Aging and Cancer Management
Part II: Research Perspectives

Robert N. Butler, M.D.
Barbara Gastel, M.D., M.P.H.

In humans and in other animals, the incidence of cancer increases with age. A human's probability of developing cancer during the next five years rises from approximately one in 700 at age 25 to one in 14 at age 65. In the United States, from 1969 through 1971, nearly half of all new cancers occurred in the tenth of the population aged 65 and above. Today, as both the proportion and total number of elderly in the population are rapidly growing, the relationship between cancer and aging assumes increasing medical and social importance.

Research has provided tantalizing clues to this relationship, but it remains largely unfathomed. Although theories abound, we are uncertain whether age-related changes lead to cancer, whether both aging and cancer result from a common process, or whether the two phenomena are linked only by the requirement of a lengthy period for development.

Studies of both cancer and aging share many disciplines and resources, and research in one field can contribute to the other. As the study of diseases often provides insight into normal processes, cancer research may help to elucidate aging. Conversely, research on aging and on cancer in the aged may aid in understanding all cancers. As suggested by Alex Comfort, in many circumstances the combination of research on aging and on cancer may be most efficient.

This paper first presents several approaches that are common to research on both cancer and aging, and that are useful in studying their relationship. Then, building largely on the first section, it discusses two areas, immunology and mutation, to which both phenomena may be closely related.

Cell Biology, Biochemistry and Genetics

Cell biology, biochemistry, genetics, and related basic sciences have provided valuable clues into the mechanisms of aging and cancer and their possible relationship. The study of cells in culture has been important to research on both cancer and aging and to the comparison of aged and malignant cells. Transformed cells and some tumor cells continue to replicate indefinitely in vitro. In contrast, non-neoplastic cells that have undergone many passages in culture—and have therefore been used as a model

Dr. Butler is Director, National Institute on Aging, National Institutes of Health, Bethesda, Maryland.
Dr. Gastel is a Special Assistant, Office of the Director, National Institute on Aging, National Institutes of Health, Bethesda, Maryland.
for aged cells—lose their proliferative capacities. However, this model of cellular aging—and thus the comparison—may not be valid, as prolonged culture might result not in senescence but rather in differentiation.

A review article by Pitot mentions several other cellular and biochemical differences and similarities between aging and cancer. Whereas aged cells exhibit relatively stable karyotypes and may contain inactive enzyme molecules, neoplastic cells often have unstable karyotypes and do not appear to contain such altered proteins. Various studies have suggested that possible similarities between aged and neoplastic cells include abnormal stability of messenger RNA templates, changes in the metabolism of certain drugs, and alterations in the hormonal regulation of various enzyme levels.

Studies correlating life span with biochemical processes that are related to carcinogenesis have yielded intriguing results. Schwartz found an inverse correlation between various species' life spans and their fibroblasts' ability to convert 7,12-dimethylbenz(a)anthracene (DMBA) to a mutagenic form. Similarly, Hart and Setlow observed a direct correlation between the capacity for DNA excision-repair—a process that may play a role in the prevention of tumors—and the life spans of various mammalian species.

The study of genetic diseases also may provide valuable insights. Investigation of conditions such as Werner's syndrome and ataxia telangectasia, which manifest both in some features of premature aging and early onset of some types of neoplasms, may yield useful information. Down's syndrome may also be a useful model. The study of xeroderma pigmentosum, a group of genetic conditions characterized by defective excision-repair of DNA, appears particularly promising. When exposed to ultraviolet light, patients with this disease develop both cutaneous cancers and premature aging of the skin. Some patients also suffer from accelerated aging of the nervous system and premature death of nerve cells. The severity of the neurological abnormalities appears to reflect the degree of deficiency in DNA repair.

The study of the mechanisms by which viruses induce tumors—thus freeing cells from the restraints normally imposed by senescence—may also increase our understanding of aging, cancer, and their relationship. In addition, research on slow viruses and on age-related changes in cell-virus interactions may prove instructive.

Animal Studies
Animal research is basic to the study of both aging and cancer and offers an excellent opportunity for the development of common resources. Spontaneous cancers occurring in aged animals may be more valid models of human tumors than are those induced by carcinogenic agents, and the use of animals permits manipulation of various genetic and environmental factors.

Use of standardized, well-characterized strains of aged animals should allow both aging and cancer to be studied in the same animals and the results of separate studies of each to be correlated. Hollander has discussed the need for such standardization of animal use and reporting in cancer research.
**Praomys (Mastomys) natalensis**, a rodent that exhibits a wide range of neoplastic and degenerative diseases. Similarly, Baba and von Haam state that rabbits, which exhibit a high incidence of endometrial carcinoma, may serve as a useful model of this disease. Hollander also emphasizes the importance of specifying the maximum age and 50 percent survival time of the strain of animals used, instead of merely describing them as "old" when they reach a particular age.

Studies of animals have permitted systematic evaluation of the effects of genetic composition and of environment. On comparing mice having slight genetic differences, Smith and Walford concluded that the major and minor histocompatibility gene regions appear to influence life span and rate of aging, as well as the age-specific and total incidences of various spontaneous tumors. Animals have likewise been useful in studies of the effect of diet on carcinogenesis and aging; for example, caloric restriction has been shown both to increase life span and to decrease tumor incidence.

Animal studies have also suggested that predisposition to cancer and to aging may be intimately related. Exposure of male mice to mammary tumor virus did not result in the development of tumors, but was associated with a decreased life span. In AKR mice, which have a short mean survival time and generally die with leukemia, treatment with polyacids significantly reduced the incidence of leukemia but did not change survival time.

Furthermore, animal research may help to determine whether susceptibility to carcinogens changes with age. Peto et al began application of benzpyrene to the skin of mice at various ages; they concluded that the increase in tumor incidence with age reflected duration of exposure and was independent of age at the start of exposure. In contrast, Ebbesen's studies of mice suggest that aging may increase the susceptibility of tissue to carcinogens. This researcher placed skin grafts from syngeneic 2- and 14-month-old donors on 2-month-old recipients. Application of DMBA to the grafts 12 months later resulted in papillomas, which occurred on a greater proportion of grafts from the older donors. In addition, repeated treatment with DMBA was associated with a significantly greater number of carcinomas on such grafts.

Animal models also may be useful in establishing the effects of antitumor therapy on aging organisms. In one such study, Teller et al compared the effectiveness of several chemotherapeutic agents in young and old mice bearing transplanted tumors; contrary to the general trend, one of the drugs was more effective in the old mice. Yuhas and Ullrich showed that the antitumor effects of the immunostimulant Corynebacterium parvum were weaker in old than in young mice bearing lung and mammary tumors. Additional animal research on the effectiveness of various types of cancer treatment—including surgery, hormonal therapy, and radiotherapy—may be of help in the design of appropriate treatment regimens for aged patients.

**Epidemiology**

Epidemiology has helped to characterize the quantitative relationships between cancer and aging and to identify the correlates of each. However, there are many opportunities for further research.

Better statistics on the age-related incidence of and mortality from cancer may increase our understanding. In the past, most death rates have placed all persons above age 75 or 85 in a single category; however, the American Cancer
Society now is gathering detailed mortality data on the very old.\textsuperscript{21} One major question is whether the apparent declines in cancer incidence and mortality in the very old are valid or are artifacts.

International comparisons may provide valuable clues to the impact of both genetic and environmental factors. Particular care must be taken, however, in studying areas with incompletely developed data collection systems. For example, an apparent decline in cancer incidence in Ibadan, Nigeria after age 45 seemed actually to be an artifact introduced by the older residents’ preference of traditional medicine over hospital care.\textsuperscript{22} Inclusion of anthropologists and other social scientists on epidemiologic teams in these geographic areas may improve the quality of such data.

Epidemiologic research might also elucidate common mechanisms of aging and carcinogenesis. For example, exposure to sunlight is associated with both aging of and cancer of the skin.\textsuperscript{23} Perhaps ironically, postmenopausal estrogen use—prescribed to alleviate age-associated changes—can increase the risk of endometrial cancer;\textsuperscript{24} investigation of the carcinogenicity of various medications commonly used by the aged may be worthwhile. Studies of elderly groups also have helped to determine the lag times between exposure to carcinogens, such as asbestos and industrial chemicals, and the development of cancer. Research on the relation of nutrition to cancer and to aging may also be productive.

Cancer can exhibit different characteristics in the old and in the young. It may be useful to determine why cancers of the colon\textsuperscript{25} and breast\textsuperscript{26} appear to be less aggressive in the older than the younger patient, whereas cancers of the cervix\textsuperscript{27} and thyroid\textsuperscript{28} seem to show the opposite tendency, and different types of leukemia predominate in the elderly and in children.\textsuperscript{29} More sophisticated and critical studies of these and other age patterns are needed. In addition, analysis of age patterns in the spontaneous regression of tumors may provide valuable insights.

Finally, epidemiologic studies may be useful in determining the types and costs of care required by the aged, particularly those with cancer.

Statistical Approaches

Statistical analysis of epidemiologic data may yield useful models of the relationship between aging and cancer. One such effort, Burton’s analysis of cancer mortality statistics from 25 countries, suggests that most types of malignant tumors begin to develop at random times throughout life and have incubation periods of at least 20 to 50 years.\textsuperscript{11} Statistical analysis of epidemiologic figures for conditions such as gingival recession and colorectal cancer has led Burch et al to conclude that both malignant diseases and age-associated degenerative conditions result from somatic gene mutations affecting central control mechanisms and thus giving rise to multicentric disease.\textsuperscript{28}

Endocrinology

Hormonal status can modify both tumor behavior and manifestations of aging. The apparent differences in cancers of the breast and cervix before and after the menopause, and the effects of exogenous estrogens, suggest that hormones affect cancers of the female reproductive organs. The characteristics and age pattern of prostate cancer also may reflect the influence of hormonal factors. Perhaps hormones do not act as true carcinogens, in the sense of initiating tumors, but resemble tumor promoters.\textsuperscript{29}

Diagnosis and Therapy of Cancer in Humans

Establishment of appropriate laboratory values for the aged is basic to the accurate diagnosis of cancer. For example, not knowing that carcinoembryonic antigen levels tend to increase with age\textsuperscript{30} could lead to an unfounded suspicion of cancer. Conversely, the mistaken belief
that old age produces anemia can result in failure to diagnose a gastrointestinal carcinoma.\textsuperscript{31,32}

The effectiveness of diagnostic methods in the aged also deserves investigation. One study, for example, showed that because of age-related changes in the female genital tract, colposcopy is less useful in diagnosing cervical neoplasia in elderly than in younger women.\textsuperscript{33} Decision theory,\textsuperscript{34} a mathematical approach, may prove useful in determining at which ages to screen populations and which methods of diagnosis and treatment are most effective.

Older patients often have been excluded from clinical trials, in part to spare them from possible adverse effects. However, their inclusion in such studies is important in developing appropriate treatment regimens for the elderly. For example, the belief that older adults with acute granulocytic leukemia rarely respond favorably to chemotherapy has recently been challenged by a study showing that such treatment produces similar remission rates in each 10-year age group over age 50 and in younger patients.\textsuperscript{35}

**Immunology and Mutagenesis: Two Possible Links**

Consideration of findings in various disciplines suggests that two of the links between cancer and aging involve immunology and mutagenesis.

**Immunology**

Multiple lines of evidence imply that the age-related decline in immune function,\textsuperscript{36} which some theories consider to be the basis of aging, contributes to the increased incidence of cancer with age. At present, this immunologic decline does not appear to be the major responsible factor, but it may play a role in the development of certain tumors in some patients.

Perhaps the best known formulation of the relationship of cancer, aging and immune function is Sir Macfarlane Burnet's concept of "immune surveillance,"\textsuperscript{37} which suggests that with age the immune system—particularly its thymus-dependent components—becomes less effective in eliminating abnormal cells that are capable of giving rise to malignant tumors. Several types of data support this theory, but contradictory findings suggest that it is not sufficient.

Various observations imply the existence of one or more immunologic links between aging and cancer. The findings that many immunosuppressant agents foster cancer and that many carcinogens are immunosuppressive\textsuperscript{38} suggest that immunosuppression and carcinogenesis may be causally related or share a common mechanism. Smith and Walford's conclusion that the histocompatibility gene regions, which are related to immune function, influence rates of aging and tumor development\textsuperscript{14} also implies an immunologic link.

Multiple studies in animals have shown simultaneous, age-related declines in immune function and rises in tumor susceptibility. Teller and his coworkers have found evidence of this phenomenon in aging, random-bred Swiss mice.\textsuperscript{39} Similarly, Perkins and Cacheiro have reported an association between age-related declines in tumor resistance and in various measures of immunocompetence in BALB/c mice.\textsuperscript{40} Keller observed that \textit{in vitro} macrophages from senescent rats showed less cytotoxicity against various target cells, including tumor cells, than did those from younger animals.\textsuperscript{41} Similarly, the results of preliminary studies at the National Institute on Aging's Gerontology Research Center suggest that as humans age, the ability of their lymphocytes to kill human tumor cells declines.\textsuperscript{42} Gozes and Trainin found that spleen cells from young C57BL/6 mice inhibited, whereas those from old animals enhanced, the growth of transplanted tumor cells.\textsuperscript{43} Furthermore, the observation by Jaroslow et al that lymphomatous spleen cells from aging mice can inhibit the response of normal spleen cells to antigenic stimulation \textit{in vitro}\textsuperscript{44} contributes to the evidence that not only might
decreased immunity predispose to cancer, but also that age-associated cancers may diminish immune function. Although work in animals has established that age-associated decreases in immune function and increases in tumor susceptibility accompany each other, a causal connection has not been proven.

Other animal research provides evidence against the role of immunologic decline in the age-related increase in cancer incidence. Based on their observations of the relationship between duration of carcinogen exposure and incidence of cancer, Peto et al concluded that environmental factors are sufficient to account for the age pattern of cancer incidence; they state that failing immune surveillance and other effects of aging itself need not be postulated.1 Ebbesen's studies showing that susceptibility to DMBA carcinogenesis depends on the age of the host rather than that of the host17,18,45 also refute the importance of immunologic factors.

Epidemiologic evidence, as reviewed by Fraumeni and Hoover,66 also suggests that although immunologic factors may predispose to some neoplasms, in general the immune surveillance concept does not appear valid. Although persons who are receiving immunosuppressive agents and those who suffer from immunodeficiency syndromes are at increased risk of certain types of cancers (in particular, lymphoproliferative neoplasms), their incidence of other cancers is not elevated. Nor does the risk of cancer rise after thymectomy. Furthermore, analysis of epidemiologic data suggests that the cumulative effects of environmental insults can account for most of the age-associated increase in cancer incidence.

The immune surveillance theory recently has received increasing criticism;29 it does not appear to be widely accepted, and Burnet himself has subsequently advanced a theory more dependent on mutagenesis than on immune function.8 Nevertheless, age-related changes in the immune system may play an important, if more restricted, role in the genesis of some age-related neoplastic processes.

Furthermore, age-related changes in immune function may have important implications for therapy. Immunologic approaches may be less effective in the older patient, as suggested by the animal work of Yuhas and Ulrich.20 In addition, age-related changes in immune capacity may modify the effectiveness and the immunodepressive impact of other modalities of antitumor therapy and may alter the rate of healing and the risk of infection following cancer surgery.

Mutagenesis

Mutagenesis appears to provide the tightest link between aging and cancer and may be essential to the mechanisms of both. Smith recently remarked that most contemporary theories of aging—including the error, immunologic, radical, cross-linking and mutation theories—revolve around mutation and differ only in the mechanism postulated or the consequence deemed crucial.47 All known ultimate carcinogens are mutagenic,29 and as discussed above, the abilities to activate the carcinogen DMBA6 and to perform excision repair on DNA7 have been correlated with the life spans of various species.

Other evidence also supports the importance of mutagenesis. In xeroderma pigmentosum, the skin and sometimes the nervous system9 age prematurely and cutaneous cancers appear early in life. The mathematical model of Burch et al suggests that both malignant diseases and age-associated degenerative conditions are the results of somatic gene mutations affecting central control mechanisms.28 Likewise, Burton's model is compatible with the rise in cancer incidence with age as the cumulative effect of mutations occurring randomly throughout life.11 Peto's animal work1 also seems consistent with such conclusions.

Burnet has attempted to relate cancer and aging through the theory of intrinsic mutagenesis,8 which states that in each species the enzymes involved in DNA replication make mistakes at a distinctive rate. Burnet proposes that this
rate—established by natural selection, perhaps to create the proper degree of diversity of immunoglobulins—determines the rate at which cancer, immunologic decline, and various other conditions develop with age.

Thus, mutagenesis may be central to both cancer and aging and may account for the observed association of the two. However, the details of such a relationship remain hazy, and implications for control of cancer and other age-associated conditions are largely unexplored.

**Conclusion: An NIA Perspective**

Aging and cancer appear to be closely linked, and research on many fronts has helped us to begin understanding their relationship. The National Institute on Aging (NIA), one of the eleven National Institutes of Health, is developing resources for, planning, funding and conducting additional research related to aging and cancer in a wide variety of disciplines—including immunology, cell biology, genetics, biochemistry, nutrition, pharmacology, endocrinology, and the behavioral and social sciences. Standardized cells and aged animals for research on aging, cancer, and other topics are available through the NIA; and the NIA strongly encourages that ages of animals be stated in research reports.

In collaboration with the National Cancer Institute, the Epidemiology, Demography, and Biometry Program of the NIA hopes to expand our knowledge of the epidemiology of cancer in the aged, particularly as it relates to nutrition. Also, in September 1979 the NIA held a Consensus Development Conference on estrogen use and postmenopausal women, at which the risk of cancer was considered.

It is the Institute's hope that the association between cancer and aging may enable us to understand both of these phenomena and thus improve human health in old age and throughout life.

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