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Toxic exposures and psychiatric disease — lessons from the epidemiology of cancer

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Toxic chemicals such as lead, methyl mercury, organic solvents, manganese, kepone, and the organophosphates are recognized to cause psychiatric disease. Whether such associations are exceptional, or if in fact a high proprtion of all psychiatric illnesses are of toxic environmental etiology, and therefore potentially avoidable, is not known. Epidemiologic studies of cancer, particularly analyses of geographic variations in mortality, of variations in incidence in migrant populations, of trends over time, and of induction by environmental agents suggest that extragenetic environmental factors (tobacco, alcohol, drugs, diet, radiation, air pollution, and industrial chemicals) may account for the majority of all human cancers. Similar application of epidemiologic techniques to the study of psychiatric illnesses might yield etiologic clues in relation to toxic environmental exposures and may also suggest approaches to disease prevention.

Key words: Epidemiology — Environmental Toxins — Psychiatry — Cancer.

Major advances in cancer biology and epidemiology and considerable progress toward cancer control have stemmed from the recognition that chemical agents can cause cancer. Percival Pott (1775), a British surgeon, reported the first association between cancer and an environmental chemical. Pott noted that the "climbing boys" of London, teen-aged lads and young men employed as chimney sweeps, had experienced a devastating incidence of cancer of the scrotum. He attributed development of those tumors to soot exposure. Subsequently, Rehn (1895) noted a high frequency of cancer of the urinary bladder among workers in the aniline dye industry. He also attributed the tumors he saw to occupational chemical exposures. More recently, etiologic associations have been recognized between benzene and leukemia (*Delore & Borgomano* (1928)), asbestos and lung cancer (*Egberg & Geiger* (1936)), arsenic and cancer of the skin, lung and liver (*Hill & Faning* (1948)), *Roth* (1958)), bis-chloromethyl ether (BCME) and lung cancer (*Figueroa et al.* (1973)), and vinyl chloride monomer and angiosarcoma of the liver (*Creech & Johnson* (1974). Most importantly, in terms of the number of persons affected, cigarette smoking has been found to cause cancer of the lungs, bladder, larynx, and esophagus (*Doll & Hill* (1956)).

Toxicologic studies stimulated by those clinical and epidemiologic observations have led to fundamental gains in the understanding of cancer biology. Benzo-(a)-pyrene, a polynuclear aromatic hydrocarbon found in soot, has been found to induce skin cancer in experimental animals (*Kennaway* (1924)). Likewise, beta-napthylamine, a chemical intermediary in aniline dye manufacture, has been shown to cause cancer of the bladder

in experimental animals (*Hueper et al* (1938)). Each of these compounds has been found capable of reacting with DNA in exposed cells so as to alter the structure of the double helix and thence to cause errors in DNA replication (*Weinstein* (1981)). Somatic mutations result, and a consequence of certain somatic mutations is malignant transformation. The understanding of such mechanisms is a first step toward development of a biochemical basis for control of cancer.

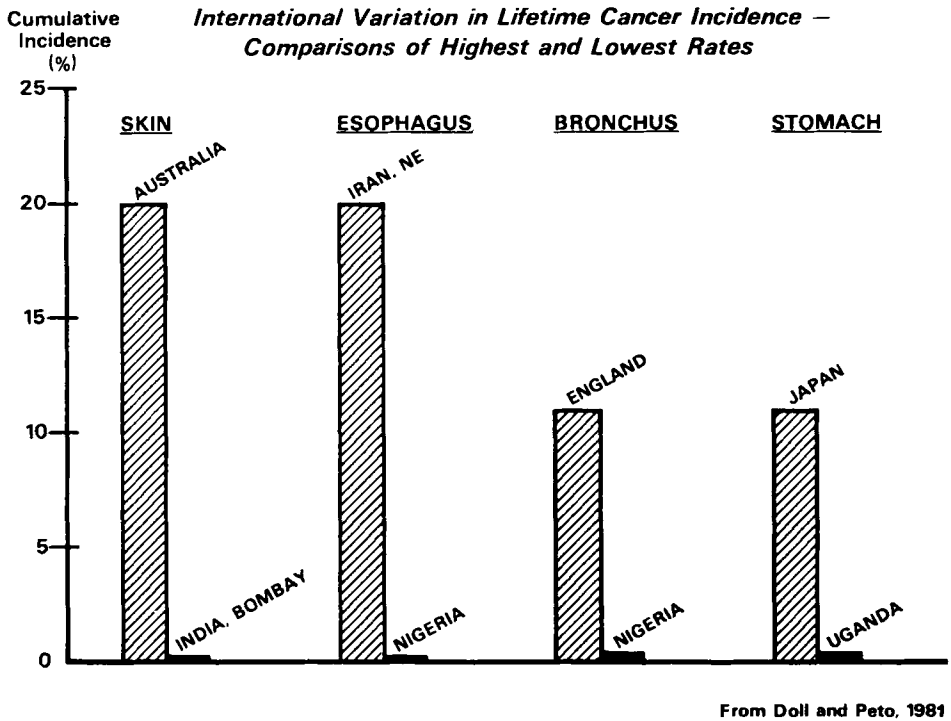
The recognition of environmental carcinogenesis has also had a profound influence on the study of cancer epidemiology. No longer must most cancer be regarded as an inescapable consequence of aging. Instead it is now realized that chemical carcinogenesis is not exceptional, and that well over half of all human cancers — and perhaps as many as 80 to 90 percent worldwide — are caused by extragenetic, environmental exposures (*Doll & Peto* (1981)). Such "environmental factors" are considered to include not only industrial chemicals and pollutants, but also such other influences as diet, alcohol, tobacco, drugs, and radiation. The most stimulating implication of this hypothesis is that a very high proportion of all human cancer may be preventable by the conceptually simple practice of reducing eposures to carcinogens.

In psychiatry, etiologic thinking in regard to chemical exposures appears to be relatively in its beginnings. Certain psychiatric disorders have long been recognized to be of chemical etiology — erethism in persons exposed to inorganic mercury (*Bidstrup* (1964)), suicide among workers in contact with carbon dislulfide (*Vigliani* (1954)), and toxic psychoses in persons inhaling tetraethyl lead (*Cassells & Dodds* (1946)). More recently, low-dose exposure to lead has been found to cause intellectual impairment, behavioral disorders, and impaired school performance (*Needleman et al.* (1979), *Winneke* (1979), *Yule et al.* 1981), *Landrigan et al.* (1975)); manganese has been found to produce a syndrome resembling Parkinson's Disease (*Cook et al.* (1974)); the pesticide kepone has been shown to produce nervousness, tremors, impaired memory, and opsoclonus (*Cannon et al.* (1978)); chronic exposure to organic solvents has been found to produce a neuropsychological syndrome characterized by fatigue, irritability, slowed reaction times, and altered electroencephalograms (*Axelson et al.* (1980), *Seppäläinen & Harkonen* (1976), *Seppäläinen & Tolonen* (1974)); and scalp irradiation during childhood has been associated with mental retardation and psychiatric disease (*Ron et al.* (1982)).

The recognition of these specific neuropsychiatric syndromes associated with environmental exposures suggests that toxic environmental agents may be directly or indirectly responsible for the etiology of many more still unrecognized psychiatric diseases. Exploration of this hypothesis should prove most exciting, because if successful it will permit the identification and specific diganosis of disease entities which have until now been consigned to vague categories of psychiatric illness of undetermined origin. A further impetus to the identificatin of psychiatric syndromes of toxic environmental etiology is that such disorders ought to be amenable to prevention and, in some instances, to specific treatment.

The evidence for a relationship between cancer and the environment has been developed over the past three decades through a long series of clinical, epidemiolgic, and toxicologic studies (*Doll & Peto* (1981)). Valuable lessons were learned in the process, and those lessons may prove useful for the investigation of possible eiologic associations between psychiatric disorders and environmental exposures. With that possi-

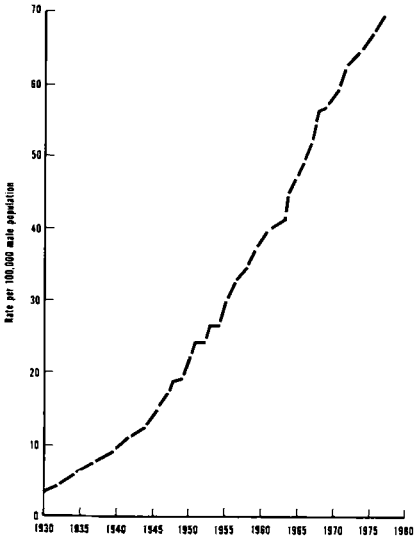
FIGURE 1



From Doll and Peto, 1981

FIGURE 2

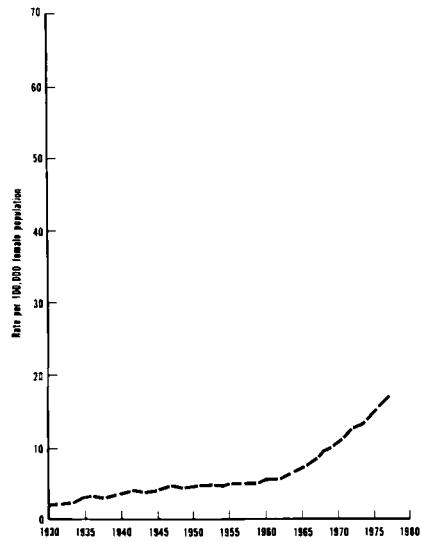
AGE-ADJUSTED LUNG CANCER DEATH RATES* FOR SELECTED SITES MALES, UNITED STATES, 1930-1977



Sources of Data: U.S. National Center for Health Statistics and U.S. Bureau of the Census
*Adjusted to the age distribution of the 1970 U.S. Census Population

FIGURE 3

AGE-ADJUSTED LUNG CANCER DEATH RATES* FOR SELECTED SITES FEMALES, UNITED STATES, 1930-1977



Sources of Data: U.S. National Center for Health Statistics and U.S. Bureau of the Census
*Adjusted to the age distribution of the 1970 U.S. Census Population

bility in mind, I shall in this paper review the several lines of evidence which have linked human cancer to toxic environmental exposures.

Cancer and the Environment

Four types of epidemiologic study (*Doll & Peto* (1981)) have provided data on the role of environmental factors in the etiology of cancer:

1. *Studies of geographic variation*

For most anatomic sites, there is an enormous variation in the incidence of cancer from one nation to another. For example, esophageal cancer occurs 300 times more frequently in northeastern Iran, where it is practically epidemic (*Kmet & Mahboudi* (1978)) than in Nigeria — the country with the lowest reported incidence (Figure 1). Stomach cancer is approximately 25 times more frequent in Japan, the nation with highest incidence, than in Uganda. Finally, skin cancer is more than 200 times more frequent among Australians, in whom the cumulative lifetime incidence is greater than 20 percent, than among Indians resident in Bombay.

Also within a nation great regional variation is evident in mortality from certain cancers (*Mason et al.* (1975)). Thus in the 1950's mortality from cancer of the lung and bronchi among white males in the United States was much higher than in most of the nation in the port cities of the east, south, and west coasts. Heavy smoking in those urban environments plus exposure to asbestos in the wartime shipyards appear to have accounted for most of that excess (*Blot et al.* (1978)). Also in the U.S., isolated counties with excess lung cancer mortality were noted in the Rocky Mountains; on further investigation, most of those excesses were found to have occurred in communities surrounding arsenic-emitting copper smelters. Also a lung cancer excess was noted in rural, central Washington State, in the Pacific Northwest; additional study indicated that lead arsenate inseciticide spray which had been applied there to apple orchards was the probable etiological factor. Bladder cancer in males was found to be heavily concentrated in the mid-Atlantic states, particularly in New Jersey. Further analysis indicated that most of that excess mortality was centered in counties with a concentration of chemical industries (*Hoover & Fraumeni* (1976)); the presumed etiologic exposure was to aniline derivatives. Among white women, high mortality from cancer of the mouth was observed across the southeastern states. Subsequent studies showed that this regional excess was due to the habit prevalent among women in the South of taking snuff (tobacco) and holding it for long periods of time between the gums and the buccal mucosa (*Winn et al.* (1981)).

Demonstration of national or regional variation in cancer frequency does not by itself not confirm the contribution of extragenetic factors to the etiology of cancer. Studies of geographical variation are only descriptive. They do not address the possibility that differing genetic constitutions in various populations may influence the observed variations in cancer incidence. Such studies do, however, provide valuable clues, and they suggest etiologic hypotheses for further, more definitive analyses.

2. *Migrant Studies*

Evaluation of migrant populations provides a second technique for separating environmental from genetic factors in studies of cancer etiology. A considerable advantage of

migrant studies over analyses of geographic variation is that they examine persons of identical genetic stock living in differing environmental milieux.

In studies of cancer among migrants the observed incidence of disease has tended in most instances to change within one to two generations from that observed in the home country to that typical of the new land. For example, in Japanese immigrants to the United States, the rate of stomach cancer has been observed to fall within two generations from the high incidence found in Japan to a much lower rate approaching that of the United States Caucasian population (*Doll & Peto* (1981)). Over the same generations, however, the annual incidence rates for cancers of the breast and colon were found to increase approximately fourfold among Japanese immigrants from the low rates incident in Japan to approach the much higher rates encountered in U.S. Caucasians. Other migrant studies have shown that among Polish immigrants to Austalia, the high rate of carcinoma of the stomach seen in Poland practically disappears within one generation, and that among British emigrants to the tropics, the incidence of skin cancer in much higher than among Britons in Britain.

Migrant studies have also proven useful for assessing the importance of extragenetic etiologic factors in diseases other than cancer. It has, for example, been observed among men of Japanese ancestry that the occurrence of cardiovascular disease is quite high in California, of intermediate frequency in Hawaii, and the lowest of any industrialized country in the world in Japan. Further study has shown that these differences correlate with systematic variations in smoking, diet, and cultural behavior; thus among Japanese-Americans, the lowest rates of cardiovascular disease were observed among those practicing the most traditional Japanese customs and behavior (*Marmot & Syme* (1976)).

3. *Trends Over Time*

Incidence rates of several cancers have changed markedly over time. Lung cancer among white males in the United States (Fig. 2) rose sharply in the years following World War II. This epidemic appears to have reflected increased cigarette smoking, which became widespread during the war years, as well as exposure to asbestos. More recently mortality rates for lung cancer in white males in the United States have begun to decline, while those in black males have increased rapidly, particularly in the younger age groups (*Blot & Fraumeni* (1982)). Those changes may reflect recent alterations in smoking behavior. Finally, lung cancer mortality rates have just begun in the past decade to rise alarmingly in American women (Fig. 3) as sexual equality has become the norm in the consumption of tobacco.

4. *Identification of Specific Causes*

The strongest, yet simplest confirmation of the role of environmental factors in cancer etiology comes from studies which have indentified specific environmental exposures as the cause of particular types of cancer. More than 30 human carcinogens have been so identified. Among the more well known are radiation (causing leukemia, breast cancer, thyroid cancer, and cancers at many other sites), benzene (leukemia), vinyl chloride (hepatic angiosarcoma), estrogens (endometrial carcinoma), bischlororomethylether (lung cancer), and benzidine (bladder cancer) (Table 1). Exposures to these carcinogenic agents are most easily documented among occupationally exposed populations. Ex-

Table 1. *Confirmed Human Carcinogens**

Aflatoxin	Immunosuppressive Drugs
Alcoholic Drinks	Ionizing Radiations
Alkylating Agents	Isopropyl Oil
— Cyclophosphamide	
— Melphalan	Leather Dust
Anabolic Amines	
Aromatic Amines	Mustard Gas
— 4 aminodiphenyl	
— Benzidine	Nickel
— Beta-naphthylamine	
Arsenic	Phenacetin
Asbestos	Polycyclic Hydrocarbons
	— Coke oven missions
Benzene	— Soots, tars and oils
Beryllium	Parasites
Betel Nut and Lime	— Schistosoma hematobium
Bis (chloromethyl) Ether	— Chloronorchis sinesis
Bis (chloroethyl) Sulfide	
	Rubber Manufacture
Cadmium	
Chloromethyl Methyl Ether	Tobacco Smoke
Chromium	
Chloronaphazine	Uranium
	Ultraviolet Light
Estrogens	Vinyl Chloride Monomer
— Natural	Virus (Hepatitis B)
— Diethyl stilbestrol (DES)	
	Wood Dust

* From: *Key et al.* (1977), *Doll & Peto* (1981), *Weinstein* (1981), and *Farber* (1981)).

posures are however, not resticted to the workplace and, for example, pleural mesothelioma has occurred in persons exposed to asbestos fibers transported home from a dusty factory on workmen's shoes and clothing (*Anderson et al.* (1974)); likewise tobacco smoking occurs generally in the population. Theoretically the identification of a specific chemical carcinogen should make the prevention of its associated cancers a straightforward matter of avoidance of exposure.

DISCUSSION

The proportion of psychiatric ilnesses which might be caused by exposure to neurotoxic environmental agents is not yet known. It is not yet possible to determine whether the recognized associations between certain toxic chemicals and neuropsychiatric diseases are exceptional occurrences or whether these associations are merely the harbingers of a large and still poorly recognized problem (*Damstra* (1978)). To date, relatively few of the 4 million known chemical compounds or of the 60,000 compounds in widespread commercial use have been examined as to their chronic neuropsychiatric toxicity (*Davis & Magee* (1978)). Even fewer have been assessed as to their potential selective toxicity to vulnerable subgroups within the population such as the very young or very old

Table 2. *Numbers of Persons Potentially Exposed to Neurotoxic Chemicals — United States.*

Children:*	
Inorganic Lead (Paint	450,00
*Adult Workers**:*	
Lead	
Lead Oxides	1,300,000
Lead Carbonate	183,000
Lead Naphtenate	1,280,000
Lead Acetate	103,000
Metallic Lead	1,394,000
Mercury	
Mercury Sulfide	8,900
Mercuric Nitrate	10,100
Mercuric Chloride	51,000
Metallic Mercury	24,000
Organic Mercury	280,000
Solvents	
Carbon Tetrachloride	1,379,000
Dichloromethane	2,175,000
Tetrachloroethylene	1,596,000
Styrene	329,000
Trichloroethylene	2,783,000
Aromatic Hydrocarbons	3,611,000
Aliphatic Hydrocarbons	2,776,000
Industrial Alcohols	3,851,000
All Pesticides (Formulation)	17,100

*Data from the Centers for Disease Control.
**Data from the National Occupational Hazards Survey, National Institute for Occupational Safety and Health.

(*Damstra* (1978)). Also procedures for assessment of the neurotoxicity of chemical compounds newly introduced to the marketplace are probably insufficiently sensitive to detect the more subtle subclinical effects that may result from chronic low-dose exposures. The number of persons potentially exposed to the known neurotoxins in an industrialized society is enormous (Table 2). If only a small fraction of those exposed suffer psychatric disease as a result of their exposure, then the problem of psychiatric illness caused by exposure to environmental neurotoxins will prove to be neither small nor isolated.

Two decades ago most cancers were considered to be the inevitable result of aging. Specific relationships of cancer to industrial chemicals and to cultural practices were recognized but were considered to be unusual and rather irrelevant (*Farber* (1981)). Today after a period of intense clinical, epidemiological, and toxicological study, it has come to be recognized that well over half of all human cancers — and perhaps as many as 80 to 90 percent worldwide — are caused by extragenetic, environmental exposures (*Doll & Peto* (1981)). It is recognized that the association between environmental exposures and cancer is complex and may frequently require interaction between an environmental agent and certain poorly defined endogenous or host factors (*Weinstein* (1981)).

Further delination of the scope and nature of psychiatric impairments which may be caused by environmental neurotoxins will require carefully designed, multinational epidemiological studies of the sort which have been conducted for evalution of the etiology of cancer. Such studies might be conducted under the aegis of the World Health Organization (*Tomatis* (1982)).

The identification, diagnosis, and prevention of psychiatric diseases of toxic environmental origin will require that psychiatrists around the world consider the possibility of neurotoxic etiology in the evaluation of every patient who presents with psychiatric illness of unknown cause. Only through astute clinical observation, coupled with careful ascertainment of environmental and of occupational exposure histories will new psychiatric syndromes of neurotoxic etiology come to be identified.

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