

Theory explaining cancer partly retracted

Inability to repeat certain experiments, possibility that others were doctored force researchers to withdraw some of biochemical cancer theory

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A new theory to explain the deranged biochemistry at work in tumor cells—a theory so elegant that it had much of the cancer research community buzzing with excitement early this year—now is being partly retracted under admittedly painful circumstances. Despite persistent efforts, certain experiments on which the theory is based cannot so far be repeated and, worse, a few of them to contain doctored mate-

"The situation is not a good one," says Cornell University biochemist Efraim Racker, the senior investigator involved in the research. Right now everything is "very, very confusing," he adds. "We are withdrawing some of our papers. A good deal of it may be wrong . . . but it isn't all wrong. I have no choice but to withdraw it until we establish what we can reproduce."

Racker, some of his immediate colleagues, and other scientists who have collaborated with them are only reluctantly willing to discuss openly the circumstances leading up to the decision to retract some of the papers. They cite fear of legal reprisal as one reason for this reluctance. But many of them also clearly are shaken by the mere possibility that some experimental results might have been faked.

Nonetheless, a few unequivocal actions are being taken. Two manuscripts, one submitted to the *Journal of Biological Chemistry* and the other to have appeared as a Cold Spring Harbor Symposium paper, are being withdrawn, according to Volker M. Vogt, an assistant professor in the Cornell department who was part of a team that included Racker, Racker's graduate student Mark Spector,

and Vogt's graduate student Robert B. Pepinsky. Two other papers, which appeared during July in *Science* [213, 303 (1981)] and in *Cell* [25, 9 (1981)], are being retracted by means of letters to the two publications.

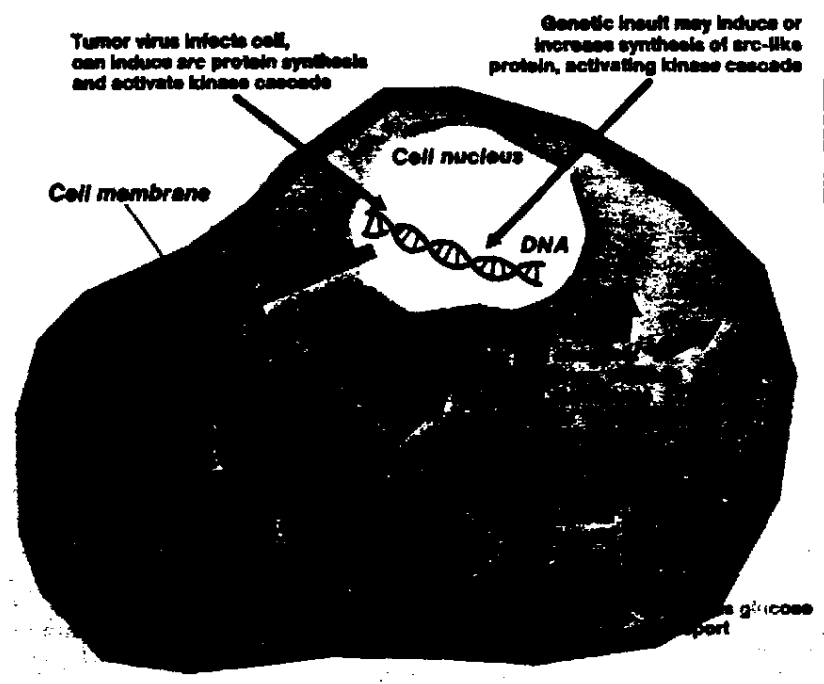
Meanwhile, graduate student Spector has been barred at least temporarily from doing research in Racker's lab. "I have asked him to wait before coming back," Racker says. No other official action has been taken yet. Spector, who is called "brilliant" and "gifted" by those close to him, including Racker, was supposed to receive his doctoral degree about now, according to Cornell biochemistry department chairman Richard E. McCarty. But the process was held up for technical reasons (not all of the necessary documents had been submitted) before any of the current doubts about this collaborative research effort surfaced. "I can't say what will happen," McCarty says. "I imagine it will take weeks; wheels grind slowly in academe."

In February, Racker agreed to

discuss the Cornell team's research with C&EN for an article summarizing recent progress in tumor virology and toward understanding fundamental biochemical mechanisms in cancer cells (C&EN, March 16, page 16). Though much of the Cornell work then was unpublished, news of it was coming rapidly into public view. Both Racker and graduate student Spector were giving public seminars. And the still-faster telephone news circuit also was at work. Enthusiasm was inducing even skeptical scientists to drop hints at press conferences about the Cornell work and its exciting implications.

Some of those scientists admit to feeling stung now. But most of them also are quick to defend the healthiness of cancer research in general. "The field is still doing nicely . . . people have been very careful," says one scientist. "This work appeared to give an unexpected intellectual unity to the field. Whether it holds up, who knows? If our thinking has been influenced by these claims, we must

Elegant protein cascade explaining cancer now doubted



Sept. 7, 1981 C&EN

URL 05145

figure out how much to jettison," he adds. "But some of it has been very stimulating."

The Cornell claims, before the current difficulties arose, appeared to bring a new unity to cancer research. They tied together much earlier findings in the scientific literature about abnormal energy metabolism in cancer cells with many of the results from the past decade or so of research on tumor-causing viruses.

The Cornell team said that a series of enzymes in cells act in a cascade in which the enzymes are phosphorylated by adenosine triphosphate molecules (ATP). An important result of that cascade, they also said, was that a sodium-potassium-ion-pumping, ATP-using protein in cells becomes phosphorylated and thus is rendered inefficient in cancer cells. The Cornell team also presented evidence, much of it based on complex experiments using antibodies as analytical tools, that some of the proteins in that cascade (all of whose members were enzymes that act as kinases) were similar or the same as certain proteins made by tumor viruses.

"A gene product, either a kinase itself or an activator of a kinase, starts a cascade of phosphorylation which increases glycolysis [an anerobic form of energy metabolism] and other metabolic pathways and alters components of the cytoskeleton, which in turn affects structure and membrane processes such as ion transport," Racker and Spector wrote in their *Science* paper. And the case also was made there that protein kinases acted as "pleiotypic mediators," meaning they exerted and controlled several activities at once in cancer cells.

That same paper in *Science* began with a quotation from G. K. Chesterton that now sounds hauntingly ironic: "There are no rules of architecture for a castle in the clouds." Unfortunately, the irony was not intentional. Racker especially, but also his colleagues, now is paying dearly as he combs through the ruins of that castle trying to see what remains intact.

"I must take the scientific responsibility," Racker tells C&EN. Thus far, during an intense effort that began late in July, a few of the results that the Cornell group claimed earlier have been confirmed, he says.

"I have confirmed the phosphorylation of the β subunit of the sodium-potassium ATPase by a protein kinase from Ehrlich ascites tumor cells prepared by Mark Spector," Racker writes in a letter submitted to *Science*. "I have established

that the phosphorylated amino acid on the β subunit is tyrosine." Racker also writes that he has repeated parts of other experiments that involved the exchange of material between his lab and that of George Todaro, who is chief of the laboratory of viral carcinogenesis at the National Cancer Institute. Their recent experiments confirm that a low-molecular-weight activator protein, obtained by Todaro, increases activity of kinase enzymes in the cascade, Racker says. But, he notes: "These experiments will have to be repeated with enzyme preparations and an activator of known purity."

Other experiments have not been verified so far. They include experiments with antibodies, attempting to identify cell kinase proteins (or their subunits) as being similar or identical to tumor virus proteins. "I am also not certain of the correctness of some of the physical-chemical properties ascribed to the protein kinases," Racker says. "It will take us many months before we know what is correct."

"We have been sifting through the rubble and ashes over the past five weeks," says Vogt of the Cornell group. "Once you distrust anything, you tend to distrust all of it—it's very painful for us."

The serious troubles began when Vogt got involved in doing more of the experiments with his own hands. He'd been precluded from such involvement before the summer, he says, because of teaching duties and the need to spend time preparing grant applications. "We had had a lot of trouble reproducing experiments," he says, "so I wanted to have a personal hand in them."

Vogt participated in one experiment involving the separation and analysis of radioactively labeled proteins. "Right away I came up with a discrepancy," he says. Samples supposedly contained proteins labeled with radioactive isotopes of phosphorus-32. But instead of phosphorus-32, Vogt found radioactive iodine in the samples. "When I started to analyze, I found the wrong thing there," he says.

Other similar evidence, obtained in other labs, also gives hints that incorrect isotopes were used in various experiments. But everyone involved is exercising extreme caution before making any public accusations of intentional wrongdoing. Indeed, there is a great deal of confusion about various materials. Nonetheless, because at least some samples are unequivocally mislabeled, and possibly deliberately doctored, virtually no

one is confident about the worth of testing them further. Racker, Vogt, and others agree that they must start "from scratch" to test what will hold up.

"Everybody is confused, disappointed, and intensely skeptical," one scientist not at Cornell says, adding that it's important to keep straight that much of the recent excitement that the Cornell scheme contributed to is based on very solid research. The Cornell work gave a new focus to the findings of others.

"From my point of view, scientifically everything in the Cornell papers is extraordinarily complex and difficult," says another scientist in the field. "Trying to reproduce something that complex is extremely difficult. Just be cautious, and give them a chance to work it out." He and others urge that Racker and his colleagues be given ample time to repeat and to sort through all of the pertinent data. However, a few scientists also say privately that it is unfortunate that Racker ignored early warning signals along the way. Racker says that he performed some of the early experiments himself and so grew to trust in the rapid progress that was being made. Some critics say that progress was much too fast to be trusted. This criticism, however valid it may be, is of course offered with the clarity of hindsight. The same critic admits: "You can't live in science without attributing honesty to your coworkers. You can be skeptical, but you can't live looking at everything as being made up." There is general agreement that Racker and Vogt are innocent victims.

Other scientists in the field also are viewing themselves as the willing believers, and thus victims of a powerfully attractive intellectual idea that now is being cast into doubt. Ironically, that insight helped to stimulate those scientists tremendously during the past few months, even giving some of them ideas for new projects. "That's the Catch 22 to this whole business," says one of those scientists. "Those projects don't rest on these [now believed to be faulty] data, but on the biochemical and intellectual approach. And it has proved to be rewarding."

For the time being, the coherent framework pieced together by the Cornell scientists must be set aside. One seemingly promising scientific career probably will be abruptly truncated. But the scientific enterprise, despite its ability to attract adversity, also is amazingly able to get back on course. □

explains Eschenmoser, that despite their apparent complexity, they readily form by themselves, provided the necessary precursor molecules are available.

Eschenmoser and his coworkers also are investigating other corrinoid structural features that may have "autogeneous character."

All natural porphyrinoids, as well as vitamin B₁₂, are known to be biosynthesized from one particular isomer of a tetrapyrrolic macrocycle called uroporphyrinogen. Living organisms such as bacteria can assemble this uroporphyrinogen isomer from a simple monopyrrolic precursor. Moreover, Mauzerall and others have shown that this same precursor can be converted easily to a mixture of four uroporphyrinogen isomers under simple chemical conditions—conditions that might have existed on primeval Earth. Of these four isomers, the one that forms in the greatest amount turns out to be the one of biological importance. This coincidence may not be accidental, according to Eschenmoser and other scientists. It is possible, he suggests, that the statistically preferred isomer—the one formed in largest amount in an abiotic environment—may have been "selected to become biosynthesized" after organisms found uroporphyrinogens to be biologically "useful and important for survival." These rudimentary organisms may simply have chosen the uroporphyrinogen isomer that was most abundant, and incorporated it into their biochemistry. □

Studies of cancer risk in chemists assessed



1981 ACS ANNUAL MEETING

Various epidemiological studies over the past dozen years have been probing the connection between the occupation of chemist and the risk of cancer. Now studies are being made and existing ones are being extended and expanded. But as yet very little in the way of a conclusion can be drawn from them.

Shelia K. Hoar of the environmental epidemiology branch of the National Cancer Institute sums up the current situation: "We can con-

Swedish mortality study finds chemists show excess of leukemias/lymphomas and brain tumors

Cause of death	Chemists		Mining engineers/ metallurgists		Architects	
	Observed	Expected	Observed	Expected	Observed	Expected
All causes	83	103.8	48	74.9	59	87.8
All cancer	32	24.2	17	17.5	11	20.5
Digestive	8	9.2	4	6.7	3	7.9
Pancreatic	2	1.6	0	1.1	2	1.4
Respiratory	3	4.0	4	3.6	5	3.4
Prostatic	3	1.5	0	1.1	1	1.4
Urinary	3	1.8	2	1.2	0	1.5
Brain	5	1.2	2	0.9	1	1.0
Lymphatic/hematopoietic	7	3.2	2	2.3	0	2.7
Hodgkin's	3	0.7	0	0.5	0	0.5
Circulatory	22	40.4	10	29.5	20	35.1
Accidents	15	21.9	16	15.5	15	17.6
Other causes	14	17.3	6	12.4	13	14.6

clude that there are some excess risks associated with the occupation of chemist. At this point, we cannot differentiate between effects of chemical exposures and socioeconomic or other factors related to being a chemist."

Hoar discussed the studies for the Division of Chemical Health & Safety. Included was a recent study of her own, conducted with Sidney Pell of the epidemiology section in the medical division at Du Pont, Wilmington. That effort was a retrospective cohort study of mortality and cancer incidence among men and women employed at Du Pont as chemists in 1959 (C&EN, Aug. 17, page 34).

All told there have been eight studies, including the Du Pont one. The other seven:

- Death certificates of some 3600 members of the American Chemical Society whose deaths were reported in C&EN from 1948 to 1967 were examined in 1969 by epidemiologists from the National Cancer Institute.

- A study of occupational mortality in the state of Washington from 1950 to 1971 included chemists.

- There was a similar study of occupational mortality in the state of California from 1959 to 1961.

- In Sweden, a retrospective cohort study was made of mortality among graduates during three decades from two Swedish schools of chemical engineering.

- Registrar General's occupational mortality study in England and Wales in 1970 to 1972 included chemists.

- Also from Great Britain, preliminary reports were made of a proportional mortality study of 938 de-

ceased members of the Royal Institute of Chemistry.

- A study of mortality by occupation level and cause of death among men 20 to 64 years of age in the U.S. in 1950 included chemists.

Together, the studies suggest that excess cancer risk is associated with the occupation of chemist. But, Hoar notes, all eight studies have their strengths and weaknesses.

For example, professional chemist societies include both persons heavily exposed to a wide variety of chemicals and persons with little or no chemical exposure. Occupations given on death certificates are often inaccurate. Several of the studies are based on proportional mortality rates, which can appear elevated as a result of deficits in other causes of death. Also, some studies are based on small numbers.

Thus, Hoar says, little can be concluded from any study alone. Still, she says, when all eight studies are considered, patterns in the morbidity and mortality data become apparent.

The studies show that chemists generally have lower mortality overall and lower mortality due to lung cancer. Half the studies show excess mortality for all cancers combined, half do not.

Lymphatic and hematopoietic cancers (leukemia), colon cancer, cerebrovascular disease, and suicide occur more frequently than expected in most of the studies. The studies, Hoar notes, have very sparse data for bladder cancer, a site often associated with chemicals. The two reports that have data for the disease show that bladder cancer occurs more frequently among chemists.

Hoar points out that better expo-

sure histories are needed to determine the factors responsible for the associations seen in the chemist studies. When more time has elapsed, she suggests, and additional subjects have developed illnesses and died, the Du Pont data could be reanalyzed by department and process. Efforts should be made, she says, to characterize occupational exposures beyond job title and department affiliation through industrial hygiene data.

One effort that continues is the Swedish study, first published in 1976 (*Lancet*, 7991, 916 (1976)). The study is being carried out by G. Robert Olin, director of the occupational health and safety department at the pharmaceutical firm Astra Inc., Södertälje, Sweden, and a professor in the preventive occupational medicine unit in the department of heat technology at the Royal Institute of Technology, Stockholm.

Olin told the Division of Chemical Health & Safety that since the original study appeared it has been expanded in several ways. The original cohort, he says, has been widened and the followup period lengthened. The original study was of chemistry graduates for three decades—1930's, 1940's, and 1950's—from the Royal Institute of Technology.

Olin now has included two other academic cohorts for comparison. The first consists of architects, a group of academics who have been educated in the same city, the same university, during the same period of time, and who can generally be considered to belong to the same social strata as the chemists. The only apparent difference between the two groups, Olin explains, is the chemical exposure that occurred among all chemists, at least during their four or five years of education.

The second additional cohort consists of male mining engineers and metallurgists, who also were educated at the Royal Institute of Technology. The idea behind including this group is that it holds an intermediate position in relation to chemical exposure, at least during the education years.

The total number of chemists involved from the three decades is 820. To this now have been added data for 581 mining engineers/metallurgists and 657 architects.

Besides adding the two groups to the study, Olin has extended and analyzed data from a followup to the study until the end of 1977.

Olin points out the "very positive results" occurring among the cohorts. For all three, the total mortality is low relative to the general population and

there is no significant difference between them. The main explanation, he says, seems to be a lowered rate of deaths due to circulatory diseases—a particularly interesting finding, he notes, since it has been believed until recently that the higher social classes in industrial societies were more prone to circulatory diseases.

As for cancer mortality, it accounts for a fifth of the deaths among the architects—identical to the proportion found in the general population. For chemists, however, the cancer rate is higher in comparison to the general population and significantly higher in comparison to the architects. Mining engineers fall between the two groups and their cancer rate is significantly elevated when compared to the architects.

Olin notes that there is no increase of lung cancers in any of the three cohorts, thus diminishing the possibility that smoking could be the major explanation for the differences among them.

Among the mining engineers and

metallurgists, there is no single cancer type that can account for the increase in cancer cases, relative to those of the architects. However, among the chemists two types of malignancies account for most of the relative increase of cancer deaths: leukemias/lymphomas and brain tumors.

Olin says that preliminary data for 1978 and 1979 are now available. During these two years, 13 more chemists have died, four from cancer. One of these cancer cases was glioma, bringing the total among the cohorts to six. And one death was due to a leukemia, bringing the total to eight.

The followup of the three cohorts is continuing, Olin says. During 1977 and 1978, the surviving chemists answered retrospective questions concerning life habits and chemical exposure. The participation rate was an acceptable 85%, Olin says, so there is the possibility for a better evaluation in the future of the relationship between life style, or chemical exposure, and various causes of death.

Lanthanide, actinide organometallics studied



1981 ACS ANNUAL MEETING

The organometallic chemistry of the lanthanide and actinide group elements is under study in many different laboratories. New information about how these elements interact with organic molecules and the potential chemical applications for these interactions was presented in several different sessions of the Inorganic Chemistry Division.

Roger E. Cramer, chemistry professor at the University of Hawaii, Manoa, for example, described the organouranium complexes he and colleagues have prepared. These researchers have been studying uranium phosphoylide complexes for several years, and now have prepared one of these complexes, $(\eta^5\text{-C}_5\text{H}_5)\text{-UCHP}(\text{CH}_3)_2(\text{C}_6\text{H}_5)$, with a carbon-uranium bond so short (2.29 Å) that it should be considered a multiple bond. Complexes with multiple carbon-metal bonds, called alkylidenes, are known for many transition metals, though they are not common, Cramer points out. Their compound is the first alkylidene of an actinide element to be observed.

The chemists have begun to investigate how similar the chemistry of their uranium alkylidene complex is to that of better-studied transition metal alkylidenes. They find, not unexpectedly, that the uranium-carbon bond is a very reactive one. For instance, carbon monoxide can insert into this bond under mild reaction conditions. (In toluene solution, the reaction can occur at 25 °C and 1 atm pressure of carbon monoxide.) Similar insertion reactions have been seen for alkylidenes of zirconium and tantalum, Cramer says.

The Hawaii chemists have other evidence of the reactivity of the carbon-uranium bond in their compound: It reacts with methyl iodide to produce an organouranium iodide salt and a phosphonium salt, and it reacts with other halogens, including halocarbons. The other organouranium complexes that the group has investigated—those that contain carbon-uranium single bonds—do not react with halocarbons. The uranium alkylidene complex also reacts with carbon dioxide, stannous chloride, and several other mild reagents.

Another group studying the organometallic chemical reactions of organoactinide complexes is that of Tobin J. Marks, Robert L. Burwell Jr., and associates at Northwestern University. This group has been investigating the effect of supporting