Cancer in the Elderly: Basic Science and Clinical Aspects

The incidence of cancer increases progressively with age. Rearrangements of genomes have been found to accompany cellular aging. These factors, in concert with age-dependent alterations in immune function and host defense, may help to explain the increased risk of malignant disease in aged persons. The clinical presentation and natural history of neoplasia are also affected by aging. This conference reviews recent developments in these areas, examines the effects of drug use in the elderly and implications for management, and discusses current information on how age may influence the response of cancer to therapy.

Dr. David A. Lipschitz (John L. McClellan Memorial Veterans Hospital, and University of Arkansas for Medical Sciences): Great strides have been made recently in cancer therapy. Judicious use of surgery, radiotherapy, and chemotherapy have increased remission rates and cures for leukemias, lymphomas, small cell lung cancer, and breast cancer, to name but a few. Although aggressive curative therapy is frequently justified in younger patients, this approach may not always be appropriate for the older patient. Neoplasia is most frequent in persons beyond age 65. Furthermore, the mode of presentation, natural history, and response of the cancer to therapy may often be different in this population. This conference explains why neoplasia is more prevalent in the elderly by addressing the mechanisms of cellular aging and emphasizes the importance of ascertaining the specific biologic age of each patient in order to design a treatment plan optimized to the individual.

Mechanisms of Cellular Aging

Drs. Samuel Goldstein and Robert Reis (John L. McClellan Memorial Veterans Hospital, and University of Arkansas for Medical Sciences): Aging of all multicellular organisms, including humans, is accompanied by overt physiologic decline or by more subtle decrements detectable in all organs after appropriate provocative tests (1). Because each physiologic variable represents the summation of several processes, each changing during life within limits determined by intrinsic genetic mechanisms and extrinsic perturbations, great individual variation may occur (2). This variability also applies to the incidence of age-dependent diseases, which climbs exponentially after age 30; these diseases predominantly involve atherothrombotic and malignant processes (3). The number of occult pathologic lesions per person increases even more rapidly with age (4), but only a few emerge above the "clinical horizon" to be diagnosed during life (5).

DECREASED CELLULAR REPLICATION WITH AGE

At the cellular level the general trend is toward decreased replicative ability and shrinkage of stem cell compartments in all types of cells (5). During fetal life, tissue expansion is accomplished by proliferation of diverse cells with similar growth rates that peak just before birth (Figure 1). Growth of virtually all organs ceases during adolescence as the somatic proportions of adulthood are attained. Thereafter, tissue homeostasis is maintained with only a fraction of the mitotic activity occurring that is seen during intrauterine life, except after cell injury or in enlightened physiologic demand.

Parenchymal and supporting cells can be classified into three main types on the basis of their mitotic capacity in adulthood: continuously mitotic, such as gastrointestinal, hematopoietic, epidermal, and spermatogenic cells; intermittently mitotic, best exemplified by hepatic parenchymal and renal tubular cells; and nonmitotic, such as neurons and cardiac and skeletal muscle cells. Against this backdrop of gradually diminishing replicative ability, carcinogenesis poses a paradox, in essence, "runaway" replication of cells. Indeed, senescence features an increasing number of multifocal hyperplasias (6) that culminate, in rare cases (rare with respect to the $10^{13}$ cells in our bodies, but common for each person), in malignant neoplasms.

In this review we attempt to explain a major concomitant of biologic aging, malignant disease, in light of available data from epidemiologic, cellular, and molecular research. Evidence is presented to support the hypothesis that aging involves genomic rearrangements that are often subtle. Because aging is a universal process, such rearrangements are reproducible and perhaps similar to those that accompany certain kinds of development and cytodifferentiation. In contrast, the rising risk of malignancy with age reflects the lifelong accumulation of DNA rearrangements or other somatic cell mutations.
that can occasionally cause cell transformation. Although this transformation immortalizes the cells in terms of growth, it is profoundly deleterious to the patient.

The relation between chromosomal alteration and malignancy is well documented (7). Moreover, several inherited human disorders that feature chromosomal breakage and a high frequency of malignant disease are now known to involve various abnormalities in DNA repair or recombination (8). Less widely recognized is that many of these same genetically determined syndromes also have an early onset and accelerated progression of biologic aging in one or more organ systems (5), adding yet another link in the association between malignancy and aging (9). This relationship strongly suggests that alterations in the integrity of the genome, either by deleting or scrambling DNA sequences, lead to the loss of genetic information required for control of cell division and thereby bring forward in time both a normal process, cellular aging, and an abnormal process, cancer. Whereas virtually all of these inherited disorders are relatively rare, the heterozygous carrier state is much more common, as is implicit in the Hardy-Weinberg equation (10). For example, in the rare autosomal recessive disorder ataxia telangiectasia, which has a gene frequency of approximately 1 in 40,000, the carrier state occurs in 1% of the population (11). Indeed, these carriers are at a substantially higher risk than the population at large for the development of malignant diseases of various organs (11). More recently, a similar increased risk for various internal as well as skin malignancies has been found for carriers of the gene for xeroderma pigmentosum (12).

Therefore, if we take all heterozygous carriers for the breakage syndromes alone, a substantial number of per-

Figure 1. Mitotic capacity of cells during various stages of the life-span. Cells are classified according to their mitotic capacity after somatic growth ceases as continuously mitotic (dashed line), intermittently mitotic (solid line), or nonmitotic (dotted line). Upward arrows indicate discrete events on a time scale that is otherwise a gradual and continuous sequence; downward arrows indicate stimuli for cell division. From Goldstein (2); reproduced with permission of the New England Journal of Medicine.

Tissue Culture Studies in Human Aging

Over 2 decades ago Hayflick and Moorehead (16) showed that normal human fibroblasts have a limited capacity to multiply in vitro. Subsequently, Hayflick (17) and others (6, 18, 19) have shown an inverse relation between the number of cell doublings of several fibroblast strains and the age of the donor; that is, the older the person is, the fewer doublings his cultured cells achieve before replicative senescence (Figure 2). Furthermore, cells propagated from persons with inherited disorders of premature senescence show shortened lifespans compared to those of age-matched controls. Thus, physiologic age (the collective effect of lifelong genetic and environmental influences) rather than chronologic age is the prime determinant of the cellular lifespan.

When fibroblasts are starved for serum or deliberately crowded without subculture, they cease to divide. However, when such arrested cells are allowed to resume active replication after various times in the nonreplicative state, they go on to register the same total number of replications as do continuously dividing cohorts (20). Clearly, their calendar time has been extended. Thus, fibroblasts in vitro and perhaps replicating cells in vivo have a critical limit of total cell divisions. The faster they divide, the sooner they reach this limit and become senescent. It follows that acceleration of cell turnover for any reason, whether due to intrinsic genetic defects or extrinsic stimuli (particularly in vulnerable tissues such as vascular and epithelial surfaces), will hasten the advent of age-related diseases (atherosclerosis and cancer, respectively).
Molecular Events in Cellular Aging

Despite their inevitable loss of replicative capacity during serial passage, fibroblasts appear to maintain a grossly stable diploid karyotype on cytogenetic analysis. However, more sensitive analyses at the molecular level have shown a generalized loss of highly repetitive DNA sequences during replicative aging. Three broad classes of DNA exist in the human genome: highly repetitive DNA sequences, present in $10^5$ to $10^6$ copies but whose function remains poorly understood, despite their abundance (they comprise about 25% of the genome); middle repetitive DNA, present in 10 to $10^4$ copies per genome and including genes for ribosomal DNA and transfer RNA; and “unique” sequences, which include most of the genes that code for proteins such as hemoglobin, enzymes, and surface antigens.

The loss of highly repetitive DNA has been shown in specific sequences located at the centromeres of chromosomes (hR1 satellite sequences) (21) and at other indeterminate sites in the genome (22). Additionally, total repetitive sequences, as assessed by kinetic analysis (21), become 20% to 30% depleted during the replicative lifespan of several human fibroblast strains. After excluding alternative explanations including DNA divergence, base modification, cell cycle changes, or loss of specific chromosomes, we conclude that these sequences are deleted from the genome.

To explore the nature of this DNA instability, we used a low-repetition sequence interspersed among certain highly repetitive DNA (23). This sequence was isolated after its identification in the human genome within a cluster of the highly reiterated Alu repeat family of sequences present in $10^6$ copies per genome. A novel polymorphism of this inter-Alu sequence was seen in tissues of single donors and between lymphocytes of different leukemic and normal donors in both the banding pattern and copy number. This polymorphism was visualized as variability in the length of DNA fragments generated after digestion by several restriction endonucleases and different intensities of autoradiographic bands. Much of this variability was traced to circular extrachromosomal molecules containing the inter-Alu sequence (23, 24). However, an alternative possibility, that they reside at interspersed genomic locations, could not be excluded. These observations represent an important milestone in studies of human DNA and are consistent with the idea that the inter-Alu/Alu repeat cluster is mobile.

On examining total cellular DNA of six human fibroblast strains at early and late passage with the inter-Alu probe, we found an approximately constant number of copies within the chromosomal (genomic) bands. However, four of six cell strains showed additional discrete bands appearing for the first time or increasing at late passage (24). The sizes of these bands after restriction endonuclease digestion ranged from 1.6 to 8 kilobase pairs, and the degree of amplification also varied from strain to strain. Notably, all fibroblast strains maintained an essentially diploid karyotype throughout passage, yet showed evidence of subtle DNA rearrangements. Various experiments have characterized these DNA sequences as extrachromosomal circular elements (24).

To extend these observations to “real” aging of somatic cells, we examined circulating blood lymphocytes from young and old normal donors. Chromosomal inter-Alu copies ranged from 2 to 40 copies per cell with no obvious correlation to donor age. However, a pronounced age dependency was seen in a single additional band at 4.8 kilobase pairs (Figure 3) that appeared in the DNA of 16 of 24 elderly donors, aged 61 to 91 years. None of the 18 young donors, aged 21 to 31 years, showed this extra-chromosomal band. More recent experiments have localized most, if not all, of these circular DNA forms to B lymphocytes rather than T lymphocytes.

These results augment the growing evidence of genomic plasticity in human somatic cells and, for the first time, show remarkable correlations with cellular aging both in vitro and in vivo. Developmentally, the most profound alterations in gene structures yet reported occur during B-cell differentiation. Joining of several dispersed DNA segments in a vast number of permutations leads simultaneously to the diversification and specificity associated with major immunoglobulin classes and individual clonal types (25). In fact, immunoglobulin gene rearrangements during B-cell ontogeny probably lead to the excision of specific segments and their appearance as circular DNA (26, 27). These circular DNA elements may occasionally undergo homologous recombination with genomic DNA, presumably mediated by this repetition sequence, which results in the insertion of circular DNA molecules into the genome as a linear sequence. Indeed, specific chromosomal translocations occur in many malignant disorders and, in the case of B-cell neoplasias, often involve immunoglobulin genes and oncogenes at the break points (7).
Experiments in our laboratory are exploring whether the circular DNA in old-donor lymphocytes contains sequences homologous with those of various immunoglobulin genes and oncogenes.

In contrast to the striking rearrangements during immunoglobulin gene ontogeny, no evidence has been seen of DNA rearrangement in other genes during vertebrate development. However, experiments on nuclear transplantation are of great interest. Nuclei of somatic cells have been regarded as totipotential and therefore fundamentally similar to those of the germ line. But whereas transplantation of nuclei from a tadpole midgut cell to a fertilized egg or early blastula can lead to development of a normal frog, the fraction of viable embryos produced in this way never exceeds 2%, a limitation that may reflect the proportion of totipotent stem cells in the donor tissue. Moreover, no one has ever succeeded in producing a normal animal from nuclei taken from an adult somatic cell (28). Therefore, subtle gene rearrangements during development may lead to irreversible commitment of somatic cells to a given line of gene expression with reciprocal loss of totipotent function. By the same token, aging of somatic cells may proceed as a terminal differentiation with progressive narrowing of options. In such a determined mechanism, excision or rearrangement of DNA sequences, such as the highly reiterated hRI and Alu sequences, might lead to diminished DNA replication, cellular senescence, and ultimately, physiologic decline. However, appearance of the DNA elements as extrachromosomal circles that can undergo autonomous replication would enhance the opportunity for random aberrant insertions within a rare cell leading to abnormal DNA replication, the focal hyperplasias of aging (6), and in even rarer clones, malignant transformation.

It seems likely that other mechanisms are involved in senescence besides change in the number of DNA sequences and their spatial configuration. We and others have shown imperfect transmission of DNA methylation patterns from cell generation to generation, particularly in the vicinity of unique genes coding for specific proteins within a fraction of clones (22, 29). If DNA methylation is important in maintaining gene repression, then demethylation may lead to leaky expression of normally silent genes in individual clones, even though leakiness for any gene may be low or undetectable in a background of polyclonal cell populations.

In conclusion, it is reasonable to suggest that biologic aging is a physiologic process, an epilogue of development originating within the genome (2). The inherited load sets the limits for the basic genetic program. Mutations associated with the chromosomal breakage syndromes predispose persons to accelerated turnover of mitotic cells, followed by genomic rearrangements and the early advent of polyclonal, hence multifocal, malignancy. But the specific malignancy seen depends not only on the differentiated cell target but also on the cumulative and specific nature of the environmental exposure. In short, aging and carcinogenesis proceed along an uneven front, occurring sooner in some cells and later in others of the same differentiated class. Future studies should show the specific nature of genomic changes during aging of each cell type and explain the relation of these changes to malignant transformation.

The Immune System During Aging

Dr. Marc Weksler (Cornell University School of Medicine): Now is an exciting time to be an oncologist. Within the next few years, an understanding of the molecular basis of malignant transformation may come within our grasp. Understanding the organization of the genome may also reveal much about the biology of aging. In a real sense, cellular senescence and malignant transformation, finite and infinite cell survival, are two sides of the biologic coin. The tools of molecular genetics show that the biology of senescence and malignancy are converging.

The first part of this review outlines the dramatic changes in immune structure and function that occur with age. The second describes recent work from my laboratory that suggests chromosomal instability is increased in lymphocytes from elderly as compared with young humans. This phenomenon may be related to the age-associated increase in cancer.
IMMUNE STRUCTURE AND FUNCTION

The involution of the thymus is the central event in the senescence of the immune system. Fifty years ago Edith Boyd (30) documented the change in the mass of the human thymus that accompanies human growth and development. She measured the cellular mass of the thymus in healthy persons who had died suddenly and found that the mass of the thymus was well maintained until about 15 years of age. At sexual maturity the involution of the thymus begins and then progresses so that by 50 years of age only about 10% of cellular mass of the thymus remains. The pace of thymic involution relative to lifespan is the same in experimental animals, beginning at sexual maturation and ending in midlife.

In 1960, Good and colleagues (31) and Miller (32) independently discovered that the thymus was a central organ of immunologic development. Two functions of the thymus are now recognized: the secretion of a family of polypeptide hormones, and differentiation of precursor T cells that come from the bone marrow and mature within the microenvironment of the thymus. Thymopoietin, a 49-amino-acid polypeptide, has been studied, sequenced, and synthesized by Gideon Goldstein (33). The level of thymic hormone activity has been measured in the blood of humans from birth to old age (34). The concentration of this hormone in blood is constant from birth until about age 30; thereafter, a linear decline occurs, so that by age 60 no hormone is detectable in the blood of healthy persons.

The involution of the thymus results not only in the decline of thymic hormone concentration in the blood but also in the loss of the capacity of the thymus to differentiate T cells of early lineage. Nearly all thymocytes in young humans have acquired the capacity to bind sheep erythrocytes, a mark of maturation. With age, increasing numbers of thymocytes fail to acquire this marker of maturation. Because of the failure of the thymus to cause differentiation of precursor T cells, increased numbers of T cells of early lineage appear in the blood of old humans (35).

Although the total number of T lymphocytes does not change with age (probably because T lymphocytes are very long lived), the distribution of T-cell subpopulations is altered. Not only are the numbers of immature T cells in the blood increased, but the ratio of regulatory T cells changes. Thus, the percentage of T cells expressing the T4 determinant increases with age and the percentage of T cells expressing the T8 determinant falls (36). The lower numbers of T8 cells may be related to the increased prevalence of aut antibodies and the increased incidence of benign monoclonal gammopathies that accompany aging.

The function as well as the structure of the immune system change with age. More than 50 years ago the titer of antibodies to sheep erythrocytes in sera from humans of varying age was measured, and the level of anti-sheep erythrocyte antibodies was highest in persons between 15 and 25 years of age and then declined with age (37). Fifteen years ago Rowley and colleagues (38) confirmed these findings by showing that the natural antibody to bacterial flagellin declined with age, but they also showed that the percentage of persons with antinuclear antibody increased with age. They suggested that aging was associated with a decreased response to foreign antigens and an increased response to autologous antigens. The disordered humoral immune system is also shown by the increased incidence of benign monoclonal gammopathy with age. The age-associated incidence is probably related to the loss of thymic function. A small percent of old mice, like humans, have benign monoclonal gammopathies. As Radl and colleagues (39) have shown, neonatal thymectomy leads to an earlier onset and a higher frequency of monoclonal gammopathy. It is reasonable therefore to believe that thymic involution contributes to the increased occurrence of autoantibodies and benign monoclonal gammopathies in the elderly.

Cell-mediated immune function also undergoes senescence. One half of healthy persons over age 60 have impaired delayed cutaneous hypersensitivity. Furthermore, lymphocytes from elderly patients with tuberculosis are impaired in in-vitro proliferative response to the purified protein derivative of the mycobacteria. This important observation suggests that aging is associated with an intrinsic defect of the lymphocyte and not the effect of an aged host environment on a normal immune system. It is important to note that the functional assay used to assess immune competence involved the proliferation of T cells. Leonard Hayflick (17) had suggested that the loss of the replicative potential was an important marker of cellular senescence; the increasing compromise in immune function with age resulted from a loss of the proliferative capacity of lymphocytes.

Our first immunobiologic study of aging made use of two T-cell mitogens, phytohemagglutinin and pokeweed mitogen, which stimulate the proliferation of T lymphocytes (40). T lymphocytes from old persons incorporated significantly less 3H-thymidine than did T lymphocytes from young persons. Although young and old persons had equal numbers of T cells in blood, fewer T lymphocytes from old donors were activated by mitogen. Furthermore, those T lymphocytes from old donors that were activated divided fewer times in culture than did the activated T lymphocytes from young donors (40). Some of the T cells from old donors that were not activated were post-mature; others were premature and came from the bone marrow after the thymus had lost its capacity to cause differentiation. These cells gain immunocompetence if exposed to thymic hormone. Certain immune functions of old mice were restored by exposing spleen cells from old animals or the old animals to thymic hormone (41).

Our interpretation of the impaired incorporation of 3H-thymidine as a basic proliferative defect associated with immune senescence was set back when it was found that lymphocytes cultured with mitogens and exposed to 3H-thymidine suffered cell cycle arrest (42). The impaired incorporation of 3H-thymidine by T cells from old donors might reflect increased sensitivity of T cells from old donors to ionizing radiation rather than a proliferative defect.
we confirmed that $^{3}\text{H}}$-thymidine caused cell cycle arrest of T lymphocytes in culture with mitogen (43). In the absence of $^{3}\text{H}}$-thymidine, 16% of T cells from old or young persons that had been incubated for 96 hours in phytohemagglutinin were in the G2 or M phase of the cell cycle. In the presence of $^{3}\text{H}}$-thymidine, 26% of T cells from young donors and 40% from old donors were in these phases. The increased number of cells in G2 or M reflects cell-cycle arrest, and the greater number of cells from old persons in G2 or M in culture showed the increased susceptibility of cells from old donors to cell cycle arrest (43). Subsequently, we did show a proliferative defect by flow cytometry in the absence of radioactive isotopes.

We have studied the nature of the increased susceptibility of old lymphocytes to $^{3}\text{H}}$-thymidine (43). $^{3}\text{H}}$-thymidine is incorporated into the DNA of chromosomes and acts as an internal source of radiation, causing striking chromosomal damage in dividing cells. Cytogenic comparison of the number of cells in metaphase from young and old lymphocyte cultures exposed to $^{3}\text{H}}$-thymidine has shown that despite the equal incorporation of $^{3}\text{H}}$-thymidine into chromosomes from young and old donors, far more chromosomal damage was seen in cultures from old donors. This finding suggests that chromosomal stability is decreased in the elderly (43). Additional evidence suggests a loss of chromosomal stability with age. First, although the mean DNA content of lymphocytes from old and young donors is the same, the DNA content of individual cells is significantly more variable in cells from old donors (44). Second, sister chromatid exchange is greater in cells from old as compared to young donors (45).

A relationship between chromosomal aberrations and neoplastic disease is becoming clearer. Nearly 20 years ago Nowell (46) noted an abnormal karotype in patients with chronic myelocytic leukemia. Now, many other nonrandom chromosomal alterations have been associated with cancer. Many investigators now believe that most, if not all, tumor cells have characteristic chromosomal aberrations, and such chromosomal rearrangements are believed to confer selective advantage to neoplastic cells for cell growth. The selective advantage is attributable in some cases to the fact that the oncogenes code for growth factors on their cell surface receptors.

The increased susceptibility of cells from old persons to chromosomal damage by $^{3}\text{H}}$-thymidine suggests increased susceptibility not only to chromosomal rearrangement but also to the toxic consequences of irradiation and radiomimetic drugs. The degree of cell cycle arrest or chromosomal damage induced by $^{3}\text{H}}$-thymidine may be used as a "chromosomal tolerance test" to judge the susceptibility of persons to cancer and drug toxicity. In the future, oncologists may choose therapies not only on the basis of sensitivity of the tumor cell to cytotoxic drugs but also on the basis of lack of toxicity of these drugs for normal cells.

**Drug Use in Elderly Patients**

Dr. Rubin Bressler (University of Arizona School of Medicine): Drug use in the elderly demands special therapeutic considerations. Age-drug interactions may result from age-dependent changes in organ function. Moreover, because elderly patients often have more than one chronic disease, it is not unusual for them to take several medications often prescribed by different physicians who are unaware of the other prescriptions. This polypharmacy has potential for deleterious drug-drug interactions (47-49). These considerations are particularly relevant to the elderly patient with cancer who is taking antineoplastic drugs that have narrow therapeutic indices.

The elderly have considerably more adverse drug reactions (48, 50, 51). These reactions may be the result of progressive physiologic changes that occur during aging and affect tissue reactivity as well as sensitivity and tolerance to a drug (48, 49). In addition, functional changes that occur with aging may change the pharmacokinetic elimination characteristics of drugs (52-57). However, relatively little information is available regarding the influence of aging on tolerance to cytotoxic chemotherapy.

Marked age-related deterioration in the function of the cardiovascular, respiratory, renal, and immune systems has been shown to limit adequate compensatory responses to excess drug actions (47, 58-63). Obviously, the cardiovascular, pulmonary, hepatic, and renal systems play important roles in responses to drugs in all age groups, and their diminished function in the aged should be expected to modify responses to drugs because of changes in drug distribution, metabolism, clearance, and organ sensitivity (47-49, 52, 57).

**ALTERED PHARMACOKINETICS AND PHARMACODYNAMICS**

Age-related changes in pharmacodynamics and pharmacokinetics are of particular importance in the elderly patient with cancer. With respect to pharmacodynamics, modifying factors such as blood supply to the tissue and tissue fibrosis can greatly influence drug actions. The compromised cerebral, renal, and cardiac circulations in the aged may result in altered responses of these organs to drugs given in the usual effective concentration range.

Alterations in pharmacokinetic variables, such as drug distribution, metabolism, and excretion, can modify drug concentrations at receptor sites (sites of drug effects on tissues and organs). Few instances of significant problems with drug absorption have been seen in the elderly (48, 49).

**Drug Distribution:** The apparent volume of distribution of a drug is a derived term that indicates how a drug is distributed in the tissues relative to the plasma. The distribution is drug specific but altered by body size, composition of tissues (water, muscle, lipid), and tissue binding of drugs. Several pathologic states, including congestive heart failure and chronic renal disease, affect volume of distribution, as does aging (47, 48). In general, changes in volume of distribution with aging are unpredictable.

The percentage of adipose tissue in total body weight increases with aging, which tends to prolong the total duration of action of some drugs with large volumes of
Table 1. Drug Interactions in the Elderly

<table>
<thead>
<tr>
<th>Primary Drug</th>
<th>Interacting Drug</th>
<th>Effect</th>
<th>Mechanism</th>
</tr>
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<tbody>
<tr>
<td>Corticosteroids*</td>
<td>Anacids</td>
<td>Steroid effect reduced</td>
<td>Inhibition of absorption</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Cyclophosphamide</td>
<td>Digoxin effect reduced</td>
<td>Inhibition of absorption</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>Anacids</td>
<td>Lincomycin effect reduced</td>
<td>Inhibition of absorption</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Rifampin</td>
<td>Steroid effect reduced</td>
<td>Stimulation of drug metabolism</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Barbbituates</td>
<td>Anticoagulant effect reduced</td>
<td>Stimulation of drug metabolism</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Cinetidine</td>
<td>Benzodiazepine effect increased</td>
<td>Pharmacodynamic effects of drugs on tissue responses</td>
</tr>
<tr>
<td>Carmustine*</td>
<td>Cytarabine*</td>
<td>Carmustine effect increased</td>
<td>Synergistic effects on DNA metabolism</td>
</tr>
<tr>
<td>Phenyoxytin</td>
<td>Isoniazid</td>
<td>Phenyoxytin toxicity increased</td>
<td>Inhibition of metabolism</td>
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<tr>
<td>Methotrexate*</td>
<td>Salicylates</td>
<td>Methotrexate toxicity increased</td>
<td>Inhibition of renal excretion</td>
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<tr>
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<td>Salicylates</td>
<td>Hypoglycemic effect increased</td>
<td>Inhibition of renal excretion</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Salicylates</td>
<td>Anticoagulant effect increased</td>
<td>Displacement of albumin binding</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Amphotericin B</td>
<td>Hypokalemia; digoxin toxicity</td>
<td>Pharmacodynamic effects of drugs on tissue responses</td>
</tr>
<tr>
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<td>Thiazide diuretics</td>
<td>Decreased lowering of blood</td>
<td>Pharmacodynamic effects of drugs on tissue responses</td>
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<td>Propranolol</td>
<td>Bradycardia and hypotension</td>
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</tr>
<tr>
<td>Mercaptopurine*</td>
<td>Allopurinol</td>
<td>Mercaptopurine effect increased</td>
<td>Pharmacodynamic effects of drugs on tissue responses</td>
</tr>
</tbody>
</table>

*Chemotherapeutic agent.

distribution, such as diazepam, chlorpromazine, and digoxin (61-66). For most poorly lipid-soluble drugs, including acetaminophen, phenylbutazone, warfarin, and sulfamethizole, no significant differences in distribution have been found. However, in the most extensive study reported, both the initial and steady-state volumes of distribution of diazepam increased linearly with age (67). On the other hand, a marked reduction in the apparent volume of distribution of propicillin, a poorly lipid-soluble drug, in elderly persons was attributed to lesser degree of tissue distribution (67).

Drug Metabolism and Hepatic Blood Flow: Drugs and other xenobiotics are acted upon by liver enzymes that convert them to water-soluble compounds more easily excreted by the kidney and gallbladder (68). These metabolites may be more or less active, but they are usually inactivated by the process. Several antitumor agents require activation, for example, conversion of cyclophosphamide to 4-hydroxycyclophosphamide.

The mass and blood flow of the liver both decline with age (up to 40%) (48, 57); however, the metabolic capacity of this organ is great, and changes in drug metabolism with age are not as easily predicted as are decrements in renal function. Activity of the hepatic metabolizing enzymes is less inducible in older persons who smoke cigarettes, as evidenced by studies of antipyrine and propranolol (48, 56, 68-70). Metabolism of quinidine, theophylline, nortriptyline, and some benzodiazepines is also reduced in the elderly (48, 57, 65, 71). Chemotherapeutic agents metabolized by the liver include fluorouracil, doxorubicin, dianorubicin, vinblastine, vincristine, and etoposide.

Hepatic blood flow falls with increasing age, resulting in increased potency and duration of action of certain drugs that are highly extracted by the liver after gastrointestinal absorption (72-76). These drugs are rapidly cleared on “first-pass” uptake and have low oral bioavailability (47, 48, 72). Some examples of this type of drug are lidocaine, propranolol, amitriptyline, chlorpromazine, verapamil, morphine, and isoproterenol.

Renal Excretion: With aging, substantial decreases occur in both glomerular filtration rate and renal blood flow (77, 78). These age-related changes in renal function are the most definitively proven pharmacokinetic deficiencies in the elderly (66, 71, 79, 80). Drugs that are primarily cleared by these routes must be used with caution. Commonly used anticancer drugs cleared by the kidney are cisplatin, methotrexate, and bleomycin.

End-Organ Sensitivity: Although the elderly are widely believed to be more sensitive to drugs, few data exist on this subject. Excess sedation due to diazepam, chlor-diazepoxide, and flurazepam has been reported in persons over 70 years of age. Some of these effects can be explained by pharmacokinetic changes that have been described earlier, but an enhanced central nervous system response seems to occur as well (65, 81, 82). No information is available on the effect of age on end-organ sensitivity to chemotherapeutic agents. As described below, the higher prevalence of bone marrow toxicity in persons after chemotherapy for certain neoplasms may indicate increased sensitivity of hematopoietic cells to chemotherapeutic damage.

Unequivocal changes in sensitivity to warfarin appear to occur with age. One epidemiologic study (83) initially suggested increased sensitivity to warfarin in the elderly, but a later report showed that the pharmacokinetics (clearance and protein binding) of warfarin are unchanged but that the elderly have a prolonged and increased anticoagulant response to a single dose of warfarin (84). The elderly were shown to have a greater degree of inhibition of synthesis of vitamin-K-dependent factors than did a younger group (83).
In contrast, older persons are less sensitive to the effects of infused isoproterenol and less responsive to the beta-blocking effects of propranolol (85). The currently available information does not allow any generalizations about drug sensitivity in the elderly.

**DRUG INTERACTIONS**

Drug-drug interactions may occur in elderly patients with cancer, resulting in either augmentation or decrease of pharmacologic activity. These interactions may occur in a setting of multi-drug therapy used for the many chronic disease states found in elderly persons. Drug interactions can arise from drug effects on the absorption, distribution, biotransformation, or excretion of other drugs, but interactions can also be used as beneficial contributions to therapy. However, undesirable or unsuspected interactions that are deleterious to the patient must be anticipated in elderly patients receiving a large number of drugs and having impaired homeostatic mechanisms.

Drug interactions may be of the pharmacodynamic or pharmacokinetic type. Pharmacokinetic effects are those that potentiate or diminish the activity of other drugs and that are mediated by drug actions on the absorption, distribution, excretion, metabolism, or protein binding of other drugs. Both types are more frequent and more severe in the elderly due to a lesser capacity for compensatory responses (Table 1) (47-49, 80, 86).

The avoidance of adverse drug reactions in the elderly is a worthwhile goal. Careful attention to the special jeopardy of the elderly patient can minimize these reactions. Adverse reactions can be avoided by minimizing drug use. Drugs should be used for major problems in which the gain-risk balance is clear, and not for minor discomforts that can be treated by other means. Both prescription and nonprescription drug use should be monitored. In addition, elderly patients should be treated with lesser doses of drugs, because steady-state levels of drugs are achieved at lower doses in these patients.

The many alterations of drug action and changing physiology that occur with aging complicate the prediction of individual patient responses to drugs. An appreciation of these complexities can improve therapeutic and diagnostic skills and judgment in managing the older patient with cancer. Further studies of pharmacodynamics and pharmacokinetics of anticancer drugs in the elderly are clearly needed.

**The Effect of Age on Prognosis**

Dr. Barbara A. Nelan (University of Arkansas for Medical Sciences): Cancer is one of the most serious illnesses affecting the elderly. Data show that the older a person becomes, the greater the probability of developing cancer (87). It has been noted that 50% of all cancers occur in persons over the age of 65, and close to 60% of all cancer deaths occur in persons over 65 years of age. Lung cancer is the major cause of cancer deaths in men aged 65 to 80. After age 80, prostate cancer death rates exceed those of lung cancer. Colorectal cancer is the third main cause of cancer deaths in older men and the leading cause in older women. Other predominant causes of cancer deaths in older women are breast, uterine, ovarian, and pancreatic cancer.

The medical profession will continue to be faced with a growing number of aging patients with cancer. Today, 11% of the population, or 23 million Americans, are 65 years of age or older. In 50 years, this percentage is expected to rise to 18%, or 55 million. Moreover, significant age shifts are occurring within the older segment of our population, so that a greater number of persons will be 75 years and older.

**SURVIVAL**

A key question concerns the effect of age on prognosis of the patient with cancer. There are conflicting reports on this question. With respect to breast cancer, some data suggest that age may have a favorable effect because of a higher incidence of estrogen-receptor-positive tumors with age (88). Although this conclusion was supported by data from a study done in British Columbia, it was not supported by those from Japan (88). For multiple myeloma, survival rates in Austria were found to be similar for young and old patients, when referring strictly to cause of death due to multiple myeloma (89). Most studies of prostatic cancer indicate that age is not a determinant of prognosis (90, 91), but for certain other neoplasms, the elderly have a worse prognosis than younger patients. For example, response rate is decreased in elderly patients with lymphoma (92, 93) and acute lymphoblastic leukemia (94, 95). Similarly, older patients with thyroid cancer and melanoma have decreased survival (96).

Several factors might influence survival in elderly patients with cancer. There may be a difference in biology of certain tumors with aging, and intercurrent medical illnesses may compromise the elderly patient’s ability to withstand the effects of cancer or treatment interventions. When the patient seeks medical attention can also affect prognosis, because the stage of cancer at diagnosis is known to be an important prognostic factor. Therefore, if the elderly delay seeking medical care, they may present with a more advanced stage. Available data suggest that generally stage at presentation is as likely to be localized in the elderly as in younger patients (97), but two exceptions have been recognized: In carcinomas of the cervix and colon, the elderly are more likely to present with more advanced disease. With cervical carcinoma, this latter presentation may be due to decreased use of Papanicolaou smears for screening in older women (97). Efforts should be made to develop methods to screen for cervical and colorectal carcinoma in the elderly.

**TOXICITY TO CHEMOTHERAPY**

Relatively little attention has been given to study of the optimal management of elderly patients with cancer. With respect to chemotherapy, it is not clear whether elderly patients differ from younger patients in responsiveness or tolerance. Various factors might be anticipated to decrease responsiveness to cancer chemotherapy. Noncompliance can be more of a problem in the elderly, underdosing with chemotherapeutic drugs may be more
prevalent, and the biology of tumors may be different. Decreased tolerance of antineoplastic therapy might also be expected. Both renal and pulmonary function decrease with age, bone marrow cellularity decreases, and pharmacokinetics are altered.

Toxicity to chemotherapy was retrospectively studied in elderly patients treated on six Eastern Cooperative Oncology Group protocols for lung, breast, or colorectal carcinoma (98). In the lung cancer and colorectal carcinoma protocols, “elderly” was defined as greater than 70 years of age, but in the two breast cancer protocols, only patients aged 60 to 65 years were in the elderly group (patients over 65 were excluded by eligibility criteria). No increase in frequency or severity of toxicity in elderly patients was found. The younger and older age groups were similar in important clinical variables, such as performance status, prior radiotherapy, and presence of liver metastases. However, the patient population was selected in terms of protocol eligibility criteria that required normal renal, hepatic, and cardiovascular function and excluded patients with significant concomitant illnesses. These criteria exclude many elderly patients and therefore this sample was not representative of the general elderly population.

Although a significant difference in toxicity was not found in elderly patients, hematologic toxicity was 36.7% in older patients with breast cancer compared with 28.3% in younger patients. This difference could conceivably have been greater if patients over age 65 had been included in these studies. Studies including patients over 65 are therefore needed to address this question.

Responsiveness of elderly patients to chemotherapy was not shown by the study of the Eastern Cooperative Oncology Group protocols (98), because three of the six protocols involved tumors that show little response to chemotherapy. In contrast, striking evidence has been seen for the effect of age on response and survival in patients with Hodgkin’s disease. Patients over the age of 40 with advanced Hodgkin’s disease have a decreased survival compared with younger patients, when treated with MOPP (mechlorethamine, vincristine, procarbazine, prednisone) combination chemotherapy (92). Similar findings have been reported for patients over age 60 (93). In two clinical trials by the Cancer and Leukemia Study Group B (93), 385 previously untreated patients with advanced Hodgkin’s disease were treated with several multi-drug regimens. Dosages were not decreased for age, but rather standard dosage adjustments were made for myelosuppression. In 205 patients under age 40, the complete remission rate was 70%. In 107 patients between ages 40 and 59, 66% had a complete remission, and in 73 patients over 60, only 40% responded.

Little information is available on the responsiveness to chemotherapy of other types of cancer as a function of age. Patients over age 70 with small cell carcinoma of the lung responded to combination chemotherapy even in the presence of intercurrent medical illnesses (99), but this study was a retrospective analysis of elderly patients treated with different combinations of chemotherapy and did not include a similar group of younger patients. In breast cancer, response to specific chemotherapeutic agents may vary with age. Older women respond less well to melphalan, cyclophosphamide, methotrexate, and fluorouracil than do young women (100). In contrast, two studies by the Southwest Oncology Group (101, 102) indicate that older patients respond better to doxorubicin, either as a single agent or in combination chemotherapy, than do younger patients. The responsiveness of elderly patients with acute nonlymphocytic leukemia to chemotherapy is controversial. Some studies have reported similar complete remission rates and median remission durations in older and younger patients (103-105), whereas others have found decreased remission rates in older patients (94, 95).

SUMMARY

A problem common to all these studies is the selection bias. Many elderly patients are excluded because of arbitrary age limitations or because they are considered too old or too frail for treatment. However, entry of eligible patients of all ages should be encouraged for development of optimal cancer treatment regimens for the elderly (106).

Many elderly patients appear older or younger than their actual age. It may be that tolerance and response to cancer chemotherapy vary more with physiologic age than chronologic age in elderly patients. The assessment of physiologic age has been a focus of attention for many years; however, variables that most closely estimate physiologic age remain controversial, and further study is needed in this area (107).

In summary, the studies discussed above leave many questions unanswered regarding cancer chemotherapy in the elderly. To address these questions, prospective clinical trials should be designed to include solid tumors sensitive to chemotherapy, so that there is a reasonable probability of observing age-related effects. Entry into these studies of all eligible patients from the entire age spectrum should be encouraged.

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