Brain tumor risk in petrochemical workers

Epidemiologists struggle to sort out tenuous evidence that points to elevated incidence of brain tumors among petrochemical workers

Jeffrey L. Fox
C&EN, Washington

The current effort to show a link between exposures to petrochemicals and the incidence of brain tumors among workers in the petrochemical industry is stretching epidemiology to its limits.

Some critics even argue that epidemiologists risk a tumble by leaning somewhat beyond the reasonable limits of their science. This possibility was apparent at the recent workshop sponsored by the New York Academy of Sciences at which was assembled a blue-ribbon group of epidemiologists and other authorities familiar with brain tumor incidence in humans and in experimental animals (C&EN, Nov. 3, page 6). Some observers at the workshop could not help concluding that establishing a firm link between brain tumor incidence and employment in the petrochemical industry may prove very difficult. Moreover, even if established, that link may represent the result of practices long since outmoded. Many naive and dangerously sloppy procedures of several decades ago have been eliminated.

C&EN staff photos

Robbins: bring the best minds together

But sloppy procedures still exist, and other procedures that are genuinely thought to be safe well might be otherwise. Thus, the petrochemical industry—and any other industry, for that matter—must rely on imperfect early warning systems, such as those mustered by epidemiologists, to ferret out potential health hazards in the workplace.

Epidemiologists often refer to their preliminary surveys as "hypothesis generating" devices. The current hypothesis, being voiced by epidemiologists working for the Occupational Safety & Health Administration, for the National Institute for Occupational Safety & Health, and for the National Cancer Institute, is that the incidence of brain tumors among petrochemical employees is anywhere from 1.5 to 2.5 times higher than the incidence in the general population. Several other epidemiologists, some of them employed by the petrochemical industry but others without such ties, do not find evidence for elevated incidence. These disagreements were by no means reconciled during the New York Academy of Sciences workshop.

"Polarizations came to mind during preparation of this meeting," says workshop organizer and epidemiologist Irving P. Selikoff. "We're conscious of this. But we were taught it was good to find causes of disease. Now, when causes in industry are found, there's no automatic pat on the back." There are also no automatic pats on the back when someone finds the obverse, no evidence for causes, he could have added.

Epidemiologic evidence regarding brain tumors is anything but straightforward. Many factors could serve to show the intense analytic efforts under way at the Texas petrochemical plants, including facilities run by Union Carbide in Texas City and Dow Chemical in Freeport but also at other installations owned by Texaco, Mobil, and Gulf Oil.

For instance, the incidence of brain tumors in the general population in the U.S. is on the rise, according to

Maltoni: dosage and route are important

Lawrence Garfinkel of the American Cancer Society. The rise is not a sharp one; it applies more to men than women; and it follows no immediately obvious pattern. Also, the apparent rise in incidence might be due, in part, to improved diagnostic procedures and to better reporting of cancers.

Quibbling about statistics and how to analyze them is just the sort of activity that preoccupies many of the epidemiologists now scrutinizing the petrochemical industry. There are plenty of good reasons for the quibbling—scarce data, reliance on old records of questionable validity, and sharp differences on how to approach an issue are all factors.

"It is clear there is a rise in the risk of brain cancer," asserted NIOSH's Anthony Robbins at the beginning of the workshop. "From the point of view of the workers, we've been too slow in recognizing that risk. We are attracting attention to this issue [by having a public workshop]—not to blame anyone. But until you bring the best minds together, you don't solve the problem."

What Robbins said was echoed often during the three-day meeting, particularly by his colleagues from NIOSH and OSHA. Their concerns, quite properly, revolve around the principle of ensuring the health of workers. But those concerns can act like a centripetal force, continually drawing one's attentions back to

Animal studi s provid troublesome hints

Ideally, the results of carefully controlled animal studies of carcinogens will complement epidemiology, confirming suspicions about humans by referring to systematic data about mice and rats.

But a good case may be made that animal studies are sometimes misleading and can be prejudicial to the epidemiologist. For example, humans might be more, less, or altogether insensitive to a particular chemical that induces cancer in rats and mice. How often such discrepancies crop up is not so important here. The point is that the existence of bad or even good animal studies can send epidemiologists off on an oriented search, but a wild goose chase nevertheless.

To anyone who is strict about the conduct of scientific investigations, the question of initial biases—of whatever nature—is bound to be troublesome. Thus, conscientious epidemiologists are likely to find themselves trapped in a paradox: wanting and needing helpful clues about enigmatic human health problems, but also wishing to avoid one of the worst pitfalls in science—namely, relying on false premises.

There is plentiful animal data for the epidemiologists searching for causes of human brain tumors to review. Scientists have identified several dozen chemical compounds that can cause brain tumors in various animals, including mice, rats, hamsters, rabbits, and nonhuman primates. When tested, however, many of these chemicals do not cause cancer consistently from one type of animal to another. Moreover, the anatomic site of tumors caused by a particular agent can vary from one species of animal to another. This lack of consistency is fairly commonplace in animal testing programs. It's a complicating factor that helps to muddy otherwise limpid clues now available.

Not all brain tumors are alike. The major kind of tumor being followed in the epidemiologic studies is called a glioma. The spontaneous incidence of gliomas in mice is "exceedingly low," according to Italian toxicologist, Cesare Maltoni of the University of Bologna. Thus, the incidence of gliomas arising after exposure to various chemicals is a relatively reliable test system, he says. Nonetheless, that incidence also varies according to how the chemicals are administered to the animals—by feeding, injection, implantation, or inhalation. "It is important to know the dosage and route by which a carcinogen gains entrance," Maltoni emphasizes.

Other observations of animals undoubtedly will complicate the assessment of the human health question. For example, there is the matter of varying susceptibility to particular cancer-causing agents during an animal's life span. "Embryos and newborn animals are far more sensitive to many agents than are adult animals," Maltoni notes, referring to the incidence of central nervous system tumors.

This age-dependent variation in susceptibility is pronounced in *Erythrocebus patas*, a species of reddish, African monkey being studied by Jerry M. Rice and colleagues at the National Cancer Institute in Bethesda, Md. "We cannot get central nervous system tumors by injection of carcinogens into adults," he says about such animals. "They need to have very early exposure during gestation to develop tumors later, two to three years after birth."

To Rice, these results suggest that there may be periods in life when humans are particularly or peculiarly susceptible to developing certain kinds of tumors. Thus, induction of brain tumors in adults "might have occurred very much longer in the past," he notes.

What all this means regarding workplace exposures to putative carcinogens and the incidence of brain tumors is difficult to say. And when these observations are tied into a widely held view of how cancer develops, the story looks even more complex.

Many scientists believe that cancer develops in two phases, called initiation and promotion. An early event, initiation, caused by one type of chemical, may not cause a tumor unless followed by exposure to (usually) other types of chemicals, called promoters. Thus, the search for a single type of workplace exposure to explain brain cancer incidence might be misguided.

Imagine the following situation. One group of adults, when children, either had a particular disease, took a certain medicine, or was exposed to some other "initiating agent," whereas another group of adults avoided that agent. Then during adulthood, members from both groups were met with an onslaught of many "promoting agents." Some such promoting agents might be found in the workplace, particularly when that workplace is a petrochemical facility. But other kinds of workplaces and altogether different kinds of environments also might provide some of the adults with deleterious promoting agents. Sorting through all these possibilities to identify the culprit agents could prove a formidable challenge.

Studies of animals are introducing further complications. For example, some scientists contend that virus particles are associated with chemically induced brain tumors in mice. Other scientists dispute the importance and even the existence of such particles. Their importance to human brain tumors is unknown.

Other observations are puzzling. Why, for instance, does a particular chemical produce primarily brain tumors without affecting other organs? Access of the chemical to such organs partly accounts for their differing sensitivity. But other metabolic influences, including either different activation or detoxification in various organs, also could be important, according to Paul Kleihus of the University of Frieburg in West Germany. Thus, for instance, enzymes in the brain cells of rats are slow to rid DNA there of certain kinds of damage. Long-lived damage might lead to brain tumors during the later life of such animals.

By far, the most puzzling phenomenon is one noted by Maltoni and his colleagues. Varying the dose and the means by which it's administered for some carcinogens can cause systematic fluctuations in brain tumor incidence in animals. Thus, an elevated dose of vinyl chloride, for example, induces few (or no) brain tumors, whereas a lower dose may induce many such tumors. This "masking" phenomenon departs significantly from the typical observation that tumor incidence rises directly in proportion to the dose of carcinogen an animal receives. If such a phenomenon pertains to human brain cancer, the search for pertinent workplace hazards may be tortuous indeed. □

workers and their environment. Thus, well-intentioned beliefs can predispose one to look for clues more zealously in one place than in another. This is not meant to say that OSHA or NIOSH officials are tailoring their investigations to distort the truth. But these epidemiologists clearly are instilled with the belief that the workplace, particularly a modern petrochemical facility, can and must be safeguarded.

That committment, which was on clear display among many of the federal officials at the workshop, is naturally even stronger among officials of unions representing the petrochemical workforce. "We must identify the job places where cases of brain cancer have appeared to see if there's a common denominator," says Raphael Moure of the Oil, Chemical & Atomic Workers International Union. "What are the locations in the plant?" Once that's known, he says, "conditions can be improved and exposures minimized." Like Moure, Sheldon Samuels of AFL-CIO now *assumes* that the risk for brain tumors is elevated for workers in pet-

Thomas: analyses suggest elevated risk

rochemical plants. "The failure to identify specific agents is a disappointment, but not an insurmountable difficulty," he says.

Although a fear about elevated brain cancer incidence certainly is justifiable, the statements of the two union officials indicate they have already gone from fear, to belief, to plan of action. Here again, their professional commitments more or less make that course inevitable. But it comes when many of the epidemiologists are arguing over whether there is any elevated risk. If the risk is the same as that faced by the general population, it seems a rather striking challenge to the petrochemical industry to improve the workplace.

"I'm puzzled by the widespread nature of the problem [of brain tumor incidence]," says H. Michael Utidjian of Union Carbide. "It seems widespread over many populations and work classes, sometimes extending to white collar workers. I don't know of any other case of occupationally related cancer where it's appeared over such a wide range of workplaces." It is "oversimplistic," he adds, to say conclusively that brain tumors are due to exposures in the chemical industry.

Several epidemiologists have concluded that brain tumor incidence, at least among some petrochemical workers, is not elevated. For example, one such study was conducted by Chi-Pang Wen of Gulf Oil's medical and health resources division of the company's oil refinery in Texas—the same installation included in an NCI survey. Wen says his study "represents the largest retrospective cohort study of refinery workers to date in North America in terms of length of observation (44 years of employment experience) and person-years of observation." And he concludes that "the results indicate no increased risk of brain tumors among workers at this Texas refinery."

He and NCI's Terry L. Thomas (and her collaborators) differ sharply in their conclusions. "Our analyses suggest that refinery workers have an elevated risk of brain cancer," Thomas says. And it's possible that current studies "underestimate" that risk, she adds.

Eventually, their differing conclusions have to be reconciled: They are, after all, looking at overlapping (albeit not identical) populations. Hence, it seems that discrepancies in analytic methods and in deciding what information to include stand in the way of reconciliation.

Yet other epidemiologists, looking at different workplaces, come up with all kinds of puzzling clues. Michael R. Alderson of the Institute of Cancer Research in the U.K. has surveyed eight refineries there and concludes there is no increased risk for brain cancer, although preliminary evidence for increases in malignant melanoma (skin cancer) is being followed up, he says. "But even if you accept some of the U.S. data, the problem of brain cancer is in no way like other hazards."

Hints from other surveys provide a kaleidoscope of incongruent observations. Women more than men employed in the Swedish chemical industry might be at greater than normal risk for brain cancer. Workers in the rubber tire building industry in the U.S. are also at greater than normal risk, says Thomas Mancuso of the University of Pittsburgh School of Public Health. But so are workers in the electrical machinery and also paper (and allied products) industries. And so also are workers in certain segments of the transportation industry, according to epidemiologists at the University of Southern California in Los Angeles.

Wen: results indicate no increased risk

Epidemiology is very much an outgrowth of clinical medicine. According to one wag, epidemiologic surveys are often really "hunches, shored up with statistics."

However, the fact is that many clinicians have hit upon important medical treatments by following up their hunches. The same phenomenon may be at work among the epidemiologists scrutinizing brain cancer incidence. Hence, the possibility that they are onto something means that their surveys, no matter how preliminary, cannot be disregarded.

All of this close scrutiny also may serve a broader purpose. For example, Selikoff and his colleague William J. Nicholson at Mount Sinai School of Medicine in New York City find evidence of higher incidence for other kinds of cancer besides brain tumors among several groups of industrial workers: "Brain tumors may be 'the canary' for locating other cancer risks," Nicholson says. Thus elevated risks of diseases, such as lung cancer and malignant melanoma, cited by several of the epidemiologists at the New York Academy of Sciences workshop well could prove to be a more significant public health problem than brain cancer. □

Many chemicals induce brain tumors in animals

2-Acetylaminofluorene
Acrylonitrile
1-Aryl-3,3-dialkyltriazenes
Azoethane[a]
Azoxyethane[a]
Azoxymethane
Butylnitrosourea
Cycasin
1,2-Diethylhydrazine
Diethylnitrosamine[a]
Diethyl sulfate[a]
Dimethylbenzanthracene
Dimethyl sulfate[a]
Elaiomycin
Ethyl methanesulphonate
Ethylnitrosobiuret[a]
Ethylnitrosourea[a]
1-Methyl-2-benzyl-hydrazine[a]
Methyl methanesulphonate
Methylnitrosourea[a]
Methylnitrosourethane (intraplacental)
Procarbazine[a]
Propane sultone
Propylene imine
Pyrrolizidine alkaloids
Vinyl chloride

a These chemicals can cross the placenta to induce brain tumors in offspring. Source: Victor Alexander et al., NIOSH

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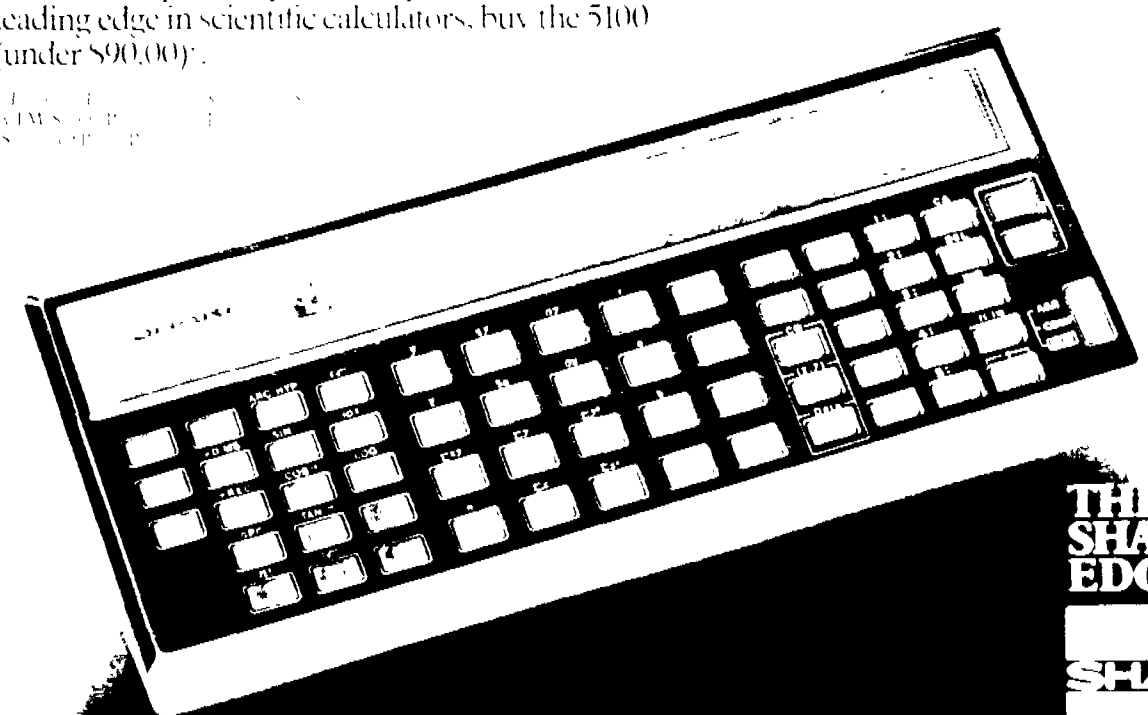

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