The Present Status of Pathology In Environmental Health

PAUL KOTIN, MD, BETHESDA, MD

IT HAS LONG been recognized that environmental agents may be crucially associated with the pathogenesis of disease in man. During the past half century, the problem of their adverse effects has increased in an alarming manner and the need for assessment of the hazards they pose is growing in urgency. Industrialization of society and advances in chemistry have made possible the synthesis of an almost infinite number of organic compounds which are introduced into our environment in numerous ways: (1) S[illegible]tic chemicals are in ever-expanding use [illegible]d additives and preservatives, and as coloring agents in consumer products with a consequent marked increase in dietary and cosmetic exposure of the population. (2) Pharmacological agents, both natural and synthetic, are being administered to patients for increasingly prolonged periods of time, often measurable in sizable segments of the total life span. The long-range low-level toxicity of these agents is a matter of concern. (3) Fertilizers and pesticide residues in foods are increasing as a result of their expanded use and little is known of their chronic effect. (4) Pollution of the atmosphere and water supplies threatens these critical and limited environmental resources. Toxicity is also being observed as a result of exposure to natural substances including microbiological food contaminants, the reaction products of chemicals within foods formed incidental to prolonged storage and diversified use, and toxic components of heretofore geographically restricted exotic foods. The problems of these potential hazards are many and complex. In the instance of synthetic agents used in consumer products, virtually all have presumed beneficial effects or contribute to progress, as the basis for their introduction. Thus, removal from the environment may be undesirable, or, in certain cases impossible at present. Host reaction to these agents may vary from a transient, acute, or subacute response to long-term toxicity with associated degenerative disease or carcinogenesis. The public health implications are of major concern to responsible governmental and nongovernmental agencies.

The changing characteristics of the environment and the manner of human exposure have rendered traditional pharmacologic and toxicologic approaches only partially adequate to solve the problem. There are several reasons for this. First, exposure involves all age groups including the fetus, affected transplacentally, the neonate with undeveloped detoxification mechanisms and resultant hypersusceptibility and possibly a proclivity for disease in later adult life, and the adult with impaired resistance as a result of antecedent or concurrent inflammatory or degenerative disease. Second, exposure to low subthreshold concentrations of potentially hazardous agents may extend over the total-life span in certain instances, and third, it is recognized that certain chemicals may manifest delayed toxicity, and further may potentiate or inhibit the toxic effect of other agents. The need for broadening the base for toxicity studies beyond traditional LD_{50} approaches is all too apparent.

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From the National Cancer Institute, National Institutes of Health, US Department of Health, Education, and Welfare.

Reprint requests to National Cancer Institute, Bethes[illegible] 20014 (Dr. Kotin).

Down's syndrome is associated with an increased risk to leukemia and, Wilm's tumor is associated with a spectrum of congenital malformations. Evidence suggests that environmental teratogenic and carcinogenic influences may have a common meeting ground in their effect on the embryo and fetus. The pathogenesis and overt manifestations of these conditions traditionally fall within the discipline of pathology.

During the past decade, there has been remarkable progress in studies devoted to the viral etiology of cancer. Independent of the ultimate status of viruses in the pathogenesis of cancer, the role of other environmental agents as oncogenic factors is unequivocally established. It is the pathologist alone who can provide the skill necessary for distinguishing the preneoplastic from the neoplastic lesions and further describe the morphogenic sequence in the ultimate development of cancer. Equivalents of the relation of arsenical keratosis to arsenical cancer probably exist for other environmental cancer, but the stigmata may be more subtle. The techniques of pathology need application to the identification and characterization of these "borderline" states.

The limited use of pathology in the investigation of environmental disease is clear when one recognizes that even in those schools of public health oriented to the study of industrial disease, only a few have pathologists as full-time staff members. Industries with large-scale programs devoted to the investigation of the biological effects of their products similarly lack the advice of pathologists. A critical review of the contents of scientific journals devoted to environmental health provides impressive evidence of the need for pathology in the study of diseases in this area. The great need and opportunities for pathologists are especially well illustrated by several problems in environmental health. In each, determination of the exact nature of the hazard was critically dependent upon the services of the pathologist. The circumstances of exposure and nature of the hazard were broad, involving occupational groups, the general population, and nonhuman animal species.

Pesticides.—For several years prior to the publication of *Silent Spring* concern was expressed over the effect of residual concentrations of pesticides in foods, water supplies, and contaminated atmosphere. The chemical structure of numerous pesticides makes them suspect as potential carcinogens in addition to acute toxins. Pesticide groups include chlorinated hydrocarbons, complex organic compounds with epoxy linkages, and carbamates. The problem of low-grade long-range toxicity is of serious concern because of storage and accumulation of pesticides in visceral organs, fat depots, and the central nervous system. The existing controversy over the carcinogenicity of dieldrin specifically denotes the indispensible role of the pathologist in the assessment of a potential human hazard as the following questions indicate: Can the proliferative lesions produced in experimental animals following ingestion of this and similar agents be classified as neoplasms? Are they malignant? Have they relevance for man in terms of either pathogenic or morphological similarities?

Cigarette Smoke.—The association of cigarette smoke with increased risk due to the lung cancer is well documented. Pathology can contribute critically in elucidating the pathogenesis of this disease. As with cancer of the cervix, a series of progressive morphological changes of the lung have been described in surgical and autopsy specimens and their counterparts induced in experimental species. Particularly gratifying has been the identification of a parallelism between the morphological changes and the extent of environmental exposure. The reversal of lesions associated with a reduction in risk to lung cancer following cessation of exposure is a most significant observation. Despite the elegant techniques in biochemistry, pharmacology, and toxicology which have been applied to the investigation of lung cancer, this morphological parameter is the most accurate measurable index of environmental exposure and risk.

Opportunities for cancers in pathology in the fields of environmental and occupational health are greater than ever before. In addition to the instances cited above, one could list many areas of growing concern that require both experimental and clinical investigation. Governmental agencies at virtually all levels suffer from the lack of availability of trained pathologists. Congress has recognized the public health implications of exposure to environmental agents

The relevance of the foregoing to teaching, research, and clinical application of pathology is constricted only by the limitations one selects in defining the discipline. While the sources of the biological insults are increasing in number and character, and the panorama of exposure is changing in character, the principles of response to injury as recognized pathologically still apply. Within the recent past there has been a growing belated recognition of the major need for scientists trained in pathology for work in environmental health. Opportunities for study exist in the experimental laboratory with research at the subcellular, cellular, and host level, and gross and histologic observations in the surgical pathology laboratory and the morgue. Studies in the experimental laboratory uniquely combine to provide the pathologist with an opportunity to unite experimental and clinical pathological observations with environmental histories so that pathogenesis in its broadest sense can be elucidated. The problem of the adverse effect of environmental agents on living organisms is necessarily the concern of numerous disciplines of which pathology is but one; nevertheless, its contribution in terms of pathological physiology as well as morphologic diagnosis cannot be overemphasized.

The magnitude of the potential, if not in fact, the indispensibility of pathology and the opportunities available for the pathologist can be illustrated by several recent environmental problems. As will be seen, assessment of the exact nature of the hazard was critically dependent upon the contribution of the pathologist. In the past, the role of pathology in the study of environmental health was essentially restricted to gross and microscopic description of lesions associated with occupational exposure. Pneumoconiosis, occupational cancer, and acute or chronic toxicity of visceral organs in restricted occupational groups, depended in large measure on pathological studies for their identification. The scope of the contribution of pathology has broadened through the introduction of experimental pathology and by the expansion of the group at a risk from a limited occupational sphere to one involving all ages of the general population.

While the end-point of the effect of an adverse environmental agent is a morphologically demonstrable lesion as a rule, elucidation of its pathogenesis is necessary before the role of the environment can be properly assessed and appropriate prophylactic measures can be undertaken. Environmental agents may gain entry into the host through the skin or any of the several body orifices. Their effects, however, may be manifest at distant as well as local anatomic sites. The behavior of chemical carcinogens denotes this especially well. Cancers may develop at the site of (1) initial tissue contact (skin: polycyclic aromatic hydrocarbons in petroleum products), (2) elective deposition or localization (marrow: benzol in chemical industries; bone: radium in watch painters), (3) metabolism and detoxification (liver: azo dyes in coloring agents, and chlorinated hydrocarbons in pesticides), or (4) excretion (urinary bladder: aromatic amines in dye manufacturing industries).

Agents which are carcinogenic also induce, to a greater or lesser degree, acute, subacute, or chronic changes as well. These changes may occur locally or systemically and vary from transient focal cellular necrosis with repair, to massive cellular necrosis ultimately leading to incomplete repair or possibly host death. The systemic effect particularly at the lethal level confronts pathologists with the problem of ascribing death to more or less specific causes. For example, the continuing controversy over the relative contribution of polluted urban air to increased mortality in such large urban areas as Los Angeles and New York is, in part, due to the inability of the pathologist to establish a cause of death which, with some degree of certainty, incriminates or exonerates environmental factors. The recognized association of antecedent or intercurrent cardiopulmonary or hepatic disease with abnormal responses to the low concentrations of environmental agents points to biological mechanisms that the pathologist is specially trained to pursue and identify. The relationships of chronic bronchitis to pulmonary cancer, of hepatic necrosis and cirrhosis to liver cancer, and of thyroid disease to thyroid cancer are of more than academic interest since environmental factors have been incriminated in the pathogenesis of the first of each pair.

Numerous studies have established an association between certain congenital malformations and an increased risk to specific neoplasms.

and this has resulted in (*a*) the enactment of the Delaney Amendment which permits no tolerance for carcinogenic agents added to foods, (*b*) revision of FDA requirements demanding evaluation of both short- and long-range toxicity with added tests for teratogenicity and (*c*) expansion of biological research activities in the fields of air pollution and water pollution.

Since enactment of the legislation, industry has repeatedly been faced with decisions requiring biologic and medical judgments. These have generated questions directed specifically to Governmental research and enforcement agencies. Such questions include: (1) What is the significance of induced animal tumors in relation to cancer in man? (2) What is the significance of chronic toxicity in animals in relation to man when circumstances of human exposure are not identical? (3) What are the acceptable criteria for bioassay of agents for toxicity and carcinogenicity in terms of species to be studied and interaction of environmental factors? (4) Is chemical demonstration of a carcinogen equivalent to proof of biologic effect? Supplying answers to these and similar questions is difficult, and even if answers were available they would be ineffectual in the face of a severe lack of trained, professional personnel. A team approach is required for the identification and monitoring of hazards as well as for the design and implementation of research aimed at elucidating mechanisms and developing countermeasurements. Ideally, the team should be under the direction of well-trained, full-time pathologists, whether work is undertaken by government or industry. For an example, one need only refer again to the contribution of pathology to our understanding of the relationship of environmental factors to the pathogenesis of lung cancer. The need for a similar role in relating other environmental factors to both neoplastic and nonneoplastic disease is equally great. One readily recognizes that toxicologists, pharmacologists, and biochemists contribute fundamentally to our understanding of mechanisms of disease. The industrial hygienist and industrial engineer can contribute their understanding of technology to the study of environmental disease. It is primarily the approach of experimental pathology in its broadest sense that can interpret disease and utilize this information in the design of experiments to elucidate the pattern of response to environmental stimuli.

In summary, environmental hazards are no longer restricted to special occupational situations but now encompass the general population. There must be an awareness on the part of the pathologist of the possible environmental origin of human disease. In addition, there exists a need for the development of technique to meet the more stringent requirements being established to protect the general population. Pathology in its broadest sense must play a critical role in this and environmental pathology as an entity is ready to join such recently recognized subareas as comparative pathology and geographic pathology.