In 1985, Kaysen and Meyers (1) stated that “the mechanisms and the full biochemical and physiologic consequences of renal senescence remain to be fully elucidated.” The present discussion highlights recent advances in cell biology that have implications for renal senescence. The study of cellular senescence is an emerging field of research with implications for aging, cancer, and chronic disease. It is the study of the limitations on the survival and function of somatic cells. Cells, tissues, organs, and organisms deteriorate over time and deteriorate more rapidly with stress. This deterioration may contribute to normal aging, chronic diseases, the performance of transplanted cells and tissues, repair of injury, and cancer. The cellular and molecular events in this deterioration may present opportunities for understanding and modifying these processes.

This article highlights recent developments and their potential relevance in nephrology. This discussion reflects in part a symposium held at the American Society of Nephrology meeting in November 1999. The issue of senescence in renal transplants has been covered elsewhere (2). Given that detailed reviews of renal senescence are available (3–7), we concentrate on basic developments in studies of somatic cell senescence in vitro and then examine their in vivo significance.

Definitions

We use the term age to mean the time elapsed since birth. The term renal senescence reflects the structural and functional phenotype associated with aged kidneys. Cellular senescence and replicative senescence refer to an in vitro phenotype of cultured somatic cells that have reached their finite limit for replication, a state that may or may not exist for similar cells in vivo. In vitro studies of aged cells, i.e., derived from an old donor, have to be distinguished from senescent cells, which have developed the in vitro senescence phenotype.

There is a difference between replicative senescence and terminal differentiation. Replicative senescence is arrived at by cell division. Terminal differentiation is a programmed phenotype, which responds to environmental clues. Whereas terminal differentiation may be a beneficial phenotype, the senescence phenotype in contrast may be a mixed blessing or even detrimental.

Molecular Events in Replicative Senescence

In Vitro

The molecular basis of the in vitro cellular senescence phenotype probably differs between cell types and between species, e.g., humans versus mice (8). Hayflick and Moorhead (9) recognized that cultured human somatic cells in vitro displayed a limitation in their number of cycles. This number of cycles was called their Hayflick number. It was lower in cells from older donors and was unaffected by pausing. Thus, human somatic cells have a mechanism for counting the number of times that they have divided, a “mitotic clock.” They stop irreversibly when this cycle number is reached, and they manifest the state of replicative senescence.

Telomere Shortening

In human cells, shortening of telomeres is critical to replicative senescence. Telomeres are DNA repeats (TTAGGG) at the ends of chromosomes that shorten in dividing normal cells. Telomeres prevent chromosome ends from being confused with DNA breaks and probably have other functions in tethering and sorting chromosomes. The ends of telomeres must be replicated by the enzyme telomerase, a ribonucleoprotein expressed in germline and in immortal cell populations that maintains telomere length constant. In 1973, Olovnikov (10) proposed the telomere theory: namely, that somatic cells were limited because they cannot fully replicate their telomeres (Figure 1). The Hayflick limit was validated by the demonstration that human fibroblasts in culture lack telomerase, shorten their telomeres with each cycle, and develop replicative senescence when telomere length becomes critical. The critical experiment was the demonstration that transfection of telomerase into cultured human cells extends their life span and replication remarkably (11), thus bypassing the Hayflick limit.

Telomeric DNA diminishes by approximately 100 bp in dividing normal somatic cells at each cell doubling. The loss of telomeres can trigger the response to DNA breaks, which results in an organized cellular state, the senescence phenotype (M1 in Figure 1). Cells that are driven to continue dividing by abnormal stimuli develop massive genomic instability or crisis (M2). Germline cells and immortal cell populations like most cancer cell lines possess mechanisms, which are either telomerase activation or an alternative mechanism, to preserve their telomere length indefinitely despite cell division, thus protecting their genome.

The state of replicative senescence in human skin fibroblasts...
includes cessation in replication, altered patterns of gene expression, and resistance to apoptosis. Senescent fibroblasts remain viable for many months, with ongoing RNA and protein synthesis. However, senescent cells cannot be stimulated to enter the S phase of the cell cycle by any combination of growth factors or physiologic mitogens. Senescent human fibroblasts show an enlarged and flat morphology and accumulate lipofuscin pigment and senescence-associated β-galactosidase (SA-β-GAL) activity.

The important alterations in gene expression are probably in the genes that control the cell cycle (see below). Other changes in gene expression include increased expression of the genes encoding Alzheimer’s β-amyloid precursor protein, certain metalloproteinases, such as MMP-1, and genes whose products contribute to the extracellular matrix, interferon responses, and inflammation. If tissue senescence in vivo is associated with similar changes, it is conceivable that the products of senescent cells could influence not only the cell loss but also the matrix changes and focal inflammation in aged tissues.

The key feature of the senescence phenotype in vitro is irreversible cessation of cell cycling. In human cells, telomere shortening is the crucial event that triggers cell cycle arrest. Telomere length for human cells has been compared to the gasoline supply of a car: It is definitely limiting but is certainly not the only mechanism for stopping. Other stresses may also induce some aspects of senescence in human cells and even more so in mouse cells as discussed below. Nevertheless, in human somatic cells in vitro, critical telomere shortening is the trigger for senescence and is responsible for the Hayflick limit.

**Mechanism of Cell Cycle Arrest in Senescent Cells**

Senescence-associated growth arrest is mediated by expression of cell cycle inhibitory genes and by downregulation of positive acting cell cycle regulators. At the center of the machinery for cell cycling are the cyclin dependent kinases (CDK), which receive and integrate regulatory signals. CDK are activated in a two-step manner. Step 1 is engagement of the regulators, the cyclins, which cause conformational changes that partially activate the kinase activity. Step 2 is the phosphorylation of a key threonine, leading to full activation. CDK inhibitors (CKI) prevent or reverse activation of CDK (Figure 2).

The protector of the genome, p53, responds to telomere shortening and controls the G1 arrest checkpoint. In response to DNA injury, p53 levels increase by a posttranscriptional mechanism. This results in the transcriptional activation of p21WAF1, a Cip1 CKI, which can mediate G1 arrest (12). Inactivation of p53 is the most common genetic event in human cancer, and p53 deficiency prevents telomere loss from inducing cell cycle arrest (13).

The retinoblastoma-susceptibility tumor suppressor protein (Rb) is a major regulator of cell cycling and the critical substrate of the CDK4 and CDK6. Rb negatively controls passage from G1 into S phase by sequestering transcription factors, such as E2F, that are required for the G1/S transition. The ability of Rb to bind transcription factors is abolished by phosphorylation (14). CDK 4 and 6 phosphorylate Rb and thus activate E2F and the cell cycle. Extension of life span beyond the Hayflick limit can be achieved by viral oncoprotein-in-

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**Figure 1. Telomere Hypothesis:** Telomerase is active in germline cells, maintaining long stable telomeres, but is repressed in most normal somatic cells, resulting in telomere loss in dividing cells. At M1, the Hayflick limit, there is a presumed critical telomere loss in one or perhaps a few chromosomes signaling irreversible cell cycle arrest. This corresponds to the phenotype of replicative senescence. Transformation events may allow somatic cells to bypass M1 without activating telomerase. When chromosomes become critically short on a large number of telomeres, cells are genomically unstable and enter crisis (M2). Rare clones that activate telomerase escape M2, stabilize their genome, and acquire indefinite growth capacity.
duced inactivation of p53 and Rb, indicating that these tumor suppressor pathways are critical mediators of the telomere shortening checkpoint response.

P16 INK4a (INK4 for “inhibitor of CDK4”) causes G1 cell cycle arrest by specific inhibition of CDK4 and CDK6, preventing Rb hyperphosphorylation and S-phase entry (15). P16INK4a is strongly associated with senescence: As mouse or human cells in vitro approach senescence, they express P16 INK4a. The gene for p16 INK4a is unusual in that it contains an alternative reading frame that allows it to encode both p16INK4a and another factor, p19 ARF 16. Telomerase activity alone is insufficient to immortalize some human epithelial cells; inactivation of Rb and p16INK4a is the second crucial step (16,17). Some oncogenes induce senescence in nontransformed human cells via p16INK4a. For example, ras-induced senescence depends on the expression of p16INK4a and p53, and raf can induce senescence in cells that lack p53 function, probably via p16INK4a alone. P53 induction by ras depends on p19ARF.

Senescence May Occur by Fundamentally Different Mechanisms in Humans Compared with Mice

Both human skin fibroblasts and mouse embryonic fibroblasts can manifest a senescence phenotype after cycling in vitro. However, the senescence state is mediated by telomere shortening in human cells but not in mouse cells (8,18). The senescent state in mouse cells resembles that in human cells at the Hayflick limit, including expression of p16INK4a, but growth arrest in mouse embryo fibroblasts occurs after fewer cycles and without appreciable telomere attrition, probably because accumulated damage from culture conditions (“culture shock”) triggers the p53 response. Thus, “senescence of cultured cells results from two sources of signals, either of which can induce the expression of a common set of inhibitors of the cell division cycle” (18). One set of triggers is extrinsic and stems from stresses from the environment. Culture stresses such as oxidant injury may simulate the stresses of life in vivo over a longer time frame. The second set of triggers is intrinsic and depends on the machinery that monitors the integrity of telomeres (a “mitotic clock”). Humans have a mitotic clock, and mice do not. Differences in the proliferative capacity of cultured mouse and human cells reflect the extent to which they respond to these signaling pathways. Rat cells may be like mouse cells, because they also have very long telomeres.

Molecular Changes in Cultured Aged Cells

Recent studies demonstrated that fibroblast lines from older humans (aged fibroblasts) displayed mitotic misregulation (19). The investigators took dermal fibroblast cell lines from young, middle-age, and old individuals and from people with Hutchinson-Gilford progeria. Using DNA microarrays of 6000 genes, they identified 61 that were upregulated or downregulated twofold in old and middle-aged versus young. Surprisingly, many regulate G2/M stage of cell cycle, suggesting that aging alters expression of genes involved in cell division. The

Figure 2. The p53-retinoblastoma (Rb) pathways: p53 is upregulated by DNA damage and/or telomere shortening. p53 is targeted by MDM2 for ubiquination and degradation. This can be prevented by p19ARF, thereby stabilizing p53. The stabilization of p53 allows induction of genes that are important for apoptosis (Bax) and growth arrest (p21WAF1/CIP1). P16INK4a interferes with D-type cyclin binding to the kinases CDK4/6 to decrease their activity and thus progression through G1/S checkpoint. Hypophosphorylated Rb represses E2F-dependent genes and blocks G1/S progression, whereas E2F alone transactivates many genes that are important for mitosis.
authors suggested that aging “may occur gradually and in mosaic patterns” (19). Such experiments have limitations in sampling, and by definition select only replicating cells, thus limiting the conclusions (20).

**Molecular Basis of the Senescence Phenotype In Vivo**

The theories of aging emphasize cumulative damage in postmitotic cells and exhaustion of the finite capacity for replication in cells with mitotic potential. Reactive oxygen species (ROS) that are generated by cellular respiration cause cumulative damage to lipids, proteins, and DNA (21). Genomic instability can result in changes in mitochondrial DNA and in loss of telomeric DNA. Some have postulated that the aging phenotype reflects an underlying genetic program-like development, but this seems less likely than the role of cumulative damage and finite repair. Studies of the genetics of aging suggest that most of aging is driven by environmental factors (22). Because aging is accompanied by a loss of cells, dysregulation of programmed cell death could play a role in aging. Alternatively, net loss of cells could reflect a finite ability to replace cells rather than excess loss. Moreover, in some cell types, senescence in vitro causes loss of their ability to undergo apoptosis as well as other abnormal features, suggesting that accumulation of senescent cells could contribute to aging and age-related diseases. Interdependence of organs through humoral factors could contribute to aging, e.g., through loss of hormone functions.

Several biomarkers of aging can be found in vivo. These include the accumulation of lipofuscin, advanced glycation end products (AGE), and SA-β-GAL. Lipofuscin, a yellow-brown pigment, probably reflects accumulation of damaged organelles and also occurs in senescent cells in vitro. Some of these features also occur in premature aging phenotypes, called segmental progerias. The molecular basis of the progerias is becoming more evident, but it is doubtful whether the mechanisms that are mutated in progerias are critical in normal aging.

The hypotheses proposed for cellular and organism senescence include either damage to intra- or extracellular molecules or programmed or epigenetic changes in gene expression. The tissue function and phenotype will reflect accumulation of damaged and/or senescent cells; loss of cells; loss of ability to respond by replication as a result of senescence in mitotic or stem cells; changes in matrix; and disorders of blood supply, inflammation, immunity, and endocrine control. Postmitotic (permanently nondividing) and mitotic (proliferation-competent) cells age by different mechanisms. Postmitotic cells that have ceased to replicate cannot undergo replicative senescence. Aging could be caused by changes in gene expression in mitotic cells, whereas damage might play a more important role in postmitotic cells. Cells in the kidney replicate at a slow rate. Studies of the expression of cycle-associated markers suggest that the tubular epithelial cells had a higher proliferation index than the glomerular cells, with the highest proliferation rate being in capillary endothelial cells (23). Nevertheless, old kidneys retain considerable replicative potential and can recover from acute injury, such as acute tubular necrosis.

Because “most if not all epithelia contain stem cells” (24), stem cells may exist in kidney epithelium. The key senescence changes that limit replication may occur in the stem cells. Then the somatic cells, which would undergo turnover, may persist and manifest abnormalities, which accumulate because these cells cannot be replaced. The tissue phenotype would include the lack of replacement of damaged cells as a result of senescence in the stem cells or at least in proliferation-competent cells, and the changes in matrix and blood vessels.

**Evidence Concerning Telomere Shortening In Vivo**

A recent study (25) found differences in the shortest telomeres and in the variation of telomere length between the fetal tissue and tissue derived from a 72-yr-old man. Telomere length was shorter and more variable for all old tissues studied, with the greatest differences observed in blood cells, e.g., average telomere length was 12.2 kbp in the fetus compared with 7.2 kbp in the 72-yr-old man.

We have shown that there is telomere shortening in kidneys with age and that the rate of loss is greater in cortex than in medulla (26). These results are of interest because aging results in a relatively greater loss of mass in cortex than in medulla. The significance of telomere loss is unclear. Although it is almost certainly important in cancer, its relevance to the renal senescence phenotype is unknown. However, given the heterogeneity in renal cell populations and the loss of nuclei with age, it is possible that telomere loss is involved in aspects of renal senescence.

**Evidence for the Importance of Cell Cycle Regulators In Vivo**

Studies on cell cycle regulatory proteins in renal glomerular disease suggest a role not only in proliferation but also in hypertrophy and differentiation of renal cells. P21WAF1/CIP1 induction could be shown after experimental glomerulonephritis and after DNA damage in cisplatin-induced acute renal injury, transient ischemic injury, or ureteral obstruction (27,28). P21WAF1/CIP1 protects by preventing DNA-damaged cells to enter the cell cycle. However, a more recent study found that in p21WAF1/CIP1 knockout mouse develops normally (32). P16 INK4a knockout mouse develops normally (32). P16 INK4a levels were not inducible by renal injury in mice. Compared
with other members of the INK4 family, p16<sup>INK4a</sup> mRNA expression is highly restricted. Our data suggest that p16<sup>INK4a</sup> is not normally expressed in young kidney or inducible by injury but is induced in some individuals with aging and disease, compatible with a role in senescence.

**Role of Oxidant Injury in the Senescence Phenotype In Vivo**

The oxidative stress hypothesis proposes that changes associated with aging are a consequence of random oxidative damage to biomolecules: nucleic acids, membranes, and proteins. *Caenorhabditis elegans* and *Drosophila* transgenic for genes encoding antioxidants have an extended life span (33,34). Oxidative damage to the mitochondria increased the rate of deleterious ROS and modifications of nucleosides, mutations, and deletions. Thus, oxidant injury may promote oxidant injury: Damage to mitochondrial DNA may lead to a derangement of mitochondrial respiratory activity leading to ROS. The majority of comparative studies have detected the highest mitochondrial DNA deletion levels in nonreplicating, high energy-demanding tissues, such as skeletal and cardiac muscle and brain (35). The number of cells affected is usually much lower (<1% of total mitochondrial DNA) than in studies of hereditary diseases in which more than 50 to 80% of the genome is mutated (36). In addition, the extent to which mitochondrial DNA deletions contribute to age-associated declines in the activities of the electron transport system complexes I to IV remains unclear.

**Accumulation of Oxidative End Products and Advanced Glycation End Products In Vivo**

Lipofuscin accumulates in postmitotic cells, located in small granules in secondary lysosomes, and consists mostly of cross-linked lipid and protein residues formed during lipid peroxidation (37). Lipofuscin accumulates in cultured rat myocytes, and accumulation is enhanced under increasing oxygen pressure (38). Antioxidants inhibit lipofuscin formation (39). Although oxidative damage to organelles seems responsible for depositing lipofuscin in lysosomes of senescent mammals, it is not clear whether it is a biomarker or a mechanism of aging. Two explanations for the increase of lipofuscin with age have been suggested. The first theory is based on the fact that lipofuscin is not totally eliminated and accumulates in postmitotic cells over time. The second suggests that lipofuscin accumulation reflects a derangement of autophagocytosis associated with decline in intralysosomal degradation, as more lysosomal volume is occupied by indigestible material (40).

Some extracellular proteins undergo oxidative modification and have a long half-life because they are rarely recycled. The modifications are initiated by the reaction of reducing sugars with free amino groups (glycation). Further nonoxidative oxidative processes result in stable, cross-linked AGE. The abundance of AGE is an excellent biomarker of age. Pentosidine, one such glycoxidation product, accumulates as a function of age and is much higher in long-lived than in short-lived species (41). Humans that have Werner’s syndrome, a disease characterized by premature senescence, have more extensive protein oxidation. Fibroblasts from Werner’s patients of all ages have levels of protein carbonyls equivalent to that in 80-yr-old control individuals (42).

Patients who have chronic renal failure or diabetes or who are of advanced age show a progressive accumulation of AGE. The development of AGE is proportional to long-term blood glucose levels in diabetic patients. However, glomerular changes occur with the exposure to AGE even in the absence of coexisting hyperglycemia. The aging changes in the kidney reflect accumulation of AGE in renal tissues, resulting in altered release of growth factors and cytokines and accumulation of oxidants and lipids (43). Although the accumulation of AGE may contribute to deterioration in renal function with age, it is not a sufficient explanation for the reduced capacity to respond to stress in the elderly. Moreover, there is little in common between the renal phenotypes of diabetes and aging.

**Do Senescent Cells Exist In Vivo?**

Attempts have been made to show that the senescent cells occur in vivo. β-GAL activity in senescent cells has been shown by enzyme histochemical staining at a pH optimum of 6.0. SA-β-GAL activity increases in human skin with replicative and physiologic age, reflecting an accumulation of senescent fibroblasts and keratinocytes in vivo (44). SA-β-GAL activity has been widely used as an in vivo senescence marker. SA-β-GAL activity was shown in retinal pigment epithelium and hepatocytes in vivo. A recent study showed specific evidence for senescent cells in rat kidney (A. Yussim, personal communication, June 2000).

**Relationship of Cellular Senescence to Tissue Senescence and Cancer**

In aging, some cells persist in a damaged form, some drop out completely, and others may remain as senescent cells. The potential importance of the persistence of senescent cells in vivo might be that they compromise the function and integrity of the tissue. Ordinarily, the organized tissue is the unit of function, not the cell. By disrupting the tissue organization, replicative senescence might disrupt function. Senescent cells could contribute to the rise in cancer by altering the tissue microenvironment or by virtue of loss of genomic integrity in these cells. In the case of dermal fibroblasts, there is a switch from a matrix-producing to a matrix-degrading phenotype (45). In addition, alteration of the balance between growth and differentiation increases the potential for neoplastic growth of cells that have acquired oncogenic mutations. The cellular senescence mechanism may be a fundamental protection against cancer. Conversely, the genomic instability of senescent cells with telomere shortening may contribute to some cancers (46).

**Does Cellular Senescence Contribute to the Phenotype of Renal Senescence?**

The aging human kidney has four features that require explanation: the phenotype of “normal” renal senescence, the high incidence of end-stage renal disease (ESRD), a high
frequency of cancer, and poor performance after renal transplantation, particularly cadaveric transplantation.

It is important to specify species when discussing kidney aging. The aging changes of the rat and other laboratory animals (6) differ from those of long-lived species, including humans. For example, the characteristic arterial changes of senescence do not develop in species that live fewer than 12 yr (47). A rigorous distinction between observations in humans and experimental animals is particularly important given the recent evidence that the cellular senescence mechanisms of mice and humans are fundamentally different.

The phenotype of renal senescence in humans is associated with loss of mass, particularly in the cortex, and cellular loss (48), an increase in heterogeneity, and the appearance of focal abnormalities. Cellular loss leads to an underestimation of the potential role of senescence mechanisms because the affected cells disappear. The principal histologic features of renal senescence are deterioration of the arteries (hyalinosis and fibrous intimal thickening of arteries and hyalinosis of arterioles), global sclerosis of glomeruli (not focal sclerosis) with reduplication of Bowman’s capsule, focal tubular atrophy with lipofuscin pigment, interstitial fibrosis, and patchy inflammation (Figure 3). The functional phenotype includes a rise in renal vascular resistance, a decline in GFR, and a rise in filtration fraction. It is not clear how these changes are related, i.e., whether glomerular sclerosis, tubular atrophy, and interstitial fibrosis are primary or secondary events. Features not found in normal human renal senescence include heavy proteinuria, hematuria, development of ESRD, focal sclerosis, and infarction as a result of arterial occlusion.

The effect of aging of kidney in an unselected human population can be described by a variety of equations, such as the Cockcroft-Gault equation (49) and the MDRD equation (50). These equations describe an unselected functional phenotype of renal senescence, which reflects the normal changes with loss of mass and function and those changes driven by age-related diseases, such as hypertension and heart failure. The selected phenotype is described by the Baltimore Longitudinal Study on Aging, which excluded all renal diseases, hypertension, and heart failure and demonstrated a mean loss of GFR of 0.75 ml/min per yr. It is important to note that a third of 80-yr-olds had normal renal function (51).

The senescence phenotype in an unselected population reflects the effect of aging and age-related diseases. Renal aging is regulated by genetic factors, intrinsic stresses, and extrinsic environmental factors. Hypertension and heart failure accelerate renal senescence (52); a general model of renal senescence must include the potential for acceleration by abnormal stresses. Thus, at some point a senescent nephron is irreversibly shut down, but what abnormality triggers this event is not clear: vascular, glomerular, tubular, or other changes. It seems possible that a physiologic shutdown mechanism is triggered, directly or indirectly, by molecular changes of senescence in the limiting cell type, as sensed by a regulatory mechanism in the nephron.

The incidence of ESRD is 100-fold higher in those older than age 65 compared with people younger than 20 (53). Nevertheless, the incidence of ESRD remains uncommon in the elderly population as a whole, approximately 1 per 1000 per year, and is not due to normal aging. This propensity can be attributed in part to the high incidence of diseases that cause ESRD in the elderly and the time dependency of their effects. It is also possible that the processes of renal senescence include a decreased ability of the aged nephrons to cope with disease stress, i.e., an interaction between disease stress and intrinsic senescence processes.

The poor performance of transplanted kidneys from older donors, particularly cadaveric donors, may be a special case of this. Terasaki et al. (54) emphasized that “the greatest adverse impact factor in cadaver kidney transplants today is donor age.” The older kidney displays increased probability of delayed graft function, acute rejection, chronic allograft nephropathy (also known as “chronic rejection”), strikingly impaired GFR, and an increased probability of early and late failure. Some of these features are attributable to the features of the older cadaveric donors, which include an increased frequency of intracerebral hemorrhage and hypertension. There is much less effect of donor age in live donor transplantation, which may reflect selection plus the lack of the special stresses of cadaveric donation. We believe that cellular senescence may contribute to the diminished ability of aged nephrons to cope with the stresses of brain death, preservation, and inflammation after cadaveric transplantation. As a result, the limiting cells in many aged nephrons reach senescence limits and the nephron irreversibly shuts down. Moreover, the transplanted kidney must continue to age, perhaps at an accelerated rate as a result of stresses such as hypertension.

Perspective

In summary, the phenotype of renal senescence is attributable to both a decline in the number of functioning nephrons and inherent limitations of age on the residual nephrons as revealed by a disease stress. This does not violate the intact nephron principle; it states only that an aged nephron has an inherent limitation because of the finite characteristics of its limiting cells. Many clinical nephrology problems in the elderly (and perhaps in diseases with high proliferative requirements) could involve an interaction between cellular senescence and disease stresses. This may contribute to the normal renal senescence phenotype, the acceleration of this phenotype by hypertension and heart failure, the high frequency of ESRD in the elderly, and the massive nephron dropout after the stresses of cadaveric donation. The relationship between cellular senescence and cancer is already well established, e.g., by virtue of the very high frequency of abnormalities of p53, p16, and Rb and the universal reexpression of telomere replication mechanisms in cancer.

Are cellular senescence mechanisms good or bad? Cellular senescence is a protection against cancer, but it can also lead to genomic instability. Thus, some cancers may arise in senescent cells. Perhaps the nephron shutdown mechanism in the normal
elderly is fundamentally good, abrogating the possibility of serious malfunction by nephrons whose cells have passed certain limits. However, senescent cells may accumulate and potentially disrupt the functioning parenchyma or extracellular matrix and evoke inflammation.

One of the appeals of studying mechanisms of cellular senescence in nephrology is the potential for predicting or intervening. Identifying those who are at risk of ESRD could be followed by strategies to reduce the stresses. It is possible that bypassing cell senescence mechanisms with drugs or gene therapy could extend the life of old kidneys faced with abnormal stresses such as cadaveric donation or renal disease. This may have to be balanced against the potential to increase renal cancer. The role of cell cycle regulatory proteins and senescence mechanisms in chronic stresses such as glomerular diseases, proteinuria, hypertension, and polycystic disease should be explored, even independent of the problem of aging.

Figure 3. Histology of renal senescence: (A) Arteriohyalinosis, (B) fibrous intimal thickening, (C) glomerulosclerosis, (D) tubular atrophy, (E) lipofuscin pigment, (F) interstitial fibrosis. (All pictures are a courtesy of Dr. Marjan Afrouzian.)


