

In pursuit of the

LONGEVITY DIVIDEND

What should we be doing to prepare for the unprecedented aging of humanity?

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Imagine an intervention, such as a pill, that could significantly reduce your risk of cancer. Imagine an intervention that could reduce your risk of stroke, or dementia, or arthritis. Now, imagine an intervention that does all these things, and at the same time reduces your risk of everything else undesirable about growing older: including heart disease, diabetes, Alzheimer and Parkinson disease, hip fractures, osteoporosis, sensory impairments, and sexual dysfunction. Such a pill may sound like fantasy, but aging interventions already do this in animal models. And many scientists believe that such an intervention is a realistically achievable goal for people. People already place a high value on both quality and length of life, which is why children are immunized against infectious diseases. In the same spirit, we suggest that a concerted effort to slow aging begin immediately – because it will save and extend lives, improve health, and create wealth. ▶



REDRAWN FROM KOLOMAN MOSER'S FROMMIES KALENDAR / ILLUSTRATIONS BY JOELLE BOLT



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The experience of aging is about to change. Humans are approaching old age in unprecedented numbers, and this generation and all that follow have the potential to live longer, healthier lives than any in history. These changing demographics also carry the prospect of overwhelming increases in age-related disease, frailty, disability, and all the associated costs and social burdens. The choices we make now will have a profound influence on the health and the wealth of current and future generations.

GERONTOLOGY COMES OF AGE

Gerontology has grown beyond its historical and traditional image of disease management and palliative care for the old, to the scientific study of aging processes in humans and in other species—the latter is known as biogerontology. In recent decades biogerontologists have gained significant insight into the causes of aging. They've revolutionized our understanding of the biology of life and death. They've dispelled long-held misconceptions about aging and its effects, and offered for the first time a real scientific foundation for the feasibility of extending and improving life.

The idea that age-related illnesses are independently influenced by genes and/or behavioral risk factors has been dispelled by evidence that genetic and dietary interventions can retard nearly all late-life diseases in parallel. Several lines of evidence in models ranging from simple eukaryotes to mammals suggest that our own bodies may well have “switches” that influence how quickly we age. These switches are not set in stone; they are potentially adjustable.

Biogerontologists have progressed far beyond merely describing cellular aging, cell death, free radicals, and telomere shortening, to actually manipulating molecular machinery and cell functions.¹ These recent scientific breakthroughs have nothing in common with the claims of entrepreneurs selling alleged anti-aging interventions they say can slow, stop, or reverse human aging (see “Your money for your life” on pg. 33 for a peek at this industry). No such treatment yet exists.

Nevertheless, the belief that aging is an immutable process, programmed by evolution, is now known to be wrong. In recent decades, our knowledge of how, why, and when aging processes take place has progressed so much that many scientists now believe that this line of research, if sufficiently promoted, could benefit people alive today.^{2,3} Indeed, the science of aging has

AGING RESEARCH FOR THE DOGS



From daschund to dane, dogs are arguably the most phenotypically variable mammalian species. That variability carries over to longevity: The tiny chihuahua can live 12–15 years compared to six or seven for its larger cousin, the Irish wolfhound. Foregoing the translation from “dog years,” adding even six or seven years to the average human life span would be significant.

Dogs face many of the same age-related conditions as humans. Don Ingram at the National Institute on Aging, who leads efforts to study aging in chimpanzees (which can live up to 60 years in captivity), says that dogs are attractive models. “They are particularly useful now for skeletal and connective tissue disorders. They also get everything from loss of hearing, loss of vision, immune dysfunction, cardiomyopathies, kidney disease, and cancer.”

Efforts to link genotype and phenotype for some disorders might be fruitful. Elaine Ostrander of the US National Human Genome Research Institute, who worked on the recent publication of the boxer genome, has recently shown that the extent of linkage disequilibrium in dogs is greater than in humans. This means that fewer single nucleotide polymorphisms are needed for association studies.

Nevertheless, paring down studies to the actual aging process could be difficult. Dogs have been burdened by breeders’ tastes in other traits. “People would say that you can’t really draw valid conclusions,” says Ostrander, “because lifespan in dogs is so perturbed by interventions of man.” —Michael O’Neill

the potential to do what no drug, surgical procedure, or behavior modification can do—extend our years of youthful vigor and simultaneously postpone all the costly, disabling, and lethal conditions expressed at later ages.

In addition to the obvious health benefits, enormous economic benefits would accrue from the extension of healthy life. By extending the time in the lifespan when higher levels of physical and mental capacity are expressed, people would remain in the labor force longer, personal income and savings would increase, age-entitlement programs would face less pressure from shifting demographics, and there is reason to believe that national economies would flourish. The science of aging has the potential to produce what we refer to as a “Longevity Dividend” in the form of social, economic, and health bonuses both for individuals and entire populations—a dividend that would begin with generations currently alive and continue for all that follow.

We contend that conditions are ripe today for the aggressive pursuit of the Longevity Dividend by seeking the technical means to intervene in the biological processes of aging in our species, and by ensuring that the resulting interventions become widely available.

WHY ACT NOW?

Consider what is likely to happen if we don't. Take, for instance, the impact of just one age-related disorder, Alzheimer disease (AD). For no other reason than the inevitable shifting demographics, the number of Americans stricken with AD will rise from 4 million today to as many as 16 million by midcentury.⁴ This means that more people in the United States will have AD by 2050 than the entire current population of the Netherlands. Globally, AD prevalence is expected to rise to 45 million by 2050, with three of every four patients with AD living in a developing nation.⁵ The US economic toll is currently \$80–\$100 billion, but by 2050 more than \$1 trillion will be spent annually on AD and related dementias. The impact of this single disease will be catastrophic, and this is just one example.

Cardiovascular disease, diabetes, cancer, and other age-related problems account for billions of dollars siphoned away for “sick care.” Imagine the problems in many developing nations where there is little or no formal training in geriatric health care. For instance, in China and India the elderly will outnumber the total current US population by midcentury. The demographic wave is a global phenomenon that appears to be leading health care financing into an abyss.

Nations may be tempted to continue attacking diseases and disabilities of old age separately, as if they were unrelated to one another. This is the way most medicine is practiced and medical research is conducted today. The National Institutes of Health in the United States are organized under the premise that specific diseases and disorders be attacked individually. More than half of the National Institute on Aging budget in the United States is devoted to AD. But the underlying biological changes that predispose everyone to fatal and disabling diseases and disorders are caused by the processes of

aging.⁶ It therefore stands to reason that an intervention that delays aging should become one of our highest priorities.

HEALTH AND LONGEVITY CREATE WEALTH

According to studies undertaken at the International Longevity Center and at universities around the world, the extension of healthy life creates wealth for individuals and the nations in which they live.⁷ Healthy older individuals accumulate more savings and investments than those beset by illness. They tend to remain productively engaged in society. They spark economic booms in so-called mature markets, including financial services, travel, hospitality, and intergenerational transfers to younger generations. Improved health status also leads to less absenteeism from school and work and is associated with better education and higher income.

A successful intervention that delays aging would do more than yield a one-time benefit, after which, one might argue, the same exorbitant health-care expenses would ensue. Life extension already achieved among animals suggests that delayed aging may produce a genuine compression of mortality and morbidity.⁸ Calorie-restricted animals not only experience a reduction in their risk of death, but also experience declines in the risk of a wide variety of age-sensitive, nonlethal conditions such as cataracts, kidney diseases, arthritis, cognitive decline, collagen cross linking, immune senescence, and many others.⁹ If this could be achieved in people, the benefits to health and vitality would begin immediately and continue throughout the remainder of the lifespan. Thus the costly period of frailty and disability would be experienced during a shorter duration of time before death. This compression of mortality and morbidity would create financial gains not only because aging populations will have more years to contribute, but also because there will be more years during which age-entitlement and healthcare programs are not used.

A MATURING SCIENCE

Centuries ago, the French naturalist Buffon observed that aging exhibits common characteristics across species. Recent work in genetics and in the comparative biology of aging confirms these impressions and provides important clues about how to develop effective interventions that delay aging. It is now clear that some of the hormones and cellular pathways that influence the rate of aging in lower organisms also contribute to many of the manifestations of aging that we see in humans, such as cancers, cataracts, heart disease, arthritis, and cognitive decline. These manifestations occur in much the same way in other animals and for the same biological reasons.¹⁰ (For more on one example see “Aging research for the dogs”). Several experiments have demonstrated that by manipulating certain genes, altering reproduction, reducing caloric intake, and changing the signaling pathways of specific physiological mechanisms, the duration of life of both invertebrates and mammals can be extended.^{11,12} Some of the genes involved, such as *PIT1*, *PROPI*, ►

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and *GHR/BP*, modulate the levels of hormones that affect growth and maturation; others, such as *p66SHC*, help individual cells avoid injury and death. No one is suggesting that alteration of these genes in humans would be practical, useful, or ethical, but it does seem likely that further investigation may yield important clues about intervening pharmacologically.

Genes that slow growth in early life – such as those that produce differences between large, middle-size, and miniature dogs – typically postpone all the signs and symptoms of aging in parallel. A similar set of hormonal signals, related in sequence and action to human insulin, insulin-like growth factor (IGF-I), or both, are involved in aging, life span, and protection against injury in worms, flies, and mice, and extend life span in all of those animals. These hormones help individual cells buffer the toxic effects of free radicals, radiation damage, environmental toxins, and protein aggregates that contribute to various late-life malfunctions.

An extension of disease-free lifespan of approximately 40% has already been achieved repeatedly in experiments with mice and rats.^{13–16} These examples provide powerful new systems to study how aging processes influence disease expression and will yield clues about where to look for interventions that can slow aging in people in a safe and effective way. Since many of the biological pathways of aging are conserved also in simple invertebrate species such as fruit flies, it should be possible to experimentally evaluate candidate intervention strategies rapidly.

Some people, including a proportion of centenarians, live most of their lives free from frailty and disability. Genetics plays a critical role in their healthy survival. Identifying variation in these subgroups of humans holds great potential for improving public health. For example, microsomal transfer protein (MTP) on chromosome 4 has been identified as a longevity modifier in a sample of centenarians¹⁷; there is strong evidence linking a common variant of *KLOTHO*, the *KL-VS* allele, to human longevity¹⁸; and it has been demonstrated that lipoprotein particle sizes promote

a healthy aging phenotype through codon 405 valine variation in the cholesterol ester transfer protein (*CETP*) gene.¹⁹

Given the speed at which the study of aging has advanced and the ability to obtain research results quickly from the study of short-lived species, scientists have reason to be confident that a Longevity Dividend is a plausible outcome of aging research.

THE TARGET

What we have in mind is not the unrealistic pursuit of dramatic increases in life expectancy, let alone the kind of biological immortality best left to science fiction novels.²⁰ Rather, we envision a goal that is realistically achievable: a modest deceleration in the rate of aging sufficient to delay all aging-related diseases and disorders by about seven years.²¹ This target was chosen because the risk of death and most other negative attributes of aging tends to rise exponentially throughout the adult lifespan with a doubling time of approximately seven years.²² Such a delay would yield health and longevity benefits greater than what would be achieved with the elimination of cancer or heart disease.²³ And we believe it can be achieved for generations now alive.

If we succeed in slowing aging by seven years, the age-specific risk of death, frailty, and disability will be reduced by approximately half at every age. People who reach the age of 50 in the future would have the health profile and disease risk of today's 43-year-old; those aged 60 would resemble current 53-year-olds, and so on. Equally important, once achieved, this seven-year delay would yield equal health and longevity benefits for all subsequent generations, much the same way children born in most nations today benefit from the discovery and development of immunizations.

A growing chorus of scientists agrees that this objective is scientifically and technologically feasible.²⁴ How quickly we see success depends in part on the priority and support devoted to the effort. Certainly such a great goal – to win back, on average, seven years of

AN AGING DRUG IN OUR MIDST?

Recent results indicate that an approved diabetes drug, metformin, may battle aging. Approved in 1995, metformin was marketed as Glucophage. Now it and generic versions are the most widely used oral medication for type II diabetes. “There is a huge natural experiment with people on metformin,” says Don Ingram, of the US National Institute on Aging. And, some data are beginning to look promising.

Animal studies with metformin show increased age and reduced tumor load, and although no clinical studies are looking directly at effects on aging, a variety of ongoing clinical trials in humans are investigating type II diabetes, metabolic syndrome, liver disease, and polycystic ovary syndrome. The UK Prospective Diabetes Study 34 showed that in patients with type II diabetes, metformin treatment

resulted in reductions in end-organ damage, myocardial infarction, and all-cause mortality. Stephen Spindler, professor of biochemistry at the University of California, San Diego, has shown that metformin out-performs short-term calorie restriction in inducing the gene-expression changes associated with long-term calorie restriction.

Not everyone is persuaded by the metformin results, however. Side effects, such as a small risk of lactic acidosis that can be fatal in certain patients, are not likely worth the risk of lifelong treatment for aging. Nir Barzilai at the Albert Einstein College of Medicine in New York says, “Metformin is a terrific drug used in a large prospective study to prevent diabetes, but this does not mean it has any effects on aging beyond its specific role in preventing one of the age-related diseases.” —Michael O’Neill

YOUR MONEY FOR YOUR LIFE

How one company carved itself a piece of the anti-aging industry pie

When it comes to aging, consumers don't slow down for science. The pleas of thousands, starving for a pill that will slow, stop, or reverse the inevitable, clog the Internet. With an insatiable desire for something that doesn't yet exist, people are using themselves as test subjects, and shelling out millions – perhaps billions – of dollars on products unsupported by science. In some cases, they may not even know what they're taking.

Case in point: a product called Protandim. When a deal between two companies to sell the product fell through, one appeared to keep the name but changed the formulation, leaving a glut of information in chat rooms, blogs, and news articles that describes Protandim, but doesn't always specify which one.

In November, Lifeline Therapeutics announced that in just three months it had sold close to \$3 million worth of the product, which retails for about \$50 for a month's supply. This represents a tiny slice of the dietary supplement industry, valued at \$20 billion in the United States alone by the Council for Responsible Nutrition, an industry trade association.

Joe McCord, a professor at the University of Colorado's Denver Health Sciences Center, takes the product, which claims to "fight cellular aging" by inducing endogenous antioxidants. In January, McCord and colleagues published the results of a study in *Free Radical Biology & Medicine*, during which he and 28 healthy volunteers took Protandim – a mixture of ashwagandha and milk thistle, bacopa, green tea, and tumeric extracts – for up to 120 days. Participants' levels of the antioxidant enzymes superoxide dismutase and catalase increased by 30% and 54%, respectively, while thiobarbituric acid-reacting substances (a measure of oxidation) fell by an average of 40%.

Nevertheless, some Protandim buyers may not know what they're taking. Years ago, Lifeline entered negotiations to market a product called CMX-1152 developed by Ceremedix, a Northeastern University-affiliated biotech in Massachusetts. CMX-1152's potential inspired news articles containing wildly optimistic predictions from Ceremedix sources.

According to a representative of Ceremedix who preferred to remain anonymous, Lifeline began calling CMX-1152 "Protandim," although it is unclear who suggested the name. After the deal between the companies fell apart (for unknown reasons) Ceremedix dropped CMX-1152, and began concentrating on other therapeutic areas. But, he says, a lingering connection to unsubstantiated anti-aging claims has likely cost the company financial backers. "[Ceremedix] does not associate itself with claims of living to 120 years," he adds. "People who made that claim are no longer with the company."

The Protandim that was introduced in February 2005 is a completely different formulation from 1152. Online searches bring up pages describing both. At one point, Lifeline filed a statement with the US Securities and Exchange Commission, saying that "several erroneous and misleading statements" were made in a Denver network broadcast, and Protandim "is in no way comprised of, or related to, Ceremedix's peptide." Company representatives from Lifeline did not return requests for comment.

Even McCord, now scientific director at Lifeline, says he thinks some consumers may confuse the products. He says he believes in Lifeline's Protandim, but stresses that it does not have a recorded effect on aging. "I wouldn't want to rule out that there might be additional years, but this is not a miracle pill."

The product is a long way from legitimacy when it comes to cellular aging, a process Protandim claims to affect "from the inside out." Steven Austad, based at the University of Texas Health Science Center and the Barshop Institute for Longevity and Aging Studies in San Antonio, calls McCord's research an "interesting beginning," but even if Protandim helps boost the body's antioxidant activity, there's no evidence that it has an effect on aging. Without placebo control, it's impossible to say whether study participants might have changed their lifestyles because they were being studied. Still, Austad gives the company credit for human testing—a step most companies selling anti-aging products don't even bother to take. —Alison McCook



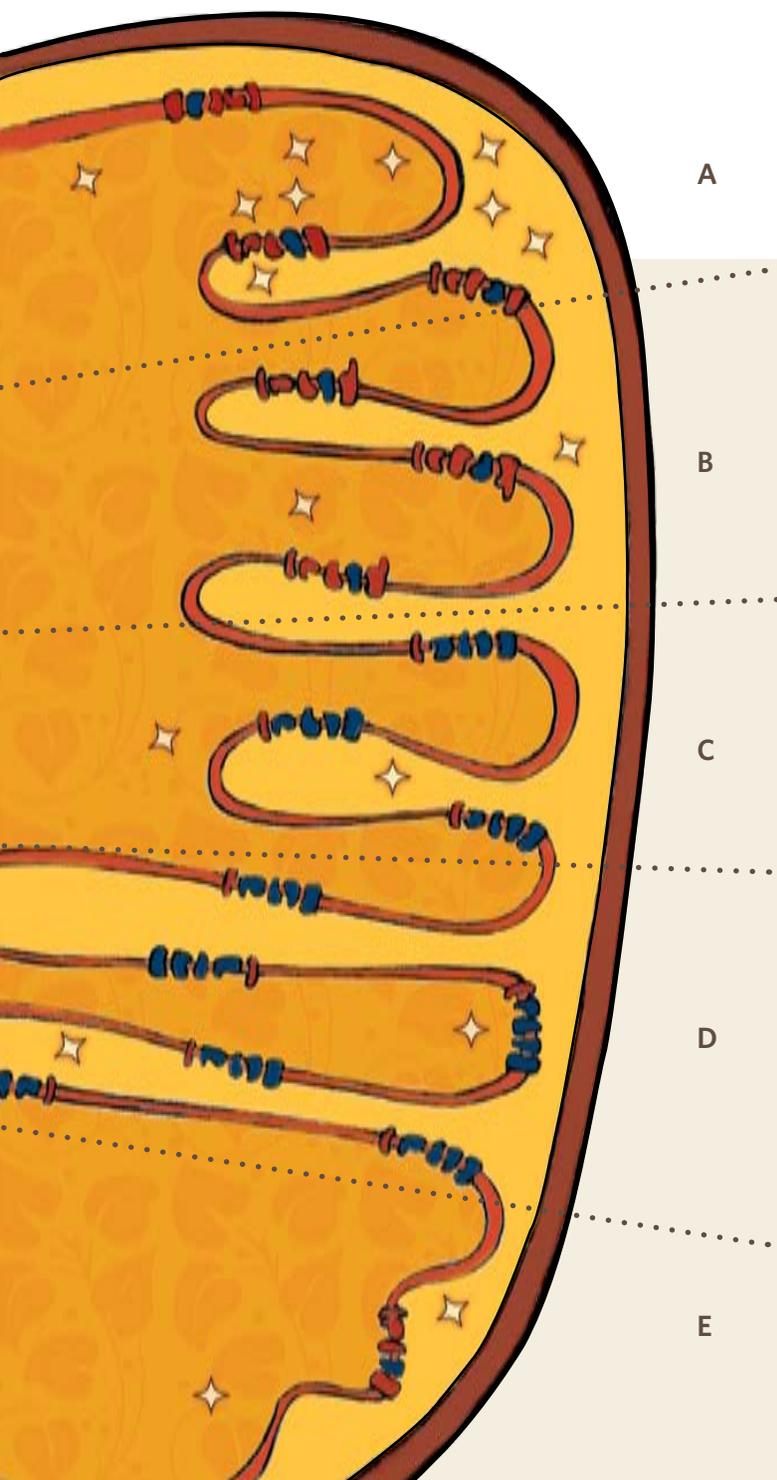
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healthy life – requires and deserves significant resources in time, talent, and treasury. But with the mammoth investment already committed in caring for the sick as they age, and the pursuit of ever-more expensive treatments and surgical procedures for existing fatal and disabling diseases, the pursuit of the Longevity Dividend would be modest by comparison. In fact, because a healthier, longer-lived population will add significant wealth to the economy, an investment in the Longevity Dividend would likely pay for itself.

THE RECOMMENDATION

The NIH is funded at \$28 billion in 2006, but less than 0.1% of that amount goes to understanding the biology of aging and how it predisposes us to a suite of costly diseases and disorders expressed at later ages. We are calling on Congress to invest \$3 billion annually to this effort, or about 1% of the current Medicare budget of \$309 billion, and to provide the organizational and intellectual infrastructure and other related resources to make this work.

Specifically, we recommend that one-third of this budget (\$1 billion) be devoted to the basic biology of aging with a focus on genomics and regenerative medicine as they relate to longevity science. Another third should be devoted to age-related diseases as part of a coordinated trans-NIH effort. One sixth (\$500 million) should be devoted to clinical trials with proportionate representation of older persons (aged 65+) that include head-to-head studies of drugs or interventions including lifestyle



PLUGGING THE MITOCHONDRIAL LEAK

Why does an elephant live twenty times longer than a mouse? Partly just because it's bigger, but even after correcting for body mass, mammals with fast metabolic rates (high oxygen consumption), such as mice, age and die swiftly, whereas animals with slow metabolic rates, such as elephants, live longer and age more slowly.

While an inverse correlation between resting metabolic rate and longevity in animals generally holds true, there are some exceptions to the rule. Birds, bats, and humans live several times longer than their metabolic rates would suggest. The reason lies in the rate at which reactive oxygen species (ROS) leak out of the mitochondrial respiratory chain, the succession of membrane-bound proteins that passes electrons from NADH to oxygen. According to Gustavo Barja at the Complutense University in Madrid, pigeons leak barely a tenth the ROS of rats, and live nearly ten times longer, yet their resting metabolic rates are similar. "ROS leakage is so low in pigeons that they can afford to have much lower antioxidant levels than rats, and still live longer," says Barja. "The question is, why are pigeon mitochondria so leak-proof?"

Mitochondria have different strategies for minimizing oxidative stress. (A) In the respiratory chain, reduced complexes (red) are generally more reactive than oxidized complexes (blue) and therefore generate more free radicals (✧). (B) Polymorphisms in mtDNA can lead to low free-radical leakage despite strongly reduced complexes. (C) Uncoupling of the respiratory chain leads to fast electron flow and low leakage due to relatively oxidized complexes. (D) Larger surface area for mitochondrial membranes, with the same number of electrons entering overall, produces mainly oxidized complexes. (E) Smaller surface area generally means more reduced complexes, but because there are fewer complexes in total available to react with oxygen, overall free-radical leakage is low.

comparisons, cost-effectiveness studies, and the development of a national system for postmarketing surveillance.

The remaining \$500 million should go to a national preventive medicine research initiative that would include studies of safety and health in the home and workplace and address issues of physical inactivity and obesity as well as genetic and other early-life pathological influences. This last category would include studies of the social and economic means to effect positive changes in health behaviors in the face of current health crises – obesity and diabetes – that can lower life expectancy. Elements of the budget could be phased in over time, and it would be appropriate to use funds within each category for research training and the development of appropriate infrastructure. We also strongly encourage the development of an international consortium devoted to this task, as all nations would benefit from securing the Longevity Dividend.

With this effort, we believe it will be possible to intervene in aging among the baby boom cohorts, and all generations after

them would enjoy the health and economic benefits of delayed aging. Such a monetary commitment would be small when compared to that spent each year on Medicare alone, but it would pay dividends an order of magnitude greater than the investment. And it would do so for current and future generations.

In our view, the scientific evidence strongly supports the idea that the time has arrived to invest in the future of humanity by encouraging the commensurate political will, public support, and resources required to slow aging, and to do so now so that most people currently alive might benefit from the investment. A successful effort to extend healthy life by slowing aging may very well be one of the most important gifts that our generation can give. ►

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The answer could have profound implications. According to Alan Wright at Edinburgh University, the cellular threshold for apoptosis is calibrated by the rate of ROS leakage: “Species that leak ROS slowly have a lower rate of apoptotic cell loss in degenerative conditions, including those that apparently have nothing to do with oxidative or nitrosative stress.” Analyzing single mutations in 10 different degenerative conditions across five species, Wright and collaborators found that age of onset and severity of disease correlates closely with the rate of ROS leakage. “If we could slow ROS leakage, there’s a prospect we could delay the onset of a wide spectrum of degenerative diseases,” he says.

In June 2005, Douglas Wallace’s group at the University of California, Irvine, showed that the approach could work in mammals.¹ They generated transgenic mice that overexpress the antioxidant enzyme catalase in mitochondria (to break down hydrogen peroxide). Not only are average and maximal lifespans increased by about five months, but also degenerative conditions such as cardiac pathology and cataract formation are delayed.

Other work suggests that antioxidants targeted to the mitochondria, such as mitoQ, concentrate 1000-fold in the mitochondrial matrix, where they inhibit apoptosis. But antioxidants have the potential to interfere with ROS signaling, which plays a major role in the physiology of the cell. Birds solve the problem by cutting leakage from complex I, not by raising intramitochondrial antioxidant levels.

“The critical factor determining ROS leakage is not antioxidant status but the redox state of complex I, which is the major source of ROS,” says Martin Brand at the MRC Dunn Unit in Cambridge, UK. “Redox state is dependent on numerous factors like substrate supply, ATP use, uncoupling, amount of complexes, and allosteric influences, such as Ca²⁺ activation or NO inhibition of cytochrome oxidase. So predicting the outcome depends on knowing the state of all these variables.”

Such variables explain conundrums such as the exercise paradox—why physically active people don’t die early. During exercise, the flow of electrons down the respiratory chain quickens, as does oxygen consumption. The overall effect is greater oxidation of complex I, and lower leakage.

A fall in the reduction state of complex I explains other apparent anomalies, such as the long lifespan of mice with high resting metabolic rates. Brand, working with John Speakman and colleagues at the University of Aberdeen, showed that these mice had more uncoupling proteins in their mitochondria, enabling electron flow to be uncoupled from ATP production, dissipating energy as heat. Uncoupling meant they consumed more oxygen at rest, yet they lived longer than other mice.²

Uncoupling may be important in people, too. Mitochondrial DNA haplotypes vary geographically, with some types predominant in tropical regions, others in colder climes. The pattern might reflect differing degrees of uncoupling, restricting internal heat generation in hot climates, and vice versa. A consequence might be a higher rate of ROS leak in tropical peoples, and a correspondingly higher susceptibility to degenerative conditions such as heart disease.

Intervention might be possible. Vladimir Skulachev at Moscow State University points to recent work showing that the reduction state of complex I depends strongly on the NAD⁺ and NADH levels. “Perhaps we could lower ROS leakage, and correspondingly apoptosis, by maintaining a tighter control over the NADH pool.” —**Nick Lane**

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THE TROUBLE WITH MARKERS

Evaluating a potential anti-aging therapeutic poses a unique challenge. When the endpoint is natural death, assessing efficacy in a realistic timeframe requires a surrogate, but biomarkers for aging have been elusive.

"There are no biomarkers that are very good at predicting of subsequent longevity, and that is the gold standard of what a biomarker is," says Tom Johnson of the University of Colorado at Boulder. While clinical research still rests largely on physiological status such as diastolic function, some argue that genomics or proteomics may provide more precise molecular markers.

Researchers at the Washington University School of Medicine recently showed that diastolic function in members of the Calorie Restriction Society resembled that normally seen in people 15 years younger.¹ Members of this society voluntarily adhere to a nutritionally balanced, low-calorie diet (1,300 to 2,000 per day). Diastolic function generally declines as people age, says Luigi Fontana, who headed the study. Whether such physiologic indicators translate into extended life is unclear.

Don Ingram, a senior investigator at the US National Institute on Aging, says that identification of molecular biomarkers for aging is crucial both for understanding the aging process in humans and for evaluating potentially effective interventions.

Stephen Spindler, at the University of California, San Diego, uses microarray-based gene-expression analyses in experiments on long-term calorie restriction (CR) in *Caenorhabditis elegans*.² A drug candidate that recapitulates the gene-expression changes seen in long-term CR might well be working. Spindler has shown that both short-term CR and the diabetes drug metformin do this to some degree. (see "An aging drug in our midst?" pg. 32)

Richard Miller, professor of pathology at the University of Michigan, sets the criteria higher. "You could call something a biomarker of aging if it were documented that those people who show rapid change in the marker also show rapid change in most other traits that change with age, and those who show slow change in the marker also change slowly in a wide range of other age-sensitive traits. As far as I know, there aren't any studies in mice or in people that meet these tough criteria."

Worms at least provide consistent results. Monica Driscoll at Rutgers University has shown that so-called age pigments correlate with lifespan in *C. elegans*.³ Clonal worms of the same chronological age differed markedly in their apparent health. "Some looked very healthy; others looked decrepit," Driscoll says. The decrepit worms had higher cellular amounts of age pigments, fluorescent molecules such as lipofuscin, and glycation end products that accumulate in lysosomes and generally increase with age in various metazoans, including humans.

Nevertheless, finding something definitive will remain problematic. Ingram says that the ultimate need for human trials of aging interventions "demands that the field ... become more sophisticated, using a variety of measures that can be shown to be reliable and valid." —Michael O'Neill

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