Systems

Aging

Chapter 3 - Age Related Diseases

Uri Alon

Many diseases occur almost exclusively at old age. These age-related diseases include the four horsemen cancer, diabetes, cardiovascular disease, and neurodegenerative diseases such as Alzheimer and Parkinson. Other major killers at old age are hip fractures and death from viral infections such as flu and Covid. There is also failure and fibrosis (scarring) of specific organs such as kidney, lung and liver. There is osteoarthritis, cataract, hearing loss and many more.

In this lecture, we will understand why aging is the major risk factor for these diseases and explore the universality of their dynamics.

These diseases are currently treated one by one, and we will discuss how future medicine can take a major step forward by treating aging itself to address all of these diseases at once.

Just as there are many ways to be unhappy, each age-related disease is different. Some are overgrowth of cells, like cancer, others are loss of cells like muscle and neuron degeneration. Some are common and are rare. Each is a medical speciality of its own.

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 if you haven't gotten it yet. It is calculated by considering 100,000 people without the disease at age t and asking how many will be diagnosed over the following year upto age t+1.

And now for the pattern shared between hundreds of age-related diseases:
incidence rises exponentially with age and drops at very old ages (Figure 5.1).
The slope of the exponential increase is similar for different diseases, but not identical, around 3%–8% per year. This means a doubling of incidence every decade or two.

Understanding this exponential rise is the aim of this chapter. We need to understand why age 20 is different from age 70 in ways that make these diseases so much more likely. We will also understand why incidence drops at very old ages - in contrast to the hazard of death that merely slows down.

Another goal of this chapter is to explain why aging is such a strong mechanistic driver of diseases. It doesn't cause the diseases, it generates the necessary conditions . In doing so we

will see mathematical analogies between diseases. This forms columns in the periodic table of diseases featured in my book Systems Medicine (2023).

To tackle diseases we have three lines of defense- prevention, screening and treatment. Treating a disease early is often much easier and hence screening for early disease is lifesaving (colonoscopy, mammograms, blood tests for lipids, blood pressure, glucose). Screening is making great progress with new blood-based markers such as circulating cancer DNA and Alzheimer proteins. So if you care about longevity, please don't die of a screenable disease.

Treatment is also being revolutionised - after decades of slow progress- finally moving the needle on treating Alzheimer's (anti-amyloid antibodies), metastatic cancer (immunotherapy), and obesity and diabetes (glp1 agonists, sglt2 inhibitors).

But the holy grail is prevention - the best defense is not to get the disease at all. And we will see how slowing aging can potentially prevent or delay all of these diseases elegantly, at once.

DISEASES CAUSED BY THRESHOLD CROSSING OF SENESCENT CELLS HAVE AN EXPONENTIAL INCIDENCE CURVE

To understand age-related disease incidence, we will use our houses and trucks model. Itay Katzir developed this model for diseases during his PhD with me (Katzir et al. 2021).

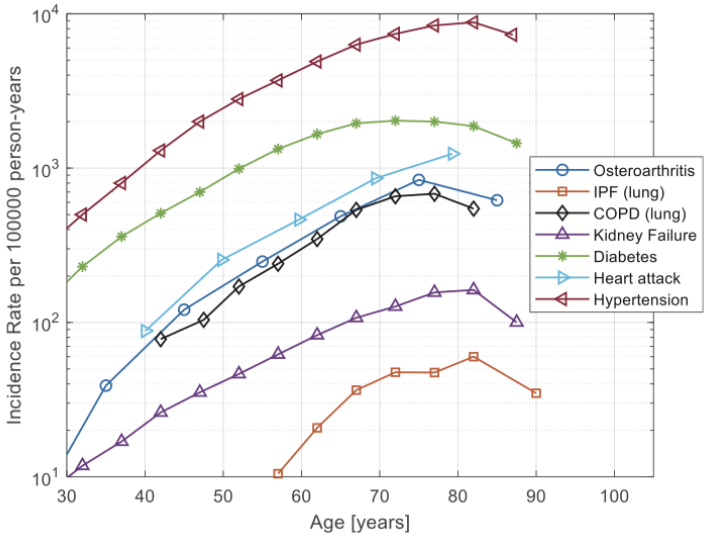


Figure 5.1

The basic idea is that diseases of old age are due to a phase transition (also known as a bifurcation) in which the stress of aging- inflammation, overloaded trucks, stem cell exhaustion - pushes a parameter of a physiological circuit beyond a threshold. Once the threshold is crossed, the circuit behavior changes catastrophically: cells grow without control as in cancer or die without control as in degenerative diseases.

Aging indeed affects the parameters of physiological circuits. In particular, senescent cell load X induces systemic inflammation and reduces regeneration, which changes circuit parameters. Above a certain level of x, the circuit undergoes a bifurcation-its healthy steady state becomes unstable and pathology emerges. Therefore, 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** Xd .

Although each disease has its own threshold Xd , the underlying senescent cell dynamics are common to all diseases. These dynamics are described by the saturating removal model with its houses, garbage and trucks. When the concentration of senescent cells X crosses the disease threshold, the individual gets the disease (Figure 5.2). Each individual crosses the threshold at different times, due to the stochastic nature of the dynamics of senescent cells.

The time of disease onset is therefore the time when senescent cell concentration first crosses the threshold Xd – a first-passage time problem.

Conveniently, 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 Xd rises exponentially with age, with an exponential slope of approximately
$\alpha \approx \frac{\eta X d}{\epsilon}$. The reason is the same- the older you are the more garbage and the fewer coin flips of noise are needed to cross the threshold.

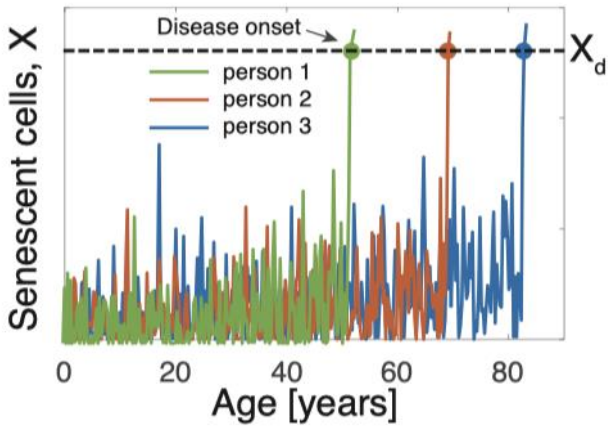


Figure 5.2

Here η and ϵ are the senescent cell production (houses) and noise parameters.

This explains the exponential rise of disease incidence curves. Since diseases have different exponential slopes, each disease must have its own threshold Xd . The disease threshold must

not exceed the death threshold Xc=17, otherwise the model would predict that death precedes the disease, and we would not observe the disease.
the disease threshold is this be smaller than the death threshold, and therefore the exponential slope of incidence is predicted to be smaller than the slope of the death hazard, 9% per year. Indeed almost all age related diseases have slopes of 3-8% per year as mentioned above.

DECLINE OF INCIDENCE AT VERY OLD AGES IS DUE TO POPULATION HETEROGENEITY

If this were all, everyone would cross the disease threshold 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. It is the chance to get the disease in a lifetime- small for rare diseases and close to one for very common ones like cataract. Some conditions are rare with low φ , such as kidney disease which happens in a few percent of the population, others like hypertension and osteoarthritis are common, with φ exceeding 0.1. The precise value of the susceptibility depends on genetic and environmental factors, as we will discuss.

The notion of a susceptible fraction is a form of population heterogeneity, as studied 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 Xd . The remaining population has higher values of the disease threshold that are not reached during normal aging.

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. This results in the decline in incidence rate.

The model thus has two parameters for each disease: the disease threshold and the susceptibility (see math appendix for more details)

We can now find the best-fit values of X d and φ for a given empirical incidence curve and see how well the disease-threshold model captures the data. In fact susceptibility only determines the numeral height of the incidence, and its shape- slope,
One pt and age of maximal
Incidence- are determined by a
Single number for each disease the threshold - Xd.

THE MODEL DESCRIBES WELL THE INCIDENCE CURVES OF HUNDREDS Of AGE-RELATED DISEASES

To test this model requires a global set of incidence curves. We are lucky to have access to the large medical record database from Clalit health services - a nationwide database of several Million people over 20 years.

The data includes about 900 disease categories that are 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 (Figure 5.5).

The disease-threshold model captures the data well (Figure 5.5). It 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 Xd ranges between 12 and 16.

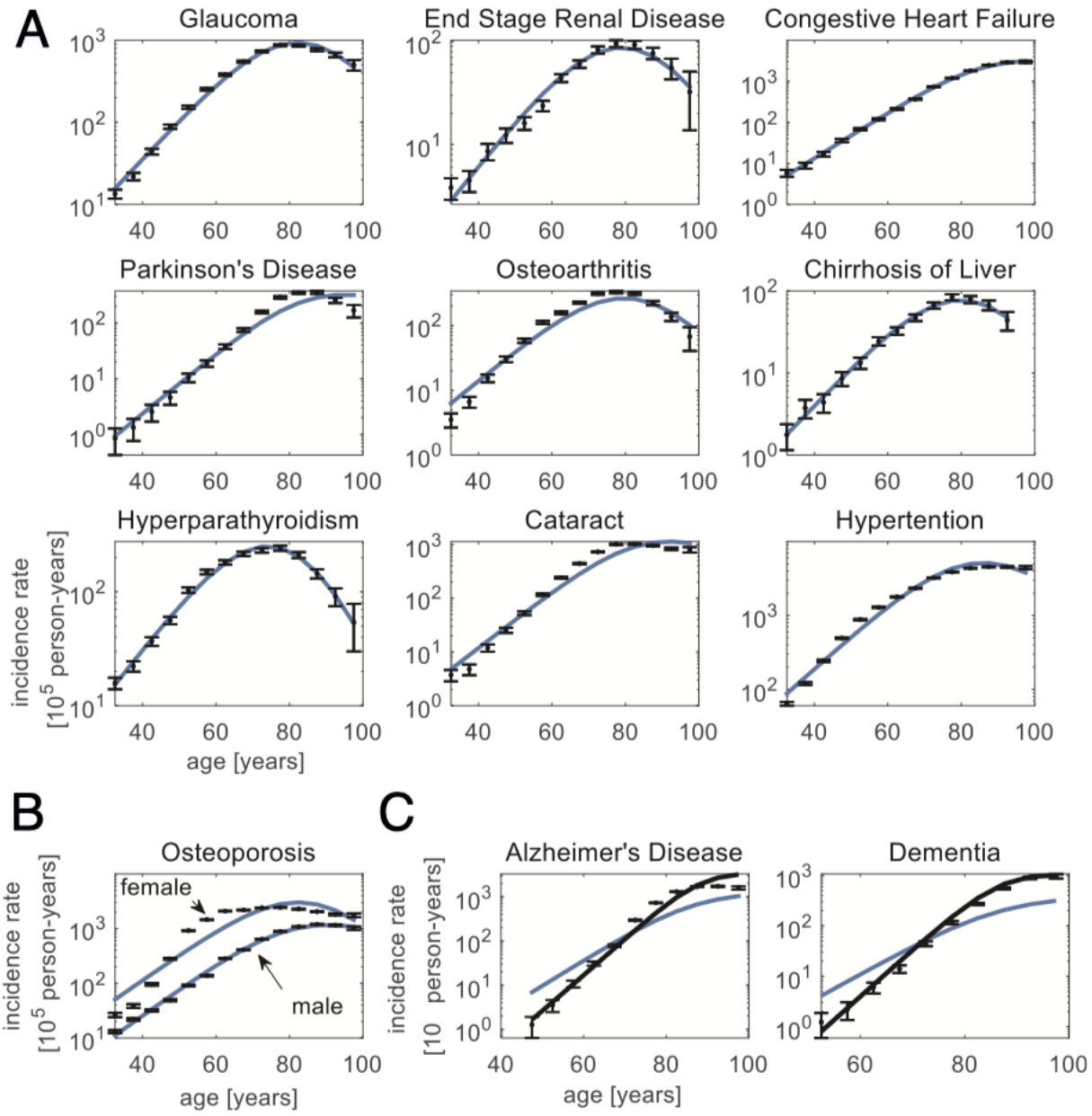


Figure 5.5

The model does not, however, describe well the incidence of several age-related diseases. A notable example is osteoporosis in women (Figure 5.5B). The incidence curve rises sharply after age 50, due to effects of menopause, in a way that the model cannot capture. On the other hand, osteoporosis in men is well described by the model (Figure 5.5C). This suggests that menopause-related changes go beyond the current framework. We will devote a chapter to menopause.

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 d = 20 that exceeds the threshold for death X death =17 (black line in Figure 5.5C). The best fit with the maximal Xd values equal to the death threshold underestimates the incidence slope (blue lines in Figure 5.5C).

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 makes sense because the brain is a protected organ with its own version of immune function. One candidate for this brain-specific damage might be accumulation of defective lysosomes, mitochondria and protein aggregates in neurons causing neuroinflammation. This is consistent with the damaged mitochondria and protein aggregates that are found in neurodegenerative diseases.

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

In fact, it is amazing that with one number Xd, the model captures the entire shape of each curve. For example, consider 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 (Figure 5.5). But the data shows otherwise: the steeper the curve, the later the peak incidence. Why? Because steeper incidence curves happen to begin lower, as defined by their intercept, namely the extrapolated incidence at age zero (See Figure 5.5, age = 0).

Remarkably, the disease-threshold model exhibits this pattern. The steeper the slope, as described by a higher disease threshold Xd , the later the peak incidence (Figure 5.6) and the lower the intercept- just as in the data.

This can be seen mathematically too (appendix) The reason is that the slope rises linearly with the disease threshold, but the intercept at age

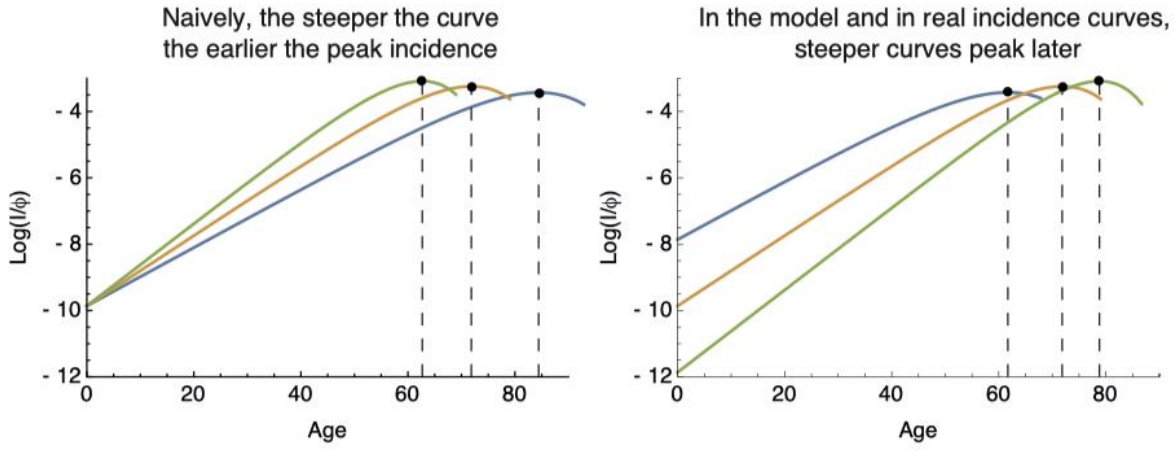


Figure 5.6

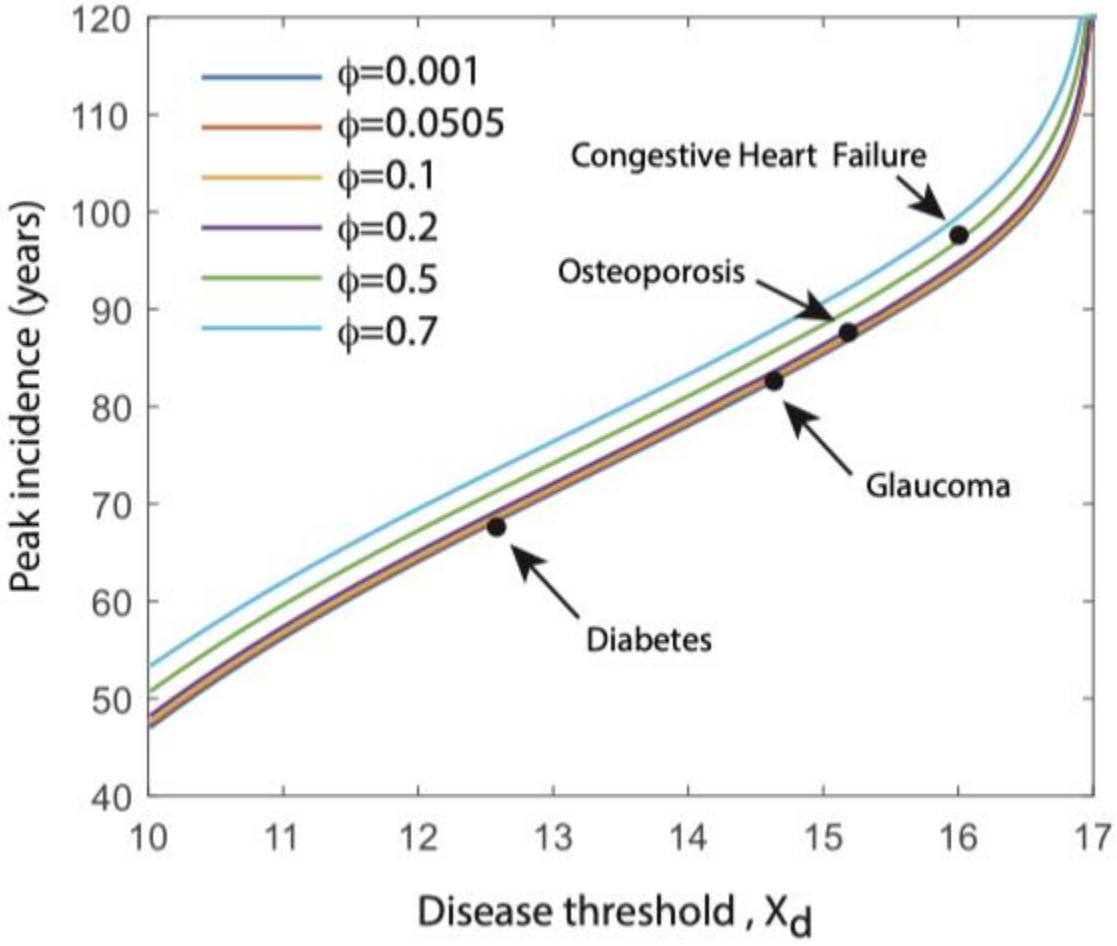


Figure 5.7

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

But how exactly does each specific disease occur when senescent cells cross a threshold? We need to link senescent cells to 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 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. The right conditions for cancer to thrive include inflammation, when normal cells slow their growth and cancer cells can shine.

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 a million 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.

The 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.

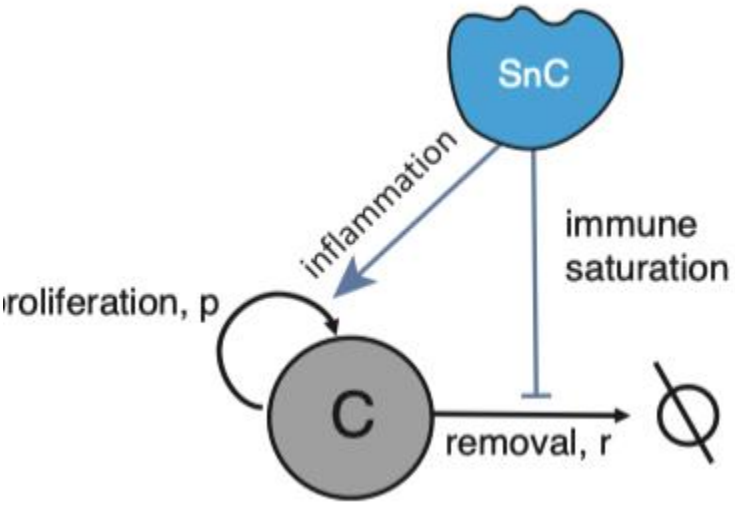
More shockingly, there are many cells with a full set of cancer driver mutations in healthy young tissues. But these cells do not progress to cancer. For example sampling of colon crypts showed that about 1% of crypt cells in healthy mid aged individuals have cancer mutations but they very rarely develop into colon cancer. about 30% of skin cells have driver mutations for basal cell carcinoma PMID: 38571416

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 (Figure 5.8). 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 (Figure 5.8). This is called a knife's-edge equation: the fate of cancer cells switches from death to thriving once production exceeds removal- a sharp bifurcation .

Both growth and removal of cancer cells are affected by senescent cell load X. With age, rising senescent cell levels overload the trucks- the NK cells and macrophages- inhibiting the capacity of the immune system to remove cancer cells. Trucks cannot keep up with the demand for cancer removal services. Thus, cancer removal rate r drops with the number of senescent cells, r = r(X) .



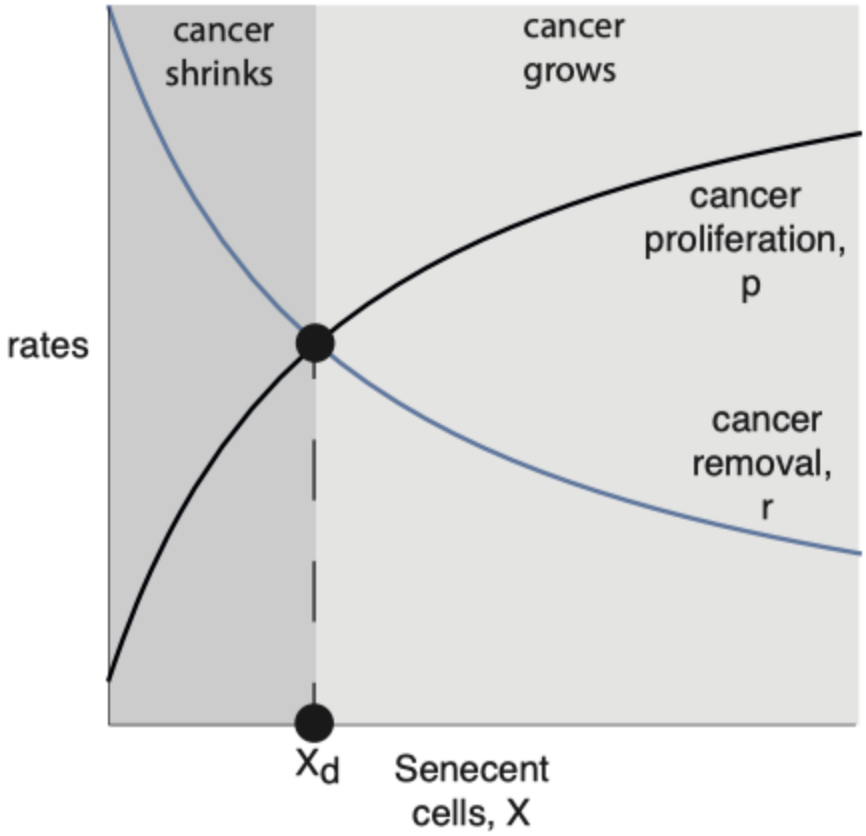


Figure 5.8

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, increasing proliferation p and lowering removal r, push cancer toward the threshold where proliferation exceeds removal.

The senescent cell level where this occurs is our disease threshold Xd (Figure 5.8).

Individuals susceptible to a given form of cancer include those with genetic factors (e.g., BRCA mutations for breast and ovarian cancer) or exposure to environmental factors such as smoking for lung cancer and UV for skin cancer. Obesity also increases the risk of many types of cancer.

These factors increase the probability of sporadic occurrences of the cancer cells in the tissue, or the propensity of cancer to proliferate. 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 ($R^2 > 0.9$) (Figure 5.9). The typical values of Xd are 13–15, and the susceptibilities for different types of cancer range from 10^{-4} to 0.1. Note once more that the higher the slope the lower the intervention the incidence curves as expected.

There are several types of cancer with a poor fit to the model (Figure 5.9b), 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.

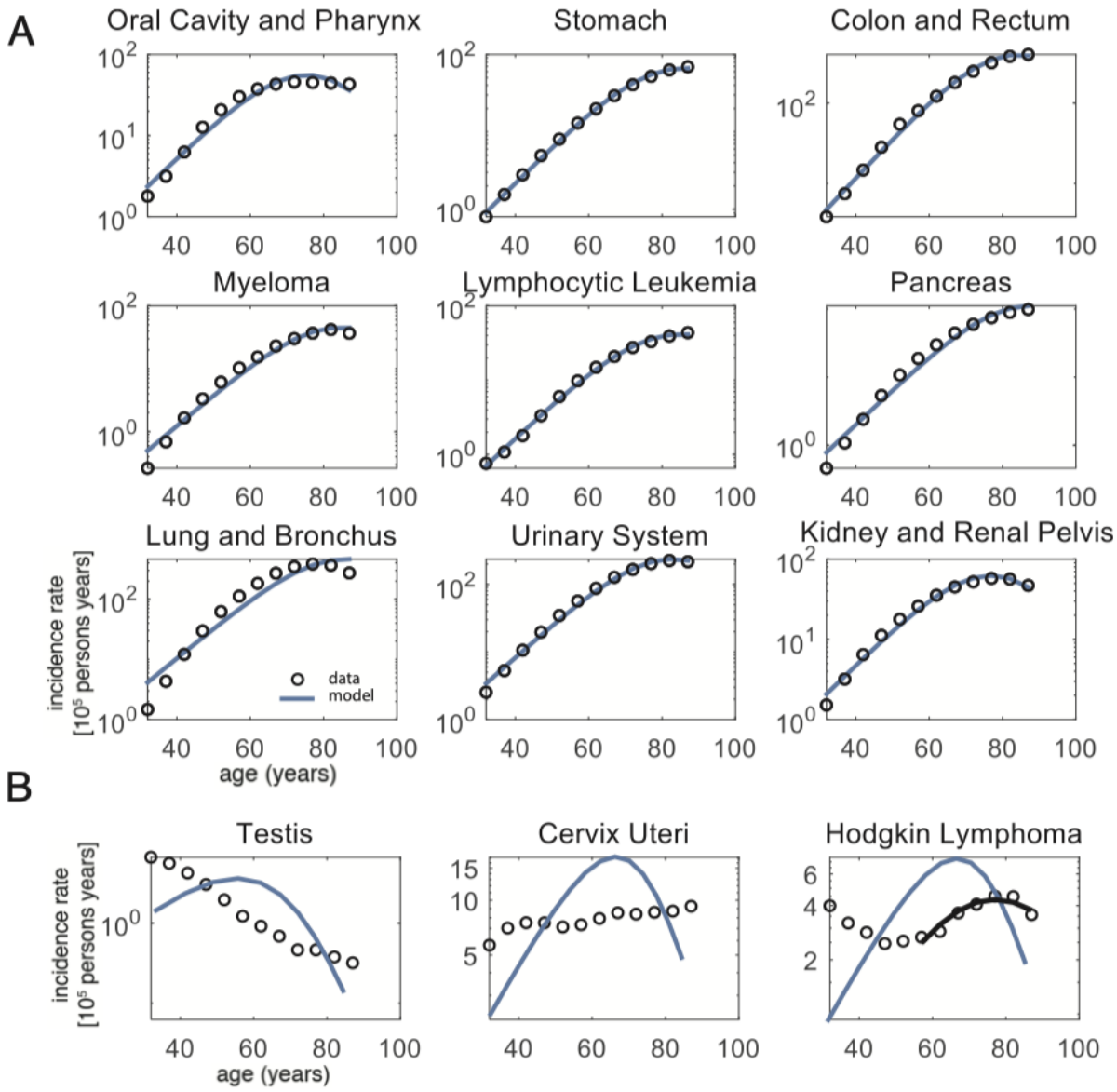


Figure 5.9

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. In many infectious diseases, mortality rate rises exponentially with age (Figure 5.10).

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-edge equation as cancer cells,

$dN/dt = (p - r) N.$

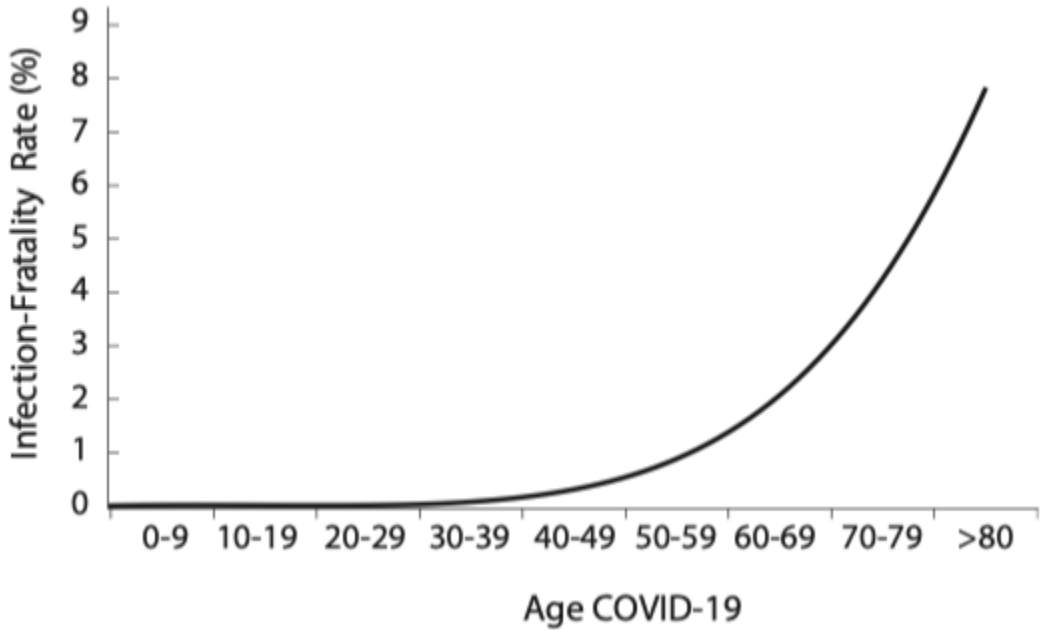


Figure 5.10

Infections become deadly when they grow exponentially, that is when p > r. The host is then 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 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 X d is reached, where removal equals proliferation r (X d) = 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 belongs to the same mathematical class – they are eliminated at young ages but have a phase transition at a critical point Xd , where they grow exponentially, giving rise to the observed incidence curves.

A similar picture applies to degenerative diseases

Other age related diseases originate form the same equation but with catastrophic removal of cells instead of unchecked growth. These are degenerative diseases and fibrotic diseases.

With age SASP factors released by X cause slowdown of stem cell renewal - slowed regeneration. Many tissues depend on stem cell replenishment - such as lung cells that bring in oxygen and the chondrites in weight-bearing joints like knees or hips. These tissues face mechanical stresses of breathing and weight bearing. At young ages there is no problem - removal of cells is easily compensated by renewal from the stem cells. However with age the maximal proliferation capacity of the stem cells drops. In most individuals it never drops below removal.

But in those with risk factors- smokers for lungs, obese for joints- removal is so high that renewal drops below removal at a critical level of X, namely Xd. At that point cells die more than are made. The tissue tries to fill up the hole- by scarring in IPF, and brittle fibers in the knees that lead to breaks in the cartilage and osteoarthritis.
The timescale of the catastrophe (the decline after Xd is crossed) is determined by the removal Rate of the cells- months in the lung, years in the knee. Despite their vastly different organs, these diseases are mathematically analogous.

Risk factors raise the incidence curve parallel to itself- high BMI raises the susceptibility phi, and not the threshold. More details in the appendix.
Let’s take a nice deep sigh of relief.

Removing garbage CAN delay 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.

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 Figure 5.20).

Even killing only half of the senescent cells once every month rejuvenates by decades. This works even if we assume, as in Figure 5.20, 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 (Figure 5.21).

Now there was nothing special about the disease we picked for Figures 5.20 and. Removing senescent cells should similarly reduce the incidence of all age-related diseases.

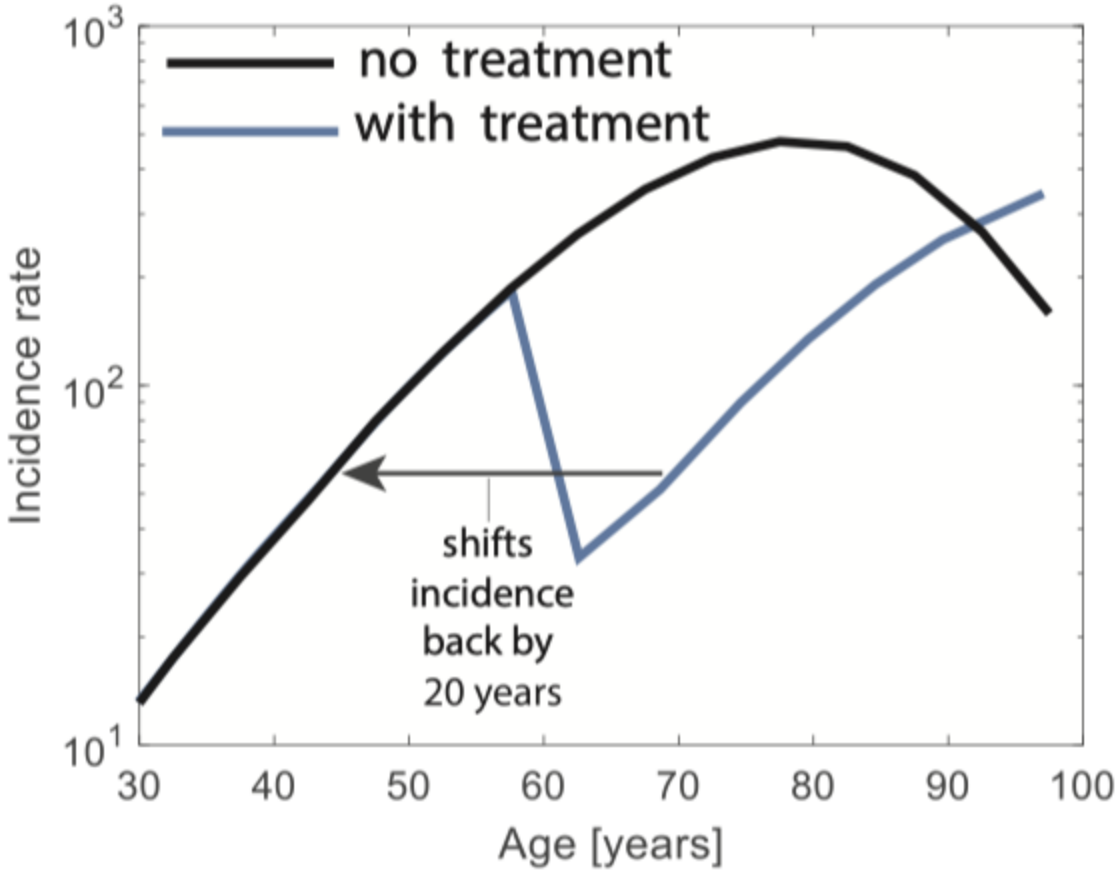

no treatment
with treatment
Incidence rate
10^3
10^2
10^1
shifts
incidence
back by
20 years
30
40
50
60
70
80
90
100
Age [years]

Figure 5.21

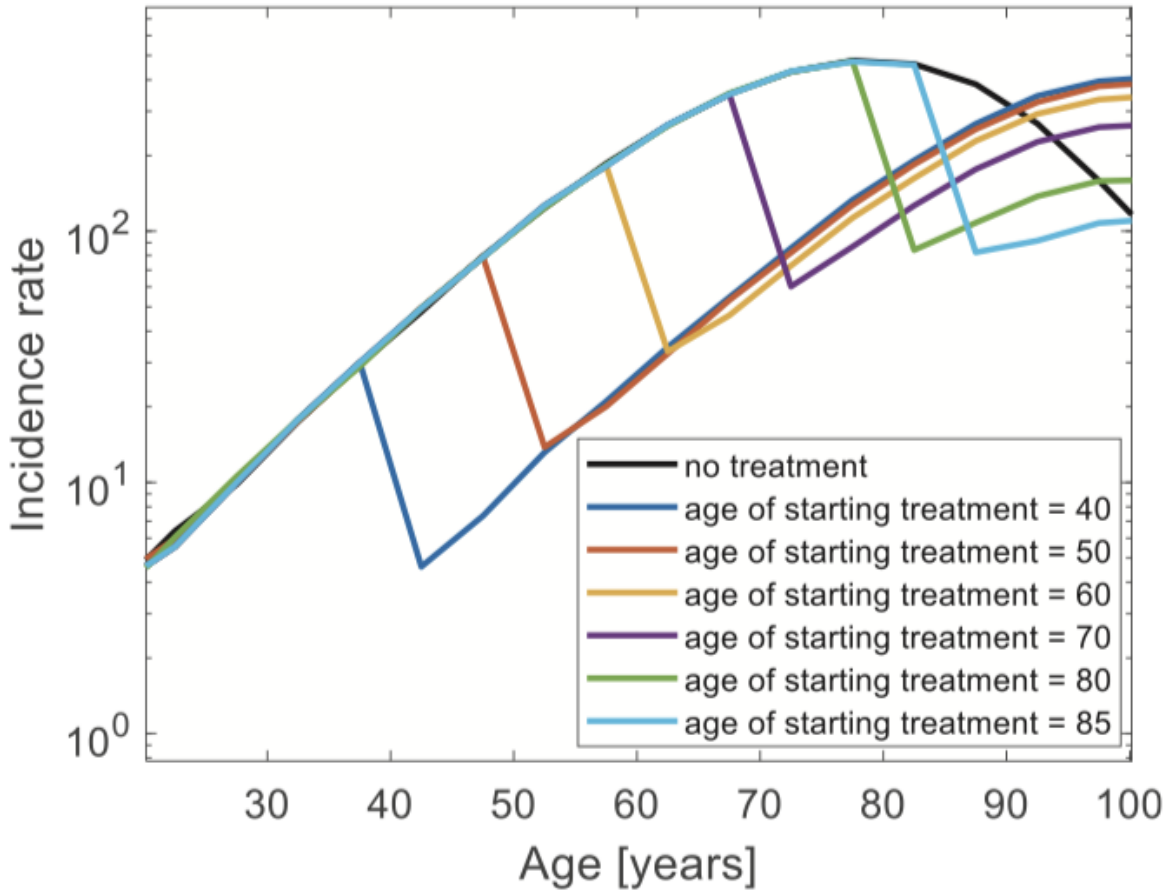


Figure 5.22

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.

Appendix 0
Attia outlive chapter 2
Medicine in 1900 focused on infectious diseases which were big killers. Most of the improvement since has been due to their mitigation by antibiotics and vaccines- if you subtract death from the top 8 infectious diseases, overall mortality declines relatively little over the 20th century, Gordon 2016. The spike at 1918 is the Spanish pandemic.

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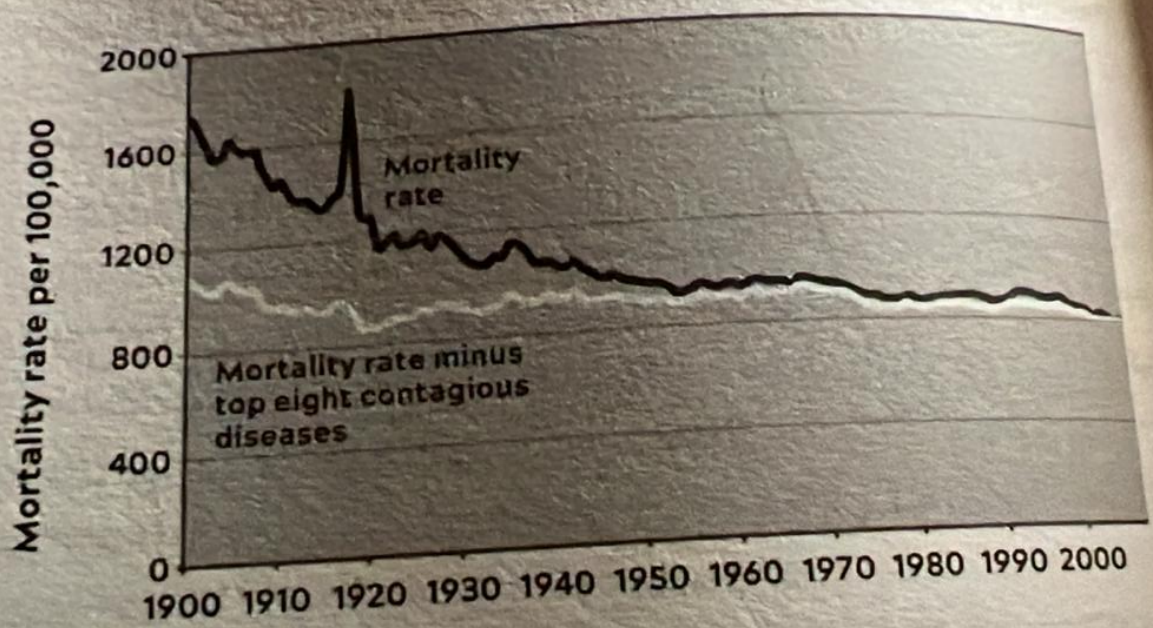
Figure 1. **Change in Mortality Rates Since 1900**



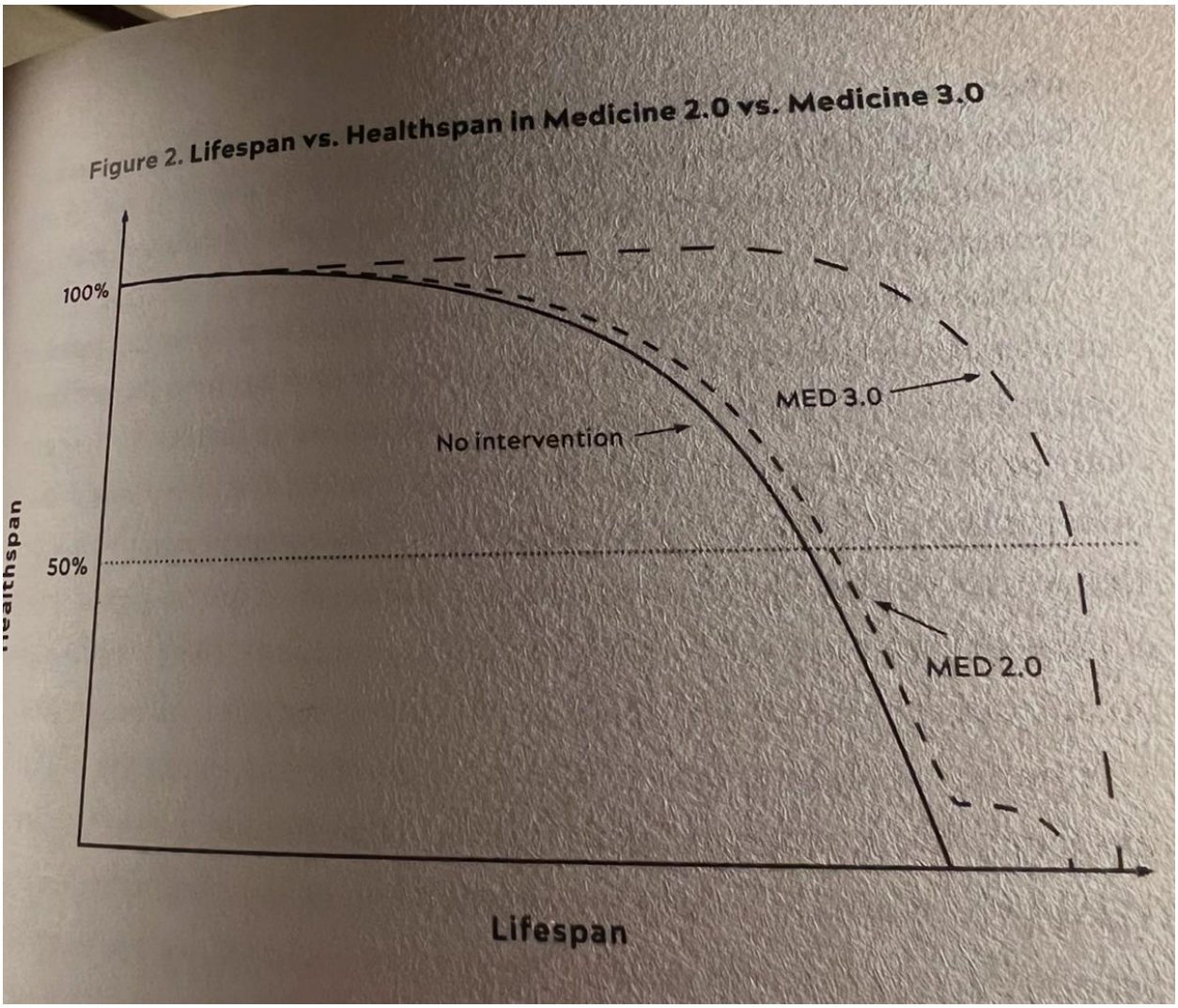
This graph shows how *little* real mortality rates have improved since 1900, once you remove the top eight contagious/infectious diseases, which were largely controlled by the advent of antibiotics in the early twentieth century.

Source: Gordon (2016)

Attia outlive chapter 3

Natural course health declines, reaching halfway around age 70 (in our linear decline if it starts at 30 ends at 110 you get halfway at 70!)
Below that halfway point it's not easy to do the things you enjoy.
Medicine 2.0 extends a little due to our comfortable lifestyle, and when you get chronic disease can extend- but at a point where health is low- the marginal decade.

The dream is to desire the health curve- more area under the curve you can enjoy a last bonus decade. You can work or do meaningful things and the period of low function is short.



Appendix 1

P

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”

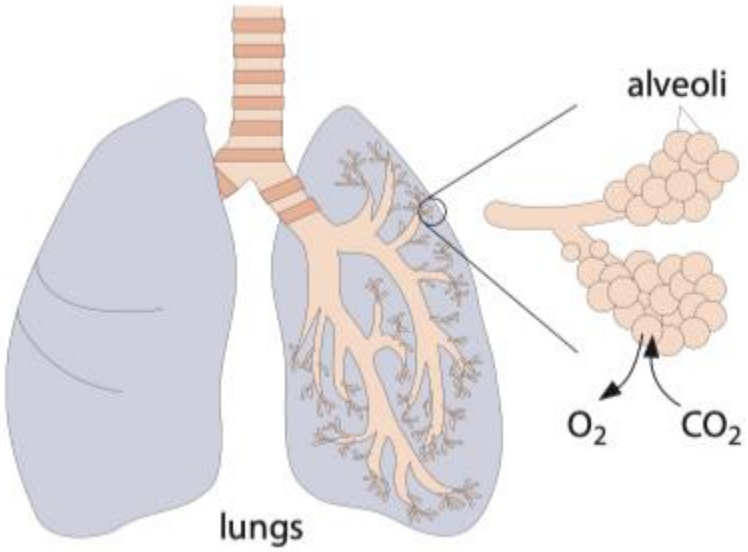
means disease of unknown cause, “pulmonary” means lungs, and “fibrosis” means excess scarring.

In IPF, lung capacity is progressively lost due to the scarring of tissue that is essential for breathing (Martinez et al. 2017). It is a chronic progressive disease that has no cure; patients often die within 1–3 years. The lifetime susceptibility to IPF is about $\varphi = 10{-}4$. Its incidence rises exponentially with age and then drops (Figure 5.1).

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 (Figure 5.11). The alveoli let oxygen from the air go into the blood and let CO_2 out. The alveoli are made of a thin epithelial layer that is one-cell thick surrounded by an interstitial layer. IPF scarring occurs in the interstitial layer around the alveoli (Figure 5.12).

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 (Figure 5.13). 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 macrophages. Macrophages are ready to gobble up bacteria and particles that make it through the layer of S and D cells. The fibroblasts produce the fibers which make the elastic sheath around the alveoli.



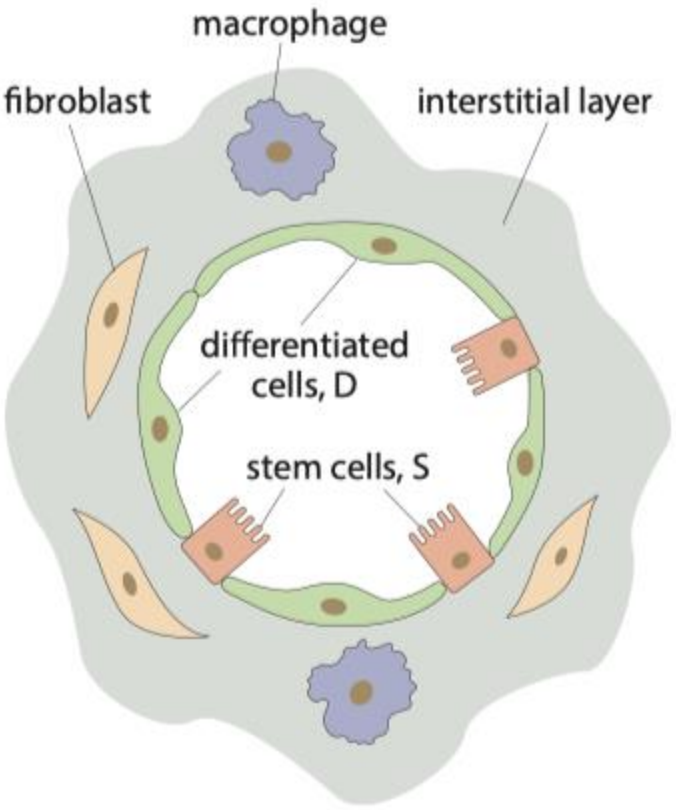
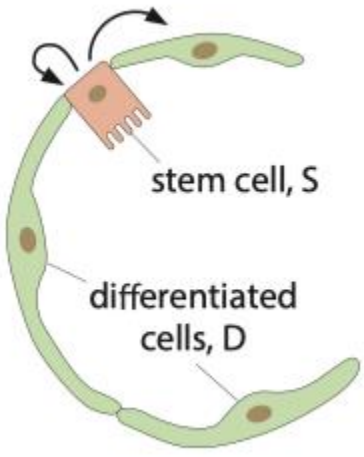


Figure 5.11

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 (Figure 5.12). These injury signals also cause S cells to activate inflammation in the interstitial layer to start a healing process.



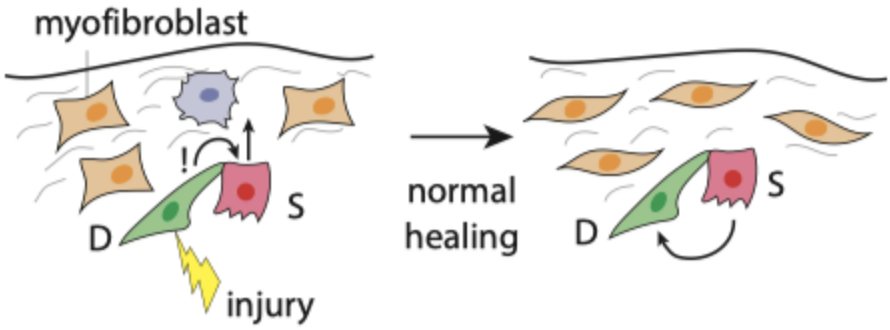


Figure 5.12

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 (Figure 5.14). 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.

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

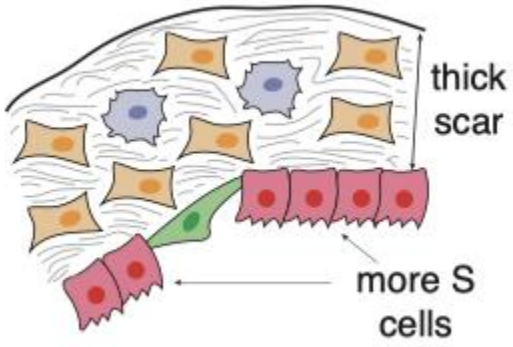


Figure 5.13

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 reduces fibrosis in IPF mouse models (HernandezGonzalez 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 (Figure 5.14).

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 (Figure 5.14).

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, the skin stem cells in the deep epithelium, and the gut stem cells tucked away at the bottom of crypts (Figure 5.14).

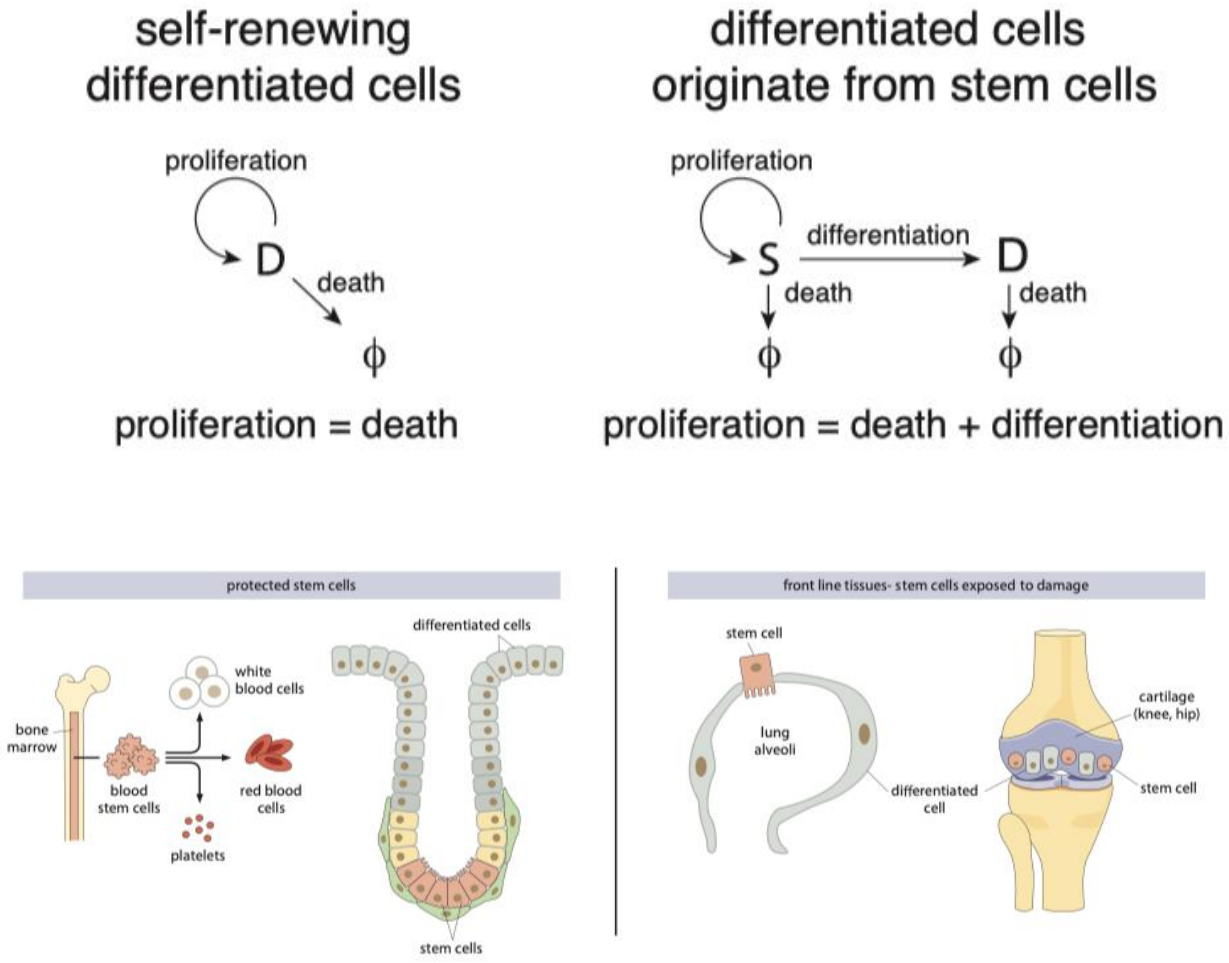


Figure 5.14

In contrast, the lung alveoli are an example of a tissue where stem cells 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

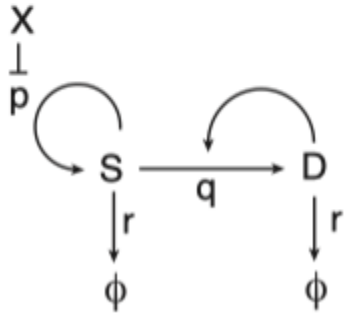
In front-line tissues, stem cells are exposed to damage and removed often. Homeostasis is harder to achieve than in tissues in which stem cells are protected, because of the high rate of removal of stem cells.

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 write down the basic equations (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:

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

$$\frac{dD}{dt} = qS - rD$$



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 TGF-beta that increase the rate of differentiation q, and thus q = q(D). This feedback acts to restore homeostasis when cell numbers are perturbedPioneering 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 to get an equation for the total number of cells S + D

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

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

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

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 (Figure 5.15).

After the collapse, tissue repair cannot proceed by regeneration because there are no more stem cells. Instead the tissue resorts to processes such as fibrosis, cell migration, and metaplasia, which are doomed to fail. Fibrosis reduces tissue function and pathology occurs.

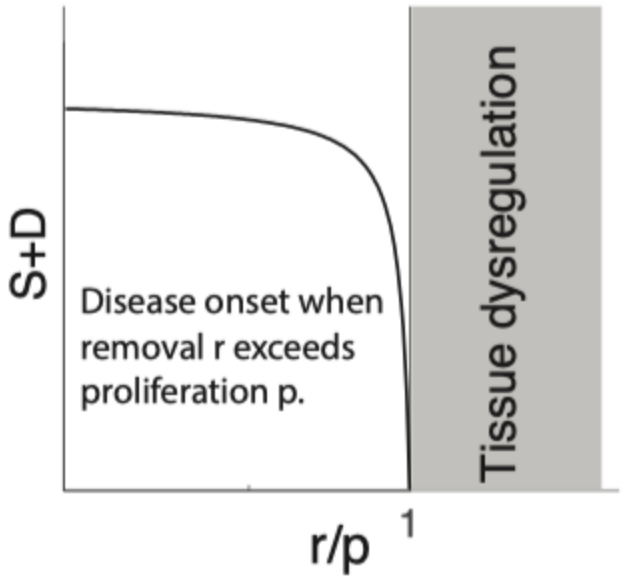
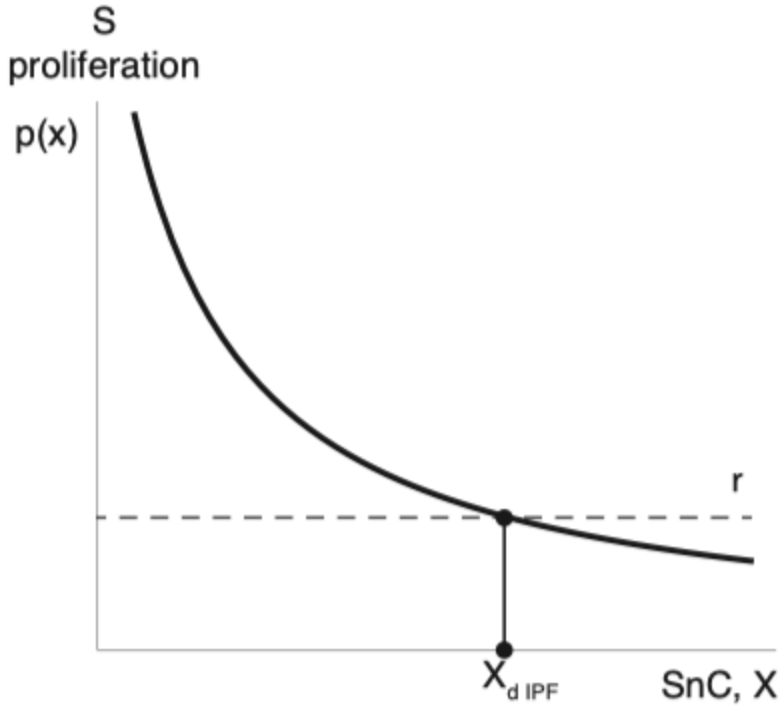


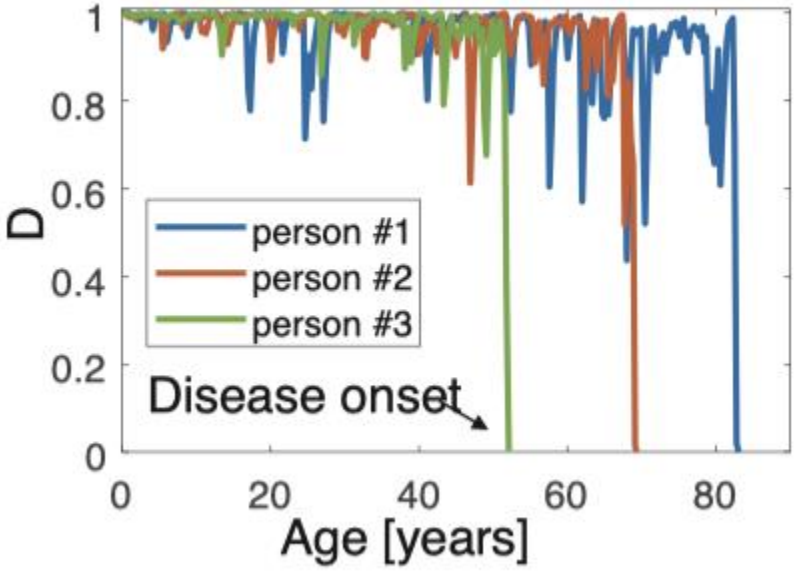
Figure 5.15

Next, we need to understand how aging can cause the crossing of proliferation and removal rates, namely the failure point. Senescent cells affect proliferation and removal in a way that pushes them toward the threshold (Figure 5.15). 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), Figure 5.15. When senescent cells cross a threshold Xd , 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 in different individuals (Figure 5.17), according to the time that senescent cells cross the disease threshold (Figure 5.17).

IPF is thus a threshold-crossing disease, and the 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 age, as is indeed observed (Figure 5.17).

The circuit also explains the clinical observation that the amount of S cells relative to D cells begins to rise before disease onset. This is due to the feedback in the system, which


S
proliferation
p(x)
r
$X_{d\ IPF}$
SnC, X


1
0.8
0.6
0.4
0.2
0
D
person #1
person #2
person #3
Disease onset
0
20
40
60
80
Age [years]

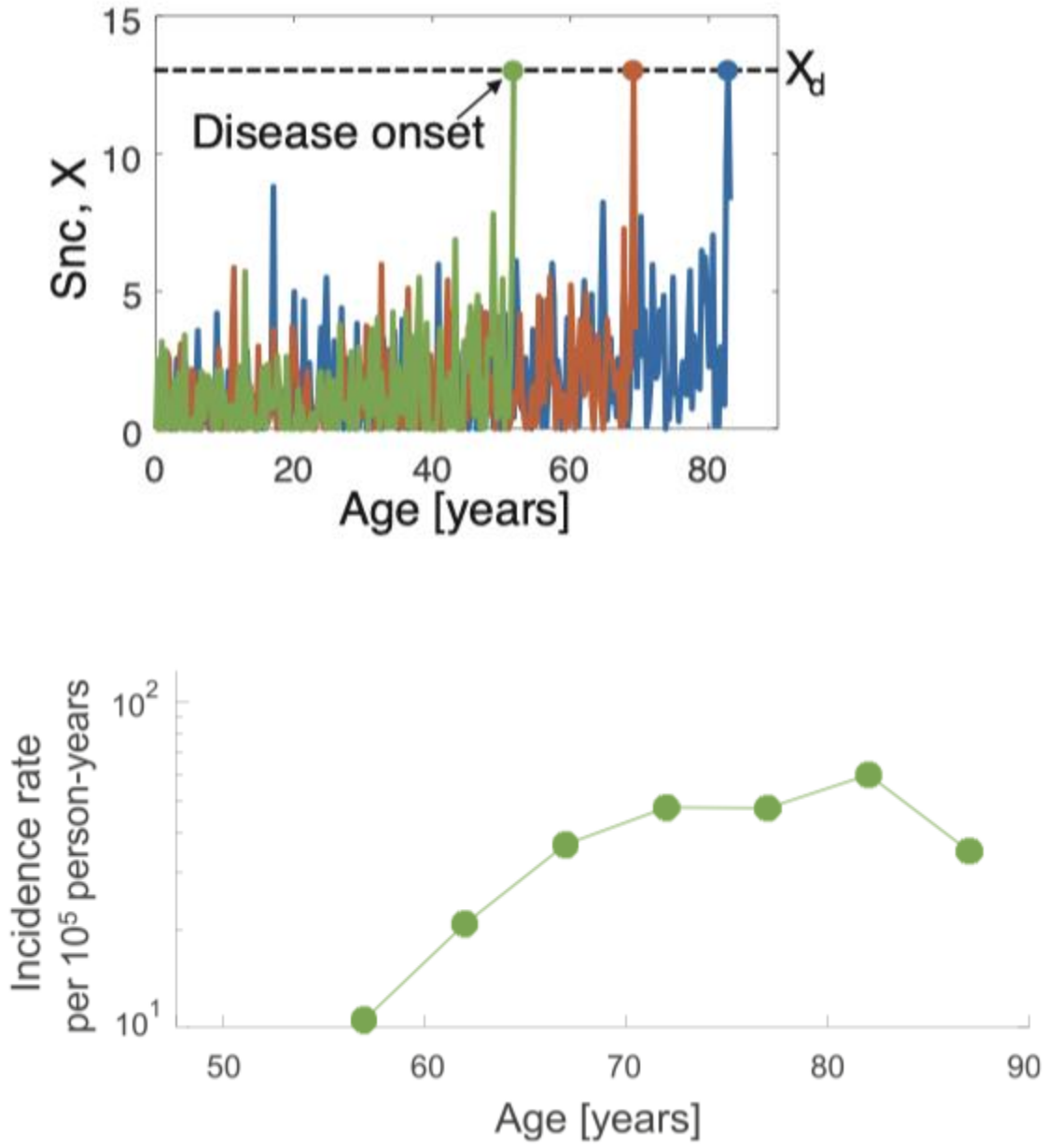


Figure 5.17

attempts to ward off the collapse by increasing stem cell numbers. This is a last-ditch attempt to supply the needed number of divisions per unit time to counteract the loss of cells.

Such a threshold for failure is less of a concern in the circuit for protected stem cells, which have low stem-cell removal rate. Thus, front-line tissues are expected to show age-related fibrotic diseases much more commonly than other tissues.

Now that we understand the origin of the disease threshold, let's also understand 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 always stays above removal. The lungs work fine, there is no disease.

But in a small 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.

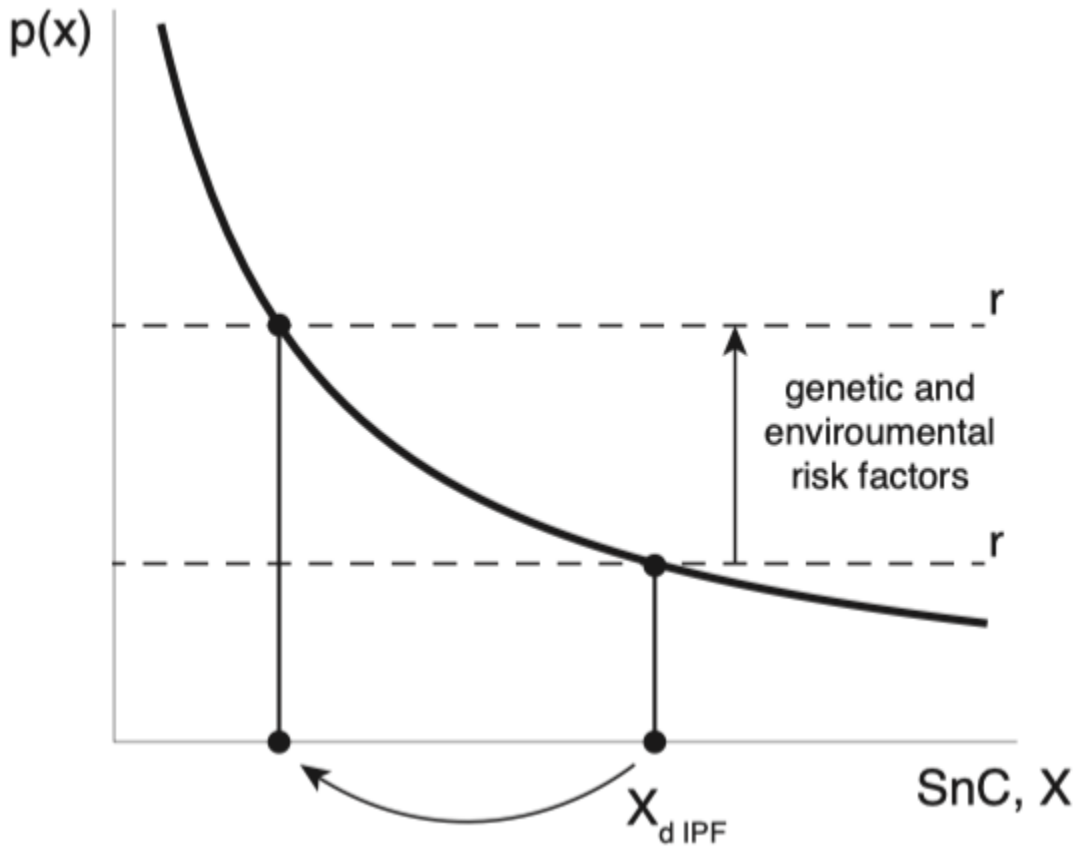


Figure 5.18

To understand this, we can examine the genetic risk factors for IPF (Martinez et al. 2017). 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 d (Figure 5.18). 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 elevated removal in IPF also explains why fibrosis begins at the outside of the lung, and then progresses inward. At the outside of the lung, the mechanical stress on the alveoli, and hence removal rate, is highest.

IPF IS MATHEMATICALLY ANALOGOUS TO ANOTHER AGE-RELATED DISEASE, OSTEOARTHRITIS

This theory of IPF can be generalized to other front-line organs, to understand a range of seemingly unrelated diseases. One such disease is a disease of the joints called 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. The disease most commonly affects joints in knees, hips, hands, and spine. Its symptoms are pain and stiffness in the joints, which can be debilitating. It is a progressive disease with no cure except joint-replacement surgery.

The joint is made of a tough fibrous cartilage. The business end of the cartilage is a smooth surface 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 age,

osteoarthritis can set in. In a process that takes many years due to the very slow turnover of the chondrocytes, D cell number declines, and the fraction of S cells increases. The S cells make tougher fibers than in normal cartilage, such as collagen-1 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 (Figure 5.19). 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. Stem cells are challenged with a high removal rate because they 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 toward their removal rate leads to a rise in the stem-cell

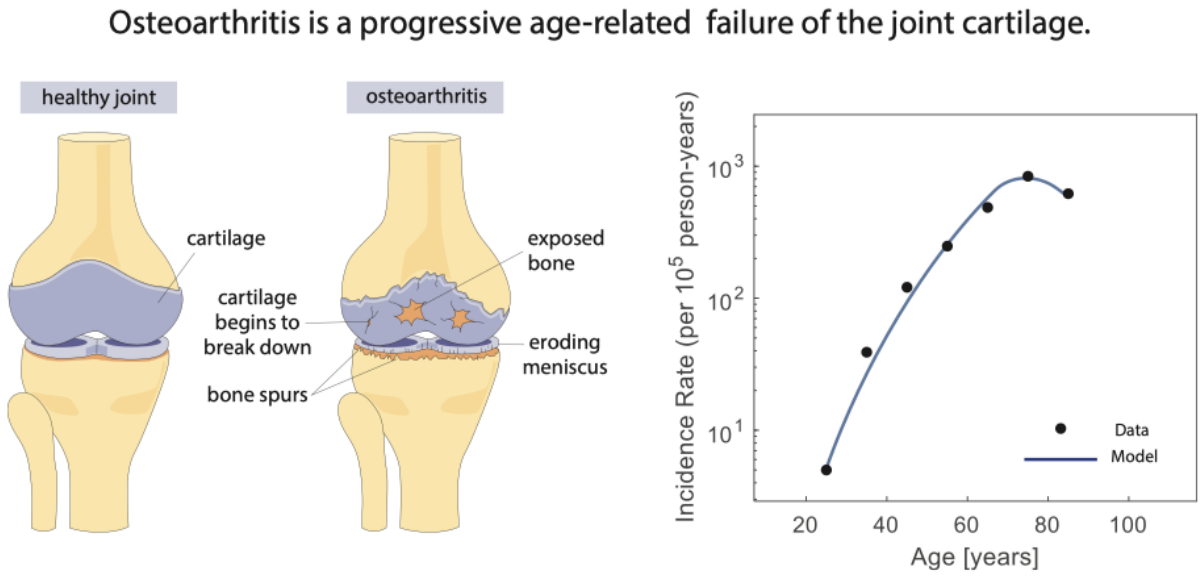


Figure 5.19

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-factor for osteoarthritis is being overweight, which increases the load on the joints (Figure 5.19). To see this, note how the higher the body-mass index (BMI, mass divided

by height squared), the larger the susceptible fraction φ ; BMI does not seem to affect the threshold.

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 as gene variants for the signaling molecules IGF1 and TGF-beta relevant to the feedback circuit that helps S and D cells maintain homeostasis.

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 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.

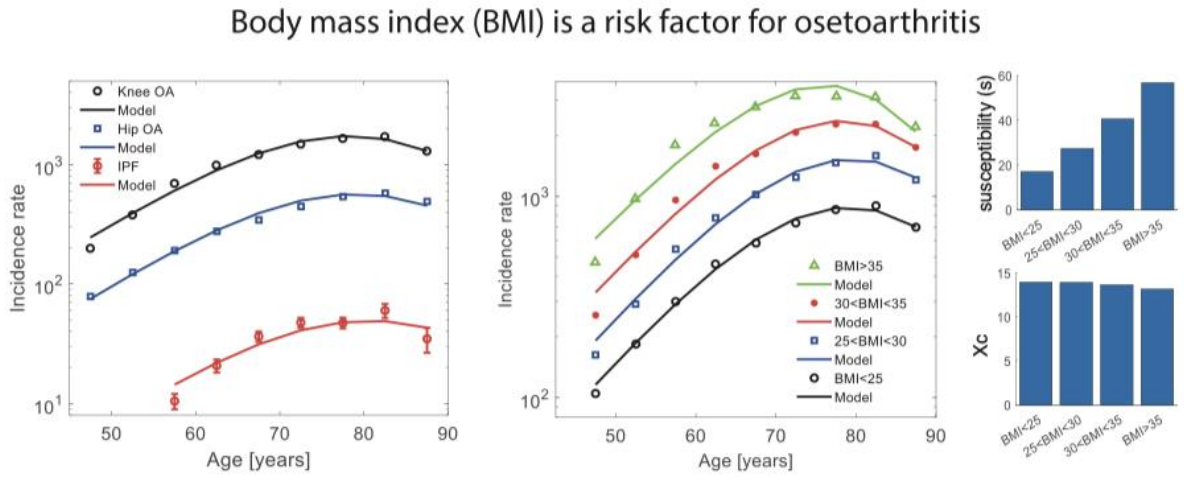


Figure 5.20

Mathematical Appendix

Let's solve the model for the incidence curve to see where the rise and fall originate. The idea is that incidence I(t) is approximately equal to the hazard h(t) – the probability to cross the disease

threshold Xd 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

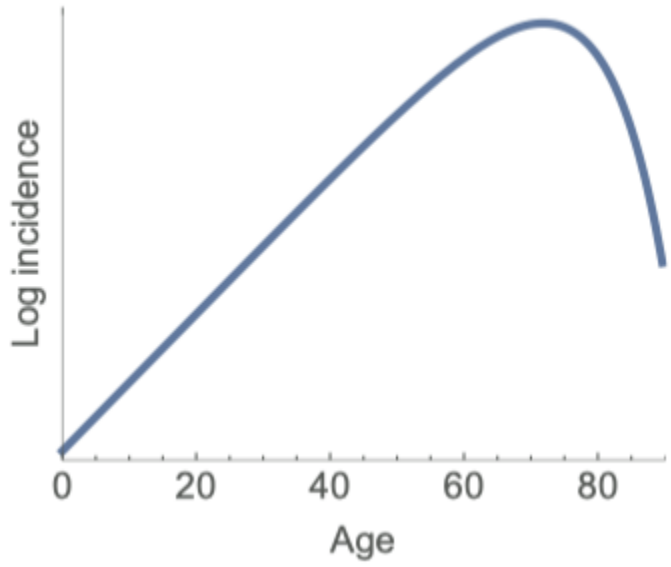


Figure 5.3

and F declines, their product is a curve with a maximum. Writing disease-free survival in terms of hazard results in an 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

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

At first, incidence rises exponentially (Figure 5.3), 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 Xd .

Using the saturated removal model of the previous chapter, we can find how the disease threshold determines the shape parameters in Eq.1: to a good approximation, the slope is α = 0.009 X d − 0.02 and the hazard intercept is log 10 h (0) = 4.14 − X d for the relevant range of disease thresholds X d between 10 and 16 (Katzir et al. 2021).

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 noise to generate enough senescent cells to cross the threshold at young ages; the zero intercept thus decays exponentially with threshold, namely $I(0) \sim e^{\frac{-\beta X_d}{\epsilon}}$.