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PROGRESS IN CANCER

NORVIN C. KIEFER, M.D.:

With this background of discussion of some of the general problems, as well as some of the specific areas such as infectious diseases and environmental hazards, it now is appropriate to turn to the degenerative diseases, which I characterized as the major disease problem of the coming decades, and consider in some detail the most important ones.

We are fortunate in having on our panel, today, two outstanding experts.

First, we are going to hear about cancer which, as a general category, ranks second among causes of death in this country today. Our speaker is the distinguished President and Director of the Sloan-Kettering Institute for Cancer Research, New York City. He received his medical degree from McGill University, following which he had his residency training in Boston and Montreal. From 1934 to 1960, he occupied various positions with the Rockefeller Institute and the Rockefeller Foundation, ultimately becoming Vice President for Clinical Studies and Physician-in-Chief to the Hospital of the Rockefeller Institute. He was appointed to his current position in 1960, and at the same time became a member of the Board of Trustees of the Memorial Sloan-Kettering Cancer Center, and also Director of and Professor of Microbiology in the Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University Medical College. He has been a member or official of over twenty local, national and international organizations, and a consultant in various capacities to the Department of Defense, the U.S. Public Health Service and the National Research Council. He has been the recipient of five medical awards, a member of the Board of Editors of several specialized medical publications, and is a member of a large number of medical and related associations.

It is a privilege to introduce to you Dr. Frank L. Horsfall, Jr.

FRANK L. HORSFALL, JR.:

When Dr. Kiefer suggested that I participate in this panel discussion before the Society of Actuaries, I was more than usually reluctant to undertake such a responsibility. The hesitation did not stem from ignorance of actuaries. Instead it arose from close personal association with some from whom I have learned much and for whom I have the highest regard. Acceptance was determined by a conviction that the sciences of mathematics, biology, physics and chemistry have a common philosophy, should be more unified and must develop a common language.

To one who has spent his mature years in study of the life sciences, an opportunity to discuss current concepts of abnormal growth with those concerned with the effects of biological processes on longevity is rarely provided. Your chief concern, I take it, is largely centered on what happens. Ours is chiefly focused on how and why; ultimately on what can be done to alter a fact of life.

I shall begin by stating certain assumptions. First, more precise data on the effects of cancer on longevity are available to you than to me. Second, interpretations and conceptual schemes are useful in evaluating current information. Third, predictions, prophesies and promises are not useful. In consequence, I shall confine my remarks to an appraisal of the present state of the art and the problems that remain to be solved.

It is, perhaps, unnecessary to state that the discovery of radioactivity initiated a revolution in the physical sciences which had remarkable and unexpected results not yet fully realized. But it must be emphasized that a comparable revolution has occurred recently in the biological sciences. The discovery that nucleic acids provide the chemical counterparts of the classical gene of heredity has had equally unexpected results. This discovery bridged the gap between the smallest unit available to biologists, *i.e.*, a virus particle, and the largest unit available to chemists, *i.e.*, a macromolecule. The distance was not great but it took a long time to span. It led also to some semantic problems which temporarily have been handled by the invention of bastard terms like "molecular biology" and "infective molecules," even "infective heredity" and "molecular disease." Of the concepts that have necessitated such odd terminology, more will be said in a moment.

Presently there are four magic terms in biology and all are related to the problems of cancer. They are: nucleic acids, genetics, viruses and immunology. What do they identify? Nucleic acids are molecular substances of large dimensions and known chemical constitution which are responsible for the continuity of life. Genetics and immunology are organized bodies of knowledge that have been thought of as independent disciplines. Viruses are the smallest, most simply constituted and most remarkable infectious agents. Now it is clear that all four terms are inseparably interrelated. Three of them, *i.e.*, genetics, viruses and immunology, identify biological phenomena which depend on the coded information-bearing capacity of the fourth, *i.e.*, nucleic acids. Genes are now thought to represent the biological counterparts of chemical fine structure in nucleic acid molecules. Viruses are considered to serve as vehicles for the transmission of information-bearing nucleic acid to host cells. Immunological reactions are believed to depend on recognition of differences in chemical structure of substances under the control of genes.

This exemplifies the syntheses that have recently emerged among disciplines that have long had too little in common. It emphasizes the value of achieving more unification of scientific knowledge. Modern biology, associated with the physical sciences and mathematics, appears to have vistas as exciting as those of modern physics. In relation to man, the implications of this new knowledge are as rich for fuller understanding of degenerative processes, malignant tumors and behavioral disorders as for infectious processes, metabolic aberrations and endocrine dysfunctions.

That nucleic acids guide and orient biological processes and function as the memory core of the genetic apparatus is now generally accepted. The discovery that a nucleic acid molecule can reproduce itself in a cell, that it carries as much coded information as 100 textbooks and that it controls its own reproduction with such precision that a mistake, *i.e.*, a mutation, occurs about once per million replications are extraordinary advances.

What has all this to do with cancer, with the problems that this uncontrolled disease presents? The first problem is this: what are the necessary and sufficient causes of cancer in man? This is obviously vital for, on the evidence of history, knowledge of cause has been the most important factor in the development of specific treatment and effective prevention.

Cancer can be induced, in animals, by infective molecules, *i.e.*, nucleic acids, separated from viruses. One type of infective nucleic acid, that from polyoma virus, can lead to the development of more than 20 different kinds of cancers in four animal species. Some 30 distinct viruses are known to be capable of inducing a variety of cancers in animals, including chickens, mice, rabbits, dogs and monkeys. The cancers so induced do not differ in any recognizable feature from those of man. They grow in an uncontrolled manner, produce metastases and lead eventually to death of the host.

When normal cells are converted to cancer cells by viruses, new properties appear which are expressed by alterations in growth rate, metabolism, chromosome number or pattern and cell form. These are handed on to the daughter cells in continuous culture and persist indefinitely. The cancerous change in cells has the hallmarks of a change in the genetic make-up of cells and so may be considered formally as corresponding to a mutation. Permanent heritable changes, *i.e.*, mutations, induced by viruses are well known and generally accepted. It is believed that part of the nucleic acid introduced by the virus is taken into a chromosome of the host cell and there alters the nucleic acid which is the cell's transmissible memory core.

Once this alteration is produced, the change persists and, unless the cell dies without progeny, is handed on in continuing series to the daughter cells.

Thus, in the instance of virus-induced cancers, we are confronted with a clear example of the heritance of acquired characters. Is this a unique example, or are there others which seem also to violate Mendel's laws? Some 17 years ago it was found that enduring heritable changes could be produced in bacteria by nucleic acids derived from other bacteria. This was in fact the first demonstration that nucleic acids provide the chemical basis of heredity and it was this remarkable discovery that led to the revolution in biology to which earlier reference was made.

In discussing viruses and cancer, emphasis has been given to investigations with animals. A major present problem is this: what relation do viruses have to cancer in man? Viruslike particles can be visualized with the electron microscope in various human cancers. Antigenic components different from those in normal tissues can be extracted from human cancers. But no cancer-inducing virus has yet been recovered from human tumors. The problem is beset with serious technical difficulties and a solution is not yet in sight. However, unless, contrary to all evidence, man is considered to be biologically unique and his tumors are thought to be wholly dissimilar to those of other mammals, it would be difficult to defend the attitude that virus research has no bearing on the cause of cancer in man.

Are there inducing factors other than viruses that are known to be associated with the development of cancer which, like viruses, lead to alterations in the genetic apparatus, *i.e.*, to the heritance of acquired characters in human cells? For years it has been known that radiant energy at certain wave lengths, particularly those of X-rays and ultraviolet light, increase the frequency of mutations and may induce cancer in animals or man. Similarly, organic chemical compounds of special types, particularly some present in coal tars, are mutagenic and also induce cancer in animals or man. In each instance, the evidence indicates that their effects are due to alterations produced in the nucleic acids that control the genetic machinery.

It needs to be emphasized that the distinguishing and unusual properties of cancer cells are closely similar regardless of the factors, whether physical, chemical or biological, that led to the cancerous change; that once such new properties have appeared they continue to be handed on to daughter cells even when inducing factors are not present. Thus, cancers in general can be considered to represent the heritance of acquired characters at the cell level. This unifying concept serves to em-