ENVIRONMENTAL CAUSES OF CANCER

BY MERRIL EISENBUDD

NATIONAL CONCERN ABOUT ENVIRONMENTAL CANCER continues unabated. Each week the public learns about new chemicals in air, water, or food that are suspected of being causes of cancer. There is good reason to be concerned. Cancer is the underlying cause for nearly one out of five deaths. As a cause of death, cancer is now second only to diseases of the heart and circulatory system—a contrast to the early years of this century when it stood eighth on the list. Humanity yearns for a way of preventing cancer and there is good reason to believe this can be achieved by control of environmental factors.

The World Health Organization in 1964 stated that most cancers are due to environmental factors, and research during the past fourteen years has supported the correctness of that conclusion. The effects of environmental carcinogens are particularly insidious because the cancer may not develop until two or more decades after exposure to the carcinogen has occurred.

Given the facts that more deaths are now due to cancer, that most cancers are caused by environmental factors, and that the environment is increasingly polluted, it might seem obvious that pollution is the principal cause for the increased percentage of cancer deaths. Surprisingly, the facts do not support this line of reasoning.

One important reason why cancer is now responsible for a higher percentage of all deaths is that mortality due to infectious disease has been greatly reduced. A person who does not die of tuberculosis, diphtheria, or typhoid fever will probably live to an older age, with a higher probability of dying of cancer.

When epidemiologists write that sixty to ninety percent of all deaths from cancer can be attributed to environmental factors, they are using the term "environment" in its broadest sense—which includes substances naturally present in foods, sunlight, cigarette smoking, excessive use of alcoholic beverages, and chemicals or radiations to which individuals are exposed in the course of their occupations. Pollution of air, food, and water by cancer-causing, industrially produced chemicals does not appear to be a major cause of cancer for the general population, despite popular belief to the contrary.

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Cancer Trends

Death rates for the major cancers in the United States since 1930 are given in Figures 1 and 2, from which it can be seen that:

- Lung cancer in men was a comparatively rare disease in 1930, but a fifteen-fold increase has occurred. The upward trend is continuing, though at a reduced rate. Lung cancer among women increased only gradually until the late 1950s but has been increasing more rapidly in recent years.
- Stomach cancer and cancer of the uterus have decreased dramatically.
- The death rates from other cancers have either remained about the same or increased slightly.

Cancer mortality rates for U.S. white males are given in Figure 3, in which the death rates are plotted against age for the biennial periods 1943-44 and 1973-74. It can be seen from the upper two curves that there has been no significant change at age 45, but that among older members of the population the death rates due to cancer increased substantially during the thirty-year interval.

The lower two curves of Figure 3 give mortality due to lung cancer for the same biennial periods. When the thirty-year interval is subtracted from the curve of total cancer mortality for 1973-74, the middle curve is obtained, which falls slightly below the curve for total mortality in 1943-44. It is thus seen that the increase in death rates from cancer is attributable to the explosive increase in lung cancer, which is due mainly to the practice of cigarette smoking.

Although widely believed, it is untrue that cancer has increased among children. Mortality due to cancer among U.S. white females was twenty percent less during 1973-74 than during 1963-64, a reduction which resulted from improvements in the treatment of childhood leukemia and Wilms' Tumor, a cancer of the kidney.

Causes of Cancer

Appreciation of the importance of environmental factors in the etiology of cancer developed slowly. The earliest report was by Sir Percival Pott, who noted in 1776 that cancer of the scrotum was usually associated with a history of chimney sweeping. Other examples of cancer due to occupational exposure to chemicals and radiations were identified early in this century, but it was not until 1938 that it was first reported that patients with lung cancer usually were heavy smokers.

An important breakthrough occurred in 1944 when it was observed that liver cancer in U.S. blacks was occurring at a rate very much lower than in Africa, suggesting that the black race does not have a genetic predisposition to this form of cancer, as had been supposed previously, but that they were exposed to some environmental factor in Africa that did not exist in the United States.

This finding stimulated other studies that revealed that the incidence of certain other cancers changed when people moved from one country to another. Thus, stomach cancer occurs with greater frequency in Japan than in the United States, but when Japanese migrate to the United States, their susceptibility to this disease is reduced to that of the U.S. population. In contrast, the Japanese have a low incidence of colon cancer in their homeland, but when they migrate to the United States, the incidence of this type of cancer approaches the rates seen in the native-born population.

The reasons for these differences are not known but are believed to be related to dietary factors.

Some of the environmental factors that cause (or prevent) cancer are cultural in origin. A high incidence of cancer of the mouth occurs among betelnut chewers in Southeast Asia. Another example is the practice of ritualistic circumcision, which greatly reduces the incidence of cancer of the penis among Jews and Moslems. The causative factor, possibly a virus associated with the smegma secreted by the foreskin, evidently also plays a role in cancer of the uterine cervix, as evidenced by the fact that this type of cancer is rare among Jewish women. The incidence of cancer of the cervix also correlates inversely with socioeconomic status, suggesting that personal hygiene may also be a factor.
Most skin cancers are due to the action of the ultraviolet component of sunlight, another environmental carcinogen, but fortunately, except for the melanomas, these are easily treated and are rarely fatal.

Marked differences in the incidences of various cancers can be observed among various ethnic groups in the United States. Cancer mortality is relatively low among Mormons and Seventh Day Adventists, sects that prohibit use of tobacco and alcohol. The predominantly Mormon state of Utah has a cancer incidence that is three-fourths that of the United States generally and is the lowest of any state.

**Tobacco Smoking**

By 1950 the relationship between lung cancer and smoking had been conclusively demonstrated in large-scale retrospective studies in which it was shown that lung cancer developed predominantly among heavy smokers. These studies were followed by a number of prospective investigations of which the most conclusive was an American Cancer Society five-year study of more than one million men and women whose smoking habits were carefully documented. A surprising finding was that in addition to lung cancer, smokers were also subject to a greater risk of developing cancers of the bladder, kidney, pancreas, liver, and stomach as well as leukemia.

The risks due to tobacco smoking are further increased by synergistic interaction with other carcinogenic substances. Lung cancer is relatively rare among nonsmoking uranium miners and asbestos workers but occurs among smokers in those trades at an incidence far higher than can be explained by either the number of cigarettes smoked or the workers' exposure to airborne carcinogens. There is also evidence that cigarette smoking increases the carcinogenic action of air pollution.

**Alcohol**

Cancers of the mouth, larynx, and esophagus occur more frequently among heavy drinkers, but the etiological relationships are confused by the association of drinking and smoking. It has been estimated that alcohol could be responsible for seven percent of all cancers among men and perhaps two percent among women.

Per capita consumption of beer has been found to be closely correlated with cancer of the rectum. The causal factor is unknown and may be something in the life style of heavy beer drinkers rather than the beer itself. This association does not hold for other alcoholic beverages.

**Naturally Occurring Substances in Foods**

Some foods contain carcinogenic chemicals of natural origin. These include bracken, the common fern, which is used in salads in the United States, New Zealand, and Japan. Some spices, oils, and constituents of tea and coffee are suspected of being carcinogenic on the basis of laboratory tests. Several fungi are known to be capable of producing tumors in experimental animals, and the aflatoxins, which have been shown to be potent carcinogens, are produced by the fungus *Aspergillus flavus* found in moldy peanuts and grains. The aflatoxins have been identified as causing liver cancer in fish, are highly carcinogenic for laboratory rats, and may be the cause of the high incidence of liver cancer in parts of Africa and the Far East. Aflatoxins have not been associated with human cancer in the United States.

There has been considerable discussion in recent years of the role of nitrosamines, which are known to be strong carcinogens in experimental animals and can be formed easily under a variety of conditions in soil or during food storage or cooking. Nitrosamines in food can possibly be produced by bacterial action from nitrates and nitrates that are added to some foods to prevent botulism. There is no epidemiological evidence that the nitrosamines cause cancer in man.

The practice of cooking food can result in the production of polycyclic aromatic hydrocarbons, a class of highly carcinogenic compounds, of which the most common is benzo[a]pyrene. This is the carcinogen that was probably responsible for the scrotal cancer observed in chimney sweeps two hundred years ago and is known to be present in the contaminants discharged into the atmosphere when fossil fuels are burned. There is no evidence that the polycyclic hydrocarbons created in food processing have produced cancer in humans but, like many other carcinogens known to be present, they must be regarded with some suspicion.

**Air Pollution**

There is evidence that urban residents are subject to a higher risk of lung cancer than people living in rural areas, but there is no general agreement as to the cause of this "urban factor," and it is not certain that the increased risk is due to air pollution, although some investigators have suggested that this is so.

The case against the argument that air pollution is responsible for the higher incidence of lung cancer in urban areas has been recently well summarized by Goldsmith and Friberg:

- a. The urban factor should be largest in those states and countries where there is the heaviest urban pollution. It is not.
- b. If exposure to urban pollution causes an augmentation in lung cancer, then the rates should
be higher in life-time urban residents than in migrants to urban areas. They are not.

c. Correlations of lung cancer rates with measured pollution should be found by studies in the United Kingdom where both lung cancer rates are high and pollution has been great. A positive correlation is found with population density, but not with pollution.

d. If the urban factor were community air pollution, it should affect women at least as much as men. It does not appear to.

e. If urban pollution by benzo[a] pyrene makes an important contribution to the urban excess, lung cancer in the locations most polluted by this material should be highest, and when the agent decreases, lung cancer should do so as well. This has not been shown to occur.18

One of the main obstacles to an understanding of the relationship between air pollution and cancer is the overriding influence of cigarette smoking. Among nonsmokers, the age-adjusted annual death rate from lung cancer is very low, in the range of three to five per 100,000 of population.16 There are traces of carcinogens in urban air, and their action may be synergistic with the effects of cigarette smoking. However, there is evidence that smokers who live in cities smoke more than those who live in rural areas and that they tend to start at an earlier age.17 This could explain why smokers who live in cities have a higher incidence of lung cancer than smokers who live in rural areas.

The particulate matter suspended in urban air contains substances that can produce cancer in laboratory animals,18 and studies indicate that the most significant carcinogens are due to a group of organic chemicals classified generally as the previously mentioned polycyclic aromatic hydrocarbons. Benzo[a] pyrene (BP), which originates mainly from combustion of fossil fuels, can be measured in the air of all cities, and the amount present correlates with the concentration of particulates.

Coal burning produces more BP than other fuels, and because the use of this fuel for space heating and power generation has diminished during the past three decades, the average concentration of BP has dropped from 6.6 μg/100 m³ to 2.5 μg/1000 during the period 1959-1967.18 The city-to-city differences in the BP levels are considerable; during the period 1958-59 the BP concentration in the air of Birmingham, Alabama, was six times greater than in Los Angeles. The difference was presumably due to the greater amount of coal consumed in Birmingham. In New York City the concentration of airborne particulates has diminished by almost ninety percent since the 1930s.19 Thus, although the BP concentrations in the New York City atmosphere have only been measured during the past few years, it may be assumed that the concentrations are much lower now than in the past. This follows from the fact that the concentration of BP is known to correlate with the concentration of airborne particulates.

<table>
<thead>
<tr>
<th>Population</th>
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<tr>
<td>&gt; 50,000</td>
<td>52</td>
</tr>
<tr>
<td>10,000 - 50,000</td>
<td>44</td>
</tr>
<tr>
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<td>43</td>
</tr>
<tr>
<td>Rural</td>
<td>39</td>
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Source: See note 21.

A curious finding of almost all investigations has been that the urban-rural gradient has much less effect on women than on men. This can be interpreted in several ways. It may be that men in urban areas are at higher lung cancer risk because they are exposed to carcinogens in the course of their occupations. It is also possible that men may be exposed to more "second-hand" smoke in the course of their business and social activities.20 In one Czechoslovakian study it was found that the air of a beer hall contained BP at levels ten to one hundred times higher than the concentration in city air.21 More data of this kind are needed.

One of the most thorough of the epidemiological studies, in which the populations were adjusted for age and smoking, showed a distinct gradient in lung cancer mortality as a function of community size. This is shown in Table 1, in which it is seen that the lung cancer incidence gradually increased from 39 to 52 per 100,000, a difference of 33 percent, as one moved from rural areas to cities having populations greater than 50,000.21

During the past 25 years, exposure to BP in community air pollution has diminished by about two-thirds, but the incidence of lung cancer has increased about twofold. The cases of lung cancer now being seen are presumably due to exposure that began more than two decades ago, and, if BP is in fact a useful indicator of the presence of atmospheric carcinogens, the rural-urban gradient should diminish in the years to come. For the time being the data suggest that if we accept rural mortality from lung cancer as a basis for comparison, the present levels of BP exposure would, at a maximum, increase the risk of lung cancer among smokers and nonsmokers alike by about two-thirds in those cities in which the BP concentrations are relatively high. For nonsmokers this is a very low additional risk, because for them lung cancer is such a rare disease. However, for a person smoking one pack of cigarettes or more per day, the urban factor can further increase the already greater risk of lung cancer due to smoking.

Cancers Produced by Medical Treatment

Cancers have resulted from medical uses of carcinogenic drugs and radiations (X-rays and radium). Thus thyroid carcinomas have developed among children who received X-ray therapy for thymus enlargement, and an elevated incidence of leukemia has been reported among children who were irradiated in fetal life during maternal pelvic X-ray examination and among patients irradiated by X-ray for treatment of an arthritic disease, ankylosing spondylitis.22 A number of other examples could be cited.

A major unresolved question is the
significance of the relatively low doses of radiation involved in routine diagnostic X-ray procedures. If it is assumed that the risk of cancer from ionizing radiation is directly proportional to the dose received and that there is no threshold, then one must assume that any radiation increases the probability of cancer production. Although many radiobiologists believe that there is a threshold dose below which the risk of cancer is not increased, prudence dictates that unnecessary exposure to radiation should be avoided.

The full extent to which cancers are caused by the use of drugs is not known. Because of epidemiological difficulties, adequate studies have been conducted for only two drugs—isoniazid (administered for treatment of tuberculosis) and the female steroidal sex hormones.23

Occupational Cancer

During the past several decades information about occupational cancer has gradually been accumulated by studying the painful experience of workers in many industries. Only in the past few years have experimental techniques developed to the point where it has become possible to predict the carcinogenicity of a substance on the basis of laboratory tests.

Some cancers occur so rarely in the general population that they can be readily identified when they appear even in small numbers due to occupational factors. Others occur in such high incidence in the general population that sophisticated statistical techniques must be used to study the health records of large numbers of employees in order to identify an excess cancer risk.

Bone cancer was quickly found among luminous dial painters24 beginning in the 1920s; because it is such a rare disease in the general population, the first few cases attracted attention since they were reported from the same community and the patients had a common history of employment. Other examples of rare cancers are angiosarcoma, a liver cancer that has been found among workers exposed to vinyl chloride in the plastics industry, and mesothelioma, a rare cancer of the linings within the chest and abdominal cavities which has been reported among workers exposed to asbestos dust.

When cancers of such an unusual kind are observed to occur in industry, it is understandable that they should attract a good deal of attention. However, they are apt to occur in fewer numbers than other cancers that are seen more frequently in the general population. There is evidence that the incidence of relatively common cancers, such as those of the lung, stomach, and urinary tract, is increased among large groups of workers in the textile, woodworking, and steel industries.25 The epidemiological studies needed to assess the overall impact of occupational factors on the statistics of cancer mortality are only beginning, but there is sufficient evidence to suggest that from one to five percent of all cancer deaths are due to occupational factors.1,26,27

It is now becoming possible to identify potential carcinogens on the basis of their chemical and physical properties. In one outstanding example, it was suspected that bis chloromethyl ether should be a potent carcinogen on the basis of its chemical structure,28 a finding that was confirmed first by tests on single-celled organisms (there is a strong correlation between the ability of a substance to produce mutagenic changes in bacteria and carcinogenic changes in mammals) and later on mouse skin.29 These quick tests were followed by inhalation experiments that showed lung cancer could be produced in laboratory rats30 and finally by epidemiological studies which disclosed that lung cancer...
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was in fact occurring in excessive incidence among industrial employees exposed to this compound.31

Of course, this is another example in which human carcinogenicity was demonstrated after the fact. We happen to be in a period where we will be repeatedly discovering new carcinogens only after the damage has been done. In the future, carcinogens will be identified before there is the opportunity for significant human exposure, and the occurrence of occupational cancer will be eliminated or at least minimized by the application of more stringent industrial hygiene controls than we practiced in the past.

Two hundred years after Pott’s observation of the high incidence of cancer among chimney sweeps, we still know much too little about the occupational causes of cancer.

Food and Agricultural Chemicals

The use of chemicals in agriculture and in the food processing and distribution industries has been of enormous benefit to public health. Chemicals make it possible to increase crop yields and help to reduce losses due to weeds, pests, molds, or other biological agents of spoilage. Other chemicals are used in packaging materials and these can contaminate food by direct contact. Some of the chemicals used by the food industries, such as coloring agents, may have only cosmetic or sales value, but others are of enormous benefit.

The fact that some of these chemicals have been found to be carcinogenic in experimental animals presents the public health and regulatory agencies with the most difficult of all problems in environmental toxicology. The subject has received widespread attention during the past decade, and properly so. Food chemicals are so widely used that almost everyone in the world is exposed to them. Because cancers may not develop for several decades after exposure, a potent carcinogenic chemical could commit an exposed population to an irreversible epidemic of cancer in the years ahead.

Background Radiation

Brief reference has already been made to cancers caused by exposure to radiation in medical practice and in the workplace. Mention should also be made of two other sources of radiation exposure—natural radioactivity and radiation resulting from the activities of the nuclear power industry.

Natural radioactivity is a ubiquitous property of the environment. Uranium and thorium and their radioactive decay products (such as radium and radon) are present in the soil, the food we eat, our drinking water, and the air we breathe. Two essential elements, carbon and potassium, are also radioactive.

The total body irradiation received by humans in most parts of the world results in a dose of about 0.1 rem per year, a figure that varies somewhat from place to place depending on the altitude above sea level and the composition of the rocks and soil. The dose increases as one moves to higher altitudes because the atmosphere becomes thinner and serves as a less effective shield against cosmic rays. The dose from the rocks and soils varies depending on the amount of radioactive minerals present.

The lungs receive a higher radiation dose than the rest of the body due to the natural presence of the radioactive gas radon. Radon exposure in many localities will deliver a dose of about 0.2 rem per year to the linings of the bronchial passageways; this is of particular interest since the bronchial passageways are where most lung cancers originate. Dose rates of nearly ten times this amount are encountered indoors, particularly if a building is made of materials with a high content of natural radium. Ironically, the indoor concentration of radon has been reported to be increasing because energy conservation requires that homes be weatherproofed. The elimination of energy-wasting drafts means a higher concentration of radon within buildings. This is another example of the actions and reactions that make it necessary for the environmental scientist to deal constantly in tradeoffs.

Radon, which has a half-life of 3.8 days, decays to Pb-210, which has a half-life of 22 years, and this radioactive
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substance is ultimately deposited on the earth's surface. It, in turn, decays to polonium-210, which is a highly radioactive substance. Only in the last few years have we begun to appreciate that humans have always been subject to this form of natural fallout and that broad-leaved plants contain relatively high concentrations of this isotope because of the deposition of Pb-210 on their foliage. Polonium-210 is deposited on the leaves of tobacco plants and becomes incorporated into cigarettes. The lungs of smokers contain measurably more polonium-210 than the lungs of nonsmokers.

Nuclear power plants in the United States are required to limit their discharges so that no individual will be exposed to more than .01 rem per year. In the case of airborne releases, the maximally exposed individual is usually a hypothetical person who is assumed to sit at the site boundary 24 hours a day throughout the year. If there is a dairy nearby, the maximally exposed individual may be a child who obtains all his milk from grazing cows from the one location. In other cases the maximally exposed individual might be a person who consumes fish or shellfish from the location where exposure to the liquid releases is maximum. Hence, if such an individual does not exceed the permissible dose, others will receive less. U.S. power plants have operated, without significant exception, well within the limits imposed by the regulations. It has been estimated that by the year 2000 the average dose received by the U.S. population will be .0002 rem per year, or about 0.2 percent of the dose received from natural radioactivity.

It may help to place the subject in better perspective by relating the maximum permissible radiation dose for the general population (.010 rem per year) to the dose ordinarily received from natural sources. In New York City there is a difference of .015 rem per year between the dose received by most residents of Brooklyn and by people living in Manhattan; most of Brooklyn is built on sand, which has a lower level of natural radioactivity than the rocky terrain of Manhattan.

Do the radiations from nature cause cancer in the general population? If so, will the small additional dose from nuclear power plants add a small but finite number of cancer cases to those caused by other environmental factors? As in the case of diagnostic x-rays, this is an unresolved question. Most of the information on which our knowledge of radiation effects is based involves relatively high doses (greater than 10 rem) administered over a short period of time. The information comes from human experience (medical uses, industrial experience, and the Japanese bombings) as well as from a vast number of animal experiments. It is not a simple matter to estimate the effects of low doses of an injurious agent received over a long period of time using data obtained at high doses administered in a few minutes or hours.

There is some evidence that the risk of cancer following radiation exposure is proportionate to dose and is independent of the rate at which the dose is received, but there is also evidence that the opposite is true—that the risk diminishes when the dose is protracted and that there is a threshold.

The first set of assumptions has been adopted in the interest of safety but most reports on the subject note that the estimates of risk based on these assumptions are conservative in that they define the upper limit of risk. The actual risk could be lower if the dose-response relationship is not linear or if the effect is reduced when the dose is protracted. Relying upon all available human data, and accepting the assumptions with respect to linearity of response and independence of dose rate, we can estimate that a dose of 1.0 rem delivered to one million persons will cause about one hundred cancers over a twenty- to thirty-year period. If the dose-response relationship is not linear or if there is a threshold or pronounced dose-rate effect, the number of cancers would be less and could in fact be zero.

It is not possible to state with certainty that there is any such thing as a safe dose of a substance capable of producing cancer. Fortunately, as the dose diminishes, the risk diminishes and the time that elapses until the cancer appears may increase.

Obstacles to Assessment

Experimental animals are the principal means by which carcinogens are tested for carcinogenicity. The doses administered in these tests can be as much as a million times higher than the dose that humans would be expected to receive, but the animal experiments are valuable for studying the mechanisms by which cancer is produced and they help to identify their relative degree of carcinogenicity.

Among the major problems are differences in the susceptibility of species: a substance that produces no effect in the rat or hamster may cause one type of tumor in the mouse and another in the cat. Some of the tumors may be
By 1950 the relationship between lung cancer and cigarette smoking had been conclusively demonstrated. It was further discovered that smokers were also subject to a greater risk of developing certain other types of cancer. Here a "smoking machine" is being used to collect cigarette smoke for testing for carcinogenic properties.

benign, but there is evidence that many such tumors in experimental animals will in time become malignant. The Environmental Protection Agency and the Occupational Safety and Health Administration have taken the position that if a chemical produces benign tumors in experimental animals, it should be assumed that the chemical is potentially capable of causing cancer in animals.

In an ideal world it would be possible to identify the "safe" dose, that is, the dose that will produce no injury to any person in an exposed population. However, it is not possible to state with certainty that there is any such thing as a safe dose of a substance capable of producing cancer. Fortunately, as the dose diminishes, the risk (probability of developing cancer) diminishes also, and there is evidence that the time that elapses until the cancer appears may also increase. Thus, at very low doses the "incubation" time may actually exceed the lifespan of the individual. If this is so, there is a "practical threshold," despite the fact that no threshold exists in theory.

The statistical problems associated with defining dose-response relationships for the low doses associated with exposure to community pollution are so formidable that an experimental approach becomes impractical. It would be necessary to test millions of animals. The cost of acquiring the experimental animals and maintaining them for their lifetime, together with the cost of examining the histological sections, would be staggering. Even if the money could be obtained, one could not find enough experimental biologists to provide the skilled attention needed for the millions of slides for which microscopic study would be required.

In 1958 Congress became impatient with the inability of scientists to provide unequivocal information about the safety of chemicals used by the food industry. A clause was added to the Food, Drug and Cosmetic Act which provided that "no (food) additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animals, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal. . . ."

It would at first seem as though this clause, which has come to be known as the Delaney Amendment, should be totally noncontroversial: what possible justification could there be for deliberately adding to our food supplies substances that are known to produce cancer in experimental animals? However, the amendment has in fact been highly controversial, with powerful arguments being presented by both the
proponents and opponents of the bill. The recent proposal to ban saccharin is reviving debate about the pros and cons of the Delaney clause.

The arguments of the proponents are rather clear-cut. It is generally true that chemicals that are known to have produced cancer in humans have also produced cancer in experimental animals. Prudence therefore requires the assumption that the reverse is also true—that most chemicals that produce cancer in experimental animals will also produce cancer in humans. The proponents of the Delaney clause also note that there is reason to believe there is no threshold—that there is no such thing as a safe dose—and that the long incubation period from the time of exposure to the time cancer develops is reason for great caution. Finally, some proponents contend that cancer is such a dreadful disease that its prevention should proceed at all costs. Risk-benefit analyses should not be considered relevant if the risk is one of contracting cancer. These are some of the principal arguments used to defend the Delaney amendment.

However, the amendment's opponents have much to say in their behalf. They note that food additives are not permissible in any concentration if cancer can be produced in any animal at any dose over any period of time. It would seem at first that this is a desirable policy. Who would want to consume a food that contains a substance known to cause cancer in experimental animals? The problem is that many substances will produce cancer in some organ of some experimental animal if administered in sufficiently high doses. For example, the cyclamates were used in "low calorie" soft drinks to the extent of 0.25 to 1 gram per 12-ounce bottle. Based on these data, it would be necessary for a human adult to consume 138 to 552 twelve-ounce bottles per day in order to consume the quantity of cyclamate known to have produced tumors in the rat.77

Another argument advanced against the Delaney amendment is that the food additive must be withdrawn from the market if it is detected as a residue in food at any concentration. Whether or not a substance can be detected depends on the available methods of analysis. From decade to decade the methods have become progressively more sensitive so that, for example, the class of chemicals known as dioxins, which could not be measured by any method in 1950, can now be detected at a level of a few parts per billion. The lower limit of sensitivity for di-ethylstilbestrol has been reduced by a factor of 100 in the past twenty years and the limit of DDT by about 1000. Thus, chemicals which could not be detected in foods in 1950 can be detected readily by the methods of analysis that are now available.

Increase in cancer death rates is due to the explosive increase in lung cancer associated with cigarette smoking.
A 1973 study by the President’s Scientific Advisory Committee noted that “the rigid stipulations of the Delaney clause springing from presently inadequate biological knowledge place the administrator in a very difficult interpretive position. He is not allowed, for example, to weigh any known benefits to human health, no matter how large, against the possible risks of cancer production, no matter how small.”

Society has not as yet developed a philosophical basis for judging the acceptability of an innovation based on benefit-risk analyses. There are many who clamor for absolute safety although we know that absolute safety is unattainable. Others find it repugnant to stomach. The explosive increase in cancer of the lung is due for the most part to the practice of cigarette smoking, although occupational exposure to carcinogens is also a significant factor.

The cases of occupational cancer seen up to the present time can for the most part be attributed to working conditions that would not be acceptable by current standards. Industrial hygiene practices have steadily improved in recent decades and the cancers now being reported from industry are the result of conditions that existed twenty or more years ago, when there was little or no effort made to screen industrial chemicals for their carcinogenicity. The mechanisms by which workroom detect carcinogens will undoubtedly continue to improve. Theoretically it may be possible some day to detect even a single molecule of a carcinogen in as large a sample as we care to collect. We must expect also that the chemical industry will continue to produce new compounds, some of which may prove to be mutagenic, tumorogenic, or carcinogenic in some laboratory species. Many questions remain to be answered. Is there a safe dose? How safe is safe? How does one translate laboratory findings into sensible regulations? These questions will require both scientific wisdom and a sense of social perspective. Regulations must be developed to assure protection of the public health. However, if the regulations are administered too zealously, society may be deprived of the benefits of many chemicals useful for assuring continued human well-being.

When epidemiologists write that 60 to 90 percent of all deaths from cancer can be attributed to environmental factors, they are using the term “environment” in its broadest sense—which includes substances naturally present in foods, sunlight, cigarette smoking, excessive use of alcoholic beverages, and chemicals or radiations to which individuals are exposed in the course of their occupations.

What about the Future?

It is reassuring to find, contrary to popular belief, that cancer among the nonsmoking population has not increased during the past thirty years. To the contrary, striking reductions have taken place in cancer incidence at two anatomical sites, the uterus and the safety can be better assured have now been made available with passage of the Occupational Safety and Health Act and the Toxic Substances Control Act. The carcinogenicity of industrial chemicals will, in the future, be evaluated in advance so that precautions can be taken that will minimize, if not totally eliminate, the risk of cancer. Occupational exposure, which is now thought to account for one to five percent of all cancers, should cause even fewer cases in the future.

The future importance of carcinogens in food, air, and water is more difficult to estimate. Our ability to make tradeoffs between benefits and costs when the costs are measured in shortened years of human life, despite the fact that the benefits may be measured in years of life extension.

ACKNOWLEDGEMENT

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NOTES


declared that as much as twenty percent of all cancer could be due to occupational factors. His estimate, based on an analysis prepared by the staffs of the National Cancer Institute, National Institute of Environmental Health Sciences, and the National Institute of Occupational Safety and Health, which became available in photocopy form a few days after the Califano statement was issued. The statement, which is based on assumptions which can only be regarded as questionable at the present, illustrates the need for better epidemiological information than now exists.


