



KRONOS LONGEVITY RESEARCH INSTITUTE

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



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HYPERTHYROIDISM IN THE ELDERLY

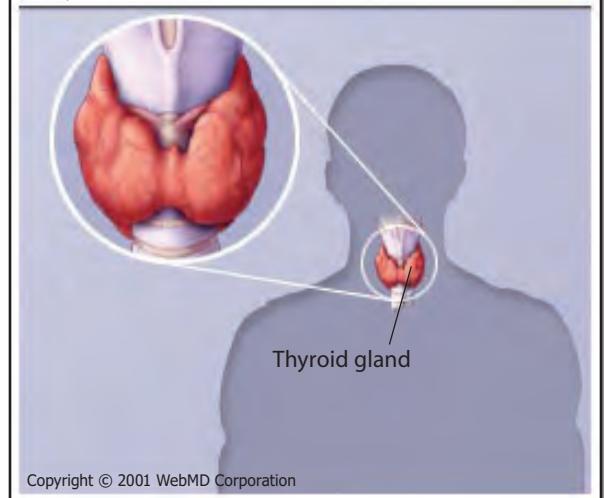
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Introduction

Hyperthyroidism (overactive thyroid gland) in the elderly is a significant health problem. In addition to previously diagnosed individuals, there exists in the general population a group of people in whom the disease exists, but has not been diagnosed. The group is very substantial, consisting of approximately two and a half to five percent of the total population. Roughly half of these have clear abnormalities on testing with compatible symptoms, which may have gone unnoticed or unreported to their physicians. The other half have normal thyroid hormone levels, but abnormal levels of a key thyroid regulator, TSH (thyroid stimulating hormone), from the pituitary gland. The group with TSH may or may not have symptoms or signs, even after extensive review of their histories and physical exams. This condition is called "subclinical" hyperthyroidism.

Thyroid Gland



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In both groups within the elderly population, the clinical picture in the hyperthyroid tends to be dominated by nonspecific (weakness, fatigue, weight loss) and/or cardiovascular manifestations (high systolic blood pressure, rapid or irregular heartbeat, sometimes congestive

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DIRECTOR'S MESSAGE

The Importance of Biomarkers of Aging

*A*s we grow older, age-related diseases such as Alzheimer's, cancer, diabetes, osteoporosis, and heart disease, become a greater and greater concern. We have all had family members or close friends experience the debilitating diseases of aging. These chronic diseases take older adults' lives slowly and painfully, one step or one disease at a time. This process causes emotional and financial strains, not only for aging individuals, but for the family members and friends who care for them as well. Providing care and support for a person with one or more of the diseases of aging is costly in every way. Can we slow the aging process down? Can we prevent or delay age-related diseases? This is the challenge that we discuss almost daily at KLRI.

In 2005, the U.S. had approximately 16,000 nursing facilities, with more than 1.4 million residents. In 2004, there were more than 36,000 assisted living facilities. The percentage of Americans over the age of 65 is expected to increase from 12.3% today to more than 18% by 2025. In 2006, alone, Medicaid is expected to have a shortfall of more than \$4.4 million in reimbursements for nursing facilities, yet nursing facility costs represented only 5.2% of Medicare expenditures in 2005. The average hours per day that a registered nurse or licensed practice nurse spends with a nursing facility resident is 1.1 hours per day.

Increased expenditures of health care dollars could improve the quality of care for the aging, and many organizations are working toward that goal today, but dollars are not unlimited. We need to consider whether an alternative strategy would improve the quality of life and health of our aging population. If we can learn how to slow the aging process and delay the onset of age-related disease so that older adults remain healthy and productively employed seven years longer than is currently the case, this would reduce costs sufficiently to eliminate the Medicaid and Medicare shortfall, and financially balance the Social Security system. Older adults want to stay active and feel needed, so it is unlikely that most would object to such a plan, if life expectancy and "health-span" were both extended by five to 10 years.

Scientific researchers have succeeded in extending the lifespans of a variety of animals, hence opening doors for interventions for the prevention of aging and age-related diseases in humans. Interestingly, animals in which life-extending interventions are carried out also experience later onset

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of age-related diseases. They stay healthy longer! However, the end-point of such research is generally the age of death of the animals. In order for such research to be carried out in humans, we will need a set of measurements indicative of biological aging, known as "biomarkers of aging" that will enable us to create an overall measure or index of aging other than mortality rate. Because individuals age differently, such an index will almost certainly consist of a battery of biomarkers of aging in different body systems that together predict age-related outcomes such as mortality or morbidity.

KLRI is working with the Alliance for Aging Research and other investigators and organizations to foster development of such an index of biological aging. Researchers will review the results of multiple tests from large human studies and move them through four basic stages, which are: nomination, validation, refinement and final evaluation. During the evaluation stage, they will assess the use of the index of biological aging for the clinical research setting. When these four steps are completed, the next stage will be exploitation.

It is in the final exploitation stage where the greatest benefits and return on investment lie. Having a validated complex index of human biological age could lead to new laboratory tests that help define standards of care and treatment, but even more importantly, will allow testing of interventions, such as new prescription drugs or nutritional supplements for anti-aging efficacy in human beings.

In the long term, we are confident that the application of age-related disease interventions will improve overall quality of life nationally and reduce prescription and health-care costs for the government, employers, health insurers, and for individuals in our maturing population. Heart disease, stroke, cancer, diabetes and Alzheimer's disease cost an estimated \$771 billion in 2003. Investment in research will save lives and money. Now that we have discovered how to treat, prevent, and/or cure most acute infectious diseases that were the great killers of the young; the next step will be conquering the diseases that plague us as we age.

You can help by writing to your congressman and senators and letting them know that you support expanding the NIH budget for the biology of aging and translational aging research, such as the development of human biomarkers of aging. Support of KLRI's research programs and of the Alliance for Aging Research and similar organizations will also make a difference. If we invest today in identifying and utilizing biomarkers of human aging, the payoff tomorrow will be tremendous.

***S. Mitchell Harman, MD, PhD
Director and President
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heart failure). In contrast, non-elderly individuals with hyperthyroidism often report excessive sweating, heat intolerance, tremulousness, change in bowel habits, change in eyes or skin, and enlargement of the thyroid gland (goiter). In general, these symptoms can be understood by thinking of thyroid hormones (there are two, called thyroxine and triiodothyronine, or T4 and T3) as regulators of the speed of bodily processes. When they are present in excess, things go too fast (like bowel contractions, heartbeats, or sweat glands, e.g.). However, these latter symptoms and findings may not be present in the elderly with hyperthyroidism. Thus, making the proper diagnosis requires alertness to the possibility that seemingly non-specific or cardiac symptoms may in fact be due to underlying hyperthyroidism. The mortality of untreated hyperthyroidism in the elderly is high, and thus proper diagnosis and treatment is essential. An additional consequence of hyperthyroidism, due to accelerated bone turnover, may be osteoporosis, especially in postmenopausal women. In fact, several researchers have reported a clear association between a history of hyperthyroid-

ism and the occurrence of hip fractures, as well as a greater mortality associated with such fractures in the hyperthyroid population.

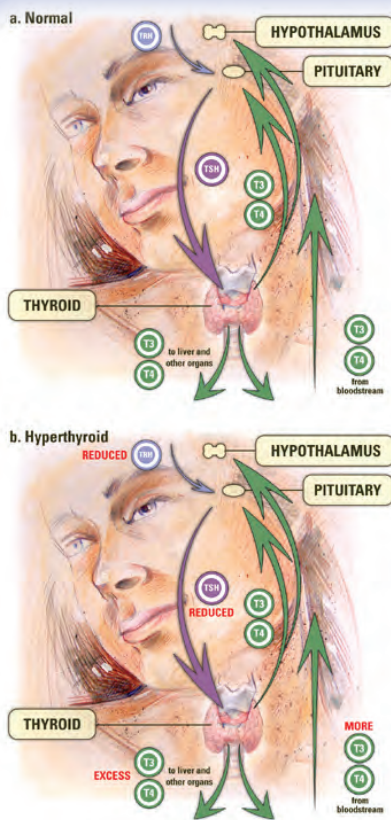
Since the prevalence of hyperthyroidism is so high in the population, and since both osteoporosis and cardiovascular disease are even more common, there is a great deal of morbidity and mortality, which can be minimized or prevented by the early diagnosis and treatment of hyperthyroidism in the elderly. In fact, this is a problem of public health proportions.

Table 1

Manifestations Of Hyperthyroidism

Weight loss*	Rapid/irregular heartbeat*
Tremor	Systolic hypertension*
Goiter	Excessive sweating
Heat intolerance	Palpitations
Shortness of breath	Tiredness/fatigue
Eye changes	Skin changes (rare)
Muscle weakness*	Hyperdefecation/diarrhea
Aggravation of osteoporosis*	

* Likely to occur in the elderly without more specific manifestations



The entity of "subclinical" disease merits some explanation. It has been known for several decades that TSH and the thyroid hormones are regulators of each other and that their interaction in what is called a negative feedback loop is responsible for keeping the hormone levels on an even keel. When thyroid hormone levels rise, due to one of the common causes of hyperthyroidism (more information later in the article), the higher concentrations suppress the production of TSH (hence "negative" feedback). This decrease in TSH, which can be recognized by appropriate testing, tends to minimize stimulation of the thyroid gland and lower the hormone levels, thus restoring the prior balance. But in the presence of alternative paths to stimulation of the gland, the lowering of TSH is often not enough to reverse the situation, and hyperthyroidism ensues. It is thought that in its very early stages, or in mild cases, the finding of a suppressed TSH can occur without elevation of the thyroid hormone levels

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to values above the normal range. This is because TSH is exquisitely sensitive to small changes in the thyroid hormone levels, and because normal values encompass a range, due to normal biologic variation from person to person.

Hence, a clinician may be faced with a hyperthyroid patient in the seventh to 10th decade of life who is doing poorly but has only non-specific symptoms such as fatigue and muscle weakness, perhaps coupled

with an irregular heartbeat due to a cardiac rhythm disturbance such as atrial fibrillation. This means that the small cardiac chambers, the atria (whose normal contraction may add as much as 10-15% to the amount of blood pumped out to the tissues by the heart), are no longer contracting effectively, but rather are just quivering. In addition to the loss of cardiac output, the stagnation of blood in these quivering chambers

may lead to clot formation, and the clots may travel in the blood stream, causing strokes, kidney damage, vision damage, etc, etc. This condition of atrial fibrillation occurs three times as often in the elderly with hyperthyroidism as in those without it. Thus, all such patients should be screened for hyperthyroidism, whether subclinical or not. And, based on the above, all elderly patients who suffer weight loss or a general decline in their state of health should also be screened for hyperthyroidism.

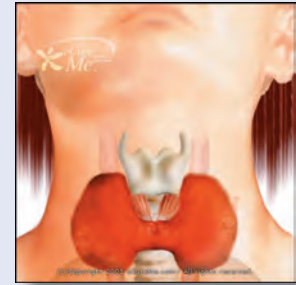
Causes Of Hyperthyroidism

The most common causes of hyperthyroidism in the population are Graves' disease, and toxic nodular hyperthyroidism. Graves' disease, which is more common in the young than in the old, is caused by the development of antibodies which stimulate the thyroid gland, independent of TSH, but via the cell component (the TSH receptor) which normally mediates the action of TSH. In a very real sense, this is an autoimmune disorder which happens to affect the thyroid gland. Nodular hyperthyroidism may occur

due to the development of functional autonomy (i.e., failure to respond to normal control signals like TSH) in one or more long-standing nodules in a goiter of many years' duration. It may also occur, though much more rarely, as a result of autonomous functioning in a single thyroid nodule. In multinodular hyperthyroidism, which is primarily a disease of the elderly, most patients show the usual biochemical findings of hyperthyroidism; a minority, however, demonstrate what is called "T3 toxicosis". In this situation, the TSH levels are suppressed, and the T3 levels are elevated, but levels of T4, or thyroxine, are normal. The hyperthyroid state is thus created and sustained by isolated overproduction of T3. T3 should thus be measured whenever hyperthyroidism is strongly suspected, but T4 levels are normal.



Normal



Abnormal

The occurrence of inflammation within the thyroid gland may cause hyperthyroidism as well. The associated tissue destruction and unregulated release of stored thyroid hormone into the blood stream may lead to a hyperthyroid condition sometimes difficult to discriminate from Graves' disease. Both have enlarged thyroids, the inflamed gland may not always be tender, and the hormone levels are often in the same range. The detection of thyroid-stimulating immunoglobulins in the blood makes the diagnosis of Graves' disease, and the finding of a low level (less than 5%) of radioiodine uptake into the inflamed gland (as opposed to the high, stimulated level in Graves'), makes the diagnosis of thyroiditis. Thyroiditis tends to occur before age 40, may recur, and is more frequent in the postpartum time frame. It is quite uncommon in the elderly.

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Exposure to iodine may precipitate hyperthyroidism. A particular cause relevant to the elderly is the drug Amiodarone. This is a very effective anti-arrhythmic agent, often used to treat atrial fibrillation and other rhythm disturbances, which are of course much more common in the elderly. The drug contains iodine, which may cause the disorder, or it sometimes is associated with an inflammatory thyroidal condition, a thyroiditis. Endocrine consultation is usually indicated when thyroid changes occur in a patient taking this drug.

In an extremely rare instance, hyperthyroidism may be dependent on excessive production of TSH. This may occur when there is a TSH-secreting tumor of the pituitary gland, or when due to non-tumorous causes, there is a dysfunction in the signaling pathway that normally regulates TSH production. The latter is often dubbed "inappropriate TSH secretion." Both of these conditions tend to occur in young or middle-aged adults rather than in the elderly.

Treatment Of Hyperthyroidism

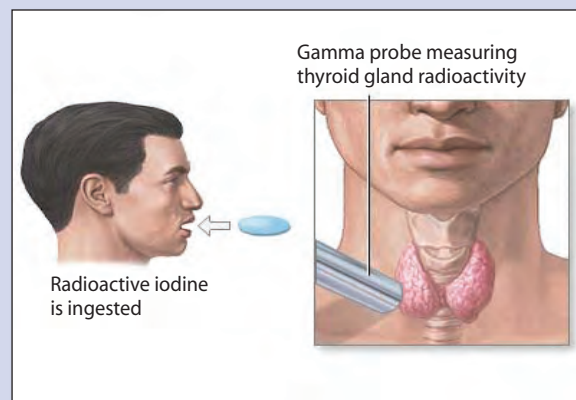
Traditionally, there have been three quite separate means of treating hyperthyroidism.

These are: the use of anti-thyroid drugs; the use of radioiodine; and surgery. When the anti-thyroid thionamide drugs (propylthiouracil, or PTU, and methimazole, or Tapazole) are used to treat hyperthyroidism, they are often combined with beta-blocking drugs, which tend to slow the heart rate and diminish the severity of sweating and of certain eye changes. The thionamides inhibit thyroid hormone synthesis, and to some extent block the metabolic step which creates T3 from T4, but overall, their effect may not be fully seen for several weeks, until already formed thyroid hormone is depleted from the gland. Hence, the frequent co-administration of beta blockers for quick short-term relief of symptoms. The thionamides may be used short-term, to prepare the patient for definitive radioiodine therapy, or long-term, even for years, by themselves, in certain clinical situations. They have been used effectively to treat Graves' disease, nodular hyperthyroidism, and Amiodarone-induced hyperthyroidism. Allergic reactions to them may occur, as with any drug. Rarely, a life-threatening side effect may occur, called agranulocytosis, in which the bone

marrow production of a type of white blood cell is shut down; fortunately, this is usually reversible if the causative drug is stopped.

Radioactive iodine has now been in use for thyroid diagnosis and treatment for roughly 60 years. Its utility is based on the fact that the thyroid hormones both contain iodine as a part of their structures; T3 having three iodine atoms/molecule, and T4 having four. When an overactive gland is exposed to a tracer dose of radioiodine, taken by mouth, a higher proportion of the dose than normal is taken up by the thyroid and incorporated into the hormones. Also, the speed with which the uptake proceeds is faster than normal. By comparison to established criteria, overactivity is usually readily diagnosed. If one uses a somewhat larger than tracer dose, one may also obtain an image of the gland, thus helping differentiate between Graves' (diffuse overactivity), nodular disease (single or multiple), or thyroiditis (suppressed uptake in the damaged, inflamed gland). Because of favorable physical characteristics of the isotope Technetium, it is now used for imaging instead of iodine; but iodine isotopes are still used for the uptake quantitation process.

For the treatment of hyperthyroidism, the doses of radioiodine used ranges from about 200 to 3000 times the tracer dose used for uptake purposes. Damage to the reproductive machinery either kills the cells outright, or impairs their ability to reproduce later. Since the cell turnover rate in the thyroid, like that in many tissues, is quite low, the latter damage may become clinically evident only years later, as replication of cells lags behind the needs of the gland for renewal.



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The practical consequence is that only about 10% of Graves' disease patients become hypothyroid promptly after radioiodine treatment, but about one to two percent per year become hypothyroid thereafter; a lag of 30 years after treatment in this generally young group is thus associated with 60-75% occurrence of hypothyroidism. Since that is fairly easy, cheap, and straightforward to treat, many endocrinologists routinely recommend radioiodine doses on the high side, and routinely start patients on replacement therapy with thyroid hormone from the initiation of radioiodine therapy.

This situation is quite different in nodular hyperthyroidism, since by definition only certain areas of the gland are overactive. In that case, the other, suppressed glandular areas are relatively "protected" by their inactivity from the effects of the radioiodine treatment, and the rate of occurrence of hypothyroidism is infinitesimally small.

Radioactive iodine has now been in use for thyroid diagnosis and treatment for roughly 60 years.

Surgery, by definition, carries risks not associated with the other treatments: hemorrhage, infection, anesthesia itself, damage to the recurrent laryngeal nerve, and damage to the parathyroid glands, which regulate calcium metabolism. These are all quite low risks, especially in the hands of an experienced thyroid surgeon, of the order of one percent or less. Still, they are not zero. Further, as more and more treating physicians have used surgical treatment of hyperthyroidism less and less (preferring to rely on radioiodine as a definitive treatment), the number

of well-experienced thyroid surgeons in practice has continued to diminish. Thus, we are arriving at a more-or-less preordained situation, in which thyroid surgery in the future will primarily be concerned with the treatment of cancer, not of hyperthyroidism.

***Laurence Jacobs, MD
KLRI Scientific Advisory Board and
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Men over 60 years of age are invited to participate in a clinical trial to study Testosterone's Effects on the Progression of Atherosclerosis in Aging Men (TEAAM Study).

Compensation provided.

... join the TEAAM

Call (602) 778-7480 to see if you qualify.

Survey Finds Surprising Results With Research Study Participation

Kronos Longevity Research Institute (KLRI) has been able to conduct several research studies with the support of our generous study participants. We would not be able to learn or perform studies without the participants who are kind enough to donate their time for the purpose of furthering aging research. We are so grateful to those who are interested in participating, but at the same time, recruiting and retaining study participants is a difficult task, often leaving us struggling to complete studies.

Surveys show that only ten percent of people who are eligible to volunteer for research studies actually participate in them and more than two-thirds of potential study participants state they have no knowledge of clinical research trials and the participation process. In a phone questionnaire of over 1,100 people, seventy percent said they would not agree to participate in a medical research study.

Several people stated that they were unwilling to participate because of the potential harm that may occur from the new treatments and methods. These concerns are rational, however, all of our study procedures and methods are approved by the Institutional Review Board (IRB), or ethical review board, which reviews, approves and monitors research involving human subjects and aims to protect the welfare of the study participants.



An informed consent is a document given at the beginning of the study to the participant. The consent form thoroughly describes all of the procedures that will be performed throughout the study and includes

any/all potential risks and harm that may be associated with them, although these risks are often slim to none. Our medical professionals are available to address any concerns and study participation is completely voluntary. All participants have a choice to drop a study at anytime during the process.



The extensive screening processes and follow-up procedures are also necessary steps to keep potential harm at a minimum. Most of our studies involve multiple in-depth scans such as the carotid intima-media thickness (CIMT) scan, which measures the degree of atherosclerosis (or the hardness from plaque in the arteries); dual energy x-ray absorptiometry (DEXA), which measures bone density; electron beam computed tomography (EBCT), which measures coronary calcium; and abdominal fat scans. Cognitive function is also measured at regular intervals throughout the studies.

At KLRI, our participants' well-being is our main priority. If any of the test results reveal a chance for potential harm to the participant, one of our medical professionals will advise for a discontinuation of the study. Currently, we are recruiting for an estrogen study, the Kronos Early Estrogen Prevention Study (KEEPS), a testosterone study, the Testosterone's Effects on the Progression of Atherosclerosis in Aging Men (TEAAM), and will be preparing to recruit for two other studies fairly soon. For additional information on any of the study procedures and extensive scans, please call 602-778-7480.

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Thank you to all the sponsors who have chosen to support KLRI with the Enlightened Age Forum event! This event wouldn't have been possible without the help of these companies:



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Who We Are!

Kronos Longevity Research Institute (KLRI) is a not-for-profit, 501(c)(3) organization that conducts 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 discoveries into clinical practice and communicates our research results to scientific and healthcare professionals and to the public so that people may enjoy longer and healthier lives.

KLRI's Vision

KLRI will be the leading independent research institute 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 scientific 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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