The Case for Programmed Mammal Aging

Theodore C. Goldsmith

tgoldsmith@azinet.com

Invited paper: Invitation date: December 30, 2008
Submitted to: Mendeleev Russian Chemistry Journal:
Special Issue on Programmed vs. Non-Programmed Aging

Submitted: February 5, 2009
Revised: February 21, 2009

Keywords: ageing, gerontology, programmed senescence, adaptive aging, aging theory

About this article and the RCJ special issue

Azinet aging theory web site:
http://www.azinet.com/aging/

The Case for Programmed Mammal Aging

Theodore C. Goldsmith

Abstract

Are the deteriorative processes associated with mammal aging purposely and actively programmed by the organism's design or are they merely a passive result of the organism's inability to better resist damage from fundamental deteriorative processes? This question has now persisted for 150 years. Historically, observational evidence generally favors active aging. However, the nature of the evolution process has been thought to preclude evolution and retention of organism design features that purposely cause deterioration or otherwise actively limit life span. More recently, discoveries such as aging genes have increased the weight of empirical evidence for programmed aging and our increasing knowledge regarding the nature of the mammal inheritance process has added to questions regarding the validity of traditional evolutionary mechanics concepts. Alternatives to traditional mechanics concepts have subsequently appeared, most of which support active aging, and theories of biological aging based on the alternative evolutionary mechanics theories have been produced.

This article compares active and passive aging concepts in light of various observations, provides an overview of the historical interaction between aging theory and evolution theory, and outlines major issues that currently exist regarding the mechanics of evolution. A specific candidate structure for an active mammal aging mechanism is presented and a specific evolutionary rationale, an evolvability theory of aging, which allows for the evolution of that mechanism, is suggested.

This issue has substantial public health implications because understanding of massively age-dependent conditions such as cancer demands understanding of the aging process. Also, active theories suggest significant additional possibilities for treatment of age-related conditions.

INTRODUCTION

Is aging "programmed", the purposeful result of some life span management system that actively limits the life of an organism or is it merely the passive result of the action of fundamental deteriorative processes? All the theories discussed here revolve around fundamental accumulative deteriorative processes including oxidation, incremental mechanical damage or wear, and other molecular damage including alterations to genes and telomere shortening. Many members of the general public favor the idea that aging is simply the result of such deteriorative processes and that humans age in essentially the same manner as automobiles or exterior paint. If considering only human aging, this idea is at least superficially attractive.

However, when considering mammals as a group it was apparent that the simple damage accumulation concept was inadequate for two reasons: First it was clear that mammals possessed maintenance and repair mechanisms that acted to repair or prevent damage from many deteriorative processes. Claws and hair grow to replace worn items.

Dead cells are replaced. Wounds heal. Infections are resisted. These kinds of maintenance processes operate over a relatively short time, on the order of days or weeks. Evidence to be described suggests that mechanisms that act to protect against age-related conditions such as cancer also operate on a short time frame.

Second, different mammals exhibit dramatically different life spans encompassing an approximately 100:1 range between humans (~80 years) and the Argentine desert mouse (*Eligmodontia typus* ~0.8 years). Although human and mouse are very different at an anatomical level they are much more similar at a cell level and even more alike at a molecular level. Why would mouse cells degrade so much faster than human cells? Why would mouse molecules deteriorate so much more rapidly than nearly identical human molecules? This led to the concept that life span differences in mammals can be explained by differences in the effectiveness of their maintenance and repair mechanisms. More rapid aging in a short-lived mammal is the passive result of combining the fundamental deteriorative processes with relatively less effective maintenance and repair mechanisms. Aging is not programmed but occurs by "default" due to the accumulation of residual un-repaired damage.

Finally, some of us believe that a specific, species-unique life span conveys benefits and that therefore mammals and other organisms developed active programmed life span management systems that purposely allow deterioration or otherwise *cause* deterioration and death. This article proposes that indeed programmed active life span management is responsible for mammal aging.

If we examine Fig. 1, the top (dashed) curve represents survival capacity (ability to withstand environment, predation, competition, and other life challenges – arbitrary units) of a typical mammal as a function of time since birth. Zero on this curve means that the organism would not survive even protected zoo conditions. Although we can argue over the shape of this curve, which presumably varies with species, we can all agree that the curve begins and ends at zero. We also can agree that the ascending portion of the curve is "programmed" as a purposeful aspect of the organism's design. The question of course is whether the descending (deteriorating) portion of the animal's life is also programmed in essentially the same way and with similar mechanization as the ascending portion.

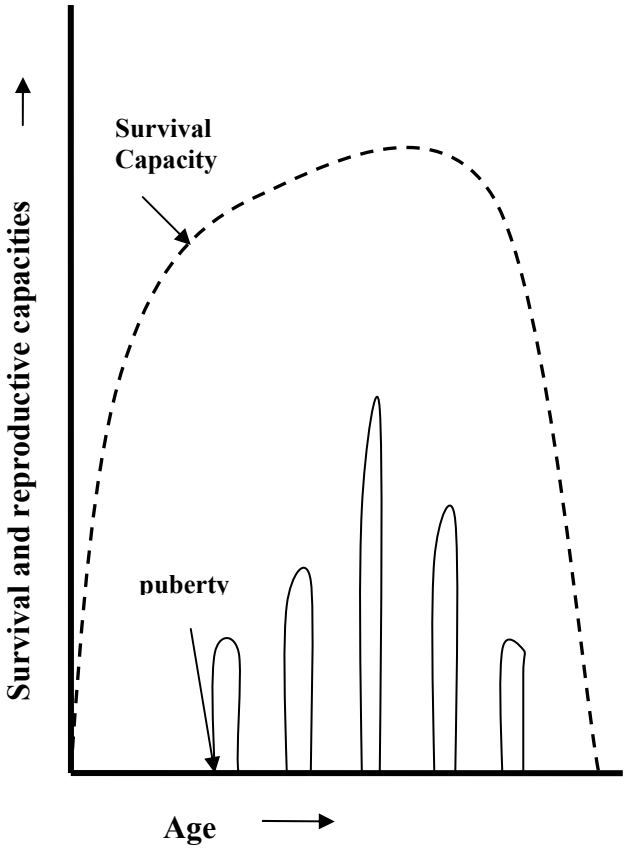

Figure 1. The survival (dashed line) and reproductive (solid lines) capacities of a typical mammal as a function of age

The lower curves (solid) in Fig. 1 describe the reproductive capacity (competitive ability to mate) of a typical mammal having annual mating seasons. The timing of these mating periods (including puberty or the age of the first mating period) is determined by some sort of "biological clock." This clock in turn is clearly affected by planetary cues that are detected by some sense function because the mating periods are synchronized to the planetary seasonal cycle. Is programmed aging also controlled by some sort of clock function or even possibly an adjunct of the same clock function that controls puberty? Both passive and active theories of aging suppose a relationship between puberty age and life span so this possibility is of special interest.

Thinking about aging theory involves examining two areas: empirical evidence and aspects of evolution theory that impact the aging issue. In general, observational evidence favors active programmed aging while traditional evolutionary mechanics theory strongly favors (actually mandates) a passive theory. This article compares the passive, non-programmed maintenance theory of aging to the active programmed theory in light of both observational evidence and evolution theory considerations.

The active theories specifically assume that there is benefit in an organism design that controls life span and that a suicide mechanism can therefore be an adaptation. They

further assume that as in the case of any other functional (performance) aspect of an organism, the optimum life span for an organism is determined by its external circumstances (such as population density, predation, food supply, etc.) as well as other interacting internal organism design characteristics such as age-at-puberty. Discussion regarding *why* such a controlled life span produces value that would be selected by the evolution process is presented in a later section of this article.

OBSERVATIONAL EVIDENCE

Primary Observation on Aging Mechanisms

The primary observation (observation 1) driving pan-mammal aging theories is that different mammal species exhibit dramatically different life spans in protected environments even though they possess very similar biochemistry and the deteriorative processes implicated in aging are largely biochemical in nature. Efforts to find physical or chemical factors such as body mass or metabolism rate that correlated well with life span were unsuccessful and it was apparent that life span was essentially an aspect of organism design. (Regarding mass, elephants and parrots have approximately the same life span. Regarding metabolism, parrots live approximately six times as long as crows.) The extremely species-unique nature of life span led to the development of *evolutionary* theories of aging in which aging theories are derived from evolutionary mechanics theories, more specifically theories that describe how organisms acquire their species-specific designs.

Active and Passive Aging Mechanism Hypotheses

This article compares two different types of mechanism proposed for gradual aging in humans and other mammals. In the passive mechanism, aging is the result of generic deteriorative processes such as oxidation, molecular disruption, genetic transcription faults, mechanical damage, and other natural processes that cause deterioration in biological systems. The gross life span differences are explained by the presence of a large number of independent anti-deterioration functions that act to prevent damage from or repair damage resulting from the generic deteriorative processes. A particular longer-lived mammal species possesses more effective anti-deteriorative functions than a shorter-lived species and therefore residual damage accumulates more slowly.

In the active mechanism concept described here, humans and other mammals possess life span management systems that actively limit life span to a species-unique value. We can think of these mechanisms as biological suicide or self-destruction mechanisms. These mechanisms can be expected to vary between species just as evolved mechanisms that provide for vision, digestion, or mobility vary between species. The generic deteriorative processes may be harnessed in implementing a life span management system in lieu of or in addition to other more direct life span limiting processes. Weismann's "programmed death" theory[1] of 1882 was the first formal proposal for an active aging mechanism.

Observation 2: Semelparous Species – Biological Suicide

Semelparous species, in which life span limitation is associated with reproduction rather than gradual deterioration, represent obvious instances of active life span management. Some mammals (marsupial mouse[2]) are semelparous (the male dies after mating), and some multi-parous species (e.g. some salmon) also possess active life span management and die after reproducing. Some suggest that the life spans of some semelparous species (e.g. some insects and plants) are passively limited by seasonal environmental conditions. The counter-argument is that other species of a similar nature are not so limited and possess multi-year life spans demonstrating that seasonal conditions are not a fundamental limitation. Others suggest that life spans of some semelparous species are limited by "exhaustion" associated with their reproductive functions. Here again, species of a similar nature accomplish the same reproductive functions and survive to be multi-parous. Further, some suicide mechanisms are known to involve complex processes such as hormone signaling and sense functions (more below). In my view the existence of obvious active suicide mechanisms in simple species suggests that others including humans possess more subtle active mechanisms. Further, since mammals are generally more complex than salmon or octopus, and possess more complex mechanisms for vision, digestion, mobility, and other functions, we would expect them to also have more complex and capable mechanisms for life span management.

Observation 3: Similarity of Aging Manifestations in Short-lived and Long-lived Mammals

Symptoms of aging (grossly increased incidence of many diseases including cancer, skin and hair conditions, arthritis, cataracts and other sensory deterioration, muscle weakness and other mobility deterioration, etc.) are generally similar between short-lived and long lived mammals. This suggests that the causing deteriorative processes all operate over a relatively short time span (less than the life span of a short lived mammal). If this were not so, short lived mammals would not display some of the manifestations. Therefore all mammals need all of the maintenance functions. Without the maintenance functions mammal life spans would be limited to a matter of months, probably less. Since the deteriorative processes and corresponding maintenance functions are respectively universally present and necessary in mammals and other complex organisms, they are an obvious choice as components of an active life span management system. Nature need only add the capability for gradually disabling the repair functions when the necessary life span has been achieved.

Consider the candidate or straw-man concept for an active mammal life span management system diagrammed in Fig. 2. In this concept, maintenance and repair functions exist to counter damage from the generic deteriorative processes. A biological clock gradually disables the maintenance functions at a species-specific age allowing the deteriorative processes to subsequently produce aging symptoms. The difference between short-lived and long-lived species is not in the maintenance functions but in the biological clock. Similar species differences exist regarding the clock that determines age

of puberty. This scheme matches observation 3 as well as the other observations and is generally more capable and flexible than the passive system.

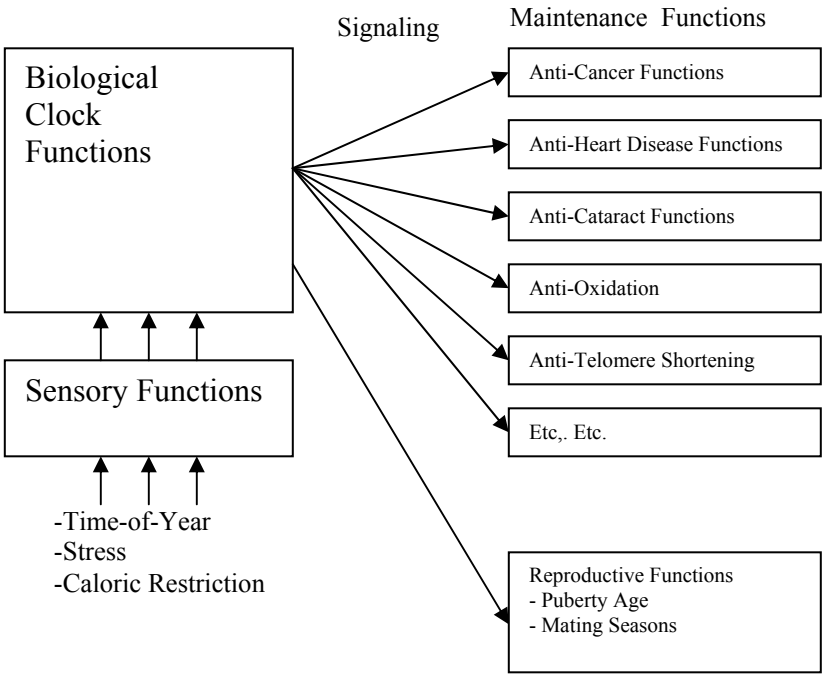

Figure 2. Candidate Active Aging Mechanism Functional Diagram

In the passive scheme, for progressively longer-lived mammals each of the many maintenance mechanisms is assumed to be in some way more effective than the corresponding mechanism in the next shorter-lived mammal and therefore capable of repairing a larger proportion of the damage addressed by that mechanism. However, damage eventually accumulates causing aging symptoms. This scheme requires an undemonstrated assumption: that each maintenance process can be incrementally improved as opposed to discrete steps of improvement. We would need "replace dead cells", "replace dead cells better", "replace dead cells better yet", and so forth. Some maintenance tasks such as telomere repair seem to be especially discrete in nature. The active scheme does not require this assumption.

Human death rates generally increase exponentially with age after maturity (Gompertz curve). However, at extreme ages (~100) the increase slows[3]. In the active concept this can be explained as a quirk in the design of the control mechanism. In the passive scheme there is no apparent reason why the rate at which un-repaired damage accumulates would behave in this manner.

Observation 4: Progeria and Werner Syndrome

Hutchinson-Guilford progeria[4] and Werner syndrome[5] are human conditions in which a single-gene defect causes acceleration of many or even (Werner) most symptoms of aging. In the active concept of Fig. 2 it is clear that such a malfunction could affect the clock function or another of the common processes involved (sensing, signaling) and therefore result in the accelerated symptoms.

In the passive scheme, it is assumed that each of the maintenance mechanisms evolved separately and independently to counter each different manifestation of aging. If cancer at too young an age was becoming a problem, the species would evolve better anti-cancer mechanisms, and so forth. It seems very improbable that a single-gene malfunction would more or less equally affect all of the independent maintenance mechanisms in the passive scheme.

Observation 5: Caloric Restriction, Exercise, and Stress

Caloric restriction, exercise, and some other instances of stress have been found to result in the counter-intuitive observation that they all increase life span[6]. In the active scheme of Fig. 2, the organism has a method for sensing these conditions and adjusting the self-destruction timer. This satisfies various adaptive (programmed) theories of aging that contend that the optimum life span for a species varies depending on local or temporary conditions. Example: The caloric restriction response improves group survival under famine conditions. Why would stress increase life span in the passive case?

Observation 6: Aging Genes

Some investigators have reported the discovery of genes that promote aging in various organisms with no individual benefit that has yet been identified. They further suggest involvement of signaling in implementing life span "regulation"[7]. These findings directly support active mechanisms.

Passive theorists contend that the "aging genes" must have some hidden individually beneficial purpose.

Flexibility Argument

One argument in favor of the active system is that it is generally more flexible in *adapting* to changes in an organism's situation. As described above, an active system could adapt non-genetically and instantaneously to local or temporary conditions that alter the optimum design-life-span for that organism. It could also genetically adapt more rapidly as follows: In the passive scheme, if an organism needed a shorter life span, we can imagine that deleterious mutations to *each* of the many maintenance mechanisms would rather rapidly (in evolution terms) accumulate thus shortening life span (requires the above described assumption that all the maintenance functions are continuously variable). However, if the need was for a longer life span, the organism would have to evolve improvements to the designs of all of its many maintenance mechanisms, a likely very much longer process. In the active concept a much simpler change to the clock could increase as well as decrease life span much more rapidly. The ability to adapt more rapidly would be a competitive advantage.

Diversity Argument

Life span is one of the most superficial of all animal characteristics. There are species that are virtually identical regarding other design characteristics (e.g. salmon varieties) and yet have grossly different life spans. This suggests that there is value in having a flexible life span management system. It also suggests that life span is controlled by a relatively small number of genes, which also favors the active concept and corresponds with observation 6. Age-at-puberty is similarly superficial.

Experimental testing

Wodinsky[8] performed experiments demonstrating that the suicide mechanism in the octopus involved hormone signaling and optical organs (implying a sensing function). The octopus females die of starvation following reproduction. They starve because they do not eat even if food is available. This behavior implies a nervous system function in which the suicide mechanism interrupts the normal hunger response. The octopus suicide mechanism therefore involves nervous system connections at both the input or sense end and at the output or actuator end.

Kenyon[9] has performed experiments demonstrating hormone signaling and sensing of external signals in the life span management of *C elegans*.

I have suggested that experiments could be performed to determine if external planetary cues affect the life span management system as suggested by Fig. 2. Short-lived organisms could be maintained under conditions that simulate a longer or shorter planetary cycle (e.g. longer or shorter day/night period) to determine if age of sexual maturity or life span would be affected.

EVOLUTION THEORY CONSIDERATIONS

Historical Notes on Aging Theory Aspects of Evolution Theory

Understanding the current situation surrounding aging theory requires an understanding of the long history in which aging theory has interacted with evolution theory.

Darwin's theory of evolution, published in 1859, is actually comprised of two distinct parts. The idea that species are descended from other species is now essentially universally accepted and supported by overwhelming observational evidence. The second part is Darwin's concept for the mechanism of evolution or *evolutionary mechanics theory*, which involved natural selection and natural variation. The mechanics concept defines the kinds of organism design characteristics that could arise through the evolution process.

Everyone understands Darwin's proposal that species evolved design characteristics that "benefited" the organism. However, since then there have developed

distinct schools of thought as to what exactly constitutes "benefit" and therefore what sorts of design characteristics could arise through the evolution process. "Orthodox" or traditional evolutionary mechanics theory holds that benefit must be narrowly defined as benefiting the ability of *individual* organisms to survive (and therefore have more opportunity to breed) or otherwise have increased probability of propagating their individual designs.

Unlike the species descendency concept, there have always been apparent discrepancies between orthodox mechanics and observations. Life span observations were among the discrepancies immediately noted. If a longer life provided benefit, why did mice not evolve the same life span as a human?

Darwin provided a rationale[10] for the general observation that organisms seemed to be designed to have a species-specific life span as well as for the semelparous species (e.g. salmon, octopus) that were more obviously designed to have a particular life span: Since his mechanics theory demanded it, there must be some hidden theory-conforming (individual) benefit to offset the individually adverse observation. Of course this was a circular "explanation." The theory was being used to predict the observation as opposed to the reverse. The same "explanation" could be used to "explain" any observation of an apparently individually adverse organism design characteristic.

At the time this was a reasonable position. There were perhaps thousands of non-conforming life span observations as opposed to millions of conforming observations. Any high-school student could easily observe myriad examples of plant and animal design characteristics that obviously aided the organism's ability to survive or reproduce and Darwin had a reasonable expectation that, eventually, conforming offsetting benefits would be discovered for the minority of apparently non-conforming observations. Subsequently, most efforts to develop evolutionary aging theories were constrained by the need to demonstrate compensating individual benefit.

By ~1950 orthodox evolutionary mechanics was well established and there was little if any scientific opposition. The multiplicity of life spans observed in mammals continued to be a major scientific mystery, an "unsolved problem of biology."

In 1952 Medawar published a concept[11] to the effect that the evolutionary effect of older animals declined with age beyond age of puberty. It was clear that an organism design in which the organism died of or suffered major adverse effects from aging prior to puberty would not be a viable design. Conversely, death from aging or adverse effects on survival that occurred well beyond puberty would have much less effect on the organism's ability to reproduce and propagate its design.

Medawar's hypothesis provided the basis for passive theories of aging. Mammal species only *needed* to live to a species-specific age loosely based on puberty age and therefore did not evolve and retain maintenance and repair mechanisms necessary for a longer life span. This provided a good fit for the primary observation (variation of life spans between mammal species). Proponents of passive theories tend to ignore all the other mammal observations and consider non-mammal species (and semelparous mammals) irrelevant to gradual mammal aging. Some proponents[12,13] of passive theories now claim that their theory has definitively solved the problem of aging and decry any dissent.

Orthodox theorists subsequent to Medawar, notably Williams[14] and Kirkwood[15], contended that while death of old age would probably have no evolutionary effect in the wild, other effects of aging (weakness, decreased mobility and sensory capability, etc.) would substantially adversely affect the survival capacity of even relatively young mammals. They therefore contended that the process that causes aging must produce some offsetting orthodox-compatible (individual) benefit and that Medawar's formulation, by itself, was inadequate. Various such benefits have been proposed. In some cases such arguments are circular formulations along the lines of: "there must be some hidden benefit." Because of Medawar's hypothesis, an offsetting benefit to a younger animal might be relatively minor relative to the massively adverse nature of aging and death.

However, in general, the evolution process is obviously capable of independently adjusting myriad different organism design parameters. Therefore, the "offsetting individual benefit" concept requires that the benefit be in some way unavoidably linked to aging such that the evolution process cannot produce the benefit without the consequence of aging. Empirical evidence of such a fixed and rigid linkage has not emerged.

The general situation was that by 1975 there were multiple competing theories of aging based on orthodox evolutionary mechanics. Opponents of orthodox aging theories have written extensively[16, 17] criticizing the logic behind Medawar's concept as well as the other theories based on that concept.

Many current proponents of passive aging theories use orthodox mechanics theory as essentially their only rationale for adopting passive aging over active aging. The following statement (Hayflick [18], et al) is typical of passive theorists: "The way evolution works makes it impossible for us to possess genes that are specifically designed to cause physiological decline with age or to control how long we live." The passive school benefits from the tendency of most scientifically trained people to reject anything that questions "the" (singular) theory of evolution and also benefits from the generally counter-intuitive nature of active aging. Medical people are especially likely to be pre-disposed toward passive aging since much of the evidence and impetus toward active aging comes from non-human models.

Meanwhile, by ~1960, even semi-plausible orthodox-conforming compensating benefits for the majority of the semelparous animal observations had still not been discovered. In addition, other apparently non-conforming observations (of individually disadvantageous or neutral design characteristics) eventually surfaced including sexual reproduction, excess male puberty age in some species, some mating rituals, altruism, and some aspects of inheritance systems[16]. In some cases the orthodox explanation remains some version of: "There must be some logical explanation." Some orthodox theorists still take the position that since the discrepant observations are in the minority, they should be ignored.

The protracted existence of thousands of non-conforming observations was not scientifically acceptable to many people. Alternatives to orthodox evolutionary

mechanics theory including group selection[19], kin selection[20], selfish gene theory[21], and evolvability theory[22] were consequently proposed between 1962 and 1995 as modifications or adjustments to orthodox theory. All of the alternatives propose that design characteristics that aid groups of the same species (beyond direct descendents) or that aid the evolution process could evolve despite some individual disadvantage. All suggest that individual benefit is not the only natural factor influencing the evolution process.

Darwin supposed that occasional mutational changes occurred in individual organisms. Some of these changes then *propagated* to exist in the entire population of a species. Natural selection or "survival of the fittest" *differentially* affected the propagation of the changes to produce the process of evolution.

Since Darwin, an enormous body of information has accumulated regarding the actual mechanics of mammal inheritance. This knowledge reveals that various design aspects of the mammal inheritance system *also* differentially affect propagation of mutational changes and therefore interact with natural selection. The discovery that the inheritance process involved a complex digital information "genetic code" scheme also resulted in evolutionary implications to be discussed.

The effect these genetics developments (some very recent) will eventually have on evolutionary mechanics theory is unknown. The overall impression is that the evolution process is much more complex and probably much more time consuming than once thought. This has the effect of increasing the plausibility of group selection by decreasing the apparent functional difference between an individual benefit and a group benefit. An evolvability theory of active aging (described below) is also substantially derived from consideration of inheritance mechanisms.

Specific biological aging theories supporting the evolution of active life span management have been developed based on group selection[23], kin selection[24], and evolvability[25,26] respectively. Several of these aging theories hold that life span management is generally beneficial, even essential, to complex species and even suggest that gradual aging is superior to semelparous life span management specifically because it is gradual and multi-system.

It is certainly true that currently there is no single generally accepted alternative to orthodox evolutionary mechanics theory. However, it is also true that there is now a wide understanding that orthodox theory has major problems; there are hundreds of journal articles extant discussing various aspects of this issue, particularly items (2) and (3) below. In my view there are major issues with orthodox evolutionary mechanics theory in three different areas:

1) There remain many apparent discrepancies between observations and predictions of the theory.
2) Orthodox theory assumes that all organisms have the same capacity for evolution – in my opinion this is provably false. Any valid mechanics theory must deal with the evolvability issue.

3) Many relatively recent discoveries in genetics science that expand our understanding of the mechanisms of inheritance plausibly impact evolution theory but have not been incorporated. These discoveries improve the case for group selection and evolvability theories.

EVOLUTIONARY BASIS FOR ACTIVE THEORIES OF AGING

As suggested above, there are several theories of active aging based on group benefits of a design-limited life span. Other theorists, cited here, have written extensively regarding these theories.

Evolvability Theory of Aging

The following is a theory of active mammal aging based on evolvability. An active, programmed aging mechanism aids the evolution process and was therefore selected and retained despite some individual disadvantage.

Evolution of Evolvability

It is generally accepted that organisms possess design features that enable the process of evolution. For example, all organisms possess the ability to pass information describing their designs to descendents, to store that information during the life of the organism, and to copy the information for distribution to multiple descendents, in addition to mechanisms that support accumulative adaptive modification of that information. The question here is whether it is possible for design properties that support or enhance the evolution process to *vary* between different organisms. If such was possible, then could not organisms evolve improvements in their ability to evolve? Would not such enhancements represent an obvious benefit in that organisms possessing them would be able to adapt more rapidly or comprehensively to changes in their environments? Would not any theory of evolutionary mechanics need to deal with variation in the capacity of organisms to evolve?

Traditional evolution theory ignores the evolvability issue. Either of two assumptions supports such a position. The first is that the capacity for evolution is a fundamental property of life that does not and can not vary between populations or species, and that therefore evolvability is a constant that does not need to be considered in devising theories of evolution. The second is that evolvability is enclosed in traditional concepts of fitness and is therefore covered by traditional theory. Arguments are presented below to the effect that neither of these assumptions is correct.

Unnatural Variation

Darwin described a property of organisms that is essential to the evolution process. He proposed that evolution was dependent on “natural variation” in inheritable design characteristics between individuals. Evolution depends on this variation because natural selection selects between the differences. If, at some point in time all the members of a

population were genetically identical, evolution in that population would not be possible, a zero-evolvability situation.

Some might say that variation is the result of mutations to the genetic data that defines organism designs, that surely all species undergo mutations, that the design of the organism does not affect this, and that therefore mutation and resulting variation is a fundamental and invariant property of life. For Darwin this was certainly a reasonable assumption. However, we now know that the variation in fitness parameters that we see in complex organisms actually results from a long list of obviously evolved mechanisms**.** Complex organisms maintain a pool of mutational differences (i.e. single nucleotide polymorphisms or SNPs) each of which is possessed by some (by definition at least 1 percent) but not all the members of the population. (The human population is thought to possess several million SNPs.) The variation we see is the result of assembling the differences in *combinations* that, through cascading the effects of multiple individual differences, produce the observed effects. The magnitude of variation produced by cascading is generally very much larger than the effect contributed by any one SNP. The mutations in the pool are in effect pre-screened by natural selection to eliminate those that result in major adverse effect and therefore consist only of those that are (considered individually) beneficial, neutral, or mildly adverse and are therefore a potentially useful part of such an assembly.

Further, we now know that nature uses a digital method for handling the organism design information and is therefore limited by the fundamental characteristics that are common to any digital data construct. One such fundamental property is that while it is relatively easy to produce a verbatim copy of digital data it is very difficult to produce meaningful, structured variation. The "analog" concept that variation is a "natural" fundamental consequence of nature does not apply to digital data. These "digital genetics" limitations[16] have required development of many complex organism design features that process the digital data in producing the observed variation. Mutations are therefore only the feedstock to a very complex system. It is clear that this "variation producing system" has evolved very dramatically between single cell prokaryotes and complex sexually reproducing species. Producing and maintaining variation even involves behaviors: An organism could have an inherited behavior pattern that caused it to seek mates that were not close relatives thus increasing variation.

The inheritance system itself represents a conflict with the idea that natural selection, selecting between phenotypic differences in individual organisms, completely explains evolution. To illustrate, a text document (also digital data) could be written completely defining the design of some complex structure. The document could then be copied and distributed to multiple builders for execution. The methods and systems used to copy and transmit the data do not affect the design of the structure; (the architect could even have written in a different language). In the same way the design of the inheritance system, which also involves a language, decoding, interpreting, merging, copying, and other complex processes does not affect the phenotypic design of organisms defined by the data it carries. Therefore, traditional evolution theory can not explain the development

and evolution of complex (sexually reproducing) inheritance systems while evolvability advantage (structured variation) does present an explanation.

Considered as the result of an evolved design characteristic, variation is individually adverse. Imagine a population of well adapted animals. We could presume that the average height of individuals (we could have picked nearly any characteristic) is nearly optimum from a fitness viewpoint. Therefore all the animals that are shorter or taller than average are less fit. Individuals in a population consisting of clones of an average animal would therefore be more fit than most of those in a population having more variation. Variation therefore benefits evolvability but detracts from fitness. Evolvability is *not* handled by traditional theory. It appears that most (possibly all) design characteristics that benefit evolvability are individually adverse or at best neutral. In the last decade, evolvability issues have been extensively discussed in scientific literature[27, 28].

So let us accept for the moment that many organism design characteristics can affect evolvability, that evolvability varies in the sort of continuous way that fitness varies, that evolvability is generally individually adverse, and that therefore the design of complex organisms must represent a compromise between evolvability and individual benefit. What other design characteristics might benefit evolvability?

Adult Death Rate

We discussed the many complex evolved design characteristics that result in each member of a sexually reproducing species possessing a different combination of all those SNP alleles. Since each has a different combination, each individual could be considered a trial or test of that specific combination. Will the individual possessing this combination live longer and breed more? This sort of logic suggests that the number of lives lived per unit time would be a factor in evolvability. A species that could live more lives could perform more tests. Therefore *death rate*, equivalent to lives lived per unit time would be an evolvability factor.

This concept needs some additional refinement. Natural selection theory says that a characteristic must be *expressed* in such a way as to affect survival or reproduction in order to be selected and that latent characteristics cannot be selected. Therefore, an organism that died prior to becoming an adult generally cannot contribute to the evolution of adult characteristics because adult characteristics are not fully expressed in juveniles. We could therefore suggest that *adult death rate* was a factor in evolvability. Design characteristics that increase adult death rate (adult lives lived per unit time) would increase evolvability. This idea suggests that any organism with an unnecessarily long life relative to the time required for maturation and reproductive capability would be at an evolvability disadvantage and generally fits the observed loose relationship between organism maturation and life span.

Some theorists point out[11] that under wild conditions, an *average* senescing animal in a typical mammal population would not have a shorter life span than that of an

non-aging version of the same mammal because of predation, food supply, and other external conditions and suggest that therefore there would not be any expressed difference between aging and non-aging to drive evolution in either direction. Population models typically used in such a formulation assume that an *average* animal will produce descendents at a fixed rate following puberty. For such a model there will necessarily be a consequent fixed *average* life span in order to maintain a stable population. Since deteriorative forces and processes clearly exist, gradual aging would be a plausible "default" result in a situation in which there was no evolutionary force to drive development and retention of maintenance and repair functions.

However, *some* individuals in a non-aging population could be expected to live very long lives and produce very many descendents. (Note that this is an individual benefit. All those descendents would carry the genes of their individual parent. The idea that aging under wild conditions *does* create an individual disadvantage caused development of competing orthodox-based theories.) Assuming a stable population and the same model as above, *many* other individuals would consequently necessarily have to die without descendents, presumably as juveniles. A non-aging population thus represents a lower adult death rate, less diversity, and in effect fewer combinations tested, an evolvability disadvantage, and suggests an evolvability purpose for organisms to evolve a system to limit life span as a compromise with individual benefit. Characteristics of complex organisms such as intelligence, immunity, and societal behaviors such as pecking order tend to worsen this situation by increasing the advantage of older individuals and further reducing diversity.

Intelligence and immunity represent cases in which an evolved inherited characteristic depends for its expressed selectable beneficial effect on acquisition of something (experience, exposure to pathogens) that accumulatively increases with age. "Intelligence quotient" embodies this concept. In the absence of a life span limitation, older individuals with their superior acquired characteristics would have an advantage over younger individuals with superior evolved characteristics, which would work against the evolution process. Evolution of intelligence and immunity would therefore appear to specially require a design-limited life span.

A related observation is that age of male puberty in many species appears to be delayed relative to the age that seems to be plausibly required merely for physical (growth) development of reproductive systems. In species in which the male protects or otherwise supports its young, a case can be made that such delay has individual benefit. In reptiles where no such male function exists, delayed male puberty is individually adverse. However, delayed male puberty would have an evolvability benefit by delaying breeding until the individual was mature, therefore expressed adult characteristics, and presumably had at least partially passed the life-test. Also, again referring to the model above, delayed puberty has an effect that is similar to and complimentary to life span restriction in improving evolvability by mediating adult death rate. Age-at-puberty and life span seem to be related in this regard. If a population had a lower age-at-puberty, *some* individuals would begin reproducing earlier, and, in a stable population, adult death rate would be reduced.

It also appears, because adult death rate is affected by external factors such as predators or food supply, that an organism that could locally or temporarily adjust life span to compensate would have an advantage. An organism that could compensate for scarcity by reducing reproduction while increasing life span would have an advantage because such behavior requires fewer resources. This is a possible explanation for the caloric restriction[6] effect.

Some mating rituals (e.g. Bighorn sheep) seem to have a similar effect in generally delaying reproduction beyond puberty age (an individually adverse effect with evolvability benefit).

Group selection[29] proposes a situation in which a future group benefit of some design characteristic trades off against a more immediate individual disadvantage to allow the propagation and evolution of an individually adverse design characteristic such as altruism. Using the traditional model (e.g. Price's equation[30]), propagation becomes progressively more difficult as the size of the group increases and the group benefit is therefore increasingly delayed relative to the individual disadvantage. How does an individually disadvantageous design characteristic propagate into a sufficiently large group for the benefit to be expressed? Subsequently, the feasibility of group selection was criticized (e.g. Williams[31]). Some orthodox theorists therefore dismiss group benefits as too "weak" and too "late" to be a feasible trade with individual disadvantage. (In connection with aging theory it is interesting to note that believers in Medawar's hypothesis consider that the individually-adverse evolutionary effect of aging is essentially negligible. Therefore orthodox believers in Medawar's hypothesis are in the logically unenviable position of having to argue that the compensating group or evolvability benefit of aging is *less than negligible!*)

Some also think of evolvability as equivalent to species-level group selection, that is, evolvability benefits the species, or benefits future species, or otherwise has benefit that is felt only in the distant future relative to the individual disadvantage. They suggest that a long-term, deferred, large-group benefit can not outweigh an immediate individual disadvantage such as a shorter life span and that therefore evolvability explanations for adaptive aging or any other individually adverse design characteristic are implausible.

However, it is clear that logically, evolvability is significantly different from group selection. Evolvability benefits the *evolution process*. Evolvability operates in a very different manner from group selection in that it acts to create conditions that must ***preexist*** (e.g. variation) in order to enable or enhance the natural selection process. The evolvability concept thus does not require a group larger than or a term longer than the fitness concept. Individual benefit, evolvability, and group selection therefore represent three different evolutionary modalities and a valid propagation model must therefore treat evolvability differently from group selection as well as differently from individual benefit. Prior analyses purporting to show that group selection is infeasible cannot be legitimately applied to evolvability without modifying them to account for the logical differences.

A conceptual hurdle involves trying to visualize how an organism that had an individual advantage (e.g. longer life span) over another organism could fail to have an

advantage in propagating its design. I find it helpful to remember that evolvability was necessary in order to create a selectable difference in the first place, and that the magnitude of that difference depended on the magnitude of evolvability present. The traditional way of thinking about or analyzing the evolution process is to ***assume the existence*** of a ***selectable*** phenotypic difference (e.g. aging vs. non-aging) and then track how natural selection operates upon that difference. This approach does not work for an evolvability characteristic because such characteristics act to create phenotypic difference (variation) or to enhance selection (see prior discussion of adult death rate, intelligence, mating rituals, delayed male puberty, etc.) Evolvability characteristics therefore act to create or set up the *initial conditions* for the scenario being analyzed. The traditional approach therefore captures the disadvantage of an evolvability characteristic without accounting for its compensating benefit, which occurred *prior* to the beginning of the analyzed scenario. To be valid for an evolvability characteristic, the analysis must encompass the entire process, not just the part extending forward from the point at which a selectable phenotypic difference exists.

Another conceptual difficulty involves envisioning how the same organism could evolve stronger muscles, keener eyesight, and other evolutionary improvements in young individuals and also simultaneously evolve purposely weaker muscles, poorer eyesight, and other deterioration in older individuals. However, some organisms (e.g. insects) have designs in which a later (adult) stage has a design in which functional characteristics (e.g. digging and burrowing capability) of earlier stages are completely missing in the adult. Evolution can accommodate grossly different and apparently conflicting requirements at different points in an organism's life. If a mammal *needed* to have strong muscles and keen eyesight in one stage of life and also needed to have weak muscles and poor eyesight at a later stage, evolution could clearly accommodate those needs.

Propagation Issues Associated with Inheritance Processes

As details of the inheritance processes in sexually reproducing species have gradually emerged it has become apparent that these complex processes could differentially affect the propagation of mutational changes and thus affect evolution. Brief examples: *Genetic linkage*[28] and *unequal crossover*[32] create a situation in which a set of mutational differences that had similar loci on a single chromosome would propagate very differently from an identical set (with phenotypically identical effect) that was more widely distributed in the genome. Further complexity is introduced by other features of inheritance systems such as *transposition*[33], duplication of genetic data, *introns*[34], and creation of *modules* or objects in genetic data[35]. These features result in moving genetic data around in a genome thus affecting genetic linkage or otherwise affect propagation. These features interact with each other and with natural selection in very complex ways and also involve processes that are "long-term" even by evolutionary standards (e.g. movement of functionally similar genes to different loci or different chromosomes in descendent species, increases in introns in more complex species, etc.) suggesting that propagation concepts that require a longer term such as group selection may eventually prove to be much more feasible than supposed by traditional theory. Many aspects of non-phenotypically-functional "junk" DNA appear to have propagation implications. Ultimately, propagation models will need to deal with these issues.

A theory of gradual aging based on individual benefit has never completely gelled despite nearly sixty years of effort. Nagging inconsistencies persist and experimental confirmation has proved elusive. Multiple competing theories (i.e. mutation accumulation[11], antagonistic pleiotropy[14], and disposable soma[15]) with their variants and proponents still exist. Other observational discrepancies with the individual benefit concept (sexual reproduction, elaborate evolved inheritance mechanisms, "acute aging" (biological suicide), some mating rituals, altruism, excessive male puberty age; *all of which have evolvability explanations*) are generally more severe but have received less attention and are typically ignored by those producing or defending aging theories based on traditional propagation concepts. Adjustments to traditional evolution theory including group selection theories[29] and the selfish gene theory[36] have been proposed in addition to evolvability concepts. *All* of these adjustments propose to reduce the impact of the individual benefit requirement in efforts to make evolution theory better fit observational evidence. It is increasingly clear that the propagation concepts used to initially develop and now used to defend the traditional aging theories are in need of extensive revision in order to fully incorporate the evolvability and other propagation issues summarized here.

Weismann proposed what is probably the first evolvability-based aging theory[1].

Skulachev[25] and I[26] have proposed evolvability theories that suggest ways in which gradual aging is superior to acute death seen in semelparous species in producing evolvability benefit. We suggest that gradual aging acts as a challenge to older animals and therefore increases the selection differential between less fit and more fit organisms.

Mittledorf[23], Bowles[17], Promislow[37], and Libertini[24] have proposed adaptive aging theories based on group selection or kin selection, and/or have written extensively criticizing the logic behind the orthodox-based aging theories.

CONCLUSIONS AND MEDICAL IMPLICATIONS

A schism has existed in the science of biology for many decades (some would say 150 years). On one side are believers in strict orthodox evolutionary mechanics theory. On the other are those who support one of the alternative theories or who otherwise have a less restrictive interpretation of the word "benefit" as it appears in the sentence: "Organisms evolve design characteristics that benefit them." Is "benefit" restricted to individual benefit or does it also encompass benefits to groups or to the evolution process? No one would be surprised if this academic argument persisted for another 150 years.

This issue essentially dictates one's position on the question of human aging. Those believing in orthodox mechanics theory are logically forced toward some version of the passive concept. The others are driven inexorably by logic, empirical evidence, and Occam's razor toward some version of the active concept.

It is now clear that this endless academic wrangling could dramatically limit the approaches we take in attempting to find treatments for age-related diseases and conditions and that therefore this argument has come to have major public health implications. How can we really understand cancer or other massively age-related

condition without understanding aging? Perhaps it is time for some sort of national or international commission to evaluate all the currently available evidence and produce a conclusion regarding aging mechanisms. There are doubtless experiments, such as described here, that could be devised to more definitively distinguish between the very different aging mechanism concepts.

The major medical issue is the degree of commonality that exists between the various diverse and apparently unrelated manifestations of aging. The passive theories (as well as the generic damage theories held by many members of the general public) lead to the conclusion that each manifestation is functionally independent of the others and thus suggest that separate attempts to treat each individual manifestation are the only valid approach to the problem of age-related conditions and diseases, a continuation of the existing medical paradigm. The active theories lead to the conclusion that there are potentially many elements of commonality between the various manifestations and that therefore agents could be found for modifying those common elements so as to simultaneously treat many different manifestations, a potentially major addition to the current approach.

While one can argue either side of the evolutionary mechanics issue it is increasingly difficult to argue, given the observational evidence summarized here, that there are no potentially treatable common factors between different manifestations of aging. Further, there are hints that some agents capable of affecting multiple diverse manifestations may already exist. Example: Statins are reported to beneficially affect human heart disease and some cancers[38]. Skulachev, et al have reported[39] that some antioxidants directed specifically at mitochondria had multiple anti-aging effects in several different organisms including mice.

References

1. Weismann, A., *Uber die Dauer des Lebens*, Jena: Fischer, 1862.
2. Cockburn, A., Lek promiscuity in a semelparous mammal, *Behavioral Biology and Sociobiology*, 1988, vol. 22, p. 195.
3. National Center for Health Statistics, *Vital Statistics of the United States, Vol 2 Mortality*, Washington: Government Printing Office, 2000.
4. Eriksson, M., Brown, W., Gordon, L., Glynn, M., Singer, J., Scott, L., Erdos, M., Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford progeria syndrome, *Nature*, 2003, vol. 15, no. 423, p. 293.
5. Gray, M., Shen, J., Kamath-Loeb, A., Blank, A., Sopher, B., Martin, G., Oshima, J., Loeb, L., The Werner syndrome protein is a DNA helicase, *Nature genetics*, 1997, vol. 17, no. 1, p. 100.
6. Spindler, S., Rapid and reversible induction of the longevity, anticancer and genomic effects of caloric restriction, *Mech. Ageing Dev*., 2005, vol. 126, no. 9, p. 960.
7. Bartke, A., The endocrine regulation of aging by insulin-like signals, *Science*, 2003, vol. 28, p. 1346.
8. Wodinsky, J., Hormonal inhibition of feeding and death in octopus control by optic gland secretion, *Science*, 1977, vol. 198, p. 948.
9. Kenyon, C, et al., Regulation of C elegans lifespan by a proteasomal E3 ligase complex. *Proc. Natl. Acad. Sci. USA*, 2007, vol. 104, no. 14, p. 5947.
10. Darwin, C., *On the Origin of Species*, New York: Random House, 1998, p. 264.
11. Medawar, P., *An Unsolved Problem of Biology*, London: H.K. Lewis, 1952.
12. Holliday, R., Aging is no longer an unsolved problem of biology, *Ann. NY Acad. Sci*., 2006, vol. 1354, p. 1.
13. de Grey, A., Calorie restriction, post-reproductive lifespan and programmed aging: a plea for rigour, *Ann. NY Acad. Sci.*, 2007, vol. 1119, p. 296.
14. Williams, G.. Pleiotropy, natural selection and the evolution of senescence, *Evolution*, 1957, vol 11, p. 398.
15. Kirkwood, T., Holliday, R., The evolution of ageing and longevity, *Proceedings of the Royal Society of London*, 1979, vol. 205, p. 531.
16. Goldsmith, T., *The Evolution of Aging 2nd ed.*, Annapolis: Azinet Press, 2006.
17. Bowles, J., Shattered: Medawar's Test Tubes and their Enduring Legacy of Chaos, *Quarterly Review of Biology*, 2000, vol. 73, p. 3.
18. Olshansky, S., Hayflick, L., Carnes, B., No Truth to the Fountain of Youth, *Scientific American*, 2004, vol. 14, p. 3.
19. Wayne-Edwards, V., *Animal Dispersion in Relation to Social Behaviour*, Edinburgh: Oliver & Boyd, 1962.
20. Hamilton, W., The Evolution of Altruistic Behavior, *American Naturalist*, 1963, vol. 97, p. 354.
21. Dawkins, R., *The Selfish Gene revised edition*, Oxford: Oxford University Press, 1986.
22. Wagner, G., Altenberg, L., Perspective: Complex adaptations and the evolution of evolvability, *Evolution*, 1996, vol. 50, no. 3, p. 967.
23. Mittledorf, J., Chaotic Population Dynamics and the Evolution of Ageing, *Evolutionary Ecology Research*, 2006, vol. 8, p. 561.

24. Libertini, G., Evolutionary explanations of the "actuarial senescence in the wild" and of the "state of senility", *Scientific World Journal*, 2006, vol. 31, no. 6, p. 1086.
25. Skulachev, V., Aging is a Specific Biological Function Rather than the Result of a Disorder in Complex Living Systems: Biochemical Evidence in Support of Weismann's Hypothesis, *Biochemistry (Mosc.)*, 1997, vol. 62, no. 11, p. 1191.
26. Goldsmith, T., Aging as an evolved characteristic: Weismann's theory reconsidered. *Med. Hypo.,* 2004, *vol.* 62, no. 2, p. 304.
27. Breakefield, P., Evo-devo and constraints on selection, *Trends Ecol. Evol.*, 2006, vol. 21, no. 7, p. 362.
28. Griffiths, A., *An Introduction to Genetic Analysis (5th ed.)*,. New York: W.H. Freeman, 1993, Chap. 5.
29. Wynne-Edwards, V., *Evolution Through Group Selection*, Oxford: Blackwell. 1986.
30. Price, G., Selection and Covarience, *Nature*, 1970, vol. 227, p. 520.
31. Williams, G., *Adaptation and Natural Selection: A Critique of Some Current Evolutionary Thought*, Princeton: Princeton Univ. Press, 1966.
32. Alkan, C., Eichler, E., Bailey, J., Sahinalp, S., Tuzon, E., The role of unequal crossover in alpha-satellite DNA evolution: a computational analysis, *J. Comput. Biol*., 2004, vol. 11, no. 5, p. 933.
33. Jurka, J., Kapitinov, V., Kohany, O., Jurka, M., Repetitive sequences in complex genomes: structure and evolution, *Annu. Rev. Genomics Hum. Genet.*, 2007, vol. 8, p. 241.
34. Mattick, J., Introns: evolution and function, *Current Opinion in Genetics and Development*, 1994, vol. 4, p. 823.
35. Newth, D., The role of translocation and selection in the emergence of genetic clusters and modules, *Artif. Life*, 2007, vol. 13, no. 3, p. 249.
36. Dawkins, R., *The Selfish Gene*, Oxford: Oxford University Press, 1990.
37. Promislow, D., Pletcher S., Advice to an Aging Scientist, *Mech. Aging Dev.,* 2002, vol. 123, p. 841.
38. Poynter, J. et al, Statins and the Risk of Colorectal Cancer, *New England Journal of Medicine*, 2005, vol. 352, p. 2184.
39. Skulachev, V., Anisimov, N., Antonenko, Y., Bakeeva, L., Chernyak, B., Erichev, B., et al, An attempt to prevent senescence: A mitochondrial approach. *Biochim. Biophys. Acta,* 2009, doi:10.1016/j.bbabio.2008.12.008.