KRONOS LONGEVITY RESEARCH INSTITUTE

Research to promote a longer, healthier life for you, your children and your grandchildren.








Vol. 9, Issue 3

Hypothyroidism in Older Adults

IN THIS ISSUE...

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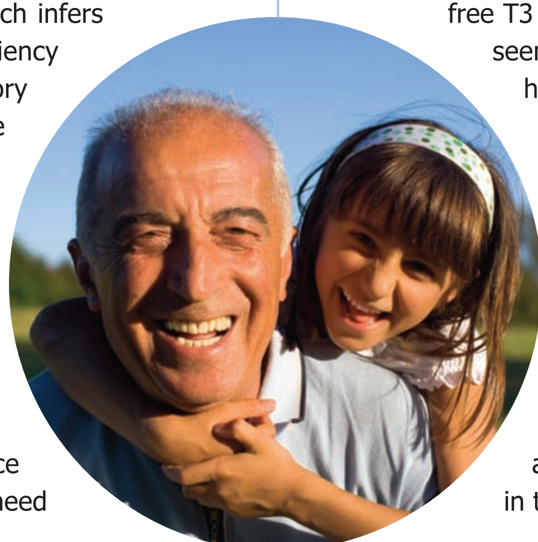
The occurrence of thyroid disease of all types increases with age. Hyperthyroidism, which was discussed in a previous issue of the *Longevity Kronicle*, though relatively common, is actually much less common than hypothyroidism. Hypothyroidism, or deficient thyroid function, has been found in many independent surveys of healthy communities to be present in an astonishing 8 to 16 percent of apparently healthy older individuals. Only a minority of the elderly has clear symptoms, which infers thyroid hormone deficiency with compatible laboratory tests. Most have abnormal characteristic laboratory tests, but no symptoms. This condition is usually called "subclinical" hypothyroidism, and despite many studies, there is still no consensus on the clinical significance of this condition or the need to treat it.



In order to understand more completely what follows, here is an abbreviated primer on thyroid function tests and their interpretation. There are two main thyroid hormones in the blood stream, thyroxine (T4) and triiodothyroinine (T3); both circulate mostly bound to various carrier proteins, and it is thought that only the free (more than 98% in both cases). An unbound fraction is able to get out of the blood stream into the tissues and exert the biologic effects that are characteristic of thyroid hormones. These free fractions are called free T4 (FT4) and free T3 (FT3). In many tissues, it seems that the truly active hormone is FT3 and that some tissues are capable of locally transforming FT4 into FT3. Thus measurement of these hormones in the blood stream, while extremely useful, may not always be the most sensitive or useful way to assess the adequacy of thyroid action in tissues.

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Director's Message

Some Thoughts about Research Funding

Medical research is exciting. All kinds of wonderful new ways of diagnosing, preventing, and treating dreaded diseases are on the horizon or right around the corner. Nearly every day the media features new discoveries or medical studies with results that seem almost like science fiction. Soon we will be able to grow brand new tissues and organs from your own stem cells; turn A, B, or AB blood donations into type O, which can be given to anyone, regardless of blood type; treat your cancer with "personalized" drugs specifically targeted to the genes that have turned the cells in your particular tumor (but perhaps no one else's) malignant; use genetic and imaging technology to diagnose Alzheimer's Disease early, before loss of memory or function, and prevent its progression. All this and more is on the horizon- right around the corner.

As the Bard wrote, "Ay, there's the rub." Medical research is expensive. Most biomedical research (as opposed to drug development) is Federally funded, mainly through the National Institutes of Health (to learn more browse www.nih.gov), with lesser amounts funded through the National Science Foundation, the Department of Agriculture (for studies of nutrition), and, yes, even the Department of Defense. But medical research competes for Federal funds as do hundreds of other priorities. The result is that the Federal budget for medical research is stagnant.. In 2007 the NIH budget was 28.8 billion dollars. Seems like a lot doesn't it? The new NIH appropriation for 2008 is 29.6 billion, an increase of 0.46% (about one-half of one percent). However, the costs of doing medical research increased last year by approximately four to five percent, so that apparent $800 million increase represents a net loss in real dollars. This means the NIH will be able to fund fewer research projects than last year.

Because I have the privilege to serve as a peer-reviewer for grant proposals to the National Institute on Aging, I am seeing this problem from both sides. When our peer-review group, the Aging System and Geriatrics study section, meets, the number of truly excellent and potentially important research proposals is never less than 30% of those reviewed. However, in 2007 there was only funding available for about 12%. Therefore, more than half of the very best research went unfunded in any review cycle. There was a time, a few years ago, when the funding line was nearly 30%. The quality of the research proposed has gotten better, not worse, since then. In this situation many investigators who have long experience doing biomedical research lose their funding, watch their carefully assembled laboratories come apart, and give up trying. Perhaps even worse, promising young scientists, the major source of excitement and innovation, become disenchanted with the low return on the amount of time and effort required to prepare grant requests and find other things to do.

Because KLRI requires funding to carry out our studies, I also experience the frustration of the applicants I referred to in the previous paragraph. Fortunately, we have a generous core of annual funding from the Aurora Foundation that enables us to pursue our current high priority projects. However funding for new initiatives and expanded activities is hard to come by. Last year KLRI applied for $4,987,559 of grant funding. Of this amount, only $38,300 was awarded, and $909,907 is still pending. The largest of these requests, to the NIH for $2,981,133 to support investigation of biochemical markers of heart

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As in many other endocrine systems, the thyroid hormone system is controlled by a negative feedback loop in which the levels of thyroid hormones are sensed by the body and adjustments are made accordingly. The pituitary hormone, thyroid-stimulating hormone (TSH), is responsible for controlling the activity of the thyroid gland and for keeping that activity within certain boundaries. When the thyroid hormone levels are low, TSH increases in order to stimulate the thyroid to compensate for that condition; and when thyroid hormone levels are high, they tend to suppress the production of TSH while minimizing ongoing stimulation of the thyroid although high hormone levels already exist. This system is designed to maintain hormone levels on a relatively even keel, within the limits set by the trigger point of the controller, TSH, which is sensitive to changes in the levels of FT3 and FT4. Of course, there is a range of values considered to be normal for all these hormones, which were established by measurements in large numbers of healthy individuals of different ages. What is normal for one person may be as much as 100% different from what is normal for another, both values being within the normal, or "reference," range. Changes in level downward for any individual may trigger an increase in TSH production even if that level does not drop below the population lower limit of normal. Another way of saying it is that TSH production is extremely sensitive to small changes in thyroid hormone levels and may therefore become abnormal when thyroid hormone levels are still within the reference range for normal.

The great sensitivity of TSH to small changes in thyroid hormone levels makes measurement of TSH the most sensitive tool we have to make the laboratory diagnosis of hypothyroidism. In the usual clinical case in which the patient has typical symptoms of hypothyroidism, the levels of FT3 and FT4 are low, and the level of TSH is high. But sometimes, with mild or subclinical disease (no or very mild symptoms), the TSH is high despite the normality of the thyroid hormone concentrations in the blood. The finding of an elevated TSH despite the normality of thyroid hormones and absence of symptoms has been dubbed "subclinical hypothyroidism." We will discuss this more later.

One other thyroid laboratory test deserves to be mentioned. This is the anti-thyroid peroxidase antibodies. These are antibodies, which are auto-immune; that is, they are produced by the body's immune system against one of its own tissues or tissue components. The reason this test is important is that autoimmune thyroid disease is by far the most common cause of hypothyroidism worldwide. The vast majority of all individuals with primary hypothyroidism (that is, hypothyroidism caused by disease of the thyroid gland) have their condition as a result of autoimmune thyroiditis. The remainder of cases are caused by thyroid surgery or radiation treatment of some sort (either radioactive iodine used to treat hyperthyroidism or external beam radiotherapy used to treat malignant tumors of the head and neck region). Most, but not all, cases of autoimmune thyroid disease can be diagnosed by finding very high blood levels of these anti-thyroid peroxidase antibodies. A very small number of cases of hypothyroidism (around 1.5 to 2 percent) are not caused by thyroid disease per se, but rather by disease of the pituitary gland leading to deficient production of TSH. Such cases are referred to as "secondary hypothyroidism." They will not be discussed at a later time.

Manifestations Of Hypothyroidism

Fatigue*	Diastolic hypertension
Weakness*	Difficulty with speech
Slow heartbeat*	Changes in tendon reflexes
Hoarseness*	Altered mental status*
Thick Skin*	Coarse hair
Pallor	Constipation
Muscle dysfunction (myopathy)	

* Likely to occur in the elderly without other signs. Sometimes only fatigue and weakness occur.

Clinical Manifestations

Useful ways to think about thyroid hormones are to regard them as analogous to an accelerator pedal in a motor vehicle or a heat generator. When they are produced in excess, all sorts of bodily processes go into overdrive, from heart rate to gut motility to sweat gland operation to anxiety and shakiness, etc. When they are underproduced, the reverse happens: the heart rate and GI motility are slowed, as are thought processes; ability to tolerate the cold is impaired; skin becomes thick and coarse, as does hair, primarily because the cell turnover in these tissues is greatly slowed down. The rate of metabolism of many drugs and medications is slowed down as well, so that conventional doses may result in high, toxic blood levels in hypothyroid individuals.

Elderly patients with hypothyroidism are less likely to have symptoms that suggest the disease than are younger individuals. Part of the reason for this is that the elderly are much more likely to suffer from other concomitant diseases, which may cause similar or identical symptoms (co-morbidity) and part is probably related to the lower level of reactivity in general.. It is very important to have a high level of suspicion in this age group, since they are so often taking medications and may require surgery, elective or emergent. Thyroid hormone deficiency, as noted above, slows the metabolic clearance of many medications, and may lead to toxicity if the disease goes unrecognized and usual doses of medication are used. Similarly, toxicity due to anesthetic agents may occur in patients with unrecognized hypothyroidism and may sometimes be life-threatening.

Diagnosis

Ordinarily, the diagnosis of hypothyroidism is made when there are compatible symptoms, coupled with laboratory evidence of low FT3 and/or FT4 plus high TSH. When all are present, the diagnosis is readily established. However, as noted, typical or characteristic symptoms may not always be present in the elderly, who may present with general decline in functioning or fatigue but without more specific symptoms. Further complicating the situation is the fact that the reference range for thyroid hormone levels established in healthy young individuals may not be quite the same for the elderly. There is some controversy here, but a reasonable synthesis of the available data suggests that FT3 and FT4 levels may be somewhat lower on average (but not outside the young reference range usually) in older patients who are healthy. Sometimes, testing to stimulate TSH production may help clarify this murky clinical situation, but here again, responses of the elderly may be lower than expected, especially in men. The elderly also display a much wider range of responses in general, than younger individuals. Furthermore, there may be changes in the activity of certain enzymes, which metabolize thyroid hormones, possibly related to selenium nutritional status (selenium is integral to the activity of these enzymes). All these factors sometimes conspire to make the interpretation of test results uncertain in the elderly.

Perhaps more problematic are the effects of non-thyroidal severe illness on these test results. First, the production of T3 is often depressed in illness requiring hospitalization and especially with severe illness requiring intensive care. FT4 and TSH may also be low, raising the question as to whether the patient is truly hypothyroidal and could benefit from judicious hormone replacement. In addition, the binding of thyroid hormones in serum is altered in severe illness further clouding interpretation of test results. Endocrinologic consultation is generally required for patients in these circumstances. Finally, if recovery from the non-thyroidal illness occurs, there may be an elevation of serum TSH levels during that recovery; this may not necessarily signal the development of hypothyroidism, but may rather turn out to be a transient elevation during the recovery process. Both pituitary and thyroid function may be depressed during severe non-thyroidal illness and transient TSH rises may be a normal feature of the recovery of pituitary TSH function.

Other, sometimes useful, ancillary tests include: thyroid antibodies (see above); serum lipids (total and LDL-cholesterol); sodium (hyponatremia may occur in hypothyroidism due to effects on kidney function); CPK (creatine phosphokinase), which may be released abnormally from muscle into the blood stream with the myopathy of hypothyroidism, and then cleared much more slowly than normal; and anemia (mostly due to abnormally slow production of blood cells by the bone marrow).

Treatment

Replacement of missing thyroid hormone is fairly straightforward in the young. A variety of preparations are available and some contain both T3 and T4. Most specialists give only T4, however, since the body converts T4 to T3 quite efficiently and giving T3 often results in supranormal blood T3 levels for several hours after each dose. In most circumstances, doses in the range of 0.75 to 1.5 micrograms per kilogram body weight per day suffice for full replacement of missing hormone. Adequacy of replacement is judged by return to the normal range of the previously elevated TSH.

In the elderly, the final maintenance dose is often lower than that in the younger individuals because of the diminished metabolic clearance rates associated with normal aging and the decrease in lean body mass (the metabolically active tissue) even when total body weight does not change. In addition, the method of administration differs, especially in those over 65 and those with a prior history of cardiac disease. In younger individuals with no co-morbidities or other complicating factors, usually the anticipated maintenance dose can be given from the start. In the elderly, however, and in those with established coronary artery disease consideration needs to be given to the increased metabolic demands imposed by thyroid hormone on the heart. Thus, one begins treatment at a low dose, and slowly increases the dose at intervals, monitoring both the TSH level and the clinical status carefully. A typical treatment schedule might involve a starting dose of 0.25 to 0.5 micrograms per kliogram per day, with increases of 12.5 to 25 micrograms per day every 4 to 6 weeks until the TSH is normalized. In this circumstance, as when the diagnosis is made, the level of TSH is a more sensitive indicator of adequacy of replacement than is the FT3 or FT4.

Occasionally, a patient with angina and hypothyroidism will experience escalation of anginal symptoms, which may ultimately limit the size of the maintenance dose to a level below the optimal amount for TSH normalization. Clinical judgement must dictate a treatment compromise in such a circumstance. Another cardiac consideration is that overtreatment in the elderly should be assiduously avoided, since even a mild degree of hyperthyroidism carries with it a 2 to 3 fold elevation in risk for the development of atrial fibrillation. TSH levels should be periodically monitored during treatment (once stabilized, yearly usually suffices), and kept above 0.1 microunit per ml. An additional reason not to overtreat is that hyperthyroidism, whether spontaneous or iatrogenic, has been associated with accelerated rates of bone loss and the development of osteoporosis.

Frequently, elderly patients are taking a number of medications, some of which may have the potential to interact with thyroid hormones. The two major modes of interaction are interference with gastrointestinal absorption of thyroid hormone (bile acid-binding resins, iron, calcium in large doses, sucralfate, aluminum hydroxide, raloxifene), and induction of enzymes which increase the metabolism of thyroid hormones (phenytoin, carbamazepine, phenobarbital, rifampin). Both of these effects tend to increase the required dosage for maintenance of a steady state. Estrogens and androgens may also influence dose requirements in hypothyroid individuals by altering the binding capacity of major binding proteins; estrogens increase that capacity, and androgens lower it. When binding capacity is increased, doses may need to increase in order to maintain a steady free hormone level; the reverse is true when binding capacity is lowered.

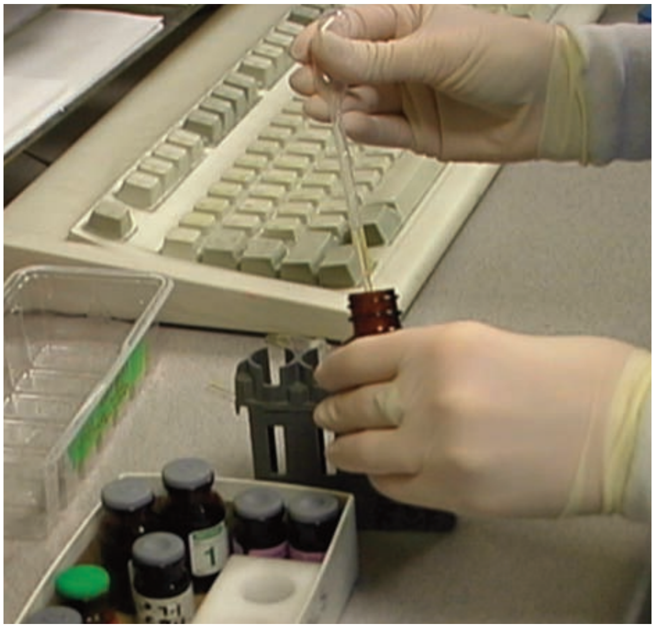
Subclinical Hypothyroidism

This topic has been extremely controversial and merits its own section. The controversy has been not about how to diagnose it, but rather about whether and how to screen for it given its very high prevalence and further about whether to treat it or not.

Clinical hypothyroidism is known to be associated with adverse changes in cardiovascular risk factors (lipids, especially cholesterol) and with progression of atherosclerosis, both central (coronary and aortic) and peripheral. It has been assumed that this is a graded association and greater cardiovascular risk is attendant upon more severe degrees of hypothyroidism. However, when the diagnosis is subclinical hypothyroidism, the literature until recently has been evenly divided on whether or not excess cardiovascular risk or frank disease is similarly associated. The factors involved in the controversy have been: small numbers of patients in a number of studies; varying periods of follow-up, some quite short; failure in many studies to stratify the severity of the process, based on the degree of TSH elevation; and a real shortage of controlled trials of administration of thyroid hormone.

Space does not permit detailed analysis of the available data, so I will simply provide my own overview of the situation. First, it does not seem biologically plausible that if overt insufficiency of the thyroid aggravates or causes cardiovascular problems, milder degrees of the same process won't do the same thing, given enough time. Further, if overtreatment is avoided (see above), thyroid hormone is among the least expensive and least harmful medications we have. So my inclination in this situation is to treat identified disease when it is found.

The definition of subclinical hypothyroidism is an elevated TSH combined with normal free thyroid hormone levels. Its population prevalence has been estimated by various observers to range between about 5 and 15% of the populations surveyed! When one divides people with this diagnosis into groups based on the degree of TSH elevation or the degree of anti-thyroid antibody positivity, it's clear that those with the highest levels of both analytes almost universally progress to overt disease over a few years and should clearly be treated when diagnosed. (For TSH, this means values above 10 microunits per milogram; since antibody values vary from laboratory to laboratory, it's not possible to specify exactly how high is high). For individuals with TSH values between about 7 and 10, it's reasonable to treat provisionally for at least 4 to 6 months, evaluating clinical response as well as laboratory response. The laboratory response should include not only TSH and FT4 levels, but also LDL-cholesterol, perhaps lipoprotein a, and any previously abnormal indicator of vascular disease, such as ultrasound evaluation of carotid artery intimal thickness, etc. For those with minimal TSH elevations (4 to 7), clinical judgment and continued observation without treatment is perfectly acceptable, since a significant fraction (about 50%) of this group will have spontaneous reversion of TSH to normal without any intervention.



Perhaps the uncertainty surrounding this topic can be more fully appreciated by summarizing two recent studies. One was the so-called Cardiovascular Health Study, a prospective cohort study of more than 3,000 people living in four different areas of the US. They had thyroid function studies once only, at the start of the study and were followed for cardiovascular problems for an average of 12.5 years. Of this population, 82% had normal thyroid function and 15% had subclinical hypothyroidism. No differences were found over time between the subclinical hypothyroidism group and the euthyroid group for cardiovascular outcomes or mortality. Obviously, the conclusion is not to treat for prevention of cardiovascular disease. Comment: Though large, this is an observational study and the findings are negative.

In contrast, a six-month study of 100 community-dwelling patients with subclinical hypothyroidism in Great Britain showed that treatment with thyroid hormone (in a double-blinded, crossover trial) significantly lowered total and low-density lipoprotein values as well as the waist-to-hip ratio, and improved arterial endothelial function as estimated by flow-mediated vessel dilatation. Thus, markers of cardiovascular risk and actual vascular functioning were both improved. Comment: This is a double-blinded controlled therapeutic trial and with positive results, but of short duration and using only surrogate/risk markers for cardiovascular disease.

Screening For Subclinical Hypothyroidism

It does not seem warranted to screen asymptomatic individuals in the general population. However, screening should be done in high-risk populations. These would include: women over 60 (much higher incidence of autoimmune thyroid disease than men); patients with a history of atrial fibrillation and/or congestive heart failure; patients with a past history of thyroid surgery or radioiodine therapy; patients over 60 with otherwise unexplained cognitive impairment; patients with a history of external beam radiotherapy for tumors of the head/neck region; and patients with a positive family history of thyroid disease.

Laurence S. Jacobs, MD
KLRI Scientific Advisor, University of Rochester

Clinical Research

How does your Participation in KLRI Studies Advance Scientific Knowledge?

Scientific information about significant health issues comes to us through the media on a daily basis. Sometimes it feels as if we're bombarded with 'facts' that appear to need our immediate attention, demanding a lifestyle change or at least a doctor's visit before it's too late. Many times these messages conflict with information we might have read at an earlier time, resulting in confusion and disbelief in the scientific process.

However, in our rapid-fire, media-responsive world, new scientific findings are often presented well before they're ready for public consumption. Sometimes food products are associated with health claims prematurely, making a trip to the supermarket seem like an ominous chore, choosing between 'good' and 'bad' foods. Here are a few recent newspaper headlines that illustrate the point: "Broccoli extract could help head off skin cancer"; "Face facts: Too much sugar can cause wrinkles"; "Find yourself packing it on, blame your friends". Headlines such as these may lead us to question whether we should immediately start eating more broccoli, swear off sugar, and/or cease dining with friends.

How can we make sense of all this information and make the appropriate choices to enhance our health and longevity? How does your participation in clinical research studies performed by KLRI contribute to scientific knowledge; specifically, how are your data evaluated and interpreted into recommendations appropriate to others? This aim of this brief review is to introduce you to the lengthy processes scientists go through prior to proposing a clinical trial and how the data from such studies are utilized. Our hope is that this information will allow you to understand the scientific information that comes your way and thus to make better choices for your health.

The scientific process follows a specifically defined method of questioning, discovery, and application that often requires years of testing and retesting before it can be translated into individual action. In the late 1500s, the philosopher Francis Bacon eloquently argued that deductive reasoning, popular at the time, should be replaced by inductive or scientific reasoning: "There are and can be only two ways of searching into and discovering truth. The one flies from the senses and

particulars to the most general axioms, and from these principles, the truth of which it takes for settled and immovable, proceeds to judgment and middle axioms. And this way is now in fashion. The other derives axioms from the senses and particulars, rising by a gradual and unbroken ascent, arriving at the most general axioms last of all. This is the true way, but as yet untried."

Translated into common language and contemporary practice, the scientific method follows a rigid outline: Observation of a problem; formulation of a hypothesis which proposes an answer to the problem; design of an experiment to test the hypothesis; collection and analysis of the data; and, arrival at a conclusion which either supports or rejects the hypothesis. Generally the experiment is repeated to insure that the results are valid prior to publication of the findings. Scientists strive to publish their results in peer-reviewed journals wherein other scientists critique and evaluate the work, deciding whether it merits publication. Peer-reviewed publications also require that sufficient methodological information be given to enable others to reproduce the study, further validating the results.

Those of you who participated in the fish-oil study, for example, might be interested to learn that the first observation of the beneficial effects of fish oil was made over 30 years ago in Greenland Eskimos, who were known to consume large amounts of fatty fish. Epidemiologic studies such as this cannot prove that consuming large amounts of fatty fish protected these individuals from cardiovascular diseases, but it can indicate that there is an association between the two factors: fish consumption and heart disease. Since that time, at least 14 additional 'prospective cohort studies' have been reported and the beneficial fatty acids in fish have been found to be protective against heart disease in 12, and to have no effect in 2, of the studies.

A prospective cohort study is a type of longitudinal study design in which groups or cohorts are selected before the disease under investigation is manifested. Examples of large-scale prospective cohort studies

include the Nurses' Health Study (120,000 nurses followed since 1976), the Framingham Study (begun in 1948 with 5200 individuals from Framingham, MA and now on its third generation) and the NHANES Studies (covering a large random sampling of various US age and ethnic groups since 1963), all of which have been useful in tracking many different conditions and outcomes, thus providing ways to test hypotheses. Scientists believed that specific fatty acids found in fatty fish lowered the risk of cardiac disease because their incorporation into cell membranes allowed great fluidity. Testing that hypothesis by utilizing blood samples taken from individuals participating in studies such as these cohort studies verified that the concentrations of the specific beneficial fats found in fish were much lower in individuals who suffered cardiac arrest compared to controls.

A more exacting method of epidemiologic study is the case-control study, in which those with a specific medical condition are compared to similar individuals without the condition. Investigators seek to determine if differences in past exposure to various factors may have contributed to the medical condition in the cases compared to controls. Case-control studies are useful for understanding the nature of conditions that develop over a long period of time, enabling researchers to look back at exposure, rather than waiting for a disease to develop over time. However, similar to prospective cohort studies, case-control studies can demonstrate associations, but they cannot prove a cause and effect relationship.

Once an association is found between a specific disease and plausible cause, studies can be designed to test the validity of the hypothesis. Often the first studies use cell lines, or animals.

Arline Salbe, PhD
Senior Clinical Research Fellow, KLRI

Who We Are

Kronos Longevity Research Institute (KLRI) is a not-for-profit, 501(c)(3) organization that con-ducts state-of-the-art clinical translational research on the prevention of age-related diseases and the extension of healthier human life. KLRI tests new strategies to detect and prevent chronic diseases associated with aging and investigates the effects of innovative interventions to slow the aging process and improve health outcomes for older persons. In addition, KLRI helps the medical and lay communities understand important aging issues. KLRI research findings support a healthier quality of life and a robust lifestyle in our senior years.

KLRI's Mission

KLRI is dedicated to understanding the human aging process and preventing age-related disease. KLRI conducts and fosters research that moves basic dis-coveries into clinical practice and communicates our research results to scientific and healthcare profes-sionals and to the public so that people may enjoy longer and healthier lives.

KLRI's Vision

KLRI will be the leading independent research insti-tute for translating basic discoveries on aging and longevity into improved preventions and treatments. We will be recognized as the thought-leader in the field of clinical gerontology and an authoritative source of sound scientific information.

Governance

A distinguished board of directors, with a unique mix of scientists, longevity specialists, and community leaders govern KLRI. There is also a scientific advisory board of recognized international experts in medical and sci-entific fields, including nutrition, exercise, hormones, bone and joint diseases, cancer and heart disease.

What Is Translational Research?

Translational research takes promising findings from the basic research laboratory and carries them forward into the clinical arena. It is the link between basic research (experiments done with animals or cultured cells, genes, etc.) and improved clinical care. It requires controlled studies of living human participants.

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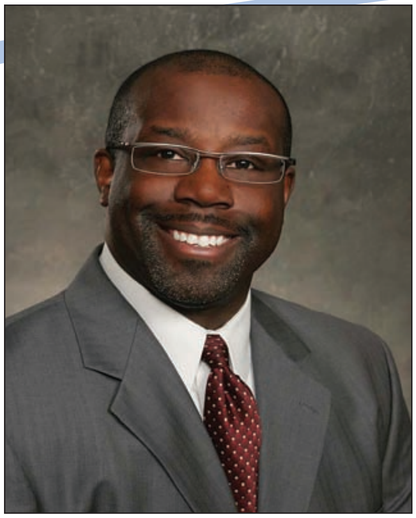


Board Member Profile

David H. Benton, JD

Fennemore Craig Law Firm

KLRI extends a warm welcome to our newest Board member — David H. Benton, an attorney at Fennemore Craig Law Firm in the Natural Resources and Environmental practice group.

Mr. Benton is interested in tracking the development of biotechnology and medical research opportunities in Arizona. He has almost ten years of scientific research experience, particularly in the development of new environmentally compliant technologies for the aerospace industry.

Previously, Mr. Benton was an Arizona Assistant Attorney General in the Environmental Enforcement Section. He provided advice and counsel in the areas of underground storage tanks, regulatory compliance and enforcement, permitting, land use regulations, as well as lobbying, administrative hearings and litigation. He also served as a lobbyist with the Arizona Supreme Court, and has worked with state and local elected officials, agency directors, and many organizations and interest groups.

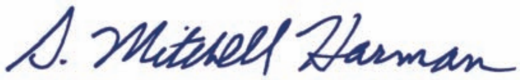
Mr. Benton is a member of the State Bar of Arizona and the Maricopa County Bar Association. He is also on the editorial board of the *State Bar Attorney Magazine.*

Mr. Benton has a Bachelor of Science degree in chemistry from California State University, Long Beach in 1986. He received his JD from the University of Arizona in 1997.

Director's Message, continued

disease in the KEEPS, was turned down, but will be resubmitted to the NIH in March. Our estimated chance of obtaining this funding is approximately 50% (which is, as I described above, the approval rate for excellent proposals).

So what is the answer? Clearly, we need to re-order our federal budget priorities as a nation if we want to maintain a first-rate biomedical research establishment and reap the benefits that it will provide. You can write your senator or congressman and express your support for expanded funding for NIH biomedical research to restore the funding line to a target of 30%. Your family, friends, neighbors, really all of us, will gain in the long run.



S. Mitchell Harman, MD, PhD
Director and President

Word Search

Instructions: Try to find these KLRI terms in the world scramble below.

Longevity **Heart** **Health** **Research** **Hormones** **Antioxidants**
Life **Memory** **Active** **Sports** **Aging**

E	R	E	S	E	A	R	C	H	E	W	U	R
K	N	U	T	R	I	T	I	O	N	Y	F	G
L	T	K	A	G	I	N	G	W	R	P	B	N
H	O	M	H	Y	H	N	P	G	T	F	D	W
C	F	N	U	B	T	O	E	V	I	X	A	S
X	Q	U	G	H	G	O	A	L	S	B	B	A
D	S	W	H	E	A	R	T	J	L	L	L	P
R	P	H	O	A	V	X	H	B	Y	I	Q	Z
O	O	N	R	L	S	I	V	G	A	F	P	X
V	R	K	M	T	A	C	T	I	V	E	R	R
X	T	M	O	H	A	U	B	Y	R	L	N	Y
G	S	T	N	A	D	I	X	O	I	T	N	A
K	P	M	E	M	O	R	Y	D	X	O	S	D
K	F	H	S	H	S	T	O	Q	L	E	P	S

Answer:

E	R	E	S	E	A	R	C	H	E	W	U	R
K	N	U	T	R	I	T	I	O	N	Y	F	G
L	T	K	A	G	I	N	G	W	R	P	B	N
H	O	M	H	Y	H	N	P	G	T	F	D	W
C	F	N	U	B	T	O	E	V	I	X	A	S
X	Q	U	G	H	G	O	A	L	S	B	B	A
D	S	W	H	E	A	R	T	J	L	L	L	P
R	P	H	O	A	V	X	H	B	Y	I	Q	Z
O	O	N	R	L	S	I	V	G	A	F	P	X
V	R	K	M	T	A	C	T	I	V	E	R	R
X	T	M	O	H	A	U	B	Y	R	L	N	Y
G	S	T	N	A	D	I	X	O	I	T	N	A
K	P	M	E	M	O	R	Y	D	X	O	S	D
K	F	H	S	H	S	T	O	Q	L	E	P	S

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