The following papers, intended for physicians and biologists not necessarily working in the field of carcinogenesis, are presented in *Public Health Reports* because of their implications for public health practitioners. The papers were prepared by members of the Field Studies Area, National Cancer Institute, Public Health Service, and they were given at a combined clinical symposium held at the Clinical Center of the National Institutes of Health on June 10, 1965.

The Human Population as a Laboratory for Studies of Carcinogenesis

PAUL KOTIN, M.D.

ENVIRONMENTAL carcinogenesis is concerned with the identification of carcinogenic hazards, elucidation of their mode of entry and mechanism of action in the host, and the characterization of populations affected by them. Variations in the occurrence of cancer in man have been identified in the past on the basis of either occupation, site of residence, special ethnic considerations, or socioeconomic or cultural characteristics. The agents responsible for the hazards have been investigated by laboratory procedures directed to pinpointing specific factors or agents in complex environments responsible for the increased risk. The identification of the chemical structures of these agents is, of course, a prerequisite to studying their gross biological effect and anatomic and metabolic fate. In the absence of epidemiologic incrimination, laboratory investigations of potential carcinogenic agents have also followed suspicion of carcinogenic action based on the chemical structure of certain compounds either naturally occurring or artificially introduced into the environment.

From a biological viewpoint, carcinogenicity is established by bioassay experiments in which the suspected agents are administered to test animals by feeding, subcutaneous or parenteral injection, skin painting, or total body exposure in appropriately designed chambers. The disciplines applied in studying environmental carcinogenesis, therefore, consist of (*a*) epidemiology, with its allied sciences of biometry and statistics, (*b*) organic and synthetic chemistry for the identification, purification, and laboratory preparation of known and suspected carcinogenic agents, and biochemistry aimed at elucidating the anatomic and metabolic fate and mechanism of action of carcinogenic agents, (*c*) experimental pathology concerned with evaluating the response of biological systems from single cells to intact hosts to carcinogenic stimuli, and (*d*) virology, aimed at identi-

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fying viruses with oncogenic potential and studying their infectivity, and the possible interaction with the immune response of carcinogens to these agents.

In the past, the various aspects of cancer research and the disciplines used in their implementation have been pursued in essentially a discrete and isolated manner. This has resulted in the accumulation of myriads of data which has not been paralleled, however, by a concomitant narrowing of the gap of extrapolation of experimental data to man. A need exists, therefore, for experimental design using all the tools of environmental and experimental carcinogenesis so that maximum extrapolation of data can be built in at the outset.

The laboratory aspects of carcinogenesis are discussed in the following papers. I should like to emphasize studies of carcinogenesis in the human population.

In studying cancer in people, one can regard the population as his laboratory which, in common with the experimental laboratory, has subjects with various characteristics who are exposed to environmental or exogenous stimuli of contrasting types and intensity aimed at different target sites within the host.

To establish the pattern of cancer in man in the human population laboratory, cancer registers or morbidity surveys using a total population as a base can be undertaken. Or, for a more limited approach, the retrospective and prospective studies using case-control methods can be used. This permits the identification of factors concerned with cancer causation behavior in a manner analogous to the experimental laboratory with the limitations, of course, that (*a*) nature or society rather than the investigator designs the experiments, (*b*) the laboratory may be an occupational environment, a small area anywhere in the world, or some cultural or sociological behavior traits, and (*c*) planned controls in the usual laboratory sense can rarely be established.

Obviously, from the papers presented here, the molecular structure of the carcinogenic compounds listed wanders all over the chemical spectrum. The site of action of a carcinogenic agent further complicates the study of environmental carcinogenesis. While carcinogenic agents may enter the host through any of the several anatomic portals of entry, resulting cancers can occur at distal as well as local sites.

Cancers may develop at the site of initial tissue contact (skin—polycylic aromatic hydrocarbons and unrefined petroleum products), site of elective deposition or localization (marrow of the bone—benzol and radium), site of metabolism and detoxification (liver—azo dyes, chlorinated hydrocarbons, aminofluorenes), or site of excretion (urinary bladder—aromatic amines). Thus, the site of cancer formation can be unrelated to the portal of entry.

In another area, increasing numbers of reports are demonstrating a relationship between congenital abnormalities and increased risk to the development of certain forms of cancer in childhood. These observations provide a basis for the design of experiments to determine whether congenital defects and neoplasms are reflections of a single event, be it genetically induced or environmentally initiated during intrauterine life. The relationship of teratogenesis to carcinogenicity can in this way be explored and, hopefully, models developed to elucidate the mechanism of each.

We are aware of the inherent limitation resulting from attempts to study in controlled experiments the activity of multiple factors in a heterogeneous host. In order to partially overcome these limitations, recent trends in carcinogenesis have been concerned with the techniques of exposure of animals to multiple carcinogenic agents from several environmental sources. This approach should be expanded. The three major classes of environmental carcinogens—chemical, physical, and biological—can be studied effectively by duplicating under laboratory conditions, as nearly as possible, the circumstances of human exposure. The feeding and parenteral administration of carcinogenic agents is time honored. Total body exposure in appropriately designed inhalation chambers is only now becoming more generally used. Chemical agents of known or suspected carcinogenic significance, including hydrocarbons, metals, natural products, and macromolecular synthetics can be aerosolized. Therefore, animals can be exposed to these agents in combination with known or suspected oncogenic and nononcogenic viruses or in association with exposure to low-level radiation.

From a chemical, physical, and now biological viewpoint, a carcinogen-free environment is an impossibility. Industrialization and urbanization have created their own special contributions to the carcinogenic burden or load to which we are exposed. Industry, in response to need and demand, is introducing into the environment an ever-expanding and increasingly complex spectrum of chemical agents which increase crop yield through fertilizers and pesticides, make food more universally available and attractive through preservatives and additives, and make consumer products more easily obtainable through synthetics and macromolecules.

The rate of introduction of new agents into the environment is going to increase rather than decrease. When to this is added the potential carcinogenic burden incidental to radioactivity in the environment, it is obvious that the most hopeful approach to cancer control is through an understanding of the total response of the host as well as the response of target cells. In this way preventive measures can be accomplished either by establishing limits to exposure or, indeed, developing host buffering or protective measures.

Education Notes

Course on Personal Protective Equipment. The University of Oklahoma will offer a course on selection, care, and use of personal protective equipment November 28–30, 1966. Sponsors include the American Industrial Hygiene Association, the University, the Public Health Service, the U.S. Bureau of Mines, and regional chapters of the American Society of Safety Engineers.

The course has been designed to guide the student from industry, agriculture, governmental agencies, and schools to the sources and to present the basic principles for proper selection of protective equipment needs.

Additional information may be obtained from Dr. Carl A. Nau, Director, Institute of Environmental Health, Medical Center, University of Oklahoma, Oklahoma City; or William Hartman, University of Oklahoma, Norman.

Applied Epidemiology for Physicians. The Communicable Disease Center, Public Health Service, is offering a course in applied epidemiology, November 14–18, 1966. The course is part of the continuing education program of the Center's Training Branch.

Directed to physicians who serve as investigators of disease outbreaks or have administrative responsibility for such investigations, this course serves both as a refresher for experienced health administrators and as an introductory medium for those new to public health. It is designed to show how epidemiologic techniques can be used in disease prevention. Program activities will include group solution of epidemiologic problems, seminars, and panel discussions.

Further information and application forms may be obtained from the Communicable Disease Center, Atlanta, Ga. 30333. Attention: Chief, Health Professions Training Section, Training Branch.

Care of Premature Infants. The Institutes for Physicians and Nurses in the Care of Premature Infants, New York Hospital-Cornell Medical Center, sponsored by the New York State Department of Health and the U.S. Children's Bureau, will begin their 18th year in the fall of 1966.

Four institutes are scheduled between October 1966 and May 1967. The sessions are 2 weeks in length for physicians and 4 weeks for nurses.

Physicians	*Nurses*
November 7–18	October 24–November 18
January 16–17	January 3–27 (Tuesday
March 20–31	March 6–31
May 8–19	April 24–May 19

Attendance at each is limited to six physician-nurse teams. Participants pay no tuition and stipends are provided to cover other expenses.

Early application for the institutes is essential because plans are contingent on the number received. For additional information write to Box 143, Institute in the Care of Premature Infants, New York Hospital, 525 East 68 Street, New York, N.Y. 10021.