I use the term **age-related diseases**, rather than **age-induced diseases** for this lecture. That is because old age brings with it a set of predispositions for specific diseases. But this is also true for neonates, adolescents, the middle aged, and during the period of infant bearing. You often hear the phrase “he died of old age” But almost always there is a specific cause of death for old animals and people, assuming it is looked for. In one survey of the extreme aged, death in these people was due mainly to cardiovascular and respiratory disease. Surprisingly, many died acutely. This has been my experience with old dogs and cats – one generally finds cause of death, or a basis for euthanasia. Rarely if ever is senescence alone a primary cause of death. Interestingly, death from cancer is less common among the very aged than in the merely old. You find age-related degenerations in all organs. Some contribute to illness or death, but most are subclinical. Human nonagenarian and centenarians, including those perceived to be healthy immediately prior to death, succumb to diseases in 100% of the cases examined.

**Age-related diseases in people and animals**

The principal age-related diseases in people above 65 years are in descending order: heart disease: 38.5%; cancer: 19.6%; stroke: 10.4%; chronic respiratory disease: 7.9%; Alzheimer's disease 0.6%. There are no comparable numbers for animals, but the range of age-related diseases in animals is species-specific. Generally, in old dogs cancer is responsible for twice as many deaths as heart disease. It is rare indeed to get dogs that die of myocardial infarction or atherosclerosis. Other common causes of death or euthanasia in dogs are musculoskeletal problems, most commonly joint disease, and behavioral problems related to aging in the central nervous system. One intriguing features of dogs is the difference in breed-specific mortality. Mongrels lived longer on average than purebred dogs, although some purebred dogs are especially long lived, such as the Jack Russell, miniature poodle and whippet. Small dogs generally live longer than medium or large breed dogs.

**Biological theories of aging**

There are multiple theories about why aging occurs, and little agreement exists. Below are several you might consider in the context of this course.

a) **Senescence genes**: There is some evidence of senescence genes. These that cause ageing are not random mutations; rather, they form tight-knit families that have been around as long as eukaryotic life has been in existence. **Cellular senescence** is the phenomenon by which diploid cells lose the ability to divide, normally after about 50 cell divisions *in vitro*. Some cells become senescent after fewer replications cycles due to DNA double strand breaks. This phenomenon is also known as replicative senescence or the Hayflick limit in honor of Leonard Hayflick who recognized the phenomenon in the 1960s. In response to DNA damage (including shortened telomeres; below), cells either age or self-destruct (apoptosis) if the damage cannot be repaired.

b) **Mutation-accumulation theory**: This was the first modern theory of ageing in mammals. Nature is unforgiving - most free-ranging animals die before old age is attained. Given this, there little reason the body should remain fit for the long haul. There is little selection pressure for traits that would maintain viability past the time when most animals would be dead anyway, eliminated by predators, disease or
accidents. The proposed mechanism involves random detrimental mutations that show their effect late in life. Unlike most detrimental mutations, these would not be efficiently weeded out by natural selection. Hence they 'accumulate' and, perhaps, cause the decline and damage we associate with ageing.

c) Antagonistic pleiotropy theory: This is a variation on the mutation-accumulation idea. Basically it suggests that some critical genes have two (or more) effects. One is beneficial and occurs early in life. Another is detrimental, exacting its cost later on. What weakens the theory is that there are some aging genes for which no benefit of any kind has been identified.

d) Disposable soma theory: This came from the analogy with disposable products: why spend money to make something durable when it is used for a limited amount of time? The theory presumes the body must budget its energy. Some is used energy for metabolism, some for reproduction, and some for repair and maintenance. With a finite supply of food, the body must compromise, and do none of these three quite as well as it would like. It is the compromise in allocating energy for cellular repair that causes the body gradually to deteriorate with age. A problem with this idea is that caloric restriction increases, rather than decreases, an animal’s longevity. It does however lower reproductive success. Another is that the amount of energy needed for cellular repair is small, compared to that needed for metabolism and reproduction.

Extrinsic and intrinsic factors in aging

Intrinsic factors in aging include telomere shortening. At the end of each chromosome are telomeres, which act like bookends. Telomeres serve to protect chromosomes and prevent them from fusing into rings or binding with each other. Telomeres shorten each time a cell divides. When telomeres become too short, DNA is damaged during replication and the cell dies. This is the basis for the Hayflick limit. Most prokaryotes avoid this problem by having circular chromosomes. Among eukaryotes, an individual’s systemic telomere length is largely determined genetically. Other determinants are age (shorter telomeres in older people), paternal age at birth (longer telomeres in individuals with older fathers at birth), and sex (shorter telomeres in men, probably due to a faster telomere attrition). A major extrinsic factor in aging of cells in tissue is free radical damage. Under normal aerobic conditions, approximately 4% of oxygen metabolized by mitochondria is converted to superoxide ion. This can be converted to hydrogen peroxide, hydroxyl radical and other reactive species, including other peroxides and singlet oxygen. These in turn generate free radicals capable of damaging structural proteins and DNA. Chemical damage to structural proteins can lead to loss of function; for example, damage of collagen in vessels may cause increased vascular wall stiffness and thereby hypertension. A similar process in the kidney might contribute to renal failure. Damage to enzymes reduces cellular functionality. Lipid peroxidation of inner mitochondrial membranes reduces the electric potential and the cell’s ability to generate energy. It is probably no accident that most but not all of the so-called "accelerated aging diseases" are due to defective DNA repair enzymes. One interesting exception is progeria in children, which involves the protein lamin A, a building block of the nuclear envelope. Progeria has some but not all of the features of aging. Few children with progeria reach 14 years of age and most die from complications of atherosclerosis, such as heart attack or stroke.

Specific age-related changes in animals

a) In one organ: the mammalian eye

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On one slide I list of the range of changes seen with age in the mammalian eye. Not all occur with equal frequency in each species. This listing is based primarily on the dog and human. Some are incidental. Others have biological significance.

- **Nuclear sclerosis** is due to compression of lens fibers in the central part of the lens, resulting in the haze seen in old dogs’ eyes. It is distinct from cataract, since that is a different process – destruction of lens fiber cells, and denaturation of crystallins. The lens also loses some elasticity, resulting in **presbyopia**. This is why for people above 50 to wear bifocal lenses. It is compounded by reduced contractility of the smooth muscles that control the shape of the lens.

- At the periphery of the retina, furthest from the optic disk and the vessels which originates there, with advancing age there is **retinal atrophy** accompanied by distinctive splitting in sensory retina called **microcystoid degeneration**. This develops in most children by 8 years of age and increases in severity with age. It is possible to get an approximate age for dogs by examining this part of the retina histologically.

- The vitreous, a gelatinous material that lies between the back of the lens and the retina, undergoes **vitreal liquefaction**. This can have consequences, as it predisposes the elderly to partial or complete retinal detachment. This leads to separation between vitreous and retina, affecting >60% of people in their 80s. Detachment then occurs when there are full-thickness breaks in the sensory retina, allowing fluid to get behind the retina. This age-related disease is called **rhegmatogenous detachment** (Gr.: **rhexis**: break).

- Another vitreal change is the accumulation of small mineralized bodies composed of calcium, sulfur and phosphorous in the vitreal gel. It is called **asteroid hyalosis** due to its resemblance to stars in the night sky. Common in old dogs, and in people in their 7th and 8th decades.

- Intraocular pressure tends to rise as people age, due to changes in the drainage angle between the iris and the cornea, putting people at risk for high intraocular pressure, or **glaucoma**.

- The number of rod photoreceptors – responsible for the detection of dim light – declines with age. As many as 30% of photoreceptor cells are lost in aged humans.

- Other changes are **hyaline degeneration** of the ciliary body and its vessels (near where the aqueous humor is formed), resulting in the accumulation of amorphous material and **arcus senilus** of the corneoscleral junction. The latter is due to lipid accumulation in the cornea, resulting in an opaque arc or ring at the edge of the cornea.

- Interesting acellular structures called **drusen** (German for geode) accumulate behind the non-sensory part of the retina. Although pretty when viewed ophthalmoscopically, too many may indicate a disease process, such as central retinal degeneration in some retrieving and herding breeds. When they occur as numerous large structures in the macula, it is sign of **age-related macular degeneration (MD)** in people. The macula is that part of the retina with the highest concentration of photoreceptors. It is responsible for central high-resolution visual acuity such as reading. Macular degeneration is the leading cause of irreversible blindness in people >50 years old in the developed world. One of the more interesting recent medical advances has been the recognition that age-related macular degeneration can be arrested. This is due in large part to better understanding of its genetics and pathophysiology, which involves proliferation of vessels behind the retina leading to vascular leakage. The **complement system**, which will be covered under inflammation, is a chemical cascade and part of the innate immune system. In simple terms and as the name partly suggests, it “complements” the activity of antibodies and white blood cells in their job of eliminating pathogens. MD is associated with mutations in several proteins that inhibit the complement cascade. One way to slow the progression of MD is to inject humanized
monoclonal antibody fragments into the vitreous to counteract the tendency for new leaky vessels to form.

b) In one species: the domestic dog. As listed in the slides, dogs have their own pattern of age-related changes. Many are incidental. Older dogs commonly have benign hyperplastic nodules of the liver. These are not considered preneoplastic, but can confuse veterinarians undertaking exploratory abdominal operations on older dogs. Splenic hyperplastic nodules are common in the aging spleen due to proliferation of large aggregates of lymphocytes, some of which can appear alarmingly atypical. Another splenic is deposition of iron plaques on elastin in the capsule. These siderotic nodules also confuse clinicians doing exploratory surgery. Some are not as innocent as they look – intrasplenic hemorrhage is common in dogs, and topographically correspond to sites of iron deposition, suggesting the loss of elasticity somehow contributes to bleeding. Some old dogs with splenic hematomas bleed into their abdominal cavity, causing illness and sometime deaths. Prostatic hyperplasia occurs in most mature and old dogs, as in people, leading to interference with urination and (in dogs) constipation. Glands may be 4 times their normal size. Pancreatic hyperplasia occurs in the exocrine pancreas, resulting in flat white plaques on the surface of the gland. Multiple changes occur in central nervous system of dogs, as well as its investing membranes, as they age. Some are a curiosity at necropsy: fibrosis and plaques of bone (osseous metaplasia) form in meningeal membranes. Age-dependent ventricular enlargement occurs in the brain of dogs above the age of 10, particularly toward the front of the brain, associated with a reduction in brain volume. Dogs, like people, develop atrophy of the frontal and prefrontal cortex, and hippocampus as they age. This is correlated with reduced cognitive function, and deposition of one form of amyloid (Aβ) in extracellular plaques. Similar material deposited the walls of blood vessels is the basis for some cases of intracerebral hemorrhage in dogs. While technically not strokes, their clinical presentation after a bleed in dogs is similar to that in people with cerebral infarction. Amyloid deposits in the brains of dogs resemble an early stage of amyloid plaques in the normal aging human brain, and in Alzheimer’s disease (AD). As in people, the amount of amyloid peptide deposition varies considerably from one geriatric dog to another. Aβ is toxic to nerve cells and may mediate cell loss and atrophy in the cerebral cortex and hippocampus. In healthy aging, which tends to affect specific parts of the brain, annual gross brain volume decreases on the order of 0.2–0.5% in humans. This process is accelerated in senile dementias such as AD. Unlike AD, however, dogs do not develop one of the disease’s hallmark lesions: neurofibrillary tangles, which occur in the cytoplasm of neurons. It is for that reason we do not refer to senile dogs as having AD. The current term is ‘cognitive dysfunction.’

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