Air Pollution—Physiological Effects

Edited by

JAMES J. McGRATH

CHARLES D. BARNES

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Department of Physiology
Texas Tech University Health Sciences Center
School of Medicine
Lubbock, Texas

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Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

William M. Abraham (107), Division of Pulmonary Disease, Mount Sinai Medical Center, Miami Beach, Florida 33140

Samarendra N. Baksi (281), Department of Physiology, Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas 79430

Milos Chvapil (223), Department of Surgery, University of Arizona Health Sciences Center, Tucson, Arizona 85724

Johannes Everse (1), Department of Biochemistry, Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas 79430

Kathleen E. Everse (1), Department of Anatomy, Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas 79430

Stephen R. Fowler[1] (243), Veterinary Toxicology and Entomology Research Laboratory, Agricultural Research Service, U.S. Department of Agriculture, College Station, Texas 77841

Donald E. Gardner (47), Inhalation Toxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Gerald A. Greenblatt (243), Department of Plant Sciences, Texas Agricultural Experiment Station, Texas A & M University, College Station, Texas 77843

[1]Present address: Department of Pathology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas 78284.

Robert F. Grover (311), Cardiovascular Pulmonary Research Laboratory, Division of Cardiology, Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80262

Guillermo Gutierrez (127), Department of Internal Medicine, The University of Michigan, Ann Arbor, Michigan 48103

Marc J. Jaeger[2] (81), Department of Physiology, College of Medicine, University of Florida, Gainesville, Florida 32610

James J. McGrath (147), Department of Physiology, Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas 79430

Richard M. Schreck (183), Biomedical Science Department, General Motors Research Laboratories, Warren, Michigan 48090

Richard L. Ziprin (243), Veterinary Toxicology and Entomology Research Laboratory, Agricultural Research Service, U.S. Department of Agriculture, College Station, Texas 77841

[2]Present address: Meakins Christie Laboratories, McGill University, Montreal, Quebec, Canada.

Preface

This volume, *Air Pollution—Physiological Effects,* is the fifth in a series prepared under the auspices of the Department of Physiology, Texas Tech University Health Sciences Center, School of Medicine. Each year, we examine an area in which research is progressing rapidly, but which has not been discussed recently in an advanced, comprehensive review. Previous volumes surveyed current work in the regulation of ventilation and gas exchange, neural control of circulation, the physiology of sleep, and the physiology of vascular smooth muscle.

In the present work, eminent investigators from industry, government, and academe review their studies of physiological responses to air pollutants. Each author presents the historical basis and theory from which his interest evolved, the current status of his specialized area, and directions of research. Furthermore, each contributor places special emphasis on critical evaluation of the experimental data in his respective area.

The contributions are organized in three sections. The first comprises a chapter exploring cellular injury, with emphasis on lung tissue. The second (five chapters) is concerned primarily with the physiological responses to the potentially toxic gases (e.g., oxidant gases, sulfur dioxide, and carbon monoxide) that are inherently part of a technologically advanced society. The third (five chapters) discusses both particulate (e.g., silica, diesel, cotton, and lead dusts) pollution, an ever increasing problem affecting an ever broader spectrum of lives, and the special physiological problems posed by working at high altitudes in dusty environments.

We expect that this volume will be useful to not only environmental health scientists but also students and researchers in areas peripheral to environmental physiology. Furthermore, we believe that the book is provocative and likely to stimulate productive research in environmental physiology.

James J. McGrath
Charles D. Barnes

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The Biochemistry of Cytotoxicity

Kathleen E. Everse and Johannes Everse

I. INTRODUCTION

Air pollutants drawn into the respiratory system may produce various effects on the alveolar and bronchial tissues. Some pollutants are chemical compounds that react with the tissue constituents and cause alterations in the chemical structure of these constituents. Examples of such pollutants are HCN, NO_2, H_2S, CO, and a large number of other inorganic and organic compounds. Other pollutants are chemically rather inert and do not promote a chemical reaction in the bodily tissues. Instead, such pollutants accumulate in the respiratory system. Examples of

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these pollutants are coal dust, asbestos, and chalk dust. Such pollutants, usually present in the form of small particles, are normally ingested by a type of phagocytic cell, the alveolar macrophages. Macrophages containing ingested material are subsequently excreted. Phagocytic cells are also able to release destructive enzymes. They do so in a futile attempt to destroy particles too large to be engulfed. These enzymes can cause damage and even death to adjacent normal lung tissue. Processes or events that cause damage to a cell and, if sustained, will ultimately result in the demise of the cell are cytotoxic processes. Many organic and inorganic compounds possess the ability to kill cells and are therefore considered to be cytotoxic.

Another class of air pollutants (although not always thought of in this manner) are living organisms such as bacteria and viruses. These pollutants, if not properly controlled by the host, can not only invade the host's tissues, but cause severe pathological conditions. The host controls this type of pollutant by using specific cells that kill the invading organisms. This process is generally referred to as cell cytotoxicity.

In this chapter we aim to discuss the cytotoxic activity displayed by various cell types that are present in higher organisms. The cytotoxic killing of cells by other cells (cell cytotoxicity) is an important and common event that occurs in higher organisms during many diseases as well as under healthy conditions.

Cell death is normally viewed as a terminal phenomenon. It should be recognized, however, that cell death is also an essential process in the normal development of multicellular organisms. The reabsorption of the amphibian tail and gills during metamorphosis and the formation of interdigital spaces during the development of many vertebrates are typical examples. Glücksman (1965) has provided a classical review listing 74 examples of cell death that occur and are necessary during normal vertebrate development. An understanding of the regulation of cell death during development is a major area of concern in the field of teratology. There are many examples where a failure of cells to die that were destined for removal or, conversely, the premature death of cells that were destined to multiply results in congenital anomalies (Menkes *et al.*, 1970).

Cytotoxic events are also part of the normal maintenance and repair processes that occur in higher organisms. Several examples of such cytotoxic processes are the removal of extravascular blood, the shedding of a snake's skin, normal cellular turnover such as the shedding of the endometrium or the removal of aged blood cells, and the process of wound healing.

Cell cytotoxicity is obviously important in the defense system of an organism; the killing of foreign invaders such as microbes and parasites

and the removal of endogenous hazards such as tumor cells are typical examples. A failure in the cytotoxic activity of the defense system may result in pathological occurrences such as bacterial, viral, and parasitic infections, as well as uncontrolled tumor invasion.

In addition to the normal processes already mentioned, there are many pathological processes that have as a result unnecessary or undesired cell death. Among these pathological processes are toxic responses to environmental hazards such as oxygen toxicity, metal poisoning, chemical injuries, radiation damage, and bacterially induced toxic shock. Also to be included among the pathological occurrences that have cell death as a component are inflammation, autoimmune diseases such as arthritis, and other diseases such as Parkinson's disease, muscular dystrophy, and ulcers. Indeed, many of the diseases affecting the animal kingdom result in some unnecessary or undesired cell death. An understanding of the mechanisms involved in cytotoxicity and the regulation of cytotoxic events will undoubtedly contribute to our understanding of these phenomena and, hopefully, to the eventual control of many of the pathological states that affect mankind.

Cellular cytotoxicity is the damage to one cell caused by another cell, a killer cell. Killer-cell activity has been implicated in many (but not all) of the examples of cell death mentioned above, both normal and pathological. There are at least two, if not more, basic types of cellular cytotoxicity: (1) an attack on the target cell membrane constituents by lysosomal-type hydrolytic enzymes, and (2) an attack on the target cell membrane constituents by active oxygen species. Many cytotoxic cells have the potential to kill by either mechanism, but the oxidative mechanism is more efficient and faster. Cell death that results from environmental hazards and in which cellular cytotoxicity has not been implicated could well be promoted by oxidative mechanisms similar to those used by cytotoxic cells.

In this chapter we hope to provide the reader with an overview of cellular cytotoxicity and of the recent advances in our understanding of the biochemical basis of oxidative cell killing.

II. CELLULAR CYTOXICITY

A variety of cell types have the capacity to be cytotoxic toward other cells. Among these are the circulating cells of the immune system such as the neutrophil, the eosinophil, various lymphocytes including the natural killer (NK) cell, and the blood monocyte. Other phagocytic cells reside in various tissues. These include the brain microglia, the Schwann

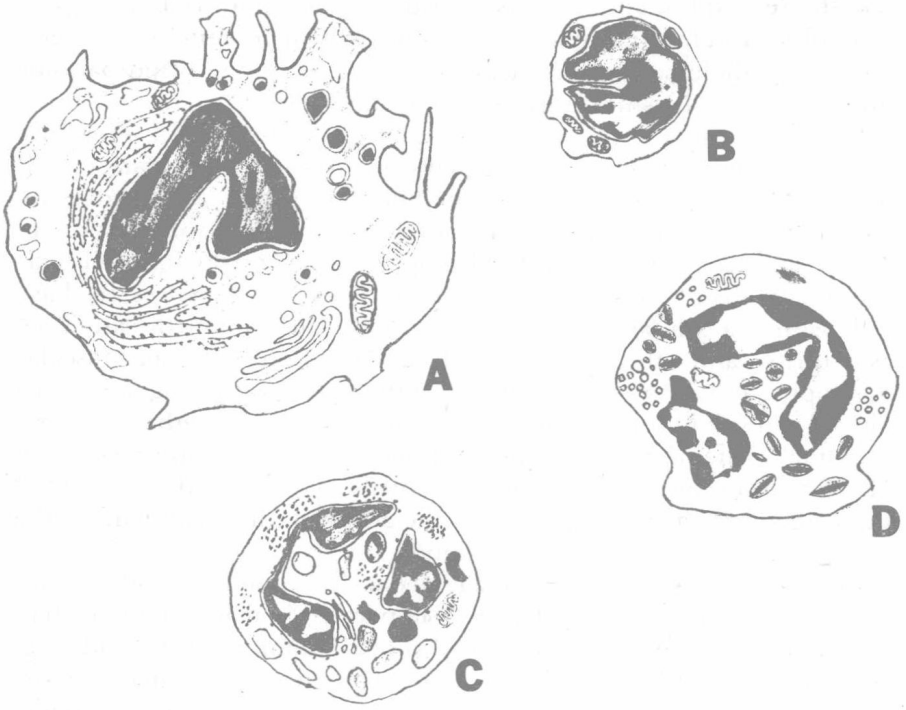

Fig. 1. Morphology and relative sizes of various leukocytes: (A) Macrophage. (B) Lymphocyte. (C) Neutrophil. (D) Eosinophil.

cells of the peripheral nervous system, and the various tissue macrophages which include the Kupffer cells of the liver, the histiocytes of connective tissue, the dendritic cells of the lymph nodes, and the alveolar and peritoneal macrophages.

The various types of killer cells of the immune system are identified and grouped according to their morphology and coloration with histochemical stains. The morphology and relative size of the cytotoxic cells are depicted in Fig. 1. Several of these cell types are further subclassified by their function, by their location, or by the presence of various antigens on their plasma membranes.

A. The Neutrophil

Neutrophils constitute the primary defense against microbial infection in mammals. They have been studied more extensively than other cytotoxic cells of the immune system, perhaps because they comprise the largest proportion of the leukocytes. They comprise 50–70% of the

white cells of the peripheral blood. Neutrophils are found scattered throughout many tissues, particularly in areas of acute inflammation.

Neutrophils belong to a group of cells called either polymorphonuclear leukocytes or granulocytes. Granulocytes are characterized by a multilobulated nucleus and many prominent cytoplasmic granules. After being stained with hematoxylin and eosin, the neutrophils show only a pale pink coloration (neutral-staining), because their cytoplasmic granules neither absorb the acidic (red) nor the basic (blue) stain. The cytoplasm of the neutrophil is rich in glycogen particles but it contains scant other cytoplasmic organelles such as mitochondria or endoplasmic reticulum.

At least two types of granules are found in the cytoplasm of the neutrophil: the azurophil (or primary) and the specific (or secondary) granules (Scott and Horn, 1970). They can be distinguished by cytochemical as well as isolation techniques. The ratio of specific granules to azurophil granules found in the mature neutrophil is approximately 2–3:1.

The neutrophil granules play an important role in the destruction of ingested bacteria. Table I lists the various components associated with the human neutrophil granules. Some differences in the composition of these granules are found between species. Note that most of the enzymes associated with the granules are hydrolytic enzymes specifically geared to the destruction and digestion of bacteria. It is also noteworthy that one of the enzymes found in the azurophil granule, myeloperoxidase, is present in amounts greater than 5% of the total dry weight of the cell (Schultz and Kaminker, 1962; Rohrer *et al.*, 1966).

A bacterial infection or an acute inflammatory response involves the mobilization of neutrophils from the bone marrow and blood vessels to the site of injury. For the first 6–24 hours, neutrophils are the predominant leukocyte at the site of tissue injury. They are relatively short-lived and disappear during the next 24 hours. Their mean half-life in the circulation is approximately 7 hours.

The main function of the neutrophil at the inflammatory site is the destruction of foreign particles or cells. The first step in the cytotoxic action of the neutrophils is their attraction to the location of the invading matter. This is accomplished by a process called chemotaxis, in which the cells move toward increasing concentrations of an attractant. The most significant chemotactic factors that induce this response in the neutrophil are bacterial products and components of the complement system. Chemotaxis proceeds until contact between the cytotoxic cell and the target cells is established.

The establishment of contact between the killer cell and the target cell initiates the process of phagocytosis. During phagocytosis, foreign

TABLE I

Human Neutrophil Granule Components[a]

Azurophil (primary)	Specific (secondary)	Membrane fraction
Acid hydrolases	Lysozyme	Alkaline phosphatase[b]
Acid β-glycerophosphatase	Lactoferrin	Acid *p*-nitrophenylphosphatase
β-Glucuronidase	Collagenase[b]	
N-Acetyl-β-glucosaminidase	Alkaline phosphatase[b]	
α-Mannosidase	Vitamin B_{12}-binding proteins	
Arylsulfatase		
β-Galactosidase		
5′-Nucleotidase		
α-Fucosidase		
Acid protease (cathepsin)		
Neutral proteases		
Cathepsin G		
Elastase		
Collagenase[b]		
Cationic proteins		
Myeloperoxidase		
Lysozyme		
Acid mucopolysaccharide		

[a] From Klebanoff and Clark (1978).

[b] There are conflicting data on the location of these components.

bodies are taken up by the phagocytic cell (endocytosis), packaged into a vacuole (phagosome), and subsequently destroyed. A brief description of the processes associated with phagocytosis may be useful.

Adherence of foreign matter to receptor sites of the phagocyte is followed very rapidly by ingestion. Pseudopodia of the neutrophil surround and engulf the particle by a process of differential adherence called the zipper mechanism (Fig. 2) (Griffin *et al.*, 1975, 1976). The net result of this mechanism is that part of the outer surface of the plasma membrane becomes the inner membrane of the phagosome.

Stossel and Hartwig (1975, 1976) have proposed a biochemical mechanism for phagocytosis. They suggest that the adherence of a foreign particle to the phagocyte activates the actin-binding protein. This activation causes a gelation of the actin at the outer edge of the plasma membrane, followed by a myosin-induced contraction of the gel toward the particle. This gelation–contraction process is initiated in the adjacent cytoplasm to form pseudopods that gradually engulf the particle (see