

ADVANCES IN MODERN TOXICOLOGY VOL. 1 • PART 2

**NEW
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IN SAFETY
EVALUATION
PART 2**

MYRON A. MEHLMAN
RAYMOND E. SHAPIRO
HERBERT BLUMENTHAL

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Part 2

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Advances in Modern Toxicology

Editor

Myron A. Mehlman

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| Vol. 1, Parts 1 and 2—Myron A. Mehlman,
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*To
Leo Friedman*

PREFACE

This is the second part of the volume published in memory of the late Leo Friedman. The chapters in this volume continue to reflect our concern with issues that may affect public health and means for their evaluation and containment.

Chapters 1-3, by Philippe Shubik, John Higginson, and J. L. Radomski, respectively deal with environmental chemicals as a causal factor in human cancer. The chapter by Thomas E. Shellenberger continues this theme in terms of hormonal exposures and the relevance of animal studies to humans. Animal studies are implicitly assumed to be predictive of what may occur in humans, and various mathematical approaches may be used in interpreting experimental animal data. These approaches are considered in the next two chapters by David W. Gaylor and Raymond E. Shapiro, and by Roy E. Albert, Fredric J. Burns, and Bernard Altshuler.

The final chapters by Arthur Furst and Ingeborg Harding-Barlow, John Autian, William Lijinsky, Bernard Davidow, and J. C. Calandra and Otis E. Fancher discuss areas of interest and problems to toxicologists. It is our hope that these volumes are a fitting memorial to the late Leo Friedman and will serve as a stimulus to the search for new tools and thinking in safety evaluation.

**NEW CONCEPTS
IN SAFETY EVALUATION**

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Chapter 1

ENVIRONMENTAL CARCINOGENESIS— PRIORITIES AND PERSPECTIVE

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I do not believe anyone will disagree with my first statement although it would seem unlikely that I will get a unanimous vote of confidence for the remainder of my remarks. It may be that I will be persuasive enough to get the majority to agree, but I would venture a degree of certainty in believing (perhaps, by now, hoping) that there will be some disagreement—even violent, emotional disagreement—with some of my statements.

The first statement is that 1975 has, indeed, been an interesting year for those of us who play an active role in the field of environmental carcinogenesis. In fact, I believe that some (and I am one) had no idea how active our role would be and how much the airline industry would benefit from the recognition that society has suddenly decided to confer on our efforts.

Recently there has been a recurring theme in statements and publications wherein certain authors claim to have been the first to point out that 70, 80, or even 90% of all cancers are doubtless due to, or at least associated with, environmental chemicals. I do not know quite why anyone would be proud to claim the authorship of such a statement, unless this person were running for political office. My previous experience indicates it is not the kind of discovery that is rated as good science. I mention this in passing to introduce you to a brief consideration of the history of this subject.

When considering what I would say here I came to the rapid conclusion that there was little I could say about the recent developments in the

This paper was presented as the keynote address at the Fourth Annual Carcinogenesis Collaborative Conference of the National Cancer Institute held in Orlando, Florida, February 23, 1976.

field—say those of the last 5 years—that would carry any great surprises. They could, of course, be the basis for one of the spirited disagreements that we all enjoy so much, but in essence most of us here know the often repeated facts and interpret them in various ways. History is the one aspect of the subject that I thought might provide me with the opportunity of saying something a little new to at least some of you. Added advantages were I could read some interesting materials that I somehow had not found time to read, and that I could reread some of the material that I had not read for a number of years and contemplate it within the context of new knowledge. Let me apologize in advance for assuming that much of what I will say is new to you. If it isn't, at least I hope that the presentation will interest you and arouse your thoughts about some new considerations.

Who started all this interest in environmental carcinogenesis? Was any one individual more responsible than any other? Or perhaps the subject was a natural development as a result of the accumulation of knowledge over the years. I have concluded that chemical factors were not really considered as possible overall causes of cancer in humans until the twentieth century. In spite of the work in the eighteenth and nineteenth centuries on occupational cancer, the extension of these discoveries to cancer in general does not seem to have occurred to anyone as even the basis for a theory that could be accorded general recognition. Even if there was a mention of such an approach it did not receive general recognition. This is not to say that individual carcinogens were not sought or that factors still included in our lists were not talked about monotonously—arsenic, tobacco (even before the epidemic of lung cancer), various oils and tar products, and so on. However, not until the start of this century did a general interest begin that waxed and waned and is now at its highest level.

If one looks through the Donner Foundation's excellent compendium of cancer research from 1900 to 1935, it is of interest to note that among the factors listed under etiology are alcohol, bilharzia, cholesterol, chromium, creosote, estrogens, dietary fat, fungi, lead, magnesium, mercury, mutagenic rays, naphthylamine, paraffins, road dust, salicylic acid, arsenics and tin, scarlet red, spermatozoa, sulfuric acid, sunlight, tetraphenylmethane, tobacco, tomato, tomato juice, and benzene.

An anonymous reference under environment reports "A contribution to the etiology of cancer; being a full report of the investigations by a committee appointed March 1898 by the Birmingham and Midland Branch of the BMA."

To be sure that I was complete in covering those factors that should be included under "environmental carcinogenesis," I looked up "environment" in various dictionaries and discovered that as time passed the term encompassed more and more aspects of our lives. The 1955 edition of the Shorter Oxford Dictionary begins with a 1603 definition: "The action of environing; the state of being environed." It would appear that at the time the word environ meant to surround or beleaguer (perhaps this explains some of our problems). The

1827 definition was "That which environs; *esp.* the conditions or influences under which any person or thing lives or is developed." The 1965 edition of Webster's Collegiate Dictionary tells us that environment is, again, "1: something that environs; 2a: The complex of climatic, edaphic and biotic factors that act upon an organism and ultimately determine its form and survival; b: the aggregate of social and cultural conditions that influence the life of an individual or community." The most recent edition of Webster's Dictionary adds to this "3: an artistic or theatrical work that involves or encompasses the spectator." As an innocent bystander who has been "encompassed" by some of the more theatrical performances, I cannot but admire the ability of the modern lexicographer. All joking aside, it is no wonder that we are having more than a little difficulty defining environmental carcinogenesis.

In spite of some disagreements with him and many misunderstandings (in my view on his part), I must start (somewhat out of historical continuity, since I will go back later to those who antedate him) with one of our great mentors in this field, Dr. Bill Hueper. When I first came to the United States I met Dr. Hueper at the National Cancer Institute. I was interested in meeting the man who made the discovery that is, I believe, perhaps next in importance to that of Yamagiwa and Itchikawa (1918). I must confess that within the next several years he had a profound influence on me and on the group that had taken refuge in the Chicago Medical School. I believe that if any one person can be given a major share of the credit for our present interest (and confusion) in environmental carcinogens, it must surely be Dr. Hueper. His book *Occupational Tumors and Allied Diseases*, published in 1942, begins with a chapter entitled "Concept and Significance of Occupational Tumors 1. The New, Artificial Environment." It presents, by and large, an original and interesting concept. It is, of course, slanted and contains one of Dr. Hueper's most unfortunate prejudices in embryo when he says, "While it may be possible that in some occupations the excessive indulgence of habits, like smoking and drinking, may play a predisposing role, *this conception should not be unduly encouraged* in view of the serious ignorance existing concerning the cause or causes of cancer in general and occupational cancer in particular" (emphasis added).

Dr. Hueper somehow managed to spot sources of environmental carcinogens. How important some of them will prove to be to cancer in humans will, in many cases, never be known.

It is astonishing to still come face to face with audiences, even physicians, who do not know that the primary cause of a single cancer is known. Mental floundering seems to occur when the subject is discussed. It does not come into focus in the context of an infectious disease or acute poisoning. Dr. Hueper knew this better than any of us and took a stance that I believe was needed in the beginning. He had to hammer home the fact that some cancers were known to be caused by chemical carcinogens and could be prevented and that doubtless many more cancers would be found to have similar causes.

I think a major question that faces us is, "Are we still in the same position? Do we still have to take extreme positions to make our point, or have the climate and the level of knowledge changed enough to enable us to discuss these problems in a properly balanced manner?" I think that the answer is "Yes and no."

To return to my quest for who said what and when, I should like to contemplate the matter of geographical pathology. I used to think that this all started at the National Cancer Institute (not to belittle the many fine contributions that have emanated from there). Our late colleague, Dr. Symeonides, a man who inspired many of us at the start of our careers, must, I believe, be given credit for the major impetus given to the study of the geographical variations in cancer incidence as a basis for investigations of etiology. However, as pointed out to me by my late colleague, Dr. Leslie Foulds, and recorded in his wonderful book *Neoplastic Development* (1969), E. F. Bashford prepared a "Draft of Scheme for Enquiring into the Nature, Cause, Prevention, and Treatment of Cancer" as his application for the newly founded Imperial Cancer Research Fund in 1902, in which he prophesied the discovery of chemical carcinogens in petroleum products and recommended studies of the "ethnological distribution of cancer." The only advance made since then has been to change the term to "geographically significant change." We have only just managed to get back to the stage in which all the facets of this logically assembled plan are being put back together. I say this at the outset to point out that much of our present endeavor is based upon a series of reasonably obvious deductions that can be made when it is known that (1) there are some established chemical causes of cancer and (2) there are geographical (and other) variations in incidence. An obvious course is to look for more chemicals associated with cancer in humans and their variations and explain them. I am not sure that we are really well organized and have benefited from the many lessons learned since the first chemical carcinogen was discovered 200 years ago.

Sir Ernest Kennaway was another inspiring man in a strange way. I was privileged to meet him when preparing the continuation of Dr. Jonathan Hartwell's compendium. He was suffering from Parkinson's disease but was extremely alert. He wished me to include the voluminous data, similar to Hartwell's, prepared by Prof. O. Neubauer. He wanted me to read through it all and proposed to stand behind me for some time while I did. I managed to escape and, in fact, could not add the data. However, it provided me with time to observe Kennaway's meticulous approach. He held a view that has taken a considerable hold, although I do not believe that most oncologists today recognize its origin. Kennaway felt that relatively low doses of weaker carcinogens occurring over a lifetime might well be responsible for many of the cancers in humans. I believe that this is an erroneous view but realize, of course, that it is popular; I stand ready to debate the issue. I bring it to your attention to point out that Kennaway essentially considered only polycyclic and heterocyclic aromatic hydrocarbon carcinogens. Although the aromatic