Encyclopaedia of Environmental Pollution

Vol. 4

ENCYCLOPAEDIA OF ENVIRONMENTAL POLLUTION

POLLUTION, DRUGS ENVIRONMENT AND HUMAN HEALTH

VOLUME - 4

S.K. SHUKLA
P.R. SRIVASTAVA

COMMONWEALTH PUBLISHERS
NEW DELHI (INDIA)

ENCYCLOPAEDIA OF ENVIRONMENTAL POLLUTION

First Published, 1997

ISBN 81-7169-446-2 (Set)

Published by:
AJAY VERMA
COMMONWEALTH PUBLISHERS
4378/4-B, Murari Lal Street,
Ansari Road, New Delhi - 110 002
Phone : 3272541

PRINTED IN INDIA

at
Taruna Enterprises
518/14, Anup Market, Maujpur, Delhi-110053

Preface

A discussion of health effects should be based on an understanding, however incomplete, of the fundamental meaning of health. It may be pertinent, therefore, to reflect that the very process of living is characterized by stresses to be found in his external environment. To "counterbalance" these stresses, highly compex physiological or internal adaptive mechanisms are evoked in order to maintain an optimal equilibrium. Fitness or 'health' of the individual depends, therefore on the effectiveness of these counterbalancing forces. Maladjust, on the normal defences disturbed function, disease and/or death.

Our total environment does not remain constant but is in a continual state of change, a state influenced increasingly by man's rapidly-growing technology, the harnessing of all forms of energy and the development and use of our natural resources. Therefore, of central interest to the present book is to analyse the health Hazards of Man's Environment in a very lucid style.

EDITORS

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Physiological Characterization of Health Hazards

Industrial growth and innovation based on scientific and engineering achievements are the means by which a technological society converts its resources into products and services which both enhance the material wealth of the nation and also provide sophisticated weaponry for its defense.

In the main, such growth raises living standards by increasing the quality and quantity of food, housing, transportation, and sanitation. By reducing toil, technology allows more leisure time for the citizens of a civilized society to enjoy educational and recreational pursuits.

On the other hand, technological progress coupled with population growth and urbanization, has introduced into the environment man-made hazards to health in the form of synthetic industrial and agricultural chemicals, toxic elements, industrial and community waste products, new sources and kinds of energy, as well as psychophysiological stresses such as crowding and noise. Detrimental effects on health of some of these stresses are immediately apparent, while other long-range effects are only dimly perceived, but considered by many as being of ominous dimensions.[1]

It is clear that our society must weigh carefully the benefits it enjoys from technological accomplishments and industrial growth against the costs it may have to pay in terms of present or future health impairment of its people stemming from man-made hazards and also from the loss of esthetic qualities of living resulting from deleterious changes in the human ecosystem.

The best available advice from authorities in various fields of science and engineering, commerce, the health professions, and the social sciences will be needed to identify, characterize, and anticipate public health hazards in the environment. Only from such informed sources can our society reach wise decisions in formulating operational plans for controlling further proliferation of environmental health hazards, and where feasible, restoring a more favourable environment.

The United States Public Health Service has long recognized its responsibility for health protection of the population not only against infectious diseases, but also against chemical and physical hazards in the community and work environments. To this end the USPHS had established action programmes for the study and control of health hazards in various categories of the environment, including water supply, milk and food sanitation, sanitary engineering, air pollution, radiological health, and occupational health.

In its report to the Surgeon General in 1962, the Committee on Environmental Health Problems (better known as the Gross Committee) outlined future national needs in environmental health and recommended substantial expansion in manpower and facilities for intramural research and training, in order to provide technical and advisory services to the states, and also to expand extramural programmes of training and research in each of these categorical areas of environment health.

A major concern of the Gross Committee, however, was the need for a far more detailed understanding than now exists of the complex interactions of man as a biological system with the multiple physical, chemical, biological, and psychosocial environmental stresses which impinge upon him individually and in social groups. The Gross Committee urged the organization within the USPHS of an Office of Environmental Health

Sciences which would include biological, physical, and social scientists as well as mathematicians whose mission would be to study and conduct research on basic problems in environmental health of common interest to the several categorical environmental health agencies within USPHS. The intent of the recommendation was that the research studies supported by this office would be more basic, longer term, and more interdisciplinary than was possible under then existing action programmes.

In 1966, Congress authorized creation of an Environmental Health Center[2] which was subsequently established within the National Institutes of Health with a National Center of Environmental Health Seiences in the Research Triangle in North Carolina, to conduct the intramural research programme together with additional funds to support extramural programmes of research and training through project and center grants to universities.

Anticipating the founding of DEHS (now NIEHS) scientists within USPHS undertook a re-evaluation of the role that physiology would play in investigations of the toxic effects of environmental agents on human health and the interplay of these agents with other environmental stresses. Their conclusion was that environmental physiology in the past had not sufficiently clarified the multiple chains of cause and effect mechanisms which exist between the exposure of man to environmental agents and the integrated response of his biological systems at the molecular, cellular, and higher levels of organization.[3]

Hence, in 1965 the USPHS proposed that the National Academy of Sciences-National Research Council undertake a broad-based critical study of the physiological underpinning of current concepts of biological responses to toxic chemicals and physical stresses.

NAS-NRC had previously taken the lead in studies in man's management of his environment and had issued two substantive reports: "The Management of National Resources" and more recently "Waste Management and Control" (the Spilhaus Report), which together with a third report emanating from the President's Advisory Committee, "Restoring the Quality of our Environment" (The Tukey Report), formed a thoughtful and comprehensive treatment of the effects of technological trends and innovations, as well as industrial expansion, on the natural environment and their resulting impact on human ecology. Specific recommendations dealt with means for identifying, predicting, and controlling deleterious changes in environment insofar as these reflect themselves in impairment of human health.

In response to the proposal of the USPHS, the Committee on Environmental Physiology of the National Research Council's Division of Medical Sciences—the latter then under the chairmanship of R. Keith Cannan—organized the Symposium on Physiological Characterization of Health Hazards in Man's Environment. With funding from the USPHS, this 2½ day meeting was held in August, 1966, at Bretton Woods, New Hampshire.

Among the participants were prominent authorities from biomedical disciplines ranging from molecular biology to human ecology, and including toxicology, biochemistry, oncology, pathology, and humun genetics, as well as several subspecialities of physiology.

In the opening plenary session, the Co-Chairmen of the Symposium, Dr. Cannan and Dr. Minard, outlined the objectives of the meeting and proposed a plan of attack to be undertaken by the assembled scientists in fulfilling the aims of the Symposium.

In contrasting the relative simplicity of protecting human health against specific agents of infection and nutritional deficiencies, which had been largely controlled through application of principles of public health and environmental sanitation, the Conference Chairmen underscored the complexity of environmental health problems now facing the nation. The participants were asked to consider and discuss perplexing questions such as these: How does one assess the long-term effect of chronic exposure to low concentrations of toxic agents acting singly or in concert with other chemical or physical agents? How does one identify susceptible subgroups within the population who may be at special risk because of age, sex, genetic background, or pre-existing physical impairments? To what extent is the aging-process itself accelerated by exposure to harmful agents acting at concentrations too low to elicit clearly more obvious signs of toxicity? To what extent are diseases of unknown etiology, such as chronic degenerative diseases affecting the cardiovascular and respiratory systems, aggravated by exposure to environmental agents?

Attention was called to growing evidence that a significant proportion of malignancies may be initiated, or promoted, by environmental factors. Unlike the great epidemic diseases of the past, present diseases associated with development and aging of the human organism are of complex etiology; multiple factors are involved and doubtless in many cases those inherent in the hosts are of primary importance. Nonetheless, a persevering search must go on to identifying and control harmful factors stemming from the environment.

Further questions were those relating to man's capacity to adapt to a changing environment. Dire predictions had been heard about the possibility of reaching some point of no return in the buildup of toxic agents in our environment. Before entertaining such suggestions seriously, one must recognize that man, like other free-living organisms, possesses an adaptive plasticity to environmental change, such that prolonged exposure to stresses may lead to an increase in tolerance. This tolerance we designate as acclimatization in the case of physical agents, such as heat and altitude, immunity in case of exposure to infectious organisms, or chemical resistance in case of exposure to drugs and toxic chemicals. The whole learning process, indeed, is a behavioural adaptation mediated through the central nervous system, which ensures the integrity of the individual in the face of environmental stresses.

Adaptive responses, moreover, occur not only over brief periods but over the life span of the individual and indeed, by genetic selection, over a period of generations.

In the course of the Bretton Woods Conference, these and other questions were freely discussed and well-established concepts vigorously challenged. Rather than attempting to present the state of the art in his special field, each principle speaker sought instead, by use of examples as models, to identify gaps in our knowledge and to point to weaknesses in existing concepts. Thus, subsequent discussion was channeled in such a way as to bring fresh insight from various related disciplines.

There were five formal sessions of the Symposium each being organized and moderated by one or two members of the Committee on Environmental Physiology. Each session concentrated on effects of environmental agents acting on mechanisms at one level of biological organization. These ranged in succession from the molecular and subcellular level, through that of cells and organ systems including discussions of absorption, transportation, metabolism, excretion and mechanism of action of environmental agents, next to the level of the intact human organism and its responses to these agents and finally to the level of populations in which discussants used epidemiologic data as indices of the range in susceptibility and adaptability in population subgroups.

By focusing in turn on ench of these levels of biological organization, participants from disciplines other than those of the principal speakers in a given session were stimulated to suggest new ideas and to propose novel experimental approaches aimed at illuminating areas of ignorance. Eventually, one may hope that investigations undertaken by interdisciplinary teams of scientists, such as those represented at the Symposium, will establish a unifying frame-work to bridge conceptual gaps between the various biomedical disciplines upon which environmental health science must be based.

The ultimate objective of environmental physiology, to repeat in essence what was stated earlier, is to develop a basis for a systematic physiologic approach to an understanding of the complex interactions between man and the multiple physical and chemical factors in his environment, and thus to provide public health agencies with the knowledge they need not only to control harmful agents in the environment but to enhance man's ability to adapt effectively to technologic and social changes.

The flavour and substance of the Symposium on Physiological Characterization of Health Hazards in Man's Environment proved to be a stimulating experience for all participants. At least the Symposium demonstrated that fruitful dialogue and provocative ideas can be generated in an interdisciplinary forum by establishing channels of communication and cross fertilization between different fields of scientific endeavour. It may be hoped, at most, that the Symposium will be viewed in retrospect as the first tentative step in establishing a sound scientific and conceptual foundation for the emerging science of environmental health.

The largest measure of credit must be shared by the individual members of the Committee on Environmental Physiology who planned each session and proved to be such skillful moderators. The Committee Chairman expresses his gratitude to the USPHS which proposed such a gathering and which provided generously for the funding.

REFERENCES

1. Now the National Institute of Environmental Health Science.
2. D. H. K. Lee (background paper for participants in the Bretton Woods Symposium).

2

Flow of Environmental Agents

In considering the flow of environmental agents in reaching their site of action, we are concerned mainly with the passage of substances across the various body membranes. Man is separated from his external chemical environment by three major membranes: the skin, the epithelium of the alimentary canal, and the epithelium of the respiratory tract. Most substances can penetrate these boundaries, but the rates of penetration vary widely.

Once a substance has penetrated an external boundary, it enters the circulation and is carried throughout the body in one or more of several forms: as freely diffusible molecules dissolved in the plasma water; as molecules reversibly bound to proteins, chylomicrons, or other constituents of the serum; as free or bound molecules contained within erythrocytes and other formed elements; or finally as molecules bound to the surfaces of the formed elements.

As a substance is brought to the various body tissues, it encounters new barriers. First, there are the membranes of the individual tissue cells; then, within these cells, the membranes surrounding the nucleus, mitochondria, and so forth. Such a succession of membranes presents a formidable barrier to the penetration of many environmental agents. Moreover, even if the internal membranes serve only to slow somewhat the rate of penetration of a particular agent, they still afford a degree of protection for the organism in that they prolong the exposure of the agent to sites of metabolic destruction and excretion.

General Principles of Membrane Penetration

The various ways in which substances move across biological membranes can be grouped under two general headings: passive transfer processes and specialized transport processes. The term "passive transfer" implies that the membrane behaves as an inert, solvent-pore boundary and that solutes cross the boundary by diffusing through the solvent regions, by diffusing through the pores, or by flowing with water through the pores. The term "specialized transport" implies that the membrane displays an active character, transporting the solute in a manner that cannot be explained in terms of the structure or solvent properties of the membranes.

Penetration of Membranes by Weak Electrolytes

Many drugs and other environmental agents are weak acids or bases and exist in solution as a mixture of the ionized and unionized forms. Since the unionized moiety is usually lipid soluble, and the ionized moiety lipid insoluble, only the unionized substance will diffuse rapidly across a lipoid membrane. The proportion of drug in the unionized form depends on the dissociation constant of the compound and on the pH of the solution in which it is dissolved. Consequently, in considering the passage of a weak electrolyte across a membrane, it is important to know the dissociation constant of the substance, as well as the lipid-to-water partition ratio of its unionized form.

Absorption from the Gastrointestinal Tract

Studies of the absorption of many drugs and other foreign organic compounds from the stomach, small intestine, and colon have revealed that the gastrointestinal epithelium has the properties of a lipoid membrane. Most drugs are readily absorbed in their unionized form, and very slowly absorbed in their ionized form. Moreover, with compounds that exist mainly as unionized molecules, the relative rates of absorption are directly related to the lipid-to-water partition ratios of the molecules.

The stomach is a significant site of absorption for many acidic and neutral compounds. For example, salicylates and barbiturates, which exist as unionized molecules in the acid gastric contents, are rapidly absorbed. In contrast, such basic drugs as the plant alkaloids and many amines, which exist largely as ions, are very slowly absorbed.

In the small intestine and colon, whose contents have a pH of 6-8, most weak acids and bases are at least partially unionized and are absorbed at rates related to their lipid solubilities. The slowest rates of absorption are seen with completely ionized drugs, such as quaternary ammonium compounds and sulphonic acids, and with lipid-insoluble molecules, such as sulphaguanidine and mannitol.

In contrast with the compounds absorbed by diffusion are several classes of substances that cross the intestinal epithelium predominantly by specialized, active transport processes. These include lipid-insoluble substances required by the organism—for example, some sugars, amino acids, pyrimidines, and inorganic ions—and the fats, which exist in the intestine largely in the form of complex micelles. Foreign organic compounds can be absorbed by these active transport processes if their chemical structures are similar enough to that of the natural substrate. For example, the antitumor compounds 5-fluorouracil and 5-bromouracil are rapidly absorbed from the intestine by the process by that transports natural pyrimidines, such as uracil and thymine. Moreover, foreign monosaccharides and amino acids have been shown to be actively absorbed from the small intestine.

Small amounts of macromolecules and particulate material are absorbed from the intestine by unknown mechanisms. For instance, resin particles as large as 5μ in diametre are absorbed to a slight extent. Moreover, it is well known from the allergic response to some foods that small quantities of intact protein can cross the gastrointestinal epithelium. The toxicity produced on ingesting the exotoxin of *Clostridium botulinum* is another example of the absorption of trace amounts membrane. Some of the substances move across the membrane as though it were a layer of lipoid material, the speed of passage being determined by the lipid-to-water partition coefficient of the substances. In contrast, a number of lipid-insoluble subtances of relatively small molecular size diffuse across the membrane as though it were interspersed with small, water-filled channels or pores, the smaller molecules crossing more rapidly than the larger ones.

Compounds can also move across membranes by a process of filtration or hydrodynamic flow. Thus, when a hydrostatic or osmotic pressure difference exists across a membrane, water flows, in bulk, through the membrane pores, dragging with it any solute molecules smaller than the pores. As an example, the water that filters across the renal glomerular membrane is accompanied by all the solutes of plasma except the protein molecules.

Although passive transfer across a lipoid-pore boundary adequately describes the penetration of membranes by many foreign organic compounds, it does not explain the rapid penetration by certain organic and inorganic ions, and some large, lipid-insoluble molecules, such as the monosaccharides. The concept of membrane "carriers" has arisen as a tentative explanation for the peculiar permeability of cell membranes to these substances. Carriers are pictured as membrane components capable of forming a complex with the solute at one surface of the membrane; the complex moves across the membrane, the solute is released, and the carrier then returns to the original surface.

There appear to be two major types of carrier transport, and, as work progresses, it will probably be found that there are many variations of these types. The type generally referred to as "active transport" has the following characteristics that distingnish it from a "diffusion process":

1. The solute moves across the membrane against a concentration gradient; that is, from the solution of lower concentration to the one of higher concentration; or, if the solute is an ion, it moves against an electrochemical potential gradient.
2. The transport mechanism becomes saturated when the concentration of solute is raised high enough.
3. The process shows specificity for a particular type of chemical structure.
4. If two substances are transported by the same mechanism, one will competitively inhibit the transport of the other.
5. The transport mechanism is inhibited by substances which interfere with cell metabolism.

Other types of carrier transport—for example, facilitated diffusion and exchange diffusion—have most of these characteristics, but they do not transport a substance against a concentration gradient.

A radically different type of specialized transport, in which cells engulf small droplets of the extracellular fluid, is the process known as "pinocytosis." It is seen in amebas, as well as in tissue cells growing in culture, and there is electron microscopic evidence that it occurs in mammalian cells within the animal. Very little is known about the physiologic significance of pinocytosis. Although the process appears to operate too slowly to account for the rapid cellular uptake of many substances, it could account for the uptake of small amounts of protein and other macromolecules. Another poorly understood form of specialized transport is the process of phagocytosis, in which some cells are able to engulf particulate or colloidal material.

Absorption from the Skin

The results of numerous studies have indicated that organic compounds penetrate the skin predominantly by passing through a lipid-like barrier. This conclusion is based on many isolated observation that lipid-soluble molecules are absorbed