Chapter 8

Age-related diseases

Many diseases occur almost exclusively at old age. These **age-related diseases** include cancer, osteoarthritis, failure of specific organs such as heart failure, kidney failure and lung failure and neuro-degenerative diseases such as Alzheimer's disease and Parkinson's disease.

In this chapter we will understand the common origin of these diseases and the universality of their dynamics. We will also discuss treatment. These diseases are currently treated one by one, and we will see how future medicine can take a major step forward by treating aging itself in order to address all of these diseases at once.

Age-related diseases are diverse and affect different systems. It is therefore striking that they share a common pattern in their incidence curves. **Incidence** is the probability to get the disease at a given age. It is often calculated by considering 100,000 people without the disease at age t and asking how many will be diagnosed over the following year.

The incidence of age-related diseases rises exponentially with age and drops at very old ages (Fig 8.1). The slope of exponential increase is similar for different diseases, but not identical, around 3-8% per year.
Understanding this exponential rise is a major aim of this chapter. We need to understand why age 30 is different from age 70 in ways that makes these diseases so much more likely. We will also understand why incidence drops at very old ages.
Another goal of this chapter is to explain the causes of several diseases of unknown origin. In doing so we will see mathematical analogies between diseases. This will form columns in the periodic table of diseases featured in the next and final chapter of our book.

Diseases caused by threshold-crossing of senescent cells have an exponential incidence curve

To understand age-related disease incidence, we will use a simple model based on the senescent cell theory of the previous chapter. This model was developed by Itay Katzir during his PhD with me (Katzir et al. 2021).

The basic idea is that diseases of old age are due to a phase transition in which a parameter in a physiological circuit crosses a threshold. Once the threshold is crossed, the circuit behaves differently: cells grow without control as in cancer or die without control as in degenerative diseases.

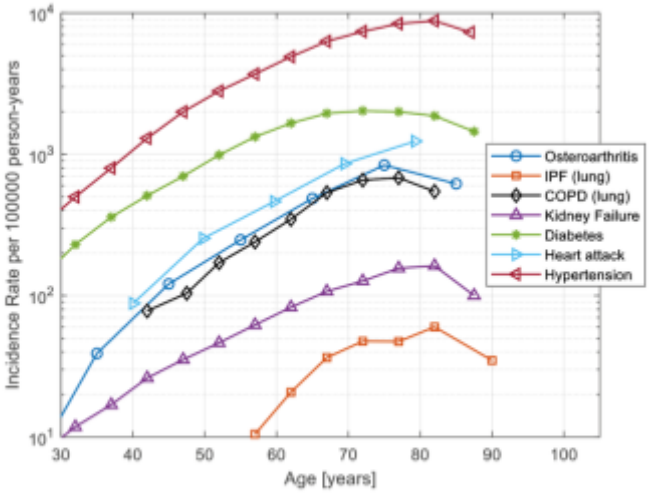


Figure 8.1: The incidence of age-related diseases rises exponentially with age and drops at very old ages.

If we accept that disease onset is a threshold-crossing event, we can ask how aging comes into play. Aging causes the parameters of the circuit to change and move towards the threshold. In particular, senescent cell load X induces systemic inflammation and reduces regeneration, which changes the circuit parameters until they cross the threshold. Thus in the model, a disease occurs when senescent cells cross a threshold that is specific for each disease. We call this threshold the **disease threshold** X_c.

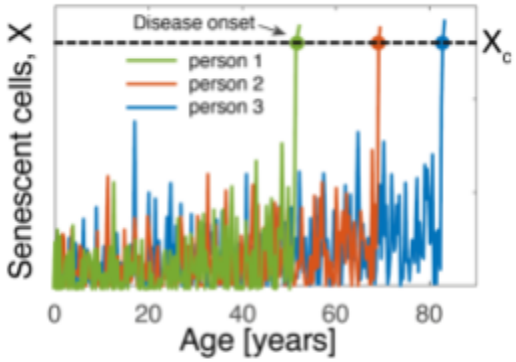


Figure 8.2: In the disease-threshold model a disease occurs when senescent cells cross a disease-specific threshold.

Although each disease has its own threshold Xc, the underlying senescent cell dynamics are common to all diseases. These dynamics are described by the saturating removal model of chapter 7, eq 7.3. When the concentration of senescent cells X crosses the disease threshold X_c the individual gets the disease (Fig 8.2). Each individual crosses the threshold at different times, due to the stochastic nature of the dynamics of senescent cells.

The time of onset is therefore the time when senescent cell accumulation first crosses the threshold X_c - a first-passage time problem.

Conveniently, we don't need to do the math again because in the previous chapter we already solved this first-passage-time problem. The solution is an exponential hazard curve—the Gompertz law—that slows at very old ages. The probability of crossing the threshold X_c rises exponentially with age, $e^{\alpha t}$, with an exponential slope of approximately

$$\alpha \approx \frac{\eta X_c}{\epsilon},$$

where η and ϵ are the senescent cell production and noise parameters.

This explains the exponential rise of disease incidence curves. Since diseases have different exponential slopes, each disease has its own threshold X_c. The disease threshold must not exceed $X_{death} = 17$, otherwise the model would predict that death precedes the disease, and we would not observe the disease.

Decline of incidence at very old ages is due to population heterogeneity

If this were all, everyone would cross the disease threshold X_c in the model and get the disease. In reality only a fraction of people ever do. This is where the second parameter in the model comes into play—only a fraction ϕ of the population are **susceptible**. The parameter ϕ ranges between zero and one. Some conditions are rare with low ϕ, others like hypertension and osteoarthritis are more common, with ϕ exceeding 0.1. The precise value of the susceptibility depends on genetic and environmental factors, as we will discuss.

The susceptible fraction stems from the notion of population heterogeneity in the fields of epidemiology and genetics. People differ in their risk for a given disease. To model this we assume that only a fraction ϕ of the population has a low disease threshold X_c. The remaining population has higher values of the disease threshold that are not reached during normal aging. We call these the *non-susceptible* fraction of the population.

The susceptible fraction explains the decline of incidence curves at very old ages. Recall that incidence is computed from the population without the disease. At very old ages, *most of those that are susceptible have already had the disease*. At very old ages the disease-free population is dominated by the non-susceptible fraction. This results in the decline in incidence rate.

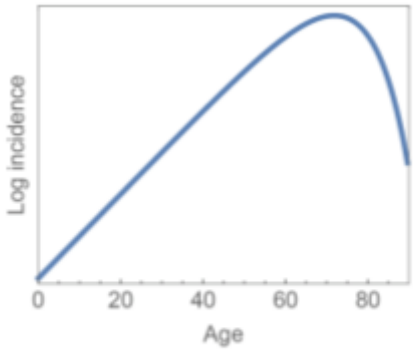


Figure 8.3: In the disease threshold model incidence rises exponentially and drops at very old ages.

The model thus has two parameters for each disease: the disease threshold and the susceptibility.

Let's solve the model for the incidence curve to see where the rise and fall originate (see Solved exercise 8.1 for more details about the approximations involved). The idea is that incidence I(t) is approximately equal to the hazard h(t) – the probability to cross the disease threshold X_c at age

t, multiplied by the disease-free survival curve F(t) – the fraction of the population who still did not get the disease. Thus $I(t) = h(t)\,F(t)$. Since h rises and F declines, their product is a curve with a peak incidence. Writing disease-free survival in terms of hazard results in this equation for the incidence

$$I(t) = \phi\, h(t) e^{-\int_0^t h(t)dt}$$

and by plugging in a Gompertz-like hazard $h = h(0)e^{\alpha t}$ we obtain an analytical incidence formula

(1) $$I = \phi h(0)\, e^{\alpha t} e^{-\frac{h(0)}{\alpha}\left(e^{\alpha t}-1\right)}$$

At first, incidence rises exponentially (Fig 8.3), until at very old ages the last term dominates, since it is an exponential of an exponential, and incidence plummets.

Note that susceptibility ϕ simply multiplies the incidence in Eq 1, and thus determines its overall height; the shape of the incidence curve, including its slope, intercept and age of peak incidence, is determined by a single parameter - the disease threshold X_c. Using the saturated removal model of the previous chapter, one can find how the disease threshold determines the shape parameters in Eq 1: to a good approximation, the slope is $\alpha = 0.009X_c - 0.02$ and the hazard intercept is $log10(h(0)) = 4.14 - X_c$ for the relevant range of disease thresholds X_c between 10 and 16 (Katzir et al. 2021).

Armed with Eq. 1 we can now find the best-fit values of Xc and ϕ for a given empirical incidence curve and see how well the disease-threshold model captures the data.

The model describes well the incidence curves of a wide range of age-related diseases

To test this model requires a global set of incidence curves. We turn to the large medical-record database from Clalit health services that we used in chapter 3 on hormone seasonality. The data includes about 900 disease categories, each found in the records of at least 10,000 people. The categories are international disease codes, called ICD9 level 2. Of these, about 200 diseases rise at least 20-fold between ages 30 and 80, and can be defined as strongly age-related diseases.

These diseases include some of the most common age-related conditions such as Parkinson's disease, glaucoma, congestive heart failure, end-stage renal disease, liver cirrhosis, cataract, hypertension and osteoarthritis (Fig 8.4).

The disease-threshold model captures the data well (Fig 8.4). The model captures more than 90% of the variation in over 90% of these diseases. The goodness of fit has a median of $R^2 = 0.97$, where $R^2 = 1$ is a perfect fit. The typical disease threshold values X_c range between 12 and 16.

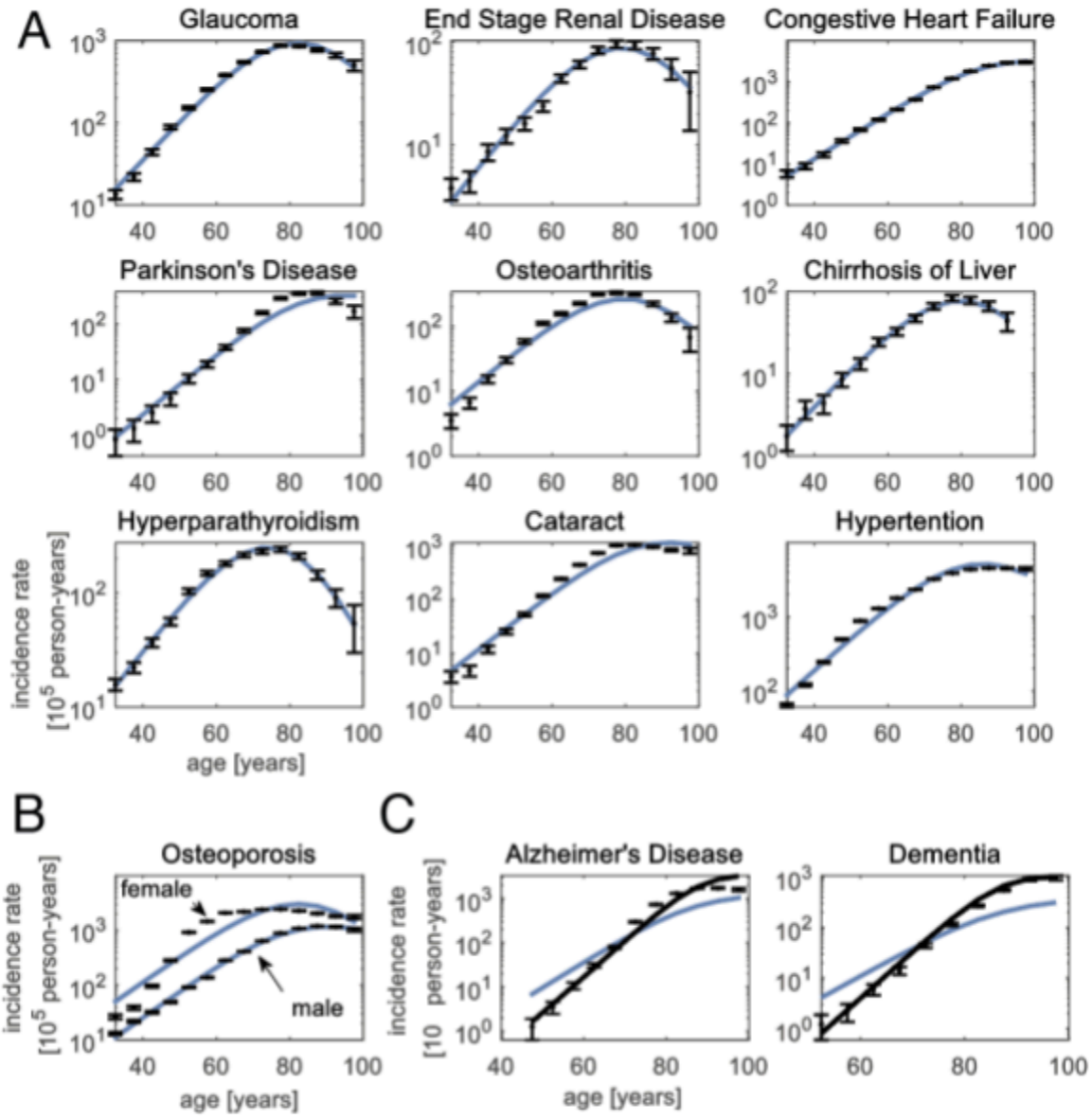


Figure 8.4: Incidence curves from the Clalit dataset are well-described by the disease threshold model (A). Exceptions are (B) female osteoporosis which rises after menopause and (C) Alzheimer's disease and dementia which require a threshold higher than the death threshold (black line). Adapted from (Katzir et al, 2021).

The model does not, however, describe well the incidence of several age-related diseases. A notable example is osteoporosis in women (Fig 8.4B). The incidence curve rises sharply after age 50, due to effects related to menopause, in a way that the model cannot capture. On the other hand, osteoporosis in men is well described by the model (Fig 8.4C). This suggests that menopause-related changes go beyond the current framework.

An interesting case occurs in Alzheimer's disease and dementia. The incidence curves of these diseases have an exceptionally large slope of about 20% per year. The model can

only explain this large slope with a disease threshold X_c =20 that exceeds the threshold for death $X_{death} = 17$ (black line in Fig 8.4C). The best fit with the maximal X_c values equal to the death threshold X_c=X_{death} underestimates the incidence slope (blue lines in 8.4C).

This suggests that the age-related factor X in dementia might be distinct from total body senescent cells and has its own saturating removal dynamics. This might make sense because the brain is a unique protected organ with its blood-brain barrier and its own version of immune function. One candidate for this damage might be accumulation of prion-like protein aggregates in neurons which saturate their mitochondrial-based removal systems. This is consistent with the damaged mitochondria and protein aggregates that are universally linked to neurodegenerative diseases.

All in all, the model seems to explain an astonishingly large fraction of the incidence curves of age-related diseases.

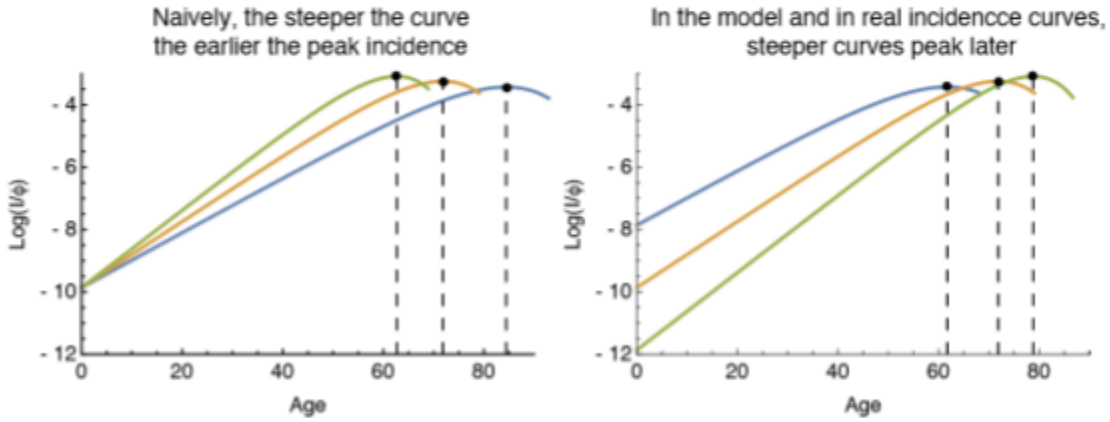


Figure 8.5: Naively, steeper incidence curves should peak earlier. In the data and the model, steeper curves peak later.

To understand what the disease-threshold model is capturing, let's explore in more detail the patterns in the incidence data. One such pattern concerns the timing of the peak incidence, and its relationship to the slope of the incidence curve. Naively, one may think that the steeper the slope, the earlier the peak incidence – steeper curves max out earlier (Fig 8.5). But the data shows otherwise: the steeper the curve, the later the peak incidence. Why? Because steeper incidence curves begin lower, as defined by their intercept, namely the

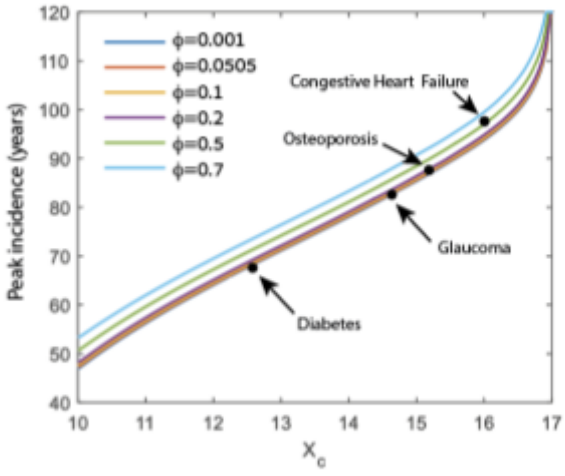


Figure 8.6: Age of peak incidence rises with disease threshold in the model and data.

extrapolated incidence at age zero (See Fig. 8.5, age=0).

Remarkably, the disease-threshold model captures this pattern. The steeper the slope, as described by a higher disease threshold Xc, the later the peak incidence (Fig 8.6). The reason is that the slope rises linearly with the disease threshold X_c, but the intercept at age zero $I(0)$ drops exponentially with this threshold. To understand this recall the analogy with a particle in a potential well: a high threshold makes it exponentially harder for for noise to generate enough senescent cells to cross the threshold at young ages; the zero intercept thus decays exponentially with threshold X_c, namely $I(0) \sim exp(-\beta X_c/\epsilon)$.

Thus, the disease-threshold model captures some of the deep patterns in the data with only two free parameters per disease, of which only one, Xc, affects the shape of the curve. This is impressive.

But how does each specific disease occur when senescent cells cross a threshold? We need to link senescent cells and the physiology of each disease. To do so, we now focus on several classes of pathologies and specify, for each case, the mechanism for their onset at the threshold-crossing.

We begin with cancer and infection. We then consider an age-related disease in which the lungs fail, called Idiopathic Pulmonary Fibrosis (IPF). Its cause is a mystery. We will use our approach to explain this disease as an outcome of fundamental principles of tissue homeostasis. We will then show that a seemingly unrelated disease of the joints, osteoarthritis, belongs to the same 'mathematical class' as IPF.

Cancer incidence curves can be explained by threshold-crossing of tumor growth and removal rates

Cancer risk rises by 4000% between age 25 and 65. The incidence curves of most cancer types show the familiar exponential rise with age and drop at very old ages. To explain this in our model, we need to find out why cancer is like a threshold-crossing phenomenon, and how senescent cells can push physiology across this threshold.

Cancer cells arise continuously in the body due to accumulation of mutations. If conditions are right, the mutant cells grow faster than their neighbors. These cancer cells are removed by immune surveillance, primarily by the innate immune cells such as NK cells and macrophages, and at later stages by adaptive immunity including T-cells. If the cancer cells manage to grow beyond a critical number of roughly 10^6 cells, they organize a local microenvironment that can prevent further immune clearance.

A classic explanation for the age-dependence of cancer is called the **multiple-hit hypothesis**: the need for several mutations in the same cell to turn it into a cancer cell (Armitage and Doll 1954; Nordling 1953). Most cancers require a series of mutations, called oncogenic mutations, in order to knock-out pathways that prevent the cell from growing out of control. Such a multiple-hit process has a likelihood that rises roughly as the age to the power of the number of mutations. Cancer in the young often occurs

because one of the mutations is already present in the germline and thus in all cells of the body.

This 'multiple hit' hypothesis, however, cannot explain why incidence drops at very old ages. It also fails to explain why cancers which require a single mutation, such as some leukemias, also have an exponentially rising incidence with age. Even colon cancer, the poster child for a multiple-mutation progression, has exponentially rising incidence with age rather than a power law.

The present theory can provide a mechanism for the incidence curves of cancers. Consider cancer cells that proliferate at rate p, and are removed at rate r (Fig 8.7). The rate of change of the number of cancer cells C equals proliferation minus removal:

$$\frac{dC}{dt} = pC - rC$$

Cancer grows when proliferation exceeds removal, $p > r$, and shrinks otherwise (Fig. 8.8). This is just the knife's-edge equation we saw in chapter 2.

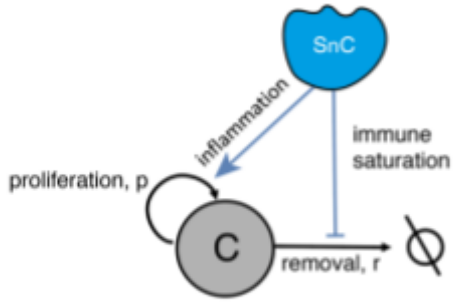


Figure 8.7: Cancer cells proliferate and are removed. Senescent cells increase proliferation and decrease removal.

Both growth and removal of cancer are affected by senescent cell load X. With age, rising senescent cell levels inhibit the capacity of the immune system to remove cancer cells. The main cells that remove early cancer cells, NK cells and macrophages, also remove senescent cells. They become saturated when senescent cells become abundant and cannot keep up with the demand for cancer removal services. The garbage trucks are overloaded. Thus, removal rate r drops with the number of senescent cells, $r = r(X)$.

A second cancer-inducing effect is chronic inflammation caused by the factors that senescent cells secrete. One may think of many cancers as an AND-gate between chronic inflammation and oncogenic mutations. Inflammation reduces the growth rate of healthy cells, giving mutant cancer cells a relative growth advantage. Many cancers arise only after chronic inflammation causes cells to become less differentiated - to undergo metaplasia. Thus, inflammation can raise cancer proliferation rate p, so that proliferation rises with senescent cell levels p=p(X).

Both effects, raising proliferation p and lowering removal r, push cancer towards the threshold where proliferation exceeds

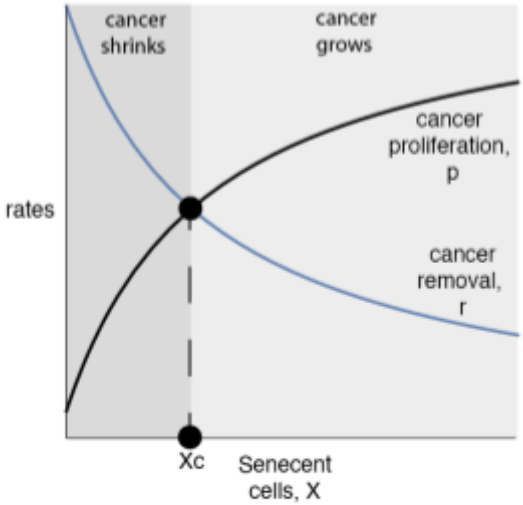


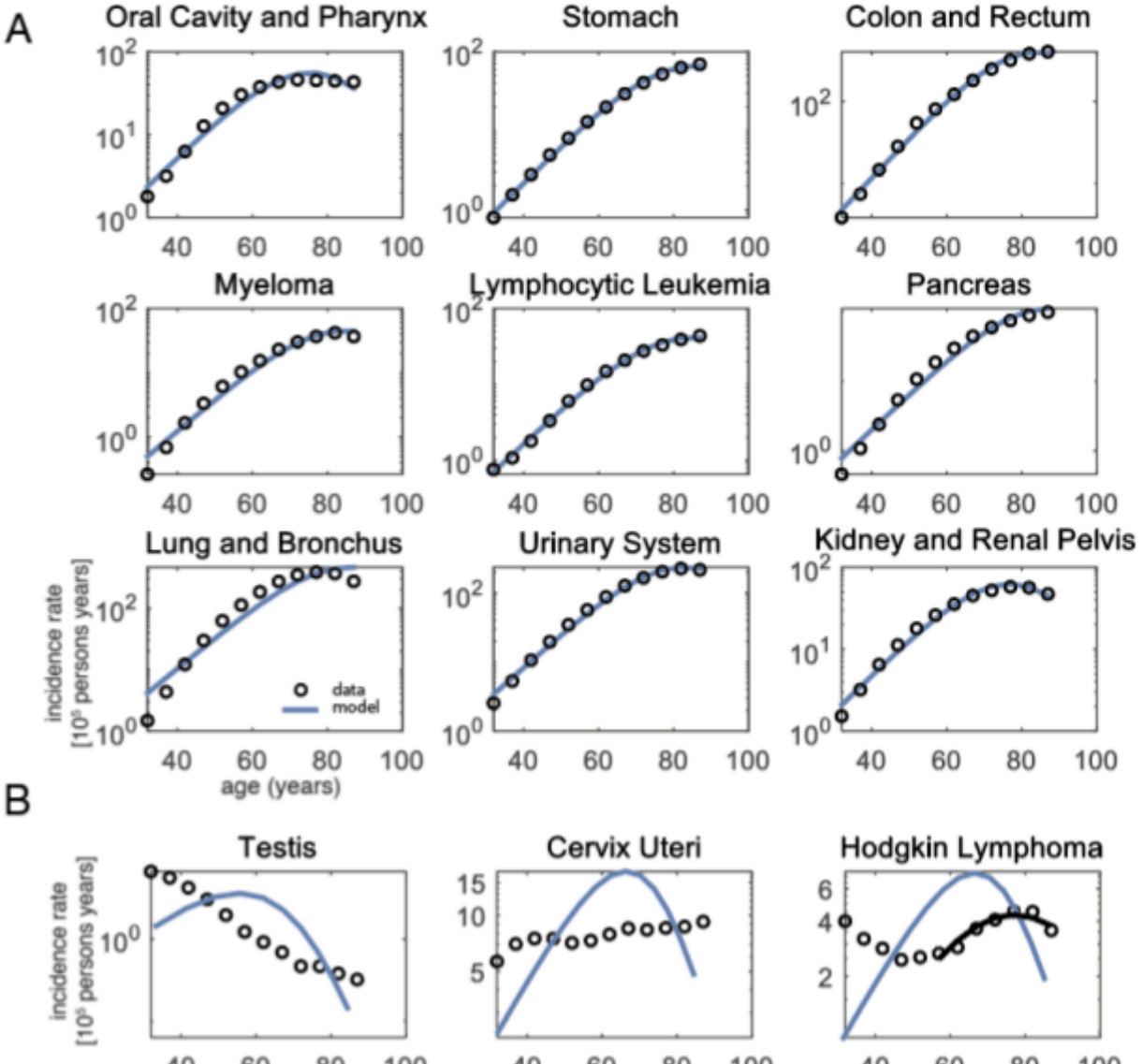
Figure 8.8: Senescent cells reduce removal and increase proliferation. When they exceed a threshold Xc, cancer starts growing exponentially.

removal. The senescent cell level where this occurs is our disease threshold X_c (Fig 8.8).

Individuals susceptible to a given form of cancer include those with genetic factors (e.g., BRCA mutations for breast and ovarian cancer) and exposure to environmental factors such as smoking for lung cancer and UV for skin cancer. These factors increase the probability of sporadic occurrences of the cancer cells in the tissue. The proliferation rate, p, and removal rate, r, both depend on conditions in the local tissue niche, as well as the mutational and epigenetic state of the cell. Hence, the more occurrences of cancer cells in the tissue, the higher the chance that $p > r$ for one of these cells, allowing it to proliferate and generate a tumor.

Cancer incidence is well documented, allowing a good test for theory. One comprehensive database, called SiteSEER, has incidence curves of 100 cancer types in the US. Of these cancers, 87 are at least mildly age-related. Of these, 66 are well-described by the disease threshold model ($R^2 > 0.9$) (Fig. 8.9). The typical values of X_c are 13-15, and the susceptibilities for different types of cancer range from 10^{-4} to 0.1.

There are several types of cancer with a poor fit to the model (Fig 8.9 B), namely cancers that are common at young ages such as testicular cancer, Hodgkin's lymphoma and cervical cancer (which has a viral origin).



All in all, the disease-threshold model seems to describe a wide range of age-related cancers very well.

Many infectious diseases have age-related mortality

A general theory such as the disease-threshold model can be used to make connections between very different diseases. To demonstrate this connection across disease classes, we consider infectious diseases, such as pneumonia, flu, and COVID-19. For many infectious diseases, mortality rate rises exponentially with age (Fig 8.10).

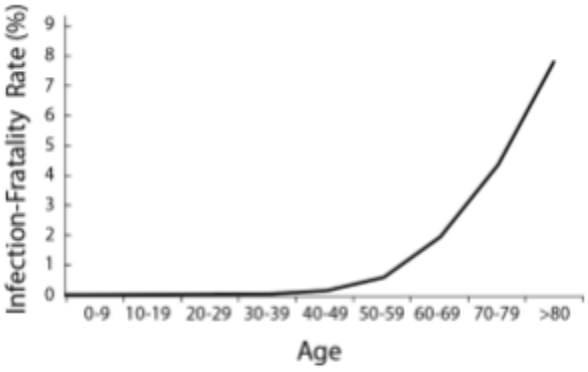


Figure 8.10: Mortality from many infections rises exponentially with age. Data for COVID-19 adapted from (XXX)

Infections are diverse. Each pathogen has ingenious ways to resist the immune system. But despite this complexity, pathogens share a mathematical unity, which is analogous to the cancer model we just saw.

A virus or bacterium has proliferation rate, p, because all pathogens come from pathogens. It is removed at rate r by the immune system. The number of pathogens N thus obeys the same knife's-edge equation as cancer cells, $dN/dt = (p - r)N$

Infections become deadly when they grow exponentially, that is when p>r. The host is killed by damage caused directly by the pathogen, or more commonly by the collateral damage unleashed by the immune system trying to fight the pathogen.

In young healthy individuals pathogen removal usually exceeds proliferation. The pathogen is handily eliminated by the immune system. However, just as in the case of cancer, senescent cells X can reduce the removal rate r(X) in multiple ways. Senescent cells overload the immune cells, including NK cells and macrophages, whose job is to fight pathogens. They also contribute to the decline of the adaptive immune system, including T-cells, with age.

Such effects lower the removal rate of the pathogen, so that r(X) decreases with X. At old age, a critical threshold Xc is reached, where removal equals proliferation r(Xc)=p. Beyond this threshold a given infection that would be removed at young ages, now has p>r and grows exponentially.

Thus, the age-dependence of both cancer and infection belong to the same mathematical class — they are eliminated at young ages, but have a phase transition to growth at a critical point Xc. The likelihood of crossing Xc rises exponentially with age, due to the first-passage-time solution of the saturating-removal model, giving rise to the observed incidence curves.

Let’s now turn to a different class of diseases, progressive fibrotic diseases. But first, to recognize that we are doing a lot of work here, let’s take a nice deep sigh of relief.

A theory for IPF, a disease of unknown origin

A striking feature of the disease-threshold theory is that it can offer new explanations for age-related diseases that are poorly understood. To see this, we consider IPF, which stands for **idiopathic pulmonary fibrosis.** Its very name indicates that the cause is unclear: 'Idiopathic' means disease of unknown cause, 'pulmonary' means lungs, and 'fibrosis' means excess scarring.

In IPF, lung capacity is progressively lost due to the scarring of tissue that is essential for breathing (Martinez et al., 2017a; Raghu et al., 2012). It is a chronic progressive disease that has no cure; patients often die within 1- 3 years. The lifetime susceptibility to IPF is about $\phi = 10^{-4}$. Its incidence rises exponentially with age and then drops (Fig 8.1).

To understand IPF, let's survey the relevant organ structure. The lung is made of branching tubes that end in small air sacs called **alveoli** (Fig 8.11). The alveoli let oxygen from the air go into the blood and let $C0_2$ out. The alveoli are made of an inner epithelial layer that is one-cell thick surrounded by an interstitial layer. IPF scarring occurs in the

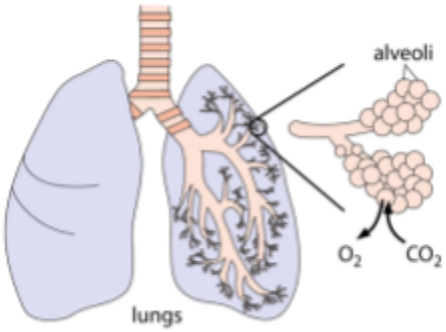


Figure 8.11: The lung is made of branching tubes called bronchi that end in alveoli that perform gas exchange.

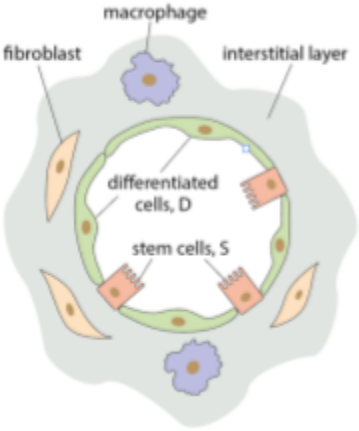


Figure 8.12: Alveoli have a thin epithelial layer surrounded by an elastic interstitial layer.

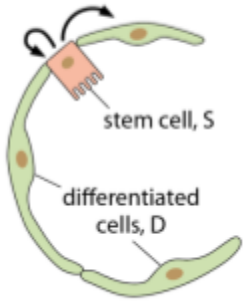


Figure 8.13: The epithelial layer is made of stem cells that renew themselves and produce differentiated cells.

interstitial layer around the alveoli (Fig 8.12).

The thin epithelial layer is made of two types of cells. The first cell type (alveolar type-1 cells) are large flat barrier cells, which we will call the differentiated cells D. The second type (alveolar type-2 cells) are smaller stem-like cells we will call S (Fig 8.13). These stem cells can divide to form new S cells or differentiate into D cells. The S cells also secrete a soapy surfactant that shields the cells from air particles and prevents collapse of the alveoli when we exhale.

The interstitial layer around the alveoli contains fibroblasts and

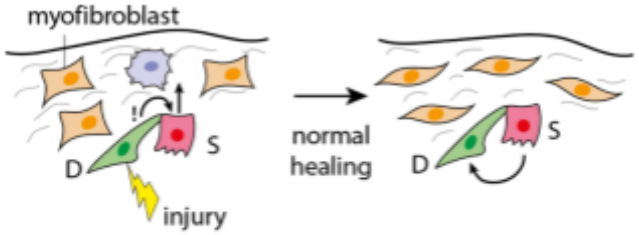


Figure 8.14: An injury causes alveolar cells to induce stem cell division and signal fibroblasts to become scar-forming myofibroblasts. In normal healing, myofibroblasts decay and the tissue is restored.

macrophages, the stars of chapter 5 on fibrosis. Macrophages are ready to gobble up bacteria and particles that make it through the epithelial layer of S and D cells. The fibroblasts produce the fibers which make the elastic sheath around the alveoli.
When there is injury to the D cells, they signal (with molecules such as TGF-beta) to S cells coaxing them to differentiate into new D cells (Fig 8.14). These injury signals also cause S cells to activate inflammation in the interstitial layer to start a healing process. The S cells signal the fibroblasts to become activated myofibroblasts, which proliferate and secrete extra fibers.

In normal healing, once the new D cells are made, the excess fibroblasts undergo programmed cell death, and the extra fibers are removed. S cells divide and renew the tissue, and the injury is repaired.
In IPF, an unknown factor causes an ongoing injury. The S cells multiply and reach higher numbers relative to D cells than in normal alveoli (Fig 8.15). They activate the fibroblasts to multiply and lay down excessive fibers, causing fibrosis. The interstitial tissue around the alveoli becomes a thick scar that reduces the ability of oxygen and CO_2 to flow in and out. It makes the alveoli stiff and less able to expand and contract. Eventually more and more alveoli become dysfunctional, leading to lung failure.

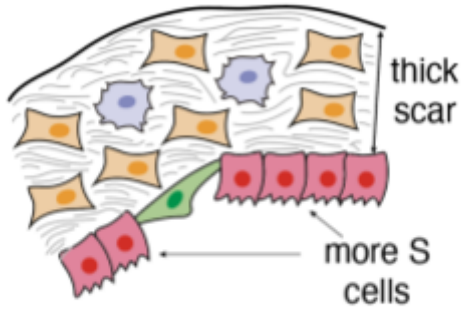


Figure 8.15: In IPF, stem cells proliferate and hyper-activate myofibroblasts causing excessive scarring and loss of alveolar function.

A major unknown in IPF is the origin of the injury. We can use what we have learned so far to make a theory for the source of the injury and explain why the risk of IPF rises exponentially with age, and why it occurs in only a small fraction of the population. We rely on research that shows that senescent cells are important for IPF: the affected alveoli have enhanced cellular senescence, especially in S cells (Martinez et al. 2017), and removing senescent cells by senolytic drugs reverses fibrosis in IPF mouse models (Hernandez-Gonzalez et al. 2021; Lopes-Paciencia et al. 2019).

We will thus explore how the accumulation of senescent cells might cause IPF. The main idea is that senescent cells slow down the rate of stem-cell proliferation; when stem-cell proliferation rate drops below removal rate, both S and D cell populations vanish -- the alveolar tissue locally reaches zero cells.

Stem cells must self-renew and supply differentiated cells

To understand IPF, we thus need to understand how stem-cell-based tissues work. Stem cells are found in organs that need to generate large numbers of cells. One class of such organs are barrier organs exposed to the outside world, like the lung, intestine and skin. Because of this exposure, cells can be damaged and need to be replaced.
These organs divide labor: the majority of cells, D, do the main tissue work, and the minority (1-5%) are stem cells, S, in charge of regenerating the D cells and themselves. Thus $S \rightarrow D$.

Stem-cell-based tissues differ from the organs we considered in part 1 of the book, where differentiated cells like adrenal cortex cells gave rise to their own kind, without need for stem cells (Fig. 8.16).

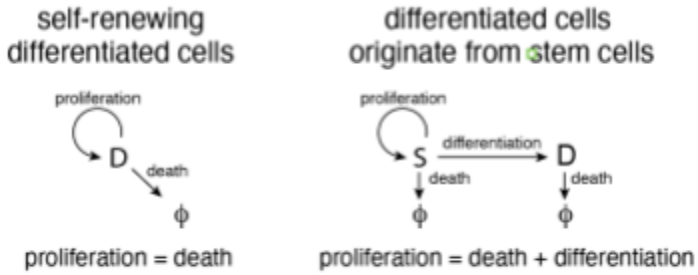


Figure 8.16: Comparison of circuits for cell types that renew themselves and cell types renewed by stem cells.

Recall that in such tissues steady state requires that cell proliferation rate equals cell removal rate, otherwise the tissue grows or shrinks. In contrast, in stem-cell based tissues, the proliferation of stem cells S must *exceed* their removal, because some of the S divisions are needed to make the D cells. For stem cells, therefore, proliferation must balance two processes: stem-cell removal plus differentiation (Fig 8.16).

The stem cell removal rate in many tissues is low because the stem cells are in a **protected niche**, where they are shielded from damage. Examples include the blood stem cells hidden in the bone marrow, skin stem cells in the deep epithelium, and the gut stem cells tucked away at the bottom of crypts (Fig. 8.17).

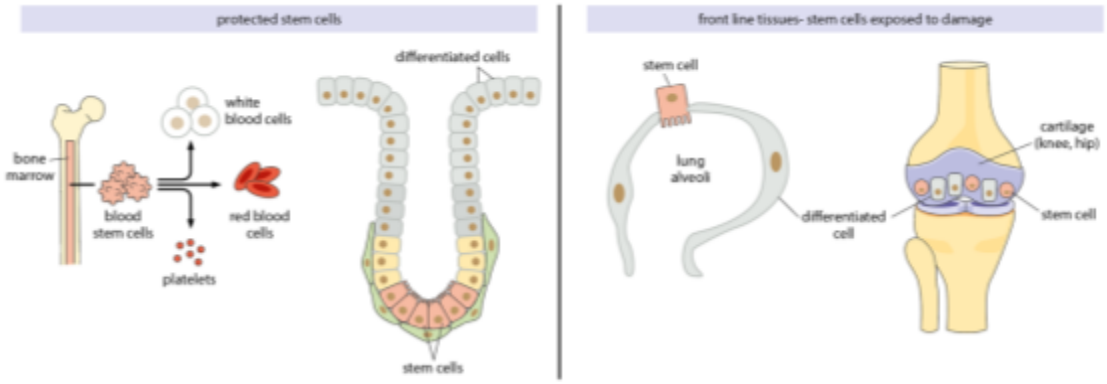


Figure 8.17: Comparison of organs with protected stem cells and organs with front-line stem cells exposed to damage.

In contrast, the lung alveoli are an example of a tissue where both S and D are on the **front lines**. Stem cells and differentiated cells are both exposed to damage, such as air particles, pathogens and the mechanical stress of breathing. There is no other choice: the alveoli must be a thin monolayer of cells to allow diffusion of gasses and can't afford a deep layer for the stem cells. We call such tissues **'front line tissues'.**

We are now ready to propose a mechanism for IPF.

Incidence of idiopathic pulmonary fibrosis can be explained by stem cell removal exceeding proliferation

In front-line tissues stem cells are exposed to damage and removed often. Homeostasis is harder to achieve than in tissues in which stem cells are protected, because of the high rate of removal of stem cells.

To understand this, let's analyze the circuit that maintains organ size in front-line tissues. We will see that front line tissues crash when removal exceeds proliferation.

Let's first write down the basic equations (Fig. 8.18) (Katzir et al., 2021). These equations account for stem cell proliferation at rate p, and their differentiation to make differentiated cells D at rate q. The removal rate of S and D cells is r:

$$(1)\ \frac{dS}{dt} = pS - rS - qS$$

$$(2)\ \frac{dD}{dt} = qS - rD$$

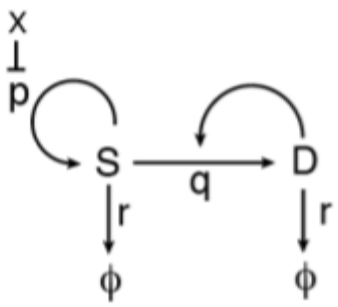


Figure 8.18: Circuit for front line tissue, in which stem cells and differentiated cells are both removed, and differentiated cells feedback on the stem cells to maintain homeostasis. Senescent cell accumulation reduces stem cell renewal.

Note that differentiation means that an S cell is lost and a D cell is gained. As a result, the $-\ qS$ term in the first equation, namely the rate of differentiation of an S to a D cell, shows up as a $+\ qS$ term in the second equation.

To maintain the proper amounts of S and D cells, there is a feedback loop. As mentioned above, D cells signal to S cells by secreting factors like TGFbeta that increase the rate of differentiation q (Zhao et al., 2013). Thus q=q(D). This feedback acts to restore homeostasis when cell numbers are perturbed, as analyzed in solved exercise 8.2. Pioneering work on such stem-cell circuits is due to Arthur Lander and colleagues (Lander et al. 2009).

We will now see that this circuit has a failure point. It breaks down when proliferation p falls below removal r -- the cell population shrinks exponentially. To see this mathematically, we bound our equation from above by a simpler equation which declines to zero. We first add the two equations Eq 1,2 to get an equation for the total number of cells S+D

$$\frac{d(S+D)}{dt} = pS - rS - rD = pS - r(S + D)$$

This addition eliminates the feedback term q(D), so our conclusions will work for any form of feedback! We increase the right-hand-side by changing S to S+D because S+D is always greater than S,

$$\frac{d(S+D)}{dt} < p(S + D) - r(S + D) = (p - r)(S + D)$$

We end up with the knife-edge equation for total number of cells T=S+D

$$\frac{dT}{dt} = (p - r)T.$$

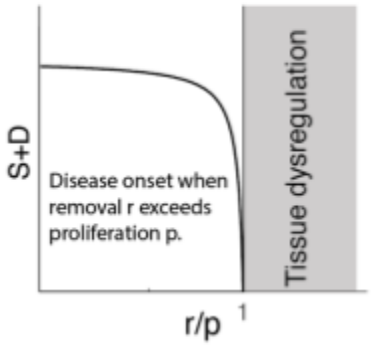


Figure 8.19: Front line tissue goes to zero cells when removal r exceeds stem cell proliferation p.

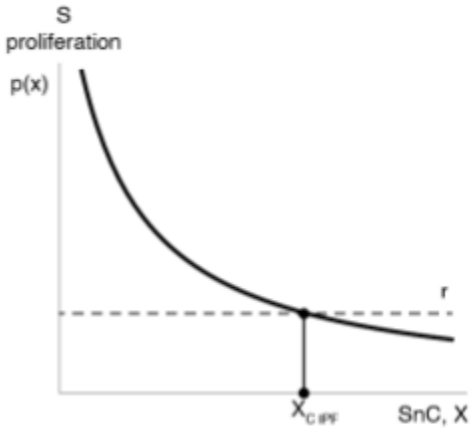


Figure 8.20: Senescent cells reduce proliferation pushing it towards removal. At a critical point Xc the tissue collapses.

Thus, when the proliferation rate falls below removal, $p < r$, the total cell number is bounded below an equation that goes to zero exponentially fast with time. Both S and D must go to zero (Fig 8.19).

After the collapse, attempts at tissue repair cannot proceed by regeneration and instead rely on processes such as fibrosis, cell migration and metaplasia. Fibrosis reduces tissue function and pathology occurs.

Next, we need to understand how aging can cause the threshold crossing of proliferation and removal rates, namely the failure point. Senescent cells affect proliferation and removal in a way that pushes the tissue towards the threshold (Fig 8.20). Senescent cells secrete SASP that slows down the proliferation of progenitor cells throughout the body. Thus, p is a declining function of X, p(X), Fig 8.20. When senescent cells cross a threshold X_c proliferation drops below removal, and tissue collapse is predicted to occur. S and D cells vanish. Simulations of the circuit with its feedback loop show how the alveolar cells D go to zero at different times for different individuals (Fig 8.21), as determined by times that senescent cells cross the disease threshold (Fig 8.22)

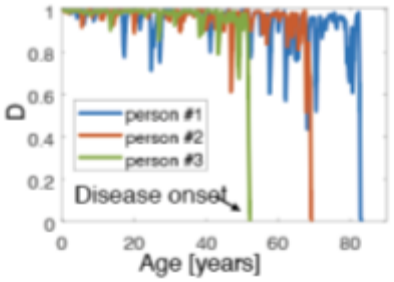


Figure 8.21: Cell number drops to zero at different times in different individuals.

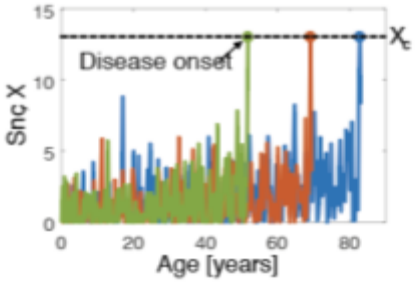


Figure 8.22: disease onset in an individual occurs when senescent cells cross the disease threshold.

IPF is thus a threshold crossing disease, and accumulation of senescent cells with age can induce this threshold crossing. According to our theory we expect an exponential rise of incidence with age, as senescent cells stochastically cross the disease threshold, with a decline at old ages. This is indeed observed (Fig 8.23).

The circuit also explains the clinical observation that the amount of S cells relative to D cells begins to rise close to the disease onset. This is due to the feedback in the system, which attempts to ward off the collapse by increasing stem cell numbers (by inhibiting differentiation q) when proliferation rate drops and approaches removal rate. This is a last-ditch attempt to supply the needed number of divisions per unit time to supply the removal rates.

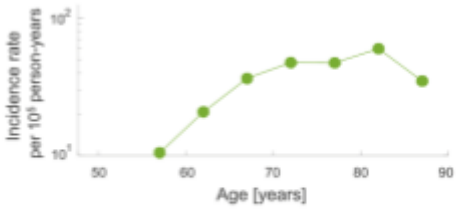


Figure 8.23 : Incidence of IPF rises exponentially and drops at very old ages.

Mathematically, we can see the rise in S relative to D cells as follows. From Eq 2 at steady state we obtain that $qS_{st} = rD_{st}$ and thus $S_{st}/D_{st} = r/q$. From equation 1 at steady state, we see that $p - r - q = 0$, and thus $q = p - r$. Combining these two facts, we find that the ratio of S to D cells at steady state diverges when proliferation p comes close to removal rate r, namely $S_{st}/D_{st} = r/(p - r)$.

Such a critical threshold for failure does not exist in the circuit for protected stem cells, with low stem cell removal rate (see exercise 8.5). Thus, only front-line tissues are expected to show progressive age-related fibrotic diseases.

Now that we understand the origin of the disease threshold, let's also understand the biological origin of the susceptibility to this disease.

Susceptibility to IPF involves genetic and environmental factors that increase stem cell death

Who is susceptible? Most people are not. Their stem cell proliferation rate is much higher than the removal rate. With age, proliferation rate drops but still stays above removal. The lungs work fine, there is no disease.

But in a fraction of people, the stem cell removal rate is higher than in the rest of the population. This is fine at young ages, because proliferation still exceeds removal. But in these individuals, aging can push proliferation down below removal, causing tissue collapse and IPF onset.

To understand this, we can examine the genetic risk factors for IPF (Martinez et al., 2017b). About 15% of IPF cases cluster within families. First-degree relatives of a patient have a 5-fold higher risk of contracting IPF.

There are two classes of gene variants that increase the risk of IPF. The first class is in the surfactant genes expressed by S cells. These variants produce unfolded surfactant proteins that damage the S cells and increase their removal rate r. Increasing cell removal rate lowers the IPF threshold X_c (Fig 8.24). Thus, these gene variants make the disease much more likely.

The other class of genetic risk variants also affects S cells. These are **telomerase** genes. Stem cells have an enzyme called telomerase that allows them to divide indefinitely, by restoring their telomeres after each division. The telomerase risk variants reduce S cell

proliferation rate p and increase their death rate r, or equivalently their removal by becoming senescent.
IPF also has environmental risk factors. Smoking doubles the risk of IPF. Smoking is mutagenic, increasing the rate of local senescent cell production, and also increasing removal rates. Exposure to toxins such as asbestos also increases removal and the risk of IPF.
The involvement of high removal in IPF also explains why fibrosis begins at the outside of the lung, and then progresses inwards. At the outside of the lung, the mechanical stress on the alveoli, and hence removal rate, is highest.
Thus, genetic and environmental risk factors for IPF tend to lower X_c . Whereas most people have a threshold that is higher than the death threshold, so that IPF never occurs, those susceptible have low Xc that is crossed at old age.

To sum up, the homeostasis circuit of a front-line tissue, such as the alveoli, is fragile to a reduction in stem cell proliferation. As proliferation drops to approach stem cell removal rate, the fraction of stem cells in the tissue rises. When proliferation drops below removal, cell numbers crash to zero, which sets off fibrosis in a doomed attempt to repair the tissue. The age-related decline in proliferation is caused, at least in part, by senescent cells that accumulate with age. The statistics of senescent-cell fluctuations explain the exponential rise of IPF incidence with age. The drop of incidence at very old ages occurs when most of those susceptible have already gotten the disease.

IPF is mathematically analogous to another age-related disease, osteoarthritis.
The understanding that IPF is due to a threshold-crossing in which removal exceeds proliferation can be generalized to other front-line organs. In this way, understanding one disease can help us understand a range of seemingly unrelated diseases.
One such disease is the joint disease **osteoarthritis**, a common condition that occurs in about 10% of those over 60 (Martel-Pelletier et al. 2016). In osteoarthritis the protective cartilage that cushions the ends of the bones wears down over time. It most commonly affects joints in knees, hips, hands and spine. The symptoms are pain and stiffness in the joints, which can be debilitating. It is a progressive disease with no cure except joint-replacement surgery.

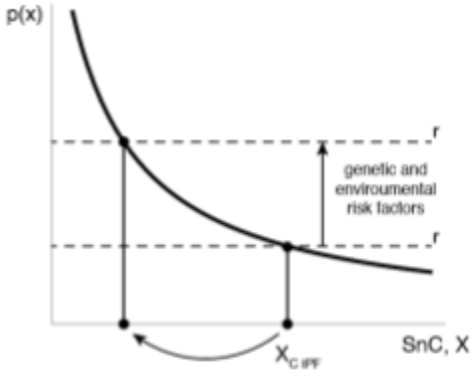


Figure 8.24: Individuals susceptible to IPF have a lower threshold due to increased stem cell removal.

The joint is made of a tough fibrous cartilage. The business end of the cartilage is a smooth edge where the two parts of the joints meet. This is the front line, where the wear-and-tear occurs. The cartilage is constantly remodeled by chondrocyte cells, D, that make the fibers for strength and elasticity, including collagen-2. These D cells are generated by stem-like progenitor cells, S (Koelling et al. 2009). The progenitor cells in the joint are at the front line, just like in the alveoli. The reason is that cells have limited mobility

through the cartilage, and thus S cells need to be close to where new D cells are needed, namely at the front line.
The joints suffer mechanical stress, especially in regions that support the body's weight. In the young, this stress doesn't do much and the joints are fine for 50 or more years. But at old ages, osteoarthritis can set in. In a process that takes many years due to the very slow turnover of the chondrocytes, D cell number reduces, and the fraction of S cells increases. The S cells make tougher fibers than in normal cartilage, such as collagen-1

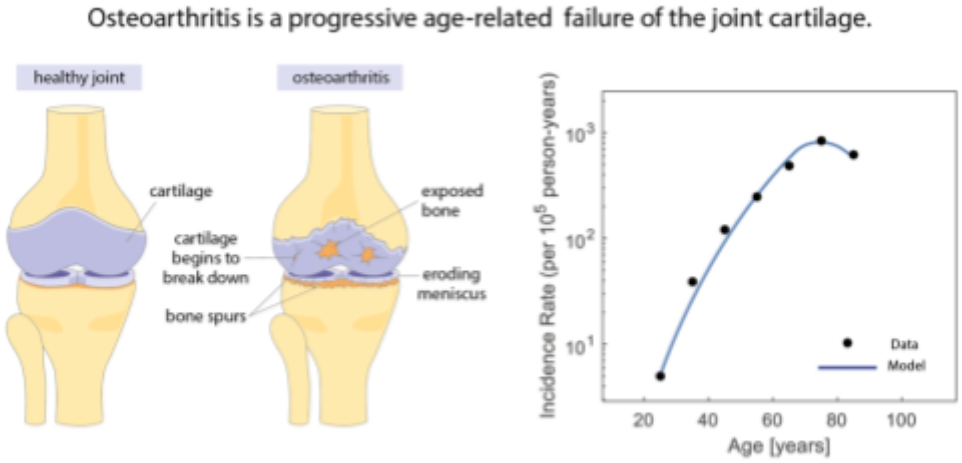


Figure 8.25: Osteoarthritis is a progressive age-related failure of the joint cartilage.

instead of collagen-2, making the tissue stiffer and less elastic. As a result, cracks form, leading to a hole that often goes right down to the bone.
This hole occurs in the part of the joint that bears the most weight, and thus has the highest cell removal rates (Fig. 8.25). People with knees that bend inward or outward have the damage at the appropriate side of the knee where load is highest.
Like IPF and virtually all age related diseases studied so far, removing senescent cells with senolytic drugs alleviates this disease in mice.
Thus, the two diseases IPF and osteoarthritis have a **mathematical analogy.** The removal rate of stem and differentiated cells is similar because both are at the front line. The removal rate varies across the organ and is highest where the most pressure occurs. Reducing the proliferation rate of S cells down towards their removal rate leads to a rise in the stem cell fraction S/D and eventually the cells are lost altogether. This reduction in S proliferation can be caused by SASP secreted by the senescent cells in the body, as well as local senescent cells in the joint.
Susceptibility to osteoarthritis, as in IPF, is due to genetic and environmental factors. The main environmental risk-factors for osteoarthritis is being overweight, which increases the load on the joints (Fig 8.26). To see this, note how the higher the body-mass index (BMI, mass divided by height squared), the larger the susceptible fraction s; BMI does not seem to affect the threshold X_c.

Genetic factors are also important, and osteoarthritis has about a 50% heritability. Risk genes include fiber components like certain collagens (including collagen-2) and other cartilage components, as well gene-variants for the signaling molecules IGF1 and TGF-beta relevant to the feedback circuit that helps S and D cells maintain homeostasis.

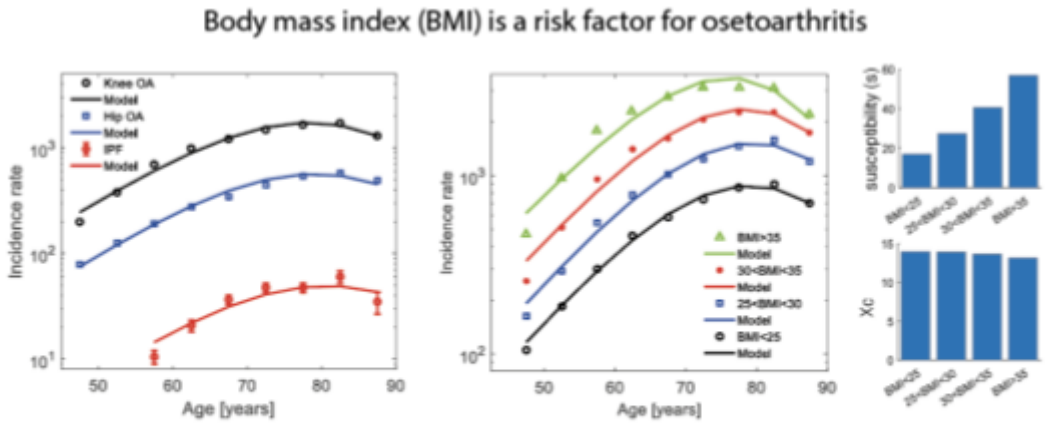


Figure 8.26: Risk of osteoarthritis rises with body mass index, by raising susceptibility not disease threshold. Adapted from (Katzir,2021).

It is intriguing that diseases as different as a lung disease and a knee disease might have common fundamental origins. In our periodic table in the next chapter, we can expect that other front-line tissues will have similar progressive fibrotic diseases. They form one column in the table.

The disease-threshold model thus reveals how diseases that seem very different are in fact deeply connected according to the type of threshold that is crossed. Cancer and infectious disease both involve exponential growth when proliferation exceeds removal. Progressive fibrotic diseases occur in the opposite transition, an exponential decline of cells when proliferation of front-line stem cells drops below their removal. When the stem cell population crashes the tissue cannot be renewed causing an injury that cannot be repaired.

We are ready to use the disease-threshold model to explore the dynamics of treatment for age related diseases.

Removing senescent cells can rejuvenate the incidence of age-related diseases by decades

Age-related diseases are currently treated one at a time. A change of paradigm is to treat them all at once by addressing their core underlying risk factor—aging itself. With our mathematical picture in hand, we can evaluate potential treatments for aging as a core process. We can ask what happens to disease incidence if senescent cells are removed.

In the previous chapter we mentioned at least three treatment strategies: reduction of senescent cell production by inhibiting the mTor pathway, senolytic drugs that kill senescent cells, and immune therapy that targets senescent cells.

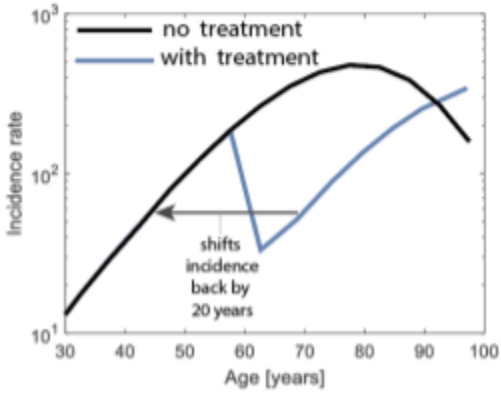


Figure 8.27: Removing senescent cells every month rejuvenates the incidence curve by two decades in simulations of the saturating removal model. In these simulations, only 25% of the senescent cells are killed by the drug.

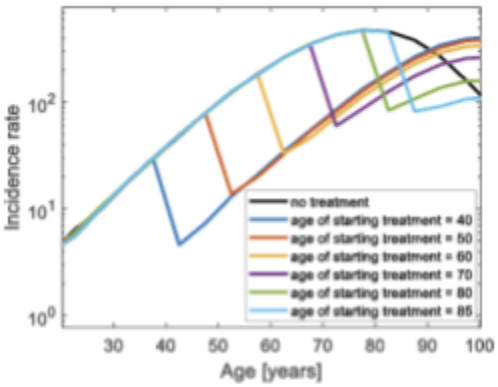


Figure 8.28: Treatment starting at old age is predicted to show rejuvenation of incidence curves.

Suppose a 60-year-old starts taking a drug once per month that removes senescent cells. We can simulate this using the saturating removal model by adding a killing term that represents removal of senescent cells due to the drug. Since senescent cells are reduced, they cross the disease threshold at older ages. This predicts dramatic consequences for disease incidence - a rejuvenation on the order of decades. The incidence curve of a typical disease shifts within months to resemble the curve of a younger population (dashed line in Fig 8.27).

Even killing only half of the senescent cells once every month rejuvenates by decades. This works even if we assume, as in Fig 8.27, that senescent cells account for only 25% of the damage responsible for the age-related disease, and the rest is due to currently unknown forms of damage not affected by the drug.

Notably, rejuvenation is predicted even when treatment begins at old ages (Fig 8.28).

Now there was nothing special about the disease we picked for Fig 8.27 and 8.28. Removing senescent cells should similarly reduce the incidence of all age-related diseases. Treating the major risk factor, aging itself, rather than treating one disease at a time can be a turning point in medicine,

Let’s take a nice deep sigh of relief to celebrate. We are ready to sum up the book in a periodic table of diseases.

Further Reading

Senescent cells and the incidence of age-related diseases. (Katzir et al. 2021)
The Geroscience Hypothesis: Is It Possible to Change the Rate of Aging? (Austad 2016)
A Disease or Not a Disease? Aging As a Pathology. (Gladyshev and Gladyshev 2016)
Pursuing the Longevity Dividend. (Olshansky et al. 2007)

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Solved example 8.1: Find an analytical form for the incidence curve and age of peak incidence for low s

The purpose of this exercise is to find an analytical form for disease incidence, using some approximations. An analytical form is often useful for understanding the more complex reality.
Let's assume that we have a cohort of susceptible individuals. The 'disease free' fraction at age t is F(t). The incidence I(t) is given by the number of disease-free individuals of age t that get the disease in the following year. The disease free individuals are made of those susceptible, ϕF(t), and those non-susceptible that survive to age t , (1-ϕ) S(t). Thus $I(t) = -\frac{\phi\frac{dF}{dt}}{\phi F+(1-\phi)S}$, where ϕ denotes the susceptible fraction in the population.

If we ignore the death rate of the non-susceptible population by setting S=1, and assume that ϕ is small, as it is for most diseases, we obtain I(t)=-ϕ dF/dt.

Let's write incidence in terms of the first-passage-time hazard rate of the disease - the number of people per year that get it out of the remaining disease free individuals, $h = -1/F\ dF/dt$. Thus $h = -d\ logF/dt$, and $F = e^{-\int_0^t hdt}$

Writing incidence in terms of hazard we have $I(t) = \phi\ h\ F$, or

$$I(t) = \phi\ h(t) e^{-\int_0^t hdt}$$

Now let's make a simple approximation for the SR-type model, by approximating the first passage time to cross a threshold goes as the Gompertz law without slowdown, $h = Ae^{\alpha t}$.
We thus find an analytical formula

$$I = \phi A\ e^{\alpha t} e^{-\frac{A}{\alpha}\left(e^{\alpha t}-1\right)}$$

Taking the log of incidence, we see a linear rise with slope α and then a drop at late times when the exponent term becomes large (Fig. 8.28)

$$log\ (I) = log\ (\phi A) + \alpha t - \frac{A}{\alpha}\left(e^{\alpha t} - 1\right)$$

We can now find the time of peak incidence. Taking $dlogI/dt = 0$ yields $\alpha = Ae^{\alpha}\ t$, and thus the time of peak incidence is $t_{max} = \frac{1}{\alpha}\ln\left(\frac{\alpha}{A}\right)$.

Solved example 8.2: Front line circuit maintains homeostasis using feedback

In order to keep the tissue at homeostasis, and in particular to maintain a proper concentration of D cells, front-line tissues need to have a feedback loop. In this feedback loop, D and S cells signal to each other by secreting molecules that affect differentiation and proliferation rates. If there are too few D cells, for example, these signals act to increase D cell production and restore homeostasis.

In the feedback loop found in the lung and joints, as well as in other stem-cell based organs like the skin, D secretes a signaling molecule that increases S differentiation (one such molecule is $TGF-\beta$, a strong signal for differentiation). S cells also secrete factors that increase their differentiation rate. Thus, differentiation rate is an increasing function of D and S concentrations, $q = q(S, D)$.

Let's see how this feedback works. Suppose there is a loss of D cells (Fig 8.29). Since D cells signal to increase differentiation, fewer D cells mean lower differentiation rate q. Thus, at first one makes even fewer D cells. This seems paradoxical. But the reduction in differentiation means that more S divisions go to making new S cells instead of D cells. S levels rise, and eventually the larger S cell population supplies more differentiation events per unit time than before the perturbation. D levels rise back. The timescale of this recovery in the alveoli is months, due to the turnover rate of about a month of the D cells (alveolar epithelial cells). In joints, the turnover time is probably much slower.

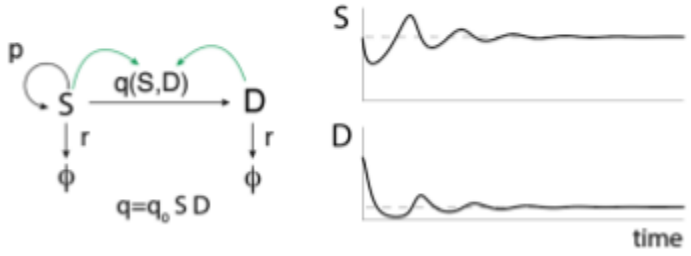

Figure 8.29: A front line tissue with feedback for homeostasis produces damped oscillations of cell numbers.

This feedback process shows damped oscillations and settles down to a proper steady state. As an aside, we can speculate, as in chapter 3, that such damped oscillations might entrain to the seasons and lead to seasonal changes in alveolar composition, with more S cells and thus more surfactant in some seasons and less in others.

We can also solve the model for various proliferation rates p to observe the rise in S and then the crash as p approaches r. We use a simple form for the feedback $q(S, D) = q_0 S D$.

Let's see what happens when the maximal proliferation rate, p, drops to approach the stem cell removal rate, r. To keep homeostasis, the feedback loop increases the number of S cells, compensating for the reduction in their proliferation rate.

When proliferation rate drops, the ratio of stem to differentiated cells S/D rises (Fig 8.30):

$$\frac{S_{st}}{D_{st}} = \frac{r}{p-r}$$

The fraction of S cells in the tissue diverges as proliferation p drops towards the S-removal rate r (Fig 8.30). When p<r, both S and D cells reach zero (Fig 8.31)

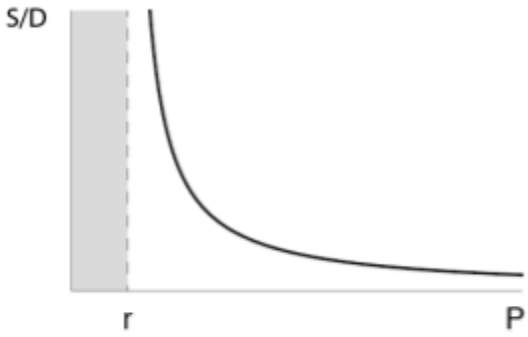

Figure 8.30: fraction of stem cells rises as the disease onset point is approached.

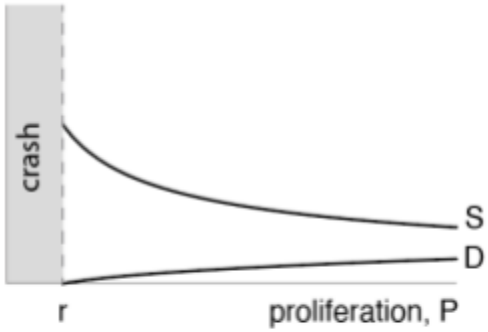

Figure 8.31: Differentiated cell numbers reach zero as disease threshold is approached.

Exercises:

8.3 Stem cell feedback that keeps constant S: Consider the following feedback loop in a labile tissue. Both stem cells and D cells secrete factors that increase differentiation rate. The differentiation rate is $q(S, D) = q_0 SD$.

(a) Write down the equations for this circuit.
(b) Simulate this circuit (or use linear stability analysis) and test whether the steady-state is stable.
(c) Show that the steady-state concentration of S cells is independent on S proliferation, p.
(d) What is the concentration of D cells as a function of p?
(e) Is the effect of this feedback biologically useful?

8.4 Oscillations in front-line tissue circuit: consider a feedback loop with a single interaction in which D increases differentiation rate $q(S, D) = q_0 SD$.

(a) Write the equations and simulate them.
(b) Explain the resulting oscillations in S and D numbers intuitively.
(c) Read about the predator-prey model in ecology called the **Lotka-Volterra** model. What is the analogy?
(d) Why are ecology population models for species population an interesting resource for modeling cell circuits?

8.5 Protected stem cells: Consider a tissue in which the stem cell removal rate r1 is negligible, whereas the D cells have a sizable removal rate r2.
(a) Suppose that a feedback loop provides a stable-steady state. What happens to the S/D ratio as S proliferation p is lowered? Is there a point of collapse?
(b) What diseases might characterize such tissues, more often than tissues with stem cells at the front line (high r1)?
(c) Design a feedback loop that provides D levels that are insensitive to variations in stem-cell proliferation p.

8.6 NK cell homeostasis circuit: NK cells are constantly produced by stem cells in the bone marrow. They have a high removal rate r2, with a lifetime of hours, unless they go

into the body's tissues and find cells that make a survival signal (IL15-IL15R). Most cells of the body produce this survival signal. When NK cells touch the donor cells, they receive the signal, and their death rate drops to zero. NK cells constantly patrol the body and go into and out of the blood stream and into the tissues.
(a) Write equations for NK cell numbers.
(b) What determines the NK cell lifetime of about a week in humans?
(c) NK cells were introduced into a mouse mutant that cannot produce its own NK cells. These cells lasted for at least six months. Explain this result.
(d) Explain how this homeostasis mechanism ensures that the number of NK cells matches the number of cells in the tissues that require NK cell surveillance.

8.7 Stem cell symmetric and asymmetric divisions: Consider the case where a stem cell can divide to form either two stem cells or two differentiated cells, 2S or 2D. This is called symmetric division. Asymmetric division is the case where there is also a third possibility of dividing to produce one D and one S cell.
(a) What is the difference in the mathematical equations for the S and D populations in the two cases?
(b) How does this affect the S/D ratio as proliferation p approaches removal r_1?

8.8 Two disease thresholds: Consider two age-related diseases with senescent cell thresholds X_{c1} and X_{c2}. Suppose the two diseases can occur in the same person (the person is susceptible to both diseases). What would you expect about the relative timing of the diseases in the same person? How would you test this hypothesis? What are some confounding factors?

8.9 Osteoarthritis: Explain why osteoarthritis occurs in certain regions of the joint. In the hip it occurs in the top part of the joint. In the knee it occurs at the inside rim in people with legs oriented slightly as an X-shape, and at the outside rim of the knee in people with a bowlegged, O-shaped configuration.

8.10 Removal rates: In healthy alveoli tissue there are approximately twice as many AT2 cells (S) than AT1 cells (D). Since S cells are smaller they make up only 7% of the surface area *Am Rev Respir Dis*. 1982). Estimate using the simple calculations in the lecture what is the ratio between S proliferation and removal rates. In the knee joint, progenitor cells (S) amount to about 4% of the total cell population, rising to about 8% in OA. What is the ratio of proliferation to removal rates?