SHATTERED:

MEDAWAR'S TEST TUBES

AND

THEIR ENDURING LEGACY OF

CHAOS

by: Jeff Bowles

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Direct all correspondence to:
Jeff Bowles
JeffBo@aol.com (email)
or
40 East Chicago #395
Chicago, Illinois 60611 USA

773-504-1137 (voice), 312-782-8217 (fax)

Web Host: Programmed Aging Theory Info
http://www.programmed-aging.org

Abstract: Medawar's 1952 paper "An Unsolved Problem of Biology" underlies most subsequent theoretical work regarding the evolution of aging; it concludes that aging is an accidental byproduct of evolution and could not have been selected for; this prevents reconciling the growing body of evidence suggesting the existence of multiple, evolved, aging systems. Medawar's paper features a well-known thought experiment using test tubes to show why aging could not have evolved for a reason. Medawar assumes that constant, random, breakage sufficiently represents lethal forces of nature; however, famine, drought, predation, disease, and accidents each uniquely affect populations. However, predation is the only evolving force that continually invents new ways to kill members of the prey populations; thus in the absence of continual evolution of novel defenses, all existing prey defenses to predation will eventually be defeated. Defenses to non-evolving or non-obligately lethal forces, however, should quickly evolve. Thus unevolving, identical test tubes cannot adequately represent biological populations. The example also ignores population booms and busts which often occur in nature. By ignoring these issues, Medawar examines only one population age distribution skewed towards younger individuals in predator-dominated environments while ignoring predator-free populations skewed towards older individuals after population crashes. Further, Medawar's test tubes lack meaningful competition for finite resources, and ignore declining fertility which occurs in all aging species. Medawar concludes that older individuals are too few in number to influence the population's gene pool for or against aging. This conclusion is found to be incorrect when variations in the age of reproductive senescence are introduced into a predator-free population.
A new thought experiment with competing strains of algae corrects for these issues and shows that aging evolved and is retained so that groups retain enough genetic variability to allow for rapid evolution of a defense to novel predation. The example shows reasons why the rate of aging is directly linked to the reproductive rate, litter size, metabolic rate, reproductive senescence, and fixed body size. It also suggests that in the absence of predation, immortality would quickly evolve if not for the evolution of highly-conserved aging systems.
Prior analysis of aging evolution is incorrect due to theorists' rejection of the idea of group selection. It is believed to be "impossible" to select for mutations that are bad for the individual but good for the group. However, mutations that are neutral to young individuals which are only deleterious if expressed at older ages can accumulate in early-mortality, predator-dominated environments. Removing the predator allows longer lifespans to occur and the eventual expression of deleterious mutations in individuals that were suppressed epigenetically at younger ages. Positive group selection then occurs amongst traits that are individually negative. Further, group selection is a universal force that occurs between local, non-interbreeding groups and not, as theorists propose, between distant groups of potentially interbreeding species. Local survivors migrate to replace extinct, related species. The antagonistic pleiotropy theory, which was created to salvage the idea of accidental aging, is examined and shown to be untenable. The hypothetical antagonistic pleiotropy genes that are beneficial to young while detrimental to old individuals, predicted to exist in the 1950's,

are unlikely to exist, have not, and likely will not be found in sufficient quantity to participate in the aging process.

Introduction

Almost no information regarding the biochemistry of aging existed when Sir Peter Medawar published his influential paper "An Unsolved Problem of Biology" in 1952. Possibly because of this, Medawar rejected the seemingly common sense position that aging is programmed and evolved for a purpose. Further, the paper promoted the counterintuitive idea that aging could not have evolved, has no purpose, and by inference, that evolution acts in a haphazard manner. This conclusion was reached after Medawar's creation and analysis of a thought experiment concerning a population of test tubes. To the author's knowledge, nobody has ever directly challenged the ideas in the thought experiment. In fact, Medawar's paper is still credited to this day as being the foundation of almost all subsequent theoretical work in the field. The paper is hailed by such theorists as Austad **(1)**, Comfort **(2)**, Hamilton **(3)**, Hayflick **(4)**, Holliday **(5)**, Kirkwood **(6**), Miller **(7)**, Rose **(8),** and Sacher **(9)**. It is also credited for helping spawn new lines of biological theory by the likes of Williams **(10)** , and Charlesworth **(11)**. And even embraced by the cautious Finch **(12)**.

Medawar is hailed as the one who finally discredited the long-standing belief originally proposed by August Weismann in the 1880's **(13)** that aging occurred for the good of the species to clear out the old to make way for the new. *Medawar's conclusions* will be challenged, and defeated in this paper and we will see in the end, that although Weismann's idea was simplistic and theoretically unsupported, it had the benefit of being based on common sense and ends up being *likely* much closer to *reality* than Medawar's conclusions.

Evolution Is Not Haphazard: The Common Sense Case For Purposeful Aging

Before we begin let's build a common sense case for the idea of purposeful aging. Can we not see that the many biological wonders of nature make the strongest case that evolution is not a haphazard process? That its results are almost never random but shaped by the requirements for species survival in a changing, limited, and hostile environment? Just consider the artistic, perfect, mimicry of leaves by some insects as the ultimate in camouflage, or the color changing ability of a chameleon, octopus, or cuttlefish. Think of the amazing adaptations of electric eels and fireflies, and Bombardier beetles that defend themselves with boiling water; Or ponder the archer fish that shoots insects out of trees with high pressure jets of water, and dolphins and bats that can see with organic sonar systems. It seems that long before man existed, evolution invented art, electricity, the light bulb, projectile weapons, radar, sonar, as well as flight. And finally, through man, evolution has created nuclear weapons, space travel, skyscrapers, computers, and whatever technological marvels we see around us. All these wonders are the products of evolution.

The purposefulness of evolved adaptations should be obvious to all who consider them. It is very difficult to name any evolved adaptation without a clear present or past purpose. If we accept that evolution does not lead to haphazard results, then it must be assumed that aging, likewise , is an evolved adaptation that has a purpose or evolution

would not allow it to occur in so many species. Purposeful aging, however, is problematic because its purpose remains unknown.

Medawar's paper provided a convincing, and easy way to escape from the difficult task of elucidating aging's purpose. It simply proclaimed that there was no purpose. This solved the problem of the unsolved problem. Unfortunately, this has not been helpful for researchers who depend on good theory to help them design good experiments. While aging research has muddled along without a cohesive theory, the state of aging theory has been , and remains in complete chaos with at least nine competing, valid theories of the cause of aging. This is Medawar's enduring chaotic legacy.

If aging was indeed an accidental "artifact of domestication" as Medawar suggests, then we should not expect to see patterns or relationships in aging rates between species. However, this is not the case; many profound relationships exist between aging rates and other variables such as body size, brain size, metabolic rate, and fecundity that can be seen in inter-species comparisons.

Another unexplained relationship is why caloric restriction has slowed the aging process in every organism tested. Is this just an evolutionary accident? Or might the response to caloric restriction of delayed aging and inhibited reproduction be considered a defense against famine? A defense to famine is eminently logical in that smaller populations consume a limited food supply less quickly, thus increasing the likelihood that some members of the population will survive until prosperity returns. If reproduction was unchecked, food supplies would dwindle faster, and total extinction would be more likely. If aging continued during a prolonged famine, survivors might be too old to reproduce when the famine abated, again leading to extinction. If evolution has a purpose in slowing aging during a famine, would it not also have a purpose for speeding it up during times of prosperity?

Also, various hormones including melatonin have been shown to be able to affect the average and maximum life spans of mice. Also glucocorticoid hormones are thought to cause the rapid death seen in semelparous species. Hormonal effects on life span also argue for the idea of programmed, as opposed to accidental, aging. Furthermore, "accidental" aging , being a very fragile concept, has even required the creation of "unique categories" such as parental or "semelparous aging" where blatant exceptions to the idea of non-programmed aging exist such as the rapid (3 days) , post-spawning, aging and death of the Pacific Salmon. By creating special categories of aging, the obvious exceptions can be hidden away, and the purposelessness of aging can be maintained.

Even early environmental clues can change the rate of aging and life span of a population of organisms. For example, populations of Drosophila that are raised in crowded vs. uncrowded conditions will have large differences in population mean and maximum life spans **(14)**.

Accidental aging has even required the almost impossible belief that the rapid human aging syndromes of progeria and Werner's Syndrome do not provide evidence that aging is programmed because there are a few differences when they are compared to normal aging. These self-deceptions go on even when a 50 year-old Werner's patient looks exactly the same as an 85 year old person with a few minor exceptions like an excess of skin ulcers and hypogonadism.

Clearly, there are many facts that indicate aging evolved and is a programmed phenomenon. So, let us now examine Medawar's paper and discover where his analysis might be lacking. Our main task is to consider the most referred to portion of his essay, Medawar's test-tubes. (I have emboldened the parts of the text that appear to be the main cause of Medawar's incorrect conclusions. The problems with the highlighted subjects should be apparent to the reader by the end of the paper.

Medawar's Test Tubes Revisited

Medawar begins.....

"I want you to now consider a population of **objects**, **living or not** which is at risk-in the sense that its members may be killed or broken-but which are potentially immortal in the sense that its members do not in any way deteriorate with ageing. Test-tubes will do, since they are clearly "mortal", and I shall peremptorily assume that they do not become more fragile with increasing age.

Imagine now a chemical laboratory equipped on its foundation with a stock of 1000 test-tubes, and that **these are accidentally and in a random manner broken at the rate of 10 per cent. per month.** Under such an exaction of mortality, a monthly decimation, the activities of the laboratory would soon be brought to a standstill. We suppose therefore that **the laboratory steward replaces the broken test tubes monthly,** and I am going to assume that he scratches on each test tube the date at which he bought it, so that its age-in-stock on any future occasion can be ascertained.

Now imagine that this regimen of mortality and fertility, breakage and replacement, has been in progress for a number of years. What will then be the age-distribution of the test-tube population; that is what will be the proportions of the various groups into which it may be classified by age? The answer is illustrated in Fig. 3 (which shows the population will have reached the stable "life-table" age distribution in which there are 100 test tubes aged 0-1 month, 90 aged 1-2 months, 81 aged 2-3 months and so on). This pattern of age distribution is characteristic of a "potentially" immortal population, i.e. **one in which the chances of dying do not change with age.** The curve it outlines is of a sort very familiar in science. Fig 3. illustrates this very elementary truism: **the older the test-tubes are, the fewer there will be of them-not because they become more vulnerable with increasing age, but simply because the older test-tubes have been exposed more often to the hazard of being broken.** Do not therefore think of a potentially immortal population as being numerically overwhelmed by **dotards**. Young animals outnumber old, and old animals those still older."

Let us stop for a moment and evaluate what has been stated...

Issue #1: Medawar implies that steady-rate, accidental breakage of random test tubes adequately represents the combination of lethal forces operating in the wild, and that young and old are equally susceptible to these forces. These assumptions lead to the single population age distribution skewed towards younger individuals described. However, there are at least five separate lethal forces in nature, famine, drought, acquired disease/parasites, accidents/natural disasters, and predation. When each force is analyzed separately, it appears that up to four of the five forces will not produce the age distribution that Medawar suggests.

Issue #2: Using test tubes that can neither learn, evolve, nor adapt to the random selection pressure of breakage in the model suggests a belief that inanimate objects can adequately represent evolving organisms.

Issue #3: Test tubes by implication are identical and equally resistant to breakage. This does not occur in most biological populations.

What needs to be done at this point to resolve these issues is to imagine how famine, drought, disease/parasites, accidents/natural disasters, and predation acting alone will affect the age distribution of a non-aging, biological population. By adding the caveat that the populations at any point in time will be limited in size due to environmental resource limits, we can arrive at meaningful conclusions…

Famine: Repeated famines should lead to the evolution of famine-resistant organisms. Also, the population size will be limited solely by food availability. In a non-aging population, after a series of booms and busts, the population will become dominated by the most famine resistant individuals. These individuals will also likely be the oldest survivors of past famines, especially if famine resistance is a somatic rather than easily inherited germline mutation. Famine, acting alone, would thus lead to a population distribution completely opposite to Medawar's youth-skewed population, especially after population crashes.

Remembering that the maximum number of individuals is fixed by the environment, we see that until the environment allows the population to grow past the point of its previous peak, that this "backwards" age distribution could be maintained indefinitely. If the environment continued to contract the population, then an even more elderly-skewed distribution would result. After population crashes in this scenario the older members would make huge contributions to the gene pool rather than the unimportant contribution of the elderly suggested by Medawar.

The author believes that evidence will be found that shows this sequence actually occurs in wild populations. After viewing at least a thousand nature programs regarding wild animal populations, it is quite apparent to the author that in famines, the young are the

first to perish. Reasons why this occurs include : maternal abandonment, and/or lactation cessation, infanticide, inability to compete for food, as well as increased predation.

Drought: Should lead to a similar age distribution pattern as famine.

Accidents/Natural Disasters: If the test tubes could learn to avoid accidents or natural disasters and/or evolve adaptations to allow them to do so, again the same "backwards" distribution pattern as famine and drought would be seen. This would occur after a large natural disaster or temporary increase in the risk of accidents wiped out most of the non-adapted younger members. (It is interesting to note that various studies suggest that some animals such as fish and snakes can predict earthquakes, and that pending earthquakes purportedly cause snakes to leave their holes).

Acquired Disease/Parasites: This is less clear, but typically, evolved resistance to regularly encountered contagious diseases and parasites should lead to the same elderly-skewed age distribution after population crashes induced by periodic outbreaks.

However, large numbers of deaths due to large-scale outbreaks might also imply a novel disease or parasite encountering a non-resistant population. This in turn would imply that a new variety of disease or parasite had evolved. In this case, the elderly members may be more at risk of losing a disproportionately large percentage of their numbers. This might be true because **the older members should have less genetic diversity as a group due to their surviving the same sequence of selection events. Younger members of the population, however, belong to a group that should have more genetic diversity due to their experiencing a smaller series of selection events.** (These ideas are highlighted because they will later be central to the elucidation of aging's purpose.) Thus, until a population evolved proper defenses to novel diseases or parasites, the most genetically homogeneous age groups (the old) could suffer more than the genetically more diverse groups (the young). In this case, the age distribution would shift towards more youthful individuals and Medawar's distribution would hold in this scenario after a crash.

We may, however, assume that any large scale lethal epidemics are examples of true evolutionary accidents. It would seem quite illogical for evolution to favor the selection of groups of diseases or parasites that are so virulent that they risk causing the extinction of their hosts. As the diseases or parasites would also become extinct unless they could move to another species. Thus, we can assume that for the most part, diseases and parasites acting alone will usually lead to an age distribution opposite to that predicted by Medawar.

So if accidents/natural disasters, disease/parasites, famine, and drought work against Medawar's age distribution in the wild, where does it come from? If one ignores aging as Medawar has because his test tubes are non-aging, we see that predation is the only unexamined lethal force.

Predation: Predation is the only factor that can lead to Medawar's age distribution pattern on a permanent basis. The youth-skewed age distribution comes from the constant interaction between predator and prey.
This occurs in the long run because the predator is the only lethal force of nature that both evolves, and requires the death of the prey for its own survival. Because predator and prey evolve in lockstep, with each new defense or offense causing the evolution of an offsetting trait in the other species, it will be most difficult for particular individuals in the prey species to get too far ahead of the predator's evolving offense. In most cases this will lead to the predator having the same chance of killing the young as compared to old. With equal chances of populations members being killed by a predator, and inability for any members to get very far ahead of the evolving predator, "predator resistance" cannot evolve, and thus we see Medawar's population age distribution materialize on a long term basis.

We have ignored the fact that predators are typically able to kill juvenile members at a much higher rate than adults in the wild. Evolution, however, has conveniently dealt with this problem by causing most species to produce far more offspring than can survive in the wild. Even with the high levels of juvenile mortality, Medawar's population distribution should still be seen in most wild populations.

Another question that is instantly raised by this analysis is whether prey species ever become separated from their predators for long periods of time during evolution. This would be required to allow for the emergence of an elderly-dominated population age distribution.

The diversity of species provides the answer. It is estimated that there are some 40 million existing species and possibly up to 40 billion extinct species **(15)**. Every species that ever existed represents a very long separation event where members of an originally contiguous population of species broke into at least two separate groups. These two groups could have no compelling reason to separate from each other, so speciation events likely occurred at random. However, a prey species would have plenty of reason to attempt separation from predators and likely did so at a rate equal to or greater than the 40 billion separation events that led to speciation.

At this point, we can state that if we ignore aging, predation is the only lethal force of nature that is enforcing Medawar's age distribution on a permanent basis in the wild. The other four lethal forces of nature, work against Medawar's distribution. Figure 1 shows Medawar's population age distribution with the percentage of surviving individuals of a specific age group being the y axis and their age cohort being the x axis:

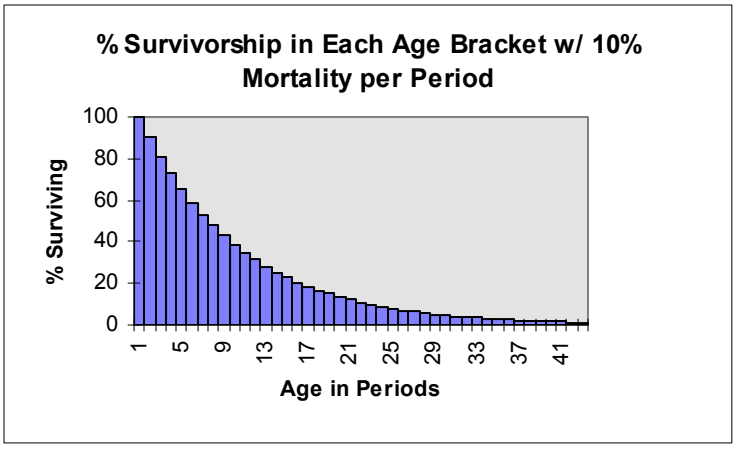

Figure 1

While a population of predator-free, non-aging, evolving organisms after a population crash caused by an unevolving or only sporadically lethal force of mortality should have a mortality distribution similar to that in Figure 2:

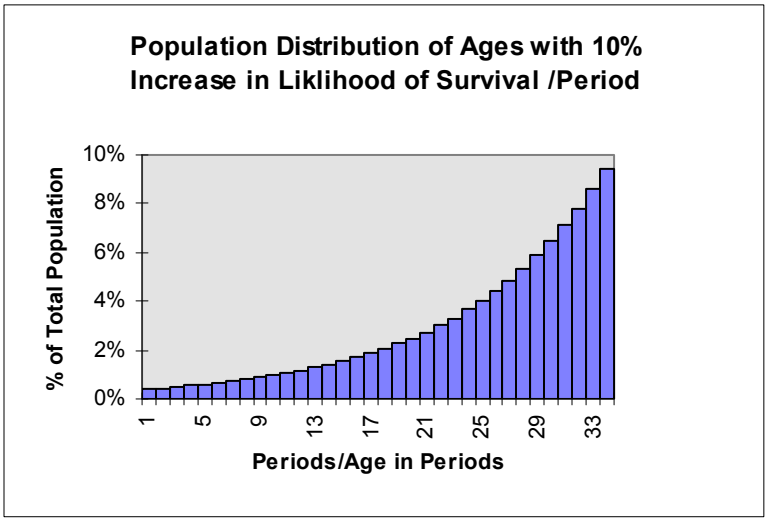

Figure 2

To Medawar's credit, he later tries to add senescence to his immortal population of test tubes by having them self-destruct at a given age, but this does little more than to truncate a minor portion of the population's tail from his original population distribution, shown as follows:

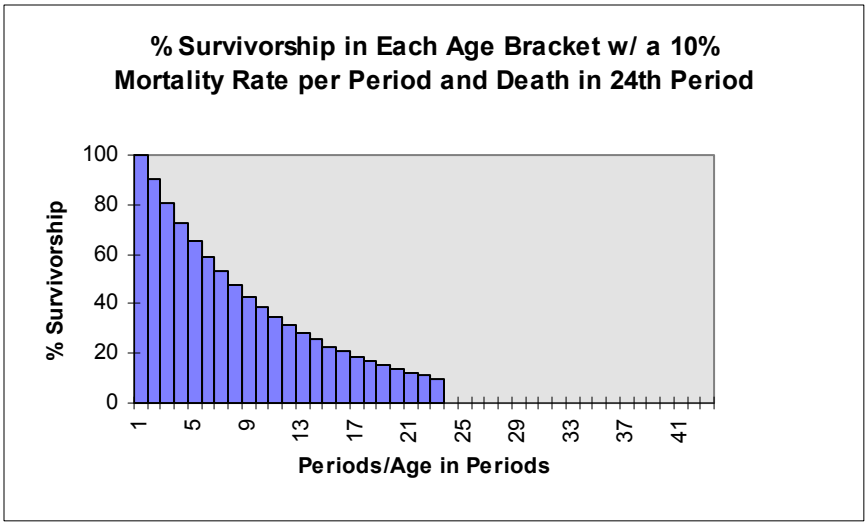

Figure 3

Medawar's continues ....

"As a first step in animating this model, I want you to imagine that these test-tubes now do for themselves exactly what the steward has hitherto been doing for them, i.e. they reproduce themselves , **no matter how**, **at an average rate of 10 per cent. per month** in order to maintain their numbers. Since the population is potentially immortal, **the rate of reproduction of its members will not vary with their age**. **It follows that each 'living' test-tube of the existing population will make the same average contribution of offspring to the test-tube population of the future. Each test-tube may lay claim to an equal share of the ancestry of future generations, and its reproductive value is invariant with its age."**

"The next step in the argument is vital. Although each individual test-tube takes an equal share of the ancestry of the future population, each age group most certainly does not. **The older the age group , the smaller is its overall reproductive value.** The group of test tubes 2-3 months old , for example makes a very much greater contribution than the group 11-12 months old. This is not because the test tubes of the senior group are individually less fertile-their fertility is ex hypothesi unchanged-but merely because there are fewer of them; and there are fewer of them not because they have become more fragile-their vulnerability is likewise unaltered-but simply because, being older, they have been exposed more often to the hazard of being broken. It is simply the old story of the pitcher and the well."

Issue #4. By assuming a constant elimination of individuals from the population at a steady rate of 10% per period (which, in reality, should be caused solely by predation in the long run), Medawar likewise assumes that reproduction will occur in the amount of 10% per period no matter what. This may be true in a predator-dominated environment with constant 10% losses, but when there is no predator, the population would quickly expand to its maximum capacity allowed by food and water resources. In a non-aging

population, at this point, no newly-born offspring could survive without another member of the population previously succumbing to starvation or drought. Given that it is the juveniles that are the first to die during famine or drought in the wild, this means that a predator-free population, with a stable food and water source, will reach a maximum sustainable size. At this point, with no births leading to viable adults, except for those few that replace individuals killed by accidents or sporadic cases of lethal illness, the non-aging population should remain unchanged indefinitely until a catastrophe of famine, drought, disease/parasites, or natural disaster occurred that temporarily reduced the population. During these rebounds from population crashes, it is the most resistant, and most likely the oldest members of the population who will survive and contribute to the future gene pool. In the case of non-aging organisms, population crashes would do nothing more than select for the older, but non-aged, adapted members.

However, for aging populations, the rebound represents a temporarily unrestricted environment where aging can be selected against (or longevity selected for) in the wild. This occurs because in unrestricted environments where average life spans exceed the age of reproductive senescence, those with postponed reproductive senescence will produce more offspring. If reproductive senescence is linked to maximum life span (a recent study suggests this is true in humans **(16)**, and a new, seemingly viable and unified theory of aging **(17)** relies upon and supports this concept), then longer life spans can evolve in this manner.

Medawar continues.....

"Some of the consequences of the decline in the reproductive value of older age groups will be apparent when I take the next step in animating my test-tube model. The test-tubes are no longer thought of as immortal; on the contrary, after a certain age, **as a result of some intrinsic shortcoming,** they suddenly fall to pieces. For the time being we shall assume that they disintegrate without premonitory deterioration. What will be the effect of this **genetically provoked** disaster upon the well-being of the race of test tubes? It must be my fault if the answer does not appear to be a truism-that it depends upon the age at which it happens. **If disintegration should occur five years after birth, its consequences would be virtually negligible,** for under the regimen which we have envisaged less than one in five hundred of the population is **lucky** enough to live so long. Indeed, if we relied upon evidence derived solely from the natural population of the test-tubes, we should probably never be quite certain that it really happened. We could make quite certain, as we do with animals, only by domesticating our test-tubes, shielding them in a padded box as pets.

If disintegration should occur one year after birth, an age which is reached or exceeded by about one quarter of the population, the situation would be fairly grave but certainly not disastrous; after all, by the time the test-tubes have reached the age of twelve months they have already made the greater part of their contribution of offspring to the future population. But with disintegration at only one month, the consequences would obviously be quite catastrophic."

"This model shows , I hope, how it **must** be that the force of natural selection weakens with increasing age-even in a theoretically immortal population, provided only that it is exposed to real hazards of mortality. If a genetical disaster that amounts to breakage happens late enough in individual life, its consequences may be completely unimportant."

After some digression he continues....

"A relatively small advantage conferred early in the life of an individual may outweigh a catastrophic disadvantage withheld until later. Go back to the test-tube model for a moment, and compare two competing test-tube populations. Both suffer the same average mortality of 10 per cent., and one has, as hitherto, the average monthly birth-rate of 11 percent, but the price paid for this hardly profligate increase of fecundity is the spontaneous bursting asunder of each member at age two. Which population will increase more rapidly in numbers-the potentially immortal, or the mortal population with a birth-rate only one-tenth part higher than the other's? The simplest calculations show that it is the latter."

There are a number of issues to be examined in this last paragraph, some of which have already been touched on at length...

The first issue is that the last paragraph seems to be intentionally constructed in such a manner as to provide a result consistent with the premise of the paper. As we will demonstrate, many other number sets that can be generated within the bounds of common sense will lead to an opposite result where immortals conquer the mortals.

Medawar initially assumes an immortal population that cannot expand due to equal birth and death rates. Of course, given a constant immortal population, it should not be too difficult a task to create a mortal population that can overtake it. All the mortals have to do is to expand at any rate within an unlimited environment, and the desired result is achieved: ***No advantage to immortality if the mortals have a slight advantage in birth rate.*** This will be shown to be a very debatable proposition.

However, as simple as the problem is for the mortals, it is a difficult result to achieve. First, the immortals are restrained with equal birth and death rates. Next , the age of spontaneous death has to be placed well out of the reach of the normal life span of almost all of the mortal population at a point where 92% have already been killed by the environment. By placing the age of death so far out, it guarantees that death from "aging " will have no effect. Let's correct these problems and take another look.

To make things fair, give the immortals a birth rate increase of "mere a tenth part higher " so its net growth rate (births-deaths) will be 1% compounded per period. Now, generously allow the mortals to grow twice as fast at 2% compounded per period. Now, just select a reasonable age of death for the mortals and see what happens....

Let's derive our age of death by examining our familiar human population. If aging begins around 50 at the age of menopause, and menopause is the evolutionary equivalent

of death (the inability to reproduce) and 120 is the maximum possible life span of humans, then an age of death at 50/120 of the maximum life span would have no evolutionary consequences. Assuming 30 months as the maximum possible life span of these test tubes (where the environment would have killed about 96% of them) then the age of death (or menopause) can be placed at 12 rather than Medawar's 24 months. What happens now?

Starting with a population of 100 members each, after 12 months, the mortal population will see about 28 members die of old age from the original population of 100 plus the 26 new net births leaving a net population of 98. Of course the immortals will have grown to about 113. So with just a few changes of assumptions that certainly fall within the bounds of common sense, completely different results are possible. But actually it gets worse.

If the environment in the above example was limited , as it should be, to where only a fixed number of test-tubes can exist, an even more striking and contradictory result will be obtained....

Assume mortal and immortal test tubes fill a box to capacity. No reproduction can occur in this case until a mortal test tube shatters. In this box, one can place any starting number of mortal and immortal test-tubes in any ratio and assign the highest possible advantage in birth rate to the mortal test tubes that can be imagined, and in all cases, as long as the immortal test tube(s) can reproduce at any rate, they(it) will eventually drive the mortal test tubes to extinction. This suggests that there is an unrelenting, and vigorous push by natural selection for immortal life forms. For whatever reason, Medawar avoids this inescapable conclusion.

Without reasonable competition from other test tubes, there is no platform from which to address the association between litter size and aging. If test tubes either die from aging, or are killed by predators which leads to turnover in the population, every death creates an opportunity for a competing species to fill the slot. The faster the population turnover from aging or predation, then the more openings that occur that competitors can fill. As was just suggested, non-aging, predator-free groups with any positive population growth rate will extinct competing groups with turnover. Groups with turnover can postpone this inevitability with increased reproduction rates and litter sizes. But even at a 1,000 to 1 greater reproduction rate, just 1,000 generations would be needed to take over all the openings from the group with aging and/or predation-induced turnover.

Given the overwhelming advantage that accrues to immortal populations, and the fact that most lethal forces promote population distributions that select for longevity, we see that the natural state of all life forms in the absence of predation is immortality. Was the world ever dominated by immortal organisms? If so, it should have occurred 1.2 to 4.0 billion years ago when unicellular/algae-like aquatic life forms dominated the planet as "primordial ooze". Prior to the evolution of predation, maybe 1.2 billion years ago, open seas and unlimited sunlight provided an unrestricted environment. The initial advantage

of immortality would be in allowing non-aging individuals to make larger contributions to the gene pool.

Once unchecked reproduction led to crowding, additional offspring *could* not survive unless another individual died; in this environment, immortality became a requirement for species survival. Those that never aged and died could permanently retain their place in the floating canopy. Dying individuals of aging species would all be replaced by immortal organisms even if the aging species had a million to one advantage in the reproductive rate. It would merely take a million ~~***years***~~ ***generations t***o happen.

Were they really immortal? Today we find Redwood trees aged 3,000 and Creosote bushes aged 10,000 years. Once a life form evolves a 3,000, 10,000 , or even million year life span, immortality could not be too far off. Further evidence for immortality of early life forms can be found in some types of cancer cells that once they lose some form of control, can divide indefinitely, and possibly forever in culture. These types of cells are said to be immortalized which is in contrast to non-cancerous cells that are typically limited to less than one hundred cell divisions. If we evolved from immortal single cell ancestors, then this fact would not be surprising; however if all of our ancestors were mortal, then spontaneous immortalization of cancer cells would be a true miracle. Surely, ancient life was immortal; however, this idea will not sit well with gerontological theorists, but can't we appeal to common sense to see that any skepticism towards this idea is likely unwarranted?

What would seem to be more difficult?:
-To program a single cell to divide innumerable times into a self-repairing colony of billions of integrated cells complete with bones, muscles, eyes, ears, a brain that can perform, act, move, think, mate, learn, fly, turn into a butterfly, and create an atom bomb? Or,

-To simply maintain and repair an organism after its miraculous development?

There is no question that if immortality provided even the slightest advantage to a species, whether simple or complex, evolution would quickly find a way to make it happen. And further, it should actually be a relatively simple, pre-programmed , evolutionary task. While the question commonly proposed by some of today's aging theorists is "Why do we live so long?", the question that should be being asked is in reality, "Why do we age so quickly if life's natural state is immortality?"

Our analysis of Medawar's test tube example is now complete. Although his test tube example provides an ingenious and important way of framing many relevant questions regarding aging evolution, it is only partially complete and unfortunately leads to incorrect conclusions. Medawar's major contribution to aging theory is showing that "wild", youth-skewed, population distributions allow for the "accidental" accumulation of mutations that cause aging in "protected" populations. However, only with the insight that predation alone leads to his population distribution could his analysis have been fully developed.

Unexplored Issues

Let us now examine some issues unexplored by Medawar: the fixed body size of aging organisms and declining fertility. (Here, aging implies loss of function with age, not just a maximum life span).

In the 1930's, Bidder **(18)** strongly promoted the idea that organisms that grow throughout their lives such as some fish, sharks, trees, or tortoises experienced constant renewal through the growth and thus, did not age. However, animals with fixed body sizes begin to age once growth ceases. (Note: the case of the Fulmar, a bird with a fixed body size that does not age but simply expires at age 50, shows that fixed body size>aging is not a universal phenomenon .) Excluding the Fulmar, animals with fixed body sizes, in addition to aging, experience declining fertility. However, in continually growing animals: increased age leads to increasing fertility **(19)**. Our examination of the two different population distributions, young-dominated in a predatory environment vs. old-dominated in a post-crash, predator-free environment point to an explanation for these observations.

A predator-free population will benefit by increasing the genetic contribution of its oldest members who have successfully survived the various unevolving lethal forces of nature as well the various diseases or parasites that do not require the individual's death. The older a member gets, the more proven are his genes. Thus, evolution "wants" him to reproduce more as he ages. In populations free of predators and novel diseases, there is a premium on genetic homogeneity, as there are a limited number of positive mutations that can occur that defend against unevolving forces. Once all the positive mutations are found, further change becomes detrimental. Furthermore, in limited environments only a certain amount of biomass can be "occupied" by a population. If body size can increase indefinitely with age, one finds that the older, proven, animals, will occupy the most biomass, thus reducing the available biomass for younger, smaller, unproven individuals. This insures that the gene pool is dominated by the genes of the older, most fit, individuals.

Predator-dominated environments are different because predators continually evolve new ways to counter prey defense. Predation is an adapting, continuously lethal, force of mortality; Thus, predator-dominated environments place a premium on genetic variability in the prey. Genetic variability prevents prey extinction caused by a novel predator offense simultaneously defeating the defenses of an entire prey population.

A continuously youth-dominated population will lead to increased genetic variability because young members' have not endured the long, series of genetically-homogenizing selection events that older members have. Thus more genetic variability exists in younger age cohorts. This implies that not only does predation lead to Medawar's youth-dominated age distribution, but that this distribution also acts as a defense to predation-induced extinction (extinction at the local level primarily and occasionally on larger scales).

Now, if genetic variability is advantageous, it can also be increased by having more individuals per population. If a population can only occupy a fixed amount of biomass, more individuals could be created by fixing the maximum body size at an optimal, smaller level as compared to having a smaller number of large individuals. Thus, we can see how both aging and a fixed body size lead to increased genetic diversity given a limited available biomass.

Declining fertility, also helps to maintain increased genetic diversity. By introducing declining fertility with age, Medawar's youth-dominated age distribution will be retained in a population in a reproductive sense even if predation had temporarily abated and older members began accumulating. By preventing reproduction of older members, (or by promoting its counterpart of accelerating the reproduction of the young) the reproductive gene pool will retain its diversity by avoiding contributions from the genetically homogenized elderly. As will be argued later, however, during extended predator-free periods, the elderly will have to be cleared out by somatic aging to make way for the young.

One final issue is Medawar's assertion that the elderly's genetic contribution in his example is too small to affect the gene pool of the group, and that aging cannot be selected for or against. This may be true in an hypothetical population of identical, non-aging members in an unrestricted environment without declining fertility. However, by adding more realistic assumptions, and compounding through the generations, an opposite conclusion can be reached which may more accurately represent nature's true state. We will show that if an individual can acquire just the slightest advantage in its ability to reproduce, then evolution, acting in a natural setting, can quickly compound the slight advantage into virtual saturation of the population.

Let us add declining fertility to Medawar's distribution and the important question then becomes how big a lifetime contribution to the gene pool has the elderly group made? We will see that only a few members of the population have to reproduce at later ages to cause a major shift in the gene pool over time towards longer reproductive lives. Then if we can then show that maximum life span is tied to maximum reproductive life span then we, in turn, will have found the way in which longevity can evolve.

Beginning with Medawar's distribution let us now assume that most individuals can have only 2-offspring per life time no matter how long they live while just a very few can manage 3-offspring per lifetime. Individuals will have 3-offspring only if they harbor a rare mutation and reach an old age. Let us also assume that the population is temporarily separated from its predators and the population can expand unabated. After 10 generations, a single 3-offspring parent would have about 60,000 descendants while a single 2-offspring parent would have only about 1,000 descendants.

Now let's look at it another way, by introducing a series of booms and busts: If their were (100) 2-offspring individuals for every (1) 3-offspring individual one might guess that the 3-offspring parents genes could never catch up to 2-offspring parent genes due

to their rarity. Now this might be true in a perpetually unrestricted environment, but if the unrestricted environment was always cut off at some maximum limit, and then followed by the elimination of a large portion of the population, a repeating cycle of temporary unrestricted environments and crashes would occur. Under this scenario, the 3-offspring genes would quickly crowd out the 2-offspring genes, and longevity would evolve quickly. Just how quickly?

We begin with (100) 2-offspring parents and (1) 3-offspring parent and we allow them and their progeny to freely reproduce for four generations. After four doublings and four triplings, there would then exist a population of (1,600) 2-offspring members and (81) 3-offspring members. Now we randomly kill 90% of them and we end up with (160) 2-offspring parents and (8) 3-offspring parents. Notice the incidence of 3-offspring genes has increased from 1% to 5% after four generations and one crash. Now if we repeat the process from this point we get (2,560) 2-offspring parents, and (648) 3-offspring parents; kill off 90% to get (256) 2's to (65) 3's, an increase in incidence of longevity genes from 5% to 20%. One more iteration and we get (4,096) of the 2's and (5,265) of the 3's. Thus the 3-offspring genes have overtaken the 2-offspring genes in just 12 generations with three crashes. Now it will only take only a few more iterations or a little genetic drift to completely wipe out the 2-offspring genes (or the aging genes that limited their reproduction). As has been mentioned, selection for longevity or immortality in a predator-free environment is not just a slight bias, but as we can see, an irresistible, rapid , and relentless force that evolution must continually suppress to avoid its occurrence.

So if, in the absence of a predator, or even in the face of periodic predation, longevity should evolve so rapidly, why does the maximum life span of most animals, including humans, seem to increase at a glacial pace if at all? Shouldn't thousand, or million year life spans quickly evolve? This would happen if aging did not provide such a powerful defense to predation or its return by increasing genetic diversity,. Because of its advantages, aging is highly conserved in prey species.

(Note: Compounding can also occur in the opposite direction. If an earlier age of reaching fertility increased lifetime reproduction potential, genes (or hormone patterns) for delayed fertility would be quickly diluted out of the population. If this force was unopposed, as it is in Medawar's distribution, by periods of old-dominated population distributions or variations in reproductive senescence, pressure for earlier fertility would cause all life to de-evolve into short-lived cancer-like cells that reproduced in big bursts (are Mayflies and Pacific Salmon heading in this direction?).

Now, selection for both earlier fertility or delayed reproductive senescence, if unrestrained, would race off uncontrolled in both directions to increase offspring. This would lead to life forms that were fertile from birth, without reproductive senescence, ultimately leading to immortality.

Finally, unopposed selection for delayed reproductive senescence alone as would be seen in purely old-dominated populations would lead to immortality and eventually sterility.

Because life forms like these are extremely rare or do not exist, we can conclude that the age of reaching fertility and the age of reproductive senescence are linked. If one variable evolves towards increasing lifetime reproduction potential, the other linked variable changes to reduce lifetime reproduction potential. This in turn implies that most groups have evolved this linkage to survive environments requiring alternating periods of young vs. old population age-distributions. Groups with this linkage would out-compete groups without during periods of changing predation levels.

Medawar's distribution, induced by either predation or aging, defends against novel predation by maintaining increased genetic diversity. Aging (as programmed death), however, also provides a defense to periodic predation by increasing population turnover during predator-free periods which accelerates the process of genetic drift. Accelerated genetic drift allows the rapid saturation of the population with traits that defend against predation prior to its return. Another of the author's papers **(20)** examines this idea in more detail.

A New Thought Experiment Links Aging, Reproduction, Metabolic Rate , and Body Size

Medawar's model is lacking for two primary reasons: neither the test tubes nor their environment evolve. To create a more useful thought experiment, an empty ocean, and a colony of algae provide a better starting point. Can hypothetical primitive algae be relevant to the study of human aging? If human life descended from algae-like single cells which dominated the planet for 2.8 billion years they should be quite relevant indeed. 2.8 billion years covers about 70% of the totality of human evolution. So let us now begin with a new thought experiment:

Assume that algae evolve and reside in an empty ocean which provides an unrestricted, predator-free environment with unlimited solar energy. The algae can evolve into different strains over time. Rapidly expanding strains would be first to cover the globe. Maximum expansion is achieved by increasing reproductive and decreasing death rates; this eventually leads to rapidly proliferating, immortal (non-aging) algae.

Now say, after a billion years, that the entire earth is covered with two strains of algae: one blue, the other green. Both are prolific reproducers and immortal. Now imagine that equal sized masses of blue and green algae come into contact and settle in a harbor. Then an earthquake dislodges some land that turns the harbor into a loch. Further, because there is no room for any new offspring, a form of contact inhibition evolves in both strains that inhibits reproduction unless there are available openings. At this point we see that an unending stalemate would seem to be the likely course of evolution.

Continuing, assume that over time both colonies of algae lose some of their reproductive capacity due to mere chance (this frees us from exploring the myriad of scenarios that lead to evolutionary dead ends). Also, in this particular loch, the blue algae now, when not contact-inhibited, proliferate at only 1/2 the rate of the green algae. At this point however, reproduction rates are irrelevant as all individuals are immortal; there are no

predators, and thus there are no openings to fill. All the algae can do is to sit and wait. But wait for what?

Somewhere, somehow, a predator eventually evolves that only prey on green algae (possibly the predator evolved from light-starved, ocean-dwelling algae that resided at lower levels). Now assume that a storm blows a green algae predator into our loch.

As quickly as the predator eats, the remaining green algae reproduce and fill any openings created in their floating canopy. However, whenever green algae is eaten near blue algae, the blue algae attempts to reproduce as well. Normally, the blue algae and the predator will drive the green algae to extinction when blue fills all the spaces given up by green during green's predator-induced population turnover. The predators, unable to eat the blue would then starve, and then the unchanging blue algae would dominate the loch for eternity.

However, remember that we assumed that green can reproduce 2 times faster than blue. In this case, green can delay its extinction for twice as long. For every spot that opens up, two greens for every one blue are waiting to fill it. Some groups of green algae would then evolve even faster reproductive rates than the ones that provide the 2 to 1 advantage. These more prolific green algae could then stave off extinction for much longer periods. Thus we see the logic for the linkage between population turnover caused by predation or aging and reproduction rates. For a single cell to increase its reproduction rate it would likely have to increase its metabolic rate. Gerontologists have long noticed across species that faster metabolic and reproductive rates are both related to faster aging rates. In larger, multi-celled organisms, faster reproductive rates manifest themselves in accelerated gestation as well as increased litter sizes.

Accelerated metabolic rates that lead to faster reproductive rates allow for single cell organisms to protect the environmental openings caused by predation or aging from being filled by their slower-replicating competitors. Likewise in multi-celled organisms, larger litter sizes will serve a similar function.

So we have at last revealed a salient point about aging and fecundity:

- *Faster population turnover caused by predation or aging must be associated with increased reproductive rates or litter sizes to prevent extinction caused by habitat-competition with lower-turnover competitive species.*.

(Note: links between aging and reproductive rates also may act to prevent the evolution of a "super -predator". Another paper by the author **(21)** defines a super-predator as a species whose highly efficient predation technique combined with overpopulation results in its own extinction.)

Now assume that the green algae, through increased reproduction, can hold its own with the blue algae even with a predator nipping at its heels. The green algae, with its much higher, age-random mortality rates will assume Medawar's population age

distribution. This leads to increased genetic diversity which allows a predator defense to emerge which we will assume is poison. Assume now, that one green algae has become poisonous to the predator if eaten. If this poisonous algae ends up in the center of an isolated mass of non-poisonous algae away from the predator , the poisonous algae will not be able to expand its numbers because it is contact-inhibited by the surrounding, non-aging algae, and might never encounter the predator until it was too late to do any good.

Also, this situation would be dangerous because if predation levels increased, all the edible green algae might be eaten before the poisonous one could expand its numbers. Eventually a predator might get to the poisonous algae, but possibly after the rest of the colony was wiped out. The scenario would conclude with several (temporarily) surviving predators, a single dead predator killed by the poisonous algae, and the extinction of all the green algae.

This end result suggests there should be a strong selection pressure at the group level for reproductive senescence which would allow a greater variety of individuals to reproduce. Reproductive senescence would insure that all the genetic diversity did not go to waste. By simply limiting the times that all algae can divide, the single poisonous algae would be more likely to be get a chance to reproduce, even in a crowded, contact-inhibited population mass. Furthermore, simple reproductive senescence alone would not ensure that the poisonous algae could reproduce, unless the poisonous algae happened to be located near an area where openings became available. If non-aging, reproductively senescent edible green algae happened to surround the poisonous algae, reproduction would still be inhibited. What is needed here, as Weismann proposed, is a way to clear out the old to make way for the new. Somatic aging fits this bill. While somatic aging is not likely different from reproductive aging in single cell organisms, the two forms of senescence, appear to diverge in more complex organisms due to the selection pressures just described.

The primitive somatic/reproductive senescence system for single cell algae may have consisted simply of telomeres that are non-coding segments of DNA that are found on the ends of the linear chromosomes of eukaryotes. With each round of cell division, the could telomeres shorten. When short enough, the coding DNA is damaged, reproduction ceases and/or death ensues.

In humans, a fixed number of ova in females acts similarly to telomeres in algae, both set a limit on maximum potential offspring. In the evolutionary short run, if increased population turnover was required to defend against predation, the increased number of turnover-induced openings could be defended by increasing the rate of reproduction which would likely require an increase in the metabolic rate. Increased reproductive rate could occur in higher organisms through decreased gestation time and/or increased litter sizes. However, preprogrammed reproductive senescence, either through telomere length, or fixed number of ova, sets a limit on the total number of offspring per life time regardless of the rate and timing at which they are produced. Thus, an earlier reproductive effort would lead to an earlier onset of reproductive senescence. (Interesting

relationships will likely be found by studying species-specific maximum potential offspring per reproductive lifetime.)

If cell division leads to both reproduction and aging in single cell organisms, then we may have uncovered yet another important rule:

-*Reproduction and aging in all aging organisms are most likely timed by the same mechanisms.*

Thus, reproduction and aging, which are driven by cell division in single cell organisms, should also be driven by reproduction-related mechanisms in higher organisms (such as hormones). The author makes a case for this in another paper **(22)**. And even though hormones may drive the aging process in higher animals, they probably do so ultimately by modulating tissue specific rates of cell division and/or apoptosis via controlling the level of cytosine methylation of DNA, histone deacteylation, and / or telomere shortening. This can be assumed if one accepts the idea that evolution builds on top of previously evolved systems rather than creating new ones from scratch.

Now, the previously discussed body size/life span relationships can also be incorporated into our model . To begin this process we can add periodic storms that blow off large portions of algae from the loch and deposit them on the shores where they die. This creates openings to fill unless a defense to wind-induced mortality can evolve. Assume then that a mutant algae emerges which loses its contact inhibition and its progeny remain partially connected to it during cell division; this would then give us the beginnings of multi-cellular organisms. These mutants would have the advantage of increased mass and possibly a means to anchor themselves to each other or to the loch bottom, thus leading to wind resistance. Selection for ever increasing individual body size given a fixed colony biomass will lead to a smaller population and reduced genetic diversity; this would be advantageous in a predator free environment, especially with competition from other smaller groups. However, upon reintroduction of a predator, that can feed on both the large multi-celled organisms, and their smaller competitors, the larger organisms will be the first to become extinct. Because populations of the larger number of smaller organisms with fixed body sizes should have more genetic diversity, they are more likely to evolve a defense to novel predation. Thus, we can see that prey species that benefit from increased genetic diversity, should have fixed, smaller, body sizes.

Species that have avoided predation for long periods through isolation, special defenses, or being a top predator, such as isolated fish clams, tortoises, or sharks, evolve indeterminate body sizes because their populations benefit from reduced genetic diversity. Birds and bats, which also have excellent defenses to predation would probably also have evolved indeterminate growth if not for aerodynamic limits on their body sizes.

So far, our example has explained the relationship seen between aging rate, body size, metabolic rate, reproductive senescence, gestation rate, and litter size. The example also

suggests that, if not for aging, predator-free populations would quickly lose their youth-dominated distribution and assume an old-dominated age distribution during and after population crashes/declines. And finally, we have shown that the evolutionary advantage of immortality in these situations is so strong that longevity should rapidly evolve in the absence of predation. Most of this corresponds to relationships that are seen in nature. However , the glaring exception to our analysis is that we know that there are few if any immortal life forms. The big question is why not?

One might guess that maintaining the predator-induced distribution between episodes of predation prevents extinction of the group upon return of the predator. This could be a huge survival advantage when compared to groups that lose this age distribution pattern. While the logic in this guess may be correct, it still does not explain why individuals must age and die. For if we assume a constant environment, the youth-skewed distribution could just be frozen into place on a static, immortal population to await the next predator encounter. So why aging, and death?

Because environmental resources vary, population sizes vary, and cycles of deaths of and births would be created. Here, simple reproductive senescence without somatic aging or death would suffice to maintain a proper age distribution in reproductively capable individuals. However, over time, the percent of reproductively able individuals would shrink as reproductively senescent individuals accumulated. This would lower genetic diversity and put the group at risk. Again, we see that the purpose of somatic aging and death is to clear out the old. One fascinating conundrum is why human menopause which occurs at age 50, is so dramatically smaller than the maximum life span of about 120. Why doesn't evolution clear everyone out by age 50? While there may be several reasons for this, one interesting idea to consider is that an accumulation of slow-moving elderly can act as a buffer to predation. If predators can be satisfied with just a few sacrifices, the elderly could be just one more line of defense between the predator and younger, faster, fertile individuals. Now that we have completed the analysis of our new thought experiment we can examine the underlying assumptions that led to the almost universal acceptance of Medawar's accidental aging.

Antagonistic Pleiotropy-A Black Box

Accidental aging requires a black box in which to store all the contradictions and inconsistencies inherent in the idea. The black box is a theory called antagonistic pleiotropy.

Antagonistic pleiotropy allows aging to exist without a purpose. It suggests that genes that are beneficial for youthful reproduction become detrimental in old age: a Dr. Jekyll and Mr. Hyde transformation . Medawar touched on this idea which was more fully developed in 1957 by Williams **(23).** If you try to look inside the black box one finds that it is full of what one could only call magic genes. These are genes that make you fertile and strong as a youngster and that amazingly do an about face and make you frail and sick as an adult. The idea that a single gene that can do all this, however, is very difficult to believe. Have any of these magic genes been found?

Supposed evidence of their existence was found by Rose . Fruit flies were selected for longer life spans and as a result fertility in their younger years decreased **(24)**. Thus, it was claimed, genes that are beneficial to youthful reproduction were selected against, which in turn eased their detrimental effects in later years. This then "proved" the existence of the magic Jekyll and Hyde genes.

There is an a priori assumption in Rose's fruit fly example, that has previously been implied here to be incorrect, that increased fecundity in early ages is a positive trait regardless of the environment (it assumes an unlimited supply of eggs per lifetime in the evolutionary short run). Also, no satisfactory explanations as to how these genes might operate or time the expression of deleterious effects at older ages has ever been put forth. The only thing close to a mechanism mentioned by theorists is the often encountered wisdom that *"there is a tradeoff between investing resources in reproduction or in somatic maintenance"*. (This should be news to immortalized cancer cells, the non-aging Fulmar, or organisms with indeterminate body size). Further, it is assumed that longer life spans emerged due to selection for new mutations that occurred in barely an evolutionary blink of the eye, in the flies' antagonistic pleiotropy genes.

If Rose was selecting for a trait other than life span, such as an extra head, green legs, or a stinger, he would have certainly had to carry on the experiment longer than a just a few years. It would likely have taken a few hundred human lifetimes. What was likely being selected for was alterations in an existing system that alters aging and fertility rates in response to environmental conditions and predation levels. What was being selected for was not new genes or mutations, but likely natural, within-population, variations in lifetime hormonal profiles that simply accelerate or delay the expression of a linked group of reproduction and aging genes. Slowing the expression of genes that trigger fertility would simultaneously slow the triggering of genes that induce aging at later ages if they are both timed by the same mechanism. That mechanism is likely reproduction-related hormones. However, if we assume that aging is accidental and not programmed, then aging genes cannot exist alone and must be merged with and be the accidental byproduct of fertility genes.

So, ignoring the fruit fly "proof", what would be convincing proof of the existence of these magic genes? One simply needs take a look at any of the genes that cause the following in humans: gray hair, wrinkles, cataracts, Alzheimer's, muscle atrophy, diabetes, heart disease, stroke, baldness, hypertension, cancer, prostrate hypertrophy, depression, immune dysfunction, osteoporosis or loss of hearing, vision, or teeth, and show the corresponding benefit that it imparts to children, or to human fertility and the theory will be saved.

Further, beneficial mutations are likely exceedingly rare. Most mutations are either neutral or harmful and selected against. Neutral mutations, can simply accumulate in the genome with no effect. The idea of a mutation that is neutral in the young but magically becomes detrimental in the old at first seems unlikely, but if one adds age-related

epigenetic suppression of gene expression, young-neutral/old-detrimental mutations seem quite possible

This then leads us to the less likely idea of mutations that are beneficial to a young organism that then somehow become harmful later in life: most likely a logical if not statistical impossibility. It is probably safe to say that even if genes exist with both positive/early and negative/later effects, they should be overwhelmed in number by genes that are early/neutral with negative/later effects.

The prior summary of eighteen human aging symptoms is small enough to fit into a single long sentence while being reasonably comprehensive. If it has taken 4 billion years to accumulate such a small number of aging genes, they must not be a common occurrence. If the genes that cause these 18 aging symptoms truly had beneficial effects in younger years, wouldn't we expect to see thousands, if not millions more of the more likely young-neutral mutations that cause aging in adults? Where are the vast number of these more likely aging genes and why aren't they on the list? The only thing missing form the list are the magic, non-existent antagonistic pleiotropy genes.

Where Have We Gone Wrong?

Medawar's idea of accidental aging has been expanded upon to produce a large body of theory which, unfortunately, is flawed from the start. The world of accidental aging, has produced many viable, competing theories of aging relating to: mitochondria, hormones, free radicals, telomeres, apoptosis, stress, metabolic rate, immunology, and many others. Mountains of evidence exist suggesting that each is correct, yet proponents of one theory, knowing the strength of their case, often believe other theories must be wrong. Aging theory is a chaotic mess with no resolution in sight. Obviously something is very wrong, and it must be at the theoretical level. But how could so many have been misled for so long without a fight? The problems in aging theory all stem from a bigger problem in biology which is the belief that group selection is not a viable evolutionary force. And while arguments against group selection certainly seem logical on the surface, a more thorough analysis shows that these arguments are most likely incorrect.

Group selection has long been thought to be a hypothetical, and unimportant factor in evolution due to its unlikely occurrence except under highly unlikely scenarios **(25)** and its dependence on the impossible selection of something that is bad for the individual because it is good for the group. The "unlikely scenarios" objection assumes group selection would occur from competition between two variants of the same species. This would require the assumption, for example, of aging and non-aging groups of say, deer, occupying the same or nearby territories without destroying their differences through gene transfer between groups.

The "unlikely scenarios" objection can be overcome by simply stating that group selection occurs between groups of non inter-breeding local species, i.e. groups of deer in competition with local groups of cattle, rabbits, ants, and/or elephants. With this in mind, one can see that group selection is a universal force. It is the local, aging groups

that cause the extinction of local, non-aging groups with predation being the selecting force. The aging species can then migrate to areas where its non-aging relatives have been driven to extinction by their local, aging competitors. This is how group selection for aging likely occurs.

Also the argument of the supposed impossibility of selecting for traits that are deleterious to the individual even though they are good for the group can be countered. In the case of a predator-induced, young-dominated, population, the accumulation of neutral mutations that become deleterious at ages past the average age of death imposed by predators does not affect the reproduction of the individuals dying at young ages. To the individual in a predatory environment, these potentially deleterious mutations are neutral and therefore can accumulate. The only time the deleterious mutations work against the individual are when the individual has entered a predator-free environment and lives longer than normal. It is in predator free periods where positive group selection occurs for these (now) individually-deleterious traits. Initially, group selection will lead to the evolution of retained aging systems that kill individuals at the proper time during predation-free periods which benefits the group, but eventually, without periodic predation selecting for aging at the group level, selection against aging at the individual level will occur, aging is lost, and longevity begins to evolve.

In Conclusion

At this point, the case can be made that the tree of accidental aging theory, planted by Medawar fifty years ago, with all its obscuring branches leaves and limbs, has been uprooted and will soon whither away and die . In its place, a new seed has been planted. This seed should grow into a simple, and elegant theory of purposeful aging producing a tree of aging knowledge which will integrate and fuse all of the many sub-branches of aging theory into a viable, unified , and cohesive body of science.

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