ADVANCES IN PATHOBIOLOGY 7

# AGING, CANCER AND CELL MEMBRANES

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# Dedication

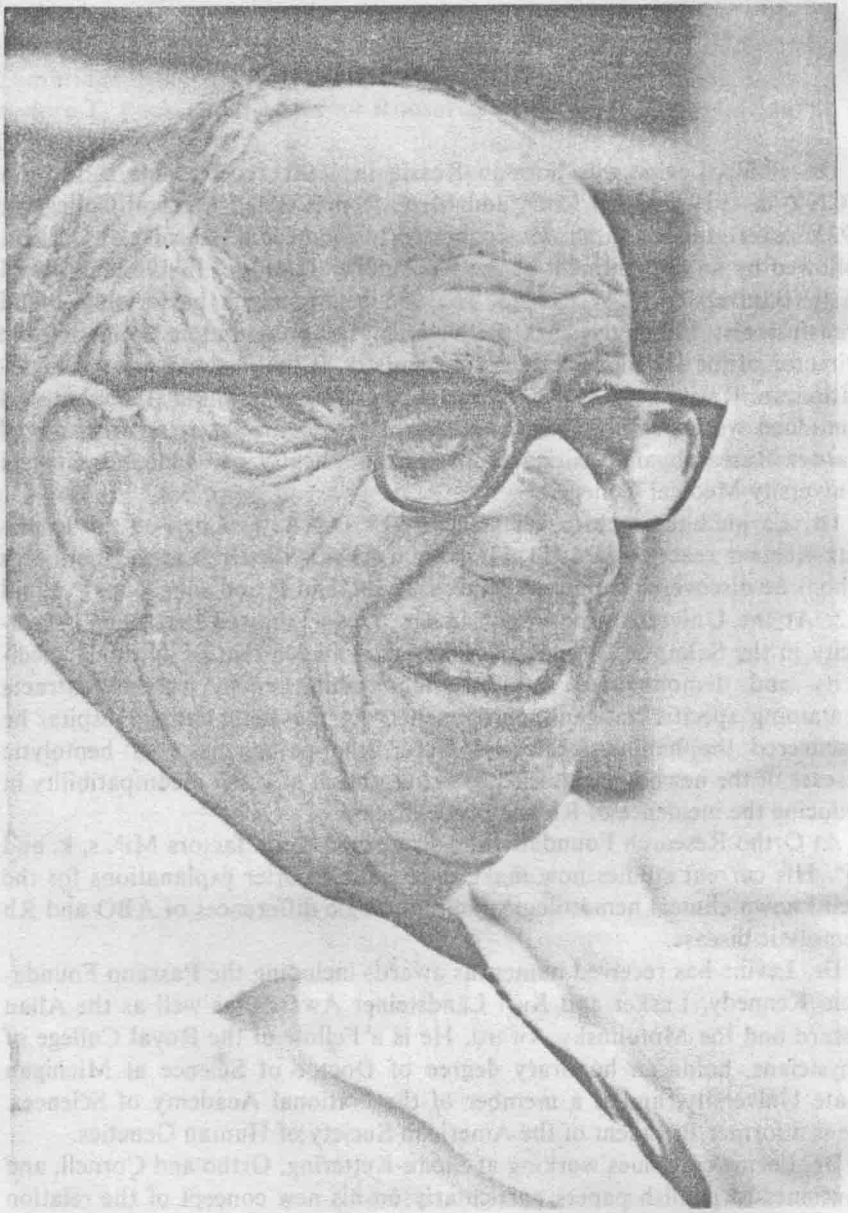
Dr. Philip Levine was born in Russia in 1900, received his B.S. from CCNY in 1919 and his M.D. and M.A. from Cornell Medical College in 1923. After graduation he was appointed to the Medical faculty at Cornell, followed by an appointment at the Rockefeller Institute. In 1932 he moved to the University of Wisconsin. In 1935 he became a bacteriologist and transfusionist at the Newark Beth Israel Hospital and in 1944 became Director of the Division of Immunochemistry at the Ortho Research Foundation in Raritan, N.J. He retired from this position in 1965 but has continued work as visiting investigator at the Sloan-Kettering Institute of Cancer Research and visiting fellow in the Faculty of Medicine, Cornell University Medical College.

Dr. Levine's research career started with Dr. A. F. Coca on the Prausnitz-Kustner reaction in 1924. He later worked with Dr. Landsteiner, with whom he discovered the blood factors M, N, and P and subgroups A1 and A2. At the University of Wisconsin Dr. Levine showed that phage specificity in the Salmonella group of bacteria paralleled that of antibody specificity and demonstrated specific phage inhibition by soluble extracts containing specific antigenic components. At the Beth Israel Hospital he discovered the human Rh blood factor, the pathogenesis of hemolytic disease of the newborn, and the protective action of ABO incompatibility in reducing the incidence of Rh hemolytic disease.

At Ortho Research Foundation he discovered blood factors $Mi^a$, s, k, and $Tj^a$. His current studies now make it possible to offer explanations for the well-known clinical hematologic and pathologic differences of ABO and Rh hemolytic disease.

Dr. Levine has received numerous awards including the Passano Foundation, Kennedy, Lasker and Karl Landsteiner Awards, as well as the Allan Award and the Motolinsky Award. He is a Fellow of the Royal College of Physicians, holds an honorary degree of Doctor of Science at Michigan State University, and is a member of the National Academy of Sciences. He is a former President of the American Society of Human Genetics.

Dr. Levine continues working at Sloan-Kettering, Ortho and Cornell, and continues to publish papers particularly on his new concept of the relation of blood groups to malignancy. His outstanding career in genetics and hematology, particularly in the elucidation of innumerable blood factors and especially the Rh factor, present a record to be emulated by all young investigators in this field. His warm, vibrant personality endears him to a host of friends and innumerable acquaintances, which increase steadily



throughout the years with his continuing travels. In 1978 he was made an Honorary Life Member of the New York Academy of Sciences. In August 13–18 of 1978, a one-week symposium entitled "Cell Surface Antigens and Cancer" was held in Aspen, Colorado and dedicated in honor of Dr. Levine; it is reflected in this volume.

# Philip Levine, M.D., F.R.C.P.

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# Response

On this occasion I wish to express my deep appreciation to Drs. King and Puck for organizing in my honor this impressive conference on "Cell Membranes." This year of the conference, 1978, represents my fiftieth year in academic research. In 1923 I ventured forth in my career with the guidance of Arthur F. Coca, Professor of Immunology at Cornell University Medical College, founder of the *Journal of Immunology* and pioneer in the field of allergy or "atopy."

It was Dr. Coca who referred me to Dr. Karl Landsteiner after assuming his position as a member of the Rockefeller Institute. Dr. Landsteiner wanted to resume studies on individual differences in human red cell antigens and their role in selecting compatible donors for transfusion—a subject he dropped after his discovery of the ABO system in 1901. He was convinced that numerous antigens existed on the red blood cell membrane and he had developed technical procedures for their demonstration. What he required was a source of normal human blood and the services of a young physician who knew how to perform venipunctures.

In late summer of 1925 I was interviewed by the great Theobald Smith (Simon Flexner had not yet returned from Europe). Needless to state, it took me a year or so to adjust to Landsteiner's scientific discipline. In the course of my adjustment period, Landsteiner found an occasion to pay me an unexpected compliment when he stated: "Dr. Levine [he was always very formal], you do not know how to tell a lie." In short, this describes the background of training which has enabled me to continue to still be productive 46 years after starting a career of independet research in 1932 at the University of Wisconsin, in a field far removed from human blood groups. He was vigorously opposed to my hopes to compete with him in research on blood groups, and so he urged me to open up my own area of research. We finally agreed that I should confirm or deny Burnet's failure to prove the parallel specificity of bacteriophage and antibodies in the Salmonella group of organisms. Using more sensitive technics, I promptly succeeded in 1933 in demonstrating the parallel specificities.

At this conference I am giving form and substance to the self-nonself concept in cancer and immune complex disease. Thus I take exception to Burnet's theory of "Immunological Recognition of Self"—the title of his Nobel Award Address published in *Science*, February 3, 1961, p. 307. In my view, self is not recognized as foreign. When altered, as in cancer or by the environment, such as by viruses or certain drugs, self is now converted to nonself. This then leads to its recognition as foreign, with an immune response and antibody production followed by formation of immune complexes as described in the proceedings of this conference.

*Philip Levine, M.D., F.R.C.P.*

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# Contents

Part I

# BIOLOGY OF AGING

## Cellular and Molecular Changes, Genetics, Immunology, Neurobiology

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# Introduction

In recent years biologic research in the field of aging has greatly profited from new knowledge and technics contributed by rapidly expanding areas such as cellular and molecular biology. Consequently, studies in aging consist now of a wide variety of approaches both theoretical and experimental, evaluating genetic and epigenetic mechanisms in the process of senescence. These studies utilize biologic systems which include human subjects, animal models, cultured cells, and cellular macromolecules and attempt to correlate Aging with a variety of structural and functional endpoints. Both cellular and extracellular regulatory mechanisms are being explored, with some attempts to modulate the process of senescence.

The aim of the present symposium has been to try to focus on some of the key problems and approaches currently prevailing in the area of the biology of aging and to bring together investigators from diverse yet related fields.

The life-spans of multicellular organisms vary widely and can be modified by numerous genetic and environmental factors (see Sacher, Hart, Martin, Shock, Cutler). These include diseases (see Yunis, Makinodan, Finch, Brody, Martin, Hayflick), changes in the immune system (see Yunis, Makinodan, Harrison), diet (see Andres, Yunis), genetic instabilities and cumulative damage to cellular DNA and proteins (see Strehler, Hart, Martin, Sacher, Hayflick, Hirsch), neuroanatomic and neurochemical modifications (see Brody, Finch) and responsiveness to homeostatic regulators such as hormones (see Roth, Finch, Cristofalo, Yunis, Makinodan). Clearly, the initiation, expression and modulation of aging are attributable to multiple events and no single genetic or environmental factor will uniformly accelerate all facets of aging.

From a biologic point of view, the process of aging is associated with structural and functional impairments which occur in a living organism and are expressed in gradual deterioration and decline in performance. The functional manifestation of this loss is multiple, occurring at all levels of biologic organization and in all processes, with different rates in species of different life forms but not markedly different when species maximum lifespan is normalized (see Sacher, Hart). Longevity has evolved as a positive trait with the increase in body and brain sizes, lower reproductive rates, and longer maturation periods (see Sacher). Differences in longevity between individuals or between genotypes within a species are not due to differences in rates of aging (see Sacher) or to differences in amount of exposure, damage or in targets exposed (see Hart), but rather to variation in resistance to stress and capacity to cope with it (see Sacher, Hart) or to pre-

vailing differences in the ability to modulate accumulated genetic damage and the resulting deleterious effects in physiologic function and fidelity of information (see Hart, Strehler, Hirsch).

The close relation between species longevity and their constitutional characteristics (see Hart, Sacher, Cutler) suggests that the real causes of aging are presented in the organisms from the beginning and may be related to specific organs, tissues and cells (see Strehler, Hayflick, Cristofalo, Harrison, Makinodan, Yunis, Finch, Brody). Cytogerontology studies (see Hayflick) suggest that in cell culture, cellular life-span is an inherent property of the cell, inversely proportional to the age of the donor or maximum life-span of the species, and that it can be modulated by appropriate hormonal environments (see Cristofalo).

Cellular capacity to repair DNA damage is related to life-span (see Hart, Sacher) as observed in animals which are close taxonomically yet differ in life expectancy, or in cultured cells derived from these species. A genetically timed clock which may adhere to a cellular limited life-span (see Hayflick) has also been suggested to operate in the immune system, in the T-dependent lymphoid cells (see Yunis, Makinodan).

When evaluated on a molecular level, the process of aging is believed to be closely related to modifications in the gene structure and its stability and expression to the ability of cells and thus all higher levels of biologic organization to maintain the initial fidelity of the information content of their cellular macromolecule (see Hart, Martin, Finch, Hirsch). These are regulated in part by DNA-chromatin organization, and are significant both in development and senescence (see Hart, Strehler, Martin), influenced by many forms of damage such as cross linking of macromolecules (see Hart, Martin, Strehler, Cutler) mediated for example by free radicals, and other agents, the result being genetic instability (see Hart, Strehler, Martin, Hayflick) and numerous modifications of gene expression which may differ from cell to cell. These modifications may play a role in a variety of intrinsic clocks (see Finch, Hayflick, Yunis, Harrison), possibly residing in the nucleus (see Hayflick) and being organ- or cell-specific (see Harrison); in the differentiated state of cells, closely linked to senescence (see Strehler, Hart, Makinodan, Yunis, Brody), in diseases (see Martin, Finch, Makinodan, Yunis, Hart), in immunologic competence (see Makinodan, Yunis, Harrison), in neuroanatomic integrity (see Brody) or neuroendocrine function (see Finch) and hormonal response of cells (see Roth, Cristofalo). All these are major determinants and play a role in the individual's ability to cope with the environment both mentally (see Brody, Finch) and physically (see Makinodan, Yunis, Andres, Finch, Brody), and thus could modify life expectancy.

While cellular RNA, DNA proteins and lipids are all possible targets for molecular senescence (see Hart, Strehler, Hirsch, Martin, Finch), DNA damage is suggested to play a key role in the aging process (see Hart,

Strehler, Hirsch), similar to its key role in development (see Hart, Strehler), where a sequential activation and repression of a variety of decoding abilities prevail. Since various kinds of differentiated cells differ from each other in their ability to decode particular "words" in the genetic code, there would exist differences between cells in their loss of capacity to replicate and to respond to challenge (see Strehler). Thus, in the immune system (see Makinodan, Yunis, Harrison), the number of stem cells remains relatively constant throughout life, but functional decline occurs with age in a subpopulation of T cells. A drop in mitotic index and a rise in a suppression index are observed, indicating that the senescent process takes effect in the differentiation pathway of the T cell (see Makinodan). The stability of B cell function, however, is not affected similarly with age (see Makinodan), as seen also following tissue transplantation in genetically defined old and young mice (see Harrison); still, it cannot be ruled out that stability of B cell function may be altered in individuals or specific organs (see Makinodan). Moreover, the age-related decline of both humoral and cell-mediated immune responses (see Makinodan, Yunis) may both be attributable to the functional impairment in the T cell subpopulation and its differentiated pathway and not to changes in the B cell function (see Yunis).

Similarly, in the nervous system, age-associated decline in neurologic loss is area-specific, related to its embryologic development (see Brody) and restricted to a minority of brain cells (see Finch, Brody). The age-related changes are reflected in loss of RNA content and alterations in catecholamine neurotransmitters—events which can be linked to a variety of neurologic disturbances and sickness (see Finch).

It became clear during the symposium that the process of aging presents some of the more puzzling problems since its initiation in multifunctional target macromolecules is manifested by a correspondingly wide variety of expressions. Hormone receptors, both external and internal, are decreased (see Roth), hormonal balance is impaired (see Yunis, Finch), a waning in immunologic vigor is observed (see Makinodan, Yunis), and a modification in the repairability of DNA which may be associated with carcinogenesis takes place (see Hart). Diet (see Andres, Yunis) and diseases such as infectious diseases, autoimmunity and cancer often manifest themselves, as a result of some of the above events and possibly in part due to the expression of genetic controls residing in the major histocompatibility complex (see Yunis). These multiple genetic and environmental factors (see Hart) may determine the longevity of an individual and efforts to intervene and modulate them and to increase life-span are being made both *in vivo* (see Yunis) and *in vitro* (see Cristofalo).

*The Editors*

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