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Environmental Pollutants and the Epidemiology of Cancer

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Cancer etiology involves the interplay of genetic and environmental factors. Striking geographic differences and changes in cancer incidence over time have led epidemiologists to infer that probably the major etiologic component is environmental. Recent experiences with vinyl chloride, kepone, and polybrominated biphenyl illustrate the problems involved in epidemiologic studies of proven or suspected environmental carcinogens. While epidemiologic studies will continue to be an essential means for monitoring potential human risks, the long latent periods involved in human carcinogenesis severely limit the usefulness of such approaches for disease prevention. While *in vitro* and animal test systems can never fully supplant human studies, they represent our only means for detecting potential carcinogenicity before human exposure has become widespread or long established.

By promising to detect environmental hazards before human exposure occurs, mutagen testing should be far more effective than epidemiologic studies as a technique for preventive medicine. This, of course, is because epidemiologic studies can take place only after exposure occurs, and usually only after disease develops.

The disease prevention shortcomings of epidemiology are particularly noticeable in the field of cancer. Usually 10-20 years can be expected to pass before cancer develops following initial exposure to a carcinogenic agent, and the interval will inevitably be longer before clinical and epidemiologic observations suggest cause–effect relationships. In the meantime, human exposures continue, and economic adjustments take place which make preventive measures difficult once carcinogenicity is finally recognized. The relation of cigarette smoking to lung cancer continues to be a major case in point.

I would like to discuss selected aspects of cancer epidemiology as it concerns environmental pollutants, using as illustration three environmental problems with which I am familiar: vinyl chloride monomer (VCM), kepone, and polybrominated biphenyl (PBB).

First, however, some general comment is in order regarding the role of environmental factors in cancer etiology. Cancer is a complex set of diseases, and its causes are equally complex. Undoubtedly any given case can be regarded as the result of interacting intrinsic and extrinsic causes, host resistance and genetic constitution interacting with environmental exposures to radiation and chemicals. Currently, environmental exposures are regarded as accounting for 80–90% of cancer causation. The basis for this idea comes from epidemiologic analysis of cancer rate differences in different parts of the world (*1*) and of cancer rate changes over time (such as lung cancer) or in migrant groups (*2*). Rapid change and large geographic differences in the absence of major genetic variation seems compatible only with environmental etiology.

In the United States, for example, wide variations in cancer incidence are evident in cancer mortality data charted by county for the years 1950–1969 (*3*). Possible environmental etiologies include variations in diet and in personal habits such as smoking, as well as local differences in exposure to occupational carcinogens and to chemical pollutants in air and water. Epidemiologic studies to date have suggested various correlations that are currently being investigated further: for example, the county distribution of petroleum industries correlates with white male rates for cancers of lung, nasal cavity, and skin (*4*), while colon cancer and postmenopausal breast cancer show patterns compati-

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ble with socioeconomic level and hence perhaps with differences in diet (*5*).

On the whole, such observations are quite indirect, merely suggesting associations and indicating directions for further research. It also must be recognized that the data on which such analyses are based are far from ideal. They represent cancer deaths that occurred 10–30 years ago (and hence were diagnosed several years on the average before that) and, by virtue of coming from death certificate records, are of decidedly uneven quality. In certain parts of the country far more accurate cancer incidence data are now becoming available. Nonetheless, when one considers latent intervals, even the best cancer incidence data reflect carcinogenic events occurring in the 1950's. By the same token, the 1950–69 mortality data, which have stimulated much current work in cancer epidemiology, arise from carcinogenic exposures that took place in the 1930's and 1940's.

In addition to latency, intensity of exposure or dose is a central consideration. Often the strength of epidemiologic observations relate to the extent to which they can show that disease risk is a function of exposure dose. Exposure levels are also important in terms of threshold dose or that level at which risk is not increased. Often dose considerations are such that links between risk factor and human disease are epidemiologically discernible only in highly exposed occupational groups.

Vinyl Chloride Monomer

The discovery of VCM causes human cancer illustrates both the practical importance of occupational studies from a dose-response viewpoint as well as the significance of latency considerations. The VCM human cancer discovery was essentially an epidemiologic matter. The epidemiologic observation was extremely simple, merely the description in December 1973 of three cases of hepatic angiosarcoma (HAS) in VCM polymerization workers at the B. F. Goodrich plant in Louisville, Kentucky (*6*). That this observation was etiologically convincing related both to the extreme rarity of this particular tumor (less than 0.1 case per million persons per year) and to the high VCM exposure of polymerization workers. These exposures, of course, dated back for many years prior to cancer diagnosis, an average of about 20 years latency for the first 16 cases recognized in the United States (*7*). This latency corresponded closely with growth in PVC production since World War II. Subsequent reports of animal exposure studies reinforced initial epidemiologic observations (*8*).

Since that time, attention has focused on potential human risk from VCM exposures at lower dose levels. Essentially no further epidemiologic evidence has appeared linking human cancer directly to VCM except to confirm the high exposure polymerization-worker situation. No evidence for increased HAS occurrence over time, particularly in geographic proximity to VCM production or polymerization facilities, has been found either in the U. S. or in Great Britain (*9, 10*). It was found, however, that HAS occurs about twice as often in males as in females and usually at younger ages. Such findings suggest the general importance of occupational exposures in causing this particular tumor. Since most cases have no clear connection with VCM exposure, it follows that other occupational carcinogens are involved. One such material appears to be arsenic (*11*).

Kepone

Obviously, the delayed nature of human carcinogenesis greatly hampered the control of VCM exposure. Epidemiologically, therefore, it is most useful if potential carcinogens also have acute health effects. There then exists the chance that acute toxicity will lead to curtailed exposure and hence curtailed carcinogenic potential. The recent kepone episode illustrates such a situation. Between March 1974 and July 1975 grossly excessive and uncontrolled occupational exposure to this chlorinated hydrocarbon insecticide took place at a small chemical plant in Hopewell, Virginia. Of a total of 133 workers exposed, 57% (76 workers) developed acute neurologic illness involving tremor and nervousness (*12*). Similar illness had previously been observed in laboratory animals (*13*). The plant was closed in July 1975, by which time, however, extensive environmental pollution had already taken place. This involved not only airborne pollution in the neighborhoods surrounding the plant, but water pollution of the entire James River by way of the Hopewell sewage treatment system. Epidemiologic surveys of exposed populations showed detectable blood kepone in persons living near the plant as well as in sewage workers and in the kepone workers themselves and their families. Levels ranged as high as 0.033 ppm in neighborhood residents and as high as 11.8 ppm in insecticide workers. Highest levels were in clinically affected workers.

Subsequent findings of hepatic tumors in kepone-exposed laboratory animals (*14*) have heightened suspicion that this material poses a carcinogenic risk for humans. Fortunately the acute health problems associated with this episode have led to curtailment of future exposures. There still

remains the epidemiologic task, however, of following prospectively the health of persons already exposed, especially the occupational cohort, with respect to eventual cancer incidence. This is not a simple task, even for a cohort of limited size. Plans for such work are presently being formulated.

Polybrominated Biphenyls

A larger population followup problem is posed by the Michigan PBB situation. The potential of PBB exposure for health disturbance, whether acute, subacute, or chronic, is still uncertain, despite several studies of the affected population. However, the similarity of PBB to polychlorinated biphenyl (PCB) and the fact that PCB appears to cause hepatic cancer in experimental animals (*15*) make cancer a distinct possibility for PBB-exposed persons 15 to 20 years hence. The episode had its origins in Michigan during the early summer of 1973 when 500–1000 lb of the flame retardant hexabromobiphenyl, mistaken for dairy feed supplement, was mixed with cattle feed distributed to dairies throughout Michigan, particularly in the west-central and northeastern parts of the state (*16*). The error was not discovered and public health action not taken until April 1974. In the meantime, widespread illness had occurred in diary cattle and other farm animals. Quarantine control measures were instituted over the ensuing year. During that time, it was necessary to destroy large numbers of PBB-contaminated animals and farm produce. The resulting economic dislocations and public concern continue to affect the state.

At the present time the great majority of Michigan residents, particularly in the populous lower peninsula, appear to have ingested PBB as a result of its wide distribution in the state's food supply. An early indication of the wide dispersal of the chemical in the population came in an epidemiologic survey of quarantined and nonquarantined farms conducted in 1974 soon after contamination was discovered. Although serum PBB levels were substantially higher in residents of quarantined farms, 80% of residents of nonquarantined farms also had detectable levels.

Unlike the kepone episode, no acute human disease has yet been documented as a result of PBB ingestion. Despite numerous anecdotal reports of human illness associated with PBB, symptoms appear to bear no relationship to body levels of PBB. Epidemiologic studies have detected no increase in birth defect incidence or fetal deaths following the incident. Likewise, no clearly associated pediatric effects have been seen, despite the fact that PBB concentrates in fatty tissues and hence in mother's milk.

Studies continue with respect to the possibility that PBB-caused illness may exist in the Michigan population. Chief among these studies have been continuing surveys of persons from quarantined farms, persons who consumed contaminated food directly from quarantined farms and workers at the chemical plant that produced the PBB. In addition, a medical survey of 3000 randomly selected Michigan households is planned for early 1978 to assess further the possibility that PBB may have produced adverse health effects in the general population.

Primary attention is being given, however, to the possibility of an eventual increased incidence of cancer in persons exposed to high levels of PBB. A cohort of about 4000 Michigan residents, largely from the above-mentioned high-PBB exposure groups, has been enrolled in long-term followup by the Michigan Department of Public Health (*17*). Ultimately the cancer experience of this group will be examined in relation to serum and fat levels of both PBB and PCB and in comparison with a nonexposed group of 2000 residents of Iowa. Such a prospective study, of course, is difficult, expensive, and time-consuming and will require sustained support at various levels of government over the next 15-20 years.

Conclusion

This brief review seeks to illustrate some of the approaches used in epidemiologic studies of environmental carcinogenesis. Some approaches, as with kepone and PBB, start with exposed populations and measure disease frequency, the so-called prospective or cohort approach. Others, as illustrated by VCM studies, start with cases of cancer and measure extent of toxic exposure, the retrospective or case history (case-control) approach. Still other studies describe patterns of cancer occurrence by such means as cancer maps and then seek correlations with potentially related population characteristics. All of these approaches are part of epidemiologic methodology and, as I pointed out initially, all are predicated on the existence of prior human exposure or prior disease occurrence. In this regard, major limiting factors involve concepts of latency and of exposure dose.

By identifying potential risks prior to human exposure or human disease, mutagen testing should eventually lighten the responsibility which is currently assigned to epidemiology for detecting environmental cancer problems. Such laboratory procedures, of course, can never fully supplant the need for human epidemiologic studies. To the extent that human observations will always be re-

quired to monitor the effectiveness of preventive health systems and to test suggested human cause-effect associations, human epidemiologic studies will remain an essential ingredient in the field of environmental carcinogenesis.

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