Comprehensive Immunology 1

Immunology and Aging

Edited by TAKASHI MAKINODAN

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TAKASHI MAKINODAN
Baltimore City Hospitals
Baltimore, Maryland
and
Veterans Administration Wadsworth Hospital Center
and University of California at Los Angeles

and
EDMOND YUNIS
Sidney Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

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Contributors

Robert E. Anderson Department of Pathology, University of New Mexico School of Medicine, Albuquerque, New Mexico, and the Albuquerque V.A. Hospital

Kay E. Cheney Department of Pathology, University of California School of Medicine, Los Angeles, California

William E. Doughty Department of Pathology, University of New Mexico School of Medicine, Albuquerque, New Mexico, and the Albuquerque V.A. Hospital

Nicola Fabris Experimental Gerontology Center, INRCA, Ancona, Italy

Gabriel Fernandes Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota

Richard K. Gershon Department of Pathology, Yale University School of Medicine, New Haven, Connecticut

Robert A. Good Sloan-Kettering Institute for Cancer Research, New York, New York

Leonard J. Greenberg Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota

W. Hijmans Institute for Experimental Gerontology of the Organization for Health Research TNO, Rijswijk, The Netherlands

Katsuiku Hirokawa Department of Pathology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan

C. F. Hollander Institute for Experimental Gerontology of the Organization for Health Research TNO, Rijswijk, The Netherlands

John W. Jutila Department of Microbiology, Montana State University, Bozeman, Montana

Marguerite M. B. Kay Laboratory of Cellular and Comparative Physiology, Gerontology Research Center, National Institute on Aging, National Institutes of Health, PHS, U.S. Department of Health, Education and Welfare, Bethesda, and Baltimore City Hospitals, Baltimore, Maryland

Ian R. Mackay Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research, and The Royal Melbourne Hospital, Victoria, Australia

Takashi Makinodan Baltimore City Hospitals, Baltimore, Maryland, and Veterans Administration Wadsworth Hospital Center and University of California at Los Angeles.

John D. Mathews Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research, and The Royal Melbourne Hospital, Victoria, Australia

Charles M. Metzler Department of Pathology, Yale University School of Medicine, New Haven, Connecticut

Patricia J. Meredith Department of Pathology, University of California School of Medicine, Los Angeles, California

Gary M. Troup Department of Pathology, University of New Mexico School of Medicine, Albuquerque, New Mexico, and the Albuquerque V.A. Hospital

Roy L. Walford Department of Pathology, University of California School of Medicine, Los Angeles, California

Senga F. Whittingham Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research, and The Royal Melbourne Hospital, Victoria, Australia

Edmond J. Yunis Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota; Present address: Sidney Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

Jorge J. Yunis Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota

Preface

In the classic sense, immunity is the ability of an organism to resist disease. On the one hand, we must distinguish between age and disease; on the other hand, the interaction between them is of considerable theoretical and practical interest. To the gerontologic research community, therefore, immunity also becomes the ability of an organism to resist age. Were the immune and other protective systems of the body able to maintain themselves over the course of time, and if there were no degradation related to age, the everyday loss of energy and vitality that occurs in the lives of older people as a consequence of viruses, arthritis, and other debilitating circumstances would be greatly lessened. The objective of gerontologists is not just to extend the life span but rather to improve the vigor, health, and quality of life.

To date, we have not developed a single index to measure immunity that is of use clinically in the evaluation of older people and of their immunologic competence. It may not be surprising that just such a clinical index may be available in the not-too-distant future. We can also look forward to the assembling of a greater body of information explaining how and why the immune system fails with age while, paradoxically, the incidence of autoimmune diseases increases with age. It is this latter phenomenon that may play a part in a wide range of chronic diseases from rheumatoid arthritis to senile dementia. In addition, we may see the development of a system of "adoptive immunity" in which an immune state is produced by transferring immunologically active lymphocytes or sera from an immunized donor to a nonimmunized recipient. Conceivably, children might then donate their "youthful" immunity directly to their parents. The future of many disciplines will depend on the further development of the field of immunology:

- To the medical historian, the steps in the elucidation of immunity have reflected the opening of an entire era of medical discovery in bacteriology.
- To the epidemiologist, the understanding of immunity has meant immunizations and vaccinations that have contributed significantly to the increased life expectancy of the twentieth century.
- To the public health policy maker, techniques for the further enhancing of the immune capacities of the body could extend the productive, healthy, and vigorous middle years and reduce what is a personally distressing and socially expensive period of dependency in old age.
- To the psychiatrist, breakthroughs in the elimination of autoimmune disorders might mean the prevention of senile dementia, or primary neuronal

degeneration, the condition (or conditions) so destructive to personality and memory.

- To the clinician, the development of a means to bolster the immune system with age could lead to the amelioration of many of the daily discomforts and illnesses of older patients.
- To the scientist, further knowledge about immunity and age would represent important steps in the enhancement of our understanding of the molecular and cellular biology of aging.

This volume, edited by Dr. Takashi Makinodan and Dr. Edmond Yunis, contains many outstanding contributions by the world's leading immunologists. We are grateful to have their attention focused on the relatively new but highly promising field of gerontology.

Robert N. Butler, M.D.
Director
National Institute on Aging

Contents

1

Biology of Aging: Retrospect and Prospect

TAKASHI MAKINODAN

1. Introduction

Aging can be defined as a time-dependent process whereby one's body can no longer cope with environmental stress and change as easily as it once could. Hence loss of physiological adaptability is one of the hallmarks of aging. Suffice it to say, aging is rapidly becoming the most critical issue socioeconomically and biomedically on this planet. It is not surprising, therefore, that in recent years increasing attention is being given to biomedical gerontology, as attested by the creation in 1974 of the National Institute on Aging in the United States.

The goals of most biomedical gerontologists are to extend the productive years of one's life at the expense of the unproductive years of life and to enable one to age graciously with a minimum of mental and physical disabilities. One may ask: What are the productive years of life? Obviously this will vary in part with one's profession. According to Lehman (1953), writers, for example, reach their peak in their second and third decades of life, while heads of religious organizations reach their peak in their seventh and eighth decades. However, when we refer to the productive years of one's life, we are generally thinking in terms of the second to the fifth decades. In any event, to achieve our goals, we need to understand (a) the processes that cause the human body to deteriorate with time, (b) whether the deterioration can be interfered with, and, if so, (c) how and when.

In this introductory chapter, an attempt will be made to present (a) a brief overview of biology of aging, (b) molecular theories of aging, and (c) reasons why the immune system is an excellent model for studies of cellular and molecular etiology of aging, pathogenesis of aging, and approaches to improve the quality of the terminal phases of life.

TAKASHI MAKINODAN • Baltimore City Hospitals, Baltimore, Maryland, and Veterans Administration Wadsworth Hospital Center and University of California at Los Angeles.

2. Past Research Activities

TAKASHI MAKINODAN

2.1. Life Span Analysis

Early research was centered primarily about population analysis with focus on the life span of different species. This research revealed that each species has a finite and unique life span; e.g., a mayfly has a life span of about a day, a mouse about 3 years, a dog about 20 years, a horse about 40 years, and a human about 110 years. Moreover, the average life span is generally significantly shorter than the maximum life span, and variation between individuals within a species is large. These findings indicate that the life span is genetically regulated and the difference between the maximum and average life span in a species reflects the influence of environment to a great extent.

Support for the genetic basis comes from studies of monozygotic and dizygotic progenies of parents with long and short life spans (Kallman, 1961). These studies revealed that (a) the intrapair life span difference is smaller in monozygotic than dizygotic twins, (b) the life expectancy of progenies of parents with a longer life span is longer than that of progenies of parents with a short life span, and (c) the cause of death is about twice as similar in monozygotic as in dizygotic pairs.

Since the turn of the century, the survival curve is becoming more rectangular or "boxlike" in shape (Figure 1); i.e., the average life span is increasing significantly but the maximum life span is not. This is due to control of deleterious environmental factors through effective dietary, hygienic, and vaccination programs and, in addition, through the use of antibiotics since the late 1940s. If the boxlike trend continues, it is possible that in the near future most of us will live to about the same age, e.g., 90 ± 5 years.

Actuarial analysis of human life spans reveals that different diseases kill off the aging population at increasing but at relatively similar rates (Kohn, 1971). This means that as the maximum life span is approached, individuals will die but the disease they will die of is fortuitous, suggesting that the maximum life span cannot be extended significantly by controlling the environmental factors. This suspicion is borne out by a recent U.S. Bureau of Census report (Siegel and O'Leary, 1973). According to this report, if the cause of death through malignant neoplasma is eliminated today, a child born tomorrow will have an increase in life expectancy of only 2.3 years and an adult 65 years old tomorrow will have an increase of only 1.2 years! Moreover, if all four major causes of death of the aged (i.e., cardiovascular–renal diseases, heart diseases, vascular diseases affecting the central nervous system, and malignant neoplasms) can be eliminated today, there will be only a 20-year gain in life expectancy of babies born tomorrow.

Based on these considerations, it should be apparent that the long-held fear that "breakthroughs" in aging research will enable people to live longer and contribute significantly to the existing problem of population explosion is not justified. The estimates above show that even by increasing the mean life expectancy to its *maximum* the population will increase by no more than 15–20%, and this increase will be only for a brief period of time. In short, population explosion is a socioeconomic problem, for countries with high standards of living seem to contribute relatively little to this problem (Figure 2).

2.2. Organisms and Organs

Physiological functions generally decline with age in a linear fashion. One of the fundamental issues that has confronted biomedical gerontologists over the years is whether the decline in various functions is initiated by the decline in function of only a few cell types or tissues or whether each tissue senesces independently of other tissues. Many investigators, on the basis of actuarial data, feel that aging of individuals is caused by a senescence time clock built into only a few cell types.

2.3. Tissues and Cells

In an attempt to resolve this issue, Krohn (1962) transplanted the skin of old mice into young, healthy mice in a serial manner. He found that the skin has a life span longer than the mouse from which it originated. This means that skin ages *in situ* because of factors extrinsic to it. Comparable results have been reported subsequently with several other tissues including bone and prostate tissues (Franks, 1970). Of course, there have been reports that certain tissues possess a limited *in*

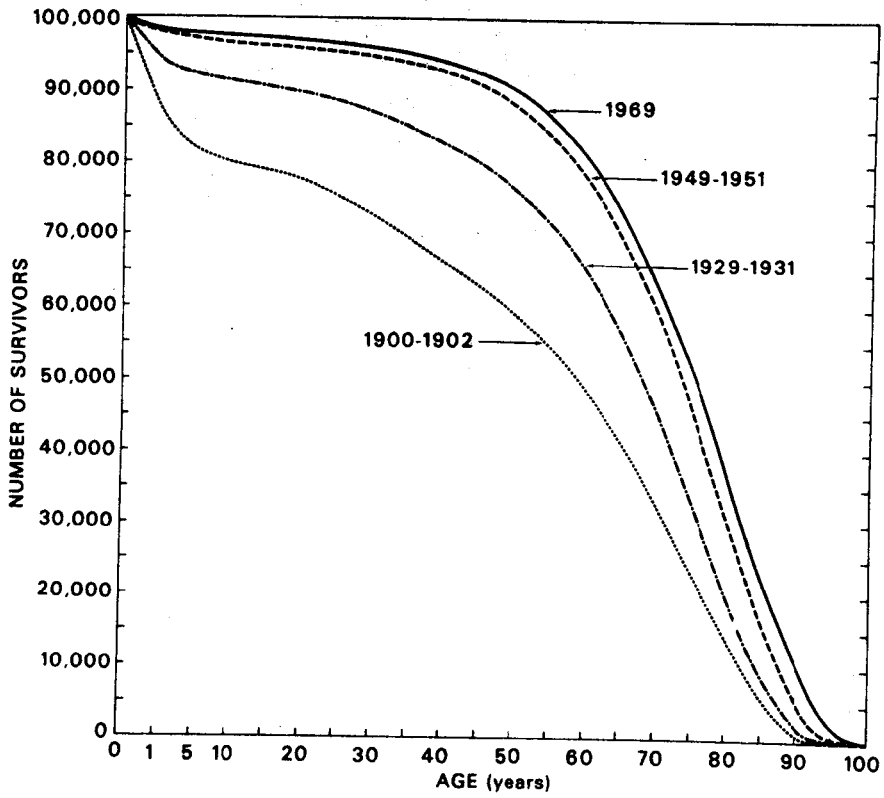

Figure 1. Expectation of life span in the United States, 1900–1969 (Golenpaul, 1973). Curves beyond 80 years of age were kindly extrapolated by Dr. Phillip I. Good and Dr. Noel R. Mohberg of the Upjohn Company, Kalamazoo, Michigan, through the use of extreme value theory for minima.

vivo transfer life (Siminovitch *et al.*, 1964; Cudkowicz *et al.*, 1964; Daniels *et al.*, 1975), suggesting that some tissues age because of changes intrinsic to them. However, the recent study of Harrison (1975) on *in vivo* transfer life span of hematopoietic stem cells of young and old mice indicates that the *in vivo* transfer life span of a tissue is due to the number of traumatic experiences a tissue undergoes during its transfer handling rather than to the *in situ* age of the tissue.

Perhaps a better approach in resolving this issue is to assess senescence of a homogeneous cell population in a defined *in vitro* culture condition. To this end,

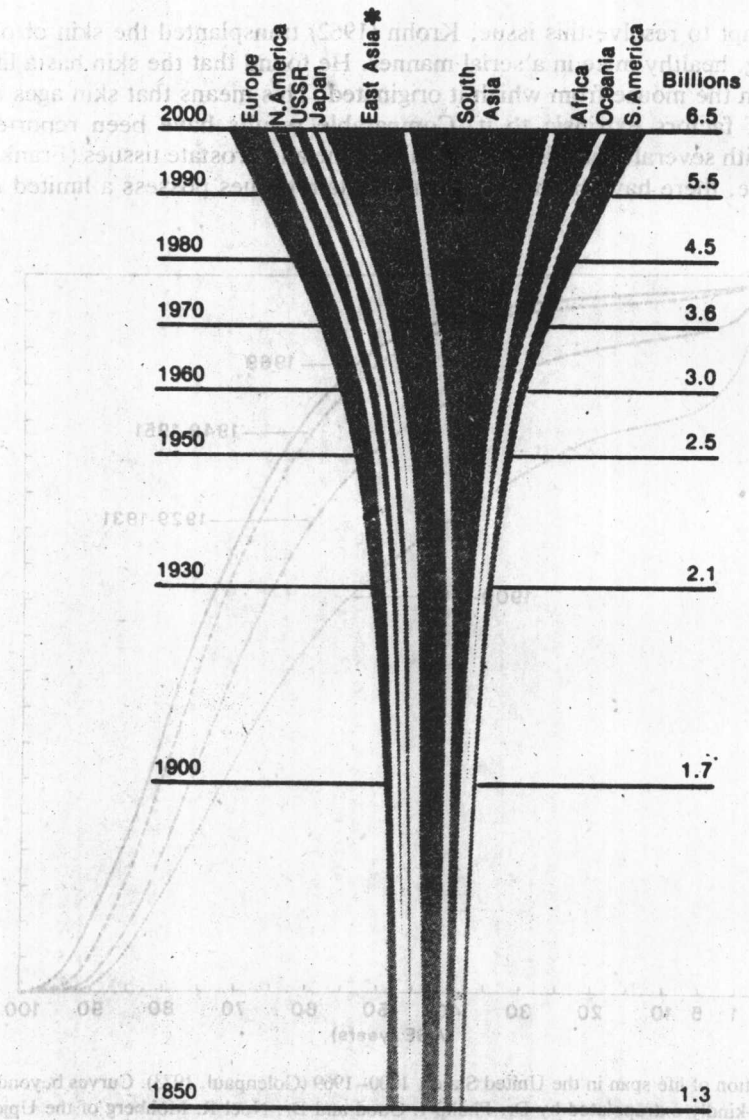

Figure 2. Estimated growth and regional distribution of the world's population, 1850–2000 (with permission from the Federation of American Scientists). *Excluding Japan.

there has been a burst of activities over the past decade centered on the fibroblast, the cell of choice over other cycling cells, resting cells (liver and kidney cells), and postmitotic cells (neurons and heart muscle cells). Hayflick (1965), who addressed himself to the issue of *in vitro* life span of human fibroblasts, found that the cultures undergo about 50 doubling passages before they die (i.e., on the average, one fibroblast can generate 10^{15} fibroblasts or 1 metric ton of fibroblasts). In an attempt to demonstrate that death of passaged fibroblasts is due to a time clock built into them, he mixed fibroblasts that had previously undergone x number of passages with marker fibroblasts that had previously undergone y number of passages and determined the number of passages each type is still capable of undergoing. He found that the former went $(50-x)$ more passages and the latter, $(50-y)$ more passages. These results strongly suggest that the *in vitro* proliferative life span of human fibroblasts is governed by a time clock built into them. The current issues are whether the time clock is in the nucleus or the cytoplasm and whether activation of the clock is genetic or stochastic?

3. Theories on Mechanisms of Aging

In looking back it would appear that the multitude of theories that emerged following studies at the organismic and organ levels stymied rather than enhanced the field of gerontology. Thus, rather than deliberate on the individual theories, it would be more fruitful to focus our attention at the genetic information and processing levels, since aging must emanate at the molecular level.

The various theories can be divided into two broad types. One is that it is an orderly, genetically programmed event which is the consequence of differentiation, growth, and maturation (e.g., Kanungo, 1976). The other is that it is a stochastic event resulting from accumulation of random errors (e.g., Orgel, 1963). Most gerontologists today seem to favor the former, although definitive evidence for or against either type of theory is still lacking. Aging can initiate at the transcriptional level, where it can be manifested as a mutation, DNA deletion, macromolecular crosslinking of DNA, etc. It can also initiate at the translational level where it can be manifested by altered RNA polymerase, tRNA, and tRNA synthetase, etc. It can also initiate at the posttranslational level, where it can be manifested by stochastic alteration of certain vital, slowly-turning-over macromolecules. These could include enzymes that are essential for protein synthesis and DNA repair.

4. Present Research Activities

Since much phenomenological study has been completed, especially at the organismic, organ, and tissue levels, present studies seem to be centered on the mechanism(s) of aging at the cellular and molecular levels. There are several areas of research that appear very promising. They include: (a) age effects on the regulatory role of the neuroendocrine system, (b) *in vitro* cellular aging with emphasis on the role of regulatory factors and site of initiation of the aging process, (c) drug sensitivity with emphasis on receptors, (d) age effects on resting cells with emphasis on their impaired adaptive enzyme systems, and (e) age effects on the immune system, which will be discussed in the subsequent section.

Relative to studies on the mechanism of aging, studies on pathogenesis of aging

and on approaches in minimizing the deteriorative processes of aging are very limited for want of better understanding of the etiology of aging.

5. The Immune System, a Cellular and Molecular Aging Model par Excellence

Biomedical gerontologists are now investigating many physiologic systems. Many of those who are biologically oriented are hopeful that there may be at most only a few mechanisms responsible for the various manifestations of aging of individuals and diseases associated with it. Those who are clinically oriented are hopeful that there will be ways in delaying the onset of, lessening the severity of, or preventing the diseases of the aged. Of all the systems being examined systematically, the immune system is perhaps the most attractive from both biologic and clinical points of view. The reasons are compelling:

1. The immune system, which is intimately involved in adaptation of the body to environmental stress and change, declines in its efficiency in performing certain functions.
2. Associated with the decline is the rise in susceptibility to viral and fungal infections, cancer, and autoimmune and immune complex diseases, which can interfere with many physiological functions of the body.
3. We probably know more about differentiation, ontogenetic, and phylogenetic processes of the immune system at the cellular, genetic, and molecular levels than any other system.
4. The immune system is amenable to precise cellular and molecular analysis and therefore offers great promise for successful manipulation.
5. There is a reasonable chance that a delay, reversal, or decrease in the rate of decline in normal immune functions may delay the onset and lessen the severity of diseases of aging, and there are several approaches available.

6. Conclusion

An attempt has been made to present a brief overview of the field of biomedical gerontology, retrospectively and prospectively. It should be apparent that it is a relatively new field in molecular biomedicine and that the aged are becoming the most critical socioeconomic issue of the world. Therefore, it is anticipated that many more investigators will become involved, and hopefully their participation will accelerate the progress of research on aging.

Currently, much research activity is centered on the mechanism(s) of aging at the cellular and molecular levels, since many phenomenological studies at the organismic, organ, and tissue levels have been completed. As our knowledge of aging increases, it is anticipated that research on molecular pathogenesis and approaches in minimizing the deteriorative processes of aging will increase.

Of the various systems being investigated, the immune system is one of the most promising, for it is a well-defined system in which to study cellular and molecular mechanisms of aging. It is also intimately involved with many of the diseases of the aged and offers several approaches to minimizing the deteriorative processes of aging.