Cancer Among Metabolic Events

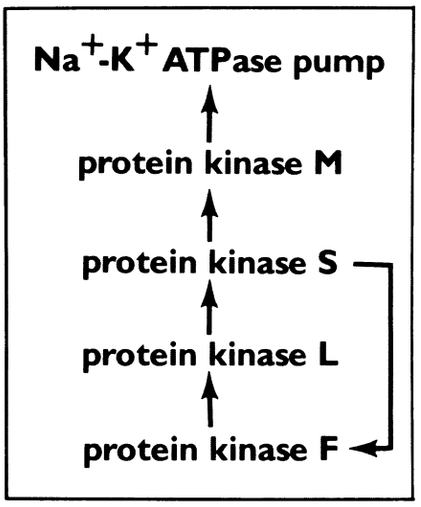
A single bad player in the orchestra of a cell's biochemical reactions can make the cell malignant. But from where in the ensemble does the discord arise? In research bringing together classical biochemistry and modern molecular biology, scientists are finding the first strong clues locating, among the metabolic pathways of a cell, events leading to the cell's transformation to malignancy.

At a seminar at the National Institutes of Health last week, Mark Spector of Cornell University described his recent research to an enthusiastic crowd, many members of which had heard of the still-unpublished results through the scientific grapevine. Although the seminar's arranger had deliberately chosen a relatively drab, or as he said "benign," title to go on the NIH events calendar, there was not even standing room at the talk given in the library of the Laboratory of Tumor Virus Genetics on the outskirts of the Bethesda campus. People sat on the chairs and table tops, crouched on the floor and perched on low bookcases, and still listeners crowded outside the doors.

Spector described one portion of the biochemical web now implicated in the transformation of some cells to a cancerous state. It is a cascade of reactions culminating in the transfer of a phosphate group to a protein complex that carries ions across the cell membrane. The cascade also adds phosphate groups to several other proteins, including one that is part of the cell's scaffolding, the cytoskeleton, so modification of these reactions can cause a variety of changes in a cell.

Efraim Racker and colleagues at Cornell were led to investigate these reactions by the observation that the ion pump, called the Na^+-K^+ ATPase, operates inefficiently in some tumor cells. They discovered that in a mouse tumor, but not in normal mouse brain, one subunit of the pump has a phosphate group attached. The addition of this phosphate turned out to be the finale of a cascade — four enzymes each catalyzing activation by phosphorylation of the next. The series resembles other cascades in cell metabolism that amplify biochemical signals, although Spector says the pattern is likely to be more complex. He already knows that one of the enzymes phosphorylates two of the others.

Phosphorylations are common means by which a cell controls biochemical reactions. But the ones Spector and Racker are investigating are not the garden variety. Traditionally a phosphate group is attached to the amino acid serine in a protein molecule. The active form of all four protein kinases in the cascade, however, has a phosphate group attached to a different amino acid, tyrosine.



A cascade of enzymes: Each activates the next. The cancer-causing genes of some animal viruses are closely related to members of this cascade.

This finding was provocative to cancer investigators. One set of enzymes was already known to attach phosphate groups to tyrosine. It is the proteins produced by the cancer-causing genes of some animal viruses called "retroviruses," and it is thought that these viral genes are pirated versions of cellular genes, important in development, that have been removed from normal control (SN: 3/7/81, p. 149).

Spector finds that in some cases the virus-encoded enzymes are very similar, if not identical, to the enzymes he and Racker have identified in the cascade. For example, one viral gene that transforms cells produces an enzyme closely related to protein kinase F; others produce an enzyme similar to each of the other three protein kinases. These results lead to the exciting hypothesis that uncontrolled production of any of these kinases can make a cell cancerous.

The cascade leading to phosphorylation of the Na^+-K^+ ATPase is not expected to be a universal mechanism for cell transformation, but it may set the style for others. Spector has recently examined 34 lines of animal cells growing in laboratory culture. Some, but not all, of the cells derived from tumors showed high levels of phosphate incorporation, and therefore may contain excess amounts of one of the cascade kinases.

Stanley Cohen at Vanderbilt University School of Medicine also has recently discovered a point in cellular metabolism where retroviruses could disrupt normal cell functions. He finds a similarity between the product of a cancer gene and an enzyme whose activity is stimulated when epidermal growth factor binds to its membrane receptor. Both enzymes phosphorylate tyrosines on at least one shared substrate. The enzymes don't seem to be identical, but, as Michael Bishop of the University of California at San Francisco says, "They are playing on the same keyboard."

"We really don't know what's going on yet," Spector cautions. But he and others are excited by the new possibilities. While chemicals and other viruses could have entirely different effects, it may be that they all cause cancer by creating discord, each in its own way, on a limited number of biochemical keyboards shared with normal developmental control. □

Progress against hepatitis B virus

When the hepatitis virus infects humans acutely, it causes debilitating disease and sometimes death. When it infects humans chronically, it seems to cause liver cancer. One way to fight this virus is with a vaccine, and researchers continue to report success in development of a vaccine that appears to be both safe and effective.

Jean Crosnier of Necker Hospital in Paris and his co-workers report in the Feb. 28 LANCET that they have found, in a double-blind, placebo-controlled trial, that a vaccine made from hepatitis B surface antigen was highly effective in protecting medical staff members at kidney dialysis centers against acute hepatitis B virus infection. Such staff members are at especially high risk of the disease. Of 318 subjects, 164 got three monthly injections of the vaccine and 154 got corresponding placebo injections. Whereas 12.3 percent of the placebo group came down with acute hepatitis B infection, only 3.6 percent of the vaccine-treated group did — a highly significant difference statistically. No hepatitis infection was observed after the 63rd day in vaccinated subjects. Success with a similar vaccine already has been reported (SN: 10/11/80, p. 231), and it now appears that vaccines made from inactivated hepatitis B antigens will eventually be used not only to protect persons at high risk of acute hepatitis B virus infection, but also to protect persons who are at high risk of becoming chronic carriers of hepatitis B virus and thus developing liver cancer.

Other scientists are working on techniques to make a hepatitis vaccine that is more abundant and less expensive than that now available, and also one that would be even more effective because it

would consist not only of the hepatitis B surface antigen but of a virus core protein. At the recent meeting in San Francisco of the First International Congress for Recombinant DNA Research William J. Rutter of the University of California at San Francisco described such an approach. He and his colleagues put two viral genes in tandem into a plasmid. One gene coded for the hepatitis B surface antigen and the other for a molecule closely related to a protein found in the viral core. To turn on operation of these genes, Rutter included in the plasmid a regulatory stretch of DNA called the trp-promoter. It can direct the bacterial cell to devote most of its protein synthesis to the viral genes. Rutter reports bacterial production of "significant quantities" of both the hepatitis B surface antigen and the core protein, as opposed to low levels of hepatitis B surface antigen purified from virus particles taken from hepatitis B carriers or as previously made in bacteria with recombinant DNA techniques (SN: 5/26/79, p. 344). Because both the hepatitis B surface antigen and the virus core protein have been detected in hepatitis patients, Rutter hypothesizes that a two-protein vaccine might be more effective than one made only of hepatitis B surface antigen.

Insights into hepatitis B virus's role in causing liver cancer are emerging from the lab of William S. Robinson of Stanford University Medical School. At the recent meeting in Dallas of the American Society for Microbiology Robinson reported that liver cancer is 300 times more prevalent among persons persistently infected with hepatitis B virus than among control subjects. Other researchers have found that hepatitis B viral DNA is integrated into the DNA of cancerous liver cells but not into the DNA of noncancerous liver cells (SN: 8/6/80, p. 102). Although both lines of research suggest that hepatitis B virus can cause liver cancer, Robinson points out that a viral cancer-causing gene per se may *not* be responsible for turning a liver cell into a cancer cell. One reason to think this is not the case is that while a cancerous liver cell's DNA contains all of the hepatitis B viral DNA, and while all of the viral DNA is transcribed into RNA, only some of the RNA is translated into proteins, notably the hepatitis B surface antigen; yet this selective pattern of gene translation has also been observed in some noncancerous liver cells. Instead, the hepatitis B virus may turn a liver cell into a cancer cell by a nonspecific mechanism, Robinson speculates. For instance, because the viral DNA is integrated into the cellular DNA, it might interrupt cellular DNA functions, and this interruption in turn might be what makes the cell cancerous.

"So I'm not at all sure," Robinson told SCIENCE NEWS, "that there is a gene in this virus that is directly responsible for changing cell function in a sense that we call [cancerous] transformation." □

Coffee and cancer: A brewing concern

People who drink coffee may be at double or triple the risk of developing pancreatic cancer, a rare but lethal disease, according to epidemiologists at the Harvard School of Public Health. If their "unexpected" finding is confirmed, and "[i]f the distribution of coffee consumption in our control group reflects that in the general population," the Harvard group says, "we estimate the proportion of pancreatic cancer that is potentially attributable to coffee consumption to be slightly more than 50 percent." But before banning the brew, remember that the jury is still out. Even Brian MacMahon and his Harvard colleagues point out that other data must be evaluated "before serious consideration is given to the possibility of a causal relation" between coffee and cancer.

MacMahon's project, described in the March 12 NEW ENGLAND JOURNAL OF MEDICINE, was actually designed to reexamine the incidence of pancreatic cancer in relation to its victims' smoking habits and to explore whether alcohol consumption plays a confounding role. The survey involved 369 pancreatic-cancer patients and a "control" group of 644 hospitalized patients with other ailments. Each was asked about smoking habits. Questions also probed the frequency with which each consumed alcoholic beverages prior to onset of the disease, the age span over which they drank and the beverage they consumed most often. Data about tea and coffee habits were limited to the typical number of cups consumed before onset of their current disease became evident.

The researchers observed no link between pancreatic cancer and use of alcohol, tea, pipe tobacco or cigars. There appeared to be a "weak positive association" between cigarette smoking and the disease—also noted in at least two earlier studies—though "only the data for women showed a significant dose-response relation." Coffee consumption was another matter.

Coffee-drinking men — regardless of how much they drank — showed a "flat" but statistically significant excess risk of pancreatic cancer over men who avoided the brew. But among women coffee drinkers, pancreatic-cancer risk increased in proportion to how much coffee they consumed. Combining both sexes, the pancreatic-cancer risk (adjusted for age and sex) showed no elevation for non-coffee drinkers, a doubling (2.1) for those drinking a cup or two daily and more than a three-fold increase for those downing at least five cups a day. MacMahon plans a follow-up study hoping to confirm or rebut these findings.

Another recent epidemiological study (SN: 1/31/81, p. 71), this one by Irving Kessler and Ruey Lin at the University of Maryland, also suggests that "one or more constituents (or contaminants) of coffee may contribute to the risk of pancreatic cancer." Because so many pancreatic-cancer patients in their study drank decaffeinated coffee, solvents such as the animal carcinogen trichloroethylene — used in decaffeinating coffee — "come immediately to mind," the researchers said. But many other factors were also linked with the cancer.

What does all this mean to the hard-core coffee addict? "Prognosis of [pancreatic] cancer is very unfavorable and therefore even a preliminary finding such as that of Dr. MacMahon's study arouses great concern," says a National Cancer Institute announcement. In fact, pancreatic cancer accounts for about 20,000 deaths in the United States annually, more than any other except colorectal, lung and breast cancers. However, NCI adds, "caution should be exercised regarding overreacting to a preliminary finding until results of further studies are reported."

But Kessler offers a further note of caution in interpreting the Harvard group's findings. After looking at a "whole constellation" of risk factors, he concludes that "there is substantial evidence" for believing that most human pancreatic cancers result from no one single factor—such as coffee drinking—but rather from a synergistic host of interacting factors. □

Metal drops that dig into graphite

Chemical reactions go faster with catalysis. That arouses the interest of physical chemists, who want to know how the catalyst speeds things up. It also attracts the interest of industrialists who see more efficient industrial processes in prospect. So as Reese Terrence Keith Baker of the Exxon Research and Engineering Co. in Linden, N.J., pointed out at the meeting this week in Phoenix of the American Physical Society, a study of the effects of metals in increasing the reaction rate of gasification of graphite can have a number of purposes. Such catalytic reaction rates may determine how long graphite structures will last, particularly in an oxygen-aiding atmosphere. Knowledge of such rates could aid development of better ways of removing graphite from places where it collects during coking and other such processes. Finally, the work may help in finding the best catalyst for gasification of coal. Gasification is often said to be the best way to make a nonpolluting fuel from coal.

In the course of their work, Baker and his co-workers have developed a tentative model for the mechanism of graphite gasification catalysis, which is always a most fascinating physical chemical point, and they have found that under the conditions of the experiment the solid metals