ROBERT W. MILLER*

National Cancer Institute, National Institutes of Health, U.S. Public Health Service, Bethesda, Maryland

ENVIRONMENTAL AGENTS IN CANCER

Advertising men would despair at the image of epidemiology. Product recognition is poor among many potential consumers. Even those who know epidemiology best recurrently question its name and scope.[1-4] Other scientists tend to underestimate it as a means for testing or developing ideas about the origins of disease. In this capacity, epidemiologic research seems most potent when closely linked with clinical and laboratory studies, each using to the fullest the information derived from the others.

Because epidemiology concerns people, its research is mainly observational rather than experimental. Studies must be created from natural circumstances. This report exemplifies such studies as they pertain to the environmental origins of cancer. For convenience, the observations are grouped according to the resources from which they come.

HOSPITAL CHARTS

By abstracting hospital records of cancer patients, (a very inexpensive procedure), certain cancers have been found to occur excessively in persons with specific noncancerous ailments. The recognition of these concurrences provides new opportunities to examine the origins of the cancer with respect to what is known about the etiology of the associated diseases. It was only ten years ago that the excessive rate of leukemia among mongols was first documented.[5,6] The subsequent discovery of an extra chromosome in mongolism has contributed to the belief that certain forms of leukemia are related to chromosomal aberrations. This knowledge is of value in studying the mechanism by which environmental agents induce leukemia. For example, the leukemogenic effect of ionizing radiation is presumably related to the capacity of radiation to induce cytogenetic abnormalities that may persist for years.[7] It would be of interest to determine if other potential leukemogens, such as benzene, chloramphenicol, phenylbutazone, or certain

* Chief, Epidemiology Branch, Field Studies, National Cancer Institute.
Received for publication 21 April 1965.

viruses also produce cytogenetic abnormalities. Conversely, agents known to produce chromosomal abnormalities can be evaluated for their oncogenic effects.

Wilms' tumor, a neoplasm of childhood, also occurs excessively with certain congenital malformations—aniridia, hemihypertrophy, genitourinary-tract anomalies, and nevi.[8] The pattern of these associations is indicated in Figure 1. It will be noted that genitourinary-tract defects occur excessively with Wilms' tumor, hemihypertrophy, or aniridia, but that hemihypertrophy and aniridia do not occur excessively together. In consequence, one may study the etiology of the tumor with respect to the seemingly disparate

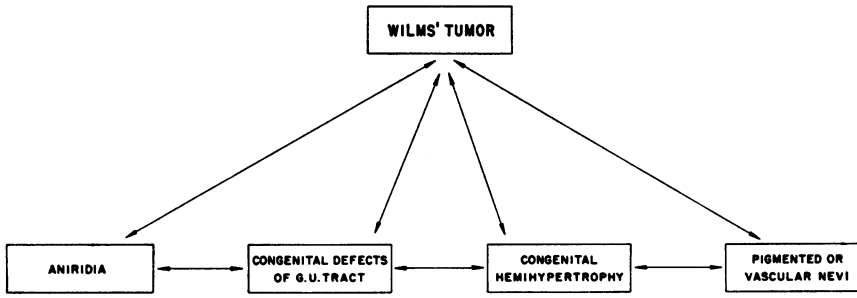

FIG. 1. Congenital malformations associated with Wilms' tumor and with one another.

origins of aniridia and hemihypertrophy. On the other hand, nevi and hemihypertrophy are associated with one another and each is independently associated with Wilms' tumor. There must, then, be something in common to the etiology of this triad of diseases.

The coexistence of the anomalies with Wilms' tumor indicates that the neoplasm was induced when the anomalies were, namely, before the end of the first trimester of pregnancy. Consequently, in seeking environmental agents which may have induced Wilms' tumor in childhood, it may be well to concentrate the search on the early part of pregnancy. The environment may, of course, exert its effect before conception, as it apparently does in mongolism. This malformation is usually attributed to meiotic nondisjunction, which occurs in the ovum. An environmental influence is indicated, however, by the marked increase in the frequency of mongolism with increasing maternal age, a relationship first found in 1909 from an examination of hospital records.[9]

MORTALITY STATISTICS

There is a dramatic change in the mortality rates from leukemia during the first few years of life. Among U. S. white children, there is a sharp rise to a towering peak at four years of age and then an equally rapid decline (Fig. 2). Court Brown and Doll[10] have shown that the peak in England

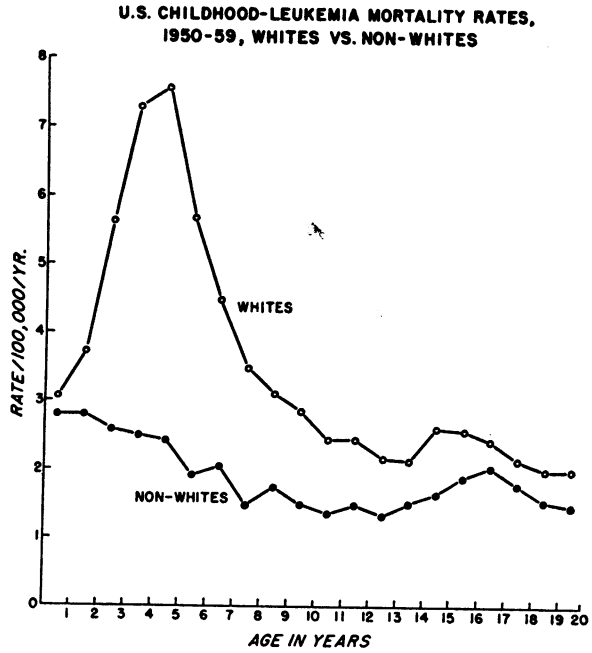

FIG. 2. U. S. mortality rates from childhood leukemia, 1950-1959, by single year of age; comparison of whites and nonwhites.

and Wales did not exist before 1920. It subsequently became progressively more pronounced there and in the United States. Because no such increase has occurred among U. S. nonwhites or in Japan, it was suggested[10] that a leukemogen was introduced into the environment or became effective about 40 years ago, and that U. S. nonwhite children and Japanese children were either not exposed or not susceptible to it.

Slocumb and MacMahon[11] have presented data that indicate the peak in leukemia mortality rates among U. S. white children may result *not* from a disproportionate *increase* at about 4 years of age but from a *decrease* in cases reported among those under 3 years of age. In any event the peak has become recognizable among white children, and acute lymphocytic

leukemia is apparently entirely responsible for it since there is little variation during the childhood years in the rates for acute myelogeneous leukemia.[10] The rise in mortality so soon after birth suggests that the search for environmental influences be concentrated on the prenatal period and

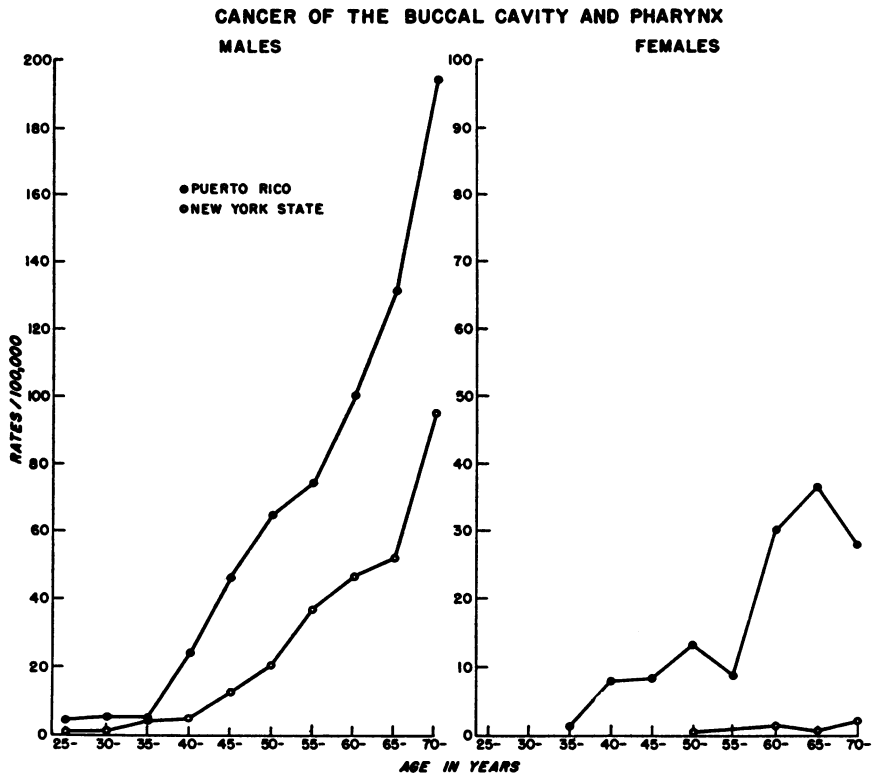

FIG. 3. Incidence rates for cancer of the buccal cavity by age and sex; comparison of Puerto Rico, 1962, and New York State exclusive of New York City, 1960. Sources: Control del Cancer Informe Anual, 1962-1963; Division de Control del Cancer, Department de Salud de Puerto Rico; and Cancer in New York State Exclusive of New York City, 1941-1960; Bureau of Cancer Control, New York State Dept. of Health.

in the first year of life. However, some cases of childhood leukemia may be determined before conception, as indicated by the excessive occurrence of the disease among mongols, in whom the cytogenetic defect is usually present before the zygote is formed.

CANCER REGISTRIES

Occasionally, cancer registries provide data through which new leads to the etiology of cancer can be derived or tested. From registry data it is now clear that in Puerto Rico there is a marked excess of cancers of the

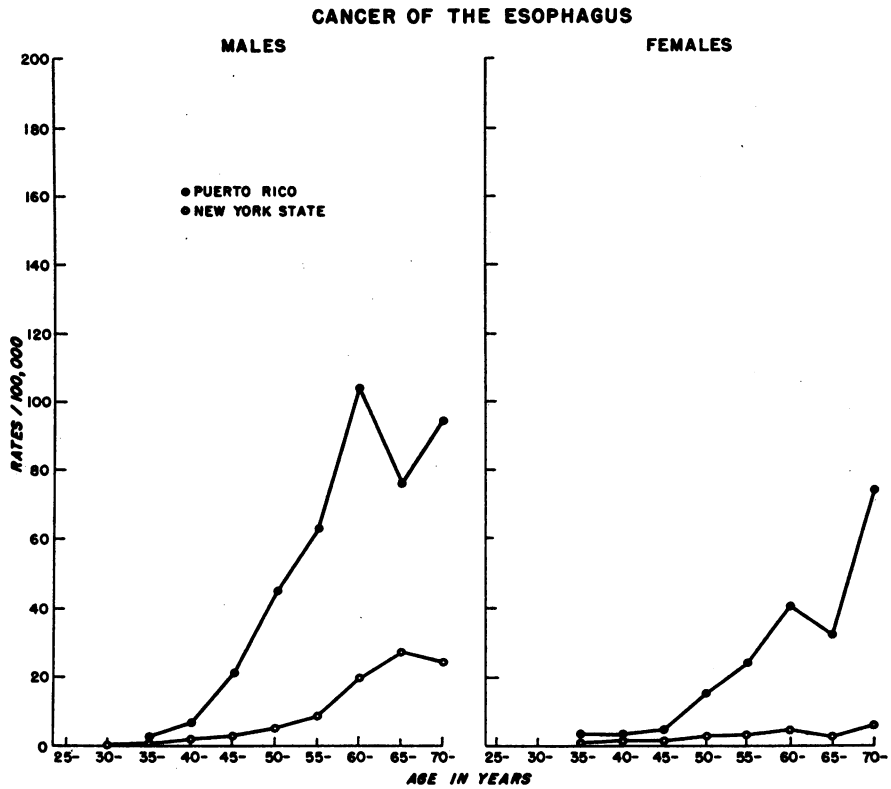

FIG. 4. Incidence rates for cancer of the esophagus by sex and age; comparison of Puerto Rico, 1962, and New York State exclusive of New York City, 1960. Same data sources as in Fig. 3.

buccal cavity and of the esophagus as compared with New York State, excluding New York City (Figs. 3 and 4). Among about 2.5 million people living in Puerto Rico there is, on the average, one new case a day of cancer at either of the two sites; the increase in rates is primarily in the lowest socio-economic class. Through a retrospective study, an evaluation is to be made of the differences in the histories of cases as compared with matched controls, and it will be determined if the differences are similar, whether the cases have cancer of the oral cavity or of the esophagus.

Studies in New York City by Keller and Terris[12] have shown that there is an association between liver cirrhosis and buccal-cavity cancer. This has led Dr. Paul Kotin, Associate Director for Field Studies at the National Cancer Institute, to suggest that as in animal experimentation, injury to the human liver interferes with the metabolism of chemical carcinogens, thus increasing their capacity to induce neoplasia of another site—a possibility that can perhaps be elucidated by the case-control study now being planned by the Director of the Puerto Rican Cancer Registry.

Data from the Connecticut Tumor Registry have recently been used to answer specific questions concerning the viral etiology of childhood leukemia. Bailar and Gurian[13] found no differences in leukemia incidence with respect to month of birth, indicating that if the disease is due to a virus infection at about the time of birth, there is no seasonal variation in its prevalence. Ederer, Myers, and Mantel[14] were unable through their newly developed statistical procedure to detect any tendency for childhood leukemia cases in Connecticut to cluster over a 15-year period. The same technique when applied to poliomyelitis or infectious hepatitis showed the numbers of clusters to be immensely greater than would occur by chance. Such observations as these, and there are many,[15] do not disprove the viral etiology of childhood leukemia, but they do help to characterize the cause, whatever it is.

FOLLOW-UP STUDIES OF MILITARY VETERANS

A great asset in the study of the etiology of disease is the Follow-up Agency of the National Academy of Sciences-National Research Council. This organization has access to the military and Veterans-Administration (VA) records of about 24 million men who have served in the Armed Forces since World War I. Largely because of benefits claimed by the families of veterans, more than 95 per cent of the deaths among this huge population are known to the VA, which has the death certificates on file. In studies of morbidity, 70-80 per cent of veterans will complete mail questionnaires concerning their health, and a high proportion of the men will appear at VA hospitals for special re-examinations.

The Follow-up Agency is about to begin a study in collaboration with scientists at Yale University, Oregon University, and the National Cancer Institute to evaluate the influence of a variety of environmental agents in carcinogenesis. Use will be made of selected records of the 120,000 veterans of World War II who have since died of cancer. Table 1 lists some of the diseases and exposures to be investigated, their normal frequencies, and the basis for suspecting each event in the genesis of cancer.

TABLE 1. EVENTS DURING WORLD WAR II MILITARY SERVICE TO BE STUDIED FOR THEIR RELATIONSHIP TO CANCER OCCURRENCE AMONG VETERANS

Events recorded during military service	*Estimated per cent expected among controls*	*Reason for suspecting relationship of event to carcinogenesis*
Yellow fever vaccination*	25.0	Some eggs used in the manufacture of yellow fever vaccine contained viruses which are oncogenic in fowl.
Transfusions**	7.6	Blood-borne viruses, as in mouse leukemia, may be transmissible by transfusion.
Infectious hepatitis**	.2	Study of sequelae of infectious hepatitis suggests a decreased frequency of cancer in general.[16]
Infectious mononucleosis†	.1	Particles similar to mouse-leukemia virus occur in the blood of patients with infectious mononucleosis.[17]
Herpes simplex infection for which medical attention was sought†	.03	Herpes simplex virus produces many cytogenetic defects[18] and heightens the carcinogenic effect of methylcholanthrene in mice.[19]
Radiation treatment†	— ‡	Radiation is known to be leukemogenic in man.[15]
Occupational chemical exposures†	— ‡	Mustard gas is a known respiratory carcinogen in man;[20] benzene is probably a human leukemogen;[21] other chemicals are carcinogenic in laboratory animals.
Parasitic infestation†	— ‡	Clinical observations in Egypt indicate that *Schistosoma hematobium* disposes to bladder cancer.[22]
Antecedent chronic diseases†	— ‡	Clinical observations suggest a relationship, for example, between malignant disease and autoimmune diseases[23] or certain congenital malformations.[24]

* Yale University component.
** Oregon University component.
† National Cancer Institute component.
‡ Not determined.

In the retrospective phase of the study, a VA death index will be used to assemble a roster of 3,500 names of men who have died of cancer since 1950. Cases and matched controls will be compared with respect to information abstracted from their military-service records concerning illnesses and exposures during the war. An evaluation will be made of the relationship between cancer occurrence and viruses that may have been transmitted by egg-grown yellow fever vaccine or by blood transfusion. The retrospective study will not be a sensitive detector of associations between cancer and such less common events as infectious hepatitis or infectious mononucleosis. Therefore, a series of prospective (cohort) investigations has been designed to detect a twofold or greater excess of cancer following certain diagnoses made during the war. The diagnostic files maintained by the Surgeon General of the Army will be used to assemble the names of thousands of men with each disease of interest. These names will be matched against the VA master index to learn of the deaths by cause. The results will be of interest not only with respect to cancer but also to other diseases.

In a prospective investigation now in progress, the effects of radiation are being evaluated among about 6,500 men trained during World War II as radiology technicians as compared with an equal number of men trained as hematology or pharmacy technicians. To date no influence on total mortality or causes of death has been detected.[25] These results are somewhat reassuring since the radiology technicians in general were subjected to substantially greater radiation exposures than are patients who undergo diagnostic X-ray procedures. As a measure of the genetic effect of radiation, questionnaire data are being evaluated to determine if there has been a shift in the sex ratio of liveborn children of the radiology technicians. Disturbance of the sex ratio is thought to be the best available epidemiologic indicator of radiation-induced genetic damage.[26] When males are exposed to radiation, lethal mutants that occur on the X-chromosome can be transmitted only to their daughters. The Y-chromosome, which the sons receive, is thought to be relatively inert with respect to lethal mutants.[26] On the basis of this reasoning, daughters of irradiated males would experience an increased fetal mortality, and consequently the sex ratio (M/F) of liveborn infants would rise.

These examples indicate that some ideas about environmental influences on disease occurrence in man can be tested either prospectively or retrospectively through the use of military and veterans' records. The influence of inheritance on diseases of adult males can also be made through the Agency's registry of about 15,500 twins who served in the Armed Forces during World War II. The zygosity of each twin pair is now being esti-

mated so that concordance rates for specific diseases among identical twins can be compared with those for fraternal twins. If inheritance influences the disease frequency, the concordance rates will be higher in the group of identical twins.

RESOURCES IN JAPAN

There are exceptional resources in Japan for epidemiologic studies into the origins of a variety of chronic diseases. Through the use of the family registry system (*koseki*), follow-up studies of mortality, reproduction, and the survival of offspring are more easily made in Japan than they usually are in other countries.[27,28] Each family is registered in its traditional ward office. To that office comes either the original or a copy of all vital certificates pertaining to members of the family even when they have moved elsewhere in Japan. Thus follow-up of vital events can be made by writing to local ward offices, and there is no need to contact the person under study. The fee is about 15 cents per record.

In estimating the influence of the environment on the occurrence of a disease, it is helpful to know to what extent inheritance plays a role. In areas of the world where inbreeding occurs, the influence of inheritance on relatively rare diseases, such as Wilms' tumor, can be estimated by determining if a group of persons having the disease was more often born of consanguineous parentage than usual (matched control series). Japan is such an area; about 5 per cent of the marriages are between first cousins and another 2 per cent between first-cousins-once-removed or second cousins. The effect of consanguinity on cancer occurrence has not yet been well studied. The *koseki* record can be used to construct the pedigree to determine precisely if the parents of a person were cousins. In an evaluation of the effect of inbreeding on child health, the pedigrees of about 500 children were so studied in one year in Nagasaki by two clerks and a physician.[28]

The extent to which the environment affects the occurrence of cancer can be evaluated by studying the rates of type-specific cancers among the Japanese in Japan as compared with those who have migrated to Hawaii or Los Angeles. When a difference in rates is found, case-control studies can be conducted simultaneously in the new and old countries. The results, when contrasted, may reveal differences in relative risk with respect, for example, to items of diet. Such studies of cancer of the stomach are now being conducted in Japan, and among Japanese-Americans in Hawaii and Los Angeles by the Biometry Branch of the National Cancer Institute.

The National Institute of Industrial Health in Japan has access by law to employment records,[29] a circumstance of importance in studying industrial exposures that may produce miscarriages, congenital malformations, or cancer. Thus, one does not have to negotiate with the employer before gaining access to factory records. In the experimental laboratory it has been shown[30] that N-methyl formamide, a solvent widely used in the nylon and plastics industries, when painted on the rat's tail during pregnancy, causes 90 per cent of the embryos to be resorbed. The *koseki* record of female employees exposed to this solvent in Japan could provide a measure of the frequency of childless marriages, the survival of liveborn children, and the survival of the exposed employee (the chemical may also be carcinogenic). Since there would be no need to interview the employee, this study could be made without creating anxiety.

A more dramatic example concerns a study already in progress. It had its beginning in 1952 when an intern at Hiroshima University discovered that his patient, who was 30 years old, had lung cancer. In what seems at first to have been a naive question, the intern asked the patient why he, such a young man, had lung cancer. The patient said that it was probably because he had worked for 16 months during the war at the mustard gas factory 50 miles from Hiroshima. The intern and his professor thought this possibility deserved further study. They visited the factory and, although it had closed eight years before, the smell of the gases manufactured there could easily be detected. They learned that protective clothing was often not worn or was incompletely effective. A large proportion of the workers had severe respiratory symptoms during their employment and afterwards. From a former supervisor the Hiroshima investigators obtained the names of several hundred of the 2,000 former factory employees. Among this group 172 deaths were ascertained, 28 of which were attributed to respiratory-tract cancer which affected the paranasal sinuses, tongue, pharynx, larynx, trachea, and bronchi.[20] Despite the lack of adequate denominators to date, the excess of respiratory-tract cancer among the former mustard-gas workers is too large to be denied.

Nineteen of these cases were studied at autopsy. Figure 5 shows the location of the neoplasms found. The lung tumors were of the squamous cell type or undifferentiated cell type, and none were in the periphery of the lungs. Thus, a radiomimetic agent, mustard gas, has produced cancers of the same anatomic and histologic character as those that have occurred excessively as a result of radiation exposure among U. S. uranium miners.[31] The duration of exposure to mustard gas among those with respiratory-tract cancer ranged from 16 months to 17 years, and the latent period

between first employment at the factory and diagnosis ranged from 12 to 33 years. In an extension of the study now being planned, a better definition will be sought of the relationship of cancer occurrence to duration of exposure and to latent period. An evaluation will also be made of the

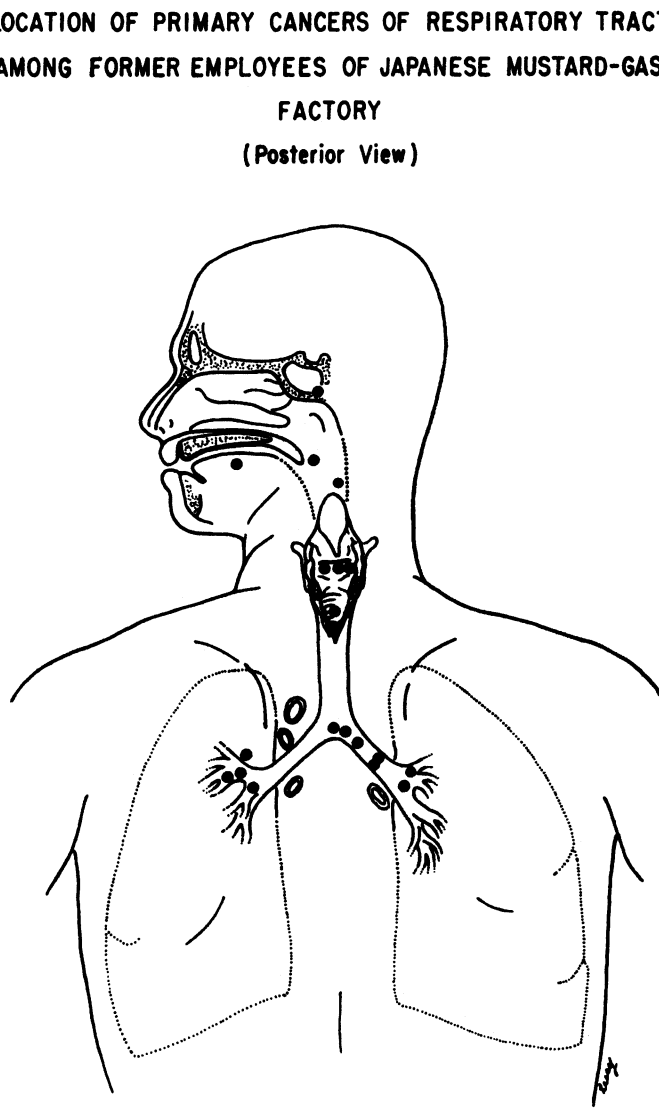

FIG. 5. Anatomic distribution of 19 respiratory-tract neoplasms at autopsy among former workers at a Japanese mustard-gas factory. (Adapted from Wada, S., *et al.*[20])

carcinogenic effect of mustard gas on organs other than those of the respiratory tract. There is a suggestion from the data already published that there may be an excess of cancer of the liver, esophagus, and skin. To expand the sample size, use will be made of the technique of the New Jersey State Health Department in its study of osteogenic sarcoma among women who painted radium dials on watches in the 1920's. As former mustard-gas workers are interviewed, each will be asked to name as many co-workers as he can recall and to respond to a series of questions designed to jog his memory of them.

Another extension of the study stems from observations made in the experimental laboratory. There it has been shown that nitrogen mustard is a powerful mutagen[33] and teratogen.[33] Plans are now being developed in Japan to evaluate the effect of mustard-gas exposure on sterility during employment, miscarriage rates, congenital malformation rates, survival of offspring, the sex ratio of offspring, and cytogenetic abnormalities in the tissues of the workers.

The results obtained will be important not with respect to mustard-gas exposure, which is uncommon, but for the broader biologic implications. 1) An excess of neoplasia at sites other than the respiratory tract will add to the evidence that chemical carcinogens in man are not organ-specific. 2) There will be new information as to the length of the latent period which can be compared with the latent periods of other human carcinogens. 3) Characteristics of persons who developed neoplasms as compared with those who did not may reveal circumstances other than mustard-gas exposure that contribute to neoplasia. 4) In a single study the oncogenic *and* teratogenic effects of a chemical will be evaluated, a circumstance which brings attention again to the overlap between these two abnormal processes. 5) The genetic concept of the influence of paternal exposure to a mutagenic agent on the sex ratio of offspring, as described above, can be put to a good test because the exposures in this instance were great and prolonged. 6) Because mustard gas imitates the effects of ionizing radiation, whatever is learned from the study of the former factory workers may be applicable in the study of the delayed consequences of radiation which, coincidentally, is being conducted nearby among the survivors of the atomic bomb.

THE ATOMIC BOMB CASUALTY COMMISSION

The most convincing evidence that ionizing radiation can induce leukemia in man comes from the studies of the atomic bomb survivors in Hiroshima and Nagasaki.[34] The response was proportionate to the dose and, unlike studies involving X-ray exposures for medical purposes, there were no

variables known that could confound the interpretation. As yet there has been little evidence that the exposure induced cancers of other sites, the chief exception being the thyroid, in which microscopic foci of neoplastic cells have been reported.[85]

The Atomic Bomb Casualty Commission (ABCC) has done much more than study the effects of radiation. By the example it has set for epidemiologic inquiry into the effects on man of a dramatic environmental agent, the ABCC has greatly widened familiarity with this research approach. On-the-job experience has persuaded a substantial number of its former staff members to devote their careers to related research.

In recent years Yale University has made a large contribution to this exceptional field study. Dr. George B. Darling, Professor of Human Ecology at the University, has been a most able Director of the Commission since 1957. Four faculty members from the Department of Internal Medicine have served in succession as the head of the corresponding department at ABCC and have guided it to its present state of clinical and epidemiologic sophistication. One member of the Department of Epidemiology and Public Health has served on the biostatistics staff in Hiroshima, and several recent graduates from the School of Medicine have been assigned to ABCC each year as officers in the U. S. Public Health Service. It may be of interest one day to study the delayed effects on Yale University of exposure to the ABCC.

SUMMARY

Through the use of a variety of existing data resources, specific ideas about the environmental origins of cancer can be tested through epidemiologic research. The observations so made are helpful in determining the applicability to human carcinogenesis of concepts developed in the experimental laboratory. Conversely, epidemiologic research can provide new ideas concerning carcinogenesis that may be further explored by laboratory study.

REFERENCES

1. Terris, Milton: The scope and methods of epidemiology. *Amer. J. publ. Hlth,* 1962, *52,* 1371-1376.
2. Payne, A. M.-M.: The scope and methods of epidemiology. *Amer. J. publ. Hlth,* 1962, *52,* 1502-1504.
3 Editorial: Opinions and discussions. *Amer. J. publ. Hlth,* 1963, *53,* 1696.
4. Paul, J. R.: Social medicine. *Lancet,* 1964, *2,* 1392.
5. Krivit, W. and Good, R. A.: Simultaneous occurrence of mongolism and leukemia: report of nationwide survey. *J. Dis. Child.,* 1957, *94,* 289.

6. Wald, N., Borges, W. H., Li, C. C., Turner, J. H., and Harnois, M. C.: Leukaemia associated with mongolism. *Lancet,* 1961, *1,* 1228.
7. Buckton, K. E., Jacobs, P. A., Court Brown, W. M., and Doll, Richard: A study of the chromosome damage persisting after X-ray therapy for ankylosing spondylitis. *Lancet,* 1962, *2,* 676-682.
8. Miller, R. W., Fraumeni, J. F., Jr., and Manning, M. D.: Association of Wilms's tumor with aniridia, hemihypertrophy and other congenital malformations. *New Engl. J. Med.,* 1964, *270,* 922-927.
9. Shuttleworth, G. E.: Mongolian imbecility. *Brit. Med. J.,* 1909, *3,* 661-665.
10. Court Brown, W. M. and Doll, Richard: Leukaemia in childhood and young adult life. *Brit. med. J.,* 1961, *1,* 981-992.
11. Slocumb, J. C. and MacMahon, Brian: Changes in mortality rates from leukemia in the first five years of life. *New Engl. J. Med.,* 1963, *268,* 922-925.
12. Keller, A. Z. and Terris, Milton: The association of alcohol and tobacco with cancer of the mouth and pharynx. Presentation at annual meeting of American Public Health Association on October 6, 1964.
13. Bailar, J. C., III and Gurian, J. M.: Month of birth and cancer mortality. *J. nat. Cancer Inst.,* 1964, *33,* 237-242.
14. Ederer, Fred, Myers, M. H., and Mantel, Nathan: A statistical problem in space and time: do leukemia cases come in clusters? *Biometrics,* 1964, *20,* 626-638.
15. Miller, R. W.: Radiation, chromosomes and viruses in the etiology of leukemia. Evidence from epidemiologic research. *New Engl. J. Med.,* 1964, *271,* 30-36.
16. Turner, R. H. and Beebe, G. W.: To be published.
17. Benyesh-Melnick, Matilda, Smith, K. O., and Fernbach, D. J.: Studies on human leukemia. III. Electron microscopic findings in children with acute leukemia and in children with infectious mononucleosis. *J. nat. Cancer Inst.,* 1964, *33,* 571-579.
18. Hampar, Berge and Ellison, S. A.: Chromosomal aberrations induced by an animal virus. *Nature (Lond.),* 1961, *192,* 145-147.
19. Tanaka, S. and Southam, C. M.: Joint action of herpes simplex virus and methylcholanthrene in production of papillomas in mice. *J. nat. Cancer Inst.* 1965, *34,* 441-451.
20. Wada, S., *et al.*: Neoplasms of the respiratory tract among poison gas workers. *Hiroshima Igaku,* 1963, *16,* 728-745.
21. Vigliani, E. C. and Saita, Giulio: Benzene and leukemia. *New Engl. J. Med.,* 1964, *271,* 872-876.
22. Mustacchi, Piero and Shimkin, M. B.: Cancer of the bladder and infestation with *Schistosoma hematobium. J. nat. Cancer Inst.,* 1958, *20,* 825-842.
23. Talal, Norman and Bunim, J. J.: The development of malignant lymphoma in the course of Sjögren's syndrome. *Amer. J. Med.,* 1964, *36,* 529-540.
24. Lubs, H. A., Jr.: Testicular size in Klinefelter's syndrome in men over fifty. Report of a case with XXY/XY mosaicism. *New Engl. J. Med.,* 1962, *267,* 326-331.
25. Jablon, S. and Miller, R. W.: Mortality patterns among radiology technicians: An 18-year controlled follow-up study. Presented at the annual meeting of the American Public Health Association on October 8, 1964.
26. Neel, J. Van G.: *Changing Perspectives on the Genetic Effects of Radiation.* Springfield, Ill., Chas. C. Thomas, 1963.
27. Yanase, T.: The use of the Japanese family registry for genetic studies. In: *The Use of Vital and Health Statistics for Genetic and Radiation Studies.* Proceedings of the seminar sponsored by UN-WHO held in Geneva, 5-9 Sept. 1960. New York, United Nations, 1962, pp. 119-133.
28. Schull, W. J. and Neel, J. Van G.: *The Effects of Inbreeding on Japanese Children.* New York, Harper and Row. 1965.

29. Cited by Tsuchiya, Kenzaburo: The relation of occupation to cancer, especially cancer of the lung. *Cancer,* 1965, *18,* 136-144.
30. Thiersch, J. B.: Review of certain classes of chemicals which damage the mammalian embryo. Presented at the annual meeting of The Teratology Society on June 11, 1964.
31. Wagoner, J. K., Archer, V. E., Lundin, F. E.,and Holiday, D. A.: Radiation as the cause of excess lung cancer among uranium miners. *New Engl J. Med.* In press.
32. Auerbach, C.: Mutagenic effects of alkylating agents. *Ann. N. Y. Acad. Sci.,* 1958, *68,* 731-761.
33. Murphy, M. L., Del Moro, Ada, and Lacon, Corinne: The comparative effects of five polyfunctional alkylating agents on the rat fetus, with additional notes on the chick embryo. *Ann. N. Y. Acad. Sci.,* 1958, *68,* 762-781.
34. Brill, A. B., Tomonaga, Masanobu, and Heyssel, R. M.: Leukemia in man following exposure to ionizing radiation: summary of findings in Hiroshima and Nagasaki, and comparison with other human experience. *Ann. intern. Med.,* 1962, *56,* 590-609.
35. Angevine, D. M. and Jablon, Seymour: Late radiation effects of neoplasia and other diseases in Japan. *Ann. N. Y. Acad. Sci.,* 1964, *114,* 823-831.

DISCUSSION: ROY M. ACHESON*

I think you will agree that Dr. Miller has played his role of anchor man between the viruses of the morning and the chronic diseases of the afternoon with considerable distinction. True to the title assigned to him, he has listed agents which any of us in the course of our everyday life may meet and which, if we meet too often, may cause a cancer in us. Some of these, such as irradiation and bad rum, are relatively common hazards; some such as mustard gas are exotic. But it is not here that the importance of his paper lies. He reminded us that it is now ten years since attention was drawn to the increased risk of developing leukemia run by the mongol. He pointed out that mongolism is due to nondisjunction of a small autosome, probably chromosome 21; and of course, it is known that one form of leukemia is associated with abberrations of this same chromosome. Then he reminded us that Wilms' tumor, an uncommon cancer, is frequently associated with equally uncommon congenital abnormalities, a highly significant association of unusual events. He concluded that in considering these associations we must think of agents to which mankind is exposed, not in his everyday life, but agents which may affect the fetus long before it is born. We must think in fact of a phenomenon analagous to what Dr. Habel described as vertical transmission. Dr. Miller added in a superbly causal way "The environment may *of course* (and note the "of course") exert its effect before conception." This kind of thinking is becoming

* Professor of Epidemiology and Medicine, Yale University School of Medicine.