

LE Magazine June 2004

AS WE SEE IT

Are You Afraid of Terrorists?

For the past 32 months, the news media have carried daily accounts of the threat of terrorism. It is as though humans have already achieved biological immortality and the only risk of death we face is at the hands of terrorists.

Regrettably, this is not the case. Every day, 6,500 people die in the US, mostly from age-related diseases. The table on this page lists the nation's 15 leading causes of death in 2001.¹

The federal government has been on a spending rampage as a result of the events of September 11, 2001, that claimed nearly 3,000 American lives. In 2001, however, a total of 2,416,425 Americans died. Terrorists were responsible for approximately 0.001% of these deaths.²

We know that defense against violence will always be a human need. For the first time in history, however, we have an opportunity to dramatically extend the healthy life span of those living today. Unfortunately, the government spends relatively little on meaningful medical research, while many billions of tax dollars are being used to guard against terrorism.

What Do You Fear Most?

The American Cancer Society predicts that 563,700 cancer deaths will occur in 2004.³ This means that approximately 1,544 Americans will die every day from one of the world's most frightening diseases.

People do not just suddenly die of cancer. They often suffer through multi-year therapies that have high rates of failure. Once the diagnosis of cancer is made, a person's life is turned upside down. Chemotherapy sessions dominate the cancer victim's schedule, along with agonizing side effects and the daily fear that the cancer will not be completely eradicated.

Cancer phobia has become so prevalent that hundreds of millions of dollars are spent every year on diagnostic procedures such as colonoscopies to rule out colon and rectal cancer, head MRIs to rule out brain tumors, and whole-body scans to rule out visceral malignancies.^{4,5} These diagnostic tests are expensive, inconvenient, and often dangerous. Yet the American Cancer Society urges that more Americans undergo these diagnostic procedures in the hopes of reducing cancer mortality rates.

We at Life Extension are all in favor of diagnostics, but would like to see a more concerted effort by the government to encourage the discovery of cures for cancer, other killer diseases, and aging, instead of relying mainly on early diagnosis to improve survival rates.

In addition to spending more money to extend the healthy human life span, the government needs to loosen the reins of control that currently prevent private companies from spending more money on research. If the government continues to escalate spending to protect against terrorism while restricting privately funded scientists, the money to discover how to cure age-related diseases and aging will not be adequate.

In March 2004, we conducted a survey on a popular website visited by 500,000 people every month. When asked whether more fearful of dying from cancer or a terrorist attack, 66% of



William Faloon

15 Leading Causes of Death in the US, 2001

Rank	Cause of Death	Number	Percent of total deaths
1.	Heart diseases	700,142	29.0
2.	Cancer	553,768	22.9
3.	Cerebrovascular diseases (stroke, etc.)	163,538	6.8
4.	Chronic lower respiratory diseases (COPD, emphysema, etc.)	123,013	5.1
5.	Accidents (unintentional injuries)	101,537	4.2
6.	Diabetes mellitus	71,372	3.0
7.	Influenza and pneumonia	62,034	2.6
8.	Alzheimer's disease	53,852	2.2
9.	Nephritis, nephrotic syndrome, and nephrosis	39,480	1.6
10.	Septicemia (blood infection)	32,238	1.3

the respondents were more fearful of cancer, while 34% were more concerned about a terrorist attack.⁶ On the Life Extension website, 92% were more afraid of cancer, while only 8% were more fearful of terrorists.⁷

These survey results indicate Americans would feel much more secure knowing that cancer is more readily curable as opposed to thinking they are completely protected against terrorist attacks.

Government Interferes with Progress Against Cancer

That the federal government does not allocate more resources to finding cures for cancer is disappointing enough. But what is absolutely barbaric is how the government—and the FDA in particular—denies cancer patients access to advanced therapies.

Back in 2000, I wrote an editorial about a class of cancer drugs known as “epidermal growth factor receptor blockers.”⁸ Although the evidence then available indicated these drugs could save some cancer patients’ lives, the FDA was delaying their approval. We urged that these drugs immediately be made available to cancer victims who were willing to try experimental therapies.

As it turned out, the results from large-scale human studies were not as impressive as the initial research. The FDA, however, eventually approved both drugs—Iressa® and Erbitux®—as being effective against certain types of cancer. The problem is that over the past four years, many cancer patients who could have benefited from these drugs died because of the FDA’s delay in approving them. Erbitux®, for example, was not approved until February 12, 2004.⁹



In 1998, in another editorial that described the potential benefits of anti-angiogenesis drugs, I stated:

“The scientific evidence indicates that these (anti-angiogenesis) drugs could have been tried on cancer patients already, but political reality dictates that these potential lifesaving therapies linger in an Orwellian drug-approval quagmire. Today’s cancer patients sit in the FDA’s waiting room hoping they will be granted permission to live before they succumb to their disease.”¹⁰

In criticizing the FDA’s delay in approving new drugs, I wrote: “If a cure for cancer were found today, almost every cancer patient alive would die before the FDA approved the breakthrough

drug.”

For too many cancer victims, my prediction sadly may have turned out to be true. On February 27, 2004, the FDA approved the first anti-angiogenesis drug, Avastatin™, which works by choking off the blood supply to the tumor.¹¹ Avastatin™ is not a cure, but patients live 30% longer compared to standard therapy, and some terminal patients have lived for years.

FDA Delays Prostate Cancer Drug

Prostate cancer kills more than 30,000 American men every year.¹² Back in 2002, the results of a Phase III study showed some remarkable results. Compared to placebo, men with metastasized prostate cancer who received an immune-boosting vaccine called Provenge® were eight times more likely to go six months without disease progression than those who did not receive the vaccine. The cancer vaccine, however, was effective only in men with a Gleason score of 7 or less. (Higher Gleason scores are indicative of a more aggressive type of prostate cancer.¹³)

The FDA refused to accept the results of this study because the agency does not allow retrospective analysis of a subgroup that may have benefited from an experimental drug. To gain FDA approval, the company was forced to begin a brand new study on men with Gleason scores of 7 or less.

But the company continued to follow patients in the original study, and the results, announced in January 2004, are impressive. Of the 75 patients who entered the trial with a Gleason score of 7 or less, those receiving the Provenge® cancer vaccine were 3.7 times more likely to be alive after 30 months. This translates to 53% of the Provenge® group being alive, compared to only 14% of the placebo group. The Provenge® group also remained in pain-free remission an average of two times longer than the placebo group.¹⁴ Regrettably, this lifesaving cancer therapy may not be approved until well into 2005.



On January 26, 2004, a Wall Street Journal editorial on this deplorable delay stated:

11.	Intentional self-harm (suicide)	30,618	1.3
12.	Chronic liver disease and cirrhosis	27,035	1.1
13.	Hypertension and hypertensive renal disease	19,250	0.8
14.	Assault (homicide)	17,386	0.7
15.	Parkinson’s disease	16,544	0.7

Source: US Mortality Public Use Data Tape, 2001, National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

“We know that it works, and we know why it works. In any rational regulatory environment, that would be reason to speed Provenge® to market. But this is the FDA we are talking about. The agency that sat on Iressa®, another targeted cancer therapy, for months after an advisory panel recommended approval.”¹⁵

How the FDA Obstructs Medical Progress

Pharmaceutical companies are investing billions of dollars to develop drugs to interfere with cancer cell growth. Unfortunately, most of these drugs have failed to extend survival in late-stage cancer patients. In some of the clinical studies, tumor shrinkage is observed, but the patients still die. Experts remain convinced, however, that these drugs will eventually play a significant role in the treatment of cancer.

One reason these drugs are not working is that they usually suppress only one of the growth factors that cancer cells use to escape regulatory control. Scientists know of more than 20 growth factors used by tumors. Late-stage breast cancer cells, for example, may express as many as six different growth factors that induce angiogenesis. Cancer cells emit these growth factors to draw new blood vessels into tumors and/or overexpress receptors on their cell membranes that enable cancer cells to hyper-proliferate in response to epidermal growth factor (EGF).

Human studies have tested angiogenesis inhibitors or EGF receptor blockers on late-stage patients whose cancer cells have mutated to become highly resistant. Some physicians believe that if these drugs were tested earlier in the disease process, they would work better. One problem is that the FDA usually restricts the testing of new cancer drugs to only those patients who have failed all other proven therapies. Regrettably, we know that cancer cells mutate each time they are exposed to a new therapy. By testing new cancer drugs only on patients who have failed previous therapy, a tremendous burden of efficacy is being placed on these new compounds; that is, these drugs are expected to kill cancer cells in their most aggressive stages.

Some experts note that successful treatment using anti-angiogenesis and growth factor blockers may depend on the use of a multi-drug cocktail, one that would block all known survival factors used by cancer cells. That would parallel the success in treating AIDS, in which several antiviral drugs that work by different mechanisms are combined into cocktails that have turned the condition into a manageable disease for some people. Unfortunately, the FDA restricts most cancer trials to only one experimental drug at a time, thus prohibiting the multi-drug combination approach that would increase the probability of achieving a complete response or cure.

Based on current knowledge, it would appear logical to simultaneously test a wide range of angiogenesis inhibitors and growth factor blockers on early-stage cancer patients. Such testing might be considered at the time that other cytotoxic therapies are administered or shortly thereafter.

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Making Research a Political Issue

This year promises a lot of political debate about how many tax dollars should be committed to fighting terrorism. Yet the issue of cancer research is unlikely to be raised. For fiscal year 2004, the federal government has authorized a record defense budget of \$401.3 billion. At least one independent study, however, estimates the true cost of defense and anti-terror expenditures to be an astonishing \$754 billion in 2004—or 88% more than the much-publicized \$401.3 billion defense budget.¹⁶ This includes the Department of Homeland Security budget, security-related portions of other federal departmental budgets, and interest attributable to past debt-financed defense outlays. By contrast, the federal government has allocated a paltry \$4.8 billion for cancer research, even less for research on other killer diseases, and only a miniscule \$2.2 billion for anti-aging research.¹⁷



Since aging is the underlying cause of age-related diseases—including most cancers—the lack of funding for this type of research is truly inexcusable.

As our polls clearly indicate, the vast majority of Americans fear cancer more than terrorism. Since government spending eats up a huge percentage of the gross national product, it would appear prudent for citizens participating in the democratic process to let both incumbents and challengers know that medical research is a critical public issue. It would be nice to know at least which politicians favor spending more money on extending the healthy human life span. By making this a political issue, there is a chance that politicians may realize that taxpayers want tangible benefits from government that are in the best interests of the people.

We suggest that Life Extension members write candidates of all parties and demand to know their positions on issues such as funding more life extension research, allowing scientists in the private sector more freedom to explore new research vistas, and speeding the pathway from the research lab to the clinic. These letters should also demand FDA reform that would provide seriously ill Americans with the freedom to try experimental drugs without bureaucratic interference. You need not say you are against fighting terrorism, but rather that you are far more terrorized by the prospect of aging and disease than by political or religious extremists.

Fortune Magazine Reports: “We Are Losing the War on Cancer”

According to a groundbreaking special investigation published in the March 22, 2004 issue of Fortune magazine, America is losing the war on cancer and it is time to overhaul the battle plan.

Fortune reports that the percentage of Americans dying from cancer is about the same as it was in 1970, and reveals systemic problems that are making cancer so difficult to defeat.

The article begins by showing how researchers have amassed an enormous amount of knowledge essential to the war on cancer. The problem is that a dysfunctional cancer culture has made the search for knowledge an end unto itself rather than a means to an end. The result is a research and grant culture focused on finding the tiniest improvements to treatment rather than genuine breakthroughs, i.e., cures.

The most revealing example of this system-wide failure is that cancer researchers focus most of their effort on shrinking tumors in terminally ill patients. The bulk of research money is spent on this goal and not on understanding and arresting the process of metastasis, which kills 90% of patients. According to a Fortune examination of National Cancer Institute (NCI) grants going back to 1972, less than 0.5% of study proposals focused on metastasis. Of nearly 8,900 NCI grant proposals awarded last year, 92% did not even mention metastasis.

Fortune criticized the failure of the cancer establishment to recognize that human tumors have quickly changing DNA characteristics that enable them to mutate and develop new growth factors in order to escape eradication by most single-agent experimental therapies employed today.

All of these failures come to a head, says *Fortune* magazine, when the FDA obstructs progress by mandating rigid three-phase clinical trials that are often designed to fail. One example of this problem is the FDA's requirement that experimental

drugs be given only to end-stage cancer patients. This often precludes scientists from learning whether promising drugs could be effective in early-stage cancers that are more readily curable. The FDA clinical trial process remains the only way to get a new cancer drug approved, yet *Fortune* magazine found that scientists in the cancer community are maddeningly frustrated by it.

The *Fortune* article points out that even as research and treatment have intensified, cancer's annual death toll has risen 73% — over one and one-half times the growth of the US population. By contrast, deaths from heart disease and stroke have slowed dramatically.

Fortune concludes its in-depth report with a proposal for a radical overhaul of how America fights the war on cancer, including a transformation in the way the NCI funds research, a consolidation of the federal war chest into one bureaucracy (from five), and an overhaul of the FDA drug-testing and approval process.

The mainstream media are now recognizing what the Life Extension Foundation exposed years ago about the failure of conventional oncology research. The question is, will anyone in the federal government pay attention?

Our Work to Extend Your Life Span

Life Extension is funding millions of dollars of research each year to help keep you alive and healthy. Included in this research is the most promising approach to the control of aging and age-related diseases, which involves the use of high-density microarrays (gene chips) to measure gene expression in thousands of genes at a time. Conducted by BioMarker Pharmaceuticals, this research is based on the idea that gene expression is a fundamental process that underlies the aging process and the killer diseases related to aging.

BioMarker is using gene chips made by Affymetrix, which measure the expression of thousands of genes at a time in mice and monkeys.

The research objective is developing gene-expression profiles for the tissues of normally aging animals and comparing them with gene profiles in life span-extending models, such as mice fed a calorie-restricted diet.

Radical Effects of Caloric Restriction

Caloric restriction has produced anti-aging effects and extended maximum life span in many species, including mice, rats, and dogs. Caloric restriction has been shown to extend the maximum life span of both mice and rats up to 60%.¹⁸⁻²⁵ BioMarker is collaborating with scientists at the National Institute on Aging, who have been conducting a study of caloric restriction in monkeys to compare its effects on gene expression in monkeys and mice. This kind of comparison is helping BioMarker's scientists uncover genes that affect aging in mammals on different rungs of the evolutionary ladder. Thus far, it appears that many of the anti-aging gene-expression effects found in mice are also found in monkeys, which share about 98% of their genome with humans.

There are two models, Ames and Snell dwarf mice, where a single gene mutation that markedly reduces the output of three pituitary hormones (growth hormone, prolactin, and thyroid-stimulating hormone) has been shown to extend maximum life span up to 70%.^{26,27} That a single gene change can extend maximum life span so radically is strong evidence that only a few genes may be involved in the control of aging. BioMarker is actively searching for these genes.

Researchers Andrezej Bartke of Southern Illinois University, Richard A. Miller of the University of Michigan, and others have shown that Ames dwarf mice, which live 50% longer than normal mice, lived an additional 25% longer when fed a calorie-restricted diet.^{28,29} BioMarker is collaborating with Dr. Bartke to analyze gene expression in long-lived dwarf mice. A gene chip study of the liver in dwarf mice has demonstrated that these animals show some changes in gene expression that are similar to calorie-restricted animals, but also show changes that are different. These findings, which will soon be published in a peer-reviewed scientific journal, support the finding that caloric restriction and dwarfism extend life span in somewhat different ways,³⁰ and that the combination of these two approaches is synergistic.

Quick Screening for Anti-Aging Therapies

In an extraordinary breakthrough, BioMarker scientists found that most of the changes in gene expression caused by long-term caloric restriction (over two years) occur in the liver in only two to four weeks after placing mice on a calorie-restricted diet.³¹ This finding makes it possible for BioMarker to screen potential anti-aging therapies in less than a month—25 times faster than any other technique currently available!

The ability to screen for anti-aging therapies quickly and inexpensively is an enormous breakthrough. Pharmaceutical companies spend billions of dollars trying to discover new drugs for the treatment of cancer, heart disease, stroke, Alzheimer's disease, and other killers. They usually have to conduct lengthy, highly expensive studies on thousands of drugs in order to find even one promising new drug candidate.



Is Metformin an Anti-Aging Therapy?

BioMarker may have already found an anti-aging therapy with its unique technology platform. When BioMarker scientists screened several glucoregulatory agents used to treat diabetes, they found that the undisputed star of the group was metformin, which was twice as effective as the other drugs in reproducing the gene-expression effects of caloric restriction.³²

Further evidence that metformin may be an authentic anti-aging therapy is that a similar drug—phenformin—was found in the late 1970s to extend life span in mice by 23%. This study by Russian researchers also demonstrated a fourfold reduction in cancer incidence in the phenformin-treated mice.³³ In 2002, scientists at the National Institute on Aging presented data showing that metformin extended the life span of mice by 20%.

BioMarker is currently conducting its own study of metformin in 40 mice, seeking to determine the extent to which metformin can extend life span and reduce the incidence of age-related diseases in these animals. This study is being conducted at the University of California at Riverside under the direction of Dr. Stephen Spindler.

New BioMarker Studies of Resveratrol

Resveratrol is an antioxidant and anti-inflammatory agent found in red wine and red grapes that has been shown to protect against heart disease and cancer.³⁴⁻⁴⁷ Gene chip studies have demonstrated that resveratrol produces a striking effect on cancer-related genes. Among other effects, resveratrol activates tumor suppressor genes and genes that detoxify chemicals. It also suppresses genes that enable cancer cells to communicate with each other.

BioMarker is now preparing for a gene chip study to determine if resveratrol can mimic the gene-expression effects of caloric restriction. BioMarker scientists are collaborating with scientists at Harvard Medical School in Boston and Critical Care Research in southern California to find the best forms of resveratrol to test, and will probably also test one or two analogs of resveratrol developed at Harvard.

Is Rejuvenation Possible?

One of BioMarker's most important findings is that life-extending regimens such as caloric restriction can rapidly induce a rejuvenation profile of gene expression. Over 70 years of studies have led to the conclusion that caloric restriction gradually prevents age-related decline and that it must be followed throughout the life span to be effective. BioMarker's gene chip studies have challenged this dogma by showing that in less than a month after a calorie-restricted diet, mice generated a gene-expression profile consistent with rejuvenation.³¹

Another BioMarker study has bolstered the likelihood that anti-aging therapies may be effective in older people, who need to be rejuvenated if they are to have their healthy life spans extended. Recently, a paper by BioMarker scientists was accepted for publication in the Proceedings of the National Academy of Sciences USA. This paper reports the results of an experiment that demonstrated, for the first time, that caloric restriction can be initiated late in life in mice (19 months old) and still be as effective in extending life span and reducing the onset of tumors as caloric restriction begun early in life. This study also closely associates the genomic response, as measured by gene chip assays, with the health and longevity effects of caloric restriction, suggesting that caloric-restriction mimetics such as metformin should be able to reproduce the physiological effects of caloric restriction.

These studies are very good news for those of us who are past our physical prime. They provide striking evidence that it should be possible to develop rejuvenation therapies that are capable of making us younger, healthier, and longer lived than ever before.



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Preventing Cancer with Anti-Aging Therapies

The best experimental model to prevent the onset of cancer and other age-related diseases is caloric restriction. In every study to date in which caloric restriction extended mammal life span, it also showed dramatic anticancer effects.⁴⁸⁻⁵⁵ In its search for anti-aging therapies, BioMarker has found changes in gene expression in calorie-restricted mice that suggest several anticancer mechanisms induced by caloric restriction. One such mechanism involves "chaperone" genes, which regulate the synthesis, maturation, processing, transport, repair, and degradation of proteins. With advancing age, damaged proteins play a major role in the deterioration of the body's critical systems.



Gene expression is the first step in determining the activity and decline of the body's systems. The next step is the actions that genes have on proteins and other substances in the body. BioMarker is planning to conduct proteomic studies with specimens of tissue it preserved when conducting its previous gene chip experiments. Proteomic research will enable BioMarker scientists to trace the effects of changes in gene expression on physiologic changes in aging tissues, which will in turn allow the company to find out more about anti-aging and anti-disease mechanisms.

BioMarker is collaborating with scientists at the National Cancer Institute in the design of studies that will attempt to elucidate mechanisms that could lead to the development of new anti-aging and anticancer therapies.

A New Product to Make You Look Better Today

In this month's issue, we introduce a MicroDermAbrasion product that makes people look younger by exfoliating dead and damaged cells from the skin's surface. This exfoliate was invented by a dermatologist who tested it on hundreds of patients in order to develop the optimal particle size needed to safely expose healthier-appearing skin cells.

While MicroDermAbrasion is primitive technology compared to our genomic research, proceeds from the sale of this appearance-enhancing product help us meet the enormous costs of conducting gene expression chip studies on compounds that may enable us to slow and even reverse the aging process.

Today, almost 6,500 Americans will silently perish from cancer, heart attack, or one of the many other diseases of aging. You will not hear about this on the evening news. Instead, the media will cover stories relating to terrorism threats or isolated violent acts. Life Extension cannot do much about these problems, but we are dedicated to protecting the lives of Americans who die needlessly because of governmental ineptitude and neglect.

Every time you purchase a Life Extension product that provides you with immediate benefits, you also help fund lifesaving scientific research.

For longer life,



William Faloon.

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