# Environmental Diseases—A Pathologist's Overview and Public Health Responsibility

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THE PATHOLOGIST is particularly well fitted to the study of environmentally determined diseases in the present era of rapid change in the environment and the increasing demonstration that chemical agents and physical influences heretofore thought to be innocuous may not be so in fact. During the past several decades, the acute bacterial infections have been superseded as principal causes of illness and of death by a series of chronic illnesses, which are insidious in onset, protracted in course and manifest primarily by irreversible structural injury to tissue.

Environmental agents or factors acting over prolonged periods of time have been shown to play a causal role in the development of chronic degenerative diseases and cancer. The same is true in the development of certain congenital malformations. The chronic diseases are characterized pathologically by structural changes in tissues and organs. Under the most favorable circumstances, treatment can only slow or halt progression of these diseases; under usual circumstances, and most frequently, these clinical states prove wholly refractory to treatment. The structural changes characterizing these diseases virtually preclude "cure." In consequence, the need for understanding of pathogenesis from initial response to injury to the appearance of overt disease is imperative. Particular emphasis must be directed to identifying states in which reversibility of adverse effects may be feasible or, at the very least, organic disease has progressed minimally.

While the study of the evolution of disease is not new to pathologists, their past image in the scientific community has been more that of identifiers and cataloguers of pathologic conditions rather than students concerned with the dynamics of disease production. Actually, such specific entities as dose response to environmental in-

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Presented at the Symposium on Environmentally Induced Diseases at the Annual Meeting of the Federation of the American Societies for Experimental Biology, Atlantic City, New Jersey, April 15, 1970.

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sults, mechanisms of injury and the kinetics of the evolution of lesions are components of a continuum crucially dependent on the pathologist for evaluation and understanding. The pathologist's concern for the total host indelibly designates him as the focal point for the current multidisciplinary and multicategorical approach to the study of disease. Our interest encompasses dynamic rather than static aspects of morphologic change from gross examination to the level of ultrastructure study, with structure-function correlation as the guiding principle.

Prior to specifically noting the contributions of pathology to the understanding of the role of environmental agents or factors in the development of acute and especially chronic diseases, I would like to review some of the problems in environmental health and describe some new perspectives which characterize environmental factors as they affect human health. One can list them as a series of changes as shown in Table 1. Each of the large categories of change is further divisible into specific components.

The changing character of the environment is described in Table 2. At least four important changes in the environment can be identified. The first of these relates to the nature of the insult. Current hazards are increasingly microchemical rather than microbiologic; and, while the principles used so successfully in the control of infectious disease have some degree of application to the current situation, a new set of guidelines and criteria for evaluating the hazards must be evolved. Chemical agents for which toxicity has been demonstrated at high concentrations exist in microquantities in all compartments of our environment—air, water, food and consumer products—with potentially hazardous effects. The introduction of approximately 5000 chemical agents into the environment each year eloquently emphasizes the magnitude of the problem.

The hazards of chemical agents have been of most concern when they are present in high concentrations, and toxicologic studies have been the traditional domain of the pharmacologist and toxicologist. The concept and use of $LD_{50}$ toxicologic studies are inadequate to provide answers to newly evolving questions. Currently, the consideration of health ha•ards

Table 1—New Perspectives in Environmental Health

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| A. Changing character of the environment |
| B. Changing character of the population |
| C. Changing character of problems |
| D. Changing character of public health responsibility |

Table 2—Changing Character of the Environment

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| A. Current hazards primarily microchemical rather than microbiologic |
| B. Industrialization and urbanization of society |
| C. Multiple sources of insult |
| D. Increasing use of synthetic agents |

requires awareness that exposure to these agents occurs at concentrations well below those producing toxic responses for prolonged periods of time. Exposure to these low levels for major segments of, if not in fact, the total life span can be harmful.

Accompanying the change in the nature of the environmental hazards has been a change in the characteristics of current society. Industrialization and urbanization have not only created our big cities, but also have been responsible for the ubiquitous presence of the chemical agents to which I have alluded. Factors associated with abnormally high population density have resulted in changes in the microenvironment which have altered risks to a wide spectrum of diseases.

While a variety of chemical agents has always been present in the several compartments of the environment, it is only in the recent past that virtually all agents—metals, organic compounds, etc—have assaulted man from several sources simultaneously so that the quantification of a chemical in a single environmental site as a basis for assessing a potential hazard is of limited use and validity. Incidentally, environmental control efforts that shift chemical agents from one compartment to another do little to ameliorate their hazard. This, perhaps as much as anything, has placed health scientists and physicians in the center of the environmental health arena.

New to the environment are the ever-increasing numbers of synthetic agents. These polymeric substances synthesized from organic molecules vary in chemical and physical properties, survival in the environment and in anatomic and metabolic fate within the body. They represent a substantial threat with very little in the evolutionary sense in the way of adaptive accommodation through the eons of time.

Several aspects of the changing character of the population are described in Table 3. The first item on the slide—the uncontrolled increase

Table 3—Changing Character of the Population

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| A. Increase in size (numbers) |
| B. Increase in percentage at extremes of age (infancy and senescence) |
| C. Increase in the numbers and duration of life of persons with decreased physiologic reserve |
| D. Increased mobility of population |

in population size—requires little additional emphasis at this time. Over and above the economic and ecologic dangers associated with a very rapidly expanding population, there is the demographic problem of the effects of the increase in population density—*eg*, towns have become cities and cities have become conurbations, each with its particular pattern of risk to disease.

Paralleling the increase in the size of the population have been changes in its composition. One result of advances in medical care has been an increase in the increment of the population at the extremes of age. The increasing birth rate and decreasing infant mortality at one end of the spectrum and the effectiveness of maintenance medicine in prolonging life of patients with degenerative diseases at the other end have created two growing segments of the population, both with lowered susceptibility to the adverse effects of environmental agents. This group is further enlarged by the increase in numbers and duration of life of persons with decreased physiologic reserve. The maintenance of life in the presence of significantly decreased cardiorespiratory reserve or hepatorenal function through the judicious use of pharmacologic agents is well known; corollary to this is the reduced efficiency of the detoxification mechanisms in patients with hepatic or renal disease and the increased susceptibility of tissues and organs with parenchymal damage to continuing injury.

An aspect of the changing character of the population that has received far too little attention has been that associated with its increased mobility. Mobility in terms of our current patterns of life means spanning oceans or countries the size of the United States in a matter of hours. Again, in the absence of evolutionary adaptation, physiologic equilibrium and the ability of a tissue or an organ to withstand injury are significantly attenuated when biologic time clocks have been manipulated. Accompanying this ever-growing transiency is the mobility of a more permanent type—migration. For cancer, which is a prime example of an environmentally determined—if not caused—disease, the effects of migration on the risks for most visceral organ sites can be very great. It is unreasonable to suppose that degenerative diseases escape the effect of migration with its associated change in the environment.

A summation of Tables 2 and 3 is presented in Table 4. The changing character of the environment and of the population has combined to create a new constellation of problems related to environmental health. It is in the areas of problem solution and public health responsibility, on which I will elaborate, that the pathologist can make an indispensable contribution.

Perhaps the major new aspect of the current problems in environmental health derives from the long-term exposure of vir-

Table 4—Changing Character of the Problems

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| A. | Health hazards associated with long-term exposure to environmental agents present at concentrations below those producing rapid adverse response |
| B. | Combination effects of environmental agents from multiple sources interacting with one another and with man |
| C. | Hidden and complex nature of specific and invididual cause-and-effect relationships |
| D. | Changing patterns of morbidity and mortality resulting from changes in the environment |
| E. | Public concern over quality of health as distinguished from ill health |

tually the entire population to a wide variety of chemical and physical environmental agents present at concentrations lower than those producing immediate and quantifiable adverse responses. Effective approaches to the control of environmental disease must be predicated on this all-encompassing generalization. Traditional toxicologic studies must now be supplemented with new approaches that will permit the assessment of the effects of long-term exposure to low levels of chemical agents. Our knowledge in this area is limited at best and nonexistent at worst. It is difficult to profile and discuss in detail all of the groups of agents present in the several compartments of the environment (air, water, food and consumer products), but one certainly can pose questions concerning three crucial aspects of the problem that need to be answered: First, do any of the agents accumulate in the exposed population? Does a body burden build up? And, if so, does it create a special hazard? Second, is there a threshold that can be demonstrated for the production of adverse health effects by these agents? In discussing threshold, one must of course consider its corollary—dose response. Third, is there an increasing susceptibility to an agent as a result of continuous or intermittent exposure, even with periods of presumed recovery between exposures? We do not have many answers to this array of questions, but the experimental pathologic approach is indispensable in the search for such answers.

The problem of the combination of effects as well as the interaction of environmental agents is one of unbelievable complexity. Many agents interact with one another in the environment to yield secondary compounds—*eg*, photochemical smog from hydrocarbons, and methyl mercury from interactions of mercury with microbiologic agents. In man, the variables are multiplied. First, there is the additive effect of single specific agents coming from different environmental milieus. Second, there are the possible additive, synergistic or inhibitory effects of chemically related agents,

which react within man as a result of simultaneous or sequential exposure to them in the several environmental compartments. It is difficult to investigate additive, synergistic or inhibitory effects of two agents; for more than two agents, the task is enormous. Nevertheless, there can be no effective resolution of the problems of the role of environmental agents as disease determinants without some measure of success in understanding combinations of interaction effects.

Earlier, I emphasized that the hallmark of environmentally determined diseases—*ie*, chronic degenerative disease and cancer, is the long latent period measurable both experimentally and clinically as segments of the total life span of the host. This long time interval is conducive to obscuring and complicating the nature of any specific or individual cause-and-effect relationships. When one considers specific diseases in these categories, one readily sees that those diseases most prominent in current patterns of morbidity and mortality preclude a single cause or one-to-one relationship between an insult and a disease.

An unusual aspect in the area of the changing character of the problems that I would like to specifically comment upon is the universal concern we share as citizens as well as scientists. The control of acute infectious disease, growing periods of leisure, the broadening and improvement in education, substitution of machine for man, and computer for pen and pad have all contributed to growing concern over the quality of health and have brought us to the point where public health efforts must do more than prevent ill health—they must provide good health. Advances in the physical sciences and the health sciences have brought about a change in citizens' attitudes, which is reflected in a demand to "feel good" as well as to be healthy.

Before discussing some of the items under the changing character of public health responsibility, let me cite a few instances where pathology and pathologists have contributed crucially to th understanding of environmental diseases. Using the lung, the kidney and the liver as target sites, one can discuss the total environment with particular reference to accomplishments resulting from a modern approach that uses the disciplines of pathology.

The most prevalent chronic diseases of the lung are emphysema, cancer, bronchitis and pneumoconiosis. A long list of environmental sites and environmental agents associated with increased risk to these diseases could be prepared without really contributing much to our understanding of the dynamics of the evolution of these dis-

eases. Advances in engineering and analytic chemical technics through the use of magnetic resonance, mass spectrometry, GLC, etc have permitted microquantification of agents in the environment causally associated with increased risk to these diseases. It is the pathologist alone, however, who can provide the substantive information necessary for understanding of the nature of the injury, the local as well as systemic host response, and more important the little information that does exist on dose response. The work of Auerbach *et al*[1,2] on the relationship of smoking to lung cancer, emphysema, and bronchitis; the work of Saccomanno *et al*[3] and Kuschner[4] on the relationship of uranium mining both to the risk to lung cancer and to the peculiar histology of the human-induced lung cancer; the work of Churg *et al*,[5] Webster,[6] and Gross *et al*[7] on the relation of asbestos exposure to asbestosis, lung cancer and mesothelioma; and the work of Ishikawa *et al*[8] on the pathogenesis of coalworkers' pneumoconiosis and on geographic factors in emphysema, all elegantly denote my contention. It is of interest that each of these men—using as a starting point the traditional domain of the pathologist, a pathologic diagnosis—has provided information critical to the elucidation of the dynamic aspects of the disease entities from the initial insult to the morphologic endpoint, including data on dose response, reversibility of lesions and identification of sites of special resistance or susceptibility.

Using exposures to such metals as lead and mercury as examples, one can again cite instances of a variety of renal diseases where the investigations by pathologist—*eg*, Goyer *et al*,[9] have contributed to an understanding of the disease from the organ down to the intracellular macromolecule as well as to the interface between the environment and the target host. Structure-function correlations alone permit the profiling of the natural history of the development and progression of environmentally induced chronic disease.

The pathologist as well as the toxicologist and pharmacologist has pursued studies of the liver for the understanding of mechanisms of toxicity and pathogenesis of disease. Such endpoints of chemical injury as subacute atrophy, various types of cirrhosis and cancer of the liver have also served as the foundations for indispensable contributions to our understanding of the progression of disease, as mentioned during my discussion of pulmonary and renal studies. As an aside, I might mention that in degenerative diseases of the cardiovascular system, pathologists (*eg*, Spain *et al*[10])—all starting with a pathologic diagnosis—have contributed to our appreciation

of the dynamics of the development of arteriosclerosis and myocardial infarction as well as the role of the environmental agents in their etiology.

Let me now discuss the final group of changes as seen in Table 5. The changing character of the public health responsibility is, in essence, a summation of the preceding four tables. The changes listed in the first four tables make apparent the fact that a pure environment is an unattainable goal. Were it achievable, it would be culturally unacceptable. This forces upon those responsible for the maintenance of public health the need to establish criteria and standards to assure the quality of the environment. I might, in passing, mention again the problems associated with multifactorial exposure, the extremely broad range of susceptibility and resistance within the population and the absence of knowledge as to long-term, low-level effects. This requirement for criteria and standards has as its corollary the need for a scientific basis for their establishment since we can at best only hope for a clean environment. Not only does the protection of man demand a sound foundation as a basis for judgment, but also the economic implications of control equally emphasize the need for utmost reliability prior to the promulgation and enforcement of standards. All restrictions cost something. This cost can be paid by a single individual, a large corporation or the entire population. It also can b measured in terms of modifying the ease of life, infringement on cultural patterns and traits, encroachment on personal liberties, or affecting economic return. Those paying the cost legitimately demand assurance that the benefit will merit the cost. Those responsible for exacting the cost must be certain of the answer.

All of the foregoing has been concerned with extant and predictable health problems due to environmental influences, associated changes in morbidity and mortality and the crucial need for fundamental scientific information on which to base current control standards as well as predictive criteria. It is manifestly impossible to test each of the 5000 new chemical agents introduced into our

Table 5—Changing Character of Public Health Responsibility

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| A. | Need for criteria and standards to assure quality of environment |
| B. | Need for scientific basis for establishment of criteria and standards |
| C. | Requirement for fundamental information on which to base predictive criteria |
| D. | Assessment of problem associated with interactions of multiple agents in man |
| E. | Recognition of effect of environmental agents on man's behavior |
| F. | Major social and economic implications of control measures require scientific bases for resolving "benefit versus risk" equation |

environment each year. For the most part, these agents serve a useful purpose and include not only consumer products but also, to a very large extent, drugs. Drugs that, in contrast to those used in limited fashion and short duration for the treatment of acute illness in the past, now are taken for most of the life span—*eg*, tranquilizers, antihistamines and the "pill." Predictive criteria can only be achieved by the elucidation of fundamental mechanisms of action and the identification of principles governing the host's response to microchemical injury.

In discussing the domain of the pathologist, one can prophesy, as a certain effort in the future, the study of the effect of environmental agents on man's behavior—*ie*, functional responses. There is no doubt that fundamental macromolecular changes must account for the majority of these functional responses.

Finally, I would like to allude again to the major social and economic implications of control measures which require scientific bases for resolving the "benefit versus risk" equation. I do this as a scientist and citizen as well as a pathologist.

I would like to close with a look to the future in the field of clinical laboratory medicine, one of the domains of pathology. Community medicine, modern preventive medicine and environmental medicine are to me all synonyms for the study and application of knowledge related to current determinants of disease. Chronic diseases by definition are incurable—*ie*, diseases with parenchymal destruction with replacement of functional tissue by fibrous tissue. The earliest evidence of these diseases is usually abnormal laboratory findings rather than clinical signs, and therefore they fall within the domain of the pathologist. We as pathologists do not deal with populations as a study resource; however, we have a responsibility to those who do—the epidemiologists. We can and must provide them with the required diagnostic tools and the necessary benchmarks and hallmarks of disease prior to their clinical advent.

In summary, at all stages of response to environmental agents from the pathologic endpoint (traditional pathology) to the identification of the earliest pathologic responses for use in the study of patients (environmental pathology) including monitoring, the pathologist has a key role in the study of environmentally induced diseases.

**Summary**

Two almost simultaneous progressions of events concerned with the well-being of man are occurring and each bears a significant

relationship to the other. The first is the changing character of man's environment and the associated threats to health this represents; the second is the changing character of the population with accompanying alterations in morbidity and mortality rates in the population. The former dictates close study of the environment as a necessary prelude for intelligent and effective control, especially since the hazards to health from environmental sources now stem from microchemical rather than microbiologic agents as in the past. The latter requires an immediate and intensive review of priorities in the health sciences in general and in the field of pathology specifically. Both the clinical pathologist and the experimental pathologist can provide the integrative skills to assure that the data being generated in everincreasing amounts by biologic scientists are properly interpreted. The correlation of functional abnormalities with structural changes in response to exposure to low levels of chemical agents in the environment for long periods of tim is a mandatory prelude to appropriate public health measures to protect the general population.

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