Cancer is a disease of aging. Biologic and clinical changes that accompany aging exert a major influence on the biology and management of cancer. Although there are basic, unsolved questions regarding cellular senescence, replicative potential, and malignant transformation, perhaps the largest impetus for this increased interest is the overwhelming demographics: Our population is aging, older people have more cancer, and there are many unanswered questions about managing cancer in old people. Recent estimates from the Surveillance, Epidemiology, and End Results (SEER) Program\(^1\) indicate that the median age of patients with cancer in the United States is 70 years, and death rates from cancer at almost all sites increase with each decade (1). Despite the fact that 60% of all cancer cases and 69% of all cancer deaths occur in 13% of the U.S. population aged 65 years or older, much of what we know about cancer management, if not cancer itself, is based on studies in animals or young people.

In this review, we present certain relevant issues and topics of gerontologic research and relate them to cancer biology and clinical oncology.

**Molecular and Cellular Aging and Its Relationship to Cancer**

**Theories of Aging**

Although several theories have been proposed, none suffice to account for the complexities of aging. Life span is finite and varies generally from species to species and much less so within species. On average, mice live 2 1/2 years, monkeys 30 years, and humans about 80 years. Among the species, larger animals generally live longer than smaller animals, but within a species smaller animals generally outlive larger animals.

These features indicate the genetic influence on life span, and many of the existing theories involve acquired alteration of gene function. It is now clearly established that certain specific genes can alter life span, at least in lower animals, but whether these same genes regulate “aging” is still in question. For example, transgenic *Drosophila* that have been genetically engineered to express higher than normal levels of the free-radical scavenging enzymes superoxide dismutase and catalase live, on average, one third longer than control fruit flies (2). In less evolutionarily complex species (e.g., yeast and nematodes), the identification of specific genes that influence life span (3,4) has led to the optimistic impression that the discovery of analogous genes in higher organisms will lead to greater insights into the aging process.

It is probable that certain critical genes in humans also relate to aging and life span. Like so much of what we understand about genetic regulation of disease, clues about the genetic regulation of aging come from the analysis of clinical syndromes, in this case those of accelerated aging (progeria). These syndromes include Hutchinson-Gilford syndrome (early-onset progeria), Werner’s syndrome (adult-onset progeria), and Down’s syndrome (5). Although no progeriod syndrome manifests a complete phenotype of advanced age, the identification of the genes responsible for these particular syndromes is beginning to pay dividends by providing clues to the molecular mechanisms involved in the aging process. For example, Werner’s syndrome is now known to be caused by mutations in a single gene located on human chromosome 8 that encodes a helicase-like protein (6,7). The functional characterization of this specific protein will no doubt increase our level of understanding of the aging process. It is also known that cells containing the Werner’s defect are abnormal in transcription-coupled DNA repair (8), but it is not yet clear whether this is a primary functional defect in this disease. Analyses of the molecular differences between proge-
period syndromes in which cancer incidence is increased and those in which it is not may also provide clues on the relationship between cancer and aging (Table 1).

One intrinsic process, telomere shortening with cell division, is certainly relevant to cellular senescence and cancer (discussed below) and may also be important for organismal aging and life span. In vitro analysis of a wide variety of proliferative cells indicates that, with each successive division, the distal chromosome tip (telomere) shortens until a critical point is reached, at which the cell can no longer divide. Some cells, particularly germ cells, possibly stem cells and other long-lived cells of the body (e.g., T lymphocytes), and transformed cells, at least transiently express an enzyme, telomerase, which preserves telomere length and imparts greater replicative potential. That this process may relate to life span is suggested by the observations that, on average, fibroblasts or lymphocytes obtained from old people have shorter telomeres than those same cells obtained from young people (9–12).

Thus, the evidence indicates that there are key genes that influence aging and life span and also that there are certain intrinsic processes, such as telomere shortening, that may link cellular senescence to animal life span.

Like telomere length, there are other factors that may nonspecifically influence gene or protein function. These factors include the accumulation over time of damage due to such extrinsic factors as reactive oxygen species (13,14) or ionizing radiation (15). Indeed, the hypothesis that free-radical damage is central to aging was proposed several decades ago (13), and it remains a prevailing concept. Certainly, life extension observed in the transgenic fly experiments mentioned above (2) adds strength to the argument.

It is becoming increasingly apparent that molecular and subcellular factors considered critical to cellular senescence and organismal life span are also factors relevant to neoplastic transformation and tumor growth. Thus, genes integral in replicative senescence have been termed “tumor suppressor” genes, and free radicals, DNA repair, and telomeres are commonly described as central features in both the oncology and gerontology literature. One process, apoptosis (or programmed cell death), is a regulatory phenomenon at the heart of development (embryology), inflammation, wound healing, immunity, and neoplastic transformation, and it may be another nexus of aging and cancer. Senescent cells in vitro have proven more resistant to stimuliators of apoptosis (16) (see below). This resistance to apoptosis could lead to the survival advantage of damaged cells that would normally die; such viable, damaged cells may then accumulate additional damage that leads to transformation.

### Cellular Senescence

Much has been written about cellular senescence and the events that lead up to cell death [reviewed in (17,18)]. After a finite number of divisions, normal somatic cells invariably enter a state of irreversibly arrested growth, a process termed “replicative senescence” (19). The loss of proliferative capacity of human cells in culture is intrinsic to the cells and not dependent on environmental factors or even culture conditions (19). Unless transformation occurs, cells age with each successive division. The number of divisions turns out to be more important than the actual amount of time passed. Thus, cells held in a quiescent state for months, when allowed back into a proliferative environment, will continue approximately the same number of divisions as those that were allowed to proliferate without a quiescent period (20).

### Genes That Regulate Cellular Senescence

Senescent cells in culture assume a larger size, remain metabolically active, and are more resistant to apoptotic death than presenescent cells (16). Senescent cells cannot be stimulated to exit the G1 phase of the cell cycle and to synthesize DNA and proliferate; this reflects an inherent resistance of such cells to respond to growth factor signals rather than a failure of growth factor signal transduction. For example, the protooncogenes c-jun, c-myc, and c-Harvey-ras are inducible in senescent fibroblasts after mitogen stimulation (21–23). The mechanism of the failure to proliferate in light of an intact ability to induce growth factors remains unknown. Recent evidence, however, indicates an active inhibition of certain critical (for proliferation) transcription factors. For example, the RB tumor suppressor gene encodes a protein (pRb) that actively inhibits the E2F growth-stimulating transcription factor. Upon appropriate growth-stimulatory signals, pRb is phosphorylated by a cyclin-dependent protein kinase (Cdk) that inhibits its function and allows E2F to bind DNA and stimulate growth. However, in senescent fibroblasts, other inhibitory proteins (e.g., p21 and p16) are found to be expressed at higher than normal levels. These proteins have been shown to directly inhibit Cdk function (24,25). Thus, despite the appropriate growth signal in senescent cells, Cdk is not available to inactivate pRb, and the proliferative

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Age of onset</th>
<th>Common clinical manifestations</th>
<th>Molecular defects</th>
<th>Cancer prone?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werner’s syndrome</td>
<td>Adolescence</td>
<td>Short stature</td>
<td>Abnormal helicase and abnormal gene expression</td>
<td>Yes, particularly tumors of mesenchymal origin and leukemias</td>
</tr>
<tr>
<td>Cockayne’s syndrome</td>
<td>First year of life</td>
<td>Photosensitivity, neurodegeneration, and short stature</td>
<td>Defective gene repair, abnormal helicase, and abnormal gene expression</td>
<td></td>
</tr>
<tr>
<td>Hutchinson-Gilford syndrome</td>
<td>First year of life</td>
<td>Short stature and neurodegeneration</td>
<td>Abnormal gene expression</td>
<td>Yes, particularly osteogenic sarcomas and squamous cell carcinomas</td>
</tr>
<tr>
<td>Rothmund-Thomson syndrome</td>
<td>Neonatal period</td>
<td>Short stature and neurodegeneration</td>
<td>Abnormal overall DNA repair and increased sensitivity to x ray and UV light</td>
<td></td>
</tr>
<tr>
<td>Wiedermann-Rautenstrauch syndrome</td>
<td>Neonatal period</td>
<td>Short stature and neurodegeneration</td>
<td>Abnormal gene expression</td>
<td></td>
</tr>
</tbody>
</table>
signal provided by E2F does not appear. Certainly, other mechanisms are involved in the growth arrest of senescent cells because some growth-enhancing transcription factors are not inducible and, when exogenous E2F is provided, DNA synthesis remains inhibited (18).

Cellular Senescence and Aging

The question remains as to whether the \textit{in vitro} phenomenon of replicative senescence is relevant to the aging of an animal. One suggestive observation is that the replicative potential of fibroblasts cultured from samples of skin from old animals is less than that of fibroblasts taken from young animals (26). Furthermore, when various species are compared, replicative potential appears to be directly related to life span (27). A specific enzyme (pH6 \(\beta\)-galactosidase), which had been shown to be a useful biomarker of \textit{in vivo} senescence because it was expressed by senescent but not presenescent or quiescent fibroblasts (28), was found to have the predicted pattern of expression in skin from young and old donors \textit{in vivo} (28). Thus, there was an age-associated increase in \(\beta\)-galactosidase present in dermal fibroblasts and epidermal keratinocytes, providing an \textit{in situ} sign of replicative senescence.

Cellular Senescence and Cancer

In a recent review on this subject, Campisi (18) identified several points of experimental evidence that, taken together, cogently argue that the process of replicative senescence occurs to the exclusion of tumor development. She points to the observation that cells demonstrating patterns of normal replicative senescence are less likely to become tumorigenic when compared with either immortalized cells or cells with unusually long replicative life spans (29). Also, genes that regulate the \textit{in vitro} phenomenon of cellular senescence are recognized as \textit{in vivo} regulators of cellular proliferation. At least a few of these (e.g., p53 [also known as TP53] and RB) have been identified as tumor suppressor genes. Furthermore, many of the common oncogenes exert their tumorigenic effect by enhancing replicative life span (30). Thus, at the molecular and cellular levels, aging and cancer may be considered distinct phenotypes. However, derangements in the pathways that lead to replicative senescence can lead to uncontrolled growth. It cannot be a coincidence that senescent cells are arrested mainly in the G1 phase, and mutations involving the G1 checkpoint are extremely common in human cancer.

Clinical Aspects of Aging and Age-Related Disease

Aging Versus Disease

It is a central tenet of geriatrics that aging is not a disease. The functional declines that accompany normal aging have been well characterized [for review, see (31)] but under normal circumstances do not account for symptoms. For example, that kidney function declines with age is well recognized (32); in fact, this decline in kidney function has proven to be a useful biologic marker of aging in humans. However, clinical consequences of this change in renal function—in the absence of a disease or the exposure to an exogenous nephrotoxic agent—do not occur. Similarly, bone marrow changes with age. Marrow stem cells are fewer, and proliferative potential of progenitor cells is less (33,34). However, anemia and neutrophil or platelet abnormalities do not occur in non-diseased, elderly individuals. In fact, in rodents, serial transplantation of marrow has indicated that there is enough regenerative capacity to sustain life for several generations (33). There have also been distinct changes in measurable immune functions described with age [reviewed in (35,36)], but the clinical consequences of these changes are minimal or even nonexistent in the absence of disease.

Aging is not a disease process, but the changes in physiologic reserve that accompany aging may make an individual susceptible to disease. For example, those aging-related changes described for the immune system, although not primarily a problem, may render an individual susceptible to reactivation of tuberculosis (37,38) or herpes zoster (39) and less capable of responding to influenza vaccine with protective titers of antibody (40,41). The decline in the immune response, however, is not of sufficient magnitude or duration to account for the increased incidence of cancer in old people (42). In fact, we (43–45) and others (46–49) have shown in experimental models that immune senescence paradoxically may contribute to the observed reduced tumor growth rate and spread for a variety of tumors (see below).

Aging Versus Time

In a study published in 1985, Peto et al. (50) chose a very provocative title, “There is no such thing as ageing, and cancer is not related to it.” Although not a sustaining concept from a gerontologist’s perspective, the concept that the increased rate of cancer in older people is not a result of physiologic alterations or a decline in host reserve but is instead the consequence of accumulated carcinogenic influences over time has some merit. In fact, this concept gets at the heart of gerontology: time versus aging. Time itself is the standard by which we predict “aging,” but in fact it is commonly appreciated that cells, tissues, organs, and individual organisms “age” at different rates. In contrast, “aging” is thought of as the phenotypic change that occurs over time and results in alteration of function or appearance. By and large, these changes result in limitations in functional reserve and result in an increased susceptibility to disease. Thus, in the multiple-“hit” hypothesis, as that which has become most clearly understood for colon cancer (51), the higher incidence of disease, particularly of cancer, in older age groups is accounted for by the stochastic nature of the genetic modifications and the time it takes to accumulate sufficient alteration in cellular growth-regulatory mechanisms to result in neoplastic disease.

Although there may be truth in this concept, a body of data (discussed below) indicates the additional possibility that there is an age-related increased susceptibility to neoplasia based on altered host functions.

Aging and Cancer: the Interface

Carcinogenesis and DNA Repair

Despite the fact that the multistep model of carcinogenesis alone is sufficient to explain the increased incidence of cancer with age (as discussed above), there is no doubt that aging influences some parameters that may render an individual susceptible (or resistant) to cancer. Therefore, it is no surprise that
young and old animals differ in their susceptibility to carcinogens under experimental conditions. For example, dimethylbenzpyrene, when applied to the skin of adult or aged mice, was found to induce tumors more rapidly in the older animals (52). However, these findings and a large body of literature on similar experiments have been cataloged and analyzed by Anisimov (53,54) who was unable to discern any specific patterns regarding age and cancer susceptibility. It appears that species-to-species and strain-to-strain variations, presence or absence of critical organ (e.g., liver or kidney) dysfunction, and carcinogenic dose were much more important predictors of carcinogenesis than was host age.

This heterogeneity in carcinogenic susceptibility may also be due to inherent differences between individuals in the ability to monitor and repair damaged sites in their genetic material. There is now an increased awareness of the mechanisms by which damaged DNA is repaired [for an overview, see (55)], and age-related impairment in these mechanisms has been suggested (56). Patients with the condition xeroderma pigmentosum have a mutation in one of several DNA repair genes, and most affected individuals have defective nucleotide excision repair of UV light-damaged DNA. They experience a greater than 1000-fold excess frequency of sunlight-related skin cancers, and the tumors develop in the very young (median age, 10 years) (57). In normal people, there is an increased risk of skin cancer with age, and it has been suggested that this too reflects an age-associated impairment of the relevant DNA repair mechanisms (58).

**Angiogenesis**

It is now appreciated that the growth of solid tumors depends on the provision of an adequate vascular supply (59,60). Angiogenic stimuli, usually in the form of soluble factors, such as fibroblast growth factor (61) or lymphocyte-induced angiogenesis factor (62), stimulate endothelial cell proliferation and new vessel formation. The response to these signals has been shown to be decreased in old mice (49,63,64), and this has been considered an important factor in the age-associated reduced rates of tumor growth and spread (see below).

**Immunity and Aging**

There is also a well-characterized deficit in immune function with advancing age [for review, see (35,36)]; however, as mentioned above, the consequences are not fully established. It is apparent that otherwise healthy older individuals are more susceptible to reactivation of tuberculosis (37,38) or herpes zoster infection (39), and responses to vaccines, such as the commercially available and widely used influenza hemagglutinin, are diminished (40,41). However, it has been postulated that other age-associated diseases, such as cancer (65), atherosclerosis (66), diabetes (67), and even Alzheimer’s disease (68,69), have been related to the decline in immune function with age.

What can be said with confidence is that there are changes in T-cell function with age and that these changes result in decreased proliferation when measured *in vitro* (70). When T cells from older animals and people are studied as a population, there appears to be an accumulation of T cells with cell surface characteristics of memory cells, whereas there is a relative decrease in naive T cells (36). B-cell function, including the capacity to make and secrete antibody, remains intact, although certain intrinsic alterations, such as decreased *in vitro* colony formation (71), have been noted.

Immunoregulatory functions are affected by the aging process, and paraproteinemia and autoantibodies are observed with increasing frequency in individuals with each advancing decade. In general, the paraproteinemia (often termed ‘monoclonal gammopathy of undetermined significance’) is an indicator of dysregulated B-cell clonal expansion, but it is considered not to be the antecedent of multiple myeloma (72–74). Although monoclonal gammopathy of undetermined significance is not thought to be a malignant process itself, patients with this condition have a 2-year decline in life expectancy compared with the life expectancy of age-matched, unaffected control subjects (75). Furthermore, there is a subset of individuals within the group thought to have benign monoclonal gammopathy (15%–30%) whose disease progresses to overt myeloma after a prodrome of up to 30 years (76,77). Also, because the more typically presenting myeloma increases in incidence with advancing age, it must be distinguished from the monoclonal gammopathy of undetermined significance. Typically, this distinction can be made by examination of bone marrow, skeletal x rays, renal function, and serum B$_2$-microglobulin levels (76).

Another indication of a dysregulated immune function is the alterations in certain key cytokines, measured in plasma, culture supernatants, or in the appropriate tissue microenvironment. Notably and consistently, interleukin (IL) 2 (IL-2) levels and function decrease with age (78), and IL-6 levels increase with age (79). The decline in IL-2 levels may account for a substantial component of the measured decline in T-cell function, and the increase in IL-6 levels has been implicated in the pathogenesis of certain age-associated diseases, including osteoporosis, Alzheimer’s disease, and certain cancers including myeloma (80).

**Tumor Aggressiveness and Aging**

There has been a long-held but incompletely documented notion that cancers in older people are ‘‘less aggressive.’’ However, epidemiologic data from tumor registries or large clinical trials have not been supportive of this concept (1). This disparity between apparent decreased cancer aggressiveness in an individual patient on the one hand and the high rate of cancer mortality in older age groups on the other may be because the survival data are confounded by special problems common to geriatric populations, e.g., comorbidity, ‘‘poly-pharmacy’’ (i.e., the common practice of prescribing numerous drugs in older people), physician or family bias regarding diagnosis and treatment in the elderly, and age-associated life stresses that may be as basic as the inability to get to a medical center for treatment (81). These factors may increase death rates and counteract any primary influence that aging might have to reduce tumor aggressiveness.

Under experimental conditions, however, most tumors grow more slowly and metastasize less readily in old animals (43,44,48,49,82). But this ‘‘age advantage’’ in experimental tumor models is not universally true. For example, the growth of certain tumors, such as 3-methylcholanthrene-induced fibrosarcomas and UV light-induced sarcomas, is more rapid in older than in younger animals (83,84). In another example, rat liver epithelial tumor cells injected into the liver demonstrated sustained growth in old animals but not in young animals (85).
the UV light-induced sarcoma model, more aggressive disease in older mice is related to an age-associated decline in tumor-specific cytolytic T-cell function. In the liver tumor model, age-related microenvironmental factors other than immunity appear to be most relevant because the age difference was not apparent when the tumor cells were injected subcutaneously (85).

In general, experimental tumors that exhibit increased aggressiveness in older animals are chemically or virally induced and are highly immunogenic. In these systems, it is a disadvantage to be immune deficient, and older mice have more aggressive disease because of their less vigorous antitumor immunity. However, for other tumors, most notably those that develop spontaneously and are weakly antigenic or nonantigenic (e.g., B16 melanoma), tumor growth is less prominent in older animals.

What accounts for the age-associated changes observed in these experimental systems? It is probable that certain factors that influence tumor growth also change with age. Accordingly, endocrine, nutritional, wound-healing, and angiogenesis factors have been explored. Indeed, for some tumors, age-associated changes in these factors have been correlated with reduced tumor growth [for review, see (42)]. However, several early observations led to the seemingly paradoxical conclusion that immune senescence accounted for a large component of the observed reduced tumor growth with age. For example, B16 melanoma grew less well in congenitally immunodeficient mice (86) and in young mice rendered T cell deficient. Furthermore, when young, thymectomized, lethally irradiated mice received bone marrow or splenocytes from old donor mice, tumor growth was less when the spleen or bone marrow was from young donor mice (44,48).

It has been proposed (87,88) that competent immune cells provide factors that can augment tumor growth under certain circumstances. If a tumor is only weakly antigenic, nonspecific growth-stimulatory factors provided by lymphocytes or monocytes may actually outweigh the inhibitory forces provided by those same cells (in part because of the lack of tumor recognition). In this situation, therefore, immune deficiency does not render a host more susceptible to aggressive tumor growth and spread; in fact, it renders the host more resistant because those cells are less likely to provide the nonspecific stimulatory factors (i.e., less fertile “soil”). However, microenvironmental factors are complex, as indicated by the liver epithelial tumor model mentioned above (85). In those experiments, conditions in the liver microenvironment in old animals, as compared with young animals, favored tumor growth.

Treatment of Cancer in Older People: the Issues

The foundation for the current practice of medical oncology is largely based on results of large, multicenter, randomized clinical trials. However, despite efforts from the cooperative groups, patients entered onto trial are generally younger and presumably healthier than the typical geriatric patient with the same cancer. Furthermore, end points of these trials are frequently survival (for therapeutic interventions) or disease-specific deaths (for prevention studies), and these end points are not always suitable for older persons because of a reduced life expectancy based on age alone or on other comorbid illnesses. In fact, it is common in geriatric medicine to focus more on symptom reduction than on life span extension, a concept referred to as “compression of morbidity.”

With very few exceptions, there is no evidence that cancer is more resistant to treatment in older patients, and age alone should not a priori preclude any therapeutic approach based on the rationale that it would be less effective. One important exception is acute nonlymphocytic leukemia, which appears distinctly different in geriatric age groups. Older individuals with acute nonlymphocytic leukemia more typically present with an antecedent myelodysplastic syndrome, cytopenias, and bone marrow cytogentic abnormalities (89). Cytoreductive treatment in these patients has been unsatisfactory and is generally not recommended, unless in an investigational setting (90).

Another feature of leukemia in older people is that the neoplastic cells from these individuals more commonly express the multidrug resistance glycoprotein (Mdr1) even in apparent de novo leukemias without cytogentic abnormalities or a pro-drome of myelodysplastic syndrome (91). By multivariate analysis, the expression of Mdr1 was found to be an independent negative prognostic factor in a series of more than 200 older leukemia patients studied by the Southwest Oncology Group (91).

Changes related to age in both the biology of tumors and the biology of the host alter older patients’ responses to chemotherapy (Tables 2 and 3). Furthermore, clinicians are also paying attention to age-related changes in the immune response (Table 4) and how these changes may relate to treatment strategies that involve biologic approaches.

In general, older people require special attention with regard to treatment decisions, but this typically relates to an evaluation of organ function and reserve (to avoid toxicity) and an estimation of treatment goals in the context of existing medical conditions, comorbid illness, and functional status. In this regard however, a word of caution is in order. Decisions about treatment issues, such as aggressive therapy versus supportive therapy, should be made by the fully informed patient. It has been our experience that this is usually the case. However, physicians should be very careful not to negatively bias treatment decisions based on their own assessment of the patient’s quality of life because studies have shown that physicians are not likely to accurately estimate this parameter (120).

Summary

The striking feature of the interface between the biology of aging and the biology of cancer is that there are similarities and differences in the altered processes, but we seem to know much more about cancer than about aging at the cellular level. Thus, a thorough exposition of that interface remains elusive. An individual cell has a range of responses it can make to changes in its environment. These responses are cell division, differentiation, or death. Alterations in any of those responses can lead (ultimately after several “hits”) to cancer. Aging research has added another response to the cell’s repertoire: senescence. We do not yet know whether senescence can be subverted to lead to cancer; there are features of cell senescence that seem antineoplastic (e.g., the impenetrable G1 phase checkpoint blockade) and others that seem proneoplastic (e.g., failure of a senescent cell to undergo apoptosis). Additional study of the process of
cell senescence and its relationship to the aging phenotype should elucidate the molecular pathways involved and clarify where they overlap and diverge in aging and cancer.

The interface between clinical geriatrics and clinical oncology is obviously quite extensive, but it is characterized by large uncharted territory. The path to elucidating the interface for the benefit of our patients involves research and training.

Novel training is required because of the vast cultural differences between geriatricians and oncologists. Both the methods and the tools used by the two groups are divergent. Geriatricians generally have a high aversion to risk in their management approaches. Interventions that produce toxic effects in the patients, even transiently, are generally eschewed. By contrast, oncologists accept much narrower therapeutic indices. Most of their attempts at curative therapy involve placing the patient at some risk of an acute decline in their health status. Oncologists frequently balance highly prevalent short-term risks and potential long-term benefits, gains experienced by only a minority of treated patients. Such thinking is foreign to geriatricians.

Yet, the overlap between the disciplines of oncology and gerontology is enormous. Most cancer patients are older than 70 years. Thus, specialists in both areas provide care for older people and must utilize multidisciplinary approaches to patient management. Both oncologists and geriatricians must deal with end-of-life issues, including palliation and hospice care for their patients.

Given the large cancer-specific therapeutic armamentarium, it would seem most appropriate to incorporate principles of geriatrics into the training of medical oncologists. It would appear that a major challenge in the coming years will be to formulate a teaching program that will equip oncologists to deal with the burgeoning population of older people who have cancer.

Establishing a research agenda addressing the many questions that deal with the older patient with cancer may be of even greater urgency. As noted above, we have very little information about the influence of age on host factors that alter the biology of the cancer and the pharmacology and biologic effects of can-

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**Table 2. Chemotherapy issues in geriatric oncology**

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Pharmacodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased gastro-intestinal absorption</td>
<td>Increased incidence of drug resistance</td>
</tr>
<tr>
<td>Volume of distribution: decreased for water-soluble and increased for lipid-soluble substances</td>
<td>Increased concentration of glutathione reductase</td>
</tr>
<tr>
<td>Decreased hepatic metabolism (activation and deactivation by the P450 system. Type II conjugative reactions do not appear to change.</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Decreased protein binding from reduction of albumin concentration</td>
<td>Abnormal protein synthesis, with production of abnormal topoisomerase II</td>
</tr>
<tr>
<td>Decreased renal excretion</td>
<td>Decreased activation and increased catabolism of drugs</td>
</tr>
<tr>
<td>Decreased DNA repair of genotoxic lesions</td>
<td>Decreased renal excretion</td>
</tr>
</tbody>
</table>

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**Table 3. Potential age-related changes in the pharmacology of antineoplastic agents (92–94)**

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
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</tr>
</tbody>
</table>

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**Table 4. Issues regarding use of biotherapy in geriatric oncology**

- Modulation of the immune response (i.e., biotherapy or immunotherapy)
  - Biotherapy is particularly attractive option for use in the older patient whose natural defenses against cancer may be impaired by immune senescence (118). At present, only a limited number of such therapies are clinically available, and these options are clearly inadequate to restore a normal immune response in the aged.

- Toxic effects of commonly used biotherapeutic agents
  - Recombinant interferon alfa (rIFN α) at small doses (e.g., 3 million units, three times weekly) is well tolerated by patients of all ages. At higher doses, rIFN α causes myelodepression, malaise, fever, neuropathy, and abnormalities of liver enzymes (118). At intermediate doses, rIFN α can cause dementia in persons aged 65 years and older (119).
  - Toxic effects following administration of recombinant interleukin 2 appear to be lower in older patients than in younger patients, and perhaps this phenomenon may be related to decreased ability of interleukin 2 to induce the secretion of other cytokines from its target cells in older people.
Academic oncologists and geriatricians can establish a mechanism for creating a research agenda that begins to define the important gaps in knowledge and proceeds to fill them.

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