Multiple Factors in the Causation of Environmentally Induced Disease

Edited by

Douglas H. K. Lee / Paul Kotin

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* The untimely death of Dr. Blood before completion of this volume is much regretted.

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EDITORIAL COMMENT

As governmental and public interest in environmental quality increases, and as conservation or remedial programs are planned, a number of scientists are called upon for advice or decision in areas involving fields beyond their own personal expertise. Program managers, experienced in administration, also find themselves in need of information on technical matters that fall within their jurisdiction.

The announcement that a United Nations Conference on human environment was to be held in Stockholm in June 1972 pointed out the fact that these needs are worldwide. It stimulated the John E. Fogarty International Center of the National Institutes of Health to investigate how these needs might be met. In conjunction with the National Institute of Environmental Health Sciences, also part of the National Institutes of Health, a decision was made to prepare four books on the aspects of environmental health for which suitable résumés were not readily available.

The interplay of multiple factors in the causation of environmentally related disease was the topic selected for the fourth of the set. As for the other volumes, a small panel of experts in the field was asked to delimit the scope that should be followed, to indicate the specific topics within that scope, and to suggest other experts who could contribute to the volume. Contributors brought draft papers to a three-day workshop where the drafts were thoroughly discussed, amendments suggested, and integration among chapters developed. Extensive editing followed.

The contributors to the previous three books had a relatively easy task in that they were asked to condense existing knowledge on the particular subjects into a form that would be instructive for scientists and scientific managers who had to make decisions involving fields in which they were not themselves expert. The contributors for this fourth book had a much more difficult task. They were, in effect, asked to comment in learned fashion on a concept rather than on factual information. The concept, moreover, was one which is often invoked but seldom defined. The previous three books, in presenting relatively hard knowledge, revealed their own areas of deficiency, such as lack of information on the environmental distribution of stressors or the poor comparability of information on even closely related stressors. This book goes further in repeatedly revealing that the information necessary for good comprehension and sound recommendation is simply not readily at hand. It is believed, however, that the very demonstration of deficiencies is important, and that the development of a more adequate approach to environmental problems will result from attention being drawn to them.

After an introduction based mainly on the epidemiology of infectious disease, but applicable to other environmental factors, some diseases believed to have multiple etiological factors are reviewed in Part I. Part II goes to to the other end of

the pathological spectrum and looks at disturbances of cellular processes resulting from two or more factors operating simultaneously or in succession. Part III examines the further complicating role that storage of potentially toxic material in body tissues and its subsequent release introduce into an already complex situation. Part IV deals with some implications of multiple factor operation.

It has not been easy to preserve a balance between simplification for the nonspecialist and adequacy as viewed by the expert. The text now appearing has been checked by the contributors, but we must accept responsibility for any undue selectivity that may have occurred as well as for errors of omission or commission. We hope, however, that the text will help those who need to know the state of current knowledge on the health significance of multiple environmental factors but who do not have the time to pursue the detailed literature or to seek a compilation directed to their special needs.

Douglas H. K. Lee
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CONCENTRATION UNITS AND CONVERSION FACTORS

Metric and proportional units are used somewhat indiscriminately for indicating the concentration of toxic agents. In this volume the units preferred by the individual contributor have been retained. The reader who wishes to make comparisons between concentrations expressed in different units will find the following data useful.

In solid and liquid mixtures, proportional units refer to weights and are easily converted to metric equivalents:

1 part per million (ppm) = 1 mg/kg
1 part per billion (ppb) = 1 μg/kg
(1 kg of liquid of density 1 = 1 li)

In gaseous mixtures, however, proportional units refer to volumes, so that conversion varies with the molecular weight of the dispersed substance, temperature, and barometric pressure. The conversion formula is

1 part per million by volume
at 25°C and 760 mm HG pressure = 0.041 (molecular weight) mg/m^3

Note: The factor 0.041 represents 273/(298 X 22.4)

Particulate matter in air is often expressed in terms of millions of particles per cubic foot or per cubic meter. To convert from cubic foot to cubic meter, multiply by 35.3. (This also gives particles per cubic centimeter.)

CONTENTS

PART II. MECHANISMS OF MULTIFACTOR EFFECT

PART III. COMPLICATIONS INTRODUCED BY STORAGE OF CAUSATIVE AGENTS

CHAPTER 1. INTRODUCTION: CONCEPTS OF MULTIPLE FACTORS

BRIAN MACMAHON, Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

Almost 2400 years ago, Hippocrates pointed out the need to understand the causes of disease if we are to control it. Only in the last one hundred years, however, have we begun to make measurable progress in this direction. In this brief span of time many living and inanimate agents capable of inducing human disease have been identified. The reductions in mortality and morbidity that have followed are clear -- at least in those areas of the world fortunate enough to possess the resources to apply the knowledge for the benefit of their populations.

For many years after the beginning of this era of discovery the guiding philosophy was that each human ailment had its own particular cause, in much the same way that each force had its own equal and opposite reaction. This philosophy was most vividly expressed in the postulates of Koch -- a set of "rules" that for many decades specified the conditions that must be met if a particular microbe was to be considered the cause of a particular human illness. The concept, in general, served us well, providing the means for controlling many infectious and chemically-induced diseases.

As the list of factors known to be capable of inducing human disease has lengthened, it has become clear that a particular disease manifestation may have more than one causal antecedent. In addition we have learned that exposure to a known cause of illness does not always lead to the expression of that illness and that identification of a causal antecedent does not necessarily provide the ability

to prevent or control the ailment. We have come to recognize that the one cause-one disease model is too simple. Illness in an individual is the result of a multitude of prior circumstances -- including those multiple, independent, minor circumstances that we call chance -- and causal circumstances differ from one individual to another, even when the manifestations of their illness are indistinguishable. Seemingly minor differences in diet or in physical or chemical environment determine the reaction of a person to a given microbial or genetic stimulus, and vice versa. Indeed the causal antecedents of illness in any individual comprise a web of intertwined circumstances that in their full breadth and complexity lie quite beyond our understanding.

PRACTICAL UTILITY OF THE CONCEPT OF MULTIPLE FACTOR ETIOLOGY

It may appear that, in our recognition of the complexity of disease etiology, we have gone from one extreme to the other -- from the limited utility of the one cause-one disease model to a philosophy that, because of the limitations of our ability to comprehend, may be of no more, and perhaps even less, practical utility for the development of disease control measures. Fortunately, to develop effective control measures it is not necessary to understand the entire causal web but merely to identify significant strands, the disruption of which can lead to alteration in the whole structure. Recognition of the possibility of multiple etiology -- even when we know that we can never understand the antecedents of a particular illness in their entirety -- enormously increases the opportunities for preventive action since it increases the number of points at which such action can be effected. This is clearly illustrated by two kinds of situation:

1. A factor is identified as an unequivocal cause of disease but proves to be not manipulatable for preventive purposes. Genes generally fall into this class. It may then be possible to identify other components of the causal web that can be altered. Phenylketonuria, for example, is a disease that thirty years ago

might have been considered a single factor disease -- determined exclusively by the presence of a single recessive gene in homozygous form. Certainly it appeared that everybody carrying the required genetic combination manifested the disease. The discovery that the manifestation depended, in addition, on the presence of phenylalanine in the diet opened the way for the prevention of at least some of the disease manifestations.

2. A factor that causes disease also has desirable effects that make its elimination unacceptable, or at least less acceptable than other ways of achieving the health objective. For example, the community at large appears to find unacceptable the elimination of cigarettes as a measure to prevent the more than 100,000 deaths that these cause annually. In spite of the availability of measures directed against specific microbial causes of enteric diseases, prevention of such diseases in this country is still based on the provision of unadulterated water and food rather than on what would have to be massive vaccination programs.

The concept of multiple-factor etiology often appears to be used as a last refuge by investigators unable to identify any causal factor of significance. As such the term has a pessimistic ring. We should recognize, therefore, that the existence of multiple etiologic factors provides us more, rather than less, opportunities for preventive action.

THE CHANGING CAUSES OF DISEASE

The profile of the human environment -- and for that matter of the human gene pool -- is in a constant state of flux. The microbial and other living agents of a disease to which a typical North American is now exposed are considerably less varied and less widely distributed than those of fifty years ago. Also more homogeneous is the general ecological milieu that hosts such agents. On the other hand,