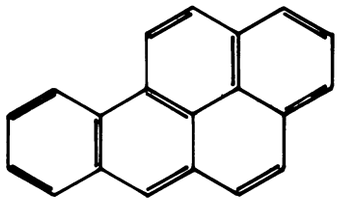
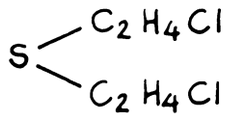
Cancer Clues from Chemical Structures

Can we predict which chemicals will turn out to cause cancer in animals?

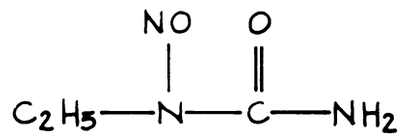
BY JULIE ANN MILLER



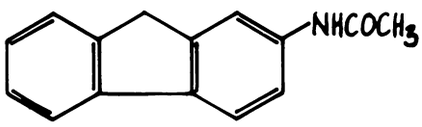
Benzo(a)pyrene



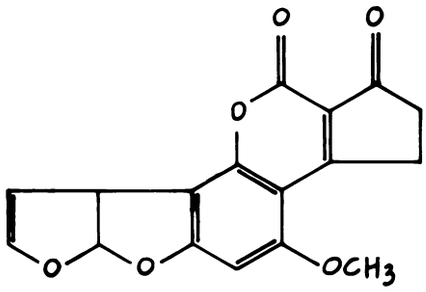
Mustard Gas



Ethylnitrosourea



2-Acetylaminofluorene



Aflatoxin B_1

No similarity is obvious among the structures of chemicals that cause cancer.

Despite the claims of cynics, everything we eat, smoke and breathe does not cause cancer. But the list of about a thousand suspected carcinogens continues to grow. Food colorings, flame retardants, pesticides join the roster. And there are already more than 30 compounds that most researchers agree cause human cancer, usually on evidence of tragic industrial exposures.

We have come some way in identifying these chemicals since 1759 when London physician John Hill wrote, "It is evident therefore that no man should venture upon snuff, who is not sure that he is not so far liable to a cancer: and no man can be sure of that."

The better known precedent for linking chemical exposure and cancer was provided by another London doctor, Percivall Pott. In 1775, he observed that young men who had been chimney sweeps had a high risk of scrotal skin cancer and he deduced that some chemicals in the soot were responsible. About 150 years later likely candidates were identified as benzo[*a*]pyrene and related polycyclic hydrocarbons.

"One cannot help being impressed by the variety of chemicals that are human carcinogens," says Charles Heidelberger of the Clinical Cancer Center at the University of Southern California. "The same is found in carcinogenesis in laboratory animals, where a bewildering number of vastly different chemical structures produce the constellation of biological effects known as cancer."

What do all the cancer-causing chemicals have in common? The answer to that crucial riddle could help identify the carcinogens among the thousands of chemicals already in the environment and the new compounds being synthesized all the time. Knowledge of the least common denominator among carcinogens could also lead biologists to the essential reactions that turn a normal cell into a cancerous one.

"When you look at the structures of chemical carcinogens you just can't see anything in common," James A. Miller of the University of Wisconsin told SCIENCE NEWS. Some carcinogens have rings of carbons, some have amine (NH_2) groups, some are even inorganic, having no carbon at all. But all these compounds can allow cells to escape from the normal controls on growth.

The ability to maintain cells in culture in a laboratory and sophisticated methods for analyzing chemical compounds have helped biologists make major advances in discovering why this group of apparently unrelated chemicals initiate cancer. In laboratory experiments cancerous cells are identified by their ability to cause tumors when they are injected into live animals. The precise description of how a chemical changes a cell so dramatically still dangles out of reach.

Duane Hopp/University of Wisconsin

James A. and Elizabeth C. Miller proposed that all carcinogens lack electrons.

The first important clue to the riddle of what all carcinogens have in common comes primarily from the work of James A. Miller and Elizabeth C. Miller. The trick is that the chemical a person eats, smokes or breathes is not necessarily the same chemical that eventually damages cells. Although a few compounds, like mustard gas, are carcinogenic without any activation, the majority of cancer-causing agents do need assistance. Ironically, it is enzymes in the body that usually change poisons into harmless molecules that, in these cases, convert an innocuous chemical into a carcinogen.

By comparing the actions of compounds in an animal and in the test tube, researchers have identified at least a dozen different internal reactions that give rise to active carcinogenic compounds. Oxygen is often added by enzymes, especially in the liver, to make foreign molecules more soluble in water and thus easier to excrete. Unfortunately, if the molecule formed is an extremely reactive carcinogen, it will immediately attack the cellular components around it.

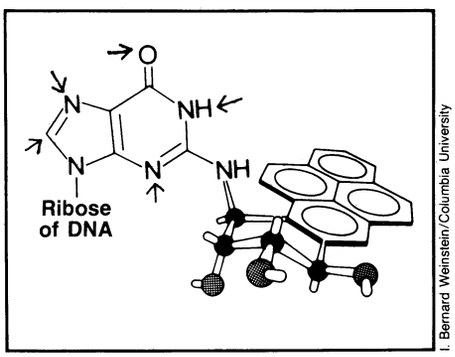
Only when scientists considered carcinogens in their final active forms could their resemblances be detected. In 1968, the Millers made a hypothesis that is now considered an axiom of cancer research. They proposed that all cancer-causing chemicals, in their ultimate forms, have a similar electronic nature. Active carcinogens are electrophiles, meaning substances with an affinity for electrons. In

Science Service, Inc. is collaborating with JSTOR to digitize, preserve, and extend access to *Science News*. www.jstor.org

contrast, the important informational molecules of a cell—DNA, RNA and proteins—have abundant electrons, and thus would be vulnerable to attack. The idea that active carcinogens lack electrons and bind to electron-rich macromolecules is one of the few unifying principles in the study of chemical carcinogenesis.

Many investigators are now looking in great detail at how carcinogenic chemicals bind to cellular macromolecules, especially to DNA. They would like to learn whether critical sites on the molecules are required for initiating cancer.

The results from various laboratories show that in a DNA molecule there are many sites vulnerable to attack. Electrophiles can bind to the sugar-phosphate backbone as well as to the bases, ring-shaped carbon and nitrogen structures. The most reactive portion of the DNA is the guanine base, in which there are six different places where carcinogens can act. The importance of these sites may depend not only on how readily they bind



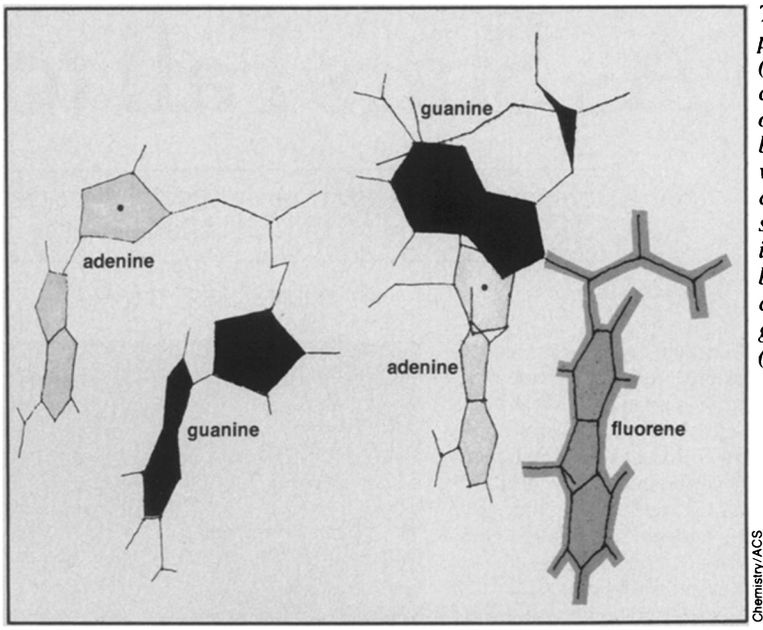
I. Bernard Weinstein/Columbia University

Benzo[a]pyrene binds to guanine at one of six possible positions (arrows).

to carcinogenic chemicals but also on activities of the cell.

Regine Goth and Manfred F. Rajewsky, in work at the Max Planck Institute in Germany, showed that the rate at which a bound carcinogen is removed from DNA may be an important factor in initiation of cancer. Ethylnitrosourea, a carcinogen that specifically attacks the nervous system, affects guanine at three positions. In the liver, guanines altered at any of these positions are eliminated relatively rapidly and cancer initiation is rare. However, in the brain, where the chemical commonly causes tumors, there is rapid repair only when guanines are altered at either of two of the positions. The researchers suggest that the third position is the site crucial to carcinogenesis, and insufficient capacity of brain cells to repair guanines altered at that site is the reason ethylnitrosourea is specific to the nervous system.

Other laboratories are looking at the structure of DNA after a carcinogen has attached. "A logical question is whether this binding produces detectable changes in the physical structure and functional properties of the modified nucleic acids," says I. Bernard Weinstein, a cancer researcher at Columbia University.



Chemistry/ACS

The normal positions (left) of constituents of DNA can be distorted when a cancer-causing substance inserts a bulky chemical group (fluorene).

Weinstein and colleagues, for example, have worked with acetylaminofluorene (AAF). That chemical was once slated to be a pesticide but was discovered to be a potent carcinogen before it was ever used. The Columbia investigators find that binding of the bulky AAF molecule appears to modify the three-dimensional structure of the DNA, so that the guanine group swings about 180° around the bond that attaches it to the rest of the DNA molecule. This shift allows the fluorene portion to take guanine's former position. Various types of DNA mutation might result, Weinstein says.

Another compound that Weinstein and collaborators have examined is benzo[*a*]pyrene (BP), a by-product of fossil-fuel combustion. BP is emitted into the air of the United States at an estimated rate of 1,300 tons per year. The most recent work, a collaborative effort among laboratories in New York, Bethesda and Chicago, gives a very detailed model showing the flat five-ringed carcinogen linked to a nitrogen at one end of the guanine. Weinstein and co-workers even distinguish between two mirror-image alternative structures. "How these polyaromatic hydrocarbon-nucleoside structures might distort the conformation and function of the modified nucleic acids remains to be determined," they caution.

Although the majority of researchers believe that carcinogens cause cancer by acting on a cell's DNA, there is still no unequivocal evidence that DNA contains the critical site. "It is a very convenient target," Miller explains, "because it is easy to see how a change in DNA could give rise to a heritable permanent change in cell characteristics, such as the inability to respond to growth controls properly." If an electrophile bound to DNA caused a change in the nucleotide sequence the next time the DNA reproduced, the error would then be fixed in totally normal DNA. "You've effected a change from now on. Unless another mutation comes along at that site, and that's statistically unlikely, you're going to have different information at that site," Miller explains.

"Personally," Weinstein says, "I believe that the effects of carcinogens on the control of gene expression may turn out to be more important than their mutagenic effects." This alternative hypothesis holds that changes in the cell proteins or RNA are the basis for transformation of a normal cell to a cancerous one. The most compelling evidence for this hypothesis is the recent discovery of conditions under which tumor cells appear to revert to a normal state (SN: 4/16/77, p. 246).

The differentiation of normal cells during development is often cited as a clear case where cellular components other than DNA affect what genetic information is expressed. The argument runs that all cells in the body have the same DNA, yet those in each tissue use different portions of the information. Supporters of the developmental or "epigenetic" theory of cancer suggest that the active forms of carcinogens interact with proteins in such a way that the normal cellular information is differently expressed.

Both schools of thought may prove partially correct. With more than 100 clinically distinct types of cancer in humans, and more in animals and plants, there is no reason why one mechanism need apply to all.

Even though the mechanisms of chemical carcinogenesis are far from settled, Miller feels that enough different classes of chemical carcinogens have been studied that chemists can at least raise a certain degree of suspicion from a given chemical's structure. "That will not prove it will be metabolized to an electrophile and yield binding," Miller says. "Nevertheless it's useful to look at structures and be aware of that possibility." □