Parker, James N., 1961-
Parker, Philip M., 1960-

Hyperthyroidism: A Medical Dictionary, Bibliography, and Annotated Research Guide to Internet References / James N. Parker and Philip M. Parker, editors

Includes bibliographical references, glossary, and index.
ISBN: 0-597-83937-9
1. Hyperthyroidism-Popular works.  I. Title.
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Acknowledgements

The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on hyperthyroidism. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.
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In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading." Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with hyperthyroidism is indexed in search engines, such as www.google.com or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about hyperthyroidism, using the most advanced research tools available and spending the least amount of time doing so.

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on hyperthyroidism.

*The Editors*

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CHAPTER 1. STUDIES ON HYPERTHYROIDISM

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on hyperthyroidism.

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and hyperthyroidism, you will need to use the advanced search options. First, go to http://chid.nih.gov/index.html. From there, select the “Detailed Search” option (or go directly to that page with the following hyperlink: http://chid.nih.gov/detail/detail.html). The trick in extracting studies is found in the drop boxes at the bottom of the search page where “You may refine your search by.” Select the dates and language you prefer, and the format option “Journal Article.” At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display “whole records.” We recommend that you type “hyperthyroidism” (or synonyms) into the “For these words:” box. Consider using the option “anywhere in record” to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the “Search in these fields” drop box. The following is what you can expect from this type of search:

- **Hypothyroidism, Hyperthyroidism, Hyperparathyroidism**
  

  Contact: Available from Medical Economics. 5 Paragon Drive, Montvale, NJ 07645. (800) 432-4570. Fax (201) 573-4956.

  Summary: This article discusses the diagnosis and treatment of thyroid illnesses. These types of illnesses are among the most prevalent of the hormonal diseases that afflict people in the United States. Although hypothyroidism and hyperthyroidism are the most widespread, hyperparathyroidism (HPT) occurs in a large number of Americans as well. Diagnosis can be complicated because numerous patients present with nonspecific signs and symptoms that closely resemble other physical and mental conditions. Primary hypothyroidism occurs from failure of the thyroid gland itself, whereas
secondary hypothyroidism results from a deficiency of pituitary thyroid-stimulating hormone. The most common cause of hypothyroidism among adult patients is Hashimoto’s thyroiditis. Other causes include drug side effects, congenital hypothyroidism, iodine excess, previous thyroidectomy, neck irradiation, and pituitary or hypothalamic disorders. Women who have type 1 diabetes are at greater risk for a temporary disorder known as postpartum thyroiditis. Signs and symptoms can be overt, subtle, or nonexistent. Diagnosis involves performing a physical examination and conducting laboratory tests. The treatment of choice for managing hypothyroidism is daily oral administration of levothyroxine. Some patients may benefit from referral to an endocrinologist. Hyperthyroidism, which is not as prevalent as hypothyroidism, is caused by Graves’ disease or diffuse toxic goiter. Other causes include pituitary tumors, pituitary resistance to thyroid hormones, neonatal hyperthyroidism, and malignancies. Signs and symptoms can be overt, subtle, or nonexistent. Diagnosis involves performing a physical examination and conducting laboratory tests. Patient referral to an endocrinologist is indicated following a positive diagnosis or when hyperthyroidism is suspected. Treatment options include radioactive iodine therapy, antithyroid drugs, and surgery. HPT, another fairly common endocrine disorder, is the most common cause of hypercalcemia. Although about 75 percent of patients have no signs or symptoms attributable to this disease, it may affect the skeletal system, kidneys, and gastrointestinal tract. The only successful treatment is surgical removal of one or more parathyroid glands. Patients who have primary HPT should be referred to an endocrinologist. 1 figure. 4 tables. 5 references.

Federally Funded Research on Hyperthyroidism

The U.S. Government supports a variety of research studies relating to hyperthyroidism. These studies are tracked by the Office of Extramural Research at the National Institutes of Health. CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to hyperthyroidism.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore hyperthyroidism. The following is typical of the type of information found when searching the CRISP database for hyperthyroidism:

- **Project Title:** AN ANIMAL MODEL FOR GRAVES’ DISEASE/OPHTHALMOPATHY
  Principal Investigator & Institution: Jaume, Juan C.; Medicine; University of Wisconsin Madison 750 University Ave Madison, Wi 53706
  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-AUG-2006

---

2 Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).
Studies 5

Summary: (provided by applicant): The ophthalmopathy of Graves' disease is a disfiguring, sight threatening condition of unclear pathogenesis and no specific or definitive therapy. Graves' disease primarily manifests with hyperthyroidism that results from the stimulation of the TSHR by specific autoantibodies that mimic the effect of TSH. Often the ophthalmopathy accompanies the hyperthyroidism. Rather than being considered two separate entities, hyperthyroidism and ophthalmopathy are different manifestations of the same underlying autoimmune process. No spontaneous animal model of Graves' disease exists. Recently, an animal model has been developed in which a proportion of individuals manifest immunological and endocrinological features of Graves' disease. We have generated and extended such mouse model. The overall goal of this proposal is to use this Graves'-like animal model to investigate critical issues of Graves' disease as is Graves' ophthalmopathy as follows: 1. Graves' ophthalmopathy in the Graves'-like mouse model. New observations suggest the immunizing cells used in the model behave as APC that constitutively express B7-1 molecules and bias the immune response to a Th1 type. These APC also have the capacity of presenting non-specific antigens present in culture medium. With this information we have modified our immunization protocol to improve specific (TSHR) antigen presentation and deviate the immune response to a Th2 type characteristic of human Graves'. We propose to: a. Study the development of Graves' disease/ophthalmopathy in both, Th1 and Th2 settings. b. Examine the role of CD40 for orbital fibroblast-B/T cell cross talk. c. Study the regulation of TSHR in orbital fibroblasts/preadipocytes. 2. Characterize TSHR antibodies in their relationship to Graves' ophthalmopathy.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF THYROID HORMONE DISEASE**
  Principal Investigator & Institution: Krueger, James M.; Professor of Neurobiology; University of Tennessee Health Sci Ctr Health Science Center Memphis, Tn 38163
  Timing: Fiscal Year 2001
  Summary: This study will determine whether sleep parameters are altered in hyperthyroid patients and, if so, whether the abnormalities return to normal during the treated, euthyroid state.
  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: COREPRESSORS AND NEGATIVE REGULATION BY THYROID HORMONE**
  Principal Investigator & Institution: Cohen, Ronald N.; Medicine; University of Chicago 5801 S Ellis Ave Chicago, Il 60637
  Timing: Fiscal Year 2001; Project Start 05-AUG-1998; Project End 30-JUN-2003
  Summary: (Taken from the applicant's Abstract): Thyroid hormone receptors (TRs) bind to thyroid hormone response elements (TREs) in the regulatory regions of genes to stimulate or inhibit gene transcription. TRs bind in the presence or absence of ligand, triiodothyronine (T3). In the absence of ligand, TRs repress transcription of genes that are positively regulated by T3. Ligand-independent repression is mediated by a class of proteins termed co-repressors, including NCoR and SMRT, which bind TR in the absence of T3. TRs also exhibit ligand-independent effects on genes negatively regulated by a thyroid hormone. One these negative TREs, TRs enhance transcription in the absence of ligand. These effects are less well defined, but appear to be mediated by
members of the co-repressor families, as well. The goals of these studies are (1) to characterize the effects of co-repressors on genes negatively regulated by thyroid hormone; (2) to identify and characterize NCoR isoforms; and (3) to determine how co-repressors interact with specific TR complexes. In these studies, we will focus on the interactions between co-repressors and TR-beta-2, a TR isoform that may play a distinct role in negative regulation. In addition, mutant TRs, found clinically in patients with syndromes of resistance to thyroid hormone (RTH) will be used to characterize interactions between TRs and co-repressor isoforms. This information will allow us to define further mechanisms underlying thyroid hormone resistance and thyroid hormone action, which will shed light on the basis of human hypothyroidism and hyperthyroidism. Moreover, an understanding of how TRs regulate gene transcription in the absence of ligand will provide further insight into the mechanisms of gene regulation in general. This project will be performed by Dr. Ronald Cohen under the guidance of Dr. Fredric Wondisford, in the Thyroid Unit and Endocrine Division of the Beth Israel Deaconess Medical Center. Dr. Wondisford has made major contributions to the understanding of the molecular mechanisms governing negative regulation of the TSH and TRH genes. There are also numerous investigators in the Endocrine Division and the surrounding Harvard Medical School community with interests in transcriptional regulation. This will provide an ideal environment to complete this project, and will provide a basis for Dr. Cohen's transition to an independent investigator.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- Project Title: EXPERIMENTAL AUTOIMMUNE GRAVES' DISEASE

Principal Investigator & Institution: Prabhakar, Bellur S.; Professor and Head; Microbiology and Immunology; University of Illinois at Chicago 1737 West Polk Street Chicago, IL 60612

Timing: Fiscal Year 2001; Project Start 01-JUN-1995; Project End 30-NOV-2003

Summary: Autoantibodies to the thyrotropin receptor can either activate thyroid gland causing hyperthyroidism or block TSH mediated activation of thyroid and cause hypothyroidism. Until several years ago, it was not possible to develop an animal mode due to the unavailability of large quantities of purified TSHR. Subsequent to cloning of human TSHR, several laboratories, including our own, have used human recombinant proteins to induce the disease in mice. These studies have provided new insights on the requirements for an optimal immune response to TSHR, resulting in thyroid perturbation. Earlier, we expressed the ectodomain of mouse TSHR (mTSHR) and showed that it is antigenically distinct from human TSHR. Recently, we expressed mTSHR on M12 cells (H-2D) and used them to immunize BALB/c mice. These mice showed significant TBII activity with concomitant raise in T4 levels. In the present study, we propose to use a soluble ectodomain of mTSHR and various cell lines expressing mTSHR, Class-II and Co-stimulatory molecules to define optimal conditions required to induce autoimmunity to TSHR. Sera will be tested for antibody production and hormonal perturbations, and thyroids will be evaluated for pathology and radioiodine uptake. We will carry out studies to evaluate the importance of CD4+ vs. CD8+ and Th1 vs. Th2 T cells. To do this, we will use selective depletion and adoptive transfer experiments, determine the relevance of cytokines, and test the ability of the protein to induce disease in Class-I and II, IFNgamma, and IL4 knockout mice available on BALB/c background. To define TSHR epitopes to which pathogenic antibodies bind, we will carry out epitope mapping studies. For this, we will employ recombinant fragments of TSHR, ectodomains of TSHR-LH/CGR chimeric proteins and cells
Studies expressing these chimeras. These proteins or their fragments will be tested in a number of different serological and bioassays. Together these studies are expected to allow establishment of an appropriate animal model to study autoimmunity to TSHR. Such a model would facilitate a thorough understanding of the regulation of the immune response to TSHR with implications for the development of novel therapeutics.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EYE IN GRAVES DISEASE--ROLE OF ORBITAL FIBROBLASTS**
  Principal Investigator & Institution: Bahn, Rebecca S.; Professor; Mayo Clinic Rochester 200 1st St Sw Rochester, Mn 55905
  Timing: Fiscal Year 2001; Project Start 01-AUG-1991; Project End 31-JUL-2004
  Summary: Graves' ophthalmopathy (GO) is an autoimmune eye disorder closed associated with Graves' hyperthyroidism. There is convincing experimental evidence that the orbital fibroblast (including the preadipocyte fibroblast subpopulation) is the target cell in GO. However, the autoantigen against which the immune response is directed is unknown. The thyrotropin receptor (TSHr) is a prime candidate to be the orbital autoantigen because its involvement would help to explain the close clinical and laboratory associations between GO and hyperthyroidism. In recent studies, the PI has demonstrated the present of TSHr mRNA and protein in orbital adipose/connective tissues from patients with GO, while TSHr expression was not apparent in normal orbital tissues. In addition, she showed that orbital preadipocyte fibroblasts, cells lacking functional TSHr, can be differentiated in vitro into mature TSHr-bearing adipocytes. These and other findings led to hypothesize that: 1) expression of TSHr in the orbit in GO is linked to the induction of adipogenesis in orbital preadipocyte fibroblasts, and that; 2) the adipocyte TSHr is the orbital autoantigen recognized by orbital-infiltrating lymphocytes in GO. The PI plans to examine these hypotheses using our system of cultured orbital preadipocyte fibroblasts derived from patients with GO. In specific aim I, she will define the fibroblast-like cells present in the orbit in GO and identify factors that modulate adipogenesis in these cells. Experiments in Aim II are designed to characterize the orbital TSHr and to clarify the link between TSHr expression and adipogenesis in the orbit. In Aim III, she will determine whether cloned orbital-infiltrating lymphocytes from patients with GO recognize TSHr, or other antigens that are processed "naturally" by autologous antigen-presenting cells. The main goal of the research program is to increase understanding of the orbital immune response in GO in order that novel and more specific therapeutic and preventive strategies for this condition might be developed.
  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: FUNCTIONAL RESPONSES OF EXTRAOCULAR EYE MUSCLES TO T3**
  Principal Investigator & Institution: Rubinstein, Neal A.; Associate Professor; Anatomy; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104
  Timing: Fiscal Year 2002; Project Start 01-DEC-1997; Project End 31-MAR-2003
  Summary: Thyroid dysfunction affects some 10 million Americans; and although the extraocular muscles (EOMs) are often involved in thyroid disease, little is known about the effects of T3 on the properties or development of EOM fibers. The effects of dysthyroidisms on the function of appendicular muscle fibers suggest that altered T3 levels should have profound influences on the performance of EOM fibers; however, there unique developmental origin, structural and functional properties and singular
Hyperthyroidism

reactions to diseases suggest that EOMs have unique rules governing gene expression. T3 regulates the contractile properties of muscle fibers by differentially activating or repressing isoforms of the myosin heavy chains (MyHCs). The transcriptional control is mediated by the thyroid receptors (TRs) and the retinoid X receptors (RXRs) which themselves exist as multiple isoforms. Preliminary data, as well as susceptibilities to disease, suggest that the response of genes to T3 in EOMs will differ from that in other muscles. We hypothesize this differential response will be related to unusual distributions of TR and RXR isoforms among fibers; altered T3 levels will lead to the expression of inappropriate MyHC isoforms, abnormal contractile characteristics and impaired vision. Proving this hypothesis requires (a) determining which MyHC genes are expressed in each EOM fiber type during development and in the adult, (b) correlating the MyHC complement of each fiber to the contractile properties of that fiber, (c) determining whether hypo- and hyperthyroidism after the expression of MyHC genes and contractile properties, (d) discriminating the TR and RXR isoforms synthesized in euthyroid and pathological conditions. Studies will isoform-specific cRNA probes and antibodies will be combined with contractile measurements of individual skinned EOM fibers to accomplish these aims. To understand how the eye performs its repertoire of motions under both normal and pathological circumstances, one must understand the synthetic capacity of each fiber and how it defines the functional properties of each fiber.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: GENETIC BASIS OF ATRIAL FIBRILLATION**
  Principal Investigator & Institution: Ellinor, Patrick T.; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114
  Timing: Fiscal Year 2003; Project Start 15-JAN-2003; Project End 30-NOV-2007
  Summary: (provided by the applicant): The candidate has a basic science background in cellular physiology and has recently completed medical residency, cardiology and electrophysiology fellowship training. He is currently a clinical research fellow and will join the staff of the Cardiology Division at Massachusetts General Hospital in July 2002. The candidate seeks to obtain formal training in clinical research methods while developing a research program to elucidate the molecular basis of atrial fibrillation. Atrial fibrillation is the most common significant arrhythmia, affecting over 2 million Americans. Although rare in youth, the prevalence of atrial fibrillation increases with age and afflicts one in ten individuals over eighty. Atrial fibrillation presents a considerable socioeconomic burden, associated with chronic medication use, nearly one fourth of all strokes in the elderly, and a reduced life expectancy in affected individuals. Most atrial fibrillation is considered secondary to other conditions such as hyperthyroidism, hypertension, cardiomyopathy or valvular disorder; however, a substantial minority of patients without obvious cause are said to have "lone" atrial fibrillation. The clinical heterogeneity of atrial fibrillation has restricted previous attempts to define the genetic etiology of this disorder. We therefore propose use of a complementary strategy of individuals and families to further define the clinical phenotypes, the genetic epidemiology, and the genetic basis of this disorder. Of patients with atrial fibrillation, we hypothesize that individuals with lone atrial fibrillation are the most likely to have a genetic component to their condition. We propose to prospectively study these individuals and their first-degree relatives in order to formally define the genetic architecture of atrial fibrillation while identifying larger kindreds suitable for positional cloning approaches. With this approach, we have characterized over one hundred probands with lone atrial fibrillation and identified
multiple extended families with inherited atrial fibrillation. Further efforts to identify the causal genes are underway. Identification of these genes will permit definition of the molecular pathways that contribute to atrial fibrillation, while the availability of the probands will enable longitudinal studies using genotypes to predict outcomes and enable detailed evaluation of gene-gene and gene-drug interactions. The ultimate goal of these complementary strategies is to lead to novel therapeutic strategies for the prevention and treatment of this common and morbid condition.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HORMONAL REGULATION OF FATTY ACID OXIDATION**
  Principal Investigator & Institution: Park, Edwards A.; University of Tennessee Health Sci Ctr Health Science Center Memphis, Tn 38163
  Timing: Fiscal Year 2003; Project Start 01-MAY-2003; Project End 30-APR-2007
  Summary: (provided by applicant): The metabolism of long chain fatty acids is profoundly altered in diabetes and hyperthyroidism. Carnitine palmitoyltransferase I (CPT-I) regulates the entry of long chain fatty acids into mitochondria and is a rate controlling step in the pathway of fatty acid oxidation. We have examined both the "liver" (CPT-Ialpha) and "muscle" (CPT-Ibeta) isoforms of CPT-I in the liver and heart respectively. Studies from our laboratory have demonstrated that CPT-Ialpha activity and gene expression are elevated in diabetes and hyperthyroidism. Our overall goal is to understand the mechanisms by which the expression of CPT-I gene isoforms and mitochondrial fatty acid oxidation are stimulated in these states. The peroxisomal proliferator activated receptor gamma coactivator-1 (PGC-1) is a transcriptional coactivator that promotes mitochondrial biogenesis. PGC-1 is expressed in metabolically active tissues such as the heart and liver. We propose to investigate the role of PGC-1 in the induction of CPT-I genes. Recently we have discovered that PGC-1 enhances CPT-Ialpha gene expression. In the liver, the abundance of PGC-1 is increased in diabetes and by thyroid hormone (T3). In these studies, we will investigate the role of PGC-1 in regulating fatty acid oxidation and define the mechanisms through which PGC-1 stimulates CPT-Ialpha gene expression. T3 is a key regulator of lipid metabolism. We have identified a thyroid hormone response element in the CPT-Ialpha promoter and discovered that elements within the first intron are crucial for liver specific induction by T3. We will define the unique role of the first intron in the T3 induction of CPT-Ialpha gene expression. Fatty acids are a primary source of energy for cardiac myocytes, and fatty acid oxidation is increased at the expense of glucose utilization in the diabetic heart. PGC-1 stimulates CPT-Ibeta gene expression. We will examine the mechanisms by which PGC-1 stimulates CPT-Ibeta gene expression in the heart. Disorders of lipid and glucose metabolism contribute to a number of clinical complications observed in diabetes and altered thyroid states. This proposal will examine novel molecular mechanism underlying alterations in the gene expression of critical enzymes in the mitochondrial pathway of beta-oxidation.
  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IDENTIFYING GENES LINKED TO AUTOIMMUNE THYROID DISEASES**
  Principal Investigator & Institution: Tomer, Yaron; Medicine; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029
  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 30-JUN-2007
Summary: (provided by applicant) The autoimmune thyroid diseases (AITD) are very common with a prevalence of - 5 percent. They include Hashimoto's thyroiditis (HT), which manifests by hypothyroidism, and Graves disease (GD), which causes hyperthyroidism. The mechanisms initiating the AITD are not completely understood. Abundant data point to a genetic susceptibility to AITD, and the applicant, has identified linkages for several AITD susceptibility loci. In the past four years we have performed genome scans on two data sets of multiplex families (102 families, 540 individuals), and mapped 8 loci showing evidence for linkage with AITD. In two of the loci we identified and investigated putative AITD susceptibility genes (CTLA-4 and CD40). The focus of the current proposal is four of the eight loci which showed the strongest evidence for linkage with AITD. The goals of our study are to identify and characterize the AITD susceptibility genes in these four loci. The specific aims of the proposed study are: 1) To resolve the genetic heterogeneity in our families at the 4 linked loci which are the focus of our studies. At all 4 loci the linkage analysis showed evidence of heterogeneity and resolving it will facilitate identification of the AITD susceptibility genes. We will subdivide the families according to various parameters (e.g. age of onset of disease), analyze these subsets separately for linkage with the four loci, and apply the Predivided-Sample Test. Resolving heterogeneity and identifying subsets of families that are uniformly linked with these loci will amplify the power of the subsequent single nucleotide polymorphism (SNP) and fine mapping analyses (Specific Aims 2 & 3); 2) To analyze two important genes (thyroglobulin and TGF-Beta3 which are located at 2 of the linked loci, and are themselves linked and associated with AITD. We will analyze the sequences of the thyroglobulin and TGF-Beta3 genes in order to identify disease-specific SNP's; 3) To fine map two additional linked loci and narrow the linked regions in order to determine appropriate candidate genes for future analyses. We have the capacity and experience to perform these studies. Our flexible relational database (IngresTM) facilitates complex linkage and association analyses. We use two ABI-310 sequencers for genotyping and sequencing, and we have experience at SNPing genes and fine mapping linked regions. We expect that these studies will lead to the identification of gene sequence variations contributing to the expression of AITD. This will allow us to understand the mechanisms initiating these diseases, and hopefully will lead to the development of new therapies targeted at the mechanisms initiating AITD.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

• Project Title: IMPACT OF HYPERTHYROIDISM ON SKELETON, MUSCLE STRUCTURE AND FUNCTION

Principal Investigator & Institution: Brennan, Michael; Mayo Clinic Rochester 200 1St St Sw Rochester, Mn 55905

Timing: Fiscal Year 2001

Summary: Clinically apparent muscle weakness and wasting occur commonly in hyperthyroidism. In order to assess the independent contributions to skeletal muscle weakness of both muscle wasting and qualitative changes in muscle contraction, we studied muscle strength and volume in a cohort of hyperthyroid patients. Data regarding the response of these parameters to normalization of serum thyroid hormone levels is currently available in 10 female patients (median age 39 yrs; range 17-92 yrs). Initial measurements were performed prior to treatment of hyperthyroidism. Repeat measurements were made within 6-9 months of the patients achieving a euthyroid state. Muscle strength was determined by Cybex II dynamometric assessment of knee flexion and extension. Lower extremity total muscle volume was measured by dual photon x-
ray absorptiometry (Lunar DPX-L) and mid-thigh muscle cross sectional area was quantitated by computerized axial tomography. Treatment of hyperthyroidism and restoration of a euthyroid state resulted in mean increases of 10% in thigh muscle cross sectional area (range 1-32%) and 12% in total lower extremity muscle volume (range 1-31%). Mean thigh muscle strength increased by 57% (range 5-197%). Mean muscle efficiency, defined as the force of muscle contraction per unit of muscle volume (Nm/cm²) is increased by 48% (range 4-183%). This finding suggests that qualitative changes in the force of contraction result in decreased muscle efficiency. Responsible mechanisms remain to be fully elucidated.

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- **Project Title: INTACT AND SCID MOUSE MODELS FOR GRAVES' DISEASE**
  Principal Investigator & Institution: Davies, Terry F.; Professor; Medicine; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029
  Timing: Fiscal Year 2001; Project Start 01-JAN-1993; Project End 31-AUG-2003
  Summary: (Adapted from the applicant's abstract) This is a competing renewal application, seeking support to continue work with models of murine Graves' disease. Two murine models will be explored: 1) A homologous TSHR immunization model. This version of the Shimojo model uses, instead of immunization with hTSHR-transfected fibroblasts, a homologous system of cell surface-expressed mouse TSHR. 2) A transgenic approach to a Graves' disease model. This model involves the scid/scid transgenic mouse expressing human rather than murine TSHR antigen. These scid-hTSHR mice will be injected with intrathyroidal lymphocytes and engrafted with thyroid tissue from patients with Graves' disease, allowing the human TSHR-Abs to interact with the transgenic human TSHR and induce thyroid overactivity. The applicant believes that the development of both an intact mouse model for Graves' disease as well as the reproduction of the human disease in scid mice will allow a series of interventional procedures to be developed to further the understanding of autoimmune thyroid disease and will provide potential therapeutic approaches to human ATD.
  Website: http://crisp.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MECHANISM OF ACTION OF THYROID HORMONE RECEPTORS**
  Principal Investigator & Institution: Koenig, Ronald J.; Professor; Internal Medicine; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274
  Timing: Fiscal Year 2001; Project Start 01-JUL-1991; Project End 30-JUN-2004
  Summary: The overall goal is to increase our understanding of how thyroid hormone (T3) regulates gene expression. T3 binds to receptors (TRs), which bind to T3 response elements (TREs) in specific target genes. TREs generally consist of two (or more) binding sites (half sites) arranged as a direct repeat, inverted repeat, or everted repeat. TRs can bind to TREs as homodimers or as heterodimers with retinoid X receptors (RXRs); the relative biological importance of each of these dimer forms is uncertain. TRs regulate transcription via two domains, AF-1 and AF-2. The function of AF-1 is poorly understood. AF-2 functions by interacting with other proteins, generally known as coactivators and corepressors. T3 alters the conformation of the TR, thereby affecting which proteins interact with this receptor. Our data suggest that certain genes are regulated by TR homodimers and others by RXR-TR heterodimers, and that this is determined by the sequence of the TRE. In addition, our data suggest that TR
homodimers and RXR-TR heterodimers have different coactivator requirements, and that half site orientation further influences coactivator requirements. These issues will be studied in yeast and in mammalian cells. Yeast are uniquely valuable because they lack the above proteins. Hence, TR, RXR, and various coactivators can be added back in defined ways to determine their effects on gene expression. Additionally, yeast are amenable to genetic manipulations that are essentially impossible in mammalian cells. However, confirmation of the findings in yeast must be made in mammalian cells, to demonstrate biological relevance. Three specific aims will be addressed: 1) Assess the mechanism of coactivator-independent (AF-1) TR function in yeast; 2) Assess the role of TRE structure and homodimers versus heterodimers in defining coactivator requirements in yeast; 3) Determine whether the key findings in the above aims apply to mammalian cells. The results should further our understanding of how T3 affects a broad range of metabolic processes in health and disease states such as hyperthyroidism and hypothyroidism.

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- **Project Title: MENTORED PATIENT-ORIENTED RESEARCH CAREER DEVELOPMENT AW**

  Principal Investigator & Institution: Liu, Zhenqi M.D.; Medicine; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2001; Project Start 01-AUG-2000; Project End 31-JUL-2005

  Summary: (Adapted from the applicant's abstract): Many disease states, including glucocorticoid excess and hyperthyroidism, are associated with accelerated protein catabolism, causing chronic muscle wasting and increasing morbidity and mortality. The exact cellular mechanisms responsible remain elusive. One of the possible mechanisms is glucocorticoid- or thyroid hormone-induced resistance to the anabolic agents in skeletal muscle. Insulin, branched chain amino acids (BCAA), balanced amino acid (AA) mixtures and insulin-like growth factor 1 (IGF-1) all have been demonstrated to retard proteolysis and/or enhance protein synthesis. The investigators propose to study the muscle's response to these four anabolic agents in the setting of acute and chronic glucocorticoid and thyroid hormone excess. The studies will be conducted in healthy human subjects with or without dexamethasone or triiodothyronine ingestion and patients with Cushing's syndrome or hyperthyroidism by examining: a) protein turnover in forearm muscle; b) the phosphorylation status of two key regulatory proteins involved in signaling mRNA translation (PHAS-I and p70 S6 kinase); and c) the activity, protein content and expression of several components in the ubiquitin-proteasome proteolytic pathway. The results should help to define the mechanisms of accelerated proteolysis associated with glucocorticoid or thyroid hormone excess. They will define: l) whether insulin, BCAA, AA mixtures and IGF-1 increase protein synthesis by stimulating phosphorylation of two key regulatory proteins involved in the protein translation initiation (PHAS-I and p70 S6 kinase); 2) whether insulin, BCAA, AA mixtures and IGF-1 retard proteolysis via blocking the ubiquitin-proteasome proteolytic pathway; and 3) whether glucocorticoid or thyroid hormone excess activates the ubiquitin-proteasome pathway and antagonizes the anabolic actions of insulin, BCAA, AA mixtures and IGF-1. By understanding the cellular mechanisms underlying the accelerated muscle catabolism and the actions of four anabolic agents in muscle, it may be possible to correct the protein wasting and to decrease the associated morbidity and mortality.

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