DILATED CARDIOMYOPATHY

A MEDICAL DICTIONARY, BIBLIOGRAPHY,
AND ANNOTATED RESEARCH GUIDE TO
INTERNET REFERENCES

JAMES N. PARKER, M.D.
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FORWARD

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."[1] 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 dilated cardiomyopathy 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 dilated cardiomyopathy, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to dilated cardiomyopathy, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on dilated cardiomyopathy. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to dilated cardiomyopathy, these are noted in the text.**

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 dilated cardiomyopathy.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/cancerinfo/ten-things-to-know**.

CHAPTER 1. STUDIES ON DILATED CARDIOMYOPATHY

Overview

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

Federally Funded Research on Dilated Cardiomyopathy

The U.S. Government supports a variety of research studies relating to dilated cardiomyopathy. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[2] 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 dilated cardiomyopathy.

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 dilated cardiomyopathy. The following is typical of the type of information found when searching the CRISP database for dilated cardiomyopathy:

- **Project Title: 4-DIMENSIONAL LV TISSUE TRACKING IN CAD FROM TAGGED MRI**

  Principal Investigator & Institution: Amini, Amir A.; Associate Professor; Barnes-Jewish Hospital Ms 90-94-212 St. Louis, Mo 63110

  Timing: Fiscal Year 2002; Project Start 01-AUG-2000; Project End 31-JUL-2003

[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).

Summary: (Adapted from Applicant's Abstract): The applicants propose to develop and validate new image analysis methods aimed at a more accurate, reproducible, and automated approach to assessment of regional left ventricular (LV) function and visualization of 3D cardiac motion from tagged MRI data of patients with coronary artery disease (CAD). The applicants have developed a number of methods for analysis of tagged MRI data which have been validated in phantoms and animal models of myocardial infarction (MI). They propose to continue development of these techniques which utilize all of the available stripe information, including tag intersections and linear tag lines, in automatically taking LV deformations and reconstructing dense displacements at all myocardial points, with the goal of routinely applying these techniques to patient data. The advantage of the developed methods is that since displacement vectors will be available at all myocardial points, indices of LV function will also be available everywhere in the myocardium. These indices can be summed over local myocardial regions resulting in segmental function scores. In human studies, the developed methods will be applied to images acquired from normal volunteers, patients with pharmacologic stress-induced myocardial ischemia, patients with old, healed MI, and patients with ischemic **dilated cardiomyopathy.** In each case, segmental wall motion as assessed by the algorithms will be compared and correlated with validated clinical techniques such as 2D echocardiography, cine-MRI, and Gadolinium (Gd) contrast MRI. Thus, the specific aims are: (a) To measure statistical distribution (mean and standard deviation) of segmental function scores from 3D + t (short-axis and long-axis) tagged MRI at rest and under pharmacologic (dobutamine) stress in normal controls. (b) To measure the function scores as determined from 2D + t (short-axis) tagged MRI during pharmacologic stress and classified into normal, hypokinetic, or akinetic classes in patients with stress-induced ischemia. These labels will then be statistically correlated to labels assigned to the same segments by 2D echocardiography and cine-NIRI. (c) To measure segmental function scores as determined from 3D + t (short-axis and long-axis) tagged NIRI at rest and classified into normal, hypokinetic, akinetic, or dyskinetic classes in patients with an old, healed MI. The labels will be statistically compared to non-nal or akinetic labels assigned to the same segment from 2D echocardiography and cine-MRI, and with Gd contrast MRI. (d) To measure the segmental function scores from 3D + t (short-axis and long-axis) tagged MRI at rest and classified into normal, hypokinetic, akinetic, or dyskinetic classes in patients with ischemic, **dilated cardiomyopathy.** The labels will be statistically compared to labels assigned to the same segment from 2D echocardiography and cine-MRI.

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

- **Project Title: ADRIAMYCIN-INDUCED MITOCHONDRIAL CARDIOMYOPATHY**

  Principal Investigator & Institution: Wallace, Kendall B.; Professor; Biochem/Mole Biol/Biophysics; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2002; Project Start 15-SEP-1997; Project End 31-MAR-2005

  Summary: (Adapted from the Applicant's Abstract): Adriamycin (doxorubicin) is a potent, broad-spectrum antineoplastic agent effective in treating a variety of cancers including both solid tumors and leukemias. However, the clinical value of this drug is limited by the development of a cumulative and irreversible **dilated cardiomyopathy** that is manifested as a progressive loss of ventricular performance in patients receiving repeated doses of the drug. Adriamycin cardiotoxicity is also characterized by a dose dependent decline in mitochondrial oxidative phosphorylation and a decrease in high-energy phosphate pools. Our hypothesis is that this results from a cumulative and

irreversible modification of regulatory factors affecting the membrane permeability transition (MPT) pore by adriamycin. The enhanced sensitivity to induction of the MPT leads to a futile, energy-depleting cycling of calcium across the mitochondrial membrane, which we suggest accounts for the dose-dependent loss of respiratory efficiency and ATP synthesis in cardiac tissue from adriamycin-treated rats. We further suggest that these mitochondrial changes contribute to the progressive inability of cardiac tissue to tolerate metabolic stress, particularly those associated with induction of the MPT such as ischemia and reperfusion. Another critical element to this adriamycin-induced mitochondrial cardiomyopathy is its irreversibility, which constitutes a very serous problem clinically in treating cases of pediatric or recurrent neoplasias. The fact that the effect of adriamycin on mitochondrial bioenergetics outlasts the persistence of drug residues in tissues suggests that adriamycin, at sufficient doses, initiates an irrevocable sequence of events that continue beyond elimination of drug. Our hypothesis is that adriamycin interacts with mitochondrial membranes to initiate a series of reactions that lead to increased rates of free radical generation. Furthermore, we suggest that this is a self-perpetuating process that increases in magnitude despite the termination of drug treatment and elimination of drug residues from the tissues. Careful and rigorous testing of these jointly related hypotheses will provide valuable insight into the pathogenesis of adriamycin cardiomyopathy and is essential to the development of mechanism-based therapeutic strategies to minimize the dose-limiting effects of this clinically important anticancer chemotherapy.

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

- **Project Title: AGING, INSULIN RESISTANCE, AND DILATED CARDIOMYOPATHY**

  Principal Investigator & Institution: Shannon, Richard P.; Professor of Medicine; Allegheny-Singer Research Institute 320 E North Ave Pittsburgh, Pa 15212

  Timing: Fiscal Year 2004; Project Start 15-JAN-2004; Project End 31-DEC-2008

  Summary: (provided by applicant): Congestive heart failure is a leading cause of morbidity and mortality in the elderly, although the mechanisms to explain the enhanced proclivity are poorly understood. It remains debatable as to whether the age-associated propensity to cardiovascular dysfunction is attributable to aging per se or the accumulation of cardiovascular risk factors that accrue over time. In particular, aging has been closely associated with the development of increased visceral adiposity that has been implicated in the pathogenesis of age associated insulin resistance. Whether age associated insulin resistance contributes to the progression of cardiac dysfunction following myocardial injury has not been explored systematically. The altered cellular actions of insulin that underlie physiological insulin resistance may have significant consequences to the failing heart. The injured myocardium develops an evolving dependence on glucose as its preferred metabolic substrate. The preference is dependent upon the efficiencies of oxidation of glucose in the generation of high-energy phosphates. This preference becomes a requirement as the ability to oxidized fat acids is limited through a series of molecular switches in key regulatory components of fatty acid transport and oxidation. We have determined that advanced, decompensated stages of **dilated cardiomyopathy** are associated with the development of myocardial insulin resistance, which limits myocardial glucose uptake and oxidation. These physiological features are associated with cellular insulin signaling abnormalities in the myocardium that are distinct from those observed in skeletal muscle and adipose tissue in other insulin resistant states. Together, aging and heart failure share the common pathophysiological features of insulin resistance. Whether the effects are additive or

synergistic in explaining the increased incidence and severity of heart failure in the elderly remains to be determined. We will determine if aging is associated with accelerated progression of heart failure in conscious dogs with pacing induced **dilated cardiomyopathy.** We will define the physiological and cellular effects of insulin resistance in the senescent myocardium during the evolution of **dilated cardiomyopathy.** Finally, we will determine if overcoming myocardial insulin resistance in the aging and failing heart will prevent the progression of **dilated cardiomyopathy.**

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

- **Project Title: AKT ACTIVATION AS TREATMENT FOR DILATED CARDIOMYOPATHY**

  Principal Investigator & Institution: Sussman, Mark A.; Professor; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 452293039

  Timing: Fiscal Year 2002; Project Start 01-JUN-2001; Project End 31-MAY-2005

  Summary: (the applicant's description verbatim): Primary degenerative changes in the failing heart include remodeling associated with loss of structural organization and cardiomyocyte apoptosis. Optimal treatment strategies must approach the long term goal of a molecular approach that promotes myocardial integrity and inhibits apoptosis to prevent ventricular dilation. Myocardial pathogenesis is inhibited by activation of Akt kinase, although the potential therapeutic effect of Akt activation has never been examined in the context of **dilated cardiomyopathy.** Recent results have demonstrated nuclear translocation of activated Akt correlates with prevention of dilation in mouse transgenic models of cardiomyopathy. The hypothesis of this proposal is that nuclear translocation of activated Akt inhibits the initiation and progression of dilation and heart failure. Insulin-like growth factor-1 (IGF-1) or the cellular oncogene Tcl-1 initiate nuclear translocation of Akt. In addition, we have discovered similar Akt activation by genistein, a phytoestrogen compound found in soy-based dietary products that exhibits estrogen agonist properties. Innovative approaches to be used involve mice that are genetically engineered or pharmacologically treated to activate Akt, with concurrent experiments to demonstrate beneficial effects of Akt activation in rescuing a transgenic mouse model of **dilated cardiomyopathy.** The specific aims are: 1) to reproducibly and precisely induce Akt activation by IGF-1, genistein treatment, and Tcl-l expression; 2) to prevent pathologic and degenerative changes by activation of Akt; 3) to show that beneficial effects of Akt activation are dependent upon induction of phosphoinositide 3-kinase. Biochemical, molecular, and confocal microscopic approaches used in combination will demonstrate the efficacy of Akt activation by the various inductive stimuli as well as the impact of the different treatments upon the pathogenesis of dilation. The significance of the study is the identification and characterization of a therapeutic pathway for treatment of heart failure, along with new approaches for the activation of Akt in the heart. This study will demonstrate the relationship between Akt activation and inhibition of cardiomyopathy, providing novel directions for therapeutic treatment to induce Akt translocation and mitigate heart failure.

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

- **Project Title: BETA-ADRENERGIC RESPONSE IN CARDIAC HYPERTROPHY/FAILURE**

  Principal Investigator & Institution: Bond, Meredith; Professor and Chair; Cleveland Clinic Foundation 9500 Euclid Ave Cleveland, Oh 44195

  Timing: Fiscal Year 2002; Project Start 01-JAN-1997; Project End 31-MAY-2005

Summary: (provided by applicant): Alterations in the signal transduction pathways which regulate Ca2+ dependent force in the heart contribute to the impaired contractile function in heart failure. These functional changes are likely to be mediated by altered phosphorylation of cAMP-dependent protein kinase (PKA) and protein kinase C (PKC) substrates. One of the major PKA/PKC substrates in the cardiac muscle cell is the thin filament regulatory protein, troponin I (TnI). As a result of conformational changes in the TnI molecular upon phosphorylation of the different PKA and PKC sites TnI, interactions between TnI with other proteins of the thin filament - and thus contractile function - are altered. In other words, TnI and its phosphorylation fingerprint represent a critical control point in the pathway regulating contractile state as a function of the incominb Ca2+ signal. We have shown that PKA phosphorylation of TnI is decreased by 25% in human heart failure. This results in increased Ca2+ affinity of troponin C (TnC), and may contribute to enhanced myofilament Ca2+ sensitivity, and prolonged relaxation of failing hearts. In contrast, PKC is reportedly increased in failing hearts; increased PKC phosphorylation of one or more sites on TnI decreases maximal actomyosin (AM) ATPase activity and thus could also contribute to impaired contraction in heart failure. However, reports on the effect of elevated PKC activity on TnI phosphorylation and cardiac function are conflicting. Finally, activity of protein phosphatases - protein phosphatase 1 (PP1) and/or PP2A - will also determine the phosphorylation state of TnI. In Specific Aim 1, we will identify the complete phosphorylation profile of TnI in failing human hearts with dilated cardiomopathy (DCM) and compare this with non-failing hearts. Electrospray ionization mass spectrometry (ESI/MS) will be used to quantify stoichiometry of the phosphorylated residues in tryptic digests of TnI obtained from failing and non-failing hearts, by a rapid one-step isolation to trop the in vivo phosphorylation state. In Specific Aim 2, we will (a) examine conformational changes that result from the combined changes of PKC and PKA phosphorylation of TnI in failing vs non-failing hearts. This will be achieved by measurement of fluorescence quenching tryptophan residues in cTnI, with selected serines and threonine mutated to aspartates or alanines, then reconstituted with human cardiac TnT and TnC. (b) The functional consequences of altered TnI phosphorylation will be assessed by measurement of Ca2+ dependent force in skinned cardiac trabeculae from failing and non-failing hearts. Specific Aim 3 will test the hypothesis that activity of TnI targeted phosphatases is altered in failing hearts. These studies should provide new information on the complete complement of changes in PKA and PKC-dependent TnI phosphorylation in human heart failure. Structural and functional outcomes of these changes plus identification of the altered phosphatase activity will shed light on mechanisms responsible for the functional decline in heart failure.

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

- **Project Title: CALCIUM CYCLING AND REGULATION OF THE CARDIAC AP**

  Principal Investigator & Institution: Winslow, Raimond L.; Professor; Biomedical Engineering; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 01-MAY-1998; Project End 31-MAR-2006

  Summary: Dilated cardiomyopathy (DCM) is the most common form of primary cardiac muscle disease, with prevalence estimated at 36.5 cases per 100,000. DCM is characterized by ventricular dilation, decreased myocardial contractility and cardiac output, and increased risk of sudden cardiac death. Ventricular myocytes isolated from failing hearts exhibit changes in expression levels of proteins involved in repolarization of the action potential (AP) and intracellular calcium (Ca2+) cycling. These changes are accompanied by reduction of junctional sarcoplasmic reticulum (JSR) Ca2+

concentration, peak intracellular Ca2+ transient amplitude, slowed diastolic Ca2+ extrusion and prolongation of AP duration. We have previously formulated a "minimal" computational model of the failing canine ventricular myocyte that incorporates experimental data on down-regulation of potassium (K+) currents and the SR Ca2+-ATPase, and up-regulation of the Na+-Ca2+ exchanger. This model is able to qualitatively reconstruct changes in AP and Ca2+ transient morphology observed in failing myocytes. Model simulations predict that down- regulation of the SR Ca2+-ATPase by itself produces significant prolongation of AP duration by reducing JSR Ca2+ level, JSR Ca2+ release and the magnitude of Ca2+-dependent inactivation of L-type Ca2+ current (ICa,L). This decreased Ca2+-dependent inactivation increases ICa,L during the plateau phase, thereby increasing AP duration. These model predictions are supported by results of preliminary experiments. This has led us to hypothesize that JSR Ca2+ level through effects on JSR Ca2+ release and Ca2+-dependent inactivation of ICa.L, modulates AP duration, and that this modulation is important under a range of conditions producing changes in JSR Ca2+ level, including heart failure. The general goal of the proposed research is to test this hypothesis by means of experiments coupled with computational modeling.

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

- **Project Title: CARDIAC KATP CHANNELS IN HEALTH AND DISEASE**

  Principal Investigator & Institution: Terzic, Andre; Professor of Medicine and Pharmacology; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2004; Project Start 01-APR-2000; Project End 31-MAR-2008

  Summary: (provided by applicant): Cardiac ATP-sensitive K+ (KATP) channels, formed by the pore-forming Kir6.2 and regulatory SUR2A subunits, are characterized by nucleotide-dependent regulation that allows the channel complex to adjust membrane excitability in response to changes in the cellular energetic state. However, it is unknown how cardiac KATP channels translate nucleotide signals into pore gating, what is the full impact of channel activity on cardiac homeostasis, and ultimately whether channel defects contribute to heart disease. In the previous funding period of this proposal we identified an ATPase activity intrinsic to the SUR2A subunit, demonstrated that deficient KATP channel function reduces cardiac tolerance to adrenergic challenge, and discovered KATP channel mutations in initial screening of patients with heart failure. Based on these findings, we here put forward the novel concept that cardiac KATP channels operate as a bi-functional channel/enzyme molecular combination serving a vital role under diverse stressors. Aim #1 will define the molecular mechanisms governing the SUR2A catalysis-based nucleotide gating of the Kir6.2 pore. Aim #2 will establish the impact of KATP channels on prevention of maladaptive structural remodeling, and preservation of energetic and electrical stability in the physiologically and pathologically stressed myocardium. Aim #3 will determine the spectrum of cardiac KATP channel mutations in patients with idiopathic **dilated cardiomyopathy,** and define the consequences of these mutations on the KATP channel/enzyme phenotype, metabolic sensing and cell adaptation to stress. To this end, we will employ murine knockout and disease models, along with genomic specimens from an existing cohort of patients with cardiomyopathy. The complementary technologies of enzymology, electrophysiology, physiological genomics, high-throughput DNA screening and functional proteomic analysis will be applied to study the cardiac KATP channel at the organism, organ, cellular and molecular levels.

Thus, this proposal will provide an integrated understanding of cardiac KATP channels in metabolic signal decoding, stress adaptation, and their impact for clinical medicine.

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

- **Project Title: CARDIOMYOPATHY IN AIDS**

  Principal Investigator & Institution: Lewis, William; Professor; Pathology; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2001; Project Start 30-SEP-1997; Project End 31-AUG-2005

  Summary: (Adapted from applicant's abstract) This project elucidates mechanisms of **dilated cardiomyopathy** (DCM) in AIDS. Cardiac infection with human immunodeficiency virus-1 (HIV-1), intramyocardial activity of HIV-1 proteins, and toxicity from antiretroviral agents each is postulated to cause AIDS DCM, Experiments in this proposal assess the individual impact of HIV-1 infection, HIV-1 proteins, and anti-AIDS therapeutics on the structure and function of the cardiac myocyte in AIDS DCM. Transgenic mice (TG) serve as key biological tools to explore mechanisms of AIDS DCM. Three TG strategies define 1) effects of targeted myocardial expression of HIV-1 using a replication-incompetent HIV-1 (NL4-3 gag/pol) driven by the cardiac specific alpha myosin heavy chain (alpha-MyHC) promoter; 2) effects of targeted cardiac specific expression of HIV-1 enzymes (e.t. protease) driven by the alpha-MyHC promoter; and 3) systemic events in AIDS DCM using a published TG that expresses replication defective NL4-3 gag/pol systemically. TGs treated with anti-HIV-1 chemotherapy help define structural and functional cardiovascular side effects contributing to AIDS DCM. AIMS address scientific questions about AIDS DCM: AIM 1 (PATHOLOGICAL): to define myocardial structural changes cellularly and subcellularly. Experiments localize and quantitate cardiac and HIV-1 mRNAs and proteins and cardiac mtDNA and mtRNA in TGs with AIDS DCM. Light microscopy, transmission electron microscopy (TEM), immuno-TEM and in situ hybridization localize HIV-1 gene products and pinpoint HIV-1 in cardiac myocyte subcellular compartments. AIM 2 (PHYSIOLOGICAL): to define cardiac performance in AIDS DCM. Isolated cardiac myocytes and work performing heart preparations identify changes in contractility and relaxation in TGs with AIDS DCM. Expression of cardiac Ca transporter proteins and their mRNAs is analyzed in isolated cardiac myocytes. AIM 3 (CELL/MOLECULAR BIOLOGICAL): to define cardiac mtDNA replication, mtRNA abundance, and mitochondrial polypeptide synthesis in AIDS DCM. Southern and Northern analysis respectively define mtDNA and mtRNA abundance in TG hearts. Biosynthetic labeling of polypeptides is determined in isolated mitochondria. Altered expression of mtRNA and mitochondrial proteins reflect altered energy genesis. (End of Abstract)

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

- **Project Title: CARDIOMYOPATHY IN DIABETES**

  Principal Investigator & Institution: Lewinter, Martin M.; Professor of Medicine and Molecular Phys; Medicine; University of Vermont & St Agric College 340 Waterman Building Burlington, Vt 05405

  Timing: Fiscal Year 2002; Project Start 01-JAN-1999; Project End 31-DEC-2003

  Summary: Patients with diabetes mellitus (DM) are subject to a high incidence of death and morbidity due to heart failure, especially following myocardial infarction (MI). These observations suggested and subsequent studies confirmed the presence of a diabetic cardiomyopathy (DBCM), indepenent of macrovascular CAD. In experimental

DBCM, multiple mechanial abnormalities and potential mechanisms have been documented. However, the manifestations and mechanisms of DBCM in patients are not well understood. Using strips of myocardium obtained from patients with CAD and DM (CAD/DM) undergoing coronary bypass grafting, we have recently shown depression of the force-frequency relationship (FFR despite the fact that basal ventricular function was normal. This myocardial abnormality in CAD/DM is similar but less severe than that observed in **dilated cardiomyopathy** and mitral regurgitation and is reversible by forskolin, indicating that its proximate mechanism is likely a defect(s) in excitation-contraction coupling (ECC). This proposal has three aims, to be undertaken in CAD/DM patients and CAD controls: 1) delineate whether there is an in vivo counterpart of in vitro FFR depression in CAD/DM, 2) systematically study the processes involved in ECC in CAD/DM and determine if identified defects cause FFR depression, and 3) test for correlations between abnormal FFR/ECC and markers of both the metabolic effects of DM and associated vasculopathy in order to begin to characterize upstream mechanisms of DBCM. Patients will be recruited at both the University of Vermont and the New York Hospital-Cornell Medical Center. We will employ an integrated, collaborative approach including in vivo and in vitro determination of the FFR, in vitro quantification of ECC, and assessment of defects in glycolysis and vasculopathy in DM myocardium. A major strength of our experimental strategy is correlation, on an individual patient basis, of in vitro FFR depression with other variables of interest. Our long- term plan is to define the steps linkin abnormal carbohydrate metabolism and/or vasculopathy in DM to DBCM and ultimately design rational treatments.

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

- **Project Title: CDI AND GAMMA DELTA+ IN VIRAL MYOCARDITIS**

  Principal Investigator & Institution: Huber, Sally A.; Professor; Pathology; University of Vermont & St Agric College 340 Waterman Building Burlington, Vt 05405

  Timing: Fiscal Year 2002; Project Start 01-APR-1998; Project End 30-JUN-2006

  Summary: (provided by applicant): Coxsackievirus B3 (CVB3) infection causes myocarditis and **dilated cardiomyopathy.** The pathogenic mechanisms of the disease are complex. Myocarditis susceptibility correlates with activation of T cells expressing the Vgamma4 T cell receptor (TCR), CD4+ Thi (IFNgamma+) and CD8+alphabeta TCR+ autoimmune cytolytic T cells (CTL). Myocarditis resistance correlates to activation of Vgamma1+ and CD4+Th2 (IL4+) cells, and the absence of autoimmune CD8+alphabeta TCR+ effectors. Vgamma4+ cells kill both CVB3-infected myocytes and CD4+Th2 cells in vitro, and comprise up to 50% of the inflammatory T cells in the heart. CD8+alphabeta TCR+ autoimmune CTL kill uninfected but not virus-infected myocytes, and are the second most populous inflammatory cells in myocarditis. Since both Vgamma4+ and CD8+alphabeta TCR+ cells are cytolytic to cardiac myocytes in vitro, either or both populations might contribute to cardiac injury in vivo. Vgamma4+ cells recognize CD1, a major histocompatibility complex (MHC) class I-like molecule which normally presents hydrophobic lipid or peptide antigens. The autoimmune CD8+alphabeta TCR+ cells recognize antigen presented by classical MHC class I molecules. The overall goal of this application is to define the relative contributions of Vgamma4+ and CD8+alphabeta TCR+ cells to myocarditis in vivo, and determine whether Vgamma4+ cells facilitate CD8+alphabeta TCR+ cell activation by promoting CD4+ Th1 cell responses. The Specific Aims are to: 1) determine the relative importance of Vgamma4+ cell mediated killing of myocytes or modulation of CD4+ cell phenotype and activation of CD8+alphabeta TCR+ CTL in myocarditis; 2) determine CD1d

expression in pathogenic versus non-pathogenic CVB3 infections and the role for lipid or peptide antigens in the CD1d-restricted Vgamma4+ T cell response; and 3) determine whether Vgamma4+ cells kill CD4+Th2 cells through CD1 -restricted responses.

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

- **Project Title: CHARACTERIZING RGS MUTATIONS IN CARDIOMYOPATHY**

  Principal Investigator & Institution: Kurrasch-Orbaugh, Deborah M.; Pharmacology; University of Texas Sw Med Ctr/Dallas Dallas, Tx 753909105

  Timing: Fiscal Year 2003; Project Start 01-JAN-2003; Project End 31-OCT-2003

  Summary: (provided by applicant): The hypothesis of this proposal is that the RGS 16 protein is an integral component of the G-alpha-q/11 signaling complex, serving as a feedback inhibitor of G-alpha-q/11 signaling in stressed cardiomyocytes, thus helping to maintain cardiac homeostasis. We propose that a point mutation in the RGS box of RGS16 (D179Y) found in patients with **dilated cardiomyopathy** alters the conformation of the interaction surface with G-alpha-q/11 and/or other proteins in the signaling complex, rendering RGS16 D179Y to function as a dominant negative protein, ultimately contributing to **dilated cardiomyopathy.** To test this hypothesis, we shall explore the following specific aims: Aim 1. We shall examine the GAP and potential dominant negative activity of D179Y and wild type RGS16 proteins in several in vitro assays, including single-turnover assays, transition-state analog binding assays, and G-alpha-q -Coupled steady state assays, and G-alpha-q -coupled MAPK activation; Aim 2. We will overexpress D179Y and RGS 16 proteins specifically in cardiomyocytes by employing the alpha-MHC promoter in transgenic mice and then characterize the onset of cardiomyocytes hypertrophy; Aim 3. We will create Rgs 16 D179Y knock-in mice and characterize the onset of **dilated cardiomyopathy;** Aim 4. We will continue to screen cardiac patients and healthy individuals to identify additional Rgs mutation. The primary objective of this proposal is to evaluate the causative role of the D179Y allele of RGS16 in the progression of **dilated cardiomyopathy.**

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

- **Project Title: CORE--PILOT PROJECT COMPONENT CORE**

  Principal Investigator & Institution: Kuhajda, Melissa; University of Alabama in Tuscaloosa Tuscaloosa, Al 35487

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2007

  Summary: CORE ABSTRACT NOT PROVIDED

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

- **Project Title: CORE--PILOT PROJECT STUDY CORE**

  Principal Investigator & Institution: Payton, Benjamin F.; Tuskegee University Tuskegee Institute, Al 36088

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2007

  Summary: CORE ABSTRACT NOT PROVIDED

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

- **Project Title: CO-STIMULATORY REGULATION OF IMMUNE FUNCTION & TOLERANCE**

  Principal Investigator & Institution: Dong, Chen; Immunology; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2002; Project Start 01-DEC-2001; Project End 30-NOV-2006

  Summary: (provided by applicant): The molecular mechanisms by which the immune system discriminates self from non-self are not understood. The breakdown of these mechanisms can result in autoimmune disease. CD4+ helper T (Th) cells are key regulatory players in various forms of autoimmune disease. Th cell activation, differentiation and function are regulated by costimulatory molecules. CD28, a receptor for B7 gene products, plays a major role in initiating T cell immune responses. CTLA4, which binds B7 with a higher affinity, is induced after T cell activation and plays a role in down-regulating T cell responses. PD-1 is an inhibitory receptor for a B7 homologue, B7-Hl. Mice deficient in PD-1 develop **dilated cardiomyopathy** and lupus-like proliferative arthritis and glomerulonephritis. Inducible co-stimulator (ICOS), a third member of the CD28/CTLA4 family, is expressed on activated T cells. Its ligand, B7H, is another B7-homologue expressed on B cells and induced in nonlymphoid tissues by tumor necrosis factor (TNF). Recently, we generated and analyzed ICOS-deficient mice. ICOS is required for humoral immune responses after immunization with several antigens. ICOS-/- mice exhibited greatly enhanced susceptibility to experimental autoimmune encephalomyelitis (EAE), suggesting that ICOS plays a preventative role in inflammatory autoimmune diseases. Thus, members of the B7 costimulator family play essential roles in immune activation and function. We are particularly interested in the new members of this family that engage receptors on activated T cells and are also expressed in nonlymphoid tissues. We hypothesize that these molecules provide mechanisms by which T cell function and tolerance are regulated in the effector phase. We propose to study immune regulation by these B7 homologues. We will determine the role B7H plays in regulation of humoral immunity and autoimmunity and test if B7H expressed on B cells stimulates T-cell help for humoral immunity and autoimmunity. We will define the site and phase during EAE autoimmunity in which ICOS functions to contain inflammation, and assess if B7H expressed by inflamed tissues during the effector phase of EAE provides a protective mechanism of peripheral tolerance. B7JH is a novel member of the B7 family we discovered that is most homologous to B7-H1. B7JH is restrictedly expressed in the liver. We will determine if B7JH is a second ligand for PD-1, and construct B7JHI-deficient animals to assess its function in immune tolerance in the liver. These studies will advance our knowledge of the regulation of T-cell function and tolerance, and may lead to a greater understanding of autoimmune diseases.

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

- **Project Title: COXSACKIE MYOCARDITIS AND VIRAL PERSISTENCE IN THE HEART**

  Principal Investigator & Institution: Whitton, J Lindsay.; Professor; Scripps Research Institute Tpc7 La Jolla, Ca 92037

  Timing: Fiscal Year 2002; Project Start 01-JAN-1998; Project End 31-DEC-2002

  Summary: Coxsackieviruses, members of the picornavirus family, are important human pathogens. Coxsackievirus B3 (CVB3), is a common associated factor in human subacute, acute, and chronic myocarditis. In young adults CVB3 infections may cause cardiac arrhythmias and acute heart failure; and chronic disease may supervene, leading

to **dilated cardiomyopathy,** requiring transplantation, or to death. To better understand the pathogenesis of this disease, several mouse model systems have been established, which appear to parallel many aspects of the human disease process. We have begun to investigate the mechanisms underlying CVB myocarditis. The goals of this proposal are: 1. To further investigate the immune determinants of CVB3 myocarditis. What viral proteins do CD4+ and CD8+ T cells recognize, and how do these cells interact? Is the Fas pathway involved in disease? 2. To investigate the roles of antibodies and T cells in control of CVB3 infection and disease. Which virus proteins can protect against CVB? Is priming of CD8+ T-cell immunity beneficial or harmful? 3. To determine the cells infected during acute and persistent CVB3 infection. Does CVB interact with B cells early in infection? What other cells are infected? What cells are infected during virus persistence? 4. To begin evaluation of the nature of persistent CVB3. We have developed a system in which persistently-infected mice contain high levels of infectious virus. Does this persisting virus differ from the original? 5. To evaluate treatments for persistent CVB3 infection. Antibody- deficient humans often suffer from chronic picornavirus infections, which are frequently refractory to treatment. Our mouse model of persistence in the absence of B cells will be used for testing different treatment regimens.

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

- **Project Title: CYTOKINES AND LV RECOVERY IN RECENT ONSET CARDIOMYOPATHY**

  Principal Investigator & Institution: Mcnamara, Dennis M.; Director, Heart Failure Research Program; Medicine; University of Pittsburgh at Pittsburgh 350 Thackeray Hall Pittsburgh, Pa 15260

  Timing: Fiscal Year 2002; Project Start 01-MAY-2002; Project End 31-MAR-2007

  Summary: (provided by applicant): For patients presenting with the recent onset of primary **dilated cardiomyopathy,** the presence of myocardial inflammation may suggest a potentially self limited and reversible process, and patients with acute "myocarditis" may actually have a better probability of left ventricular recovery than those with more chronic disease. The poor sensitivity of endomyocardial biopsy has limited its clinical utility, and circulating plasma cytokines are potentially more sensitive indicators of a reversible myocardial inflammatory process. This proposal will investigate the hypothesis that the assessment of plasma cytokines in recent onset **dilated cardiomyopathy,** can help to prospectively delineate patients with greater likelihood of myocardial recovery. Specific Aim 1 will assess the correlation of baseline plasma cytokine levels (TNFa, TNF receptors, and IL-6) with echocardiographic measures of left ventricular systolic and diastolic function. The study will enroll 120 patients with recent onset idiopathic **dilated cardiomyopathy** or myocarditis with an LVEF less than or equal to 0.40. This will evaluate the hypothesis that plasma cytokines in recent onset cardiomyopathy are markers of cardiac inflammation and will correlate with more profound perturbations of myocardial function. Specific Aim 2 will evaluate the hypothesis that patients with more active myocardial inflammation (higher plasma TNFa) upon presentation, are more likely to have significant recovery of left ventricular systolic function at 12 month follow up. Echocardiographic assessment will be repeated at 6 and 12 months after entry. In addition we will evaluate the hypothesis that patients with higher plasma IL-6 levels will have a poorer event free survival during subsequent follow up. Specific Aim 3 will explore the hypothesis that polymorphisms of cytokine genes, in particular those in the TNFa and IL-6 promoters, will effect levels of their respective mediators, and will subsequently influence clinical outcomes.

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

- **Project Title: CYTOSKELETAL BASIS OF VENTRICULAR ARRHYTHMIAS**

  Principal Investigator & Institution: Vatta, Matteo; Pediatrics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2004; Project Start 01-JUL-2004; Project End 30-JUN-2006

  Summary: (provided by applicant): Sudden cardiac death accounts for more than 300,000 deaths in the United States alone. Arrhythmias due to primary structural diseases such as **dilated cardiomyopathy** (DCM) followed by other non-structural cardiac diseases, such as long QT syndrome (LQTS) and Brugada syndrome (BS) must be considered as likely causes of sudden cardiac death. Cytoskeletal proteins such as dystrophin, the major link between the sarcomere and the sarcolemma in cardiac cells, have been involved in sudden cardiac death. Other dystrophin associated proteins, such as alpha1-syntrophin, when altered, could fail to provide correct anchorage and localization for ion channels on the plasma membrane. We hypothesize that alpha1-syntrophin mutations can cause both ventricular dysfunction and arrhythmias. In particular our aims are: 1) to evaluate for genetic abnormalities in alpha1-syntrophin as causing DCM, LQTS and BS. We hypothesize that alpha1-syntrophin mutations cause DCM, LQTS and BS. Specific Aim #1: To evaluate for genetic abnormalities in alpha1-syntrophin as determinants of ventricular arrhythmias with or without structural damage. Specific Aim #2: To perform functional analysis in alpha1-syntrophin mutant models of cardiomyopathy and ventricular arrhythmias. Specific #3: To evaluate the effect of mechanical unloading on cardiac reverse remodeling in alpha1-syntrophin mutant models. We will screen alpha1-syntrophin gene for mutations in 200 DCM, LQTS and 100 BS probands. We expect to identify mutations in alpha1-syntrophin as the cause of DCM, LQTS and BS; 2) to perform functional analysis in alpha1-syntrophin mutant models of DCM, LQTS or BS. We hypothesize that alpha1-syntrophin mutations cause protein structural changes leading to cytoskeletal network disruption and ion channels displacement. Identifying cytoskeletal mecahnisms involved in malignant arrhythmias, could lead to the design of novel drugs and the employment of therapeutic means, resulting in a better patients management.

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

- **Project Title: DNA VIRUS AS VECTORS FOR CARDIOVASCULAR DISEASES**

  Principal Investigator & Institution: Wilson, James M.; Professor; Medicine; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

  Timing: Fiscal Year 2004; Project Start 15-MAY-2000; Project End 30-JUN-2009

  Summary: (provided by applicant): This competing renewal application builds on substantial progress that was made in the initial cycle of this grant in the development of gene transfer to heart and liver for treating heart disease and atherosclerosis. The structure of the grant has not changed in the renewal with includes projects by Drs. Wilson, Sweeney and Rader as well as Vector, Cell Morphology and Administrative Cores. The goals of the current cycle of this P01 have been realized resulting in 63 publications. The renewal application builds on this progress. The overall goal of the renewal grant is the development of effective gene therapy for cardiovascular disease, which can be achieved by targeting the heart and liver. An important theme in the renewal is that one needs to understand the biology and pathogenesis of the vectors systems used and the target diseases in order to realize this goal. In Project 1, Dr. Wilson will exploit their recent discovery of a new family of AAVs broadly distributed throughout non-human primate populations to create better vectors for targeting heart and liver and to learn more about the biology of natural AAV infections in the context of

the use of AAV vectors. Dr. Sweeney, in Project 2, will develop methods to target cardiac myocytes with vectors to further define the mechanisms underlying the progressive development of **dilated cardiomyopathy** and failure following myocardial infarction and the hypertrophy that develops in the setting of chronic pressure overload. In Project 3, Dr. Rader will utilize techniques of liver directed gene transfer to study and potentially treat two diseases of apoB-containing lipoproteins: familial hypercholesterolemia and abetalipoproteinemia. Vectors developed in Project 1 will be evaluated in terms of the needs of Projects 2 and 3. The Vector Core will produce and characterize materials used in all projects while the Cell Morphology Core will provide support in the in vivo analysis of gene transfer and characterization of vector preparations.

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

- **Project Title: DYNAMIC EXPRESSION PROFILING IN THE INTACT HUMAN HEART**

  Principal Investigator & Institution: Bristow, Michael R.; Professor of Medicine; Medicine; University of Colorado Hlth Sciences Ctr P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 30-JUN-2004

  Summary: (provided by applicant): The mechanisms responsible for progressive myocardial dysfunction and remodeling of the cardiomyopathic, failing human heart are unknown. In general, these pathophysiologic mechanisms are likely to involve alterations in myocardial gene expression. Numerous recent studies have demonstrated that, in order to be meaningful, gene regulation and expression must be examined in the intact heart. The overall objective of this proposal is to investigate, in human subjects with myocardial failure from a **dilated cardiomyopathy** phenotype, the utility of gene expression profiling performed longitudinally as phenotype is dynamically modulated. We propose that "dynamic expression profiling" can identify gene categories as well as specific individual novel genes whose altered expression is potentially causally related to phenotypic improvement. The proposal tests one general hypothesis supported by preliminary data: that "improvement in the **dilated cardiomyopathy** phenotype is associated with an increase in metabolic category gene expression, and a decrease in expression within cytoskeletal, extracellular matrix, signal transduction, growth factors, transcription /translation/nucleotide synthesis, and cell cycle/apoptosis gene categories." Three Specific Aims in the proposal deal respectively with identification of categories of genes, individual genes, and kinetics of gene changes associated with phenotypic improvement in idiopathic **dilated cardiomyopathy** in response to 0-blocking agents. A 4th Aim compares mRNA quantitation between the Affymetrix GeneChip method and quantitative RT-PCR, for 38 genes. We have developed techniques to measure the expression of a large number of target genes in small quantities of human ventricular myocardium that can be obtained serially from the intact heart by right ventricular (RV) endomyocardial biopsy, using Affymetrix GeneChips and quantitative RT-QPCR. We have demonstrated that RT-QPCR used in a serial, longitudinal fashion is able to identify genes whose altered expression is a potential explanation for contractile dysfunction and chamber/myocyte remodeling. We have also demonstrated the utility of expression profiling in serial, longitudinal studies where phenotype is modulated by treatment, and we provide evidence that this approach is superior to "static" expression profiling performed within the context of a cross-sectional design.

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

- **Project Title: DYSTROPHIN-GLYCOPROTEIN COMPLEX IN CARDIOMYOPATHY**

  Principal Investigator & Institution: Michele, Daniel E.; Physiology and Biophysics; University of Iowa Iowa City, Ia 52242

  Timing: Fiscal Year 2003; Project Start 01-MAY-2003; Project End 31-MAR-2004

  Summary: (provided by applicant): The long term objective of this proposal is to understand the molecular basis of inherited cardiomyopathies, particular those associated with mutations in components of the dystroglycan-glycoprotein complex. The dystroglycan-glycoprotein complex provides a link from the cytoskeleton to the extracellular matrix. Mutations in components of this complex, such as delta sarcoglycan, cause recessive forms of muscular dystrophy. Interestingly, heterozygous mutations in the same delta sarcoglycan can also cause **dilated cardiomyopathy** without muscular dystrophy. The basis for the tissue specificity of these mutations and the mechanism behind sarcoglycan associated **dilated cardiomyopathy** is unclear. Furthermore, muscular dystrophy patients with mutations in enzymes that glycosylate dystroglycan and whose activity is necessary for dystroglycan to bind extracellular ligands, also have a high prevalence of cardiomyopathy. This proposal tests the hypothesis that the link between the cytoskeleton and the extracellular matrix 'through dystroglycan, specifically in cardiac myocytes, is critical 'to the development of cardiomyopathy. The proposed research will test the dominant-negative and tissue specific effects of delta sarcoglycan mutations on the attachment of alpha-dystroglycan to the transmembrane complex using isolated muscle cell gene transfer. In addition, the tissue specific role of dystroglycan glycosylation in the link to the extracellular matrix and the development of cardiomyopathy will be tested in the myodystrophy mouse. Finally, tissue specific gene targeted mice will be generated to determine if the link from cytoskeleton to matrix through dystroglycan, is necessary and sufficient in a tissue specific manner, to cause and explain the development of DGC associated cardiomyopathy.

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

- **Project Title: EFFECT OF CARDIOMYOPATHY MUTATIONS ON MYOSIN AND ACTIN**

  Principal Investigator & Institution: Trybus, Kathleen M.; Professor; Molecular Physiol & Biophysics; University of Vermont & St Agric College 340 Waterman Building Burlington, Vt 05405

  Timing: Fiscal Year 2004; Project Start 01-JUL-2004; Project End 30-JUN-2008

  Summary: (provided by applicant): Point mutations in both the beta-cardiac myosin heavy chain and in alpha-cardiac actin lead to either familial hypertrophic cardiomyopathy (FHC) or **dilated cardiomyopathy** (DCM). To arrive at a definitive mechanism for the primary cause of these two diseases, we propose to undertake an extensive kinetic, mechanical, and structural analysis of mutated cardiac myosins and actins. Aim 1 will examine the effect of isoform backbone on function by comparing the R403Q mutation in an alpha- or a beta-murine cardiac myosin heavy chain (MHC) isoform obtained by over-expression in transgenic mice. Mutated MHCs will be HIS-tagged at the N terminus to facilitate isolation by metal chelate affinity chromatography. The mutant myosins will be characterized enzymatically by steady-state and transient kinetics, and mechanically by measurements of velocity and average force. Structural differences between wildtype and mutant myosin isoforms will be investigated by computer-based fitting of crystal structures into 3D-reconstructions of actomyosin complexes obtained by electron cryomicroscopy. Similar analyses will be extended to

point mutations leading to FHC (G741 R, R453C) and DCM (S532 and F764). For a better understanding of the functional consequences of a point mutation in human myosin, Aim 2 will analyze myosin isolated from transgenic rabbits that express a human beta-cardiac myosin (R403Q) gene. In parallel, several new strategies for expression of human beta-cardiac myosin in vitro will be explored, including use of the Drosophila S2 expression system, and the addition of chaperones to increase the yield of striated muscle myosin isoforms. Aim 3 will seek to characterize the effect of point mutations in actin that lead to FHC or DCM. alpha-cardiac actin expressed in the baculovirus/insect cell system allows us to investigate the effect of mutations in the correct backbone, rather than in the currently used yeast actin system. Alterations to actin's intrinsic filamentous structure, and to its interactions with myosin, will be assessed by many of the same approaches as described for the myosin mutations.The overall goal of the proposal is to elucidate how mutations implicated in FHC and in DCM affect the mechanical performance of myosin and actin, and to determine if any correlation can be made between the effect of the primary mutation and the ultimate disease phenotype.

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

- **Project Title: EM & TIRF ANALYSIS OF ARP2/3 COMPLEX AND ACTIN ASSEMBLY**

  Principal Investigator & Institution: Goode, Bruce L.; None; Brandeis University 415 South Street Waltham, Ma 024549110

  Timing: Fiscal Year 2004; Project Start 01-JUL-2004; Project End 30-JUN-2009

  Summary: (provided by applicant): In all eukaryotes, actin is assembled into highly dynamic thin filaments, which are organized into networks that provide polarity and force to drive different cellular processes (e.g., cell migration, cytokinesis, muscle contraction, and endocytosis). The proper regulation of actin assembly and actin cytoskeletal function is impaired in many disease states, particularly those relevant to heart, lung, and blood research. Mutations in human WASp (Wiskott Aldrich Syndrome protein), a stimulator of actin related protein (Arp) 2/3 complex-medicated actin assembly, cause defects in neutrophil cell motility and loss of immune function. In asthma, calcium levels rise in response to histamine release and induce smooth muscle contraction in respiratory tracts of the lungs. Defects in actin itself are linked directly to **dilated cardiomyopathy** and heart failure, and mutations in key actin regulators (e.g., cofilin) lead to muscle denervation and dystrophy. Thus, understanding the biochemical basis of actin assembly is an important first step in defining how these pathological processes disrupt normal function in these tissues. Studies in the budding yeast Saccharomyces cerevisiae have been instrumental in dissecting the functions of key actin regulators, because combined genetic and biochemical approaches can be used. The objectives of this research career award (RCA) are to expand the specific aims of an existing R01 (Regulation of Actin Assembly in Budding Yeast) by introducing two new microscopy tools to study the structure and mechanism of action of Arp2/3 complex. Total internal reflection fluorescence (TIRF) microscopy will be used to study actin filament polymerization and branching by Arp2/3 complex and its regulation by WASp, Abp1, and coronin in real time. Electron microscopy and single particle image analysis will be used to study the structures of mutant Arp2/3 complexes with impaired activities and in vivo defects. The funding of this proposal would significantly enhance the ability of the PI to accomplish these goals by reducing his teaching and administrative duties. The interdisciplinary nature of this research program necessitates central involvement of the PI in training of students and postdocs in techniques and

areas in which they are inexperienced. The PI will be directly involved in the integration of TIRF microscopy and single particle imaging into his research program.

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

- **Project Title: ETHANOL & AIDS CARDIOMYOPATHY--MITOCHONDRIAL CONNECTION**

  Principal Investigator & Institution: Wallace, Douglas C.; Professor; Ecology and Evolutionary Biol; University of California Irvine Irvine, Ca 926977600

  Timing: Fiscal Year 2002; Project Start 03-JUL-1999; Project End 30-JUN-2004

  Summary: Chronic ethanol (EtOH) exposure and AIDS exposure are known to cause cardiomyopathy, and to act synergistically when combined. Moreover, both ethanol and AIDS exposure have been observed to inhibit mitochondrial function, alter mitochondrial structure, and increase oxidative stress. Inhibition of mitochondrial oxidative phosphorylation reduces mitochondrial energy production and increases mitochondrial reactive oxygen species (ROS) generation, which have been linked to hypertrophic cardiomyopathy and **dilated cardiomyopathy,** respectively. Therefore, we hypothesize that both ethanol and AIDS exposure induce cardiomyopathy by reducing mitochondrial energy production through the direct disruption of OXPHOS and the indirect inhibition of OXPHOS by mitochondrial ROS. To test this hypothesis, we propose to challenge mice harboring various genetic defects in mitochondrial energy production and ROS detoxification to chronic ethanol, murine AIDS (MAIDS), and ethanol plus MAIDS exposure. The four strains will include (1) wildtype mice, (2) mice deficient (-/-) in the mitochondrial heart-muscle isoform of the adenine nucleotide translocator (ANT1), (3) mice partially deficient (+/-) in the mitochondrial Mn superoxide dismutase (MnSOD), and (4) mice deficient (-/-)in the glutathione peroxidase (GPx). The ANTI-defect reduces mitochondrial ATP availability to the heart and predisposes to hypertrophic cardiomyopathy. The MnSOD-defect increases mitochondrial ROS production and leads to **dilated cardiomyopathy.** The GPx1 -defect increases cardiac cytosolic hydrogen peroxide levels and increases the potential for viral myocarditis. Control, ethanol, MAIDS, and ethanol + MAIDS exposed mice will then be analyzed for cardiac pathology, changes in cardiac mitochondrial OXPHOS, increased cardiac oxidative damage, and alterations in the expression of mitochondrial and oxidative stress gene expression. If the ANT -/- animals develop a more severe hypertrophic cardiomyopathy and an increased predilection to **dilated cardiomyopathy** an ethanol and MAIDS exposure then this will indicate that mitochondrial energy deficiency is important in cardiomyopathy. If the MnSOD +/- animals have an increased frequency of **dilated cardiomyopathy,** then this will implicate mitochondrial ROS toxicity. If the GPx1 -/- animals have an increased incidence of myocarditis, then this will indicate that cytosolic oxidative stress is important in induced cardiomyopathy.

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

- **Project Title: FAMILIAL DILATED CARDIOMYOPATHY: DETECTION/GENE MAPPING**

  Principal Investigator & Institution: Hershberger, Ray E.; Professor of Medicine/Cardiology; Medicine; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2002; Project Start 01-MAY-1998; Project End 30-APR-2007

  Summary: Heart failure brings considerable morbidity and mortality and consumes a large quantity of health care resources, yet the underlying molecular mechanisms of

heart failure remain poorly defined. Heart failure results most commonly from **dilated cardiomyopathy,** and one common form is idiopathic **dilated cardiomyopathy** (IDC). Of patients with IDC, 20-50 percent have family members similarly affected. This condition, termed familial **dilated cardiomyopathy** (FDC), implicates a genetic cause. Indeed, for FDC with autosomal dominant inheritance, six disease genes (cardiac actin, desmin, lamin A/C, delta- sarcoglycan, beta-myosin heavy chain, and cardiac troponin T) have been implicated, and genetic linkage has identified 10 additional FDC loci. Despite this progress, it is likely that the these disease genes represent a only fraction of FDC cases, and a comprehensive understanding of the molecular mechanisms for FDC has not yet been achieved. Thus, identification of additional disease-associated FDC genes is imperative. An FDC research program was established in 1993 at Oregon Health Sciences University. We have prospectively identified and clinically characterized 50 FDC families of which five are African-American. Of the 50, 10 have 6 or more living affected members and 40 have 1-4 living, affected individuals. Several large pedigrees of adults and children have been selected for gene mapping. To date we have identified novel lamin A/C mutations in two FDC families, and a three base pair deletion in cardiac troponin T in one FDC family. The specific aims of this competitive renewal are to (1) perform clinical screening and characterization of additional pedigrees with FDC. All clinical processes to identify large FDC families and to obtain clinical cardiovascular information of both adults and children, usually through screening activities conducted by our group, are in place and have been extensively tested and optimized. Following clinical screening, subjects are categorized as affected, unaffected, unknown or indeterminate. Emphasis has been placed on the identification and characterization of FDC pedigrees and loci in African-Americans, a racial group where relatively little cardiomyopathy research has been performed despite substantial cardiac disease with worse outcomes, and no large families have been reported with FDC. We further propose to (2) map the genes responsible for FDC in several FDC pedigrees, of which linkage and additional gene mapping studies are in progress.

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

- **Project Title: FAMILIAL DILATED CARDIOMYOPATHY:GENETIC CHARACTERIZATION**

  Principal Investigator & Institution: Taylor, Matthew R.; Pediatrics; University of Colorado Hlth Sciences Ctr P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2002; Project Start 13-SEP-2002; Project End 31-AUG-2007

  Summary: (provided by applicant): The candidate for the K23 Award possesses a background in both Internal Medicine and Clinical Genetics. His primary career goal is to develop the requisite skills to successfully pursue independent clinical investigation in the area of adult genetic disorders. A thoughtfully designed career development plan encompassing formal training in clinical investigation, human genetics, computer database design, and medical ethics is outlined in this application. Complementing this aspect of the proposal is a research plan examining the genetic contributions to idiopathic **dilated cardiomyopathy** (IDC). IDC is an important and common cause of congestive heart failure. Furthermore, a substantial proportion of IDC cases (35-58%) are the result of single gene mutations; nine such genes have been linked to the disease. However, the relative contributions of each gene to the overall prevalence and phenotype of IDC are currently unknown. Such information is critical to improving the clinical diagnosis, genetic counseling, and practical management of IDC. The research proposed will elucidate the genetic epidemiology of mutations in the known relevant genes and will characterize the genotype-to-phenotype correlations that exist in both

familial and sporadic cases of IDC. The approach is founded upon an existing comprehensive database that contains clinical, pedigree, laboratory, and DNA data for over 90 families. High-throughput mutation screening for mutations in described genes will be performed on the database DNA to expose the genetic epidemiology. Skills acquired in the career development phase of the award will permit further refinement of this computer database. The mutation data will be merged with the comprehensive clinical information stored in the database to uncover relationships between genotype and clinical phenotype. The research will be performed at the University of Colorado under the mentorship of Dr. Luisa Mestroni, who is a faculty cardiologist with extensive research experience and numerous publications in this field. In addition, a diverse collection of consultants has been assembled to provide ongoing expertise that is sensitive to the needs of both the research and career development plans of the candidate.

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

- **Project Title: FUNCTIONAL PHENOTYPING OF CARDIOMYOPATHY BY MRI**

  Principal Investigator & Institution: Yu, Xin; Medicine; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2004; Project Start 05-DEC-2003; Project End 30-NOV-2008

  Summary: (provided by applicant): The focus of this proposal is to determine the role of dystrophin-glycoprotein complex (DGC) in extracellular matrix remodeling and its impact on the three-dimensional myocardial fiber structure and ventricular wall motion. Using state-of-the-art MR technology (diffusion tensor MRI and cardiac tagging), we seek to characterize changes in myocardial fiber structure due to remodeling of the extracellular matrix in cardiomyopathic hearts with defects in DGC and associated proteins, and to elucidate the impact of such structural changes on regional myocardial contractility. Histologic and immunocytochemical methods will be employed to elucidate molecular/cellular changes that underlie the macroscopic structural changes and functional alterations. Four rodent models of **dilated cardiomyopathy** (DCM), the T0-2 DCM hamster (delta-sarcoglycan-deficient), the mdx mouse (dystrophin-deficient), the mdx/utm mouse (dystrophin/utrophin double knockout), and the dy/dy mouse (laminin alpha2-deficient), will be characterized on a 4.7T research scanner. Computational modeling will be employed to directly correlate functional abnormalities to changes in cardiac structure that occur at microscopic levels in elucidating the mechanisms that are responsible for myocardial dysfunction in DCM. Our specific aims are: 1. To characterize functional and structural changes in cardiomyopathic Syrian hamster (T0-2) at distinct stages of the disease using both MRI and immunohistological methods; 2. To document longitudinal changes in myocardial structure and regional ventricular wall motion in mdx, mdx/utrn, and dy/dy mouse; 3. To use experimental data and computational models to predict myocardial wall stress and to determine passive and active material properties of normal and diseased hearts. This is a multi-disciplinary project that involves both technology development and investigation of a common cardiovascular disease with integrative approaches. Experimental and computational approaches will be applied to understand cellular mechanisms of pathophysiological processes that are responsible for their functional manifestations in vivo. Methods developed in this proposal will provide new means in elucidating the molecular mechanism of cardiac dysfunction not only in DCM but also in other cardiovascular diseases.

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

- **Project Title: GENDER-BASED REGULATION OF AUTOIMMUNE MEMORY**

  Principal Investigator & Institution: Tuohy, Vincent K.; Associate Staff; Cleveland Clinic Foundation 9500 Euclid Ave Cleveland, Oh 44195

  Timing: Fiscal Year 2002; Project Start 01-JUN-2002; Project End 31-MAY-2006

  Summary: (provided by applicant): Gender differences in the immune response are particularly evident in autoimmunity where females show increased susceptibility for developing autoimmune disease but males are predisposed to a poorer prognosis. This sex-based divergence in both disease susceptibility and disease outcome is not well understood yet is clearly evident in several diseases having prominent autoimmune features, including multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Graves' disease, and DCM. The experiments proposed in the current application are designed to address the basis for the differential prognosis of males versus females with autoimmune disease. To this end we have developed a murine EAMC model in which male SWXJ mice show prolonged maintenance of cardiac self- recognition and develop a high incidence of DCM, whereas female mice show aborted maintenance of T cell autoimmune memory and significant protection from the development of DCM. Thus, we hypothesize that the poor prognosis in males with autoimmune disease is due to their enhanced ability to maintain autoimmune T cell memory and persistence of inflammatory self-recognition. In Specific Aim 1, we will determine the mechanism by which differential gender- based maintenance of self-recognition occurs in male versus female SWXJ mice with EAMC. In Specific Aim 2, we will determine how the patterns of autoimmune memory may be altered by immune and non-immune manipulations. In addition, we will determine whether persistence of memory causes DCM and whether the gender-based differential development of autoimmune memory may be therapeutically manipulated to alter disease outcome. We believe that our proposed studies will lead to a better understanding of how autoimmune memory is maintained or aborted by gender-defined conditions. Such information may ultimately serve as a basis for therapeutic intervention during the development of autoimmune disease.

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

- **Project Title: GENE EXPRESSION PROFILES IN THE FAILING HUMAN HEART**

  Principal Investigator & Institution: Lowes, Brian D.; Medicine; University of Colorado Hlth Sciences Ctr P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2003; Project Start 15-SEP-2003; Project End 31-AUG-2008

  Summary: (provided by the applicant): The mechanisms responsible for progressive myocardial dysfunction and remodeling of the cardiomyopathic, intact failing human heart are unknown. The mechanism(s) behind Beta-blocker related improvements in myocardial function and reversal of remodeling also remains unknown. In general, the pathophysiologic mechanisms responsible for progressive myocardial failure and remodeling are likely to involve signaling mechanisms, which alter myocardial gene expression. Similarly, the molecular basis for improvement in myocardial function and remodeling following treatment with Beta-blocking agents also is likely due to time-dependent changes in myocardial gene expression. Numerous recent studies have demonstrated that, in order to be meaningful, gene regulation and expression must be examined in the intact heart. The overall objective of this proposal is to identify, in human subjects with myocardial failure, gene expression profiles associated with changes in myocardial function. This proposal investigates 1) the expression of over 12,000 genes in the failing human heart relative to nonfailing controls 2)changes in gene

expression associated with Beta-blocker related improvement in myocardial function. Using microarray analysis we are able to measure the expression of a large number of genes in small quantities of human ventricular myocardium that can be obtained serially from the intact heart by right ventricular (RV) endomyocardial biopsy. We have demonstrated that in situations where left and right ventricular function are concordant, directional changes in gene expression are similar in RV free wall, RV septal endomyocardium, and LV free wall, indicating that RV septal endomyocardial biopsy samples may be used to investigate changes in RV or LV free wall gene expression. Thus, this proposal has the ability to determine the molecular mechanisms responsible for myocyte dysfunction in the intact human heart. Furthermore, this proposal has the ability to provide information relevant to the mechanisms responsible for Beta-blocker-related improvements in myocardial dysfunction.

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

- **Project Title: GENES THAT CONTROL CARDIAC CELL NUMBER--EIA TRANSGENICS**

  Principal Investigator & Institution: Field, Loren J.; Professor; Medicine; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

  Timing: Fiscal Year 2002; Project Start 01-JAN-1999; Project End 31-DEC-2003

  Summary: Clinical recovery from myocardial infarction is thwarted, in part, by inability of surviving ventricular myocytes to reconstitute functional cardiac mass through a corresponding, compensatory increase in cell number. This highlights the limited capacity to restore cardiac mass by hypertrophy alone, and deleterious effects associated with hypertrophy that further impair survival. On-going myocyte loss also appears likely as an eventual contributor to end-stage heart failure. Conventional therapies for heart failure are aimed at rescuing jeopardized myocardium, optimizing mechanical load, or augmenting the mechanical performance of surviving myocytes. In principle, strategies to increase the number of functional ventricular myocytes have potential for a clinical benefit. (This theme is among the highest priorities expressed by the NHLBI Special Emphasis Panel on Heart Failure Research and the present RFA.) Three complementary, gene-based approaches have been brought to bear on the problem of cardiac cell number in this Collaborative RO1-transdifferentiation, manipulation of cell cycle constraints, and interference with pathways for programmed cell death (apoptosis). Viral delivery of cardiogenic transcription factors and upstream cardiogenic signals will be explored by Dr. Robert Schwartz. Drs. Michael Schneider and Loren Field will use gain-and loss-of- function mutations to dissect the "post-mitotic" phenotype in vivo, and will use co-precipitation or interaction cloning to isolate the endogenous cardiac proteins affecting cell cycle exit. Dr. Konstantin Galaktionov, an expert on Cdc25, will study molecular regulators of the G2/M transition, a second checkpoint that must be overcome for cell number to be increased. Mechanisms and countermeasures for cardiac apoptosis will be tested by Dr. Doug Mann, with emphasis on **dilated cardiomyopathy** triggered by overexpression of tumor necrosis factor alpha, and on investigations of human myocardium.

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

- **Project Title: GENES THAT CONTROL CELL NUMBER--GI/S CHECKPOINT**

  Principal Investigator & Institution: Schneider, Michael; Professor; Medicine; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2002; Project Start 30-SEP-1998; Project End 31-AUG-2003

Summary: (Adapted from the applicant's abstract) Clinical recovery from myocardial infarction is thwarted, in part, by inability of surviving ventricular myocytes to reconstitute functional cardiac mass through a corresponding, compensatory increase in cell number. This highlights the limited capacity to restore cardiac mass by hypertrophy alone, and deleterious effects associated with hypertrophy that further impair survival. Ongoing myocyte loss also appears likely as an eventual contributor to end-stage heart failure. Conventional therapies for heart failure are aimed at rescuing jeopardized myocardium, optimizing mechanical load, or augmenting the mechanical performance of surviving myocytes. In principle, strategies to increase the number of functional ventricular myocytes have potential for a clinical benefit. (This theme is among the highest priorities expressed by the NHLBI Special Emphasis Panel on Heart Failure Research and the present RFA.) Three complementary, gene-based approaches have been brought to bear on the problem of cardiac cell number in this Collaborative R01- transdifferentiation, manipulation of cell cycle constraints, and interference with pathways for programmed cell death (apoptosis). Viral delivery of cardiogenic transcription factors and upstream cardiogenic signals will be explored by Dr. Robert Schwartz. Drs. Michael Schneider and Loren Field will use gain- and loss-of-function mutations to dissect the "postmitotic" phenotype in vivo, and will use co-precipitation or interaction cloning to isolate the endogenous cardiac proteins affecting cell cycle exit. Dr. Konstantin Galaktionov, an expert on Cdc25, will study molecular regulators of the G2/M transition, a second checkpoint that must be overcome for cell number to be increased. Mechanisms and countermeasures for cardiac apoptosis will be tested by Dr. Doug Mann, with emphasis on **dilated cardiomyopathy** triggered by overexpression of tumor necrosis factor alpha, and on investigations of human myocardium. (End of Abstract)

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

- **Project Title: GENETIC ANALYSIS OF DILATED CARDIOMYOPATHY**

  Principal Investigator & Institution: Jha, Sanjay; Children's Hospital (Boston) Boston, Ma 021155737

  Timing: Fiscal Year 2002; Project Start 09-JUL-2001; Project End 31-MAY-2007

  Summary: (provided by applicant) Dilated cardiornyopathy (DCN4) is a disease characterized by cardiac chamber dilation and deterioration of systolic function. it accounts for 10,000 deaths annually In the United States, and is an etiologically heterogeneous disorder with a strong genetic component. The central goals of this project are to identify genes involved in the pathogenesis of DCM, and to obtain the necessary training in cardiovascular genetics over a proposed five year period, to prepare for a career as an independent investigator. Research will focus on four specific alms critical for identification of genes involved in DCM pathogenesis. 1) Ascertainment and phenotypic characterization of individuals and families with DCM. Families and sporadic cases suitable for genetic analyses will be identified from congestive heart failure and transplant clinics at1he University of Utah and University of Pennsylvania system hospitals. 2) Identification of new DCM loci using genetic linkage analysis in large kindreds. Genome-wide linkage scans using highly polymorphic markers will be performed on large DCM families that do not link to known loci. 3) Positional cloning of a DCM gene on chromosome 3p. The critical genetic interval for a DCM locus previously identified by this laboratory will be cloned. Candidate genes identified in the region will be screened for mutations that co-segregate with the disease phenotype in the family where linkage was established. 4) Identification and mutation screening of candidate genes in familial and sporadic DCM populations. We will identify genes,

which on the basis of physiologic rationale, may play central roles in DCM pathogenesis. The candidate genes will be screened for mutations in our patient population. The principle investigator has completed training in clinical cardiology. This application now proposes to build on his research background in Drosophila developmental genetics obtained in the laboratory of Dr. David Hogness. Over a five year period, an expertise in genetic approaches to understanding the molecular pathogenesis of dilated cardlomyopathy will be developed. The candidate's sponsor, Dr. Mark Keating, is a recognized leader in the field of cardiovascular genetics. An advisory committee consisting of two other senior scientists, Dr. Mark Leppert and Dr. Michael Parmacek, will provide additional scientific and career guidance. The Department of Human Genetics at the University of Utah is a center for the study of genetic diseases and provides an outstanding environment for the candidate to develop into an independent investigator. (End of Abstract)

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

- **Project Title: GENETICS STUDIES OF FAMILIAL DILATED CARDIOMYOPATHY**

  Principal Investigator & Institution: Mcnally, Elizabeth M.; Associate Professor; Medicine; University of Chicago 5801 S Ellis Ave Chicago, Il 60637

  Timing: Fiscal Year 2002; Project Start 01-FEB-2000; Project End 31-JAN-2004

  Summary: Many etiologies lead to the development of **dilated cardiomyopathy.** Idiopathic **dilated cardiomyopathy** arises from intrinsic muscle disease in the presence of normal coronary arteries and the absence of a clear toxic or immunologic insult. Approximately 30 percent of idiopathic **dilated cardiomyopathy** patients have first degree relatives that also show evidence of cardiac dilatation with or without symptoms of congestive heart failure. Supporting this, genetic loci have been significantly associated with familial **dilated cardiomyopathy** (FDC). Positional cloning efforts are underway to increase our understanding of the molecular mechanisms that underlie familial **dilated cardiomyopathy.** Through genetic linkage analysis, we have identified a region of chromosome 6q23 that is associated with **dilated cardiomyopathy,** conduction system disease that produces progressive atrio-ventricular block and a mild, adult onset, slowly progressive muscular dystrophy. We have constructed a physical map of this region of chromosome 6 and evaluation of candidate genes is underway. We have also discovered a second region, chromosome 2q22, that is associated with **dilated cardiomyopathy** and ventricular arrhythmias. We propose to refine the genetic interval, identify candidate genes and, through mutation analysis, identify the gene responsible for chromosome 2-associated FDC. The FDC-gene product will be studied for expression patterns in both normal and diseased tissue. The murine homolog of the FDC-gene will be determined. We will also establish a clinical and DNA database of **dilated cardiomyopathy** patients. This database will be used to determine the role of certain mutations in the development of the cardiomyopathic process. While genetic heterogeneity is present in FDC, the study of genes responsible for this disorder will reveal whether multiple cellular mechanism lead to cardiomyopathy. Additionally, in families with **dilated cardiomyopathy,** we find a prodrome of arrhythmias prior to the onset of cardiac dilatation and congestive heart failure. By developing genetic markers, we will identify those at risk for arrhythmia and most like to benefit from pacemaker and/or implantable defibrillator treatment.

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

- **Project Title: GENOMICS OF CARDIOVASCULAR DEVELOPMENT, ADAPTION**

  Principal Investigator & Institution: Izumo, Seigo; Director of Cardiovascular Research; Medicine; Harvard University (Medical School) Medical School Campus Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 30-SEP-2000; Project End 31-JUL-2004

  Summary: The goal of this PGA is to begin linking genes to function, dysfunction and structural abnormalities of the cardiovascular system caused by clinically relevant, genetic and environmental stimuli. The principal biological theme to be pursued is how the transcriptional network of the cardiovascular system responds to genetic and environmental stresses to maintain normal function and structure, and how this network is altered in disease. In Specific Aim 1, the investigators will take a multidisciplinary approach combining well-defined mouse models of cardiomyopathy and vasculopathy with an integrated analysis of physiology, pathology, and RNA expression profiling to search for prototypical patterns of gene expression in response to various genetic and non-genetic perturbations. In Specific Aim 2, the investigators will perform transcriptional profiling using human myocardium and vascular tissues obtained at the time of cardiac transplant or biopsy, and compare the transcriptional profile data with those of various mouse models. In Specific Aim 3, the investigators will screen for mutations that cause cardiovascular malformations with particular emphasis on hypertrophic cardiomyopathy, **dilated cardiomyopathy,** and selected sets of patients with congenital heart disease. In Specific Aim 4, the investigators will examine 200 candidate genes, identified by the mouse and human expression studies, in 2093 individuals drawn from the Framingham Heart Study. In these studies, a single nucleotide DNA polymorphism analysis (SNP) will be correlated with echocardiographic evidence of left ventricle mass, ventricular function, cardiac chamber size and aortic root size. The data generated by all of the above studies will be analyzed by state-of-the-art informatics to search for logics for common as well as disease specific pathways. The data will be extensively annotated and made freely available to the scientific community through the interactive website. In summary, this PGA will generate a high quality, comprehensive data set for the functional genomics of structural and functional adaptation of the cardiovascular system by integrating expression data from animal models and human tissue samples, mutation screening of candidate genes in patients, and DNA polymorphisms in a well characterized general population. Such a data set will serve as a benchmark for future basic, clinical and pharmacogenomic studies.

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

- **Project Title: GI SIGNALING AND CARDIOMYOPATHY**

  Principal Investigator & Institution: Conklin, Bruce R.; J. David Gladstone Institutes Box 419100, 365 Vermont St San Francisco, Ca 94103

  Timing: Fiscal Year 2002; Project Start 01-JUL-1998; Project End 30-JUN-2003

  Summary: (adapted from the applicant's abstract): Human **dilated cardiomyopathy** (DCM) is associated with increased Gi protein levels, increased Gi signaling, and auto-antibodies that activate signaling by GI- coupled receptors. The goal of this proposal is to test the hypothesis that Gi signaling can cause DCM. Control of Gi signaling has been achieved by expressing in the heart a Gi-coupled receptor that has been specifically designed to be a Receptor Activated Solely by a Synthetic Ligand, or RASSL. The first RASSL (R1) is based on a Gi-coupled, kappa- opioid receptor. R1 contains mutations that reduce affinity for natural peptide agonists and yet allow activation by the drug

spiradoline. Cardiac-specific, conditional expression of R1 in transgenic mice is achieved with a tetracycline-controlled expression system utilizing the a-myosin heavy chain promoter. Activation of R1 signaling by spiradoline administration results in acute slowing of heart rate and complete atrioventricular block, which are known effects of Gi signaling. Preliminary studies show that prolonged signaling by R1 causes a lethal form of congestive heart failure with anasarca (up to 60% weight gain), contractile dysfunction, and the histopathological features of DCM. The Gi signaling-induced cardiomyopathy can be phenotypically reversed by suppressing R1 expression, creating the potential for studies of disease recovery as well as disease onset. Specific Aims are: (1) to determine if receptor- stimulated Gi signaling in the heart can cause the characteristic anatomical, physiological and histopathological changes of DCM using echocardiography, perfused hearts, isolated heart tissue strips, quantitative morphometric analysis, gene expression, and biochemical markers of cardiomyopathy; (2) to determine if the DCM is influenced by the spatial or temporal nature of the Gi signal, by altering the anatomical location of the Gi signal, inducing continuous Gi signaling with a mutationally activated form of Gi, and reducing continuous basal Gi signaling by expressing a new RASSL (R2) that has a lower susceptibility to endogenous peptide agonists; and (3) to determine if a mouse heart with Gi-induced DCM can regain normal function on a physiologic, histologic, and cellular level.

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

- **Project Title: GI SIGNALING IN CARDIOMYOPATHY AND CARDIOPROTECTION**

  Principal Investigator & Institution: Baker, Anthony J.; Associate Professor; Northern California Institute Res & Educ 4150 Clement Street (151-Nc) San Francisco, Ca 941211545

  Timing: Fiscal Year 2002; Project Start 01-AUG-2002; Project End 31-JUL-2007

  Summary: (provided by applicant): In humans, chronically increased signaling through Gi-coupled receptors is associated with congestive heart failure (CHF) caused by idiopathic **dilated cardiomyopathy** or ischemic cardiomyopathy following myocardial infarction. However, the mechanisms responsible are unclear. Our working hypothesis is that chronically increased Gi signaling causes impaired excitation-contraction (ec) coupling. To test this hypothesis we will combine physiological measurements of cardiac muscle function with a novel transgenic mouse model in which a modified Gi-coupled receptor (Ro1) is targeted to the heart. Expression of Ro1 is regulated by a tetracycline-controlled expression system (tet-system). We have recently shown that chronic Ro1 expression causes CHF and major abnormalities of Ca2+ transients and contraction. In contrast, acute Ro1 expression causes significant protection against ischemia/reperfusion injury, suggesting a dual role for increased Gi signaling in cardioprotection and disease. For this proposal we will determine the ec-coupling mechanisms and Gi signaling mechanisms involved in CHF and cardioprotection. Using single myocytes, cardiac trabeculae, and Langendorff perfused mouse hearts, we will determine the effect of Ro1 expression on Ca2+ transients and determine the mechanisms responsible by localizing abnormalities to specific Ca2+ handling processes. We will determine the effect of Ro1 expression on Ca2+-responsiveness and determine the mechanisms responsible by localizing abnormalities to specific contractile and regulatory proteins. Using the tet-system to turn off Ro1 expression after induction of CHF, we will determine the extent to which ec-coupling abnormalities are reversible. To elucidate signaling mechanisms, we will determine which of the major Gi pathways in the heart (Gi2 and Gi3) are involved; and whether signaling via the G protein alpha

subunit and/or the betagamma dimer is involved. Using 3 model systems we will investigate Gi signaling effects (both deleterious and beneficial) and the ec-coupling- and signaling mechanisms involved in: Aim 1. CHF caused by Ro1 expression; and recovery after terminating Ro1 expression. Aim 2. Acute Cardioprotection caused by Ro1 expression. Aim 3. CHF caused by ischemic cardiomyopathy. This research will provide new information on the dual role of Gi signaling in both heart failure and cardioprotection which may help identify new strategies to treat heart disease.

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

- **Project Title: IDENTIFYING A GENE FOR CANINE CARDIOMYOPATHY**

  Principal Investigator & Institution: Jakobs, Petra M.; Medicine; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2002; Project Start 10-JUL-2002; Project End 30-JUN-2006

  Summary: (provided by applicant): Atrial fibrillation (AF) causes significant morbidity, disability, and mortality related to heart disease and stroke in the human population. **Dilated cardiomyopathy** (DCM) is characterized by ventricular dilatation and systolic contractile dysfunction and is an important cause of heart failure. In some canine breeds, DCM is a relatively common, lethal disease. A recent study of 500 Irish Wolfhounds (IW) found that 24% had DCM; 88% of these affected dogs also had AF. The DCM/AF phenotype appears to be inherited as an autosomal dominant trait. We have collected DNA and clinical data from a large family of IW in which AF and progressive DCM is segregating. Our hypothesis is that a mutation in a single gene causes DCM/AF in IW, and we propose to map this gene by linkage analysis and to use the tools of positional cloning and candidate gene analysis to identify the gene. One of the most common genetic causes of human DCM is mutation in the lamin A/C gene. The phenotype caused by lamin A/C mutations in such patients also includes conduction system disease and therefore resembles the DCM/AF phenotype in IW. In preliminary studies, we have excluded lamin A/C as the locus of the defect in IW. Hence our proposed work presents an ideal opportunity to identify a novel DCM/AF disease gene. If successful, this may lead to improved knowledge of the mechanisms of DCM and AF in humans.

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

- **Project Title: INDUCIBLE NO SYNTHASE IN CARDIAC ALLOGRAFT REJECTION**

  Principal Investigator & Institution: Cannon, Paul J.; Professor of Medicine (With Tenure); Medicine; Columbia University Health Sciences Po Box 49 New York, Ny 10032

  Timing: Fiscal Year 2002; Project Start 01-MAY-1996; Project End 30-JUN-2003

  Summary: (adapted from the applicant's abstract): The general objective of the proposed research in this renewal application is to investigate the role of the inducible isoform of nitric oxide synthase (iNOS) in the biochemistry and pathobiology of cardiac allograft rejection. The central hypothesis to be tested is that NO produced by iNOS in macrophages infiltrating the myocardium and in the cardiac myocytes augments the myocardial inflammation and contributes to the death of cardiac myocytes. We have demonstrated: 1) that iNOS mRNA, protein, and enzyme activity are induced in endothelial cells, infiltrating macrophages and cardiomyocytes in rejecting cardiac allografts, and 2) that iNOS induction is accompanied by impaired ventricular function and death of heart muscle cells which occurs both by necrosis and by apoptosis. We now propose to investigate mechanisms responsible for necrosis, apoptosis, and iNOS expression during heart transplant rejection. Aim #1 is to investigate, using cultured cardiomyocytes and rat and mouse heterotopic cardiac transplantation models, the

hypothesis that activation of polyadenosine 5' -diphosphoribose synthetase (PARS) by nitric oxide contributes to the necrosis of cardiac myocytes in vitro and during cardiac allograft rejection. Aim #2 is to investigate the hypothesis that myocardial inflammation, necrosis and apoptosis during cardiac allograft rejection are ameliorated using mice as allograft donors and recipients that are unable to express iNOS (iNOS-ko mice). Aim#3 is to investigate the hypotheses that apoptosis of cardiomyocytes triggered by NO can be inhibited by sem-selective iNOS inhibitors, by transfection with Bcl-2, and by administration of caspase inhibitors. Aim #4 is to investigate the interplay between iNOS and COX-2 in modulating prostaglandin and thromboxane synthesis during cardiac allograft rejection, the role of CD154-CD40 interaction in the expression of iNOS and COX-2 in cardiomyocytes and the effect of COX-2 expression on cardiomyocyte apoptosis in cardiac allograft rejection. The proposed experiments may provide new insights concerning the role of iNOS in pathobiology and potential therapy of cardiac allograft rejection and they may also be relevant to other cardiac diseases in which iNOS is expressed such as myocardial infarction and **dilated cardiomyopathy.**

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- **Project Title: INFLAMMATION AND IMMUNITY IN DILATED CARDIOMYOPATHY**

  Principal Investigator & Institution: Cooper, Leslie T.; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2004; Project Start 01-JUL-2004; Project End 30-JUN-2005

  Summary: (provided by applicant): This is an application for partial funding of an American Heart Association sponsored workshop on "Inflammation and Immunity in Dilated Cardiomyopathy" to be held in May 2004 at the Hyatt Hotel in Bethesda, Maryland. The objective of this meeting is to bring together internationally-recognized experts in the fields of virology, cardiac pathology, cardiac molecular immunology, diagnostic imaging, epidemiology, and clinical trial design to discuss the current understanding of the pathogenesis, diagnosis and treatment of dilated cardiomyopathy(DCM). Specific efforts have been made to ensure the participation of women and underrepresented minorities. The specific aims of this workshop are 1) to review the current understanding of cardiac inflammation and immunity as related to DCM at the cellular and molecular level, and to identify the most promising and critical areas for future clinical research efforts in the field. 2) To disseminate the workshop recommendations through publication and webcast. A copy of the final report will be provided to the NHLBI and Office of Rare Diseases (ORD) staff to help in the development of future programs. **Dilated cardiomyopathy** (DCM) is an important cause of heart failure with an estimated prevalence of 36 cases per 100,000 in the USA. Over the past 12 years since the last NHLBI-sponsored workshop on this subject, there has been increasing evidence that abnormalities in cellular and humoral immunity contribute to the pathogenesis of DCM. However, these advances in the understanding of the pathogenesis and pathophysiology of DCM have not affected clinical diagnosis and treatment. Therefore, it is timely to organize a workshop to review the advances of the past decade in cardiac immunopathology as they impact the diagnosis and treatment of DCM. The long-term overall goal of this workshop is to translate advances in molecular and cellular mechanisms of disease into improvements in the diagnosis and treatment of patients with DCM.

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

- **Project Title: MAPPING NOVEL DISEASE GENES FOR DILATED CARDIOMYOPATHY**

  Principal Investigator & Institution: Olson, Timothy M.; Assistant Professor; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2002; Project Start 15-JUL-2002; Project End 30-JUN-2005

  Summary: Dilated cardiomyopathy (DCM) is a heritable, genetically heterogeneous disorder causing congestive heart failure. Current medical therapy has minimal impact on prognosis and cardiac transplantation is the only definitive treatment for end-stage disease. The molecular and cellular mechanisms underlying DCM are poorly defined, but the importance of single gene defects in disease pathogenesis is becoming increasingly apparent. The objective of this study is to identify novel DCM genes by genetic linkage and mutational analyses. The first aim is to determine the chromosomal location of novel familial DCM genes. This will be accomplished by genome-wide genotyping and genetic linkage analyses in 3 large families with autosomal dominant DCM. Previously identified DCM genes have been excluded in these families. The second aim is to identify mutations in novel genes that cause familial DCM by linkage and sequence analyses of candidate genes mapping to DCM loci. Once novel genes for familial DCM are identified, the third aim will be to determine the role of these genes in a large cohort of unrelated patients with familial and sporadic DCM. High throughput DNA sequence analyses will be performed to identify additional inherited and de novo mutations. The long-term objectives of this work are to gain new insights into molecular mechanisms for heart failure and to improve prediction, prevention, and treatment of DCM.

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

- **Project Title: MECHANICAL REGULATION OF DILATED CARDIOMYOPATHY**

  Principal Investigator & Institution: Omens, Jeffrey H.; Medicine; University of California San Diego La Jolla, Ca 920930934

  Timing: Fiscal Year 2002; Project Start 01-FEB-2001; Project End 31-JAN-2005

  Summary: Dilated cardiomyopathy is a disease of the heart that in most cases leads to decreased cardiac function and eventually to congestive heart failure. Mechanical factors such as stress and strain have been implicated as regulatory factors in diseases such as cardiac hypertrophy. The overall hypothesis of this proposal is that mechanical factors play a significant role in the tissue remodeling associated with **dilated cardiomyopathy** and cardiac failure. Sophisticated computational models in conjunction with experimental studies in rodents with different etiologies of heart failure (both genetic and surgically-induced) will help elucidate the role of mechanical factors in the progression of cardiac dilation and failure. The following hypotheses will be tested: (1) **Dilated cardiomyopathy** and eventual heart failure are mediated by mechanical loads on the heart, and the transition from a compensated hypertrophic state to cardiac failure is dependent on a critical level of stress or strain. Studies of cardiac function before and after this transitory phase can determine which mechanical factors are important. (2) A change in residual stress has important consequences for regional function in the heart, and may be a mechanism of dysfunction in heart failure. We will investigate this possibility by quantifying geometry and tissue structure in the stress-free state of the ventricle during the transition from dilation to failure, and use mathematical models to predict subsequent abnormal changes in diastolic and systolic wall stresses. (3) We expect that changes in. regional myocyte orientation, both at the cellular and global levels, are mechanisms of cardiac dilatation and failure. To test this hypothesis, local

myocyte disarray and regional variations in laminar sheet orientation will be measured during the transition to failure. We will incorporate these measures into computational models of the heart, and then independently alter the myocyte orientation in the model, and compare the functional results with those obtained experimentally. We propose that these regional structural changes accompanies dilatory heart failure, and are mechanisms behind the reduction in fiber shortening and the ability of the wall to thicken during systole.

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- **Project Title: MECHANISM OF ARRHYTHMIAS IN THE SETTING OF HEART FAILURE**

  Principal Investigator & Institution: Pogwizd, Steven M.; Associate Professor; Medicine; University of Illinois at Chicago 1737 West Polk Street Chicago, Il 60612

  Timing: Fiscal Year 2002; Project Start 09-AUG-1991; Project End 31-JUL-2003

  Summary: The goal of the proposed studies is to define the electrophysiologic and subcellular mechanisms underlying nonreentrant initation of ventricular tachycardia (VT) in the failing heart and its modulation by adrenergic stimulation. In the preceding grant interval, we have performed 3- dimensional mapping studies in arrhythmogenic experimental models of cardiomyopathy and in the failing human heart and demonstrated that VT initiates by a nonreentrant mechanism that is enhanced by catecholamines. The applicant has isolated myocytes from failing hearts and found alterations in Na/Ca exchange activity and intracellular calcium handling that could underlie the development of an arrhythmogenic transient inward current (Iti). Studies will be performed both in an arrhythmogenic rabbit model of nonischemic cardiomyopathy and in the failing human heart. The contribution of Alpha1-, Beta1- and Beta2-adrenergic receptor stimulation to arrhythmogenesis in the failing heart will be determined by in vivo 3-dimensional mapping and in vitro electrophysiologic studies. Measurement of Alpha1-, Beta1-, and Beta2- adrenergic receptor density with microscopic resolution using autoradiographic techniques will determine whether the density of adrenergic subtype receptors parallel the arrhythmogenic effects of adrenergic subtype stimulation. To delineate how alterations in sarcoplasmic reticulum (SR) calcium flux, Na/Ca exchange activity and a calcium-activated chloride current lead to activation of a Iti in the failing heart, and to determine how the activation of Iti is enhanced by adrenergic stimulation, whole cell voltage clamping and measurement of intracellular calcium and SR calcium content will be performed in myocytes isolated from myopathic hearts. Lastly, to determine whether nonreentrant activation is due to triggered activity arising from delayed afterdepolarizations (as opposed to early afterdepolarizations or abnormal automaticity), studies will be performed in a novel isolated heart preparation in which transmural mapping in vitro will be combined with recording of monophasic and transmembrane action potentials. The results of these studies will provide new insights into the nature of nonreentrant activation in the failing heart and of the subcellular alterations that underlie adrenergic enhancement of arrhythmogenesis. The results will also provide the foundation for novel therapeutic approaches directed at nonreentrant activation that would be useful in the prevention of sudden death in patients with cardiomyopathy.

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

- **Project Title: MECHANISMS OF DILATED CARDIOMYOPATHY IN CREB A133**

  Principal Investigator & Institution: Reed, Guy L.; Associate Professor; Medicine; Harvard University (Medical School) Medical School Campus Boston, Ma 02115

Timing: Fiscal Year 2002; Project Start 30-SEP-1998; Project End 31-AUG-2004

Summary: Dilated cardiomyopathy (DC) represents an important cause of cardiovascular morbidity and mortality and consumes a disproportionate share of medical resources in this country. Despite recent advances in the treatment of DC, this disorder has a poor prognosis with 5 year mortality rates of 20-50 percent. Progress in understanding the pathophysiology of DC and in devising new therapies for this disorder has been limited by our relative lack of understanding of the molecular pathophysiology of the disease and by the lack of a small animal model which closely resembles the anatomical, physiological, and clinical features of the human disease. We have recently shown that transgenic mice expressing a dominant-negative form of the CREB transcription factor (CREBA133) under the control of the cardiac-specific alpha-MHC promoter reproducibly develop DC that resembles many of the anatomical, physiological and clinical features of human DC. In the studies described in these 3 collaborative R01 applications we propose to use this new mouse model to better understand the molecular pathways by which CREB regulates cardiac myocyte homeostasis and how perturbations in these pathways produce DC. Specifically we will 1) elucidate the CREB-dependent signaling pathways that are required to maintain cardiac myocyte homeostasis and determine how these pathways are perturbed in the CREBA133 mice with DC, 2) determine the role of apoptosis in the CREBAl33 DC and test the hypothesis that the cardiomyopathic phenotype can be ameliorated by expression of anti-apoptotic genes in the heart, 3) study excitation-contraction coupling, contractility, and calcium homestasis in the CREBA133 cardiac myocytes, 4) understand the myofibrillar and SR defects underlying cardiac myocyte dysfunction in the CREBA133 mice, 5) study ventricular remodeling and LV-arterial coupling during the development of DC in the CREBA133 mice, and 6) determine the effects of exercise conditioning, gender, and different modes of inhibiting the renin angiotensin system on progression of DC in the CREBA133 mice. These studies represent the continuation of an established collaboration between molecular biologists (Leiden), cell physiologists (Moss) mouse and human physiologists (Lang, Spencer) and clinical cardiologists (Leiden, Lang, Spencer) the Universities of Chicago and Wisconsin. Taken together the results of this work should provide us with important new insights into the molecular mechanisms underlying human DC and CHF.

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- **Project Title: MECHANISMS OF TROPOMYOSIN INDUCED HYPERTROPHY**

  Principal Investigator & Institution: Wieczorek, David F.; Associate Professor; Molecular Genetics, Biochemistry & Microbiology; University of Cincinnati 2624 Clifton Ave Cincinnati, Oh 45221

  Timing: Fiscal Year 2003; Project Start 01-AUG-2003; Project End 30-JUN-2007

  Summary: Cardiac muscle contraction is dependent upon a cooperative interaction between thick and thin sarcomeric proteins. Mutations in tropomyosin (TM), an essential thin filament protein, cause both skeletal and cardiac myopathies, including familial hypertrophic cardiomyopathy (FHC). We have deve oped novel mouse mode s whereby these mutations induce concentric or **dilated cardiomyopathy.** Our long-term objective is to understand how specific amino acid changes in TM disrupt sarcomere assembly and function, thereby triggering the enactment of a cardiac hypertrophic response. The Specific Aims of this proposal are: (1) To address how TM mutations in non-troponin T binding regions lead to cardiac hypertrophy; the focus of Specific Aim 1 is to develop mouse models encoding genetically altered TM to enhance the understanding of the role TM plays in the sarcomere during both normal and

pathological conditions. (2) To identify changes in gene expression that occur in response to sarcomeric induced cardiac hypertrophy. Specific Aim 2 will identify new and current genes that are transcriptionally activated/repressed following sarcomeric impairment and the onset of the cardiomypathic response. (3) To identify the chromosomal regions containing modifier genes associated with FHC a-TM180 hypertrophic cardiomyopathy. Using genetically inbred transgenic mouse lines which demonstrate marked differences in cardiac hypertrophy, the focus of Specific Aim 3 is to identify the chromosomal regions containing the gene(s) that modulate development of cardiac hypertrophy. Our research focuses on the importance of TM during mechanical and biochemical activity of normal and diseased cardiac muscle. We employ murine models that provide invaluable information on in vivo function of TM in the intact sarcomere. Our comprehensive approach will extend the understanding of the molecular mechanisms that are involved in the development and prevention of cardiac hypertrophy following mutations in the TM sarcomeric thin filament protein.

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- **Project Title: METABOLIC PHENOTYPE SWITCH IN HEART FAILURE**

  Principal Investigator & Institution: Recchia, Fabio A.; Assistant Professor; New York Medical College Valhalla, Ny 10595

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2008

  Summary: The overall theme of this Program Project Grant is the identification of abnormalities of myocardial energy metabolism that occur with heart failure, and the effects of these abnormalities on left ventricular function and remodeling. The severely decompensated heart switches to a fetal metabolic phenotype, characterized by downregulation of free fatty acid (FFA) oxidation and enhancement of glucose oxidation. Two important questions remain unanswered: 1) it is not known whether this metabolic alteration is an adaptive or maladaptive mechanism, nor if it plays a role in the progression from compensated to decompensated heart failure (HF); and 2) the molecular mechanisms responsible for the altered metabolic phenotype of the failing heart are poorly understood. Our preliminary data indicate that chronic partial inhibition of FFA oxidation delays the onset of decompensation in a canine model of **dilated cardiomyopathy.** We have also shown a reduction in the protein expression of retinoid X receptor-alpha (RXRalpha), a key regulator of the FFA oxidative pathway, in end-stage pacing-induced HF. The overall goal of this Project is to test the hypothesis that changes in expression and activation of RXRalpha and of its obligate co-receptor peroxisome proliferator receptor-alpha (PPARalpha) are key determinants of the altered myocardial metabolic phenotype in HF and play an important role in the progression toward cardiac decompensation. Studies will be performed in dogs with pacing-induced HF. The first specific aim is to determine the time course of alterations in myocardial metabolic phenotype and in protein expression and activation of RXRalpha and PPARalpha at sequential time points during the progression of HF and after post-pacing recovery. Changes in hemodynamics, cardiac function and substrate metabolism measured in vivo will be correlated with the activity of key enzymes of the substrate oxidative pathways and with the expression and activation state of RXRalpha, PPARalpha measured in snap-frozen cardiac biopsies. The second specific aim is to determine whether early myocardial switch to preferential oxidation of carbohydrate delays the progression of HF. During development of HF, myocardial FFA oxidation will be partially suppressed at pre-mitochondrial or intra-mitochondrial level. The third specific aim is to determine whether a sustained activation of RXRalpha or PPARalpha can prevent the alterations in myocardial metabolic phenotype and accelerate the

progression of HF. RXRalpha and PPARalpha will be alternatively activated by specific ligands administered during the development of HF.

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- **Project Title: MITOCHONDRIAL OXIDATIVE STRESS AND NEURODEGENERATION**

  Principal Investigator & Institution: Melov, Simon; Assistant Professor; Buck Institute for Age Research Novato, Ca 94945

  Timing: Fiscal Year 2002; Project Start 15-AUG-2000; Project End 31-JUL-2005

  Summary: (Verbatim from the Applicant's Abstract) Oxidative stress has been hypothesized to be a major factor in the etiology of many progressive age related neurodegenerative diseases including Alzheimer and Parkinson disease, amytrophic lateral sclerosis, Friedreichs ataxia, and the prion diseases. The chief source of oxidative stress within the cell is the mitochondrion. The main ROS produced is the superoxide radical (O'~) which under normal circumstances is reduced to H2O2 via the mitochondrial form of superoxide dismutase (Sod2). We have previously reported that inactivation of this gene results in neonatal lethality accompanied by a **dilated cardiomyopathy,** hepatic lipid accumulation, oxidative DNA damage, organic aciduria, spongiform encephalopathy, gliosis, and mitochondrial enyzmatic abnormalities. We have also demonstrated that many of these phenotypes can be ameliorated by synthetic antioxidant treatment. The long term goals of these studies are to 1) understand the molecular targets of mitochondrial oxidative stress both at the genetic and protein level within the brain, & 2) characterize the efficacy of synthetic antioxidants in preventing many of the CNS disorders which present due to mitochondrial oxidative stress within the brain. The specific aims are 1) Characterize the metabolism of the affected areas of the brain to determine if there is a metabolic differential relative to unaffected areas; 2) Determine whether cell loss contributes to the progression of the spongiform changes; 3) Characterize at the biochemical and enzymatic level the changes due to mitochondrial oxidative stress within the brain and the efficacy of various synthetic antioxidants in attenuating such changes; 4) Investigate gene expression changes in the brain in relation to endogenous mitochondrial oxidative stress via microarray analysis. Experimental methods include; growth and harvesting of Sod2 mutant mice and controls with and without synthetic antioxidant treatment, histopathological analysis, stereological cell counting, metabolic measurements via 2-deoxyglucose labeling, biochemical analysis of mitochondria from control and experimental groups, and microarray analysis of RNA from control and experimental groups of both affected and unaffected areas.

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

- **Project Title: MODIFIER GENES IN HEART FAILURE**

  Principal Investigator & Institution: Rockman, Howard A.; Professor; Medicine; Duke University Durham, Nc 27710

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 30-JUN-2006

  Summary: (provided by applicant): Heart Failure is a clinical syndrome characterized by progressive ventricular dilatation, depressed cardiac function and premature death. Importantly, variation in the development of heart failure and in the long-term survival irrespective of etiology indicates that additional unidentified genetic factors play a significant role in the phenotypic expression. Unfortunately, these modifier genes have been recalcitrant to direct identification in human populations. In this regard, genetic studies in animals models of disease can identify candidate modifier genes and provide

an insight on the genetic interactions that cause phenotypic variation in the humans. The goal of this proposal is to identify genetic modifiers of human heart failure. To accomplish this goal we will use a well-characterized murine model of heart failure created by the overexpression of a calsequestrin (CSQ) transgene to simulate a monogenetic disorder of inherited **dilated cardiomyopathy.** The phenotype of the CSQ model demonstrates many of the "hallmark" features of **dilated cardiomyopathy** including progressive cardiac dysfunction, shortened lifespan and abnormalities in beta-adrenergic receptor signaling. Although the model is not one caused by a natural occurring single-gene mutation in humans, it is one that recapitulates the human heart failure phenotype and importantly, is highly dependent on the genetic background. Accordingly, the goal of this project is to use the CSQ mouse to identify modifier genes that contribute to the severity of heart failure in the human population. The following specific aims are proposed: 1) to identify modifier genes in the CSQ mouse model of heart failure that confer susceptibility to premature death. Quantitative Trait Loci mapping has already shown strong linkage of survival to a narrow region on chromosome 2. 2) to identify modifier genes in the CSQ mouse model of heart failure that delay susceptibility to both cardiac dysfunction and premature death. Quantitative Trait Loci mapping has already shown strong linkage of cardiac function and survival to a broad region on chromosome 3 and 8. 3) to test whether modifier genes influence phenotypic variation in human heart failure, we will examine whether genetic polymorphisms identified in the mouse correlate with outcome in patient populations with heart failure. Genetic epidemiology will be performed in collaboration with the Duke Center for Human Genetics.

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- **Project Title: MOLECULAR CONSEQUENCES OF SARCOMERE PROTEIN GENE MUTATIONS**

  Principal Investigator & Institution: Seidman, Jonathan G.; Professor of Genetics; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 01-FEB-2002; Project End 31-JAN-2003

  Summary: The central focus of this project is to define the signaling pathways that lead from sarcomere gene mutation to hypertrophic cardiomyopathy, **dilated cardiomyopathy, dilated cardiomyopathy** and/or heart failure. During the previous grant period we demonstrated that mutations in sarcomere protein genes cause familial hypertrophic cardiomyopathy (FHC). Many, if not all, FHC-causing mutations, create poison polypeptides that become incorporated into the growing sarcomere and create defective sarcomeres. However, we do not understand how these defective sarcomeres lead to dramatic changes in cardiac morphology and function. Some individuals bearing these mutations can live for many years without demonstrating any clinical signs of disease, while others develop disease symptoms early in childhood. To create tools to study these signaling pathways we have create two lines of mice; each line of mice bears a mutation that causes FHC in man. One line bears the Arg403Gln mutation in the alpha-cardiac myosin heavy chain gene, and the other line bears a truncation mutation in the cardiac myosin binding protein C gene. Heterozygous mice bearing these mutations develop features of FHC, whole homozygous mice bearing these mutations develop **dilated cardiomyopathy** and in one case, heart failure. We propose a series of experiments that should define the signaling pathways activated in these sarcomere defective mice. Specifically we propose to: 1) Identify molecules involved in the pathways that lead to **dilated cardiomyopathy** in MyBPC T/T mice and alphaMHC/403/403 mice. 2) Identify molecules in the pathways that lead to cardiac

hypertrophy in heterozygous MyBPC/T/+ mice and alphaMHC/403/+ MICE. 3) Assess the mechanisms by which cyclosporin induces rapid development of cardiac hypertrophy in sarcomere protein gene mutant bearing mice. 4) Define the phenotype of compound heterozygous MyBPC/T/+ mice and alphaMHC/403/+ mice. 5) Assess treatment phenotype of compound heterozygous MyBPC/T/+ mice and alphaMHC403/+ mice. 5) Assess treatment modalities and environmental factors that affect the cardiac response to sarcomere protein gene mutations. During the past few years we, in collaboration with other projects and Core facilities supported by this SCOR center, have developed the methods necessary to characterize these murine models. In particular, we have benefitted from associated with Core B which provide echocardiographic facilities which are essential for evaluation of mouse cardiac structure and Core C which performed histologic analysis which are a significant part of phenotype analyses. Further, our choice of disease gene models came from studies performed in collaboration with project 1. The analysis of cardiac function were originally conducted in collaboration with Dr. Ingwall. In the next granting period we, in collaboration with projects 3 (Dr. Ingwall) and 4 (Dr. Neer) will evaluate further these mutant mice using expertise and equipment available in the Core facilities. In summary, we propose to continue our efforts to define the signaling pathways that lead to and from sarcomere protein gene mutation to **dilated cardiomyopathy,** FHC and heart failure. We recognize that these studies will receive significant benefits from our close association with the SCOR center.

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- **Project Title: MOLECULAR EPIDEMIOLOGY OF DILATED CARDIOMYOPATH**

  Principal Investigator & Institution: Mestroni, Luisa; Director and Associate Professor; Medicine; University of Colorado Hlth Sciences Ctr P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2002; Project Start 01-JAN-2002; Project End 31-DEC-2005

  Summary: This proposal addresses the molecular epidemiology of **dilated cardiomyopathy** by determining the frequency of disease gene mutations, and the genotype/phenotype correlations in the patient population, and their clinical relevance. Idiopathic **dilated cardiomyopathy** (DCM) is a disease affecting the cardiac muscle and is a primary cause of heart failure leading to heart transplant. The etiology of DCM is mainly unknown, but the disease is frequently inherited and genetically heterogeneous. Linkage studies have identified 17 FDC disease loci including a locus mapped by the P.I.'s laboratory on chromosome 9 in a large kindred with autosomal dominant FDC. Thus far, 8 disease genes have been identified: the P.I.'s laboratory has contributed to the discovery of mutations in dystrophin gene leading to X-linked FDC, and more recently, has discovered lamin A/C gene mutations in patients with FDC and variable skeletal muscle involvement. Other investigators have reported mutations in cardiac actin, delta-sarcoglycan, desmin, tafazzin, beta-myosin heavy chain and troponin T leading to FDC. However, the prevalence, type and clinical relevance of cytoskeletal gene mutations in FDC, and in the overall DCM population are unknown. This application proposes a series of experiments designed to test the following hypotheses: 1) gene mutations are a frequent cause of FDC, 2) different gene mutations may have different frequency, different prognostic value, and different clinical relevance, 3) several FDC genes are still unidentified, and they are likely to encode cytoskeletal proteins. The Specific Aims of this proposal are: 1) to investigate of a cohort of patients with FDC and to evaluate their relatives to determine the inheritance pattern, the phenotype, the natural history, and recruit for molecular genetics studies; 2) to identify and characterize novel genes

causing FDC using a candidate gene approach and a positional candidate cloning approach; 3) to analyze the molecular epidemiology of known and novel disease genes by studying the prevalence, type, and genotype/phenotype correlation of the FDC gene mutations in a large patient population with or without a familial trait. Clinical data, DNA and, in the case of FDC, lymphoblastoid cell lines have already been collected from 478 subjects, and we anticipate the enrollment of 20 to 30 new families/year. The experimental methods include mutation screening of known and novel candidate genes, positional cloning of the FDC gene on chromosome 9 by linkage and association studies, analysis of the frequency and genotype/phenotype correlations using a large database designed for these studies. The identification of the genes and mutations responsible for DCM will greatly increase the understanding of the molecular basis of this disease and will allow for the development of new molecular- based diagnostic and therapeutic strategies.

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- **Project Title: MOLECULAR MECHANICS OF FHC & DCM MUTANT ACTOMYOSIN**

  Principal Investigator & Institution: Warshaw, David M.; Professor and Chariman; Molecular Physiol & Biophysics; University of Vermont & St Agric College 340 Waterman Building Burlington, Vt 05405

  Timing: Fiscal Year 2004; Project Start 15-DEC-2003; Project End 30-NOV-2007

  Summary: (provided by applicant): The goal of this proposal is to provide a molecular basis for the clinical impact that point mutations to cardiac actin and myosin's molecular structure have on patients afflicted with familial hypertrophic (FHC) and **dilated cardiomyopathy** (DCM). FHC is characterized by a thick, hypercontractile ventricular wall, whereas DCM patients have ventricles that are thin and hypocontractile. To understand how point mutations within actin or myosin result in such drastically different pathologies, information about the molecular mechanics of the mutant actomyosin motor is required. Our approach will take advantage of both transgenic mice and the Baculovirus system to express mutant cardiac actin and myosin that have single amino acid substitutions found in either FHC or DCM. Using state-of-the-art laser trapping techniques in an in vitro motility assay in force clamp mode, we will measure the force:velocity relationship of a small myosin ensemble (<50 molecules) as it interacts with a single actin or regulated thin filament. These data will provide an estimate of the maximum power that can be produced by a mutant actomyosin motor. Any alterations in power will be probed at the level of a single myosin molecule to determine if changes have occurred to the inherent motion generating capacity or to the rates of actomyosin transitions. Since the chosen mutations are localized throughout the myosin heavy chain (FHC: R403Q, R453C, G741R; DCM: S532P, F764L), we will directly pinpoint crucial intramolecular domains that are important to myosin's ability to generate force and motion. With actin being a key element in force production and thin filament regulation, mutations to actin that lead to FHC (E99K, A331P) and DCM (R312H, E361G) will be assessed for their impact on actin flexural rigidity, actomyosin power production, and thin filament regulation. These studies will help determine whether the impact of these point mutations on actomyosin's mechanical performance results in functional alterations that are common and distinct for a given form of hypertrophy so that one triggers a cascade of events resulting in either FHC or DCM.

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- **Project Title: MOLECULAR MECHANISM OF APOPTOTIC CARDIOMYOPATHY**

  Principal Investigator & Institution: Dorn, Gerald W.; Professor; Internal Medicine; University of Cincinnati 2624 Clifton Ave Cincinnati, Oh 45221

  Timing: Fiscal Year 2002; Project Start 15-DEC-1998; Project End 30-NOV-2002

  Summary: In tissue culture, cardiomyocyte hypertrophy occurs in response to mechanical stretching or exposure to Gq activating cardiotrophic factors. In vivo cardiac hypertrophy in hemodynamically overloaded hearts is also mediated in part by autocrine or paracrine activation of Gq coupled receptors. However, the reasons for decompensation and failure of cardiac hypertrophy which is initially "compensatory" are not known. Recently it was observed that Gq signaling at levels exceeding those which stimulate cardiomyocyte hypertrophy causes apoptotic cardiomyocyte death, suggesting a plausible mechanism for hypertrophy decompensation. We have created transgenic mice overexpressing the alpha subunit of Gq (Galphaq) and observed autonomous activation of protein kinase C (PKC) and development of nonfailing cardiac hypertrophy recapitulating molecular, cellular and functional features of pressure overloaded hearts. When Gq signaling and PKC activity were further enhanced, transition to a **dilated cardiomyopathy** occurred with widespread cardiomyocyte apoptosis. Thus, Galphaq overexpressors represent a unique model of cardiac hypertrophy resulting purely from autonomous activation of intrinsic signaling pathways, in which manipulation of these signaling events causes apparent apoptotic heart failure. We will utilize this transgenic model to: (SA numberl) Determine the effects of Gq-coupled receptor agonists verses peptide growth factors on cardiomyocyte hypertrophy or apoptosis, and on cardiac anatomy and function; (SA number2) Identify critical downstream mediators of cardiomyocyte apoptosis in agonist-stimulated Galphaq overexpressors by assaying the expression and activities of candidate kinases and apoptosis signaling proteins; (SA number3) Determine the apoptotic effects of cardiomyocyte PKC alpha, delta and epsilon signaling in comparison with signaling through Bax by combined transgenesis of Gaphaq with dominant negative PKCs or the apoptotic inhibitor Bcl-x1; (SA number4) Rescue Galphaq-mediated hypertrophy decompensation and cardiomyocyte apoptosis by restoring adenylyl cyclase activity through combined transgenesis with adenylyl cyclase type 5.

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

- **Project Title: MOLECULAR MECHANISMS IN T. CRUZI CARDIOMYOPATHY IN AIDS**

  Principal Investigator & Institution: Tanowitz, Herbert B.; Professor; Pathology; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2004; Project Start 01-JAN-2004; Project End 31-DEC-2008

  Summary: (provided by applicant): Chagas' disease is caused by the protozoan parasite T. cruzi and is now recognized as an emerging HIV/AIDS-related, opportunistic infection. Subsequent to immunosuppression there is reactivation of dormant organisms leading to myocarditis and necrotizing encephalitis. Since HIV-infected patients receiving HAART live for many years there is the likelihood that there will be repeated episodes of reactivation as their immune status waxes and wanes. Hence, progressive myocarditis and cardiovascular remodeling and chronic cardiomyopathy will likely develop in a more rapid fashion. In this application we have defined ventricular remodeling as changes in structure and function following myocardial damage together with characteristic molecular changes. These changes are the result of inflammation and/or necrosis. T. cruzi infection of the myocardium results in a **dilated**

cardiomyopathy. Our overall objective is to examine some of the important signaling pathways involved in cardiac remodeling as a consequence of the T. cruzi infection. We plan to examine the consequences of T. cruzi-infection on cyclins in vitro, Our investigations clearly indicate that T. cruzi-induced ERK activation modulates the expression and/or activity of cyclins, which function as mediators of cellular proliferation and differentiation. Cyclins are responsible for remodeling in the cardiovascular system. Therefore, the kinetics of the expression of cyclins in infected cultured cells and co-culture systems. Since we have demonstrated that T. cruzi induces expression of cyclin D1, we will determine the molecular mechanisms involved in regulation of cyclin D 1 promoter activation in cardiac fibroblasts employing transient transfection/promoter assays. We plan to determine the consequence of T. cruzi infection on cyclins in mouse models of chagasic heart disease on. During acute T. cruzi infection there is activation of ERK, transcription factors AP-1 and NF-kB and increased expression of cyclin D 1 in the myocardium. Therefore, in the mouse model of Chagas' disease the kinetics of expression of cell cycle regulatory proteins in the cells of the myocardium of T. cruzi-infected mice will be determined and correlated with progression of cardiomyopathy. The mechanisms underlying the alterations in these proteins in the myocardium will be investigated by a variety of techniques including immune complex assays and cell proliferation experiments. The contribution of cyclin D 1 in cardiovascular remodeling will be investigated utilizing mouse models including cyclin D1 null mice and mice in which NF-r.d3 and ET-1 have been selectively deleted from cardiac myocytes. These studies will lead to a better understanding of cardiac remodeling in chagasic cardiomyopathy, an emerging opportunistic infection in AIDS. In addition, it will provide potential targets of adjunctive therapy.

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- **Project Title: MOLECULAR PHYSIOLOGY OF MYOCARDIAL TROPONIN I VARIANTS**

  Principal Investigator & Institution: Murphy, Anne M.; Director, Mitachondrial Biology; Pediatrics; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2004; Project Start 13-SEP-1999; Project End 31-MAR-2008

  Summary: (provided by applicant): Contraction of the heart occurs through regulated interactions of the myofilament proteins in response to increasing intracellular calcium concentrations. Recent studies have shown that specific post-translational modifications to the myofilament regulatory protein, troponin I are involved in the progression and development of ischemia/reperfusion injury. Furthermore, alterations in the phosphorylation of troponin I are associated with heart failure. The underlying hypothesis of this proposal is that disease related posttranslational modifications of cardiac troponin I produce abnormalities of cardiac function that may be delineated by creating and characterizing in vivo models. The long-range goal of this work is to understand the underlying molecular mechanism by which these variants alter cardiac function in order to design strategies to prevent or treat cardiac dysfunction. The dissection of the molecular pathophysiology of troponin I post-translational modifications will be approached in a series of highly collaborative integrative studies focused on modeling of myofilament disease-related proteomic changes in vivo. We will also exploit a transgenic model of troponin I proteolysis we have developed in order to dissect other potential modifiers in the progressive cardiomyopathy in these mice. To address these goals the following aims are proposed: 1. To assess genomic and proteomic changes associated with the developmental progression in the phenotype of **dilated cardiomyopathy** in the troponin I 1-193 mice, with the goal of identifying early

alterations in the genome or specific subproteomes. 2. A. To determine whether constitutive "pseudo" phosphorylation of troponin I at protein kinase A sites protects the heart from deleterious effects of heart failure including a diminished force frequency response and delayed relaxation in response to increased afterload. B. To determine whether alterations in site-specific phosphorylation of troponin I by protein kinase A and protein kinase C associated with heart failure have a primary deleterious effect on cardiac muscle function in vitro and myocardial function in vivo. C. To determine the effect of a novel phosphorylation of troponin I at Serine 150 by p21activated kinase in vivo. This work should provide insight into the in vivo effects of specific post-translational modifications of the myofilaments, which contribute to pathophysiology of ischemic myocardial diseases and heart failure. In the long-term this will contribute to the development of novel therapies.

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- **Project Title: MUTANT SARCOMERIC PROTEINS AND CARDIAC DISEASE**

  Principal Investigator & Institution: Metzger, Joseph M.; Professor; Molecular and Integrative Physiology; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2004; Project Start 14-DEC-1998; Project End 30-JUN-2008

  Summary: (provided by applicant): The long-term goal of this work is to establish a unifying primary mechanism of cardiomyopathy pathogenesis. Hypertrophic cardiomyopathy (HCM) is defined as a disease of the sarcomere. Patients with HCM have diastolic dysfunction with normal or supra-normal systolic function. In comparison, **dilated cardiomyopathy** (DCM) patients present with diminished contractile function and ventricular chamber dilation. Unexpectedly, DCM and HCM share in common six sarcomeric genes as disease loci. It is presently unknown how mutations in identical genes can result in the divergent functional outcomes of DCM and HCM. In addition, recent study shows that restrictive cardiomyopathy (RCM), a disease of the myocardium characterized by restrictive filling with normal or decreased ventricular volume, can be caused by mutations in troponin I. The working hypothesis of this proposal is that distinct primary alterations in myocyte contractile performance result from specific mutations within the same or different sarcomeric gene(s), and this underlies, at least in part, the variable clinical phenotypes in hypertrophic cardiomyopathy, **dilated cardiomyopathy,** and restrictive cardiomyopathy. The experimental plan involves an array of high-fidelity single cardiac myocyte functional assays including a novel carbon-fiber-based technique to directly determine force and power output under physiological loads in living adult cardiac myocytes. The Specific Aims are: Aim 1. To determine the primary defect(s) caused by RCM-associated single missense mutations in cTnl. Hypothesis: RCM mutants will incorporate normally into the adult cardiac myocyte sarcomere and have a dominant effect to alter myocyte contractile performance. Aim 2. To determine whether specific DCM and HCM mutations in tropomyosin (Tm) and cardiac troponin T (cTnT) will produce specific and distinct differences in cardiac myocyte performance. Hypothesis: DCM mutations in Tm and cTnT will decrease twitch force and power output, and hasten relaxation performance. HCM mutants will have opposite effects.

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

- **Project Title: MYOCYTE FUNCTION IN CARDIOMYOPATHIC CREB A133 MICE**

  Principal Investigator & Institution: Moss, Richard L.; Robert Turell Professor and Chair of Phy; Physiology; University of Wisconsin Madison 750 University Ave Madison, Wi 53706

  Timing: Fiscal Year 2002; Project Start 30-SEP-1998; Project End 31-JUL-2003

  Summary: Dilated cardiomyopathy (DC) represents an important cause of cardiovascular morbidity and mortality and consumes a disproportionate share of medical resources in this country. Despite recent advances in the treatment of DC, this disorder has a poor prognosis with 5 year mortality rates of 20-50 percent. Progress in understanding the pathophysiology of DC and in devising new therapies for this disorder has been limited by our relative lack of understanding of the molecular pathophysiology of the disease and by the lack of a small animal model which closely resembles the anatomical, physiological, and clinical features of the human disease. The investigators have recently shown that transgenic mice expressing a dominant-negative form of the CREB transcription factor (CREBA133) under the control of the cardiac-specific alpha-MHC promoter reproducibly develop DC that resembles many of the anatomical, physiological and clinical features of human DC. In the studies described in these 3 collaborative R0I applications, the investigators propose to use this new mouse model to better understand the molecular pathways by which CREB regulates cardiac myocyte homeostasis and how perturbations in these pathways produce DC. Specifically, they will 1) elucidate the CREB-dependent signaling pathways that are required to maintain cardiac myocyte homeostasis and determine how these pathways are perturbed in the CREBA133 mice with DC, 2) determine the role of apoptosis in the CREBA133 DC and test the hypothesis that the cardiomyopathic phenotype can be ameliorated by expression of anti-apoptotic genes in the heart, 3) study excitation-contraction coupling, contractility, and calcium homeostasis in the CREBA133 cardiac myocytes, 4) understand the myofibrillar and SR defects underlying cardiac myocyte dysfunction in the CREBA133 mice, 5) study ventricular remodeling and LV-arterial coupling during the development of DC in the CREBA133 mice, and 6) determine the effects of exercise conditioning, gender, and different modes of inhibiting the renin angiotensin system on progression of DC in the CREBA133 mice. These studies represent the continuation of an established collaboration between molecular biologists (Leiden), cell physiologists (Moss) mouse and human physiologists (Lang, Spencer) and clinical cardiologists (Leiden, Lang, Spencer) from the Universities of Chicago and Wisconsin. Taken together the results of this work should provide us with important new insights into the molecular mechanisms underlying human DC and CHF.

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

- **Project Title: NO AND OXIDATIVE STRESS IN HUMAN MYOCARDIAL FAILURE**

  Principal Investigator & Institution: Givertz, Michael M.; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 15-AUG-1999; Project End 31-JUL-2004

  Summary: The overall goal of this project is to determine the functional significance of myocardial nitric oxide (NO) and oxidative stress in humans with heart failure (CHF). Recent evidence suggests that NO is increased in failing human myocardium and may contribute to the pathophysiology of CHF. In addition, increased myocardial oxidative stress has been demonstrated in heart failure. In vitro studies indicate that reactive oxygen species (ROS) can exert direct toxic effects on the myocardium associated with impaired contractility, fetal gene expression and cell death. Moreover, antioxidants have

been shown to attenuate the negative inotropic effects of ROS and prevent the development of heart failure in animal models. In left ventricular (LV) failure, the heart rate- mediated increase in contractility (force-frequency relationship) is attenuated, flat or even inverted. While the failure to increase contractility with tachycardia likely contributes to the reduced cardiac output response and exercise intolerance observed in patients with CHF, the underlying mechanisms are poorly understood. In Specific Aim 1, we will test the hypothesis that increased myocardial NO synthase (NOS) activity attenuates the force- frequency relationship in humans with LV failure by measuring the changes in the peak rate of rise of LV pressure (+dP/dt) that occur with increasing heart rates before and during intracoronary infusion of NG-monomethyl-L-arginine, an inhibitor of NOS. In Specific Aim 2, we will test the hypothesis that increased myocardial oxidative stress attenuates the force-frequency relationship in humans with LV failure by determining the force- frequency relationship before and during intracoronary infusion of the antioxidant ascorbic acid. Aims 1 and 2 are invasive protocols that will assess the acute functional significance of myocardial NO and oxidative stress in heart failure. In Specific Aim 3, we will test the ability of a novel, non-invasive system to detect acute changes in contractile state by measuring LV end-systolic elastance during atrial pacing tachycardia and intracoronary dobutamine infusion in patients with **dilated cardiomyopathy.** If we show that this new technology is able to measure changes in contractility in the catheterization laboratory, we will assess its ability to detect chronic changes in LV performance by measuring end-systolic elastance before and after therapy with antioxidants and/or anti- inflammatory agents in patients with systolic heart failure.

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

- **Project Title: OXIDATIVE STRESS IN ALCOHOLIC CARDIOMYOPATHY**

  Principal Investigator & Institution: Lui, Charles Y.; Associate Professor of Medicine; To Be Determined; University of Arizona P O Box 3308 Tucson, Az 857223308

  Timing: Fiscal Year 2003; Project Start 01-MAY-2003; Project End 30-APR-2005

  Summary: (provided by applicant): Alcoholism is one of the top public health problems in the U S Although alcohol abuse can cause cardiac muscle dysfunction with a relatively high prevalence, the early disease states usually go unrecognized clinically, since patients seldom experience any symptom of congestive heart failure When the extent of cardiac dysfunction becomes clinically evident, the disease has invariably resulted in a severely enlarged heart (**dilated cardiomyopathy**) commonly described as alcohol-induced heart muscle disease or alcoholic cardiomyopathy Experimental data generally supports the notion that alcohol is the sole causative agent in the development of this disease. However, there is a growing body of evidence to suggest that cardiomyopathy, regardless of etiology, is directly or indirectly related to an increased oxidative stress to the heart as a common final pathway. Since selenium and vitamin deficiencies are common among alcoholics, possibly as a result of malnutrition and/or malabsorption, it is hypothesized that alcoholic cardiomyopathy is caused by long-term alcohol abuse in the setting of nutritional deficiency involving both selenium and vitamin E. Since selenium and vitamin E are important anti-oxidants, a deficiency state involving these two anti-oxidants will result in a decrease in anti-oxidant defense. Alcohol consumption is well recognized to be associated with an increase in free radical production. Under these two specific nutritional deficiency states, the resultant decrease in anti-oxidant defense may not be adequate in quenching/removing the free radicals generated from high alcohol intake. This resultant increase in oxidative stress may damage various organs such as the heart leading to cardiac contractile dysfunction

manifested clinically as congestive heart failure. Therefore, the present study is designed to confirm such hypothesis by feeding rats long-term high-dose alcohol and diets deficient in selenium and/or vitamin E. Pressure-volume conductance and histological studies will be performed when echocardiographic study indicates a decrease. Biochemical and molecular studies of the cardiomyopathic heart will then be performed in cardiac function and ventricular enlargement after 40 weeks of feeding. They include measuring 4-hydroxy-2-nonenal, a major product and biomarker of lipid peroxidation. To investigate if increased apoptosis occurs as a result of increased oxidative stress, two consecutive measurements of apoptotic index and caspase 3 release will be conducted first when hypertrophy is detected from serial echocardiography and again with the development of alcoholic cardiomyopathy. The results obtained from this study will not only provide unique information regarding the pathogenetic mechanism involved in the development of alcoholic cardiomyopathy, but may also yield a new model of alcoholic cardiomyopathy suitable for future studies to evaluate therapeutic options such as selenium-, vitamin E supplementation, specific anti-metabolites of alcohol, specific anti-lipid peroxidation inhibitor or specific anti-apoptosis agent for preventing the development of alcoholic cardiomyopathy as well as reversing the far more prevalent yet frequently undiagnosed stage of alcoholic cardiomyopathy.

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- **Project Title: P57KIP2 IN VENTRICULAR CARDIOMYOCYTE DIFFERENTIATION**

  Principal Investigator & Institution: Kochilas, Lazaros; Women and Infants Hospital-Rhode Island 101 Dudley St Providence, Ri 029052499

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 30-JUN-2008

  Summary: This proposal focuses on the role of the cell cycle inhibitor p57KIP2, on the differentiation of ventricular myocytes. Previous studies suggest that p57KIP2 plays an important role regulating the balance between proliferation and differentiation in the developing heart and suggests its involvement in causing a thin-walled ventricular myocardium phenotype (**dilated cardiomyopathy**) in the mouse. We hypothesize that cardiac over-expression of p57KIP2 depletes the ventricular proliferative zone and leads to a thin myocardium phenotype by causing early terminal differentiation of cardiomyocytes. The goal of this proposal is to test this hypothesis by examining the effects of p57 KIP2 over-expression in the mouse and zebrafish animal models. I will pursue two specific aims: 1. Examine the role of p57KIP2 in the generation of the thin-walled myocardium phenotype in the mouse. - First, I will analyze the pattern of expression of p57 KIP2 in established murine models of thin myocardium. -Second, I will examine the effects of p57 KIP2 over-expression in the mouse heart by inducing Cre-loxP mediated activation driven by the myosin light chain-2 ventricular (MLC-2v) promoter. 2. Identify the zebrafish p57 KIP2 homologue, isolate its full length cDNA and perform in depth analysis of this zebrafish homologue, including: -detailed analysis of its temporal and spatial expression pattern by whole mount in situ hybridization and RT-PCR. -study the effects of the constitutive and cardiac specific over-expression of p57 KIP2 in the zebrafish. -study the effects of the morpholino induced inactivation of p57KIP2 in the zebrafish. These experiments will form the foundation for further investigating the role of p57KIP2 in the settings of **dilated cardiomyopathy,** ventricular hypertrophy and cardiac regeneration. Understanding the mechanisms underlying withdrawal of cardiomyocytes from the cell cycle will be important for the treatment of a wide range of cardiovascular diseases.

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

- **Project Title: PATHOGENESIS OF AUTOIMMUNE MYOCARDITIS**

  Principal Investigator & Institution: Rose, Noel R.; Professor; Pathology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 01-DEC-2001; Project End 30-NOV-2005

  Summary: (provided by applicant): Myocarditis is a major cause of sudden death in people under 40 years of age. While some myocarditis patients recover, many of them progress to **dilated cardiomyopathy,** an often fatal condition and a frequent reason for cardiac transplantation. Many cases of myocarditis are associated with an autoimmune process in which cardiac myosin is a major autoantigen. The mechanisms leading to the immune-mediated damage to the heart, particularly the role of cytokines, are not fully elucidated. We propose to study these mechanisms using the murine model of cardiac myosin-induced experimental autoimmune myocarditis (EAM) previously established in our laboratory. The goal of the present proposal is to delineate the mechanisms by which IL-4 and IFN-gamma, prototypic Th2 and Th1 cytokines respectively, influence the disease process. Our interest in these two cytokines is based on our preliminary findings which indicate that IL-4 has a disease-promoting role in EAM, whereas IFN-gamma limits the disease. Specific aims 1 and 2 will address the role of IL-4 in EAM and the mechanisms by which IL-4 promotes disease. Specific aims 3 and 4 will examine the role of IFN-gamma and the mechanisms by which IFN-gamma limits disease. We are planning to achieve these specific aims by blocking cytokines with specific antibodies, using cytokine and cytokine receptor knock out mice, and transferring disease with antibodies and subsets of T cells. Disease outcomes will be assessed by gross and histologic examination of the hearts. In vivo assessment will include echocardiography and pressure-volume analysis. Our preliminary findings contrast with the prevailing opinion that organ-specific autoimmune diseases are driven by a Th1 response and are ameliorated by a Th2 response. The proposed study will help us understand how Th1 responses may limit and Th2 responses may promote organ-specific autoimmunity. It will also provide us with a basis for designing new therapeutic interventions in patients with myocarditis.

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- **Project Title: PATHOGENESIS OF CHAGAS HEART DISEASE**

  Principal Investigator & Institution: Engman, David M.; Associate Professor; Pathology; Northwestern University Office of Sponsored Research Chicago, Il 60611

  Timing: Fiscal Year 2004; Project Start 01-JAN-2004; Project End 31-DEC-2007

  Summary: (provided by the applicant): The protozoan parasite Trypanosoma cruzi is the etiologic agent of Chagas' disease, an illness that causes severe morbidity and death among millions of Latin Americans. The most common, and most serious, adverse effect of chronic infection with this parasite is Chagas heart disease (CHD), a **dilated cardiomyopathy** of uncertain etiology. A number of mechanisms have been proposed for the pathogenesis of CHD, two of which are the subject of considerable controversy. Because parasites are scarce in or absent from the heart tissues of Chagas' patients who succumb to heart failure, autoimmunity has been proposed to be responsible for disease pathogenesis. More sensitive techniques, such as in situ PCR and immunohistochemistry, have been used to analyze these hearts and, indeed, parasite DNA and antigen are present. These findings support the hypothesis that parasite-induced damage plus host immunity to parasite antiqens is the inflammatory stimulus. Another confounding factor is that different combinations of parasite and animal strains give different outcomes, which, in actuality, is reflective of the human disease. To test

the autoimmunity hypothesis for CHD pathogenesis, while simultaneously considering the parasite immunity hypothesis, we developed a mouse model of CHD (T. cruzi Brazil strain infection of male A/J mice) in which strong cardiac autoimmunity and parasite-specific immunity rapidly develop upon infection. Our research during the past several years indicates that (i) cardiac autoimmunity develops upon infection that is of similar magnitude and quality as that induced by immunization with cardiac proteins in adjuvant (purely autoimmune), (ii) autoimmunity involving a number of cardiac antigens develops in infected animals, (iii) autoimmunity to cardiac myosin may develop via the mechanisms of molecular mimicry and bystander activation, and (iv) selective suppression of myosin autoimmunity does not eliminate tissue inflammation in infected animals, suggesting that other autoimmune responses may be significant and/or that parasite-specific immunity hypothesis is sufficient to give tissue inflammation. The Specific Aims of our research are (i) to investigate the molecular mimicry mechanism of myosin autoimmunity in CHD, (ii) to identify additional cardiac auto-antigens and determine their roles in CHD pathogenesis and (iii) to test the autoimmune and parasite immune hypotheses for CHD pathogenesis.

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- **Project Title: PEDIATRIC HEART DISEASE NETWORK: CHOP MEMBERSHIP**

  Principal Investigator & Institution: Vetter, Victoria L.; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 191044399

  Timing: Fiscal Year 2002; Project Start 01-SEP-2001; Project End 31-AUG-2006

  Summary: (provided by applicant) As a Clinical Center in the new Pediatric Heart Disease Clinical Research Network (PHDCRN), the Children?s Hospital of Philadelphia (CHOP) will participate collaboratively with the Network to improve outcomes for children with heart disease, provide an evidential base for therapies currently used or considered, develop new therapies, and disseminate that information to the medical community. To achieve this goal, we will address the following aims: Aim 1: Develop an infrastructure and investigational team for to assure full participation in PHDCRN; Aim 2: Develop procedures and policies to assure proper implementation of approved PHDCRN protocols; Aim 3: Fully participate in the development new protocols and dissemination of information to the scientific community. Two protocols are proposed for the PHDCRN?s scientific agenda that emphasize the research strengths of the Cardiology Division, the Cardiac Center and CHOP. The short-term study investigates the use of biventricular pacing or cardiac resynchronization in children with severe congestive heart failure and **dilated cardiomyopathy.** The primary aim of the study is to evaluate the acute effects of biventricular pacing on cardiac function as measured by oxygen consumption during exercise in a 6-week randomized controlled clinical trial. After the 6-week randomized comparison, all patients are paced and longer-term effects on cardiac function, functional capacity and quality of life will be evaluated out to 12 months. The long-term project investigates whether enalapril (ACE inhibition) can reduce the time-related decline in exercise performance experienced by patients with single ventricle who have undergone the Fontan procedure. The primary aim will be to evaluate the effects of ACE inhibition over a 4-year period on maximal oxygen consumption measured during exercise testing in a double blinded randomized clinical trial design. The Children?s Hospital of Philadelphia Cardiology Division and Cardiac Center has a distinguished history of clinical innovation and excellence in cardiac care, a high volume program with expertise in all areas of pediatric cardiology including cardiac arrhythmias, echocardiography, exercise physiology catheterization including interventions, intensive care, cardiac magnetic resonance imaging, transplantation, and

surgery for heart disease. Patient care is integrated through a multidisciplinary Cardiac Center. The faculty of the Cardiac Center are experienced investigators and maintain a highly productive program of multicenter and institutional clinical trials and studies. CHOP has made major investments in the clinical research infrastructure that support essential functions in clinical investigations. These programmatic and institutional strengths support the aims and enhance the likelihood that the long-term goals of the PHDCRN will be achieved.

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- **Project Title: PORE OPENING: A TARGET FOR MITOCHONDRIAL DNA MUTATIONS**

  Principal Investigator & Institution: Zassenhaus, H Peter.; Molecular Microbiol and Immun; St. Louis University St. Louis, Mo 63103

  Timing: Fiscal Year 2002; Project Start 01-APR-2001; Project End 31-MAR-2006

  Summary: (provided by the applicant): Mitochondrial dysfunction is seen not only in late-onset neurodegenerative disease, such as Alzheimer's, Parkinson's, and Huntington's, but with aging in the normal brain as well. Since the frequency of mitochondrial DNA (mtDNA) mutations in the brain climbs hundreds to thousands of fold with age, it is widely thought that such mutations may contribute to cause mitochondrial dysfunction. To experimentally probe their pathophysiology, transgenic mice were constructed that rapidly accumulate specifically mtDNA mutations in cardiomyocytes. These mice reveal that mtDNA mutations - at frequencies commonly seen with age or disease in humans - indeed cause pathology. Characterization of mitochondria from those mice suggests a novel molecular mechanism for the pathogenesis of elevated levels of mtDNA mutations. As mutations rise so do the levels of mutant proteins encoded by the mitochondrial genome. Some of these mutant proteins will misfold. One of the major chaperones catalyzing protein folding in mitochondria is cyclophilin D (CyP-D), a peptidyl-prolyl cis/trans isomerase that also functions to regulate mitochondrial pore transition. Elevated levels of misfolded mitochondrial-encoded proteins are proposed to lead to dysfunction of CyP-D and, in turn, to dysregulation of pore transition. Catastrophic pore transition is known to cause massive disruption of calcium homeostasis in neurons and to signal cell death by apoptosis. To test these hypotheses, we propose to: 1) characterize the structural and functional alteration in CyP-D that occur when the levels of mtDNA mutations rise, 2) determine the basis for the alteration in mitochondrial pore transition that occurs when mutation levels rise, and 3) generate transgenic mice with an accelerated accumulation of mtDNA mutations in the brain to characterize the effect(s) of these mutations on the function of CyP-D and the permeability transition pore in neurons. These studies are broadly significant to understand molecular mechanisms for the pathogenesis of mtDNA mutations. Since such mutations may be an important contributing factor for many adult-onset diseases, these studies may provide insights into novel therapeutic strategies.

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

- **Project Title: PULMONARY LIMITATIONS IN CHRONIC HEART FAILURE**

  Principal Investigator & Institution: Johnson, Bruce D.; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2002; Project Start 10-JUL-2002; Project End 30-JUN-2007

Summary: (provided by applicant): The central theme of our proposal is to understand mechanisms of exercise intolerance in Chronic Heart Failure (CHF) and to ultimately use this information to help guide rehabilitation and medical management of this growing population. This is of importance because, the incidence of CHF increases 50-fold between the ages of 40 and 60 years and the disease is the nation's most rapidly growing cardiovascular disorder. Two specific aims focused on heart and lung interactions will be addressed. First, we will test the hypothesis that breathing during exercise influences cardiac function. We will test this by, a) examining the influence of transient and sustained increases in lung volume on cardiac function during exercise using continuous positive airway pressure, expiratory threshold loading and voluntary maneuvers, b) determining the effects of intra-thoracic pressure changes on cardiac output via loading and unloading the respiratory muscles using proportional assist ventilation during exercise, c) examine if a muscle chemosensitive reflex may stimulate ventilation in CHF greater than in controls by using post-exercise leg ischemia, and d) determining if the respiratory muscles "steal" blood flow from locomotor muscles during exercise by unloading respiratory muscles and measuring leg blood flow. Second, we will examine a neurohumoral basis for structural changes in the pulmonary system and altered exercise tolerance in CHF by examining a polymorphism of a key regulatory enzyme, angiotensin-converting enzyme (ACE, which exists in 2 forms, insertion-Il and deletion-DD alleles). We will test this by, a) determining if the activated renin-angiotensin system in CHF enhances ACE genotype related differences in pulmonary and cardiovascular function relative to controls, b) determining if the altered pulmonary function in the DD genotype of CHF patients is related to alterations in pulmonary vascular tone and permeability and independent of cardiac function c) examining if complete blockade of angiotensin-Il (A-Il) with A-Il receptor blockers will abolish genotype differences in the CHF subjects.

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

- **Project Title: REGULATION OF CA-SIGNALING IN MYOFILAMENTS BY TROPONIN C**

  Principal Investigator & Institution: Liao, Ronglih; Medicine; Boston University Medical Campus 715 Albany St, 560 Boston, Ma 02118

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2007

  Summary: (provided by applicant): Emerging evidence has linked mutations in myofilament proteins to the development of myocardial dysfunction and genetic cardiomyopathy. We recently have identified two novel missense mutations in human cardiac troponin C at amino acid residues 59 (E59D) and 75 (D75Y) from a patient with idiopathic **dilated cardiomyopathy.** This is the first identified mutation of troponin C in any human disease. Troponin C is responsible for transmitting the Ca2+-binding signal and triggering the contractile cycle. These missense mutations are located within the Ca2+-binding domain that regulates myocardial contraction, and result in decreased myofilament Ca2+ responsiveness. Based on our preliminary results, we hypothesize that the optimal spatial relationship between helix A and Ca2+-binding loop II must be maintained for proper TnC-regulated Ca2+ signaling in cardiac myofilaments. To test this hypothesis, we propose a systematic, multidisciplinary approach utilizing three integrated levels of investigation: isolated proteins, cardiac myocytes and transgenic animals. First, we will use a mutational model system by generating a number of troponin C mutants based on replacing specific amino acid residues located within regulatory Ca2+-binding domain and define the Ca2+-binding properties of the troponin C mutants (Specific Aim 1). Secondly, we will use adenovirus-mediated gene

delivery technique to express specific troponin C mutants in contractile apparatus to elucidate how mutations in cardiac troponin C alter myofilament Ca2+ responsiveness and myocyte contractility (Specific Aim 2). Finally, we will generate a transgenic mouse over-expressing troponin C found in IDCM heart to reveal whether troponin C mutants cause **dilated cardiomyopathy** (Specific Aim 3). The results obtained from this proposal will help us to understand the physiological role of specific structural alterations in troponin C in the regulation of Ca2+-signaling in cardiac myofilaments in normal and diseased myocardium. Furthermore, the knowledge gained here may contribute to the future development of therapeutic agents using troponin C as a target protein for the treatment of myocardial dysfunction in heart disease.

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- **Project Title: REGULATION OF NA,K ATPASE BY THE AH RECEPTOR**

  Principal Investigator & Institution: Walker, Mary K.; Associate Professor of Pharmacology And; None; University of New Mexico Albuquerque Controller's Office Albuquerque, Nm 87131

  Timing: Fiscal Year 2002; Project Start 05-AUG-2000; Project End 31-JUL-2004

  Summary: Human exposure during pregnancy to persistent environmental pollutants, like 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related chemicals, results in decreased birth weights, neurological deficits, thyroid hormone alterations, lung auscultation, and hyperpigmentation. The mechanism by which TCDD mediates developmental toxicity has not been elucidated. The basic helix-loop-helix-PAS transcription factor, aryl hydrocarbon receptor (AhR), is required for TCDD-induced teratogenicity in mice and likely mediates teratogenicity in other species. TCDD toxicity may result from alterations in gene transcription by the AhR. One potential AhR gene target that could account for some of TCDD's teratogenic effects is the Na+/K+ ATPase alpha1. Putative dioxin response elements are conserved in the 5' enhancer region of the mammalian and avian Na+/K+ ATPase alpha1 gene. In the chick embryo, TCDD reduces myocardial Na+/K+ ATPase alpha1 protein expression, induces a **dilated cardiomyopathy,** and alters ECGs, all consistent with reduced Na+/K+ ATPase activity. In mice lacking the AhR, embryos develop a hypertrophic cardiomyopathy and cardiac fibrosis which worsens with age, consistent with the potential overexpression of Na+/K+ ATPase alpha1 and development of hypertension. I will use the chick embryo and AhR null mice to test the hypothesis that the AhR regulates myocardial expression of the Na+/K+ ATPase alpha1 gene, altering cardiovascular development. The aims of this proposal are to (1) elucidate the regulation of myocardial Na+/K+ ATPase alpha1 gene in AhR null mice and in the developing chick embryo by TCDD using RT-PCR, and in vitro by promoter analysis of the avian gene; (2) determine the tissue significance of this regulation by quantitating myocardial ouabain binding sites and Na+/K+ ATPase enzyme activity in AhR null mice and TCDD-exposed chick embryos; (3) determine the functional significance by measuring blood pressure in AhR null mice and myocardial sensitivity to ouabain in TCDD-exposed chick embryos by ECG; and (4) analyze the expression of murine and avian homologues of candidates genes, whose expression is altered by TCDD in the rat embryo heart and lung as identified by Dr. Selmin, University of Arizona, by PCR-selected subtractive hybridization method and screening of gene microarrays.

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

- **Project Title: RIGHT VENTRICULAR DYSFUNCTION AND TREATMENT**

  Principal Investigator & Institution: Semigran, Marc J.; Assistant Professor; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2002; Project Start 12-APR-1999; Project End 31-MAR-2004

  Summary: Heart failure represents the results of a variety of cardiovascular diseases in which the initial insult to the myocardium may either be identifiable, such as a myocardial infarction, or unknown, such as in **dilated cardiomyopathy.** In either case, the occurrence of injury to the myocardium leads to an inexorable course of myocardial dysfunction. While most previous investigations have concentrated on the abnormalities in left ventricular function, there is evidence that right ventricular (RV) function is a more important determinant of patients symptoms and prognosis. Few therapies currently exist to improve RV performance, as currently used systemic vasodilator therapy can cause hypotension when nonselective pulmonary vasodilators are added to a patient's therapeutic regimen. Nitric oxide (NO) activates vascular smooth muscle cell soluble guanylate cyclase leading to vasodilation. The vasodilator effect of NO is limited in time by its rapid binding to, and inactivation by hemoglobin. In preliminary studies, inhaled NO has been demonstrated to be a selective pulmonary vasodilator which can improve cardiac performance and exercise capacity in heart failure patients. The goal of this proposal is to combine type 5 (cGMP- specific) phosphodiesterase inhibiton with inhaled NO to: 1. Assess the acute alterations in right ventricular function, overall cardiac performance and exercise capacity in heart failure patients treated with the combination of inhaled NO and the type 5 phosphodiesterase inhibitor sildenafil. 2. Assess the acute and chronic effects of selective pulmonary vasodilation with inhaled nitric oxide and type 5 phosphodiesterase inhibition on pulmonary artery resistance and morphology in patients with pulmonary hypertension due to pulmonary vascular disease or to left heart failure. 3. Assess the effects of acute and chronic pulmonary vasodilator and the subsequent decrease in wall stress on the activity of proteins which regulate myocyte apoptosis.

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

- **Project Title: SEX DIFFERENCES IN EARLY MYOCARDIAL REPOLARIZATION**

  Principal Investigator & Institution: Kadish, Alan H.; Professor; Medicine; Northwestern University Office of Sponsored Research Chicago, Il 60611

  Timing: Fiscal Year 2004; Project Start 01-JUL-2004; Project End 30-JUN-2008

  Summary: (provided by applicant): Sex differences in the QT interval have been known since the early 1900s. In contrast, sex differences in the ST segment consisting of a higher ST height and elevated J point have only recently been studied in detail. There are sex differences in clinical arrhythmias that may be associated with the sex ECG differences. Ventricular tachycardia is inducible in 35-40 percent of men but only 20 percent of women with coronary artery disease and LV dysfunction. Women are only half as likely as men to develop VF as a cause of cardiac arrest are. The fact that there are important sex differences in susceptibility to certain arrhythmias suggests the existence of fundamental electrophysiologic distinctions between males and females that remain to be elucidated. The overall hypothesis of the present study is that sex differences in early myocardial repolarization are rate dependent, are due to effects of sex hormones and alter the propensity to clinical arrhythmias. The following specific hypotheses will be tested. 1) A major determinant of ST height is the level of sex hormones. We will also seek to determine whether the ST elevation seen most often in athletic males sometimes called "early repolarization" is a distant clinical syndrome. 2) Sexrelated differences in

myocardial repolarization are dependent on both heart rate and autonomic tone. This aim will be accomplished by examining the heart rate dependence of ST height before and after autonomic manipulations in both men and women. 3) Androgens but not estrogens or progesterone modulate early repolarization. This aim will be accomplished by studying subjects who will undergo sex hormone therapy. 4) ST elevation that has previously been characterized as benign based on incomplete data alters the propensity to arrhythmias under appropriate pathologic conditions. In this aim, the relationship between ST elevation on the resting ECG and ventricular tachycardia and ventricular fibrillation will be examined. Studies will be performed in patients with acute and healed myocardial infarction and in patients with non-ischemic **dilated cardiomyopathy.** It is hoped that the results of this study will improve the understanding of myocardial physiology and improve risk stratification and therapy for arrhythmias by uncovering important sex related differences.

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- **Project Title: SPECIALIZED CENTER OF RESEARCH IN HEART FAILURE**

  Principal Investigator & Institution: Seidman, Christine E.; Professor; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 15-JAN-1995; Project End 31-JAN-2005

  Summary: Heart failure is a leading cause of disability and death in the U.S. affecting at least 4.7 million individuals, with an estimated 400,000 new cases each year. Progress in the prevention and treatment of heart failure has been limited in magnitude due in some part to an incomplete understanding of basic biologic phenomena and mechanisms that underlie the clinical syndrome. This Heart Failure SCOR proposal attacks the problem across a spectrum of basic to clinical studies. The theme unifying these studies is that heart failure is a continuum of molecular phenomena and cellular mechanisms. These direct the progression from an underlying cause, such as a single nucleotide substitution in the DNA of an individual with familial dilated cardiomyopathy-to the multiple disturbances of cell and organ function and regulation that comprise the clinical syndrome of heart failure, irrespective of the initial inciting cause. The participating Project Leaders have an extensive record of produce collaboration and have focused their efforts on five interactive projects with substantial efforts of interface. Dr. C. Seidman's project seeks to identify genetic causes of inherited **dilated cardiomyopathy** with the expectation that during the next granting period a common theme will emerge that explains the significant genetic heterogeneity of this condition. Dr. (Michel) Project seeks to define the role of the interactions between caveolae and myocyte signaling proteins that evolve during the development and progression of heart failure. Project 3 (Ingwall) combines biophysical, biochemical and molecular biologic tools to test the hypothesis that decreased energy reserve via the creatine kinase system impairs contractile mutated G/a0 subunits that develop **dilated cardiomyopathy** with compensatory hypertrophy. These die of heart failure within two months. Pathways that link transgene expression to heart failure in these mice will be defined. Dr. Seidman's project has developed two genetically engineered lines of mice that are models of familial hypertrophic cardiomyopathy; these mice will be studied to determine those factors that worsen cardiac hypertrophy and in some, cause **dilated cardiomyopathy** and heart failure. All projects will interact closely with Core B (Mende and Lee), which has the technology to prepare and characterize contractile function of individual myocytes as well as to obtain non-invasive imaging of murine and human hearts to evaluate cardiac function. Cardiac histology, immunohistochemistry and in situ hybridization will be provided by CORE c (Schoen) to evaluate gene expression in the

myocardium. In all of these interactive projects, the collaborating fundamental biological phenomena and mechanisms that bear on improved prevention and treatment of patients at risk. The aggregate productivity of coordinated project efforts has already exceeded the expectations of the individual components and we anticipate that these benefits will expand even further during the next granting period.

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

- **Project Title: SPECIALIZED CENTER OF RESEARCH IN HEART FAILURE**

  Principal Investigator & Institution: Mann, Douglas; Professor; Medicine; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2002; Project Start 17-FEB-1995; Project End 31-JAN-2005

  Summary: The overall objective of the current SCOR and the Proposed Renewal is to elucidate the molecular basis for the long-term adaptive response of the heart to injury, both inherited and acquired, where manifested by hypertrophy or dilitation. This proposal encompasses 5 collaborative investigations, supported by integrated core facilities to address issues fundamental to the etiology, pathogenesis and treatment of cardiac failure. Novel genes will be identified responsible for inherited cardiac disorders, familial **dilated cardiomyopathy** (FDCM) manifested in the left ventricle and arryhthmogenic right ventricular dysplasia in the right ventricle, as paradigms of **dilated cardiomyopathy,** the most common form of acquired heart failure. To date, two genes (cytoskeletal) have been identified that cause DCM, actin and desmin. Thus, cytoskeletal proteins may provide a unifying causality for DCM analogous to that of sarcomeric proteins for HCM. Accordingly, insight gained from expression of the mutant desmin in the transgenic mouse should have pathogenetic implications for DCM due to other defective cytoskeletal proteins, whether familial or acquired. While assembly and organization of the cytoskeletal components are an integral part of the cardiac growth response, their role as heretofore been ignored until the identification of the integrin signaling pathway (RhoA, Focal Adhesion Kinase, and Integrin Linked Kinase). In Dr. Schwartz' project, dominant negative mutants of these molecules will be used in cardiac myocytes and Gene-Switch transgenics to determine whether one or all of these are necessary for cytoskeletal assembly and hypertrophy. FHCM, due to over 100 mutations in seven genes, develops the secondary phenotype of increased fibrosis and hypertrophy, providing the opportunity for prevention. Renin-angiotensin system (RAS) inhibitors will be assessed in transgenics harboring the human cTNT mutation and, in preparation for future gene therapy, Gene-Switch will be used to determine if the phenotype is reversible. Growth factor(s) responsible for the secondary phenotype will be sought through subtraction hybridization. A novel pathway (TNFalpha) shown in the current SCOR to play a pivotal role in the growth response (hypertrophy) and heart failure (apoptosis), will be pursued to identify molecular interaction with RAS, both in genetic models and in patients with heart failure and to develop novel specific therapies. Strategies to achieve the aims, will utilize "state of the art" techniques: automated genetic analyzers for genotyping and DNA sequencing, BACs, YACs, and DNA microchip arrays to identify genes, the RU-486 Gene Switch to regulate expression of transgenes, PCR-generated dominant negative mutants, "gutless" tetracycline dependent adenoviral vectors, selective elimination of genes (knock-out mice), and Ta178 radionuclide angiography to assess mouse cardiac function. These studies elucidate further the molecular foundations of cardiac hypertrophy and failure and should provide a rational basis for more effective therapy.

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

- **Project Title: STEROID AS CYTOPROTECTANTS AGAINST OXIDATIVE TOXICITY**

  Principal Investigator & Institution: Chen, Qin M.; Associate Professor; Pharmacology and Toxicology; University of Arizona P O Box 3308 Tucson, Az 857223308

  Timing: Fiscal Year 2004; Project Start 01-APR-2004; Project End 31-MAR-2008

  Summary: (provided by applicant): Stress is known to cause an increase in the synthesis of corticosteroids by the adrenal glands. Although corticosteroids have been shown to contribute to the pathophysiology of suppressed Immune response and a number of psychiatric disorders, the effect of CT on the heart remains unclear. Doxorubicin (Dox) is an anti-neoplastic drug that can produce chronic cardiac toxicity which is manifested as **dilated cardiomyopathy.** An important feature of this form of cardiomyopathy is the apoptosis of cardiomyocytes. Our preliminary studies found that corticosterone (CT) pretreatment prevented Dox from inducing apoptosis of cardiomyocytes. The glucocorticoid receptor antagonist mifepristone prevented CT from inducing a cell survival response. Several forms of g!ucocorticoids, aldosterone, progesterone and retinoic acid but not estrogen, testosterone or L-thyroxin can inhibit apoptosis of cardiomyocytes. Analyses of ERK, Akt and SGK-1 activities or bcl-2 expression indicated that CT neither activated the known survival kinases nor elevated the expression of the anti-apoptotic gene bcl- 2. The conditioned medium of CT-treated cardiomyocytes shows partially cytoprotective effective. The TranSignal array approach found that CT treatment could potentially activate 21 transcription factors. We hypothesize that activation of the glucocorticoid receptor initiates transcriptional activation of survival genes in cardiomyocytes in vitro and in vivo. Specific aims of this grant include: 1) To test if CT binding causes its receptor to interact with and to activate multiple transcription factors in cardiomyocytes; 2) To test that the activation of cell survival genes contributes to CT-induced cytoprotection; and 3) To demonstrate that CT protects the heart from cardiomyopathy induced by Dox in vivo via inducing the transcription of cell survival genes. This project will combine our expertise in genomics, transcriptomics and proteomics to systematically study the linkage between the glucocorticoid receptor and cell survival mechanisms. Given the fact that stress is unavoidable in our daily life, this project will provide novel information to advance our understanding in the biological effect of corticosteroids on the heart. More importantly, since apoptosis has been shown to contribute to heart failure induced by the chemotherapy agent Dox as well as by many forms of cardiovascular disease, our finding and proposed mechanistic study will provide a hope for novel therapy against heart failure in the future.

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- **Project Title: T CELL COSTIMULATION AND REGULATION IN MYOCARDITIS**

  Principal Investigator & Institution: Lichtman, Andrew H.; Associate Professor; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2007

  Summary: (provided by applicant): Auotimmune myocarditis, which can occur after viral infection, underlies many cases of **dilated cardiomyopathy.** CD8+ cytolytic T lymphocytes mediate much of the damage in myocarditis, but the mechanisms by which naive CD8+ T cell tolerance is broken, and the regulation of autoreactive effector CD8+ T cells are incompletely understood. In this proposal, a newly developed transgenic model of myocarditis will be used to study the regulation of heart antigen-specific CD8+ T cells and to determine how several T cell costimulatory and inhibitory pathways

influence disease. Mice that express the model antigen ovalbumin (cMy-mOva) will be used in conjunction with ovalbumin peptide-specific CD8+ T cells from the OT-1 TCR transgenic mouse. Adoptive transfer of activated OT-1 cells, or naive OT-I cells followed by infections with ovalbumin-expressing virus, causes myocarditis in cMy-mOva-ova mice. Disease can be assessed by histology, serum troponin levels, ultrasonography, and mortality. There are three Specific Aims in this proposal. Specific Aim 1. Determine the role of CTLA-4 in regulation of heart-antigen specific CD+ T cells. CTLA-4 is a negative regulator of T cell activation, but little is known, about the role of this molecule in inhibiting autoreactive CD8+ T cells. In this Aim, the pathogenic potential and in vivo fate of CTLA-4+/+ and CTLA-4 OT-I cells in alpha MHC-ova mice will be compared. Specific Aim 2. Determine the role of the PD-1:PD-L 1/2 pathway in CD8+ T cell-mediated myocarditis PD-1, a newly identified member of the CD28 family, inhibits effector functions of T cells when it binds its ligands PD-L1 and PD-L2. The role of this pathway in negatively regulating heart-antigen specific CD8+ T cells in vivo will be explored using PD-L1/L2 -/- cMy-mOva mice as recipients of OT-I cells. Specific Aim 3. Determine the role of ICOS in CD8+ T cell-mediated myocarditis. ICOS, a member of the CD28 family of costimulatory molecules, may have particular importance in sustaining activation of effector T cells. In this Aim, the pathogenic potential, effector functions, and in vivo fate of ICOS -/- and ICOS +/+ OT-I cells will be compared in the cMy-mOva mouse model of myocarditis. This project will provide new information about the regulation of autoreactive CD8+ T cells, and will clarify how CD8+ T cell responses against myocardial antigens are controlled. The focus is on newly characterized T cell regulatory pathways, which are potential targets for immunotherapy of myocarditis and other autoimmune diseases.

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- **Project Title: THE CYTOSKELETON IN HAART-INDUCED CARDIOMYOPATHY**

  Principal Investigator & Institution: Bowles, Neil E.; Instructor; Pediatrics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-JUL-2007

  Summary: (provided by applicant): One of the consequences of the development of improved therapies for the treatment of HIV infection and the acquired immunodeficiency syndrome, and the associated longer survival of infected patients, has been the emergence of diseases such as myocarditis and/or **dilated cardiomyopathy** (DCM). A number of etiological agents have been proposed to be responsible for the initiation of the pathologic processes leading to the development of myocarditis and DCM in HIV-infected patients. These have included infection of myocytes with HIV or cardiotropic viruses, or cardiotoxicity resulting from drugs commonly used by AIDS patients, such as AZT. Monotherapy with AZT is uncommon today because highly active antiretroviral therapy (HAART) is a formidable clinical combination. However, AZT has been reported to cause a mitochondrial skeletal myopathy, similar to inherited skeletal myopathies, as well as myopathies secondary to inherited cardiomyopathies. Dystrophin was identified as the gene responsible for cardiomyopathy in patients with X-linked cardiomyopathy (XLCM). Dystrophin is thought to provide structural support for the myocyte and cardiomyocyte membrane. Mutations in dystrophin or dystrophin associated protein subcomplexes result in a wide spectrum of skeletal myopathy and/or cardiomyopathy in humans and animal models such as the mouse or hamster. We have recently shown in patients with DCM or ischemic cardiomyopathy that dystrophin remodeling is a useful indicator of left ventricular function. It has been reported that the 2A protease of Coxsackievirus B3, a major etiologic agent of acquired DCM, is capable of

cleaving dystrophin, resulting in sarcolemmal disruption in infected mouse hearts. Further, in murine models of DCM defects in the integrity of dystrophin and/or other components of the cytoskeleton may be important in disease pathogenesis in these models. In order to further delineate the role of cytoskeletal disruption in models of acquired DCM we are proposing the following specific aims: Specific Aim 1: Delineation of the events leading to disruption of the cytoskeleton in transgenic mice. Specific Aim 2: Characterization of the cytoskeleton in HAART-treated transgenic mice. Specific Aim 3: Role of extrinsic stimuli in the development of HAART-induced cardiomyopathy.

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- **Project Title: THE UBIQUITIN-PROTEASOME SYSTEM IN CARDIAC REMODELING**

  Principal Investigator & Institution: Wang, Xuejun; University of South Dakota 414 E Clark St Vermillion, Sd 57069

  Timing: Fiscal Year 2002; Project Start 20-SEP-2002; Project End 31-AUG-2007

  Summary: A long term goal of this proposal is to delineate the mechanisms by which protein surplus cardiomyopathies (PSCs) progress to congestive heart failure. PSCs are an emerging group of cardiomyopathies. Crystallinopathy caused by the mutation of the alphaB-crystallin (CryAB) gene, often presents as desmin-related cardiomyopathy (DRC) and exemplifies PSCs. DRC is characterized by aberrant desmin aggregation in muscle cells and this aggregation appears to play a central role in DRC pathogenesis. Notably, similar protein aggregates were also observed in human congestive heart failure (CHF) resulting from idiopathic **dilated cardiomyopathy,** a common heart disease. However, it remains unclear how abnormal protein aggregation affects myocyte functions. The current proposal focuses on the ubiquitin-proteasome system (UPS) mediated protein turnover, a cellular process essential to virtually all aspects of cell function. The central hypothesis is that aberrant protein aggregation characteristic of DRC impairs proteolytic function of the UPS, representing a nodal pathogenic process in PSCs. These specific aims will be pursued: (1) To test whether CryAB has an obligatory role in UPS function and to define a correlation (likely a causal relation) between aberrant protein aggregation and UPS impairment in intact mice. The underlying hypothesis is that aberrant protein aggregation instead of loss-of-function of CryAB impairs the UPS in crystallinopathic hearts. (2) To test a cause-effect link between aberrant protein aggregation and UPS impairment in cell culture. This is to test the hypothesis that formation of protein aggregates through expression of a mutant CryAB is sufficient to compromise UPS function. (3) To discover the identities of ubiquitylated proteins accumulated in crystallinopathy mouse hearts lusing proteomics. Underlying hypothesis is that accumulated ubiquitylated proteins include structural proteins and physiologically important regulatory proteins.

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

- **Project Title: THIN FILAMENTS WITH CARDIOMYOPATHIC MUTANT PROTEINS**

  Principal Investigator & Institution: Tobacman, Larry S.; Professor; Internal Medicine; University of Iowa Iowa City, Ia 52242

  Timing: Fiscal Year 2002; Project Start 15-JAN-2000; Project End 31-DEC-2003

  Summary: (adapted from the applicant's description): Familial Hypertrophic Cardiomyopathy (FHC) is an autosomal dominant disorder caused by mutations in any of several genes encoding the proteins of the cardiac contractile apparatus. This project

will characterize the effects of FHC-causing mutations on the in vitro function of the various thin filament proteins so far implicated in this disorder: troponin T, troponin 1, and alpha-tropomyosin. By comparing normal and mutant proteins, the project will provide some of the insight required to understand the pathophysiology of cardiac disease in these patients. Also, the applicant will use the mutations to test the mechanism by which cardiac contraction is regulated by troponin and tropomyosin. A multi-faceted study of the mutant proteins is planned, with examination of several protein-protein affinities (including thin filament binding of troponin, of troponin-tropomyosin, and of myosin Sl; troponin binary subunit interactions; effects of calcium and of myosin on these various processes), calcium affinity, myosin MgATPase regulation, folding stability, in vitro motility, in vitro force, and structural effects on the regulatory conformational switching of the thin filament as determined by 3-D reconstructions of electron micrographs. A smaller number of mutations, identified in the cardiac actin gene, have been found causative in a subset of patients with another genetic disorder: **dilated cardiomyopathy.** Mutant forms of actin will be similarly examined for alterations in interactions with tropomyosin and troponin. (1) FHC mutations occurring in two regions of troponin T will be investigated. Troponin T mutants R92Q, R92W, Al 04V, and Fl 01 I occur in or near a region of troponin T that the applicant recently identified as forming a critical portion of the troponin tail. In a different region, the effects of FHC-linked COOH-terminal truncation of 28 residues will be studied. (2) Six troponin I mutations that occur in FHC will be similarly investigated, all located in the region of troponin I that interacts with the regulatory domain of troponin C. (3) Five FHC-linked tropomyosin mutants will be created and similarly studied, as will an actin mutation that causes inherited **dilated cardiomyopathy** and that is hypothesized to interact abnormally with tropomyosin.

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- **Project Title: TISSUE RENIN ANGIOTENSIN/CHYMASE SYSTEM IN HEART FAILURE**

  Principal Investigator & Institution: Dell'italia, Louis J.; Professor; Medicine; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

  Timing: Fiscal Year 2002; Project Start 01-AUG-1995; Project End 31-JAN-2006

  Summary: (the applicant's description verbatim): The PI has studied the role of the cardiac renin angiotensin system (RAS)/chymase system in mechanisms of angiotensin II (ANG II) formation in the heart in response to volume overload heart failure. These studies demonstrated increased expression of RAS and chymase in the dog heart associated with LV dilatation (decreased wall thickness/diameter ratio), increased matrix metalloproteinase (MMP) activity, and dissolution of the fine collagen weave. Neither suppression of tissue ANG II with ACE inhibitor, nor blockade of the AT1 receptor modulated this remodeling process. Further, heterozygote ACE knockout mice (1/0), having 40 percent of tissue ACE activity compared to wild type, had a significantly lower w/t diameter ratio than wild type mice in response to volume overload. There was a failure to downregulate LV MMP activity in the 1/0 mice vs. 1/1 mice and in dogs with chronic MR. In both animal models, chymase activity was upregulated and not effected by blockade of the RAS. There is recent compelling evidence that remodeling of the extracellular matrix (ECM) is regulated by MMPs in **dilated cardiomyopathy.** Inhibition of tissue ACE, by its effect of decreasing ANG II and increasing bradykinin (BK), can promote MMP synthesis and activation. In addition, chymase can also directly cleave and activate MMPs. Thus, the hypothesis of the current proposal is that tissue concentrations of ACE and chymase mediate the LV

remodeling pattern in response to volume overload by their influence on myocardial MMP activational state. The PI will measure interstitial fluid (ISF) ANG II, BK, and MMP activational state in the conscious rat (low chymase/ACE activity ratio) and hamster (high chymase/ACE activity ratio) in response to volume overload stress. This approach combined with targeted transgenic models of variable ACE expression and increased chymase expression will relate in-vivo LV function and collagen weave by scanning EM to MMP activation. Viral vectors for chymase antisense will be utilized in the heart failure models in the rat, hamster, and mouse. In the absence of an orally effective chymase inhibitor, this approach will answer important questions regarding the physiological importance of the relative concentrations of ACE and chymase in LV remodeling in heart failure.

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- **Project Title: TITIN AND HEART FUNCTION AND DISEASE (INDIVIDUAL)**

  Principal Investigator & Institution: Granzier, Henk L.; Professor; Vet & Comp Anat/Pharm/Physiol; Washington State University 423 Neill Hall Pullman, Wa 99164

  Timing: Fiscal Year 2002; Project Start 30-SEP-1998; Project End 31-AUG-2003

  Summary: (Adapted from the applicant's abstract) Titin is a recently discovered protein that extends in the sarcomere from the Z-line to the M-line and that forms, in addition to thin and thick filaments, the third myofilament of the cardiac sarcomere. The segment of the molecule that is found in the I-band behaves elastically when sarcomere length is changed. The PI's laboratory has shown that extension of this elastic segment underlies the majority of the passive force developed by cardiac myocytes when stretched beyond their slack length. The work has also indicated that, over a considerable part of the physiological sarcomere-length range, titin-based passive force is an important contributor to the diastolic wall stress of rat myocardium. Furthermore, in rat cardiac myocytes titin also develops restoring force when sarcomeres shorten to below the slack length, indicating that titin may be able to contribute to the elastic diastolic recoil of the heart that aids in ventricular filling. Titin's importance in determining the compliance of the heart is also suggested by studies that have reported reduced expression of titin in patients with dilated cardlomyopathy. However, no systematic study has been carried out on the relation between the properties of titin (the amount of titin and its elasticity) and the altered compliance of cardiac muscle during heart disease. Altered compliance of the heart may result not only from titin, but also from changes in the cytoskeleton, as well as changes in the extracellular matrix (collagen). The investigators' aim is to study each of these components in the normal heart and in the diseased heart. They will first focus on **dilated cardiomyopathy** (DCM) using the turkey model of DCM. The investigators' preliminary work has revealed that, relative to the normal heart, the left ventricle of the DCM heart functions at much shorter sarcomere lengths, and that diastolic wall stress of the DCM heart increases more steeply with sarcomere length. These and other findings support the need to dissect the molecular origin of the diastolic properties of normal and DCM hearts. To study whether the findings can be extrapolated to other species, the canine heart will also be studied, both from normal animals and animals with DCM produced by rapid pacing. Finally, the investigators propose to study the role of titin in the altered ventricular compliance in human patients with DCM. A multi-faceted approach will be taken with mechanical, immuno-electron microscopical, and biochemical techniques at the molecular, cellular, multi-cellular and isolated heart level. (End of Abstract)

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- **Project Title: TRANSCRIPTIONAL REGULATION OF CARDIOMYOCYTE DEVELOPMENT**

  Principal Investigator & Institution: Huggins, Gordon S.; New England Medical Center Hospitals 750 Washington St Boston, Ma 021111533

  Timing: Fiscal Year 2002; Project Start 25-SEP-1995; Project End 31-JUL-2004

  Summary: (the applicant's description verbatim): The normal development of the cardiovascular system is regulated by a complex set of molecular pathways that interpret environmental and developmental signals into changes in cardiovascular gene expression. Perturbations of these signaling pathways have been implicated in a number of prevalent human cardiovascular diseases including congenital cardiac malformations, pathologic cardiac hypertrophy, and **dilated cardiomyopathy.** During the last ten years we have studied the nuclear transcription factors that regulate the development and function of the mammalian cardiovascular system. In an initial series of experiments we identified a cardiac-specific transcriptional promoter/enhancer in the 5' flanking region of the cardiac troponin C (cTnC) gene. We used this promoter to identify a set of nuclear transcription factors that appear to play important roles in regulating early cardiomyocyte development and cardiac morphogenesis. Among these was the GATA4 zinc finger protein that binds to and trans-activates a wide variety of cardiac specific transcriptional regulatory elements. Using a gene targeting approach we showed that GATA4 is necessary for the formation of the primitive ventral heart tube during early murine embryogenesis. More recently, we identified a second zinc finger protein called cardiac friend of GATA (CFOG) that is expressed in the developing heart and that binds specifically to the N-terminal zinc finger of GATA4. Similarly, Olson and coworkers recently demonstrated that GATA4 also interacts with the rel-related protein NFAT3 and that these two proteins appear to be important regulators of cardiac myocyte hypertrophy. The long term goal of the studies described in this continuing RO1 proposal is to understand the molecular mechanisms by which GATA proteins, in conjunction with other transcriptionfactors and coactivator/ repressor proteins regulate cardiogenesis and cardiac hypertrophy. Specifically we will (1) map the regions of GATA4 that are required for its central role in the heart tube formation. (2) genetically and biochemically characterize the interaction between GATA4 and CFOG and understand the effects of this interaction on the transcriptional activity of GATA4, (3) Use gene targeting to determine the roles of NFAT3 and CFOG in cardiac development and function in the mouse. Together, the results of these studies should provide novel basic insights into the molecular pathways that regulate normal cardiac development and function. They should also be relevant to understanding the molecular pathophysiology of a number of clinically important inherited and acquired cardiovascular diseases.

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

- **Project Title: VEGF TRANSFER TO PROMOTE ANGIOGENESIS IN ADVANCED CHF**

  Principal Investigator & Institution: Mccarthy, Patrick M.; St. Elizabeth's Medical Center of Boston 736 Cambridge St Boston, Ma 02135

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002; Project End 31-AUG-2003

  Summary: The clinical investigations outlined in this Project are designed to test the hypothesis that direct intramyocardial injections of naked DNA encoding for vascular endothelial growth factor (phVEGF165) in patients with advanced heart failure is safely tolerated and may in some patients lead to improvement in their clinical status. The

clinical trials that we have proposed incorporate a strategy that is designed to address patients in whom all medial measures to treat advanced congestive heart failure (CHF) have failed, leaving these patients in need of cardiac transplantation. Owing to the mismatch that currently exists between the number of patients in need of cardiac transplantation and the number of available donors, implantation of a left ventricular assist device (LVAD) Is often required for patients as a so- called "bridge" to transplantation. It is this population of patients-those undergoing LVAD implantation for advanced heart failure-that re intended to be addressed in the current Proposal. For the purpose of our clinical studies, these patients have been divided into two large subgroups, based on associated evidence on extramural coronary artery disease (CAD). Accordingly, the specific aims of this Proposal are as follows: 1. Specific Aim #1: To evaluate the safety and impact of phVEGF/165 gene transfer on LV function in patients with CHF due to coronary artery disease. 2. Specific Aim #2: To evaluate the safety and impact of phVEGF165 gene transfer on LV function in patients with CHF due to idiopathic **dilated cardiomyopathy,** excluding patients with significant narrowing of the extramural coronary arteries of primary valvular heart disease. 3. Sp4ecific Aim #3: To evaluate the efficacy of phVEGF gene transfer to allow for LVAD bridge-to-recovery (BTR) as an alternative to transplantation.

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- **Project Title: VINCULIN AND METAVINCULIN FUNCTION IN THE MYOCARDIUM**

  Principal Investigator & Institution: Ross, Robert S.; Associate Professor; Veterans Medical Research Fdn/San Diego Foundation of San Diego San Diego, Ca 92161

  Timing: Fiscal Year 2003; Project Start 18-APR-2003; Project End 31-MAR-2007

  Summary: (provided by applicant): The cytoskeleton and actin-associated proteins provide for cellular structural integrity and function as a critical link between the extracellular matrix and the contractile apparatus of the myocyte. The focal adhesion is the intersection between the extracellular matrix and the cellular cytoskeleton, and may be a pivotal point for transmission of mechanical signals and organization of the actin based cytoskeleton. Vinuclin is a key focal adhesion protein. While vinculin is found in all cells, a muscle-specific splice variant termed metavinculin is found only in smooth and cardiac muscle. The biological role of metavinculin is poorly understood and its deficiency or mutation has been linked to human **dilated cardiomyopathy.** Homozygous vinculin knockout mice die by mid-gestation with severe neural and cardiac abnormalities via an unknown mechanism. Heterozygous vinculin knockout mice survive and breed normally but have abnormal cardiac function and die suddenly. It is possible that the cardiac abnormalities are due to direct affects of the vinculin deficiency in cardiac myocytes or related to alterations in non-cardiac cells. We hypothesize that normal vinculin expression in cardiac myocytes is crucial for appropriate cardiogenesis, cardiac myofibrillogenesis and function of the mature heart and that distinct biological functions of metavinculin exist. To test this we will manipulate vinculin and metavinculin in cultured cardiac myocytes and in the murine genome. Molecular, biochemical and immunocytochemical studies of cultured cells will be performed. Analysis of intact developing mice and the adult murine heart will likewise be evaluated by molecular, morphological, biochemical and physiological techniques. We propose the following specific aims: 1. Examine the role of vinculin in cardiogenesis and post-natal function of the heart by use of currently existing global vinculin "knockout" mice. 2. Study how deletion of the vinculin gene specifically in cardiac myocytes alters cardiac form and function. 3. Evaluate the biological function of

the muscle-specific splice-variant metavinculin as distinct from vinculin, in cultured cardiac myocytes and the intact mouse.

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- **Project Title: XANTHINE OXIDASE INHIBITOR FOR CONGESTIVE HEART FAILURE**

  Principal Investigator & Institution: Novorozhkin, Alex; Inotek Pharmaceuticals Corporation 100 Cummings Ctr, Ste 419E Beverly, Ma 01915

  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 31-JUL-2003

  Summary: (provided by applicant): Congestive heart failure (CHF) is a major market opportunity for therapeutics that targets the fundamental etiology of the ventricular injury. Although the pathogenesis of CHF is complex, recent data suggest an inflammatory basis secondary to free radical generation by the purine degradative enzyme xanthine oxidase (XO). In the well-established pacing dog model, which produces a **dilated cardiomyopathy** and many of the classic features of CHF, XO activity is 4-fold increased and the weak XO inhibitor allopurinol increases dP/dt(max), preload-recruitable stroke work, and ventricular elastance. In heart failure dogs, but not controls, allopurinol decreases MVO2 and substantially increases mechanical efficiency. Taken together, these data indicate that XO inhibition is uniquely inotropic, increasing myocardial contractility while simultaneously reducing cardiac energy requirements. The resultant boost in myocardial contractile efficiency may prove beneficial in the treatment of clinical CHF. The market for allopurinol is limited by its infrequent but severe side-effects. We now report the discovery of a non-purine class of XO inhibitors that is 1,000-fold more potent than allopurinol. Preliminary data confirm that a prototype of this class profoundly reduces inflammation in experimental models of acute lung injury and enterocolitis. The central objective of this Phase I grant proposal is to establish in vivo proof of principle that the lead candidate dose-dependently improves contractile function in the classic dog model of CHF induced by chronic pacing. We will then define the pharmacodynamic profile of XO therapy, begun after the establishment of CHF. Cardiac contractility will be assessed using left ventricular pressure-volume analysis, dP/dT, stroke volume, and ejection fraction. The classic weak XO inhibitor allopurinol will be included in all studies as a reference standard. We expect that our lead non-purine ultrapotent XO inhibitor will dose-dependently improve dP/dT, with an ED5O greater than 2-fold greater than allopurinol. PROPOSED COMMERCIAL APPLICATION: Sale of $500 million per annum are anticipated in the US alone, based upon an estimate of a 1% incidence of CHF in the general population (=2.5 million potential subjects), a 10% market penetration, and an annual expenditure per patient of $2,000. The worldwide market (developed countries only) is four times larger. Given the intoleerance for allopurinol in 10% of patients, and the current absence of a second-line medication, we expect the market acceptance of a safe and effective alternative XO inhibitor to be achieved rapidly over a five year period. We believe the high price point ($6 per day) is amply justified by the lack of an alternative to allopurinol. Estimated worldwide gross sales revenues after market entry and maturation (ca. 4 years after FDA approval) are expected to equal $1-2 billion per annum.

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- **Project Title: XANTHINE OXIDASE, MYOCARDIAL GENOMICS AND HEART FAILURE**

  Principal Investigator & Institution: Cappola, Thomas P.; Medicine; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

  Timing: Fiscal Year 2003; Project Start 01-AUG-2003; Project End 31-JUL-2008

  Summary: (provided by the applicant):Cardiac hypertrophy is a central pathologic feature of congestive heart failure. Prior investigations suggest that oxidative stress induces the expression of hypertrophy genes in vitro, and may be an important cause of cardiac hypertrophy in humans. The applicant proposes to merge his interest in clinical investigation with state-of-the-art genomic approaches to determine how oxidative stress promotes cardiac hypertrophy in humans. Based on preliminary data, he will focus on xanthine oxidase as a source of myocardial oxidative stress. The central thesis of this proposal is that increased myocardial XO contributes to heart failure by stimulating the transcription of hypertrophy genes. In Aim 1, the applicant will use Affymetrix microarrays to determine genes associated with hypertrophy in failing explanted human myocardium. Multiple analytic approaches will be used, including a hypothesis-based analysis of pre-selected candidate genes, exploratory analyses, and global analyses of patterns in gene expression. In Aim 2, the applicant will demonstrate that myocardial XO activity correlates with expression of these hypertrophy genes in humans. In Aim 3, the applicant will test the hypothesis that XO inhibition with allopurinol attenuates the expression of hypertrophy genes in serial endomyocardial biopsies, and prevents an increase in cardiac mass in patients with **dilated cardiomyopathy.** These experiments will determine the transcriptional targets of XO in human myocardium, thereby clarifying the role of oxidative stress in heart failure. Moreover. they are the first steps in determining whether XO inhibition is a novel treatment strategy for heart failure. This research will be performed at the Johns Hopkins Medical Institutions under the mentorship of Dr. Joshua Hare, an expert in the field of oxidative stress in heart failure. Genomic analyses will be performed in collaboration with the HopGene PGAmApplied Genomics in Cardiopulmonary Disease. The applicant's interdisciplinary training, strong mentorship, career development program, supportive environment, and novel research plan will give him the experience and tools he needs to develop into a highly successful, independent clinical investigator.

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

E-Journals: PubMed Central[3]

PubMed Central (PMC) is a digital archive of life sciences journal literature developed and managed by the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM).[4] Access to this growing archive of e-journals is free and unrestricted.[5] To search, go to **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Pmc**, and type "dilated cardiomyopathy" (or synonyms) into the search box. This search gives

[3] Adapted from the National Library of Medicine: **http://www.pubmedcentral.nih.gov/about/intro.html**.

[4] With PubMed Central, NCBI is taking the lead in preservation and maintenance of open access to electronic literature, just as NLM has done for decades with printed biomedical literature. PubMed Central aims to become a world-class library of the digital age.

[5] The value of PubMed Central, in addition to its role as an archive, lies in the availability of data from diverse sources stored in a common format in a single repository. Many journals already have online publishing operations, and there is a growing tendency to publish material online only, to the exclusion of print.

you access to full-text articles. The following is a sample of items found for dilated cardiomyopathy in the PubMed Central database:

- **Activation of Mst1 causes dilated cardiomyopathy by stimulating apoptosis without compensatory ventricular myocyte hypertrophy.** by Yamamoto S, Yang G, Zablocki D, Liu J, Hong C, Kim SJ, Soler S, Odashima M, Thaisz J, Yehia G, Molina CA, Yatani A, Vatner DE, Vatner SF, Sadoshima J.; 2003 May 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=155047
- **Defects in caveolin-1 cause dilated cardiomyopathy and pulmonary hypertension in knockout mice.** by Zhao YY, Liu Y, Stan RV, Fan L, Gu Y, Dalton N, Chu PH, Peterson K, Ross J Jr, Chien KR.; 2002 Aug 20; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=123264
- **Defects in nuclear structure and function promote dilated cardiomyopathy in lamin A/C --deficient mice.** by Nikolova V, Leimena C, McMahon AC, Tan JC, Chandar S, Jogia D, Kesteven SH, Michalicek J, Otway R, Verheyen F, Rainer S, Stewart CL, Martin D, Feneley MP, Fatkin D.; 2004 Feb 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=324538
- **Detection of enteroviral RNA in idiopathic dilated cardiomyopathy and other human cardiac tissues.** by Weiss LM, Liu XF, Chang KL, Billingham ME.; 1992 Jul; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=443075
- **Failure of atrial natriuretic factor to increase with saline load in patients with dilated cardiomyopathy and mild heart failure.** by Volpe M, Tritto C, De Luca N, Mele AF, Lembo G, Rubattu S, Romano M, De Campora P, Enea I, Ricciardelli B, et al.; 1991 Nov; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=295653
- **Human phospholamban null results in lethal dilated cardiomyopathy revealing a critical difference between mouse and human.** by Haghighi K, Kolokathis F, Pater L, Lynch RA, Asahi M, Gramolini AO, Fan GC, Tsiapras D, Hahn HS, Adamopoulos S, Liggett SB, Dorn GW II, MacLennan DH, Kremastinos DT, Kranias EG.; 2003 Mar 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153772
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The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[6] The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

To generate your own bibliography of studies dealing with dilated cardiomyopathy, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type "dilated cardiomyopathy" (or synonyms) into the search box, and click "Go." The following is the type of output you can expect from PubMed for dilated cardiomyopathy (hyperlinks lead to article summaries):

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  Author(s): Olgun H, Ceviz N, Ozkan B.
  Source: Turk J Pediatr. 2003 April-June; 45(2): 152-4.
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[6] PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.

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CHAPTER 2. NUTRITION AND DILATED CARDIOMYOPATHY

Overview

In this chapter, we will show you how to find studies dedicated specifically to nutrition and dilated cardiomyopathy.

Finding Nutrition Studies on Dilated Cardiomyopathy

The National Institutes of Health's Office of Dietary Supplements (ODS) offers a searchable bibliographic database called the IBIDS (International Bibliographic Information on Dietary Supplements; National Institutes of Health, Building 31, Room 1B29, 31 Center Drive, MSC 2086, Bethesda, Maryland 20892-2086, Tel: 301-435-2920, Fax: 301-480-1845, E-mail: ods@nih.gov). The IBIDS contains over 460,000 scientific citations and summaries about dietary supplements and nutrition as well as references to published international, scientific literature on dietary supplements such as vitamins, minerals, and botanicals.[7] The IBIDS includes references and citations to both human and animal research studies.

As a service of the ODS, access to the IBIDS database is available free of charge at the following Web address: **http://ods.od.nih.gov/databases/ibids.html**. After entering the search area, you have three choices: (1) IBIDS Consumer Database, (2) Full IBIDS Database, or (3) Peer Reviewed Citations Only.

Now that you have selected a database, click on the "Advanced" tab. An advanced search allows you to retrieve up to 100 fully explained references in a comprehensive format. Type "dilated cardiomyopathy" (or synonyms) into the search box, and click "Go." To narrow the search, you can also select the "Title" field.

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[7] Adapted from **http://ods.od.nih.gov**. IBIDS is produced by the Office of Dietary Supplements (ODS) at the National Institutes of Health to assist the public, healthcare providers, educators, and researchers in locating credible, scientific information on dietary supplements. IBIDS was developed and will be maintained through an interagency partnership with the Food and Nutrition Information Center of the National Agricultural Library, U.S. Department of Agriculture.

The following information is typical of that found when using the "Full IBIDS Database" to search for "dilated cardiomyopathy" (or a synonym):

- **A case of polymyositis with dilated cardiomyopathy associated with interferon alpha treatment for hepatitis B.**
  Author(s): The Hospital for Rheumatic Diseases, Hanyang University, 17 Haengdong-dong, Seongdong-gu, Seoul 133-792, Korea.
  Source: Lee, Seung Won Kim, Ki Chan Oh, Dong Ho Jung, Sung Soo Yoo, Dae Hyun Kim, Seong Yoon Choe, Gheeyoung Kim, Tae Hwan J-Korean-Med-Sci. 2002 February; 17(1): 141-3 1011-8934

- **A rat model of dilated cardiomyopathy to investigate partial left ventriculectomy.**
  Author(s): Department of Cardiovascular Surgery, Matsue Red-Cross Hospital, Shimane, Japan.
  Source: Yuasa, S Nishina, T Nishimura, K Miwa, S Ikeda, T Hanyu, M Fujioka, Y Kihara, Y Sasayama, S Komeda, M J-Card-Surg. 2001 Jan-February; 16(1): 40-7 0886-0440

- **A rat model of ischaemic or dilated cardiomyopathy for investigating left ventricular repair surgery.**
  Author(s): Department of Cardiovascular Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan.
  Source: Nishina, T Miwa, S Yuasa, S Nishimura, K Komeda, M Clin-Exp-Pharmacol-Physiol. 2002 August; 29(8): 728-30 0305-1870

- **Acute dilated cardiomyopathy and central nervous system toxicity following propranolol intoxication.**
  Author(s): Toxicology Unit, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel. matyl@bgumail.bgu.ac.il
  Source: Lifshitz, M Zucker, N Zalzstein, E Pediatr-Emerg-Care. 1999 August; 15(4): 262-3 0749-5161

- **Angiotensin-converting enzyme inhibitors improve coronary flow reserve in dilated cardiomyopathy by a bradykinin-mediated, nitric oxide-dependent mechanism.**
  Author(s): Cardiovascular Research Institute, Department of Medicine, Allegheny General Hospital, Pittsburgh, Pa 15212, USA.
  Source: Nikolaidis, Lazaros A Doverspike, Aaron Huerbin, Rhonda Hentosz, Teresa Shannon, Richard P Circulation. 2002 June 11; 105(23): 2785-90 1524-4539

- **Anticoagulation in patients with dilated cardiomyopathy and sinus rhythm: a critical literature review.**
  Author(s): Division of Cardiovascular Diseases, Department of Internal Medicine, University of Florida Health Science Center, Jacksonville, FL, USA.
  Source: Sirajuddin, Riaz A Miller, Alan B Geraci, Stephen A J-Card-Fail. 2002 February; 8(1): 48-53 1071-9164

- **Anti-mitochondrial flavoprotein autoantibodies of patients with myocarditis and dilated cardiomyopathy (anti-M7): interaction with flavin-carrying proteins, effect of vitamin B2 and epitope mapping.**
  Author(s): Institute of Biochemistry and Molecular Biology, University of Freiburg, Germany.
  Source: Stahle, I Brizzio, C Barile, M Brandsch, R Clin-Exp-Immunol. 1999 March; 115(3): 404-8 0009-9104

- **Comparison of effects of ascorbic acid on endothelium-dependent vasodilation in patients with chronic congestive heart failure secondary to idiopathic dilated cardiomyopathy versus patients with effort angina pectoris secondary to coronary artery disease.**
  Author(s): The First Department of Internal Medicine, Kobe University School of Medicine, Japan.
  Source: Ito, K Akita, H Kanazawa, K Yamada, S Terashima, M Matsuda, Y Yokoyama, M Am-J-Cardiol. 1998 September 15; 82(6): 762-7 0002-9149

- **Evaluation of the regional responsivity to ryanodine of human myocardium from patients with idiopathic dilated cardiomyopathy and secondary cardiomyopathies.**
  Author(s): Department of Pharmacology, University of Padua, Padova, Italy.
  Source: Padrini, R Panfili, M Testolin, L Pesarin, F Piovan, D Magnolfi, G Livi, U Casarotto, D Dalla Volta, S Basic-Res-Cardiol. 1996 Sep-October; 91(5): 361-6 0300-8428

- **Idiopathic dilated cardiomyopathy presenting in pregnancy.**
  Author(s): Department of Anaesthesia & Intensive Care, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, China.
  Source: Chan, F Ngan Kee, W D Can-J-Anaesth. 1999 December; 46(12): 1146-9 0832-610X

- **Plasma clearance of polyfructosan and extracellular body fluid distribution in idiopathic dilated cardiomyopathy and after heart transplantation.**
  Author(s): The Heart Center, The Rigshospital, Copenhagen, Denmark. Galatius@dadlnet.dk
  Source: Galatius, S Bent Hansen, L Wroblewski, H Kastrup, J Am-J-Cardiol. 2000 April 1; 85(7): 843-8 0002-9149

- **Thiamin, selenium, and copper levels in patients with idiopathic dilated cardiomyopathy taking diuretics.**
  Author(s): Hospital Universitario Pedro Ernesto, IBRAG, Geologia - UERJ, Rio de Janeiro, RJ, Brazil. sergio@netfly.cm.br
  Source: da Cunha, S Albanesi Filho, F M da Cunha Bastos, V L Antelo, D S Souza, M M Arq-Bras-Cardiol. 2002 November; 79(5): 454-65 0066-782X

- **Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration.**
  Author(s): University of Athens Medical School, Greece.
  Source: Rizos, I Am-Heart-J. 2000 February; 139(2 Pt 3): S120-3 0002-8703

- **Transient dilated cardiomyopathy in a newborn exposed to idarubicin and all-trans-retinoic acid (ATRA) early in the second trimester of pregnancy.**
  Author(s): Department of Pediatrics (Cardiology), Texas Children's Hospital, 6621 Fannin, MC 19345-C, Houston, TX 77030, USA.
  Source: Siu, B L Alonzo, M R Vargo, T A Fenrich, A L Int-J-Gynecol-Cancer. 2002 Jul-August; 12(4): 399-402 1048-891X

Federal Resources on Nutrition

In addition to the IBIDS, the United States Department of Health and Human Services (HHS) and the United States Department of Agriculture (USDA) provide many sources of information on general nutrition and health. Recommended resources include:

- healthfinder®, HHS's gateway to health information, including diet and nutrition: **http://www.healthfinder.gov/scripts/SearchContext.asp?topic=238&page=0**
- The United States Department of Agriculture's Web site dedicated to nutrition information: **www.nutrition.gov**
- The Food and Drug Administration's Web site for federal food safety information: **www.foodsafety.gov**
- The National Action Plan on Overweight and Obesity sponsored by the United States Surgeon General: **http://www.surgeongeneral.gov/topics/obesity/**
- The Center for Food Safety and Applied Nutrition has an Internet site sponsored by the Food and Drug Administration and the Department of Health and Human Services: **http://vm.cfsan.fda.gov/**
- Center for Nutrition Policy and Promotion sponsored by the United States Department of Agriculture: **http://www.usda.gov/cnpp/**
- Food and Nutrition Information Center, National Agricultural Library sponsored by the United States Department of Agriculture: **http://www.nal.usda.gov/fnic/**
- Food and Nutrition Service sponsored by the United States Department of Agriculture: **http://www.fns.usda.gov/fns/**

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering food and nutrition. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=174&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/med_nutrition.html**
- Google: **http://directory.google.com/Top/Health/Nutrition/**
- Healthnotes: **http://www.healthnotes.com/**
- Open Directory Project: **http://dmoz.org/Health/Nutrition/**
- Yahoo.com: **http://dir.yahoo.com/Health/Nutrition/**
- WebMD®Health: **http://my.webmd.com/nutrition**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**

The following is a specific Web list relating to dilated cardiomyopathy; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **Food and Diet**

  Hypertension
  Source: Healthnotes, Inc.; www.healthnotes.com

CHAPTER 3. ALTERNATIVE MEDICINE AND DILATED CARDIOMYOPATHY

Overview

In this chapter, we will begin by introducing you to official information sources on complementary and alternative medicine (CAM) relating to dilated cardiomyopathy. At the conclusion of this chapter, we will provide additional sources.

National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (**http://nccam.nih.gov/**) has created a link to the National Library of Medicine's databases to facilitate research for articles that specifically relate to dilated cardiomyopathy and complementary medicine. To search the database, go to the following Web site: **http://www.nlm.nih.gov/nccam/camonpubmed.html**. Select "CAM on PubMed." Enter "dilated cardiomyopathy" (or synonyms) into the search box. Click "Go." The following references provide information on particular aspects of complementary and alternative medicine that are related to dilated cardiomyopathy:

- **A physiological oral magnesium supplement does not influence total serum magnesium, left ventricular ejection fraction and prognosis in patients with dilated cardiomyopathy.**
  Author(s): Fruhwald FM, Dusleag J, Fruhwald SM, Grisold M, Gasser R, Klein W.
  Source: Magnes Res. 1993 September; 6(3): 251-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8292499

- **Adult chronic lead intoxication. A clinical review.**
  Author(s): Balestra DJ.
  Source: Archives of Internal Medicine. 1991 September; 151(9): 1718-20. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1888236

- **Afterload reduction: a comparison of captopril and nifedipine in dilated cardiomyopathy.**
  Author(s): Agostoni PG, De Cesare N, Doria E, Polese A, Tamborini G, Guazzi MD.
  Source: British Heart Journal. 1986 April; 55(4): 391-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3516187

- **Analytical performance and clinical usefulness of a commercially available IRMA kit for measuring atrial natriuretic peptide in patients with heart failure.**
  Author(s): Clerico A, Iervasi G, Del Chicca MG, Maffei S, Berti S, Sabatino L, Turchi S, Cazzuola F, Manfredi C, Biagini A.
  Source: Clinical Chemistry. 1996 October; 42(10): 1627-33.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8855146

- **Cardiac complications in pediatric patients on the ketogenic diet.**
  Author(s): Best TH, Franz DN, Gilbert DL, Nelson DP, Epstein MR.
  Source: Neurology. 2000 June 27; 54(12): 2328-30.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10881264

- **Cardiomyopathy from ipecac administration in Munchausen syndrome by proxy.**
  Author(s): Goebel J, Gremse DA, Artman M.
  Source: Pediatrics. 1993 October; 92(4): 601-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8105444

- **Cell transplantation to improve heart function: cell or matrix.**
  Author(s): Li RK.
  Source: Yonsei Medical Journal. 2004 June; 45 Suppl: S72-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15250057

- **Cellular, but not direct, adenoviral delivery of vascular endothelial growth factor results in improved left ventricular function and neovascularization in dilated ischemic cardiomyopathy.**
  Author(s): Askari A, Unzek S, Goldman CK, Ellis SG, Thomas JD, DiCorleto PE, Topol EJ, Penn MS.
  Source: Journal of the American College of Cardiology. 2004 May 19; 43(10): 1908-14.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15145120

- **Conditioned nutritional deficiencies in the cardiomyopathic hamster heart.**
  Author(s): Keith ME, Ball A, Jeejeebhoy KN, Kurian R, Butany J, Dawood F, Wen WH, Madapallimattam A, Sole MJ.
  Source: The Canadian Journal of Cardiology. 2001 April; 17(4): 449-58.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11329545

- **Conditioned nutritional requirements: therapeutic relevance to heart failure.**
  Author(s): Sole MJ, Jeejeebhoy KN.
  Source: Herz. 2002 March; 27(2): 174-8. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12025462

- **Dilated cardiomyopathy complicating a case of epidermolysis bullosa dystrophica.**
  Author(s): Brook MM, Weinhouse E, Jarenwattananon M, Nudel DB.
  Source: Pediatric Dermatology. 1989 March; 6(1): 21-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2704658

- **Dilated cardiomyopathy due to type II X-linked 3-methylglutaconic aciduria: successful treatment with pantothenic acid.**
  Author(s): Ostman-Smith I, Brown G, Johnson A, Land JM.
  Source: British Heart Journal. 1994 October; 72(4): 349-53.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7833193

- **Dilated cardiomyopathy in juvenile chronic arthritis.**
  Author(s): Soylemezoglu O, Besbas N, Ozkutlu S, Saatci U.
  Source: Scandinavian Journal of Rheumatology. 1994; 23(3): 159-61.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8016592

- **Echocardiographic findings of the heart resembling dilated cardiomyopathy during hypokalemic myopathy due to licorice-induced pseudoaldosteronism.**
  Author(s): Hasegawa J, Suyama Y, Kinugawa T, Morisawa T, Kishimoto Y.
  Source: Cardiovascular Drugs and Therapy / Sponsored by the International Society of Cardiovascular Pharmacotherapy. 1998 December; 12(6): 599-600.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10410830

- **Effect of acupuncture on left ventricular size and function assessed by echocardiography in patients with stable dilated cardiomyopathy.**
  Author(s): Huang DJ, Cheng DT, Das SK, Buda AJ, Pitt B, Lee F.
  Source: J Tradit Chin Med. 1985 December; 5(4): 243-5. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3879627

- **Experimental idiopathic dilated cardiomyopathy under low-calcium condition.**
  Author(s): Yamaguchi H, Kaku H, Onodera T, Kurokawa R, Morisada M.
  Source: Experimental and Toxicologic Pathology : Official Journal of the Gesellschaft Fur Toxikologische Pathologie. 1994 August; 46(3): 223-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8000243

- **Genotypic and serotypic profile in dilated cardiomyopathy.**
  Author(s): Wesslen L, Waldenstrom A, Lindblom B, Hoyer S, Friman G, Fohlman J.

Source: Scand J Infect Dis Suppl. 1993; 88: 87-91.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8390721

- **Impaired cardiac adrenergic innervation assessed by MIBG imaging as a predictor of treatment response in childhood dilated cardiomyopathy.**
  Author(s): Acar P, Merlet P, Iserin L, Bonnet D, Sidi D, Syrota A, Kachaner J.
  Source: Heart (British Cardiac Society). 2001 June; 85(6): 692-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11359754

- **Interferon and thymic hormones in the therapy of human myocarditis and idiopathic dilated cardiomyopathy.**
  Author(s): Miric M, Miskovic A, Vasiljevic JD, Keserovic N, Pesic M.
  Source: European Heart Journal. 1995 December; 16 Suppl O: 150-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8682086

- **L-carnitine supplementation in the therapy of canine dilated cardiomyopathy.**
  Author(s): Keene BW.
  Source: The Veterinary Clinics of North America. Small Animal Practice. 1991 September; 21(5): 1005-9. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1949496

- **Long-term follow-up of patients with myocarditis and idiopathic dilated cardiomyopathy after immunomodulatory therapy.**
  Author(s): Miric M, Miskovic A, Brkic S, Vasiljevic J, Keserovic N, Pesic M.
  Source: Fems Immunology and Medical Microbiology. 1994 November; 10(1): 65-74.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7874080

- **Long-term survival effect of metoprolol in dilated cardiomyopathy. The SPIC (Italian Multicentre Cardiomyopathy Study) Group.**
  Author(s): Di Lenarda A, De Maria R, Gavazzi A, Gregori D, Parolini M, Sinagra G, Salvatore L, Longaro F, Bernobich E, Camerini F.
  Source: Heart (British Cardiac Society). 1998 April; 79(4): 337-44.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9616339

- **Response of cats with dilated cardiomyopathy to taurine supplementation.**
  Author(s): Pion PD, Kittleson MD, Thomas WP, Delellis LA, Rogers QR.
  Source: J Am Vet Med Assoc. 1992 July 15; 201(2): 275-84.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1500324

- **Reversal of Borrelia burgdorferi associated dilated cardiomyopathy by antibiotic treatment?**
  Author(s): Gasser R, Fruhwald F, Schumacher M, Seinost G, Reisinger E, Eber B, Keplinger A, Horvath R, Sedaj B, Klein W, Pierer K.

Source: Cardiovascular Drugs and Therapy / Sponsored by the International Society of Cardiovascular Pharmacotherapy. 1996 July; 10(3): 351-60.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8877079

- **Reversible dilated cardiomyopathy following treatment of atopic eczema with Chinese herbal medicine.**
  Author(s): Ferguson JE, Chalmers RJ, Rowlands DJ.
  Source: The British Journal of Dermatology. 1997 April; 136(4): 592-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9155965

- **Structure and function of contractile proteins in human dilated cardiomyopathy.**
  Author(s): Wiegand V, Ebecke M, Figulla H, Schuler S, Kreuzer H.
  Source: Clin Cardiol. 1989 November; 12(11): 656-60.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2582658

- **Successful treatment with an implantable cardioverter defibrillator for spontaneous ventricular fibrillation in dilated cardiomyopathy with very high defibrillation thresholds.**
  Author(s): Tamura K, Abe H, Nagatomo T, Nakashima Y.
  Source: J Uoeh. 2001 December 1; 23(4): 363-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11789138

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering CAM and related topics. The following is a representative sample:

- Alternative Medicine Foundation, Inc.: **http://www.herbmed.org/**
- AOL: **http://search.aol.com/cat.adp?id=169&layer=&from=subcats**
- Chinese Medicine: **http://www.newcenturynutrition.com/**
- drkoop.com®: **http://www.drkoop.com/InteractiveMedicine/IndexC.html**
- Family Village: **http://www.familyvillage.wisc.edu/med_altn.htm**
- Google: **http://directory.google.com/Top/Health/Alternative/**
- Healthnotes: **http://www.healthnotes.com/**
- MedWebPlus: **http://medwebplus.com/subject/Alternative_and_Complementary_Medicine**
- Open Directory Project: **http://dmoz.org/Health/Alternative/**
- HealthGate: **http://www.tnp.com/**
- WebMD®Health: **http://my.webmd.com/drugs_and_herbs**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**

- Yahoo.com: **http://dir.yahoo.com/Health/Alternative_Medicine/**

The following is a specific Web list relating to dilated cardiomyopathy; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **General Overview**

  Cardiomyopathy
  Source: Healthnotes, Inc.; www.healthnotes.com

  Cardiomyopathy
  Source: Prima Communications, Inc.www.personalhealthzone.com

  Congestive Heart Failure
  Source: Healthnotes, Inc.; www.healthnotes.com

  Heart Attack
  Source: Healthnotes, Inc.; www.healthnotes.com

  HIV and AIDS Support
  Source: Healthnotes, Inc.; www.healthnotes.com

- **Herbs and Supplements**

  Coenzyme Q10
  Source: Healthnotes, Inc.; www.healthnotes.com

  Coleus
  Alternative names: Coleus forskohlii
  Source: Healthnotes, Inc.; www.healthnotes.com

  Glycyrrhiza
  Alternative names: Licorice; Glycyrrhiza glabra L.
  Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

  Thymus Extracts
  Source: Healthnotes, Inc.; www.healthnotes.com

General References

A good place to find general background information on CAM is the National Library of Medicine. It has prepared within the MEDLINEplus system an information topic page dedicated to complementary and alternative medicine. To access this page, go to the MEDLINEplus site at **http://www.nlm.nih.gov/medlineplus/alternativemedicine.html**. This Web site provides a general overview of various topics and can lead to a number of general sources.

CHAPTER 4. DISSERTATIONS ON DILATED CARDIOMYOPATHY

Overview

In this chapter, we will give you a bibliography on recent dissertations relating to dilated cardiomyopathy. We will also provide you with information on how to use the Internet to stay current on dissertations. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical dissertations that use the generic term "dilated cardiomyopathy" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on dilated cardiomyopathy, we have not necessarily excluded non-medical dissertations in this bibliography.

Dissertations on Dilated Cardiomyopathy

ProQuest Digital Dissertations, the largest archive of academic dissertations available, is located at the following Web address: **http://wwwlib.umi.com/dissertations**. From this archive, we have compiled the following list covering dissertations devoted to dilated cardiomyopathy. You will see that the information provided includes the dissertation's title, its author, and the institution with which the author is associated. The following covers recent dissertations found when using this search procedure:

- **Retrovirally induced dilated cardiomyopathy in murine acquired immunodeficiency syndrome** by Beischel, Julie Marie, PhD from the University of Arizona, 2003, 125 pages http://wwwlib.umi.com/dissertations/fullcit/3089910

Keeping Current

Ask the medical librarian at your library if it has full and unlimited access to the *ProQuest Digital Dissertations* database. From the library, you should be able to do more complete searches via **http://wwwlib.umi.com/dissertations**.

CHAPTER 5. PATENTS ON DILATED CARDIOMYOPATHY

Overview

Patents can be physical innovations (e.g. chemicals, pharmaceuticals, medical equipment) or processes (e.g. treatments or diagnostic procedures). The United States Patent and Trademark Office defines a patent as a grant of a property right to the inventor, issued by the Patent and Trademark Office.[8] Patents, therefore, are intellectual property. For the United States, the term of a new patent is 20 years from the date when the patent application was filed. If the inventor wishes to receive economic benefits, it is likely that the invention will become commercially available within 20 years of the initial filing. It is important to understand, therefore, that an inventor's patent does not indicate that a product or service is or will be commercially available. The patent implies only that the inventor has "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States. While this relates to U.S. patents, similar rules govern foreign patents.

In this chapter, we show you how to locate information on patents and their inventors. If you find a patent that is particularly interesting to you, contact the inventor or the assignee for further information. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical patents that use the generic term "dilated cardiomyopathy" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on dilated cardiomyopathy, we have not necessarily excluded non-medical patents in this bibliography.

Patents on Dilated Cardiomyopathy

By performing a patent search focusing on dilated cardiomyopathy, you can obtain information such as the title of the invention, the names of the inventor(s), the assignee(s) or the company that owns or controls the patent, a short abstract that summarizes the patent, and a few excerpts from the description of the patent. The abstract of a patent tends to be more technical in nature, while the description is often written for the public. Full patent descriptions contain much more information than is presented here (e.g. claims, references, figures, diagrams, etc.). We will tell you how to obtain this information later in the chapter.

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[8]Adapted from the United States Patent and Trademark Office: **http://www.uspto.gov/web/offices/pac/doc/general/whatis.htm**.

The following is an example of the type of information that you can expect to obtain from a patent search on dilated cardiomyopathy:

- **Actin mutations in dilated cardiomyopathy, a heritable form of heart failure**

  Inventor(s): Keating; Mark T. (Salt Lake City, UT), Olson; Thomas M. (Salt Lake City, UT)

  Assignee(s): University of Utah Research Foundation (Salt Lake City, UT)

  Patent Number: 6,063,576

  Date filed: June 29, 1998

  Abstract: Two mutations in the human cardiac actin gene are disclosed which have been associated with idiopathic **dilated cardiomyopathy** (IDC) in two families. These mutations cosegregate with IDC in the two families. Both mutations affect universally conserved amino acids in domains of actin that attach to Z bands and intercalated discs. Analysis of the cardiac actin gene can be used to determine the presence in a patient of IDC resulting from mutations in this gene. Such analysis is useful in the diagnosis and prognosis of the disease in patients with mutations in this gene.

  Excerpt(s): Heart failure is a major medical problem that affects 700 thousand individuals per year in the United States and accounts for annual costs of 10 to 40 billion dollars (Abraham and Bristow, 1997). Heart failure is the primary manifestation of **dilated cardiomyopathy,** a group of disorders characterized by cardiac dilation and pump dysfunction. Half of patients with **dilated cardiomyopathy** are diagnosed with idiopathic **dilated cardiomyopathy** (IDC), isolated heart failure of unknown etiology (affecting 5 to 8 in 100,000 individuals) (Manolio et al., 1992; Kasper et al., 1994). Cardiac transplantation is the only definitive treatment for end-stage disease. The present invention is directed to ACTC and its gene products, mutations in the gene, the mutated gene, probes for the wild-type and mutated gene, and to a process for the diagnosis and prevention of idiopathic **dilated cardiomyopathy.** The instant work shows that some families with idiopathic **dilated cardiomyopathy** have mutations in ACTC. Idiopathic **dilated cardiomyopathy** is diagnosed in accordance with the present invention by analyzing the DNA sequence of the ACTC gene of an individual to be tested and comparing the respective DNA sequence to the known DNA sequence of normal ACTC. Alternatively, the ACTC gene of an individual to be tested can be screened for mutations which cause idiopathic **dilated cardiomyopathy.** The publications and other materials used herein to illuminate the background of the invention or provide additional details respecting the practice, are incorporated by reference, and for convenience are respectively grouped in the appended List of References.

  Web site: http://www.delphion.com/details?pn=US06063576__

- **Agent for gene therapy of dilated cardiomyopathy**

  Inventor(s): Toyo-Oka; Teruhiko (23-3, Kamiogi 3-chome, Suginami-ku, Tokyo 167-0043, JP)

  Assignee(s): none reported

  Patent Number: 6,589,523

  Date filed: January 25, 2001

Abstract: According to the present invention, there is provided a gene expression vector which is obtained by inserting a gene encoding sarcoglycan into an adeno-associated virus (AAV) vector. By administering the gene expression vector of the present invention to a living body in vivo, a sarcoglycan can be continuously expressed in the living body, so that the restoration of.alpha.-,.beta.-,.gamma.- and.delta.-sarcoglycan components can be accompanied and the heart function of the patient of **dilated cardiomyopathy** can be improved.

Excerpt(s): The present invention relates to an agent for gene therapy of **dilated cardiomyopathy,** more particularly, a gene expression vector which is obtained by inserting a gene encoding a sarcoglycan into an adeno-associated virus vector. Cardiomyopathy is one of the heart diseases which shows contraction dysfunction and electrophysiological dysfunction as symptoms, and includes a group of heart diseases which lead to a sever heart failure and a sudden death. Cardiomyopathy is classified into **dilated cardiomyopathy** and hypertrophied cardiomyopathy, and the study for revealing the causes of each cardiomyopathy has been made. In the case of **dilated cardiomyopathy** (DCM), in spite of progress in the therapy, the prognosis of the patients is still poor and cardiac transplantation is necessary in the deteriorated cases (V. V. Michels, et al., New Engl.J.Med. 326, 77 (1992); E. K. Kasper, et al., J.Am.Coll.Cardiol. 23, 586 (1994); M. Packer, et al., New Engl.J.Med. 334, 1349 (1996); M. Packer, et al. New Engl.J.Med. 335,1107 (1996); R. M. Graham, W. A. Owens, N.Engl.J.Med. 341, 1759 (1999)). Therefore, it is necessary to develop a novel method for therapy which can improve the patient's mortality and morbidity. Animal model is useful for developing such a novel method for therapy. Gene transfer will be promising for the therapy of some type of DCM which is caused by the gene deletion. It has been demonstrated that the deletion of.delta.-sarcoglycan (.delta.-SG) gene is the cause of DCM in hamsters (A. Sakamoto, et al., Proc.Natl.Sci.Acad.U.S.A. 94, 13873 (1997); V. Nigro, et al., Hum.Mol.Genet. 6, 601 (1997)). Also, it has been found that the breakpoint of.delta.-SG gene in TO-2 hamster which is a model animal of DCM is present in the first intron, and large region including its promoter and the first exon is deleted in TO-2 hamster (A. Sakamoto, et al., Proc.Natl.Sci.Acad.U.S.A. 94, 13873 (1997)). Furthermore, dystrophin-associated glycoprotein complex (DAGC) links intracellular contractile machinery with extracellular matrix (G. F. Cox, L. M. Kunkel, Curr.Opin.Cardiol. 12, 329 (1997); K. H. Holt, et al., Mol. Cell 1, 841 (1998); M. D. Henry, K. P. Campbell, Curr.Opin.Cell Biol. 11, 602 (1999)).

Web site: http://www.delphion.com/details?pn=US06589523__

- **Gene mutation in patients with idiopathic dilated cardiomyopathy**

  Inventor(s): Lusis; Aldons Jake (Los Angeles, CA), Philipson; Kenneth D. (Pacific Palisades, CA), Sen; Luyi (Stevenson Ranch, CA)

  Assignee(s): The Regents of the University of California (Oakland, CA)

  Patent Number: 5,639,614

  Date filed: June 7, 1995

  Abstract: A genetic mutation within the SR calcium release channel provides a test for susceptibility to idiopathic **dilated cardiomyopathy.** The test detects the presence of the mutation in a sample of nucleic acids obtained from the individual being tested. Restriction fragment length polymorphism is one technique which can be used in the test.

Excerpt(s): The present invention relates generally to the field of genetic screening for inherited disease. More specifically, the invention regards a method of identifying individuals at risk of developing idiopathic **dilated cardiomyopathy.** Idiopathic **dilated cardiomyopathy,** formerly called **congestive cardiomyopathy,** is a syndrome characterized by cardiac enlargement and congestive heart failure. Although no etiology is definable in most cases, the **congestive cardiomyopathy** is believed to represent the result of myocardial damage caused by toxic, metabolic or infectious agents. Diagnosis of this disease depends solely on the exclusion of other possible causes at a late stage of the disorder. Nearly 40% of the patients receiving heart transplants suffer from idiopathic **dilated cardiomyopathy.** Abnormal modulation of intracellular calcium has been proposed as the key mechanism underlying the systolic and diastolic dysfunctions that accompany heart failure associated with cardiomyopathy. Recently, several studies have documented the pathogenetic role of abnormal sarcoplasmic reticulum (SR) function in various cardiomyopathies. For example, Ca.sup.++ -ATPase expression is decreased in patients having end-stage heart failure caused by the various cardiomyopathies.

Web site: http://www.delphion.com/details?pn=US05639614__

- **Method of treating dilated cardiomyopathy**

  Inventor(s): Komamura; Kazuo (2-15-5, Kitayamato, Ikoma-shi, Nara 630-01, JP), Miyatake; Kunio (2-8-3, Aoshinke, Minoo-shi, Osaka 562, JP), Nakamura; Toshikazu (4-1, Takamidai, Takatsuki-shi, Osaka 569, JP)

  Assignee(s): none reported

  Patent Number: 6,036,972

  Date filed: October 14, 1997

  Abstract: The invention describes to a method of treating a patient with **dilated cardiomyopathy** comprising administering an effective amount of Hepatocyte Growth Factor (HGF).

  Excerpt(s): The present invention relates to a method of treating a patient of **dilated cardiomyopathy** comprising administering an effective amount of Hepatocyte Growth Factor (HGF). One of the critical symptoms of patients with **dilated cardiomyopathy** is a reduction of ventricular performance, resulting in an expansion of the left ventricle. The patients often have reduction in left ventricular cardiac output, increase in left ventricular diastolic pressure, and congestive heart failure. Since not all patients with **dilated cardiomyopathy** have congestive heart failure, the name of **dilated cardiomyopathy** is more practical than the name of **congestive cardiomyopathy** in this meaning. The symptom is acute or latent and the patients are likely to have intractable heart failure in the terminal stage. Pathologically, **dilated cardiomyopathy** is accompanied with diffuse or local degeneration, fibrosis and atrophy of cardiac myocardium, and the rest of cardiac myocytes is frequently found to be hypertrophied. **Dilated cardiomyopathy** is thought to be caused by the taking of excess alcohol, virus infection, spasm of microvessels, disorder of immunity and so on, however the real cause has not been clearly understood. Since some **dilated cardiomyopathy** may occur in a pedigree, it is suggested that a genetic background might be involved. **Dilated cardiomyopathy** may cause heart failure, lethal arrhythmia or thromboembolism, and its prognosis is poor. Ischemic cardiomyopathy may cause heart failure, and hypertensive heart diseases. In treatment of **dilated cardiomyopathy,** it is not enough to

control an each factor independently but is necessary to control several factors simultaneously.

Web site: http://www.delphion.com/details?pn=US06036972__

- **Mouse model for congestive heart failure**

  Inventor(s): Leiden; Jeffrey M. (51 Cresent Dr., Glencoe, IL 60022)

  Assignee(s): none reported

  Patent Number: 6,194,632

  Date filed: December 18, 1998

  Excerpt(s): The present invention relates to transgenic mice which express CREB. These transgenic mice provide a genetic model of **dilated cardiomyopathy.** Congestive heart failure (CHF) is a leading cause of cardiovascular morbidity and mortality affecting more than 4 million Americans and representing the most common reason for hospitalization of patients over the age of 65 (1, 2). Idiopathic **dilated cardiomyopathy** (IDC), a primary myocardial disease of unknown etiology characterized by ventricular dilatation and depressed myocardial contractility is an important cause of CHF with an estimated prevalence of 36 cases/100,000 (3-7). Relatively little is known about the molecular mechanisms underlying the pathogenesis of IDC. Progress in this area has been limited by the lack of animal models that closely resemble the anatomical and clinical features of the human disease. Several previously described genetically modified mice have been reported to develop cardiomyopathies. These include mice expressing mutant forms of {character pullout}-myosin heavy chain ({character pullout}-MHC), mice engineered to ectopically express the myf5 bHLH transcription factor in the heart, and mice containing targeted mutations of the muscle LIM protein (MLP) (49-51). However, the phenotypes of each of these mice differs significantly from that of the transgenic mice described herein. Unlike the transgenic mice of the present invention, which display progressive cardiac dilatation without hypertrophy, the {character pullout}-MHC and myf5 mice develop a hypertrophic cardiomyopathy with myocyte disarray and interstitial fibrosis (50, 51). Consistent with these histological findings, the {character pullout}-MHC mice display normal end systolic LV pressures and dP/dtmax but abnormal LV relaxation. These findings are highly reminiscent of the phenotype of patients with hypertrophic as opposed to **dilated cardiomyopathy.** The phenotype of the transgenic mice of the present invention also differed significantly from that of the recently described muscle LIM protein (MLP)-deficient mice which display soft, markedly hypertrophic hearts with grossly abnormal sarcomere structure within the first several weeks after birth (49). Unlike the transgenic mice of the present invention, 50-70% of the MLP-deficient mice die before 10 days of age.

  Web site: http://www.delphion.com/details?pn=US06194632__

- **System and method for treating dilated cardiomyopathy using end diastolic volume (EDV) sensing**

  Inventor(s): Rosenberg; Meir (Newton, MA)

  Assignee(s): Abiomed, Inc. (Danvers, MA)

  Patent Number: 6,314,322

  Date filed: March 2, 1998

Abstract: A system for controlling end diastolic volume of the heart is disclosed. The system includes an EDV sensor constructed and arranged to measure a parameter related to the end diastolic volume of the heart, and a heart stimulator, responsive to the EDV sensor, constructed and arranged to invoke systole when the measured parameter reaches a predetermined level, the parameter reaching that level prior to termination of diastole. Preferably, the heart stimulator may be a pacemaker. The EDV sensor may be any sensor constructed to measure a parameter related to the end diastolic volume of the heart, or another selected physiological or patho-physiological condition of the heart, including a strain sensor, a stress sensor, a dimension sensor, an impedance sensor, an optical sensor, a microwave sensor, or another sensor constructed to measure a parameter related to the end diastolic volume of the heart, or another selected physiological or patho-physiological condition of the heart. A method for controlling end diastolic volume of the heart including the steps of measuring a parameter that is related to the end diastolic volume of the heart, and invoking systole before termination of diastole when the measured parameter reaches a predetermined level is also disclosed.

Excerpt(s): The present invention relates generally to controlling congestive heart failure and, more particularly, to electrically controlling a dilated condition resulting from congestive heart failure. The heart pumps blood through a patient's body in order to carry oxygen to, and remove carbon dioxide from, cells located throughout the body. In a patient having a normal heart, the rate at which the blood is pumped through the body increases or decreases to accommodate changes in the physiological needs of the patient. That is, as the cells of the patient's body require more oxygen, the heart rate and/or stroke volume increases to pump more oxygen-rich blood to the cells. When insufficient oxygen is available from the lungs, the respiration rate may also increase to increase the rate of oxygen intake into the body. Conversely, as the demand for oxygen decreases, the heart rate decreases, providing less blood flow and, hence, less oxygen, to the cells. During a heart cycle, deoxygenated, venous blood enters the right atrium of the heart via the inferior vena cava and the superior vena cava and, during diastole, flows to the right ventricle. The pulmonary artery then delivers blood ejected from the right ventricle into the lungs. The pulmonary vein carries oxygenated blood from the lungs to the left atrium of the heart. During diastole, oxygenated blood flows from the left atrium to the left ventricle, which is filled to its end diastolic volume (EDV). During systole the left ventricle ejects oxygenated blood into the aorta.

Web site: http://www.delphion.com/details?pn=US06314322__

Patent Applications on Dilated Cardiomyopathy

As of December 2000, U.S. patent applications are open to public viewing.[9] Applications are patent requests which have yet to be granted. (The process to achieve a patent can take several years.) The following patent applications have been filed since December 2000 relating to dilated cardiomyopathy:

[9] This has been a common practice outside the United States prior to December 2000.

- **Adsorbents for dilated cardiomyopathy**

  Inventor(s): Furuyoshi, Shigeo; (Hyogo, JP), Hirai, Fumiyasu; (Hyogo, JP), Nishimoto, Takehiro; (Osaka, JP), Ogino, Eiji; (Hyogo, JP)

  Correspondence: Kenyon & Kenyon; 1500 K Street, N.W., Suite 700; Washington; DC; 20005; US

  Patent Application Number: 20040120946

  Date filed: November 15, 2002

  Abstract: The present invention has for its object to provide an adsorbent for an antibody against.beta.1-adrenoceptor and/or an antibody against M2 muscarinic receptor, which is capable of efficient and selective adsorption of an antibody against.beta.1-adrenoceptor and/or an antibody against M2 muscarinic receptor occurring in a body fluid without requiring a pretreatment of the body fluid. A further object is to provide an adsorption apparatus utilizing this adsorbent and a method for adsorbing an antibody against.beta.1-adrenoceptor and/or an antibody against M2 muscarinic receptor.An adsorbent which comprises a water-insoluble carrier and a compound, which is immobilized on said carrier, having a binding affinity for an antibody against.beta.1-adrenoceptor and/or an antibody against M2 muscarinic receptor exhibits a remarkably large adsorptive capacity.

  Excerpt(s): The present invention relates to an adsorbent designed to selectively remove an antibody against.beta.1-adrenoceptor and/or an antibody against M2 muscarinic receptor by adsorption from a body fluid (e.g. blood, plasma, etc.) and thereby encourage the treatment of **dilated cardiomyopathy** (DCM) and other diseases in which an antibody against.beta.1-adrenoceptor and/or an antibody against M2 muscarinic receptor is an exacerbating factor, an adsorption apparatus utilizing said adsorbent, and a method of adsorbing an antibody against.beta.1-adrenoceptor and/or an antibody against M2 muscarinic receptor. Dilated cardiomyopathy is a disease in which the contractility of the ventricular muscle is severely compromised to cause cardiac enlargement and, compared with hypertrophic cardiomyopathy, its prognosis is extremely poor. In Japan, persons surviving 5 years following the diagnosis reportedly account for about 50%. For the treatment of **dilated cardiomyopathy,** cardiac transplantation is preferably indicated as a radical treatment but since donations are outnumbered by cases on the waiting list, the symptomatic treatment of heart failure is a dominant treatment today. There are reported cases of improved cardiac function and prognosis following administration of an angiotensin-converting enzyme (ACE) inhibitor or a.beta.-adrenergic blocker but the demand for efficacious therapeutic drugs and treatment is still outstanding. Meanwhile, Matsui et al. reported that administration of a peptide derived from.beta.1-adrenoceptor by addition of Cys to its second loop (His Trp Trp Arg Ala Glu Ser Asp Glu Ala Arg Arg Cys Tyr Asn Asp Pro Lys Cys Cys Asp Phe Val Thr Asn Arg Cys) or a peptide derived from M2 muscarinic receptor by addition of Cys to its second loop (Val Arg Thr Val Glu Asp Gly Glu Cys Tyr Ile Gln Phe Phe Ser Asn Ala Ala Val Thr Phe Gly Thr Ala Ile Cys) to rabbits resulted in the emergence of an antibody to each administered peptide and that the heart of rabbits that died 9 months later gave findings of **dilated cardiomyopathy** (Matsui S, Fu M L. Myocardial injury due to G-protein coupled receptor-autoimmunity. Jpn Heart J. 1998;39(3):261-74), thus suggesting that these antibodies act as etiologic factors in **dilated cardiomyopathy.** Further, Wallukat, G et al. purified an antibody against.beta.1-adrenoceptor by using an adsorbent prepared by immobilizing the second-loop peptide of.beta.1-adrenoceptor (His Trp Trp Arg Ala Glu Ser Asp Glu Ala Arg Arg Cys Tyr Asn Asp Pro Lys Cys Cys Asp Phe Val Thr Asn Arg) on CNBr-activated Sepharose 4B

(Wallukat G, Wollenberger A, Morwinski R, Pitschner H F. Anti-beta 1-adrenoceptor autoantibodies with chronotropic activity from the serum of patients with dilated cardiomyopathy: mapping of epitopes in the first and second extracellular loops. J Mol Cell Cardiol January 1995;27(1):397-406). However, they did not bring the serum directly into contact with the adsorbent. They first added a 40% saturated aqueous solution of ammonium sulfate to the serum to precipitate its immunoglobulin fraction (ammonium sulfate precipitation), redissolved the precipitate, dialyzed the solution, and thereafter performed a fractional purification with the adsorbent. This suggests that if the serum or the like in the state not pretreated (ammonium sulfate precipitation and dialysis) were brought into contact with the adsorbent they had synthesized, no sufficient selective adsorption should have been obtained.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Agent for gene therapy of dilated cardomyopathy**

  Inventor(s): Toyo-Oka, Teruhiko; (Tokyo, JP)

  Correspondence: Greenblum & Bernstein, P.L.C.; 1941 Roland Clarke Place; Reston; VA; 20191; US

  Patent Application Number: 20010029040

  Date filed: January 25, 2001

  Abstract: According to the present invention, there is provided a gene expression vector which is obtained by inserting a gene encoding sarcoglycan into an adeno-associated virus (AAV) vector. By administering the gene expression vector of the present invention to a living body in vivo, a sarcoglycan can be continuously expressed in the living body, so that the restoration of.alpha.,.beta.,.gamma.- and.delta.-sarcoglycan components can be accompanied and the heart function of the patient of **dilated cardiomyopathy** can be improved.

  Excerpt(s): The present invention relates to an agent for gene therapy of **dilated cardiomyopathy,** more particularly, a gene expression vector which is obtained by inserting a gene encoding a sarcoglycan into an adeno-associated virus vector. Cardiomyopathy is one of the heart diseases which shows contraction dysfunction and electrophysiological dysfunction as symptoms, and includes a group of heart diseases which lead to a sever heart failure and a sudden death. Cardiomyopathy is classified into **dilated cardiomyopathy** and hypertrophied cardiomyopathy, and the study for revealing the causes of each cardiomyopathy has been made. In the case of **dilated cardiomyopathy** (DCM), in spite of progress in the therapy, the prognosis of the patients is still poor and cardiac transplantation is necessary in the deteriorated cases (V. V. Michels, et al., New Engl.J.Med. 326, 77 (1992); E. K. Kasper, et al., J.Am.Coll.Cardiol. 23, 586 (1994); M. Packer, et al., New Engl.J.Med. 334, 1349 (1996); M. Packer, et al. New Engl.J.Med. 335,1107 (1996); R. M. Graham, W. A. Owens, N.Engl.J.Med. 341, 1759 (1999)). Therefore, it is necessary to develop a novel method for therapy which can improve the patient's mortality and morbidity. Animal model is useful for developing such a novel method for therapy. Gene transfer will be promising for the therapy of some type of DCM which is caused by the gene deletion. It has been demonstrated that the deletion of.delta.-sarcoglycan (.delta.-SG) gene is the cause of DCM in hamsters (A. Sakamoto, et al., Proc.Natl.Sci.Acad.U.S.A. 94, 13873 (1997); V. Nigro, et al., Hum.Mol.Genet. 6, 601 (1997)). Also, it has been found that the breakpoint of.delta.-SG gene in TO-2 hamster which is a model animal of DCM is present in the first intron, and large region including its promoter and the first exon is deleted in TO-2 hamster (A.

Sakamoto, et al., Proc.Natl.Sci.Acad.U.S.A. 94, 13873 (1997)). Furthermore, dystrophin-associated glycoprotein complex (DAGC) links intracellular contractile machinery with extracellular matrix (G. F. Cox, L. M. Kunkel, Curr.Opin.Cardiol. 12, 329 (1997); K. H. Holt, et al., Mol. Cell 1, 841 (1998); M. D. Henry, K. P. Campbell, Curr.Opin.Cell Biol. 11, 602 (1999)).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Electrotherapy system, device, and method for treatment of cardiac valve dysfunction**

  Inventor(s): Adams, John M.; (Sammamish, WA), Mathis, Mark; (Kirkland, WA), Reuter, David; (Bothell, WA), Wolf, Scott J.; (Bellevue, WA)

  Correspondence: Christensen, O'connor, Johnson, Kindness, Pllc; 1420 Fifth Avenue; Suite 2800; Seattle; WA; 98101-2347; US

  Patent Application Number: 20040133240

  Date filed: January 7, 2003

  Abstract: A system for treating cardiac valve dysfunction includes a lead with electrodes in electrical communication with muscle tissue proximate to a cardiac valve to be treated. Electrical energy is delivered to the lead electrodes to stimulate contraction of the muscle tissue and thereby constrict the cardiac valve. The lead may be received within a blood vessel in the patient. Detection circuitry may detect a physiological signal in the patient for controlling the timing of delivery of electrical energy. The lead may have one or more undulations. The lead may also be combined with a prosthesis to provide a combined electromechanical cardiac valve therapy. The lead can be attached to the prosthesis or formed integrally with the prosthesis. One embodiment implanted in the coronary sinus is used to treat **dilated cardiomyopathy** of the mitral valve.

  Excerpt(s): The present invention relates generally to methods and apparatus for treatment of cardiac dysfunction, and more specifically to treatment of cardiac valve dysfunction. A mammalian heart typically includes multiple chambers through which blood is pumped into the circulatory system. A human heart includes four chambers, namely, a left and right atrium and a left and right ventricle. Blood is first pumped from the atria to the ventricles during atrial contraction. During ventricular contraction, blood is pumped from the ventricles into the circulatory system of the body. Valves separate the various chambers of a mammalian heart and control the direction of blood flow through the heart. In a human patient, for example, the left atrium is separated from the left ventricle by the mitral valve. A normally functioning mitral valve permits blood to flow from the left atrium to the left ventricle, but not vice versa. Leaflets, or cusps, that form the mitral valve close upon one another when blood is pumped from the left ventricle to the circulatory system. This closure of the mitral valve prevents backflow or regurgitation of blood into the left atrium during ventricular contraction. A normally functioning mitral valve can withstand substantial back pressure of blood when the left ventricle contracts.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Focused compression mitral valve device and method**

  Inventor(s): Adams, John M.; (Sammamish, WA), Mathis, Mark L.; (Kirkland, WA), Reuter, David G.; (Bothell, WA), Wolf, Scott J.; (Bellevue, WA)

  Correspondence: Richard O. Gray, JR.; Graybeal Jackson Haley Llp; Suite 350; 155-108th Avenue NE; Bellevue; WA; 98004-5901; US

  Patent Application Number: 20030083538

  Date filed: November 1, 2001

  Abstract: A mitral valve therapy device and method treats **dilated cardiomyopathy.** The device is configured to be placed in the coronary sinus of a heart adjacent to the mitral valve annulus. The device includes a force distributor that distributes an applied force along a pericardial wall of the coronary sinus, and a force applier that applies the applied force to one or more discrete portions of a wall of the coronary sinus adjacent to the mitral valve annulus to reshape the mitral valve annulus in a localized manner.

  Excerpt(s): The present invention generally relates to a device and method for treating **dilated cardiomyopathy** of a heart. The present invention more particularly relates to a device and method for delivering a localized force to the mitral valve annulus to reshape the mitral valve annulus. The human heart generally includes four valves. Of these valves, a most critical one is known as the mitral valve. The mitral valve is located in the left atrial ventricular opening between the left atrium and left ventricle. The mitral valve is intended to prevent regurgitation of blood from the left ventricle into the left atrium when the left ventricle contracts. In preventing blood regurgitation the mitral valve must be able to withstand considerable back pressure as the left ventricle contracts. The valve cusps of the mitral valve are anchored to muscular wall of the heart by delicate but strong fibrous cords in order to support the cusps during left ventricular contraction. In a healthy mitral valve, the geometry of the mitral valve ensures that the cusps overlie each other to preclude regurgitation of the blood during left ventricular contraction.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Isoform-selective inhibitors and activators of PDE3 cyclic nucleotide phosphodiesterases**

  Inventor(s): Movsesian, Matthew A.; (Salt Lake City, UT)

  Correspondence: Richard A. Nakashima; Blakely, Sokoloff, Taylor & Zafman Llp; Seventh Floor; 12400 Wilshire Boulevard; Los Angeles; CA; 90025-1030; US

  Patent Application Number: 20030158133

  Date filed: June 19, 2002

  Abstract: The present invention concerns methods and compositions related to type 3 phosphodiesterases (PDE3). Certain embodiments concern isolated peptides corresponding to various PDE3A isoforms and/or site-specific mutants of PDE3A isoforms, along with expression vectors encoding such isoforms or mutants. In specific embodiments, methods for identifying isoform selective inhibitors or activators of PDE3 are provided, along with methods of use of such inhibitors or activators in the treatment of **dilated cardiomyopathy,** pulmonary hypertension and/or other medical conditions related to PDE3 effects on cAMP levels in different intracellular compartments.

Excerpt(s): The present invention relates to the field of cardiovascular and other diseases. More particularly, the present invention concerns compositions and methods of identification and use of isoform selective activators or inhibitors of type 3 phosphodiesterase (PDE3). Other embodiments of the invention concern high-throughput screening for novel pharmaceuticals directed against PDE3 isoforms. In certain embodiments, the compositions and methods disclosed herein are of use for treatment of cardiomyopathy, pulmonary hypertension and related conditions. PDE3 cyclic nucleotide phosphodiesterases hydrolyze cAMP and cGMP and thereby modulate cAMP- and cGMP-mediated signal transduction (Shakur et al., 2000a). These enzymes have a major role in the regulation of contraction and relaxation in cardiac and vascular myocytes. PDE3 inhibitors, which raise intracellular cAMP and cGMP content, have inotropic effects attributable to the activation of cAMP-dependent protein kinase (PK-A) in cardiac myocytes and vasodilatory effects attributable to the activation of cGMP-dependent protein kinase (PK-G) in vascular myocytes (Shakur et al., 2000a). When used in the treatment of **dilated cardiomyopathy,** PDE3 inhibitors such as milrinone, enoximone and amrinone initially elicit favorable haemodynamic responses, but long-term administration increases mortality by up to 40% (Nony et al., 1994). This linkage of short-term benefits of PDE3 inhibition to deleterious effects on long-term survival in **dilated cardiomyopathy** is one of the most perplexing problems in cardiovascular therapeutics. However, it is thought that these biphasic effects reflect the compartmentally-nonselect- ive increases in intracellular cAMP content in cardiac myocytes current inhibitors display. Clinical trials of the use of.beta.-adrenergic receptor agonists--which, like PDE3 inhibitors, increase intracellular cAMP content in cardiac myocytes--were terminated prior to completion because of increased mortality in treated patients, while.beta.-adrenergic receptor antagonists, which reduce intracellular cAMP content, have been shown to improve long-term survival despite initially adverse haemodynamic effects. These findings suggest that both the short-term benefits and long-term adverse effects of PDE3 inhibition are attributable to increases in intracellular cAMP content in cardiac myocytes (Movsesian, 1999).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **p53 binding protein-related protein in cardiomyopathy**

  Inventor(s): Beier, David R.; (Brookline, MA), Herron, Bruce; (Nassau, NY), Rao, Cherie; (Oceanside, CA)

  Correspondence: Michael A. Sanzo; Fitch, Even, Tabin & Flannery; Suite 401l; 1801 K Street, N.W.; Washington; DC; 20006-1201; US

  Patent Application Number: 20030031680

  Date filed: June 14, 2002

  Abstract: The present invention is directed to a mouse model of **dilated cardiomyopathy** in which animals are deficient in the expression of a gene encoding a p53 binding protein-related protein (PRP). The invention also encompasses the mouse PRP gene and protein themselves as well as counterparts found in the human. The various genes and proteins can be used in making transgenic animals and in assays designed to determine the likelihood of an individual developing cardiomyopathy.

  Excerpt(s): The present application claims the benefit of U.S. provisional application No. 60/299,160, filed on Jun. 20, 2001. The present invention is directed to a mouse model of **dilated cardiomyopathy.** It also includes genes and proteins whose underexpression contributes to disease development and a variety of compositions and methods in which

these genes and proteins are used. Congestive heart failure affects over 4 million people in the United States and is the most common cause of hospitalization for patients over the age of 65. A leading cause of congestive heart failure is **dilated cardiomyopathy.** This condition is characterized by the progressive expansion of the heart muscle and an accompanying inability to maintain adequate blood flow. Patients typically complain of fatigue, shortness of breath and chest pain. There is presently no cure for this condition and up to 50% of patients die or require a heart transplant within 5 years of diagnosis.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Pd-1-lacking mouse and use thereof**

  Inventor(s): Honjo, Tasuku; (Kyoto-shi, JP), Nishimura, Hiroyuki; (Boston, MA)

  Correspondence: Sughrue Mion, Pllc; 2100 Pennsylvania Avenue, N.W.; Washington; DC; 20037; US

  Patent Application Number: 20040034881

  Date filed: September 29, 2003

  Abstract: It relates to BALB/c mice that defect programmed cell death-1 receptor (PD-1), a screening method of autoimmune disease medicine by use of these mice, IgG self-reactivity antibody that the mice produce specifically, protein specifically reacted to the antibody and produced in heart, and an diagnostic method in **dilated cardiomyopathy** by use of the protein.Because PD-1 deficient BALB/c mice spontaneously develop autoimmune disease, specifically **dilated cardiomyopathy,** they are useful to screening for medicines against these diseases.

  Excerpt(s): The present invention relates to programmed cell death-1 receptor (hereafter, it is abbreviated as PD-1)-deficient BALB/c mice and the use. More particularly, it relates to PD-1 receptor-deficient BALB/c mice, a screening method of medicines against autoimmune disease by use of the mice, IgG self-reactivity antibody of which these mice produce specifically, a protein specifically reacted to the antibody and produced in heart and an diagnostic method in **dilated cardiomyopathy** by use of the protein. Programmed cell death controlled embryologically or physiologically can be observed in all most tissues of various animals. Such programmed cell death is generally called, "Programmed cell death or Premeditated programmed cell death", and distinguished from unexpected cell death which could be caused by a pathologic mechanism. First, PD-1 has been found in mice as a receptor that cells are related to process to premeditated programmed cell death through the activation (The EMBO J., vol. 11(11), 3887-3895(1992); JP05-336973; EMBL/GenBank/DDJB Acc. No.X67914). Then, it has been found in human by using the gene of mouse PD-1 as a probe (Genomics 23:704 (1994); JP07-291996). Because PD-1 has expressed in lymphocytes with activation and has deeply related to autoimmune disease by researches of PD-1 deficient mice (International Immunology, Vol.10(10), 1563-1572(1998); Immunity. Vol.11, 141-151(1999)), it has been suggested to be used for treatments and diagnoses of decrease or accentuation of immune function, infectious disease, rejections in transplant and tumours, etc. Both mouse and human PD-1 are composed by 288 amino acids, and are type I membrane-bound 55 kDa proteins with the hydrophobic region in the penetrative area of the cell-membrane in the middle and the signal peptide (20 amino-acids) in the N-terminus. Deficient mice (called the knockout mice.) are indicated those which cannot produce the gene product in born by modifying a specific gene artificially, and are made to examine roles of factors and receptors that are the gene products.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

Keeping Current

In order to stay informed about patents and patent applications dealing with dilated cardiomyopathy, you can access the U.S. Patent Office archive via the Internet at the following Web address: **http://www.uspto.gov/patft/index.html**. You will see two broad options: (1) Issued Patent, and (2) Published Applications. To see a list of issued patents, perform the following steps: Under "Issued Patents," click "Quick Search." Then, type "dilated cardiomyopathy" (or synonyms) into the "Term 1" box. After clicking on the search button, scroll down to see the various patents which have been granted to date on dilated cardiomyopathy.

You can also use this procedure to view pending patent applications concerning dilated cardiomyopathy. Simply go back to **http://www.uspto.gov/patft/index.html**. Select "Quick Search" under "Published Applications." Then proceed with the steps listed above.

CHAPTER 6. PERIODICALS AND NEWS ON DILATED CARDIOMYOPATHY

Overview

In this chapter, we suggest a number of news sources and present various periodicals that cover dilated cardiomyopathy.

News Services and Press Releases

One of the simplest ways of tracking press releases on dilated cardiomyopathy is to search the news wires. In the following sample of sources, we will briefly describe how to access each service. These services only post recent news intended for public viewing.

PR Newswire

To access the PR Newswire archive, simply go to **http://www.prnewswire.com/**. Select your country. Type "dilated cardiomyopathy" (or synonyms) into the search box. You will automatically receive information on relevant news releases posted within the last 30 days. The search results are shown by order of relevance.

Reuters Health

The Reuters' Medical News and Health eLine databases can be very useful in exploring news archives relating to dilated cardiomyopathy. While some of the listed articles are free to view, others are available for purchase for a nominal fee. To access this archive, go to **http://www.reutershealth.com/en/index.html** and search by "dilated cardiomyopathy" (or synonyms). The following was recently listed in this archive for dilated cardiomyopathy:

- **Idiopathic dilated cardiomyopathy tied to autoimmunity**
  Source: Reuters Medical News
  Date: June 04, 2004

- **Immunosuppressive therapy for dilated cardiomyopathy should be reconsidered**
  Source: Reuters Industry Breifing
  Date: July 06, 2001
- **Mitral Regurgitation: Protective Against LV Thrombus In Dilated Cardiomyopathy Patients**
  Source: Reuters Medical News
  Date: March 11, 1998
- **Relatives Of Patients With Dilated Cardiomyopathy At Risk For Cardiac Disease**
  Source: Reuters Medical News
  Date: January 01, 1998
- **Noninvasive Predictor Of Mortality In Patients With Dilated Cardiomyopathy Identified**
  Source: Reuters Medical News
  Date: October 17, 1997
- **Molecular Basis For Dilated Cardiomyopathy Elucidated**
  Source: Reuters Medical News
  Date: April 29, 1996
- **Cause Of Dilated Cardiomyopathy Determined By Fast CT**
  Source: Reuters Medical News
  Date: January 31, 1996
- **Gene Locus Responsible For Familial Dilated Cardiomyopathy Identified**
  Source: Reuters Medical News
  Date: December 15, 1995

The NIH

Within MEDLINEplus, the NIH has made an agreement with the New York Times Syndicate, the AP News Service, and Reuters to deliver news that can be browsed by the public. Search news releases at **http://www.nlm.nih.gov/medlineplus/alphanews_a.html**. MEDLINEplus allows you to browse across an alphabetical index. Or you can search by date at the following Web page: **http://www.nlm.nih.gov/medlineplus/newsbydate.html**. Often, news items are indexed by MEDLINEplus within its search engine.

Business Wire

Business Wire is similar to PR Newswire. To access this archive, simply go to **http://www.businesswire.com/**. You can scan the news by industry category or company name.

Market Wire

Market Wire is more focused on technology than the other wires. To browse the latest press releases by topic, such as alternative medicine, biotechnology, fitness, healthcare, legal, nutrition, and pharmaceuticals, access Market Wire's Medical/Health channel at **http://www.marketwire.com/mw/release_index?channel=MedicalHealth**. Or simply go to Market Wire's home page at **http://www.marketwire.com/mw/home**, type "dilated

cardiomyopathy" (or synonyms) into the search box, and click on "Search News." As this service is technology oriented, you may wish to use it when searching for press releases covering diagnostic procedures or tests.

Search Engines

Medical news is also available in the news sections of commercial Internet search engines. See the health news page at Yahoo (**http://dir.yahoo.com/Health/News_and_Media/**), or you can use this Web site's general news search page at **http://news.yahoo.com/**. Type in "dilated cardiomyopathy" (or synonyms). If you know the name of a company that is relevant to dilated cardiomyopathy, you can go to any stock trading Web site (such as **http://www.etrade.com/**) and search for the company name there. News items across various news sources are reported on indicated hyperlinks. Google offers a similar service at **http://news.google.com/**.

BBC

Covering news from a more European perspective, the British Broadcasting Corporation (BBC) allows the public free access to their news archive located at **http://www.bbc.co.uk/**. Search by "dilated cardiomyopathy" (or synonyms).

Academic Periodicals covering Dilated Cardiomyopathy

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to dilated cardiomyopathy. In addition to these sources, you can search for articles covering dilated cardiomyopathy that have been published by any of the periodicals listed in previous chapters. To find the latest studies published, go to **http://www.ncbi.nlm.nih.gov/pubmed**, type the name of the periodical into the search box, and click "Go."

If you want complete details about the historical contents of a journal, you can also visit the following Web site: **http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi**. Here, type in the name of the journal or its abbreviation, and you will receive an index of published articles. At **http://locatorplus.gov/**, you can retrieve more indexing information on medical periodicals (e.g. the name of the publisher). Select the button "Search LOCATORplus." Then type in the name of the journal and select the advanced search option "Journal Title Search."

APPENDICES

APPENDIX A. PHYSICIAN RESOURCES

Overview

In this chapter, we focus on databases and Internet-based guidelines and information resources created or written for a professional audience.

NIH Guidelines

Commonly referred to as "clinical" or "professional" guidelines, the National Institutes of Health publish physician guidelines for the most common diseases. Publications are available at the following by relevant Institute[10]:

- Office of the Director (OD); guidelines consolidated across agencies available at **http://www.nih.gov/health/consumer/conkey.htm**
- National Institute of General Medical Sciences (NIGMS); fact sheets available at **http://www.nigms.nih.gov/news/facts/**
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines: **http://www.nlm.nih.gov/medlineplus/healthtopics.html**
- National Cancer Institute (NCI); guidelines available at **http://www.cancer.gov/cancerinfo/list.aspx?viewid=5f35036e-5497-4d86-8c2c-714a9f7c8d25**
- National Eye Institute (NEI); guidelines available at **http://www.nei.nih.gov/order/index.htm**
- National Heart, Lung, and Blood Institute (NHLBI); guidelines available at **http://www.nhlbi.nih.gov/guidelines/index.htm**
- National Human Genome Research Institute (NHGRI); research available at **http://www.genome.gov/page.cfm?pageID=10000375**
- National Institute on Aging (NIA); guidelines available at **http://www.nia.nih.gov/health/**

[10] These publications are typically written by one or more of the various NIH Institutes.

- National Institute on Alcohol Abuse and Alcoholism (NIAAA); guidelines available at **http://www.niaaa.nih.gov/publications/publications.htm**
- National Institute of Allergy and Infectious Diseases (NIAID); guidelines available at **http://www.niaid.nih.gov/publications/**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); fact sheets and guidelines available at **http://www.niams.nih.gov/hi/index.htm**
- National Institute of Child Health and Human Development (NICHD); guidelines available at **http://www.nichd.nih.gov/publications/pubskey.cfm**
- National Institute on Deafness and Other Communication Disorders (NIDCD); fact sheets and guidelines at **http://www.nidcd.nih.gov/health/**
- National Institute of Dental and Craniofacial Research (NIDCR); guidelines available at **http://www.nidr.nih.gov/health/**
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); guidelines available at **http://www.niddk.nih.gov/health/health.htm**
- National Institute on Drug Abuse (NIDA); guidelines available at **http://www.nida.nih.gov/DrugAbuse.html**
- National Institute of Environmental Health Sciences (NIEHS); environmental health information available at **http://www.niehs.nih.gov/external/facts.htm**
- National Institute of Mental Health (NIMH); guidelines available at **http://www.nimh.nih.gov/practitioners/index.cfm**
- National Institute of Neurological Disorders and Stroke (NINDS); neurological disorder information pages available at **http://www.ninds.nih.gov/health_and_medical/disorder_index.htm**
- National Institute of Nursing Research (NINR); publications on selected illnesses at **http://www.nih.gov/ninr/news-info/publications.html**
- National Institute of Biomedical Imaging and Bioengineering; general information at **http://grants.nih.gov/grants/becon/becon_info.htm**
- Center for Information Technology (CIT); referrals to other agencies based on keyword searches available at **http://kb.nih.gov/www_query_main.asp**
- National Center for Complementary and Alternative Medicine (NCCAM); health information available at **http://nccam.nih.gov/health/**
- National Center for Research Resources (NCRR); various information directories available at **http://www.ncrr.nih.gov/publications.asp**
- Office of Rare Diseases; various fact sheets available at **http://rarediseases.info.nih.gov/html/resources/rep_pubs.html**
- Centers for Disease Control and Prevention; various fact sheets on infectious diseases available at **http://www.cdc.gov/publications.htm**

NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.[11] Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic citations, full-text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine:[12]

- **Bioethics:** Access to published literature on the ethical, legal, and public policy issues surrounding healthcare and biomedical research. This information is provided in conjunction with the Kennedy Institute of Ethics located at Georgetown University, Washington, D.C.: **http://www.nlm.nih.gov/databases/databases_bioethics.html**
- **HIV/AIDS Resources:** Describes various links and databases dedicated to HIV/AIDS research: **http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html**
- **NLM Online Exhibitions:** Describes "Exhibitions in the History of Medicine": **http://www.nlm.nih.gov/exhibition/exhibition.html**. Additional resources for historical scholarship in medicine: **http://www.nlm.nih.gov/hmd/hmd.html**
- **Biotechnology Information:** Access to public databases. The National Center for Biotechnology Information conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information for the better understanding of molecular processes affecting human health and disease: **http://www.ncbi.nlm.nih.gov/**
- **Population Information:** The National Library of Medicine provides access to worldwide coverage of population, family planning, and related health issues, including family planning technology and programs, fertility, and population law and policy: **http://www.nlm.nih.gov/databases/databases_population.html**
- **Cancer Information:** Access to cancer-oriented databases: **http://www.nlm.nih.gov/databases/databases_cancer.html**
- **Profiles in Science:** Offering the archival collections of prominent twentieth-century biomedical scientists to the public through modern digital technology: **http://www.profiles.nlm.nih.gov/**
- **Chemical Information:** Provides links to various chemical databases and references: **http://sis.nlm.nih.gov/Chem/ChemMain.html**
- **Clinical Alerts:** Reports the release of findings from the NIH-funded clinical trials where such release could significantly affect morbidity and mortality: **http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html**
- **Space Life Sciences:** Provides links and information to space-based research (including NASA): **http://www.nlm.nih.gov/databases/databases_space.html**
- **MEDLINE:** Bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and the pre-clinical sciences: **http://www.nlm.nih.gov/databases/databases_medline.html**

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[11] Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINE*plus* (**http://medlineplus.gov/** or **http://www.nlm.nih.gov/medlineplus/databases.html**).

[12] See **http://www.nlm.nih.gov/databases/databases.html**.

- **Toxicology and Environmental Health Information (TOXNET):** Databases covering toxicology and environmental health: **http://sis.nlm.nih.gov/Tox/ToxMain.html**
- **Visible Human Interface:** Anatomically detailed, three-dimensional representations of normal male and female human bodies: **http://www.nlm.nih.gov/research/visible/visible_human.html**

The NLM Gateway[13]

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.[14] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type "dilated cardiomyopathy" (or synonyms) into the search box and click "Search." The results will be presented in a tabular form, indicating the number of references in each database category.

Results Summary

Category	Items Found
Journal Articles	10127
Books / Periodicals / Audio Visual	17
Consumer Health	846
Meeting Abstracts	23
Other Collections	126
Total	11139

HSTAT[15]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[16] These documents include clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.[17] Simply search by "dilated cardiomyopathy" (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

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[13] Adapted from NLM: **http://gateway.nlm.nih.gov/gw/Cmd?Overview.x**.

[14] The NLM Gateway is currently being developed by the Lister Hill National Center for Biomedical Communications (LHNCBC) at the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

[15] Adapted from HSTAT: **http://www.nlm.nih.gov/pubs/factsheets/hstat.html**.

[16] The HSTAT URL is **http://hstat.nlm.nih.gov/**.

[17] Other important documents in HSTAT include: the National Institutes of Health (NIH) Consensus Conference Reports and Technology Assessment Reports; the HIV/AIDS Treatment Information Service (ATIS) resource documents; the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Treatment Improvement Protocols (TIP) and Center for Substance Abuse Prevention (SAMHSA/CSAP) Prevention Enhancement Protocols System (PEPS); the Public Health Service (PHS) Preventive Services Task Force's *Guide to Clinical Preventive Services*; the independent, nonfederal Task Force on Community Services' *Guide to Community Preventive Services*; and the Health Technology Advisory Committee (HTAC) of the Minnesota Health Care Commission (MHCC) health technology evaluations.

Coffee Break: Tutorials for Biologists[18]

Coffee Break is a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. Here you will find a collection of short reports on recent biological discoveries. Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.[19] Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.[20] This site has new articles every few weeks, so it can be considered an online magazine of sorts. It is intended for general background information. You can access the Coffee Break Web site at the following hyperlink: **http://www.ncbi.nlm.nih.gov/Coffeebreak/**.

Other Commercial Databases

In addition to resources maintained by official agencies, other databases exist that are commercial ventures addressing medical professionals. Here are some examples that may interest you:

- **CliniWeb International:** Index and table of contents to selected clinical information on the Internet; see **http://www.ohsu.edu/cliniweb/**.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see **http://www.mwsearch.com/**.

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[18] Adapted from **http://www.ncbi.nlm.nih.gov/Coffeebreak/Archive/FAQ.html**.

[19] The figure that accompanies each article is frequently supplied by an expert external to NCBI, in which case the source of the figure is cited. The result is an interactive tutorial that tells a biological story.

[20] After a brief introduction that sets the work described into a broader context, the report focuses on how a molecular understanding can provide explanations of observed biology and lead to therapies for diseases. Each vignette is accompanied by a figure and hypertext links that lead to a series of pages that interactively show how NCBI tools and resources are used in the research process.

APPENDIX B. PATIENT RESOURCES

Overview

Official agencies, as well as federally funded institutions supported by national grants, frequently publish a variety of guidelines written with the patient in mind. These are typically called "Fact Sheets" or "Guidelines." They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. Since new guidelines on dilated cardiomyopathy can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

Patient Guideline Sources

The remainder of this chapter directs you to sources which either publish or can help you find additional guidelines on topics related to dilated cardiomyopathy. Due to space limitations, these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

The National Institutes of Health

The NIH gateway to patients is located at **http://health.nih.gov/**. From this site, you can search across various sources and institutes, a number of which are summarized below.

Topic Pages: MEDLINEplus

The National Library of Medicine has created a vast and patient-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are "health topic pages" which list links to available materials relevant to dilated cardiomyopathy. To access this system, log on to **http://www.nlm.nih.gov/medlineplus/healthtopics.html**. From there you can either search using the alphabetical index or browse by broad topic areas. Recently, MEDLINEplus listed the following when searched for "dilated cardiomyopathy":

Cardiomyopathy
http://www.nlm.nih.gov/medlineplus/cardiomyopathy.html

Circulatory Disorders
http://www.nlm.nih.gov/medlineplus/circulatorydisorders.html

Congenital Heart Disease
http://www.nlm.nih.gov/medlineplus/congenitalheartdisease.html

Heart Diseases
http://www.nlm.nih.gov/medlineplus/heartdiseases.html

Heart Failure
http://www.nlm.nih.gov/medlineplus/heartfailure.html

Heart Valve Diseases
http://www.nlm.nih.gov/medlineplus/heartvalvediseases.html

You may also choose to use the search utility provided by MEDLINEplus at the following Web address: **http://www.nlm.nih.gov/medlineplus/**. Simply type a keyword into the search box and click "Search." This utility is similar to the NIH search utility, with the exception that it only includes materials that are linked within the MEDLINEplus system (mostly patient-oriented information). It also has the disadvantage of generating unstructured results. We recommend, therefore, that you use this method only if you have a very targeted search.

The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is "crawled" and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to dilated cardiomyopathy. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for professionals and patients. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: **http://search.nih.gov/index.html**.

Additional Web Sources

A number of Web sites are available to the public that often link to government sites. These can also point you in the direction of essential information. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=168&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/specific.htm**
- Google: **http://directory.google.com/Top/Health/Conditions_and_Diseases/**
- Med Help International: **http://www.medhelp.org/HealthTopics/A.html**
- Open Directory Project: **http://dmoz.org/Health/Conditions_and_Diseases/**
- Yahoo.com: **http://dir.yahoo.com/Health/Diseases_and_Conditions/**

- WebMD®Health: **http://my.webmd.com/health_topics**

Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to dilated cardiomyopathy. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with dilated cardiomyopathy.

The National Health Information Center (NHIC)

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about dilated cardiomyopathy. For more information, see the NHIC's Web site at **http://www.health.gov/NHIC/** or contact an information specialist by calling 1-800-336-4797.

Directory of Health Organizations

The Directory of Health Organizations, provided by the National Library of Medicine Specialized Information Services, is a comprehensive source of information on associations. The Directory of Health Organizations database can be accessed via the Internet at **http://www.sis.nlm.nih.gov/Dir/DirMain.html**. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. To access DIRLINE directly, go to the following Web site: **http://dirline.nlm.nih.gov/**. Simply type in "dilated cardiomyopathy" (or a synonym), and you will receive information on all relevant organizations listed in the database.

Health Hotlines directs you to toll-free numbers to over 300 organizations. You can access this database directly at **http://www.sis.nlm.nih.gov/hotlines/**. On this page, you are given the option to search by keyword or by browsing the subject list. When you have received your search results, click on the name of the organization for its description and contact information.

The Combined Health Information Database

Another comprehensive source of information on healthcare associations is the Combined Health Information Database. Using the "Detailed Search" option, you will need to limit your search to "Organizations" and "dilated cardiomyopathy". Type the following hyperlink into your Web browser: **http://chid.nih.gov/detail/detail.html**. To find associations, use the drop boxes at the bottom of the search page where "You may refine your search by." For publication date, select "All Years." Then, select your preferred language and the format option "Organization Resource Sheet." Type "dilated cardiomyopathy" (or synonyms) into the "For these words:" box. You should check back periodically with this database since it is updated every three months.

The National Organization for Rare Disorders, Inc.

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by health topic. You can access this database at the following Web site: **http://www.rarediseases.org/search/orgsearch.html**. Type "dilated cardiomyopathy" (or a synonym) into the search box, and click "Submit Query."

APPENDIX C. FINDING MEDICAL LIBRARIES

Overview

In this Appendix, we show you how to quickly find a medical library in your area.

Preparation

Your local public library and medical libraries have interlibrary loan programs with the National Library of Medicine (NLM), one of the largest medical collections in the world. According to the NLM, most of the literature in the general and historical collections of the National Library of Medicine is available on interlibrary loan to any library. If you would like to access NLM medical literature, then visit a library in your area that can request the publications for you.[21]

Finding a Local Medical Library

The quickest method to locate medical libraries is to use the Internet-based directory published by the National Network of Libraries of Medicine (NN/LM). This network includes 4626 members and affiliates that provide many services to librarians, health professionals, and the public. To find a library in your area, simply visit **http://nnlm.gov/members/adv.html** or call 1-800-338-7657.

Medical Libraries in the U.S. and Canada

In addition to the NN/LM, the National Library of Medicine (NLM) lists a number of libraries with reference facilities that are open to the public. The following is the NLM's list and includes hyperlinks to each library's Web site. These Web pages can provide information on hours of operation and other restrictions. The list below is a small sample of

[21] Adapted from the NLM: **http://www.nlm.nih.gov/psd/cas/interlibrary.html**.

libraries recommended by the National Library of Medicine (sorted alphabetically by name of the U.S. state or Canadian province where the library is located)[22]:

- **Alabama:** Health InfoNet of Jefferson County (Jefferson County Library Cooperative, Lister Hill Library of the Health Sciences), **http://www.uab.edu/infonet/**
- **Alabama:** Richard M. Scrushy Library (American Sports Medicine Institute)
- **Arizona:** Samaritan Regional Medical Center: The Learning Center (Samaritan Health System, Phoenix, Arizona), **http://www.samaritan.edu/library/bannerlibs.htm**
- **California:** Kris Kelly Health Information Center (St. Joseph Health System, Humboldt), **http://www.humboldt1.com/~kkhic/index.html**
- **California:** Community Health Library of Los Gatos, **http://www.healthlib.org/orgresources.html**
- **California:** Consumer Health Program and Services (CHIPS) (County of Los Angeles Public Library, Los Angeles County Harbor-UCLA Medical Center Library) - Carson, CA, **http://www.colapublib.org/services/chips.html**
- **California:** Gateway Health Library (Sutter Gould Medical Foundation)
- **California:** Health Library (Stanford University Medical Center), **http://www-med.stanford.edu/healthlibrary/**
- **California:** Patient Education Resource Center - Health Information and Resources (University of California, San Francisco), **http://sfghdean.ucsf.edu/barnett/PERC/default.asp**
- **California:** Redwood Health Library (Petaluma Health Care District), **http://www.phcd.org/rdwdlib.html**
- **California:** Los Gatos PlaneTree Health Library, **http://planetreesanjose.org/**
- **California:** Sutter Resource Library (Sutter Hospitals Foundation, Sacramento), **http://suttermedicalcenter.org/library/**
- **California:** Health Sciences Libraries (University of California, Davis), **http://www.lib.ucdavis.edu/healthsci/**
- **California:** ValleyCare Health Library & Ryan Comer Cancer Resource Center (ValleyCare Health System, Pleasanton), **http://gaelnet.stmarys-ca.edu/other.libs/gbal/east/vchl.html**
- **California:** Washington Community Health Resource Library (Fremont), **http://www.healthlibrary.org/**
- **Colorado:** William V. Gervasini Memorial Library (Exempla Healthcare), **http://www.saintjosephdenver.org/yourhealth/libraries/**
- **Connecticut:** Hartford Hospital Health Science Libraries (Hartford Hospital), **http://www.harthosp.org/library/**
- **Connecticut:** Healthnet: Connecticut Consumer Health Information Center (University of Connecticut Health Center, Lyman Maynard Stowe Library), **http://library.uchc.edu/departm/hnet/**

[22] Abstracted from **http://www.nlm.nih.gov/medlineplus/libraries.html**.

- **Connecticut:** Waterbury Hospital Health Center Library (Waterbury Hospital, Waterbury), **http://www.waterburyhospital.com/library/consumer.shtml**
- **Delaware:** Consumer Health Library (Christiana Care Health System, Eugene du Pont Preventive Medicine & Rehabilitation Institute, Wilmington), **http://www.christianacare.org/health_guide/health_guide_pmri_health_info.cfm**
- **Delaware:** Lewis B. Flinn Library (Delaware Academy of Medicine, Wilmington), **http://www.delamed.org/chls.html**
- **Georgia:** Family Resource Library (Medical College of Georgia, Augusta), **http://cmc.mcg.edu/kids_families/fam_resources/fam_res_lib/frl.htm**
- **Georgia:** Health Resource Center (Medical Center of Central Georgia, Macon), **http://www.mccg.org/hrc/hrchome.asp**
- **Hawaii:** Hawaii Medical Library: Consumer Health Information Service (Hawaii Medical Library, Honolulu), **http://hml.org/CHIS/**
- **Idaho:** DeArmond Consumer Health Library (Kootenai Medical Center, Coeur d'Alene), **http://www.nicon.org/DeArmond/index.htm**
- **Illinois:** Health Learning Center of Northwestern Memorial Hospital (Chicago), **http://www.nmh.org/health_info/hlc.html**
- **Illinois:** Medical Library (OSF Saint Francis Medical Center, Peoria), **http://www.osfsaintfrancis.org/general/library/**
- **Kentucky:** Medical Library - Services for Patients, Families, Students & the Public (Central Baptist Hospital, Lexington), **http://www.centralbap.com/education/community/library.cfm**
- **Kentucky:** University of Kentucky - Health Information Library (Chandler Medical Center, Lexington), **http://www.mc.uky.edu/PatientEd/**
- **Louisiana:** Alton Ochsner Medical Foundation Library (Alton Ochsner Medical Foundation, New Orleans), **http://www.ochsner.org/library/**
- **Louisiana:** Louisiana State University Health Sciences Center Medical Library-Shreveport, **http://lib-sh.lsuhsc.edu/**
- **Maine:** Franklin Memorial Hospital Medical Library (Franklin Memorial Hospital, Farmington), **http://www.fchn.org/fmh/lib.htm**
- **Maine:** Gerrish-True Health Sciences Library (Central Maine Medical Center, Lewiston), **http://www.cmmc.org/library/library.html**
- **Maine:** Hadley Parrot Health Science Library (Eastern Maine Healthcare, Bangor), **http://www.emh.org/hll/hpl/guide.htm**
- **Maine:** Maine Medical Center Library (Maine Medical Center, Portland), **http://www.mmc.org/library/**
- **Maine:** Parkview Hospital (Brunswick), **http://www.parkviewhospital.org/**
- **Maine:** Southern Maine Medical Center Health Sciences Library (Southern Maine Medical Center, Biddeford), **http://www.smmc.org/services/service.php3?choice=10**
- **Maine:** Stephens Memorial Hospital's Health Information Library (Western Maine Health, Norway), **http://www.wmhcc.org/Library/**

- **Manitoba, Canada:** Consumer & Patient Health Information Service (University of Manitoba Libraries), **http://www.umanitoba.ca/libraries/units/health/reference/chis.html**
- **Manitoba, Canada:** J.W. Crane Memorial Library (Deer Lodge Centre, Winnipeg), **http://www.deerlodge.mb.ca/crane_library/about.asp**
- **Maryland:** Health Information Center at the Wheaton Regional Library (Montgomery County, Dept. of Public Libraries, Wheaton Regional Library), **http://www.mont.lib.md.us/healthinfo/hic.asp**
- **Massachusetts:** Baystate Medical Center Library (Baystate Health System), **http://www.baystatehealth.com/1024/**
- **Massachusetts:** Boston University Medical Center Alumni Medical Library (Boston University Medical Center), **http://med-libwww.bu.edu/library/lib.html**
- **Massachusetts:** Lowell General Hospital Health Sciences Library (Lowell General Hospital, Lowell), **http://www.lowellgeneral.org/library/HomePageLinks/WWW.htm**
- **Massachusetts:** Paul E. Woodard Health Sciences Library (New England Baptist Hospital, Boston), **http://www.nebh.org/health_lib.asp**
- **Massachusetts:** St. Luke's Hospital Health Sciences Library (St. Luke's Hospital, Southcoast Health System, New Bedford), **http://www.southcoast.org/library/**
- **Massachusetts:** Treadwell Library Consumer Health Reference Center (Massachusetts General Hospital), **http://www.mgh.harvard.edu/library/chrcindex.html**
- **Massachusetts:** UMass HealthNet (University of Massachusetts Medical School, Worchester), **http://healthnet.umassmed.edu/**
- **Michigan:** Botsford General Hospital Library - Consumer Health (Botsford General Hospital, Library & Internet Services), **http://www.botsfordlibrary.org/consumer.htm**
- **Michigan:** Helen DeRoy Medical Library (Providence Hospital and Medical Centers), **http://www.providence-hospital.org/library/**
- **Michigan:** Marquette General Hospital - Consumer Health Library (Marquette General Hospital, Health Information Center), **http://www.mgh.org/center.html**
- **Michigan:** Patient Education Resouce Center - University of Michigan Cancer Center (University of Michigan Comprehensive Cancer Center, Ann Arbor), **http://www.cancer.med.umich.edu/learn/leares.htm**
- **Michigan:** Sladen Library & Center for Health Information Resources - Consumer Health Information (Detroit), **http://www.henryford.com/body.cfm?id=39330**
- **Montana:** Center for Health Information (St. Patrick Hospital and Health Sciences Center, Missoula)
- **National:** Consumer Health Library Directory (Medical Library Association, Consumer and Patient Health Information Section), **http://caphis.mlanet.org/directory/index.html**
- **National:** National Network of Libraries of Medicine (National Library of Medicine) - provides library services for health professionals in the United States who do not have access to a medical library, **http://nnlm.gov/**
- **National:** NN/LM List of Libraries Serving the Public (National Network of Libraries of Medicine), **http://nnlm.gov/members/**

- **Nevada:** Health Science Library, West Charleston Library (Las Vegas-Clark County Library District, Las Vegas), **http://www.lvccld.org/special_collections/medical/index.htm**
- **New Hampshire:** Dartmouth Biomedical Libraries (Dartmouth College Library, Hanover), **http://www.dartmouth.edu/~biomed/resources.htmld/conshealth.htmld/**
- **New Jersey:** Consumer Health Library (Rahway Hospital, Rahway), **http://www.rahwayhospital.com/library.htm**
- **New Jersey:** Dr. Walter Phillips Health Sciences Library (Englewood Hospital and Medical Center, Englewood), **http://www.englewoodhospital.com/links/index.htm**
- **New Jersey:** Meland Foundation (Englewood Hospital and Medical Center, Englewood), **http://www.geocities.com/ResearchTriangle/9360/**
- **New York:** Choices in Health Information (New York Public Library) - NLM Consumer Pilot Project participant, **http://www.nypl.org/branch/health/links.html**
- **New York:** Health Information Center (Upstate Medical University, State University of New York, Syracuse), **http://www.upstate.edu/library/hic/**
- **New York:** Health Sciences Library (Long Island Jewish Medical Center, New Hyde Park), **http://www.lij.edu/library/library.html**
- **New York:** ViaHealth Medical Library (Rochester General Hospital), **http://www.nyam.org/library/**
- **Ohio:** Consumer Health Library (Akron General Medical Center, Medical & Consumer Health Library), **http://www.akrongeneral.org/hwlibrary.htm**
- **Oklahoma:** The Health Information Center at Saint Francis Hospital (Saint Francis Health System, Tulsa), **http://www.sfh-tulsa.com/services/healthinfo.asp**
- **Oregon:** Planetree Health Resource Center (Mid-Columbia Medical Center, The Dalles), **http://www.mcmc.net/phrc/**
- **Pennsylvania:** Community Health Information Library (Milton S. Hershey Medical Center, Hershey), **http://www.hmc.psu.edu/commhealth/**
- **Pennsylvania:** Community Health Resource Library (Geisinger Medical Center, Danville), **http://www.geisinger.edu/education/commlib.shtml**
- **Pennsylvania:** HealthInfo Library (Moses Taylor Hospital, Scranton), **http://www.mth.org/healthwellness.html**
- **Pennsylvania:** Hopwood Library (University of Pittsburgh, Health Sciences Library System, Pittsburgh), **http://www.hsls.pitt.edu/guides/chi/hopwood/index_html**
- **Pennsylvania:** Koop Community Health Information Center (College of Physicians of Philadelphia), **http://www.collphyphil.org/kooppg1.shtml**
- **Pennsylvania:** Learning Resources Center - Medical Library (Susquehanna Health System, Williamsport), **http://www.shscares.org/services/lrc/index.asp**
- **Pennsylvania:** Medical Library (UPMC Health System, Pittsburgh), **http://www.upmc.edu/passavant/library.htm**
- **Quebec, Canada:** Medical Library (Montreal General Hospital), **http://www.mghlib.mcgill.ca/**

- **South Dakota:** Rapid City Regional Hospital Medical Library (Rapid City Regional Hospital), **http://www.rcrh.org/Services/Library/Default.asp**
- **Texas:** Houston HealthWays (Houston Academy of Medicine-Texas Medical Center Library), **http://hhw.library.tmc.edu/**
- **Washington:** Community Health Library (Kittitas Valley Community Hospital), **http://www.kvch.com/**
- **Washington:** Southwest Washington Medical Center Library (Southwest Washington Medical Center, Vancouver), **http://www.swmedicalcenter.com/body.cfm?id=72**

ONLINE GLOSSARIES

The Internet provides access to a number of free-to-use medical dictionaries. The National Library of Medicine has compiled the following list of online dictionaries:

- ADAM Medical Encyclopedia (A.D.A.M., Inc.), comprehensive medical reference: **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**
- MedicineNet.com Medical Dictionary (MedicineNet, Inc.): **http://www.medterms.com/Script/Main/hp.asp**
- Merriam-Webster Medical Dictionary (Inteli-Health, Inc.): **http://www.intelihealth.com/IH/**
- Multilingual Glossary of Technical and Popular Medical Terms in Eight European Languages (European Commission) - Danish, Dutch, English, French, German, Italian, Portuguese, and Spanish: **http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html**
- On-line Medical Dictionary (CancerWEB): **http://cancerweb.ncl.ac.uk/omd/**
- Rare Diseases Terms (Office of Rare Diseases): **http://ord.aspensys.com/asp/diseases/diseases.asp**
- Technology Glossary (National Library of Medicine) - Health Care Technology: **http://www.nlm.nih.gov/nichsr/ta101/ta10108.htm**

Beyond these, MEDLINEplus contains a very patient-friendly encyclopedia covering every aspect of medicine (licensed from A.D.A.M., Inc.). The ADAM Medical Encyclopedia can be accessed at **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**. ADAM is also available on commercial Web sites such as drkoop.com (**http://www.drkoop.com/**) and Web MD (**http://my.webmd.com/adam/asset/adam_disease_articles/a_to_z/a**). The NIH suggests the following Web sites in the ADAM Medical Encyclopedia when searching for information on dilated cardiomyopathy:

- **Basic Guidelines for Dilated Cardiomyopathy**

  Dilated cardiomyopathy
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000168.htm

  Restrictive cardiomyopathy
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000189.htm

- **Signs & Symptoms for Dilated Cardiomyopathy**

  Anemia
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000560.htm

  Chest pain
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003079.htm

  Cough
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003072.htm

Decreased alertness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003202.htm

Decreased urine production
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003147.htm

Fainting
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003092.htm

Faintness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003092.htm

Fatigue
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003088.htm

Headache
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003024.htm

Hypotension
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003083.htm

Lightheadedness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003092.htm

Loss of appetite
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003121.htm

Low blood pressure
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003083.htm

Muscle
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003193.htm

Need to urinate at night
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003141.htm

Nocturia
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003141.htm

Obesity
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003101.htm

Oliguria
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003147.htm

Palpitations
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003081.htm

Shortness of breath
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003075.htm

Stress
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003211.htm

Swelling of feet
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003104.htm

Swelling of the abdomen
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003122.htm

Weakness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003174.htm

Weight gain
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003084.htm

- **Diagnostics and Tests for Dilated Cardiomyopathy**

Angiography
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003327.htm

Biopsy
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003416.htm

Cardiac catheterization
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003419.htm

Chest CT
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003788.htm

Chest CT scan
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003788.htm

Chest X-ray
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003804.htm

Coronary angiography
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003875.htm

Coronary angiography
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003876.htm

CT
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003330.htm

ECG
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003868.htm

Echocardiogram
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003869.htm

Heart biopsy
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003873.htm

MUGA
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003822.htm

Nuclear heart scan
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003822.htm

Pulse
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003399.htm

RNV
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003822.htm

X-ray
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003337.htm

- **Surgery and Procedures for Dilated Cardiomyopathy**

Heart transplant
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003003.htm

- **Background Topics for Dilated Cardiomyopathy**

Smoking
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002032.htm

Acute
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002215.htm

Auscultation
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002226.htm

Cardiovascular
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002310.htm

Palpation
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002284.htm

Percussion
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002281.htm

Smoking
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002032.htm

Online Dictionary Directories

The following are additional online directories compiled by the National Library of Medicine, including a number of specialized medical dictionaries:

- Medical Dictionaries: Medical & Biological (World Health Organization): **http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical**

- MEL-Michigan Electronic Library List of Online Health and Medical Dictionaries (Michigan Electronic Library): **http://mel.lib.mi.us/health/health-dictionaries.html**
- Patient Education: Glossaries (DMOZ Open Directory Project): **http://dmoz.org/Health/Education/Patient_Education/Glossaries/**
- Web of Online Dictionaries (Bucknell University): **http://www.yourdictionary.com/diction5.html#medicine**

DILATED CARDIOMYOPATHY DICTIONARY

The definitions below are derived from official public sources, including the National Institutes of Health [NIH] and the European Union [EU].

3-dimensional: 3-D. A graphic display of depth, width, and height. Three-dimensional radiation therapy uses computers to create a 3-dimensional picture of the tumor. This allows doctors to give the highest possible dose of radiation to the tumor, while sparing the normal tissue as much as possible. [NIH]

Abdomen: That portion of the body that lies between the thorax and the pelvis. [NIH]

Abdominal: Having to do with the abdomen, which is the part of the body between the chest and the hips that contains the pancreas, stomach, intestines, liver, gallbladder, and other organs. [NIH]

Abducens: A striated, extrinsic muscle of the eyeball that originates from the annulus of Zinn. [NIH]

Aberrant: Wandering or deviating from the usual or normal course. [EU]

Ablation: The removal of an organ by surgery. [NIH]

Abscess: A localized, circumscribed collection of pus. [NIH]

Acceptor: A substance which, while normally not oxidized by oxygen or reduced by hydrogen, can be oxidized or reduced in presence of a substance which is itself undergoing oxidation or reduction. [NIH]

Acetylcholine: A neurotransmitter. Acetylcholine in vertebrates is the major transmitter at neuromuscular junctions, autonomic ganglia, parasympathetic effector junctions, a subset of sympathetic effector junctions, and at many sites in the central nervous system. It is generally not used as an administered drug because it is broken down very rapidly by cholinesterases, but it is useful in some ophthalmological applications. [NIH]

Acquired Immunodeficiency Syndrome: An acquired defect of cellular immunity associated with infection by the human immunodeficiency virus (HIV), a CD4-positive T-lymphocyte count under 200 cells/microliter or less than 14% of total lymphocytes, and increased susceptibility to opportunistic infections and malignant neoplasms. Clinical manifestations also include emaciation (wasting) and dementia. These elements reflect criteria for AIDS as defined by the CDC in 1993. [NIH]

Actin: Essential component of the cell skeleton. [NIH]

Actinin: A protein factor that regulates the length of R-actin. It is chemically similar, but immunochemically distinguishable from actin. [NIH]

Action Potentials: The electric response of a nerve or muscle to its stimulation. [NIH]

Actomyosin: A protein complex of actin and myosin occurring in muscle. It is the essential contractile substance of muscle. [NIH]

Adaptability: Ability to develop some form of tolerance to conditions extremely different from those under which a living organism evolved. [NIH]

Adaptation: 1. The adjustment of an organism to its environment, or the process by which it enhances such fitness. 2. The normal ability of the eye to adjust itself to variations in the intensity of light; the adjustment to such variations. 3. The decline in the frequency of firing of a neuron, particularly of a receptor, under conditions of constant stimulation. 4. In dentistry, (a) the proper fitting of a denture, (b) the degree of proximity and interlocking of

restorative material to a tooth preparation, (c) the exact adjustment of bands to teeth. 5. In microbiology, the adjustment of bacterial physiology to a new environment. [EU]

Adenine: A purine base and a fundamental unit of adenine nucleotides. [NIH]

Adenosine: A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

Adenovirus: A group of viruses that cause respiratory tract and eye infections. Adenoviruses used in gene therapy are altered to carry a specific tumor-fighting gene. [NIH]

Adenylate Cyclase: An enzyme of the lyase class that catalyzes the formation of cyclic AMP and pyrophosphate from ATP. EC 4.6.1.1. [NIH]

Adipose Tissue: Connective tissue composed of fat cells lodged in the meshes of areolar tissue. [NIH]

Adjunctive Therapy: Another treatment used together with the primary treatment. Its purpose is to assist the primary treatment. [NIH]

Adjustment: The dynamic process wherein the thoughts, feelings, behavior, and biophysiological mechanisms of the individual continually change to adjust to the environment. [NIH]

Adjuvant: A substance which aids another, such as an auxiliary remedy; in immunology, nonspecific stimulator (e.g., BCG vaccine) of the immune response. [EU]

Adrenal Cortex: The outer layer of the adrenal gland. It secretes mineralocorticoids, androgens, and glucocorticoids. [NIH]

Adrenal Glands: Paired glands situated in the retroperitoneal tissues at the superior pole of each kidney. [NIH]

Adrenal Medulla: The inner part of the adrenal gland; it synthesizes, stores and releases catecholamines. [NIH]

Adrenergic: Activated by, characteristic of, or secreting epinephrine or substances with similar activity; the term is applied to those nerve fibres that liberate norepinephrine at a synapse when a nerve impulse passes, i.e., the sympathetic fibres. [EU]

Adsorption: The condensation of gases, liquids, or dissolved substances on the surfaces of solids. It includes adsorptive phenomena of bacteria and viruses as well as of tissues treated with exogenous drugs and chemicals. [NIH]

Adsorptive: It captures volatile compounds by binding them to agents such as activated carbon or adsorptive resins. [NIH]

Adverse Effect: An unwanted side effect of treatment. [NIH]

Aerobic: In biochemistry, reactions that need oxygen to happen or happen when oxygen is present. [NIH]

Aerobic Metabolism: A chemical process in which oxygen is used to make energy from carbohydrates (sugars). Also known as aerobic respiration, oxidative metabolism, or cell respiration. [NIH]

Aerobic Respiration: A chemical process in which oxygen is used to make energy from carbohydrates (sugars). Also known as oxidative metabolism, cell respiration, or aerobic metabolism. [NIH]

Affinity: 1. Inherent likeness or relationship. 2. A special attraction for a specific element, organ, or structure. 3. Chemical affinity; the force that binds atoms in molecules; the tendency of substances to combine by chemical reaction. 4. The strength of noncovalent chemical binding between two substances as measured by the dissociation constant of the

complex. 5. In immunology, a thermodynamic expression of the strength of interaction between a single antigen-binding site and a single antigenic determinant (and thus of the stereochemical compatibility between them), most accurately applied to interactions among simple, uniform antigenic determinants such as haptens. Expressed as the association constant (K litres mole -1), which, owing to the heterogeneity of affinities in a population of antibody molecules of a given specificity, actually represents an average value (mean intrinsic association constant). 6. The reciprocal of the dissociation constant. [EU]

Affinity Chromatography: In affinity chromatography, a ligand attached to a column binds specifically to the molecule to be purified. [NIH]

Afterload: The tension produced by the heart muscle after contraction. [EU]

Agonist: In anatomy, a prime mover. In pharmacology, a drug that has affinity for and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances. [EU]

Airway: A device for securing unobstructed passage of air into and out of the lungs during general anesthesia. [NIH]

Albumin: 1. Any protein that is soluble in water and moderately concentrated salt solutions and is coagulable by heat. 2. Serum albumin; the major plasma protein (approximately 60 per cent of the total), which is responsible for much of the plasma colloidal osmotic pressure and serves as a transport protein carrying large organic anions, such as fatty acids, bilirubin, and many drugs, and also carrying certain hormones, such as cortisol and thyroxine, when their specific binding globulins are saturated. Albumin is synthesized in the liver. Low serum levels occur in protein malnutrition, active inflammation and serious hepatic and renal disease. [EU]

Aldehydes: Organic compounds containing a carbonyl group in the form -CHO. [NIH]

Aldosterone: (11 beta)-11,21-Dihydroxy-3,20-dioxopregn-4-en-18-al. A hormone secreted by the adrenal cortex that functions in the regulation of electrolyte and water balance by increasing the renal retention of sodium and the excretion of potassium. [NIH]

Alertness: A state of readiness to detect and respond to certain specified small changes occurring at random intervals in the environment. [NIH]

Algorithms: A procedure consisting of a sequence of algebraic formulas and/or logical steps to calculate or determine a given task. [NIH]

Alimentary: Pertaining to food or nutritive material, or to the organs of digestion. [EU]

Alkaline: Having the reactions of an alkali. [EU]

Alkaloid: A member of a large group of chemicals that are made by plants and have nitrogen in them. Some alkaloids have been shown to work against cancer. [NIH]

Alleles: Mutually exclusive forms of the same gene, occupying the same locus on homologous chromosomes, and governing the same biochemical and developmental process. [NIH]

Allogeneic: Taken from different individuals of the same species. [NIH]

Allogeneic bone marrow transplantation: A procedure in which a person receives stem cells, the cells from which all blood cells develop, from a compatible, though not genetically identical, donor. [NIH]

Allograft: An organ or tissue transplant between two humans. [NIH]

Allopurinol: A xanthine oxidase inhibitor that decreases uric acid production. [NIH]

Alprenolol: 1-((1-Methylethyl)amino)-3-(2-(2-propenyl)phenoxy)-2-propanol. Adrenergic beta-blocker used as an antihypertensive, anti-anginal, and anti-arrhythmic agent. [NIH]

Alternans: Ipsilateral abducens palsy and facial paralysis and contralateral hemiplegia of the limbs, due to a nuclear or infranuclear lesion in the pons. [NIH]

Alternative medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used instead of standard treatments. Alternative medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Alveoli: Tiny air sacs at the end of the bronchioles in the lungs. [NIH]

Ameliorated: A changeable condition which prevents the consequence of a failure or accident from becoming as bad as it otherwise would. [NIH]

Amine: An organic compound containing nitrogen; any member of a group of chemical compounds formed from ammonia by replacement of one or more of the hydrogen atoms by organic (hydrocarbon) radicals. The amines are distinguished as primary, secondary, and tertiary, according to whether one, two, or three hydrogen atoms are replaced. The amines include allylamine, amylamine, ethylamine, methylamine, phenylamine, propylamine, and many other compounds. [EU]

Amino Acid Sequence: The order of amino acids as they occur in a polypeptide chain. This is referred to as the primary structure of proteins. It is of fundamental importance in determining protein conformation. [NIH]

Amino Acid Substitution: The naturally occurring or experimentally induced replacement of one or more amino acids in a protein with another. If a functionally equivalent amino acid is substituted, the protein may retain wild-type activity. Substitution may also diminish or eliminate protein function. Experimentally induced substitution is often used to study enzyme activities and binding site properties. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Amiodarone: An antianginal and antiarrhythmic drug. It increases the duration of ventricular and atrial muscle action by inhibiting Na,K-activated myocardial adenosine triphosphatase. There is a resulting decrease in heart rate and in vascular resistance. [NIH]

Ammonium Sulfate: Sulfuric acid diammonium salt. It is used in fractionation of proteins. [NIH]

Amplification: The production of additional copies of a chromosomal DNA sequence, found as either intrachromosomal or extrachromosomal DNA. [NIH]

Amrinone: A positive inotropic cardiotonic agent with vasodilator properties, phosphodiesterase inhibitory activity, and the ability to stimulate calcium ion influx into the cardiac cell. Its therapeutic use in congestive heart or left ventricular failure is associated with significant increases in the cardiac index, reductions in pulmonary capillary wedge pressure and systemic vascular resistance, and little or no change in mean arterial pressure. One of its more serious side effects is thrombocytopenia in some patients. [NIH]

Amylase: An enzyme that helps the body digest starches. [NIH]

Anaesthesia: Loss of feeling or sensation. Although the term is used for loss of tactile sensibility, or of any of the other senses, it is applied especially to loss of the sensation of pain, as it is induced to permit performance of surgery or other painful procedures. [EU]

Anal: Having to do with the anus, which is the posterior opening of the large bowel. [NIH]

Analog: In chemistry, a substance that is similar, but not identical, to another. [NIH]

Analogous: Resembling or similar in some respects, as in function or appearance, but not in origin or development;. [EU]

Anaphylatoxins: The family of peptides C3a, C4a, C5a, and C5a des-arginine produced in the serum during complement activation. They produce smooth muscle contraction, mast cell histamine release, affect platelet aggregation, and act as mediators of the local inflammatory process. The order of anaphylatoxin activity from strongest to weakest is C5a, C3a, C4a, and C5a des-arginine. The latter is the so-called "classical" anaphylatoxin but shows no spasmogenic activity though it contains some chemotactic ability. [NIH]

Anatomical: Pertaining to anatomy, or to the structure of the organism. [EU]

Anemia: A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

Anesthesia: A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

Aneurysm: A sac formed by the dilatation of the wall of an artery, a vein, or the heart. [NIH]

Angina: Chest pain that originates in the heart. [NIH]

Angina Pectoris: The symptom of paroxysmal pain consequent to myocardial ischemia usually of distinctive character, location and radiation, and provoked by a transient stressful situation during which the oxygen requirements of the myocardium exceed the capacity of the coronary circulation to supply it. [NIH]

Anginal: Pertaining to or characteristic of angina. [EU]

Angiography: Radiography of blood vessels after injection of a contrast medium. [NIH]

Angiotensin-Converting Enzyme Inhibitors: A class of drugs whose main indications are the treatment of hypertension and heart failure. They exert their hemodynamic effect mainly by inhibiting the renin-angiotensin system. They also modulate sympathetic nervous system activity and increase prostaglandin synthesis. They cause mainly vasodilation and mild natriuresis without affecting heart rate and contractility. [NIH]

Angiotensinogen: An alpha-globulin of which a fragment of 14 amino acids is converted by renin to angiotensin I, the inactive precursor of angiotensin II. It is a member of the serpin superfamily. [NIH]

Animal model: An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models. [NIH]

Anions: Negatively charged atoms, radicals or groups of atoms which travel to the anode or positive pole during electrolysis. [NIH]

Anomalies: Birth defects; abnormalities. [NIH]

Anthracycline: A member of a family of anticancer drugs that are also antibiotics. [NIH]

Antianginal: Counteracting angina or anginal conditions. [EU]

Antiarrhythmic: An agent that prevents or alleviates cardiac arrhythmia. [EU]

Antibacterial: A substance that destroys bacteria or suppresses their growth or reproduction. [EU]

Antibiotic: A drug used to treat infections caused by bacteria and other microorganisms.

[NIH]

Antibodies: Immunoglobulin molecules having a specific amino acid sequence by virtue of which they interact only with the antigen that induced their synthesis in cells of the lymphoid series (especially plasma cells), or with an antigen closely related to it. [NIH]

Antibody: A type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen. [NIH]

Anticoagulant: A drug that helps prevent blood clots from forming. Also called a blood thinner. [NIH]

Antigen: Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

Antigen-Antibody Complex: The complex formed by the binding of antigen and antibody molecules. The deposition of large antigen-antibody complexes leading to tissue damage causes immune complex diseases. [NIH]

Antihypertensive: An agent that reduces high blood pressure. [EU]

Anti-infective: An agent that so acts. [EU]

Anti-inflammatory: Having to do with reducing inflammation. [NIH]

Antimetabolite: A chemical that is very similar to one required in a normal biochemical reaction in cells. Antimetabolites can stop or slow down the reaction. [NIH]

Antineoplastic: Inhibiting or preventing the development of neoplasms, checking the maturation and proliferation of malignant cells. [EU]

Antioxidant: A substance that prevents damage caused by free radicals. Free radicals are highly reactive chemicals that often contain oxygen. They are produced when molecules are split to give products that have unpaired electrons. This process is called oxidation. [NIH]

Antiviral: Destroying viruses or suppressing their replication. [EU]

Anus: The opening of the rectum to the outside of the body. [NIH]

Anxiety: Persistent feeling of dread, apprehension, and impending disaster. [NIH]

Aorta: The main trunk of the systemic arteries. [NIH]

Apoptosis: One of the two mechanisms by which cell death occurs (the other being the pathological process of necrosis). Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be intrinsically programmed. It is characterized by distinctive morphologic changes in the nucleus and cytoplasm, chromatin cleavage at regularly spaced sites, and the endonucleolytic cleavage of genomic DNA (DNA fragmentation) at internucleosomal sites. This mode of cell death serves as a balance to mitosis in regulating the size of animal tissues and in mediating pathologic processes associated with tumor growth. [NIH]

Aqueous: Having to do with water. [NIH]

Arachidonic Acid: An unsaturated, essential fatty acid. It is found in animal and human fat as well as in the liver, brain, and glandular organs, and is a constituent of animal

phosphatides. It is formed by the synthesis from dietary linoleic acid and is a precursor in the biosynthesis of prostaglandins, thromboxanes, and leukotrienes. [NIH]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Arrhythmogenic: Producing or promoting arrhythmia. [EU]

Arterial: Pertaining to an artery or to the arteries. [EU]

Arteries: The vessels carrying blood away from the heart. [NIH]

Arteriolar: Pertaining to or resembling arterioles. [EU]

Arterioles: The smallest divisions of the arteries located between the muscular arteries and the capillaries. [NIH]

Arteriosus: Circle composed of anastomosing arteries derived from two long posterior ciliary and seven anterior ciliary arteries, located in the ciliary body about the root of the iris. [NIH]

Artery: Vessel-carrying blood from the heart to various parts of the body. [NIH]

Ascorbic Acid: A six carbon compound related to glucose. It is found naturally in citrus fruits and many vegetables. Ascorbic acid is an essential nutrient in human diets, and necessary to maintain connective tissue and bone. Its biologically active form, vitamin C, functions as a reducing agent and coenzyme in several metabolic pathways. Vitamin C is considered an antioxidant. [NIH]

Assay: Determination of the amount of a particular constituent of a mixture, or of the biological or pharmacological potency of a drug. [EU]

Astrocytes: The largest and most numerous neuroglial cells in the brain and spinal cord. Astrocytes (from "star" cells) are irregularly shaped with many long processes, including those with "end feet" which form the glial (limiting) membrane and directly and indirectly contribute to the blood brain barrier. They regulate the extracellular ionic and chemical environment, and "reactive astrocytes" (along with microglia) respond to injury. Astrocytes have high- affinity transmitter uptake systems, voltage-dependent and transmitter-gated ion channels, and can release transmitter, but their role in signaling (as in many other functions) is not well understood. [NIH]

Asymptomatic: Having no signs or symptoms of disease. [NIH]

Ataxia: Impairment of the ability to perform smoothly coordinated voluntary movements. This condition may affect the limbs, trunk, eyes, pharnyx, larnyx, and other structures. Ataxia may result from impaired sensory or motor function. Sensory ataxia may result from posterior column injury or peripheral nerve diseases. Motor ataxia may be associated with cerebellar diseases; cerebral cortex diseases; thalamic diseases; basal ganglia diseases; injury to the red nucleus; and other conditions. [NIH]

Atopic: Pertaining to an atopen or to atopy; allergic. [EU]

Atopic Eczema: Generic term for acute or chronic inflammatory conditions of the skin, typically erythematous, edematous, papular, vesicular, and crusting; often accompanied by sensations of itching and burning. [NIH]

ATP: ATP an abbreviation for adenosine triphosphate, a compound which serves as a carrier of energy for cells. [NIH]

Atresia: Lack of a normal opening from the esophagus, intestines, or anus. [NIH]

Atrial: Pertaining to an atrium. [EU]

Atrial Fibrillation: Disorder of cardiac rhythm characterized by rapid, irregular atrial impulses and ineffective atrial contractions. [NIH]

Atrial Function: The hemodynamic and electrophysiological action of the atria. [NIH]

Atrioventricular: Pertaining to an atrium of the heart and to a ventricle. [EU]

Atrioventricular Node: A small nodular mass of specialized muscle fibers located in the interatrial septum near the opening of the coronary sinus. It gives rise to the atrioventricular bundle of the conduction system of the heart. [NIH]

Atrium: A chamber; used in anatomical nomenclature to designate a chamber affording entrance to another structure or organ. Usually used alone to designate an atrium of the heart. [EU]

Atrophy: Decrease in the size of a cell, tissue, organ, or multiple organs, associated with a variety of pathological conditions such as abnormal cellular changes, ischemia, malnutrition, or hormonal changes. [NIH]

Attenuated: Strain with weakened or reduced virulence. [NIH]

Auscultation: Act of listening for sounds within the body. [NIH]

Autoantibodies: Antibodies that react with self-antigens (autoantigens) of the organism that produced them. [NIH]

Autoantigens: Endogenous tissue constituents that have the ability to interact with autoantibodies and cause an immune response. [NIH]

Autoimmune disease: A condition in which the body recognizes its own tissues as foreign and directs an immune response against them. [NIH]

Autoimmunity: Process whereby the immune system reacts against the body's own tissues. Autoimmunity may produce or be caused by autoimmune diseases. [NIH]

Autonomic Nervous System: The enteric, parasympathetic, and sympathetic nervous systems taken together. Generally speaking, the autonomic nervous system regulates the internal environment during both peaceful activity and physical or emotional stress. Autonomic activity is controlled and integrated by the central nervous system, especially the hypothalamus and the solitary nucleus, which receive information relayed from visceral afferents; these and related central and sensory structures are sometimes (but not here) considered to be part of the autonomic nervous system itself. [NIH]

Avian: A plasmodial infection in birds. [NIH]

Bacteria: Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccal, rodlike or bacillary, and spiral or spirochetal. [NIH]

Bacterial Physiology: Physiological processes and activities of bacteria. [NIH]

Bactericidal: Substance lethal to bacteria; substance capable of killing bacteria. [NIH]

Basal Ganglia: Large subcortical nuclear masses derived from the telencephalon and located in the basal regions of the cerebral hemispheres. [NIH]

Basal Ganglia Diseases: Diseases of the basal ganglia including the putamen; globus pallidus; claustrum; amygdala; and caudate nucleus. Dyskinesias (most notably involuntary movements and alterations of the rate of movement) represent the primary clinical manifestations of these disorders. Common etiologies include cerebrovascular disease; neurodegenerative diseases; and craniocerebral trauma. [NIH]

Base: In chemistry, the nonacid part of a salt; a substance that combines with acids to form salts; a substance that dissociates to give hydroxide ions in aqueous solutions; a substance whose molecule or ion can combine with a proton (hydrogen ion); a substance capable of donating a pair of electrons (to an acid) for the formation of a coordinate covalent bond. [EU]

Basement Membrane: Ubiquitous supportive tissue adjacent to epithelium and around

smooth and striated muscle cells. This tissue contains intrinsic macromolecular components such as collagen, laminin, and sulfated proteoglycans. As seen by light microscopy one of its subdivisions is the basal (basement) lamina. [NIH]

Basophil: A type of white blood cell. Basophils are granulocytes. [NIH]

Benign: Not cancerous; does not invade nearby tissue or spread to other parts of the body. [NIH]

Berberine: An alkaloid from Hydrastis canadensis L., Berberidaceae. It is also found in many other plants. It is relatively toxic parenterally, but has been used orally for various parasitic and fungal infections and as antidiarrheal. [NIH]

Bile: An emulsifying agent produced in the liver and secreted into the duodenum. Its composition includes bile acids and salts, cholesterol, and electrolytes. It aids digestion of fats in the duodenum. [NIH]

Bile Acids: Acids made by the liver that work with bile to break down fats. [NIH]

Binding Sites: The reactive parts of a macromolecule that directly participate in its specific combination with another molecule. [NIH]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

Biochemical Phenomena: Biochemical functions, activities, and processes at organic and molecular levels in humans, animals, microorganisms, and plants. [NIH]

Biological Phenomena: Biological functions and activities at the organic and molecular levels in humans, animals, microorganisms, and plants. For biochemical and metabolic processes, biochemical phenomena is available. [NIH]

Biological response modifier: BRM. A substance that stimulates the body's response to infection and disease. [NIH]

Biological therapy: Treatment to stimulate or restore the ability of the immune system to fight infection and disease. Also used to lessen side effects that may be caused by some cancer treatments. Also known as immunotherapy, biotherapy, or biological response modifier (BRM) therapy. [NIH]

Biological Transport: The movement of materials (including biochemical substances and drugs) across cell membranes and epithelial layers, usually by passive diffusion. [NIH]

Biopsy: Removal and pathologic examination of specimens in the form of small pieces of tissue from the living body. [NIH]

Biosynthesis: The building up of a chemical compound in the physiologic processes of a living organism. [EU]

Biotechnology: Body of knowledge related to the use of organisms, cells or cell-derived constituents for the purpose of developing products which are technically, scientifically and clinically useful. Alteration of biologic function at the molecular level (i.e., genetic engineering) is a central focus; laboratory methods used include transfection and cloning technologies, sequence and structure analysis algorithms, computer databases, and gene and protein structure function analysis and prediction. [NIH]

Biphasic: Having two phases; having both a sporophytic and a gametophytic phase in the life cycle. [EU]

Bladder: The organ that stores urine. [NIH]

Blood Coagulation: The process of the interaction of blood coagulation factors that results in an insoluble fibrin clot. [NIH]

Blood Glucose: Glucose in blood. [NIH]

Blood pressure: The pressure of blood against the walls of a blood vessel or heart chamber. Unless there is reference to another location, such as the pulmonary artery or one of the heart chambers, it refers to the pressure in the systemic arteries, as measured, for example, in the forearm. [NIH]

Blood vessel: A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

Body Fluids: Liquid components of living organisms. [NIH]

Bone Marrow: The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells. [NIH]

Bone Marrow Transplantation: The transference of bone marrow from one human or animal to another. [NIH]

Bone scan: A technique to create images of bones on a computer screen or on film. A small amount of radioactive material is injected into a blood vessel and travels through the bloodstream; it collects in the bones and is detected by a scanner. [NIH]

Bowel: The long tube-shaped organ in the abdomen that completes the process of digestion. There is both a small and a large bowel. Also called the intestine. [NIH]

Brachiocephalic Veins: Large veins on either side of the root of the neck formed by the junction of the internal jugular and subclavian veins. They drain blood from the head, neck, and upper extremities, and unite to form the superior vena cava. [NIH]

Bradykinin: A nonapeptide messenger that is enzymatically produced from kallidin in the blood where it is a potent but short-lived agent of arteriolar dilation and increased capillary permeability. Bradykinin is also released from mast cells during asthma attacks, from gut walls as a gastrointestinal vasodilator, from damaged tissues as a pain signal, and may be a neurotransmitter. [NIH]

Broad-spectrum: Effective against a wide range of microorganisms; said of an antibiotic. [EU]

Bronchi: The larger air passages of the lungs arising from the terminal bifurcation of the trachea. [NIH]

Bronchial: Pertaining to one or more bronchi. [EU]

Bronchitis: Inflammation (swelling and reddening) of the bronchi. [NIH]

Bronchodilator: A drug that relaxes the smooth muscles in the constricted airway. [NIH]

Buccal: Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

Bypass: A surgical procedure in which the doctor creates a new pathway for the flow of body fluids. [NIH]

Calcineurin: A calcium- and calmodulin-binding protein present in highest concentrations in the central nervous system. Calcineurin is composed of two subunits. A catalytic subunit, calcineurin A, and a regulatory subunit, calcineurin B, with molecular weights of about 60 kD and 19 kD, respectively. Calcineurin has been shown to dephosphorylate a number of phosphoproteins including histones, myosin light chain, and the regulatory subunit of cAMP-dependent protein kinase. It is involved in the regulation of signal transduction and is the target of an important class of immunophilin-immunosuppressive drug complexes in T-lymphocytes that act by inhibiting T-cell activation. EC 3.1.3.-. [NIH]

Calcium: A basic element found in nearly all organized tissues. It is a member of the alkaline earth family of metals with the atomic symbol Ca, atomic number 20, and atomic weight 40. Calcium is the most abundant mineral in the body and combines with phosphorus to form calcium phosphate in the bones and teeth. It is essential for the normal functioning of nerves and muscles and plays a role in blood coagulation (as factor IV) and in many enzymatic processes. [NIH]

Callus: A callosity or hard, thick skin; the bone-like reparative substance that is formed round the edges and fragments of broken bone. [NIH]

Calmodulin: A heat-stable, low-molecular-weight activator protein found mainly in the brain and heart. The binding of calcium ions to this protein allows this protein to bind to cyclic nucleotide phosphodiesterases and to adenyl cyclase with subsequent activation. Thereby this protein modulates cyclic AMP and cyclic GMP levels. [NIH]

Calsequestrin: Acidic protein found in sarcoplasmic reticulum that binds calcium to the extent of 700-900 nmoles/mg. It plays the role of sequestering calcium transported to the interior of the intracellular vesicle. [NIH]

Capillary: Any one of the minute vessels that connect the arterioles and venules, forming a network in nearly all parts of the body. Their walls act as semipermeable membranes for the interchange of various substances, including fluids, between the blood and tissue fluid; called also vas capillare. [EU]

Capillary Permeability: Property of blood capillary walls that allows for the selective exchange of substances. Small lipid-soluble molecules such as carbon dioxide and oxygen move freely by diffusion. Water and water-soluble molecules cannot pass through the endothelial walls and are dependent on microscopic pores. These pores show narrow areas (tight junctions) which may limit large molecule movement. [NIH]

Captopril: A potent and specific inhibitor of peptidyl-dipeptidase A. It blocks the conversion of angiotensin I to angiotensin II, a vasoconstrictor and important regulator of arterial blood pressure. Captopril acts to suppress the renin-angiotensin system and inhibits pressure responses to exogenous angiotensin. [NIH]

Carbohydrate: An aldehyde or ketone derivative of a polyhydric alcohol, particularly of the pentahydric and hexahydric alcohols. They are so named because the hydrogen and oxygen are usually in the proportion to form water, (CH2O)n. The most important carbohydrates are the starches, sugars, celluloses, and gums. They are classified into mono-, di-, tri-, poly- and heterosaccharides. [EU]

Carbon Dioxide: A colorless, odorless gas that can be formed by the body and is necessary for the respiration cycle of plants and animals. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Carcinogens: Substances that increase the risk of neoplasms in humans or animals. Both genotoxic chemicals, which affect DNA directly, and nongenotoxic chemicals, which induce neoplasms by other mechanism, are included. [NIH]

Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs. [NIH]

Cardiac: Having to do with the heart. [NIH]

Cardiac arrest: A sudden stop of heart function. [NIH]

Cardiac Output: The volume of blood passing through the heart per unit of time. It is usually expressed as liters (volume) per minute so as not to be confused with stroke volume (volume per beat). [NIH]

Cardiogenic: Originating in the heart; caused by abnormal function of the heart. [EU]

Cardiology: The study of the heart, its physiology, and its functions. [NIH]

Cardiomyopathy: A general diagnostic term designating primary myocardial disease, often of obscure or unknown etiology. [EU]

Cardioselective: Having greater activity on heart tissue than on other tissue. [EU]

Cardiotonic: 1. Having a tonic effect on the heart. 2. An agent that has a tonic effect on the heart. [EU]

Cardiotoxicity: Toxicity that affects the heart. [NIH]

Cardiovascular: Having to do with the heart and blood vessels. [NIH]

Cardiovascular disease: Any abnormal condition characterized by dysfunction of the heart and blood vessels. CVD includes atherosclerosis (especially coronary heart disease, which can lead to heart attacks), cerebrovascular disease (e.g., stroke), and hypertension (high blood pressure). [NIH]

Cardiovascular System: The heart and the blood vessels by which blood is pumped and circulated through the body. [NIH]

Carnitine: Constituent of striated muscle and liver. It is used therapeutically to stimulate gastric and pancreatic secretions and in the treatment of hyperlipoproteinemias. [NIH]

Case report: A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some demographic information about the patient (for example, age, gender, ethnic origin). [NIH]

Caspase: Enzyme released by the cell at a crucial stage in apoptosis in order to shred all cellular proteins. [NIH]

Catecholamine: A group of chemical substances manufactured by the adrenal medulla and secreted during physiological stress. [NIH]

Catheterization: Use or insertion of a tubular device into a duct, blood vessel, hollow organ, or body cavity for injecting or withdrawing fluids for diagnostic or therapeutic purposes. It differs from intubation in that the tube here is used to restore or maintain patency in obstructions. [NIH]

Causal: Pertaining to a cause; directed against a cause. [EU]

Causality: The relating of causes to the effects they produce. Causes are termed necessary when they must always precede an effect and sufficient when they initiate or produce an effect. Any of several factors may be associated with the potential disease causation or outcome, including predisposing factors, enabling factors, precipitating factors, reinforcing factors, and risk factors. [NIH]

Caveolae: Endocytic/exocytic cell membrane structures rich in glycosphingolipids, cholesterol, and lipid-anchored membrane proteins that function in endocytosis (potocytosis), transcytosis, and signal transduction. Caveolae assume various shapes from open pits to closed vesicles. Caveolar coats are composed of caveolins. [NIH]

Caveolins: The main structural proteins of caveolae. Several distinct genes for caveolins have been identified. [NIH]

Cell: The individual unit that makes up all of the tissues of the body. All living things are made up of one or more cells. [NIH]

Cell Adhesion: Adherence of cells to surfaces or to other cells. [NIH]

Cell Count: A count of the number of cells of a specific kind, usually measured per unit volume of sample. [NIH]

Cell Cycle: The complex series of phenomena, occurring between the end of one cell

division and the end of the next, by which cellular material is divided between daughter cells. [NIH]

Cell Death: The termination of the cell's ability to carry out vital functions such as metabolism, growth, reproduction, responsiveness, and adaptability. [NIH]

Cell Differentiation: Progressive restriction of the developmental potential and increasing specialization of function which takes place during the development of the embryo and leads to the formation of specialized cells, tissues, and organs. [NIH]

Cell Division: The fission of a cell. [NIH]

Cell membrane: Cell membrane = plasma membrane. The structure enveloping a cell, enclosing the cytoplasm, and forming a selective permeability barrier; it consists of lipids, proteins, and some carbohydrates, the lipids thought to form a bilayer in which integral proteins are embedded to varying degrees. [EU]

Cell Membrane Structures: Structures which are part of the cell membrane or have cell membrane as a major part of their structure. [NIH]

Cell motility: The ability of a cell to move. [NIH]

Cell proliferation: An increase in the number of cells as a result of cell growth and cell division. [NIH]

Cell Respiration: The metabolic process of all living cells (animal and plant) in which oxygen is used to provide a source of energy for the cell. [NIH]

Cell Survival: The span of viability of a cell characterized by the capacity to perform certain functions such as metabolism, growth, reproduction, some form of responsiveness, and adaptability. [NIH]

Central Nervous System: The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [NIH]

Cerebellar: Pertaining to the cerebellum. [EU]

Cerebral: Of or pertaining of the cerebrum or the brain. [EU]

Cerebral Cortex: The thin layer of gray matter on the surface of the cerebral hemisphere that develops from the telencephalon and folds into gyri. It reaches its highest development in man and is responsible for intellectual faculties and higher mental functions. [NIH]

Cerebrovascular: Pertaining to the blood vessels of the cerebrum, or brain. [EU]

Character: In current usage, approximately equivalent to personality. The sum of the relatively fixed personality traits and habitual modes of response of an individual. [NIH]

Chemoreceptor: A receptor adapted for excitation by chemical substances, e.g., olfactory and gustatory receptors, or a sense organ, as the carotid body or the aortic (supracardial) bodies, which is sensitive to chemical changes in the blood stream, especially reduced oxygen content, and reflexly increases both respiration and blood pressure. [EU]

Chemotactic Factors: Chemical substances that attract or repel cells or organisms. The concept denotes especially those factors released as a result of tissue injury, invasion, or immunologic activity, that attract leukocytes, macrophages, or other cells to the site of infection or insult. [NIH]

Chemotherapeutic agent: A drug used to treat cancer. [NIH]

Chemotherapy: Treatment with anticancer drugs. [NIH]

Chest Pain: Pressure, burning, or numbness in the chest. [NIH]

Chin: The anatomical frontal portion of the mandible, also known as the mentum, that contains the line of fusion of the two separate halves of the mandible (symphysis menti).

This line of fusion divides inferiorly to enclose a triangular area called the mental protuberance. On each side, inferior to the second premolar tooth, is the mental foramen for the passage of blood vessels and a nerve. [NIH]

Cholesterol: The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

Chromatin: The material of chromosomes. It is a complex of DNA, histones, and nonhistone proteins (chromosomal proteins, non-histone) found within the nucleus of a cell. [NIH]

Chromosomal: Pertaining to chromosomes. [EU]

Chromosome: Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes. [NIH]

Chronic: A disease or condition that persists or progresses over a long period of time. [NIH]

Chronic Disease: Disease or ailment of long duration. [NIH]

Chronic Obstructive Pulmonary Disease: Collective term for chronic bronchitis and emphysema. [NIH]

Chronotropic: Affecting the time or rate, as the rate of contraction of the heart. [EU]

Circulatory system: The system that contains the heart and the blood vessels and moves blood throughout the body. This system helps tissues get enough oxygen and nutrients, and it helps them get rid of waste products. The lymph system, which connects with the blood system, is often considered part of the circulatory system. [NIH]

CIS: Cancer Information Service. The CIS is the National Cancer Institute's link to the public, interpreting and explaining research findings in a clear and understandable manner, and providing personalized responses to specific questions about cancer. Access the CIS by calling 1-800-4-CANCER, or by using the Web site at http://cis.nci.nih.gov. [NIH]

Clamp: A u-shaped steel rod used with a pin or wire for skeletal traction in the treatment of certain fractures. [NIH]

Cleave: A double-stranded cut in DNA with a restriction endonuclease. [NIH]

Clinical Medicine: The study and practice of medicine by direct examination of the patient. [NIH]

Clinical study: A research study in which patients receive treatment in a clinic or other medical facility. Reports of clinical studies can contain results for single patients (case reports) or many patients (case series or clinical trials). [NIH]

Clinical trial: A research study that tests how well new medical treatments or other interventions work in people. Each study is designed to test new methods of screening, prevention, diagnosis, or treatment of a disease. [NIH]

Cloning: The production of a number of genetically identical individuals; in genetic engineering, a process for the efficient replication of a great number of identical DNA molecules. [NIH]

Coenzyme: An organic nonprotein molecule, frequently a phosphorylated derivative of a water-soluble vitamin, that binds with the protein molecule (apoenzyme) to form the active enzyme (holoenzyme). [EU]

Cofactor: A substance, microorganism or environmental factor that activates or enhances the action of another entity such as a disease-causing agent. [NIH]

Collagen: A polypeptide substance comprising about one third of the total protein in mammalian organisms. It is the main constituent of skin, connective tissue, and the organic substance of bones and teeth. Different forms of collagen are produced in the body but all consist of three alpha-polypeptide chains arranged in a triple helix. Collagen is

differentiated from other fibrous proteins, such as elastin, by the content of proline, hydroxyproline, and hydroxylysine; by the absence of tryptophan; and particularly by the high content of polar groups which are responsible for its swelling properties. [NIH]

Complement: A term originally used to refer to the heat-labile factor in serum that causes immune cytolysis, the lysis of antibody-coated cells, and now referring to the entire functionally related system comprising at least 20 distinct serum proteins that is the effector not only of immune cytolysis but also of other biologic functions. Complement activation occurs by two different sequences, the classic and alternative pathways. The proteins of the classic pathway are termed 'components of complement' and are designated by the symbols C1 through C9. C1 is a calcium-dependent complex of three distinct proteins C1q, C1r and C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names. Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

Complementary and alternative medicine: CAM. Forms of treatment that are used in addition to (complementary) or instead of (alternative) standard treatments. These practices are not considered standard medical approaches. CAM includes dietary supplements, megadose vitamins, herbal preparations, special teas, massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Complementary medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used to enhance or complement the standard treatments. Complementary medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Compliance: Distensibility measure of a chamber such as the lungs (lung compliance) or bladder. Compliance is expressed as a change in volume per unit change in pressure. [NIH]

Computational Biology: A field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make biological discoveries or predictions. This field encompasses all computational methods and theories applicable to molecular biology and areas of computer-based techniques for solving biological problems including manipulation of models and datasets. [NIH]

Computed tomography: CT scan. A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called computerized tomography and computerized axial tomography (CAT) scan. [NIH]

Computerized axial tomography: A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called CAT scan, computed tomography (CT scan), or computerized

tomography. [NIH]

Concentric: Having a common center of curvature or symmetry. [NIH]

Conduction: The transfer of sound waves, heat, nervous impulses, or electricity. [EU]

Confounding: Extraneous variables resulting in outcome effects that obscure or exaggerate the "true" effect of an intervention. [NIH]

Congestive heart failure: Weakness of the heart muscle that leads to a buildup of fluid in body tissues. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Consciousness: Sense of awareness of self and of the environment. [NIH]

Constrict: Tighten; narrow. [NIH]

Constriction: The act of constricting. [NIH]

Continuum: An area over which the vegetation or animal population is of constantly changing composition so that homogeneous, separate communities cannot be distinguished. [NIH]

Contractile Proteins: Proteins which participate in contractile processes. They include muscle proteins as well as those found in other cells and tissues. In the latter, these proteins participate in localized contractile events in the cytoplasm, in motile activity, and in cell aggregation phenomena. [NIH]

Contractility: Capacity for becoming short in response to a suitable stimulus. [EU]

Contraindications: Any factor or sign that it is unwise to pursue a certain kind of action or treatment, e. g. giving a general anesthetic to a person with pneumonia. [NIH]

Contralateral: Having to do with the opposite side of the body. [NIH]

Contrast medium: A substance that is introduced into or around a structure and, because of the difference in absorption of x-rays by the contrast medium and the surrounding tissues, allows radiographic visualization of the structure. [EU]

Controlled clinical trial: A clinical study that includes a comparison (control) group. The comparison group receives a placebo, another treatment, or no treatment at all. [NIH]

Conus: A large, circular, white patch around the optic disk due to the exposing of the sclera as a result of degenerative change or congenital abnormality in the choroid and retina. [NIH]

Coordination: Muscular or motor regulation or the harmonious cooperation of muscles or groups of muscles, in a complex action or series of actions. [NIH]

Coronary: Encircling in the manner of a crown; a term applied to vessels; nerves, ligaments, etc. The term usually denotes the arteries that supply the heart muscle and, by extension, a pathologic involvement of them. [EU]

Coronary Arteriosclerosis: Thickening and loss of elasticity of the coronary arteries. [NIH]

Coronary Artery Bypass: Surgical therapy of ischemic coronary artery disease achieved by grafting a section of saphenous vein, internal mammary artery, or other substitute between the aorta and the obstructed coronary artery distal to the obstructive lesion. [NIH]

Coronary Circulation: The circulation of blood through the coronary vessels of the heart. [NIH]

Coronary Disease: Disorder of cardiac function due to an imbalance between myocardial function and the capacity of the coronary vessels to supply sufficient flow for normal

function. It is a form of myocardial ischemia (insufficient blood supply to the heart muscle) caused by a decreased capacity of the coronary vessels. [NIH]

Coronary heart disease: A type of heart disease caused by narrowing of the coronary arteries that feed the heart, which needs a constant supply of oxygen and nutrients carried by the blood in the coronary arteries. When the coronary arteries become narrowed or clogged by fat and cholesterol deposits and cannot supply enough blood to the heart, CHD results. [NIH]

Coronary Thrombosis: Presence of a thrombus in a coronary artery, often causing a myocardial infarction. [NIH]

Coronary Vessels: The veins and arteries of the heart. [NIH]

Corpus: The body of the uterus. [NIH]

Corpus Luteum: The yellow glandular mass formed in the ovary by an ovarian follicle that has ruptured and discharged its ovum. [NIH]

Cortex: The outer layer of an organ or other body structure, as distinguished from the internal substance. [EU]

Corticosteroids: Hormones that have antitumor activity in lymphomas and lymphoid leukemias; in addition, corticosteroids (steroids) may be used for hormone replacement and for the management of some of the complications of cancer and its treatment. [NIH]

Creatine: An amino acid that occurs in vertebrate tissues and in urine. In muscle tissue, creatine generally occurs as phosphocreatine. Creatine is excreted as creatinine in the urine. [NIH]

Creatine Kinase: A transferase that catalyzes formation of phosphocreatine from ATP + creatine. The reaction stores ATP energy as phosphocreatine. Three cytoplasmic isoenzymes have been identified in human tissues: MM from skeletal muscle, MB from myocardial tissue, and BB from nervous tissue as well as a mitochondrial isoenzyme. Macro-creatine kinase refers to creatine kinase complexed with other serum proteins. EC 2.7.3.2. [NIH]

Creatinine: A compound that is excreted from the body in urine. Creatinine levels are measured to monitor kidney function. [NIH]

Cultured cells: Animal or human cells that are grown in the laboratory. [NIH]

Curative: Tending to overcome disease and promote recovery. [EU]

Cutaneous: Having to do with the skin. [NIH]

Cyclic: Pertaining to or occurring in a cycle or cycles; the term is applied to chemical compounds that contain a ring of atoms in the nucleus. [EU]

Cyclin: Molecule that regulates the cell cycle. [NIH]

Cytochrome: Any electron transfer hemoprotein having a mode of action in which the transfer of a single electron is effected by a reversible valence change of the central iron atom of the heme prosthetic group between the +2 and +3 oxidation states; classified as cytochromes a in which the heme contains a formyl side chain, cytochromes b, which contain protoheme or a closely similar heme that is not covalently bound to the protein, cytochromes c in which protoheme or other heme is covalently bound to the protein, and cytochromes d in which the iron-tetrapyrrole has fewer conjugated double bonds than the hemes have. Well-known cytochromes have been numbered consecutively within groups and are designated by subscripts (beginning with no subscript), e.g. cytochromes c, c1, C2, . New cytochromes are named according to the wavelength in nanometres of the absorption maximum of the a-band of the iron (II) form in pyridine, e.g., c-555. [EU]

Cytokine: Small but highly potent protein that modulates the activity of many cell types,

including T and B cells. [NIH]

Cytokinesis: Division of the rest of cell. [NIH]

Cytoplasm: The protoplasm of a cell exclusive of that of the nucleus; it consists of a continuous aqueous solution (cytosol) and the organelles and inclusions suspended in it (phaneroplasm), and is the site of most of the chemical activities of the cell. [EU]

Cytoprotection: The process by which chemical compounds provide protection to cells against harmful agents. [NIH]

Cytoskeletal Proteins: Major constituent of the cytoskeleton found in the cytoplasm of eukaryotic cells. They form a flexible framework for the cell, provide attachment points for organelles and formed bodies, and make communication between parts of the cell possible. [NIH]

Cytoskeleton: The network of filaments, tubules, and interconnecting filamentous bridges which give shape, structure, and organization to the cytoplasm. [NIH]

Cytotoxic: Cell-killing. [NIH]

Daunorubicin: Very toxic anthracycline aminoglycoside antibiotic isolated from Streptomyces peucetius and others, used in treatment of leukemias and other neoplasms. [NIH]

De novo: In cancer, the first occurrence of cancer in the body. [NIH]

Decarboxylation: The removal of a carboxyl group, usually in the form of carbon dioxide, from a chemical compound. [NIH]

Decompensation: Failure of compensation; cardiac decompensation is marked by dyspnea, venous engorgement, and edema. [EU]

Defense Mechanisms: Unconscious process used by an individual or a group of individuals in order to cope with impulses, feelings or ideas which are not acceptable at their conscious level; various types include reaction formation, projection and self reversal. [NIH]

Defibrillation: The act to arrest the fibrillation of (heart muscle) by applying electric shock across the chest, thus depolarizing the heart cells and allowing normal rhythm to return. [EU]

Degenerative: Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

Deletion: A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [NIH]

Dementia: An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness. [NIH]

Dendrites: Extensions of the nerve cell body. They are short and branched and receive stimuli from other neurons. [NIH]

Dental Caries: Localized destruction of the tooth surface initiated by decalcification of the enamel followed by enzymatic lysis of organic structures and leading to cavity formation. If left unchecked, the cavity may penetrate the enamel and dentin and reach the pulp. The three most prominent theories used to explain the etiology of the disase are that acids produced by bacteria lead to decalcification; that micro-organisms destroy the enamel protein; or that keratolytic micro-organisms produce chelates that lead to decalcification. [NIH]

Deoxyglucose: 2-Deoxy-D-arabino-hexose. An antimetabolite of glucose with antiviral

activity. [NIH]

Depolarization: The process or act of neutralizing polarity. In neurophysiology, the reversal of the resting potential in excitable cell membranes when stimulated, i.e., the tendency of the cell membrane potential to become positive with respect to the potential outside the cell. [EU]

Desensitization: The prevention or reduction of immediate hypersensitivity reactions by administration of graded doses of allergen; called also hyposensitization and immunotherapy. [EU]

Desmin: An intermediate filament protein found predominantly in smooth, skeletal, and cardiac muscle cells. Localized at the Z line. MW 50,000 to 55,000 is species dependent. [NIH]

Detoxification: Treatment designed to free an addict from his drug habit. [EU]

Deuterium: Deuterium. The stable isotope of hydrogen. It has one neutron and one proton in the nucleus. [NIH]

Developed Countries: Countries that have reached a level of economic achievement through an increase of production, per capita income and consumption, and utilization of natural and human resources. [NIH]

Diabetes Mellitus: A heterogeneous group of disorders that share glucose intolerance in common. [NIH]

Diagnostic Imaging: Any visual display of structural or functional patterns of organs or tissues for diagnostic evaluation. It includes measuring physiologic and metabolic responses to physical and chemical stimuli, as well as ultramicroscopy. [NIH]

Diagnostic procedure: A method used to identify a disease. [NIH]

Diaphragm: The musculofibrous partition that separates the thoracic cavity from the abdominal cavity. Contraction of the diaphragm increases the volume of the thoracic cavity aiding inspiration. [NIH]

Diastole: Period of relaxation of the heart, especially the ventricles. [NIH]

Diastolic: Of or pertaining to the diastole. [EU]

Diastolic pressure: The lowest pressure to which blood pressure falls between contractions of the ventricles. [NIH]

Diffusion: The tendency of a gas or solute to pass from a point of higher pressure or concentration to a point of lower pressure or concentration and to distribute itself throughout the available space; a major mechanism of biological transport. [NIH]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Digitalis: A genus of toxic herbaceous Eurasian plants of the Scrophulaceae which yield cardiotonic glycosides. The most useful are Digitalis lanata and D. purpurea. [NIH]

Dilatation, Pathologic: The condition of an anatomical structure's being dilated beyond normal dimensions. [NIH]

Dilation: A process by which the pupil is temporarily enlarged with special eye drops (mydriatic); allows the eye care specialist to better view the inside of the eye. [NIH]

Dipyridamole: A drug that prevents blood cell clumping and enhances the effectiveness of fluorouracil and other chemotherapeutic agents. [NIH]

Direct: 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

Discrete: Made up of separate parts or characterized by lesions which do not become blended; not running together; separate. [NIH]

Disease Susceptibility: A constitution or condition of the body which makes the tissues

react in special ways to certain extrinsic stimuli and thus tends to make the individual more than usually susceptible to certain diseases. [NIH]

Disinfectant: An agent that disinfects; applied particularly to agents used on inanimate objects. [EU]

Dissection: Cutting up of an organism for study. [NIH]

Dissociation: 1. The act of separating or state of being separated. 2. The separation of a molecule into two or more fragments (atoms, molecules, ions, or free radicals) produced by the absorption of light or thermal energy or by solvation. 3. In psychology, a defense mechanism in which a group of mental processes are segregated from the rest of a person's mental activity in order to avoid emotional distress, as in the dissociative disorders (q.v.), or in which an idea or object is segregated from its emotional significance; in the first sense it is roughly equivalent to splitting, in the second, to isolation. 4. A defect of mental integration in which one or more groups of mental processes become separated off from normal consciousness and, thus separated, function as a unitary whole. [EU]

Distal: Remote; farther from any point of reference; opposed to proximal. In dentistry, used to designate a position on the dental arch farther from the median line of the jaw. [EU]

DNA Topoisomerase: An enzyme catalyzing ATP-independent breakage of single-stranded DNA, followed by passage and rejoining of another single-stranded DNA. This enzyme class brings about the conversion of one topological isomer of DNA into another, e.g., the relaxation of superhelical turns in DNA, the interconversion of simple and knotted rings of single-stranded DNA, and the intertwisting of single-stranded rings of complementary sequences. (From Enzyme Nomenclature, 1992) EC 5.99.1.2. [NIH]

Dobutamine: A beta-2 agonist catecholamine that has cardiac stimulant action without evoking vasoconstriction or tachycardia. It is proposed as a cardiotonic after myocardial infarction or open heart surgery. [NIH]

Dose-dependent: Refers to the effects of treatment with a drug. If the effects change when the dose of the drug is changed, the effects are said to be dose dependent. [NIH]

Dose-limiting: Describes side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment. [NIH]

Double-blind: Pertaining to a clinical trial or other experiment in which neither the subject nor the person administering treatment knows which treatment any particular subject is receiving. [EU]

Doxorubicin: Antineoplastic antibiotic obtained from Streptomyces peucetics. It is a hydroxy derivative of daunorubicin and is used in treatment of both leukemia and solid tumors. [NIH]

Drive: A state of internal activity of an organism that is a necessary condition before a given stimulus will elicit a class of responses; e.g., a certain level of hunger (drive) must be present before food will elicit an eating response. [NIH]

Drug Interactions: The action of a drug that may affect the activity, metabolism, or toxicity of another drug. [NIH]

Drug Tolerance: Progressive diminution of the susceptibility of a human or animal to the effects of a drug, resulting from its continued administration. It should be differentiated from drug resistance wherein an organism, disease, or tissue fails to respond to the intended effectiveness of a chemical or drug. It should also be differentiated from maximum tolerated dose and no-observed-adverse-effect level. [NIH]

Duct: A tube through which body fluids pass. [NIH]

Dysplasia: Cells that look abnormal under a microscope but are not cancer. [NIH]

Dyspnea: Difficult or labored breathing. [NIH]

Dystrophic: Pertaining to toxic habitats low in nutrients. [NIH]

Dystrophin: A muscle protein localized in surface membranes which is the product of the Duchenne/Becker muscular dystrophy gene. Individuals with Duchenne muscular dystrophy usually lack dystrophin completely while those with Becker muscular dystrophy have dystrophin of an altered size. It shares features with other cytoskeletal proteins such as spectrin and alpha-actinin but the precise function of dystrophin is not clear. One possible role might be to preserve the integrity and alignment of the plasma membrane to the myofibrils during muscle contraction and relaxation. MW 400 kDa. [NIH]

Dystrophy: Any disorder arising from defective or faulty nutrition, especially the muscular dystrophies. [EU]

Echocardiography: Ultrasonic recording of the size, motion, and composition of the heart and surrounding tissues. The standard approach is transthoracic. [NIH]

Edema: Excessive amount of watery fluid accumulated in the intercellular spaces, most commonly present in subcutaneous tissue. [NIH]

Effector: It is often an enzyme that converts an inactive precursor molecule into an active second messenger. [NIH]

Efficacy: The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized control trial. [NIH]

Ejection fraction: A measure of ventricular contractility, equal to normally 65 8 per cent; lower values indicate ventricular dysfunction. [EU]

Elastic: Susceptible of resisting and recovering from stretching, compression or distortion applied by a force. [EU]

Elasticity: Resistance and recovery from distortion of shape. [NIH]

Elastin: The protein that gives flexibility to tissues. [NIH]

Electric shock: A dangerous patho-physiological effect resulting from an electric current passing through the body of a human or animal. [NIH]

Electrocardiogram: Measurement of electrical activity during heartbeats. [NIH]

Electrocardiography: Recording of the moment-to-moment electromotive forces of the heart as projected onto various sites on the body's surface, delineated as a scalar function of time. [NIH]

Electrolyte: A substance that dissociates into ions when fused or in solution, and thus becomes capable of conducting electricity; an ionic solute. [EU]

Electrons: Stable elementary particles having the smallest known negative charge, present in all elements; also called negatrons. Positively charged electrons are called positrons. The numbers, energies and arrangement of electrons around atomic nuclei determine the chemical identities of elements. Beams of electrons are called cathode rays or beta rays, the latter being a high-energy biproduct of nuclear decay. [NIH]

Emaciation: Clinical manifestation of excessive leanness usually caused by disease or a lack of nutrition. [NIH]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Embryogenesis: The process of embryo or embryoid formation, whether by sexual (zygotic) or asexual means. In asexual embryogenesis embryoids arise directly from the explant or on intermediary callus tissue. In some cases they arise from individual cells (somatic cell

embryoge). [NIH]

Emetic: An agent that causes vomiting. [EU]

Emetine: The principal alkaloid of ipecac, from the ground roots of Uragoga (or Cephaelis) ipecacuanha or U. acuminata, of the Rubiaceae. It is used as an amebicide in many different preparations and may cause serious cardiac, hepatic, or renal damage and violent diarrhea and vomiting. Emetine inhibits protein syntheis in eucaryotic but not prokaryotic cells. [NIH]

Emphysema: A pathological accumulation of air in tissues or organs. [NIH]

Enalapril: An angiotensin-converting enzyme inhibitor that is used to treat hypertension. [NIH]

Encephalitis: Inflammation of the brain due to infection, autoimmune processes, toxins, and other conditions. Viral infections (see encephalitis, viral) are a relatively frequent cause of this condition. [NIH]

Encephalitis, Viral: Inflammation of brain parenchymal tissue as a result of viral infection. Encephalitis may occur as primary or secondary manifestation of Togaviridae infections; Herpesviridae infections; Adenoviridae infections; Flaviviridae infections; Bunyaviridae infections; Picornaviridae infections; Paramyxoviridae infections; Orthomyxoviridae infections; Retroviridae infections; and Arenaviridae infections. [NIH]

Encephalomyelitis: A general term indicating inflammation of the brain and spinal cord, often used to indicate an infectious process, but also applicable to a variety of autoimmune and toxic-metabolic conditions. There is significant overlap regarding the usage of this term and encephalitis in the literature. [NIH]

Encephalopathy: A disorder of the brain that can be caused by disease, injury, drugs, or chemicals. [NIH]

Endemic: Present or usually prevalent in a population or geographical area at all times; said of a disease or agent. Called also endemial. [EU]

Endocytosis: Cellular uptake of extracellular materials within membrane-limited vacuoles or microvesicles. Endosomes play a central role in endocytosis. [NIH]

Endogenous: Produced inside an organism or cell. The opposite is external (exogenous) production. [NIH]

Endothelial cell: The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart. [NIH]

Endothelium: A layer of epithelium that lines the heart, blood vessels (endothelium, vascular), lymph vessels (endothelium, lymphatic), and the serous cavities of the body. [NIH]

Endothelium, Lymphatic: Unbroken cellular lining (intima) of the lymph vessels (e.g., the high endothelial lymphatic venules). It is more permeable than vascular endothelium, lacking selective absorption and functioning mainly to remove plasma proteins that have filtered through the capillaries into the tissue spaces. [NIH]

Endothelium, Vascular: Single pavement layer of cells which line the luminal surface of the entire vascular system and regulate the transport of macromolecules and blood components from interstitium to lumen; this function has been most intensively studied in the blood capillaries. [NIH]

Endothelium-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes it. [NIH]

Endotoxic: Of, relating to, or acting as an endotoxin (= a heat-stable toxin, associated with the outer membranes of certain gram-negative bacteria. Endotoxins are not secreted and are released only when the cells are disrupted). [EU]

Endotoxin: Toxin from cell walls of bacteria. [NIH]

Energetic: Exhibiting energy : strenuous; operating with force, vigour, or effect. [EU]

Enhancer: Transcriptional element in the virus genome. [NIH]

Enoximone: 1,3-Dihydro-4-methyl-5-(4-(methylthio)benzoyl)-2H-imidazol-2-one. A selective phosphodiesterase inhibitor with vasodilating and positive inotropic activity that does not cause changes in myocardial oxygen consumption. It is used in patients with congestive heart failure. [NIH]

Enterocolitis: Inflammation of the intestinal mucosa of the small and large bowel. [NIH]

Environmental Exposure: The exposure to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals. [NIH]

Environmental Health: The science of controlling or modifying those conditions, influences, or forces surrounding man which relate to promoting, establishing, and maintaining health. [NIH]

Environmental Pollutants: Substances which pollute the environment. Use for environmental pollutants in general or for which there is no specific heading. [NIH]

Enzymatic: Phase where enzyme cuts the precursor protein. [NIH]

Enzyme: A protein that speeds up chemical reactions in the body. [NIH]

Enzyme Induction: An increase in the rate of synthesis of an enzyme due to the presence of an inducer which acts to derepress the gene responsible for enzyme synthesis. [NIH]

Enzyme Inhibitors: Compounds or agents that combine with an enzyme in such a manner as to prevent the normal substrate-enzyme combination and the catalytic reaction. [NIH]

Enzyme Repression: The interference in synthesis of an enzyme due to the elevated level of an effector substance, usually a metabolite, whose presence would cause depression of the gene responsible for enzyme synthesis. [NIH]

Eosinophilic: A condition found primarily in grinding workers caused by a reaction of the pulmonary tissue, in particular the eosinophilic cells, to dust that has entered the lung. [NIH]

Epidemic: Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

Epidermis: Nonvascular layer of the skin. It is made up, from within outward, of five layers: 1) basal layer (stratum basale epidermidis); 2) spinous layer (stratum spinosum epidermidis); 3) granular layer (stratum granulosum epidermidis); 4) clear layer (stratum lucidum epidermidis); and 5) horny layer (stratum corneum epidermidis). [NIH]

Epidermolysis Bullosa: Group of genetically determined disorders characterized by the blistering of skin and mucosae. There are four major forms: acquired, simple, junctional, and dystrophic. Each of the latter three has several varieties. [NIH]

Epidermolysis Bullosa Dystrophica: Form of epidermolysis bullosa characterized by atrophy of blistered areas, severe scarring, and nail changes. It is most often present at birth or in early infancy and occurs in both autosomal dominant and recessive forms. [NIH]

Epidural: The space between the wall of the spinal canal and the covering of the spinal cord. An epidural injection is given into this space. [NIH]

Epidural block: An injection of an anesthetic drug into the space between the wall of the spinal canal and the covering of the spinal cord. [NIH]

Epinephrine: The active sympathomimetic hormone from the adrenal medulla in most

species. It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is used in asthma and cardiac failure and to delay absorption of local anesthetics. [NIH]

Epithelial: Refers to the cells that line the internal and external surfaces of the body. [NIH]

Epithelial Cells: Cells that line the inner and outer surfaces of the body. [NIH]

Epithelium: One or more layers of epithelial cells, supported by the basal lamina, which covers the inner or outer surfaces of the body. [NIH]

Epitope: A molecule or portion of a molecule capable of binding to the combining site of an antibody. For every given antigenic determinant, the body can construct a variety of antibody-combining sites, some of which fit almost perfectly, and others which barely fit. [NIH]

Epitope Mapping: Methods used for studying the interactions of antibodies with specific regions of protein antigens. Important applications of epitope mapping are found within the area of immunochemistry. [NIH]

Esophagus: The muscular tube through which food passes from the throat to the stomach. [NIH]

Estrogen: One of the two female sex hormones. [NIH]

Ethanol: A clear, colorless liquid rapidly absorbed from the gastrointestinal tract and distributed throughout the body. It has bactericidal activity and is used often as a topical disinfectant. It is widely used as a solvent and preservative in pharmaceutical preparations as well as serving as the primary ingredient in alcoholic beverages. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

Evoke: The electric response recorded from the cerebral cortex after stimulation of a peripheral sense organ. [NIH]

Excitability: Property of a cardiac cell whereby, when the cell is depolarized to a critical level (called threshold), the membrane becomes permeable and a regenerative inward current causes an action potential. [NIH]

Excitation: An act of irritation or stimulation or of responding to a stimulus; the addition of energy, as the excitation of a molecule by absorption of photons. [EU]

Exercise Test: Controlled physical activity, more strenuous than at rest, which is performed in order to allow assessment of physiological functions, particularly cardiovascular and pulmonary, but also aerobic capacity. Maximal (most intense) exercise is usually required but submaximal exercise is also used. The intensity of exercise is often graded, using criteria such as rate of work done, oxygen consumption, and heart rate. Physiological data obtained from an exercise test may be used for diagnosis, prognosis, and evaluation of disease severity, and to evaluate therapy. Data may also be used in prescribing exercise by determining a person's exercise capacity. [NIH]

Exercise Tolerance: The exercise capacity of an individual as measured by endurance (maximal exercise duration and/or maximal attained work load) during an exercise test. [NIH]

Exocytosis: Cellular release of material within membrane-limited vesicles by fusion of the vesicles with the cell membrane. [NIH]

Exogenous: Developed or originating outside the organism, as exogenous disease. [EU]

Exon: The part of the DNA that encodes the information for the actual amino acid sequence of the protein. In many eucaryotic genes, the coding sequences consist of a series of exons

alternating with intron sequences. [NIH]

Expiration: The act of breathing out, or expelling air from the lungs. [EU]

Expiratory: The volume of air which leaves the breathing organs in each expiration. [NIH]

Extracellular: Outside a cell or cells. [EU]

Extracellular Matrix: A meshwork-like substance found within the extracellular space and in association with the basement membrane of the cell surface. It promotes cellular proliferation and provides a supporting structure to which cells or cell lysates in culture dishes adhere. [NIH]

Extracellular Matrix Proteins: Macromolecular organic compounds that contain carbon, hydrogen, oxygen, nitrogen, and usually, sulfur. These macromolecules (proteins) form an intricate meshwork in which cells are embedded to construct tissues. Variations in the relative types of macromolecules and their organization determine the type of extracellular matrix, each adapted to the functional requirements of the tissue. The two main classes of macromolecules that form the extracellular matrix are: glycosaminoglycans, usually linked to proteins (proteoglycans), and fibrous proteins (e.g., collagen, elastin, fibronectins and laminin). [NIH]

Extracellular Space: Interstitial space between cells, occupied by fluid as well as amorphous and fibrous substances. [NIH]

Eye Infections: Infection, moderate to severe, caused by bacteria, fungi, or viruses, which occurs either on the external surface of the eye or intraocularly with probable inflammation, visual impairment, or blindness. [NIH]

Facial: Of or pertaining to the face. [EU]

Facial Paralysis: Severe or complete loss of facial muscle motor function. This condition may result from central or peripheral lesions. Damage to CNS motor pathways from the cerebral cortex to the facial nuclei in the pons leads to facial weakness that generally spares the forehead muscles. Facial nerve diseases generally results in generalized hemifacial weakness. Neuromuscular junction diseases and muscular diseases may also cause facial paralysis or paresis. [NIH]

Family Planning: Programs or services designed to assist the family in controlling reproduction by either improving or diminishing fertility. [NIH]

Fat: Total lipids including phospholipids. [NIH]

Fatigue: The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli. [NIH]

Fatty acids: A major component of fats that are used by the body for energy and tissue development. [NIH]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

Fibrillation: A small, local, involuntary contraction of muscle, invisible under the skin, resulting from spontaneous activation of single muscle cells or muscle fibres. [EU]

Fibrinogen: Plasma glycoprotein clotted by thrombin, composed of a dimer of three non-identical pairs of polypeptide chains (alpha, beta, gamma) held together by disulfide bonds. Fibrinogen clotting is a sol-gel change involving complex molecular arrangements: whereas fibrinogen is cleaved by thrombin to form polypeptides A and B, the proteolytic action of other enzymes yields different fibrinogen degradation products. [NIH]

Fibroblasts: Connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

Flatus: Gas passed through the rectum. [NIH]

Fluorescence: The property of emitting radiation while being irradiated. The radiation emitted is usually of longer wavelength than that incident or absorbed, e.g., a substance can be irradiated with invisible radiation and emit visible light. X-ray fluorescence is used in diagnosis. [NIH]

Fluorine: A nonmetallic, diatomic gas that is a trace element and member of the halogen family. It is used in dentistry as flouride to prevent dental caries. [NIH]

Fluorouracil: A pyrimidine analog that acts as an antineoplastic antimetabolite and also has immunosuppressant. It interferes with DNA synthesis by blocking the thymidylate synthetase conversion of deoxyuridylic acid to thymidylic acid. [NIH]

Fold: A plication or doubling of various parts of the body. [NIH]

Forearm: The part between the elbow and the wrist. [NIH]

Forskolin: Potent activator of the adenylate cyclase system and the biosynthesis of cyclic AMP. From the plant Coleus forskohlii. Has antihypertensive, positive ionotropic, platelet aggregation inhibitory, and smooth muscle relaxant activities; also lowers intraocular pressure and promotes release of hormones from the pituitary gland. [NIH]

Fractionation: Dividing the total dose of radiation therapy into several smaller, equal doses delivered over a period of several days. [NIH]

Free Radicals: Highly reactive molecules with an unsatisfied electron valence pair. Free radicals are produced in both normal and pathological processes. They are proven or suspected agents of tissue damage in a wide variety of circumstances including radiation, damage from environment chemicals, and aging. Natural and pharmacological prevention of free radical damage is being actively investigated. [NIH]

Gadolinium: An element of the rare earth family of metals. It has the atomic symbol Gd, atomic number 64, and atomic weight 157.25. Its oxide is used in the control rods of some nuclear reactors. [NIH]

Ganglia: Clusters of multipolar neurons surrounded by a capsule of loosely organized connective tissue located outside the central nervous system. [NIH]

Gas: Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

Gas exchange: Primary function of the lungs; transfer of oxygen from inhaled air into the blood and of carbon dioxide from the blood into the lungs. [NIH]

Gastric: Having to do with the stomach. [NIH]

Gastric Mucosa: Surface epithelium in the stomach that invaginates into the lamina propria, forming gastric pits. Tubular glands, characteristic of each region of the stomach (cardiac, gastric, and pyloric), empty into the gastric pits. The gastric mucosa is made up of several different kinds of cells. [NIH]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal tract: The stomach and intestines. [NIH]

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

Gene Deletion: A genetic rearrangement through loss of segments of DNA or RNA, bringing sequences which are normally separated into close proximity. This deletion may be detected using cytogenetic techniques and can also be inferred from the phenotype, indicating a deletion at one specific locus. [NIH]

Gene Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Gene Expression Profiling: The determination of the pattern of genes expressed i.e., transcribed, under specific circumstances or in a specific cell. [NIH]

Gene Targeting: The integration of exogenous DNA into the genome of an organism at sites where its expression can be suitably controlled. This integration occurs as a result of homologous recombination. [NIH]

Gene Therapy: The introduction of new genes into cells for the purpose of treating disease by restoring or adding gene expression. Techniques include insertion of retroviral vectors, transfection, homologous recombination, and injection of new genes into the nuclei of single cell embryos. The entire gene therapy process may consist of multiple steps. The new genes may be introduced into proliferating cells in vivo (e.g., bone marrow) or in vitro (e.g., fibroblast cultures) and the modified cells transferred to the site where the gene expression is required. Gene therapy may be particularly useful for treating enzyme deficiency diseases, hemoglobinopathies, and leukemias and may also prove useful in restoring drug sensitivity, particularly for leukemia. [NIH]

Genetic Code: The specifications for how information, stored in nucleic acid sequence (base sequence), is translated into protein sequence (amino acid sequence). The start, stop, and order of amino acids of a protein is specified by consecutive triplets of nucleotides called codons (codon). [NIH]

Genetic Engineering: Directed modification of the gene complement of a living organism by such techniques as altering the DNA, substituting genetic material by means of a virus, transplanting whole nuclei, transplanting cell hybrids, etc. [NIH]

Genetic Markers: A phenotypically recognizable genetic trait which can be used to identify a genetic locus, a linkage group, or a recombination event. [NIH]

Genetic Screening: Searching a population or individuals for persons possessing certain genotypes or karyotypes that: (1) are already associated with disease or predispose to disease; (2) may lead to disease in their descendants; or (3) produce other variations not known to be associated with disease. Genetic screening may be directed toward identifying phenotypic expression of genetic traits. It includes prenatal genetic screening. [NIH]

Genetics: The biological science that deals with the phenomena and mechanisms of heredity. [NIH]

Genistein: An isoflavonoid derived from soy products. It inhibits protein-tyrosine kinase and topoisomerase-ii (dna topoisomerase (atp-hydrolysing)) activity and is used as an antineoplastic and antitumor agent. Experimentally, it has been shown to induce G2 phase arrest in human and murine cell lines. [NIH]

Genomics: The systematic study of the complete DNA sequences (genome) of organisms. [NIH]

Genotype: The genetic constitution of the individual; the characterization of the genes. [NIH]

Gestation: The period of development of the young in viviparous animals, from the time of fertilization of the ovum until birth. [EU]

Gland: An organ that produces and releases one or more substances for use in the body. Some glands produce fluids that affect tissues or organs. Others produce hormones or

participate in blood production. [NIH]

Gliosis: The production of a dense fibrous network of neuroglia; includes astrocytosis, which is a proliferation of astrocytes in the area of a degenerative lesion. [NIH]

Glomerular: Pertaining to or of the nature of a glomerulus, especially a renal glomerulus. [EU]

Glomeruli: Plural of glomerulus. [NIH]

Glomerulonephritis: Glomerular disease characterized by an inflammatory reaction, with leukocyte infiltration and cellular proliferation of the glomeruli, or that appears to be the result of immune glomerular injury. [NIH]

Glucocorticoid: A compound that belongs to the family of compounds called corticosteroids (steroids). Glucocorticoids affect metabolism and have anti-inflammatory and immunosuppressive effects. They may be naturally produced (hormones) or synthetic (drugs). [NIH]

Glucose: D-Glucose. A primary source of energy for living organisms. It is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement. [NIH]

Glucose Intolerance: A pathological state in which the fasting plasma glucose level is less than 140 mg per deciliter and the 30-, 60-, or 90-minute plasma glucose concentration following a glucose tolerance test exceeds 200 mg per deciliter. This condition is seen frequently in diabetes mellitus but also occurs with other diseases. [NIH]

Glutathione Peroxidase: An enzyme catalyzing the oxidation of 2 moles of glutathione in the presence of hydrogen peroxide to yield oxidized glutathione and water. EC 1.11.1.9. [NIH]

Gluten: The protein of wheat and other grains which gives to the dough its tough elastic character. [EU]

Glycolysis: The pathway by which glucose is catabolized into two molecules of pyruvic acid with the generation of ATP. [NIH]

Glycoprotein: A protein that has sugar molecules attached to it. [NIH]

Glycoside: Any compound that contains a carbohydrate molecule (sugar), particularly any such natural product in plants, convertible, by hydrolytic cleavage, into sugar and a nonsugar component (aglycone), and named specifically for the sugar contained, as glucoside (glucose), pentoside (pentose), fructoside (fructose) etc. [EU]

Glycosylation: The chemical or biochemical addition of carbohydrate or glycosyl groups to other chemicals, especially peptides or proteins. Glycosyl transferases are used in this biochemical reaction. [NIH]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Graft: Healthy skin, bone, or other tissue taken from one part of the body and used to replace diseased or injured tissue removed from another part of the body. [NIH]

Graft Rejection: An immune response with both cellular and humoral components, directed against an allogeneic transplant, whose tissue antigens are not compatible with those of the recipient. [NIH]

Grafting: The operation of transfer of tissue from one site to another. [NIH]

Granulocytes: Leukocytes with abundant granules in the cytoplasm. They are divided into three groups: neutrophils, eosinophils, and basophils. [NIH]

Growth factors: Substances made by the body that function to regulate cell division and cell

survival. Some growth factors are also produced in the laboratory and used in biological therapy. [NIH]

Guanylate Cyclase: An enzyme that catalyzes the conversion of GTP to 3',5'-cyclic GMP and pyrophosphate. It also acts on ITP and dGTP. (From Enzyme Nomenclature, 1992) EC 4.6.1.2. [NIH]

Habitual: Of the nature of a habit; according to habit; established by or repeated by force of habit, customary. [EU]

Haptens: Small antigenic determinants capable of eliciting an immune response only when coupled to a carrier. Haptens bind to antibodies but by themselves cannot elicit an antibody response. [NIH]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Heart failure: Loss of pumping ability by the heart, often accompanied by fatigue, breathlessness, and excess fluid accumulation in body tissues. [NIH]

Heart Transplantation: The transference of a heart from one human or animal to another. [NIH]

Heartbeat: One complete contraction of the heart. [NIH]

Helix-loop-helix: Regulatory protein of cell cycle. [NIH]

Hemiplegia: Severe or complete loss of motor function on one side of the body. This condition is usually caused by BRAIN DISEASES that are localized to the cerebral hemisphere opposite to the side of weakness. Less frequently, BRAIN STEM lesions; cervical spinal cord diseases; peripheral nervous system diseases; and other conditions may manifest as hemiplegia. The term hemiparesis (see paresis) refers to mild to moderate weakness involving one side of the body. [NIH]

Hemodynamics: The movements of the blood and the forces involved in systemic or regional blood circulation. [NIH]

Hemoglobin: One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal conentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

Hemoglobinopathies: A group of inherited disorders characterized by structural alterations within the hemoglobin molecule. [NIH]

Hemorrhage: Bleeding or escape of blood from a vessel. [NIH]

Hemostasis: The process which spontaneously arrests the flow of blood from vessels carrying blood under pressure. It is accomplished by contraction of the vessels, adhesion and aggregation of formed blood elements, and the process of blood or plasma coagulation. [NIH]

Hepatic: Refers to the liver. [NIH]

Hepatitis: Inflammation of the liver and liver disease involving degenerative or necrotic alterations of hepatocytes. [NIH]

Hepatocytes: The main structural component of the liver. They are specialized epithelial cells that are organized into interconnected plates called lobules. [NIH]

Hereditary: Of, relating to, or denoting factors that can be transmitted genetically from one generation to another. [NIH]

Heredity: 1. The genetic transmission of a particular quality or trait from parent to offspring. 2. The genetic constitution of an individual. [EU]

Heterodimers: Zippered pair of nonidentical proteins. [NIH]

Heterogeneity: The property of one or more samples or populations which implies that they are not identical in respect of some or all of their parameters, e. g. heterogeneity of variance. [NIH]

Heterozygote: An individual having different alleles at one or more loci in homologous chromosome segments. [NIH]

Histamine: 1H-Imidazole-4-ethanamine. A depressor amine derived by enzymatic decarboxylation of histidine. It is a powerful stimulant of gastric secretion, a constrictor of bronchial smooth muscle, a vasodilator, and also a centrally acting neurotransmitter. [NIH]

Histamine Release: The secretion of histamine from mast cell and basophil granules by exocytosis. This can be initiated by a number of factors, all of which involve binding of IgE, cross-linked by antigen, to the mast cell or basophil's Fc receptors. Once released, histamine binds to a number of different target cell receptors and exerts a wide variety of effects. [NIH]

Histidine: An essential amino acid important in a number of metabolic processes. It is required for the production of histamine. [NIH]

Histology: The study of tissues and cells under a microscope. [NIH]

Histones: Small chromosomal proteins (approx 12-20 kD) possessing an open, unfolded structure and attached to the DNA in cell nuclei by ionic linkages. Classification into the various types (designated histone I, histone II, etc.) is based on the relative amounts of arginine and lysine in each. [NIH]

Homeostasis: The processes whereby the internal environment of an organism tends to remain balanced and stable. [NIH]

Homogeneous: Consisting of or composed of similar elements or ingredients; of a uniform quality throughout. [EU]

Homologous: Corresponding in structure, position, origin, etc., as (a) the feathers of a bird and the scales of a fish, (b) antigen and its specific antibody, (c) allelic chromosomes. [EU]

Hormonal: Pertaining to or of the nature of a hormone. [EU]

Hormone: A substance in the body that regulates certain organs. Hormones such as gastrin help in breaking down food. Some hormones come from cells in the stomach and small intestine. [NIH]

Hormone therapy: Treatment of cancer by removing, blocking, or adding hormones. Also called endocrine therapy. [NIH]

Humoral: Of, relating to, proceeding from, or involving a bodily humour - now often used of endocrine factors as opposed to neural or somatic. [EU]

Humour: 1. A normal functioning fluid or semifluid of the body (as the blood, lymph or bile) especially of vertebrates. 2. A secretion that is itself an excitant of activity (as certain hormones). [EU]

Hybrid: Cross fertilization between two varieties or, more usually, two species of vines, see also crossing. [NIH]

Hybridization: The genetic process of crossbreeding to produce a hybrid. Hybrid nucleic acids can be formed by nucleic acid hybridization of DNA and RNA molecules. Protein hybridization allows for hybrid proteins to be formed from polypeptide chains. [NIH]

Hybridomas: Cells artificially created by fusion of activated lymphocytes with neoplastic cells. The resulting hybrid cells are cloned and produce pure or "monoclonal" antibodies or T-cell products, identical to those produced by the immunologically competent parent, and continually grow and divide as the neoplastic parent. [NIH]

Hydrogen: The first chemical element in the periodic table. It has the atomic symbol H, atomic number 1, and atomic weight 1. It exists, under normal conditions, as a colorless, odorless, tasteless, diatomic gas. Hydrogen ions are protons. Besides the common H1 isotope, hydrogen exists as the stable isotope deuterium and the unstable, radioactive isotope tritium. [NIH]

Hydrogen Peroxide: A strong oxidizing agent used in aqueous solution as a ripening agent, bleach, and topical anti-infective. It is relatively unstable and solutions deteriorate over time unless stabilized by the addition of acetanilide or similar organic materials. [NIH]

Hydrolysis: The process of cleaving a chemical compound by the addition of a molecule of water. [NIH]

Hydrophobic: Not readily absorbing water, or being adversely affected by water, as a hydrophobic colloid. [EU]

Hydroxylysine: A hydroxylated derivative of the amino acid lysine that is present in certain collagens. [NIH]

Hydroxyproline: A hydroxylated form of the imino acid proline. A deficiency in ascorbic acid can result in impaired hydroxyproline formation. [NIH]

Hypercholesterolemia: Abnormally high levels of cholesterol in the blood. [NIH]

Hyperpigmentation: Excessive pigmentation of the skin, usually as a result of increased melanization of the epidermis rather than as a result of an increased number of melanocytes. Etiology is varied and the condition may arise from exposure to light, chemicals or other substances, or from a primary metabolic imbalance. [NIH]

Hyperpnea: Increased ventilation in proportion to increased metabolism. [NIH]

Hypersensitivity: Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that particular antigen. [NIH]

Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Hyperthyroidism: Excessive functional activity of the thyroid gland. [NIH]

Hypertrophic cardiomyopathy: Heart muscle disease that leads to thickening of the heart walls, interfering with the heart's ability to fill with and pump blood. [NIH]

Hypertrophy: General increase in bulk of a part or organ, not due to tumor formation, nor to an increase in the number of cells. [NIH]

Hypotension: Abnormally low blood pressure. [NIH]

Hypoxanthine: A purine and a reaction intermediate in the metabolism of adenosine and in the formation of nucleic acids by the salvage pathway. [NIH]

Idarubicin: An orally administered anthracycline antibiotic. The compound has shown activity against breast cancer, lymphomas and leukemias, together with potential for reduced cardiac toxicity. [NIH]

Idiopathic: Describes a disease of unknown cause. [NIH]

Immune response: The activity of the immune system against foreign substances (antigens). [NIH]

Immune Sera: Serum that contains antibodies. It is obtained from an animal that has been

immunized either by antigen injection or infection with microorganisms containing the antigen. [NIH]

Immune system: The organs, cells, and molecules responsible for the recognition and disposal of foreign ("non-self") material which enters the body. [NIH]

Immune Tolerance: The specific failure of a normally responsive individual to make an immune response to a known antigen. It results from previous contact with the antigen by an immunologically immature individual (fetus or neonate) or by an adult exposed to extreme high-dose or low-dose antigen, or by exposure to radiation, antimetabolites, antilymphocytic serum, etc. [NIH]

Immunity: Nonsusceptibility to the invasive or pathogenic effects of foreign microorganisms or to the toxic effect of antigenic substances. [NIH]

Immunization: Deliberate stimulation of the host's immune response. Active immunization involves administration of antigens or immunologic adjuvants. Passive immunization involves administration of immune sera or lymphocytes or their extracts (e.g., transfer factor, immune RNA) or transplantation of immunocompetent cell producing tissue (thymus or bone marrow). [NIH]

Immunochemistry: Field of chemistry that pertains to immunological phenomena and the study of chemical reactions related to antigen stimulation of tissues. It includes physicochemical interactions between antigens and antibodies. [NIH]

Immunodeficiency: The decreased ability of the body to fight infection and disease. [NIH]

Immunogenic: Producing immunity; evoking an immune response. [EU]

Immunohistochemistry: Histochemical localization of immunoreactive substances using labeled antibodies as reagents. [NIH]

Immunologic: The ability of the antibody-forming system to recall a previous experience with an antigen and to respond to a second exposure with the prompt production of large amounts of antibody. [NIH]

Immunology: The study of the body's immune system. [NIH]

Immunophilin: A drug for the treatment of Parkinson's disease. [NIH]

Immunosuppression: Deliberate prevention or diminution of the host's immune response. It may be nonspecific as in the administration of immunosuppressive agents (drugs or radiation) or by lymphocyte depletion or may be specific as in desensitization or the simultaneous administration of antigen and immunosuppressive drugs. [NIH]

Immunosuppressive: Describes the ability to lower immune system responses. [NIH]

Immunosuppressive Agents: Agents that suppress immune function by one of several mechanisms of action. Classical cytotoxic immunosuppressants act by inhibiting DNA synthesis. Others may act through activation of suppressor T-cell populations or by inhibiting the activation of helper cells. While immunosuppression has been brought about in the past primarily to prevent rejection of transplanted organs, new applications involving mediation of the effects of interleukins and other cytokines are emerging. [NIH]

Immunosuppressive therapy: Therapy used to decrease the body's immune response, such as drugs given to prevent transplant rejection. [NIH]

Immunotherapy: Manipulation of the host's immune system in treatment of disease. It includes both active and passive immunization as well as immunosuppressive therapy to prevent graft rejection. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

Implantation: The insertion or grafting into the body of biological, living, inert, or radioactive material. [EU]

In situ: In the natural or normal place; confined to the site of origin without invasion of neighbouring tissues. [EU]

In Situ Hybridization: A technique that localizes specific nucleic acid sequences within intact chromosomes, eukaryotic cells, or bacterial cells through the use of specific nucleic acid-labeled probes. [NIH]

In vitro: In the laboratory (outside the body). The opposite of in vivo (in the body). [NIH]

In vivo: In the body. The opposite of in vitro (outside the body or in the laboratory). [NIH]

Incision: A cut made in the body during surgery. [NIH]

Induction: The act or process of inducing or causing to occur, especially the production of a specific morphogenetic effect in the developing embryo through the influence of evocators or organizers, or the production of anaesthesia or unconsciousness by use of appropriate agents. [EU]

Infancy: The period of complete dependency prior to the acquisition of competence in walking, talking, and self-feeding. [NIH]

Infantile: Pertaining to an infant or to infancy. [EU]

Infarction: A pathological process consisting of a sudden insufficient blood supply to an area, which results in necrosis of that area. It is usually caused by a thrombus, an embolus, or a vascular torsion. [NIH]

Infection: 1. Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response. The infection may remain localized, subclinical, and temporary if the body's defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute, or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system. 2. An infectious disease. [EU]

Inferior vena cava: A large vein that empties into the heart. It carries blood from the legs and feet, and from organs in the abdomen and pelvis. [NIH]

Infiltration: The diffusion or accumulation in a tissue or cells of substances not normal to it or in amounts of the normal. Also, the material so accumulated. [EU]

Inflammation: A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion. [NIH]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

Innervation: 1. The distribution or supply of nerves to a part. 2. The supply of nervous energy or of nerve stimulus sent to a part. [EU]

Inotropic: Affecting the force or energy of muscular contractions. [EU]

Insight: The capacity to understand one's own motives, to be aware of one's own psychodynamics, to appreciate the meaning of symbolic behavior. [NIH]

Insulator: Material covering the metal conductor of the lead. It is usually polyurethane or silicone. [NIH]

Insulin: A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

Insulin-dependent diabetes mellitus: A disease characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both. Autoimmune, genetic, and environmental factors are involved in the development of type I diabetes. [NIH]

Integrins: A family of transmembrane glycoproteins consisting of noncovalent heterodimers. They interact with a wide variety of ligands including extracellular matrix glycoproteins, complement, and other cells, while their intracellular domains interact with the cytoskeleton. The integrins consist of at least three identified families: the cytoadhesin receptors, the leukocyte adhesion receptors, and the very-late-antigen receptors. Each family contains a common beta-subunit combined with one or more distinct alpha-subunits. These receptors participate in cell-matrix and cell-cell adhesion in many physiologically important processes, including embryological development, hemostasis, thrombosis, wound healing, immune and nonimmune defense mechanisms, and oncogenic transformation. [NIH]

Intensive Care: Advanced and highly specialized care provided to medical or surgical patients whose conditions are life-threatening and require comprehensive care and constant monitoring. It is usually administered in specially equipped units of a health care facility. [NIH]

Intercostal: Situated between the ribs. [EU]

Interferon: A biological response modifier (a substance that can improve the body's natural response to disease). Interferons interfere with the division of cancer cells and can slow tumor growth. There are several types of interferons, including interferon-alpha, -beta, and -gamma. These substances are normally produced by the body. They are also made in the laboratory for use in treating cancer and other diseases. [NIH]

Interferon-alpha: One of the type I interferons produced by peripheral blood leukocytes or lymphoblastoid cells when exposed to live or inactivated virus, double-stranded RNA, or bacterial products. It is the major interferon produced by virus-induced leukocyte cultures and, in addition to its pronounced antiviral activity, it causes activation of NK cells. [NIH]

Interleukin-6: Factor that stimulates the growth and differentiation of human B-cells and is also a growth factor for hybridomas and plasmacytomas. It is produced by many different cells including T-cells, monocytes, and fibroblasts. [NIH]

Interstitial: Pertaining to or situated between parts or in the interspaces of a tissue. [EU]

Intestinal: Having to do with the intestines. [NIH]

Intestinal Mucosa: The surface lining of the intestines where the cells absorb nutrients. [NIH]

Intestines: The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

Intoxication: Poisoning, the state of being poisoned. [EU]

Intracellular: Inside a cell. [NIH]

Intraocular: Within the eye. [EU]

Intraocular pressure: Pressure of the fluid inside the eye; normal IOP varies among individuals. [NIH]

Intravenous: IV. Into a vein. [NIH]

Intrinsic: Situated entirely within or pertaining exclusively to a part. [EU]

Intubation: Introduction of a tube into a hollow organ to restore or maintain patency if

obstructed. It is differentiated from catheterization in that the insertion of a catheter is usually performed for the introducing or withdrawing of fluids from the body. [NIH]

Invasive: 1. Having the quality of invasiveness. 2. Involving puncture or incision of the skin or insertion of an instrument or foreign material into the body; said of diagnostic techniques. [EU]

Involuntary: Reaction occurring without intention or volition. [NIH]

Iodine: A nonmetallic element of the halogen group that is represented by the atomic symbol I, atomic number 53, and atomic weight of 126.90. It is a nutritionally essential element, especially important in thyroid hormone synthesis. In solution, it has anti-infective properties and is used topically. [NIH]

Ion Channels: Gated, ion-selective glycoproteins that traverse membranes. The stimulus for channel gating can be a membrane potential, drug, transmitter, cytoplasmic messenger, or a mechanical deformation. Ion channels which are integral parts of ionotropic neurotransmitter receptors are not included. [NIH]

Ionization: 1. Any process by which a neutral atom gains or loses electrons, thus acquiring a net charge, as the dissociation of a substance in solution into ions or ion production by the passage of radioactive particles. 2. Iontophoresis. [EU]

Ions: An atom or group of atoms that have a positive or negative electric charge due to a gain (negative charge) or loss (positive charge) of one or more electrons. Atoms with a positive charge are known as cations; those with a negative charge are anions. [NIH]

Ipecac: A syrup made from the dried rhizomes of two different species, Cephaelis ipecacuanha and C. acuminata, belonging to the Rubiaciae family. They contain emetine, cephaeline, psychotrine and other isoquinolines. Ipecac syrup is used widely as an emetic acting both locally on the gastric mucosa and centrally on the chemoreceptor trigger zone. [NIH]

Ischemia: Deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel. [EU]

Isoenzyme: Different forms of an enzyme, usually occurring in different tissues. The isoenzymes of a particular enzyme catalyze the same reaction but they differ in some of their properties. [NIH]

Isoproterenol: Isopropyl analog of epinephrine; beta-sympathomimetic that acts on the heart, bronchi, skeletal muscle, alimentary tract, etc. It is used mainly as bronchodilator and heart stimulant. [NIH]

Kallidin: A decapeptide bradykinin homolog produced by the action of tissue and glandular kallikreins on low-molecular-weight kininogen. It is a smooth-muscle stimulant and hypotensive agent that functions through vasodilatation. [NIH]

Karyotypes: The characteristic chromosome complement of an individual, race, or species as defined by their number, size, shape, etc. [NIH]

Kb: A measure of the length of DNA fragments, 1 Kb = 1000 base pairs. The largest DNA fragments are up to 50 kilobases long. [NIH]

Kinetic: Pertaining to or producing motion. [EU]

Labile: 1. Gliding; moving from point to point over the surface; unstable; fluctuating. 2. Chemically unstable. [EU]

Laminin: Large, noncollagenous glycoprotein with antigenic properties. It is localized in the basement membrane lamina lucida and functions to bind epithelial cells to the basement membrane. Evidence suggests that the protein plays a role in tumor invasion. [NIH]

Latency: The period of apparent inactivity between the time when a stimulus is presented

and the moment a response occurs. [NIH]

Latent: Phoria which occurs at one distance or another and which usually has no troublesome effect. [NIH]

Left ventricular assist device: A mechanical device used to increase the heart's pumping ability. [NIH]

Lesion: An area of abnormal tissue change. [NIH]

Lethal: Deadly, fatal. [EU]

Leukemia: Cancer of blood-forming tissue. [NIH]

Leukopenia: A condition in which the number of leukocytes (white blood cells) in the blood is reduced. [NIH]

Levocardia: Location of heart in left hemithorax with apex pointing to the left, but with situs inversus of other viscera and defects of the heart, or corrected transposition of great vessels. [NIH]

Life cycle: The successive stages through which an organism passes from fertilized ovum or spore to the fertilized ovum or spore of the next generation. [NIH]

Ligaments: Shiny, flexible bands of fibrous tissue connecting together articular extremities of bones. They are pliant, tough, and inextensile. [NIH]

Ligands: A RNA simulation method developed by the MIT. [NIH]

Linkage: The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

Lipid: Fat. [NIH]

Lipid A: Lipid A is the biologically active component of lipopolysaccharides. It shows strong endotoxic activity and exhibits immunogenic properties. [NIH]

Lipid Peroxidation: Peroxidase catalyzed oxidation of lipids using hydrogen peroxide as an electron acceptor. [NIH]

Lipodystrophy: A collection of rare conditions resulting from defective fat metabolism and characterized by atrophy of the subcutaneous fat. They include total, congenital or acquired, partial, abdominal infantile, and localized lipodystrophy. [NIH]

Lipopolysaccharides: Substance consisting of polysaccaride and lipid. [NIH]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Liver scan: An image of the liver created on a computer screen or on film. A radioactive substance is injected into a blood vessel and travels through the bloodstream. It collects in the liver, especially in abnormal areas, and can be detected by the scanner. [NIH]

Localization: The process of determining or marking the location or site of a lesion or disease. May also refer to the process of keeping a lesion or disease in a specific location or site. [NIH]

Localized: Cancer which has not metastasized yet. [NIH]

Locomotion: Movement or the ability to move from one place or another. It can refer to humans, vertebrate or invertebrate animals, and microorganisms. [NIH]

Locomotor: Of or pertaining to locomotion; pertaining to or affecting the locomotive apparatus of the body. [EU]

Longitudinal Studies: Studies in which variables relating to an individual or group of

individuals are assessed over a period of time. [NIH]

Loop: A wire usually of platinum bent at one end into a small loop (usually 4 mm inside diameter) and used in transferring microorganisms. [NIH]

Lucida: An instrument, invented by Wollaton, consisting essentially of a prism or a mirror through which an object can be viewed so as to appear on a plane surface seen in direct view and on which the outline of the object may be traced. [NIH]

Lung volume: The amount of air the lungs hold. [NIH]

Lupus: A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

Lymph: The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [NIH]

Lymphadenopathy: Disease or swelling of the lymph nodes. [NIH]

Lymphatic: The tissues and organs, including the bone marrow, spleen, thymus, and lymph nodes, that produce and store cells that fight infection and disease. [NIH]

Lymphatic system: The tissues and organs that produce, store, and carry white blood cells that fight infection and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes and a network of thin tubes that carry lymph and white blood cells. These tubes branch, like blood vessels, into all the tissues of the body. [NIH]

Lymphocyte Count: A count of the number of lymphocytes in the blood. [NIH]

Lymphocyte Depletion: Immunosuppression by reduction of circulating lymphocytes or by T-cell depletion of bone marrow. The former may be accomplished in vivo by thoracic duct drainage or administration of antilymphocyte serum. The latter is performed ex vivo on bone marrow before its transplantation. [NIH]

Lymphocytes: White blood cells formed in the body's lymphoid tissue. The nucleus is round or ovoid with coarse, irregularly clumped chromatin while the cytoplasm is typically pale blue with azurophilic (if any) granules. Most lymphocytes can be classified as either T or B (with subpopulations of each); those with characteristics of neither major class are called null cells. [NIH]

Lymphoid: Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop. [NIH]

Magnetic Resonance Imaging: Non-invasive method of demonstrating internal anatomy based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy and emit them as radiowaves which can be reconstructed into computerized images. The concept includes proton spin tomographic techniques. [NIH]

Major Histocompatibility Complex: The genetic region which contains the loci of genes which determine the structure of the serologically defined (SD) and lymphocyte-defined (LD) transplantation antigens, genes which control the structure of the immune response-associated (Ia) antigens, the immune response (Ir) genes which control the ability of an animal to respond immunologically to antigenic stimuli, and genes which determine the structure and/or level of the first four components of complement. [NIH]

Malabsorption: Impaired intestinal absorption of nutrients. [EU]

Malignant: Cancerous; a growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malnutrition: A condition caused by not eating enough food or not eating a balanced diet. [NIH]

Mammary: Pertaining to the mamma, or breast. [EU]

Matrix metalloproteinase: A member of a group of enzymes that can break down proteins, such as collagen, that are normally found in the spaces between cells in tissues (i.e., extracellular matrix proteins). Because these enzymes need zinc or calcium atoms to work properly, they are called metalloproteinases. Matrix metalloproteinases are involved in wound healing, angiogenesis, and tumor cell metastasis. [NIH]

Medial: Lying near the midsaggital plane of the body; opposed to lateral. [NIH]

Mediate: Indirect; accomplished by the aid of an intervening medium. [EU]

Medical Records: Recording of pertinent information concerning patient's illness or illnesses. [NIH]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

Melanocytes: Epidermal dendritic pigment cells which control long-term morphological color changes by alteration in their number or in the amount of pigment they produce and store in the pigment containing organelles called melanosomes. Melanophores are larger cells which do not exist in mammals. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

Membrane Proteins: Proteins which are found in membranes including cellular and intracellular membranes. They consist of two types, peripheral and integral proteins. They include most membrane-associated enzymes, antigenic proteins, transport proteins, and drug, hormone, and lectin receptors. [NIH]

Memory: Complex mental function having four distinct phases: (1) memorizing or learning, (2) retention, (3) recall, and (4) recognition. Clinically, it is usually subdivided into immediate, recent, and remote memory. [NIH]

Meninges: The three membranes that cover and protect the brain and spinal cord. [NIH]

Menopause: Permanent cessation of menstruation. [NIH]

Menstrual Cycle: The period of the regularly recurring physiologic changes in the endometrium occurring during the reproductive period in human females and some primates and culminating in partial sloughing of the endometrium (menstruation). [NIH]

Mental: Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

Mental Health: The state wherein the person is well adjusted. [NIH]

Metastasis: The spread of cancer from one part of the body to another. Tumors formed from cells that have spread are called "secondary tumors" and contain cells that are like those in the original (primary) tumor. The plural is metastases. [NIH]

Metoprolol: Adrenergic beta-1-blocking agent with no stimulatory action. It is less bound to plasma albumin than alprenolol and may be useful in angina pectoris, hypertension, or cardiac arrhythmias. [NIH]

Microbe: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microbiology: The study of microorganisms such as fungi, bacteria, algae, archaea, and viruses. [NIH]

Microorganism: An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms. [NIH]

Microscopy: The application of microscope magnification to the study of materials that cannot be properly seen by the unaided eye. [NIH]

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [NIH]

Milrinone: A positive inotropic cardiotonic agent with vasodilator properties. It inhibits cAMP phosphodiesterase activity in myocardium and vascular smooth muscle. Milrinone is a derivative of amrinone and has 20-30 times the ionotropic potency of amrinone. [NIH]

Mitochondria: Parts of a cell where aerobic production (also known as cell respiration) takes place. [NIH]

Mitochondrial Swelling: Increase in volume of mitochondria due to an influx of fluid; it occurs in hypotonic solutions due to osmotic pressure and in isotonic solutions as a result of altered permeability of the membranes of respiring mitochondria. [NIH]

Mitosis: A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

Mitotic: Cell resulting from mitosis. [NIH]

Mitral Valve: The valve between the left atrium and left ventricle of the heart. [NIH]

Modeling: A treatment procedure whereby the therapist presents the target behavior which the learner is to imitate and make part of his repertoire. [NIH]

Modification: A change in an organism, or in a process in an organism, that is acquired from its own activity or environment. [NIH]

Molecular: Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

Molecular Structure: The location of the atoms, groups or ions relative to one another in a molecule, as well as the number, type and location of covalent bonds. [NIH]

Molecule: A chemical made up of two or more atoms. The atoms in a molecule can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms. [NIH]

Monitor: An apparatus which automatically records such physiological signs as respiration, pulse, and blood pressure in an anesthetized patient or one undergoing surgical or other procedures. [NIH]

Monocytes: Large, phagocytic mononuclear leukocytes produced in the vertebrate bone marrow and released into the blood; contain a large, oval or somewhat indented nucleus surrounded by voluminous cytoplasm and numerous organelles. [NIH]

Mononuclear: A cell with one nucleus. [NIH]

Morphogenesis: The development of the form of an organ, part of the body, or organism. [NIH]

Morphological: Relating to the configuration or the structure of live organs. [NIH]

Morphology: The science of the form and structure of organisms (plants, animals, and other forms of life). [NIH]

Motility: The ability to move spontaneously. [EU]

Mucosa: A mucous membrane, or tunica mucosa. [EU]

Multiple sclerosis: A disorder of the central nervous system marked by weakness, numbness, a loss of muscle coordination, and problems with vision, speech, and bladder control. Multiple sclerosis is thought to be an autoimmune disease in which the body's immune system destroys myelin. Myelin is a substance that contains both protein and fat (lipid) and serves as a nerve insulator and helps in the transmission of nerve signals. [NIH]

Murine Acquired Immunodeficiency Syndrome: Acquired defect of cellular immunity that occurs in mice infected with mouse leukemia viruses (MuLV). The syndrome shows striking similarities with human AIDS and is characterized by lymphadenopathy, profound immunosuppression, enhanced susceptibility to opportunistic infections, and B-cell lymphomas. [NIH]

Muscle Contraction: A process leading to shortening and/or development of tension in muscle tissue. Muscle contraction occurs by a sliding filament mechanism whereby actin filaments slide inward among the myosin filaments. [NIH]

Muscle Denervation: The resection or removal of the innervation of a muscle or muscle tissue. [NIH]

Muscle Fibers: Large single cells, either cylindrical or prismatic in shape, that form the basic unit of muscle tissue. They consist of a soft contractile substance enclosed in a tubular sheath. [NIH]

Muscle Proteins: The protein constituents of muscle, the major ones being ACTINS and MYOSIN. More than a dozen accessary proteins exist including troponin, tropomyosin, and dystrophin. [NIH]

Mydriatic: 1. Dilating the pupil. 2. Any drug that dilates the pupil. [EU]

Myelin: The fatty substance that covers and protects nerves. [NIH]

Myocardial Contraction: Contractile activity of the heart. [NIH]

Myocardial Diseases: Diseases of the myocardium. [NIH]

Myocardial infarction: Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

Myocardial Ischemia: A disorder of cardiac function caused by insufficient blood flow to the muscle tissue of the heart. The decreased blood flow may be due to narrowing of the coronary arteries (coronary arteriosclerosis), to obstruction by a thrombus (coronary thrombosis), or less commonly, to diffuse narrowing of arterioles and other small vessels within the heart. Severe interruption of the blood supply to the myocardial tissue may result in necrosis of cardiac muscle (myocardial infarction). [NIH]

Myocardial Reperfusion: Generally, restoration of blood supply to heart tissue which is ischemic due to decrease in normal blood supply. The decrease may result from any source including atherosclerotic obstruction, narrowing of the artery, or surgical clamping. Reperfusion can be induced to treat ischemia. Methods include chemical dissolution of an occluding thrombus, administration of vasodilator drugs, angioplasty, catheterization, and artery bypass graft surgery. However, it is thought that reperfusion can itself further damage the ischemic tissue, causing myocardial reperfusion injury. [NIH]

Myocardial Reperfusion Injury: Functional, metabolic, or structural changes in ischemic heart muscle thought to result from reperfusion to the ischemic areas. Changes can be fatal to muscle cells and may include edema with explosive cell swelling and disintegration, sarcolemma disruption, fragmentation of mitochondria, contraction band necrosis, enzyme washout, and calcium overload. Other damage may include hemorrhage and ventricular arrhythmias. One possible mechanism of damage is thought to be oxygen free radicals. Treatment currently includes the introduction of scavengers of oxygen free radicals, and injury is thought to be prevented by warm blood cardioplegic infusion prior to reperfusion. [NIH]

Myocarditis: Inflammation of the myocardium; inflammation of the muscular walls of the heart. [EU]

Myocardium: The muscle tissue of the heart composed of striated, involuntary muscle known as cardiac muscle. [NIH]

Myofibrils: Highly organized bundles of actin, myosin, and other proteins in the cytoplasm of skeletal and cardiac muscle cells that contract by a sliding filament mechanism. [NIH]

Myopathy: Any disease of a muscle. [EU]

Myosin: Chief protein in muscle and the main constituent of the thick filaments of muscle fibers. In conjunction with actin, it is responsible for the contraction and relaxation of muscles. [NIH]

Natriuresis: The excretion of abnormal amounts of sodium in the urine. [EU]

NCI: National Cancer Institute. NCI, part of the National Institutes of Health of the United States Department of Health and Human Services, is the federal government's principal agency for cancer research. NCI conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at http://cancer.gov. [NIH]

Necrosis: A pathological process caused by the progressive degradative action of enzymes that is generally associated with severe cellular trauma. It is characterized by mitochondrial swelling, nuclear flocculation, uncontrolled cell lysis, and ultimately cell death. [NIH]

Neonatal: Pertaining to the first four weeks after birth. [EU]

Neoplasms: New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms. [NIH]

Nervous System: The entire nerve apparatus composed of the brain, spinal cord, nerves and ganglia. [NIH]

Networks: Pertaining to a nerve or to the nerves, a meshlike structure of interlocking fibers or strands. [NIH]

Neural: 1. Pertaining to a nerve or to the nerves. 2. Situated in the region of the spinal axis, as the neutral arch. [EU]

Neurodegenerative Diseases: Hereditary and sporadic conditions which are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of the affected central or peripheral nervous system structures. [NIH]

Neuroglia: The non-neuronal cells of the nervous system. They are divided into macroglia (astrocytes, oligodendroglia, and schwann cells) and microglia. They not only provide physical support, but also respond to injury, regulate the ionic and chemical composition of the extracellular milieu, participate in the blood-brain and blood-retina barriers, form the myelin insulation of nervous pathways, guide neuronal migration during development, and exchange metabolites with neurons. Neuroglia have high-affinity transmitter uptake systems, voltage-dependent and transmitter-gated ion channels, and can release transmitters, but their role in signaling (as in many other functions) is unclear. [NIH]

Neurons: The basic cellular units of nervous tissue. Each neuron consists of a body, an axon, and dendrites. Their purpose is to receive, conduct, and transmit impulses in the nervous system. [NIH]

Neuropathy: A problem in any part of the nervous system except the brain and spinal cord. Neuropathies can be caused by infection, toxic substances, or disease. [NIH]

Neurotransmitter: Any of a group of substances that are released on excitation from the axon terminal of a presynaptic neuron of the central or peripheral nervous system and travel across the synaptic cleft to either excite or inhibit the target cell. Among the many

substances that have the properties of a neurotransmitter are acetylcholine, norepinephrine, epinephrine, dopamine, glycine, y-aminobutyrate, glutamic acid, substance P, enkephalins, endorphins, and serotonin. [EU]

Neutrophil: A type of white blood cell. [NIH]

Niacin: Water-soluble vitamin of the B complex occurring in various animal and plant tissues. Required by the body for the formation of coenzymes NAD and NADP. Has pellagra-curative, vasodilating, and antilipemic properties. [NIH]

Nifedipine: A potent vasodilator agent with calcium antagonistic action. It is a useful anti-anginal agent that also lowers blood pressure. The use of nifedipine as a tocolytic is being investigated. [NIH]

Nitric Oxide: A free radical gas produced endogenously by a variety of mammalian cells. It is synthesized from arginine by a complex reaction, catalyzed by nitric oxide synthase. Nitric oxide is endothelium-derived relaxing factor. It is released by the vascular endothelium and mediates the relaxation induced by some vasodilators such as acetylcholine and bradykinin. It also inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium. Nitric oxide activates cytosolic guanylate cyclase and thus elevates intracellular levels of cyclic GMP. [NIH]

Nitrogen: An element with the atomic symbol N, atomic number 7, and atomic weight 14. Nitrogen exists as a diatomic gas and makes up about 78% of the earth's atmosphere by volume. It is a constituent of proteins and nucleic acids and found in all living cells. [NIH]

Norepinephrine: Precursor of epinephrine that is secreted by the adrenal medulla and is a widespread central and autonomic neurotransmitter. Norepinephrine is the principal transmitter of most postganglionic sympathetic fibers and of the diffuse projection system in the brain arising from the locus ceruleus. It is also found in plants and is used pharmacologically as a sympathomimetic. [NIH]

Nuclear: A test of the structure, blood flow, and function of the kidneys. The doctor injects a mildly radioactive solution into an arm vein and uses x-rays to monitor its progress through the kidneys. [NIH]

Nuclei: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nucleic acid: Either of two types of macromolecule (DNA or RNA) formed by polymerization of nucleotides. Nucleic acids are found in all living cells and contain the information (genetic code) for the transfer of genetic information from one generation to the next. [NIH]

Nucleic Acid Hybridization: The process whereby two single-stranded polynucleotides form a double-stranded molecule, with hydrogen bonding between the complementary bases in the two strains. [NIH]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Observational study: An epidemiologic study that does not involve any intervention, experimental or otherwise. Such a study may be one in which nature is allowed to take its course, with changes in one characteristic being studied in relation to changes in other characteristics. Analytical epidemiologic methods, such as case-control and cohort study designs, are properly called observational epidemiology because the investigator is observing without intervention other than to record, classify, count, and statistically analyze results. [NIH]

Oncogene: A gene that normally directs cell growth. If altered, an oncogene can promote or

allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure to carcinogens. [NIH]

Oncogenic: Chemical, viral, radioactive or other agent that causes cancer; carcinogenic. [NIH]

Operon: The genetic unit consisting of a feedback system under the control of an operator gene, in which a structural gene transcribes its message in the form of mRNA upon blockade of a repressor produced by a regulator gene. Included here is the attenuator site of bacterial operons where transcription termination is regulated. [NIH]

Opportunistic Infections: An infection caused by an organism which becomes pathogenic under certain conditions, e.g., during immunosuppression. [NIH]

Organ Culture: The growth in aseptic culture of plant organs such as roots or shoots, beginning with organ primordia or segments and maintaining the characteristics of the organ. [NIH]

Organelles: Specific particles of membrane-bound organized living substances present in eukaryotic cells, such as the mitochondria; the golgi apparatus; endoplasmic reticulum; lysomomes; plastids; and vacuoles. [NIH]

Ossification: The formation of bone or of a bony substance; the conversion of fibrous tissue or of cartilage into bone or a bony substance. [EU]

Ouabain: A cardioactive glycoside consisting of rhamnose and ouabagenin, obtained from the seeds of Strophanthus gratus and other plants of the Apocynaceae; used like digitalis. It is commonly used in cell biological studies as an inhibitor of the NA(+)-K(+)-exchanging atpase. [NIH]

Ovalbumin: An albumin obtained from the white of eggs. It is a member of the serpin superfamily. [NIH]

Overexpress: An excess of a particular protein on the surface of a cell. [NIH]

Ovum: A female germ cell extruded from the ovary at ovulation. [NIH]

Oxidants: Oxidizing agents or electron-accepting molecules in chemical reactions in which electrons are transferred from one molecule to another (oxidation-reduction). In vivo, it appears that phagocyte-generated oxidants function as tumor promoters or cocarcinogens rather than as complete carcinogens perhaps because of the high levels of endogenous antioxidant defenses. It is also thought that oxidative damage in joints may trigger the autoimmune response that characterizes the persistence of the rheumatoid disease process. [NIH]

Oxidation: The act of oxidizing or state of being oxidized. Chemically it consists in the increase of positive charges on an atom or the loss of negative charges. Most biological oxidations are accomplished by the removal of a pair of hydrogen atoms (dehydrogenation) from a molecule. Such oxidations must be accompanied by reduction of an acceptor molecule. Univalent o. indicates loss of one electron; divalent o., the loss of two electrons. [EU]

Oxidation-Reduction: A chemical reaction in which an electron is transferred from one molecule to another. The electron-donating molecule is the reducing agent or reductant; the electron-accepting molecule is the oxidizing agent or oxidant. Reducing and oxidizing agents function as conjugate reductant-oxidant pairs or redox pairs (Lehninger, Principles of Biochemistry, 1982, p471). [NIH]

Oxidative metabolism: A chemical process in which oxygen is used to make energy from carbohydrates (sugars). Also known as aerobic respiration, cell respiration, or aerobic metabolism. [NIH]

Oxidative Phosphorylation: Electron transfer through the cytochrome system liberating free

energy which is transformed into high-energy phosphate bonds. [NIH]

Oxidative Stress: A disturbance in the prooxidant-antioxidant balance in favor of the former, leading to potential damage. Indicators of oxidative stress include damaged DNA bases, protein oxidation products, and lipid peroxidation products (Sies, Oxidative Stress, 1991, pxv-xvi). [NIH]

Oxygen Consumption: The oxygen consumption is determined by calculating the difference between the amount of oxygen inhaled and exhaled. [NIH]

Pacemaker: An object or substance that influences the rate at which a certain phenomenon occurs; often used alone to indicate the natural cardiac pacemaker or an artificial cardiac pacemaker. In biochemistry, a substance whose rate of reaction sets the pace for a series of interrelated reactions. [EU]

Palliative: 1. Affording relief, but not cure. 2. An alleviating medicine. [EU]

Palsy: Disease of the peripheral nervous system occurring usually after many years of increased lead absorption. [NIH]

Pancreas: A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the Islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

Pancreatic: Having to do with the pancreas. [NIH]

Parasite: An animal or a plant that lives on or in an organism of another species and gets at least some of its nutrition from that other organism. [NIH]

Parasitic: Having to do with or being a parasite. A parasite is an animal or a plant that lives on or in an organism of another species and gets at least some of its nutrients from it. [NIH]

Parathyroid: 1. Situated beside the thyroid gland. 2. One of the parathyroid glands. 3. A sterile preparation of the water-soluble principle(s) of the parathyroid glands, ad-ministered parenterally as an antihypocalcaemic, especially in the treatment of acute hypoparathyroidism with tetany. [EU]

Parathyroid Glands: Two small paired endocrine glands in the region of the thyroid gland. They secrete parathyroid hormone and are concerned with the metabolism of calcium and phosphorus. [NIH]

Paroxysmal: Recurring in paroxysms (= spasms or seizures). [EU]

Particle: A tiny mass of material. [EU]

Pathologic: 1. Indicative of or caused by a morbid condition. 2. Pertaining to pathology (= branch of medicine that treats the essential nature of the disease, especially the structural and functional changes in tissues and organs of the body caused by the disease). [EU]

Pathologic Processes: The abnormal mechanisms and forms involved in the dysfunctions of tissues and organs. [NIH]

Pathologies: The study of abnormality, especially the study of diseases. [NIH]

Pathophysiology: Altered functions in an individual or an organ due to disease. [NIH]

Pedigree: A record of one's ancestors, offspring, siblings, and their offspring that may be used to determine the pattern of certain genes or disease inheritance within a family. [NIH]

Pelvis: The lower part of the abdomen, located between the hip bones. [NIH]

Pentoxifylline: A methylxanthine derivative that inhibits phosphodiesterase and affects blood rheology. It improves blood flow by increasing erythrocyte and leukocyte flexibility. It also inhibits platelet aggregation. Pentoxifylline modulates immunologic activity by

stimulating cytokine production. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Percutaneous: Performed through the skin, as injection of radiopacque material in radiological examination, or the removal of tissue for biopsy accomplished by a needle. [EU]

Perfusion: Bathing an organ or tissue with a fluid. In regional perfusion, a specific area of the body (usually an arm or a leg) receives high doses of anticancer drugs through a blood vessel. Such a procedure is performed to treat cancer that has not spread. [NIH]

Pericardium: The fibroserous sac surrounding the heart and the roots of the great vessels. [NIH]

Peripheral Nervous System: The nervous system outside of the brain and spinal cord. The peripheral nervous system has autonomic and somatic divisions. The autonomic nervous system includes the enteric, parasympathetic, and sympathetic subdivisions. The somatic nervous system includes the cranial and spinal nerves and their ganglia and the peripheral sensory receptors. [NIH]

Phagocyte: An immune system cell that can surround and kill microorganisms and remove dead cells. Phagocytes include macrophages. [NIH]

Pharmacodynamic: Is concerned with the response of living tissues to chemical stimuli, that is, the action of drugs on the living organism in the absence of disease. [NIH]

Pharmacologic: Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

Phenotype: The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

Phosphates: Inorganic salts of phosphoric acid. [NIH]

Phosphodiesterase: Effector enzyme that regulates the levels of a second messenger, the cyclic GMP. [NIH]

Phospholipases: A class of enzymes that catalyze the hydrolysis of phosphoglycerides or glycerophosphatidates. EC 3.1.-. [NIH]

Phospholipids: Lipids containing one or more phosphate groups, particularly those derived from either glycerol (phosphoglycerides; glycerophospholipids) or sphingosine (sphingolipids). They are polar lipids that are of great importance for the structure and function of cell membranes and are the most abundant of membrane lipids, although not stored in large amounts in the system. [NIH]

Phosphorus: A non-metallic element that is found in the blood, muscles, nevers, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

Phosphorylated: Attached to a phosphate group. [NIH]

Phosphorylation: The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

Physiologic: Having to do with the functions of the body. When used in the phrase "physiologic age," it refers to an age assigned by general health, as opposed to calendar age. [NIH]

Physiology: The science that deals with the life processes and functions of organismus, their cells, tissues, and organs. [NIH]

Picornavirus: Any of a group of tiny RNA-containing viruses including the enteroviruses and rhinoviruses. [NIH]

Pigmentation: Coloration or discoloration of a part by a pigment. [NIH]

Pilot study: The initial study examining a new method or treatment. [NIH]

Pituitary Gland: A small, unpaired gland situated in the sella turcica tissue. It is connected to the hypothalamus by a short stalk. [NIH]

Placenta: A highly vascular fetal organ through which the fetus absorbs oxygen and other nutrients and excretes carbon dioxide and other wastes. It begins to form about the eighth day of gestation when the blastocyst adheres to the decidua. [NIH]

Plants: Multicellular, eukaryotic life forms of the kingdom Plantae. They are characterized by a mainly photosynthetic mode of nutrition; essentially unlimited growth at localized regions of cell divisions (meristems); cellulose within cells providing rigidity; the absence of organs of locomotion; absense of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plasma: The clear, yellowish, fluid part of the blood that carries the blood cells. The proteins that form blood clots are in plasma. [NIH]

Plasma cells: A type of white blood cell that produces antibodies. [NIH]

Platelet Activation: A series of progressive, overlapping events triggered by exposure of the platelets to subendothelial tissue. These events include shape change, adhesiveness, aggregation, and release reactions. When carried through to completion, these events lead to the formation of a stable hemostatic plug. [NIH]

Platelet Aggregation: The attachment of platelets to one another. This clumping together can be induced by a number of agents (e.g., thrombin, collagen) and is part of the mechanism leading to the formation of a thrombus. [NIH]

Platelets: A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

Pneumonia: Inflammation of the lungs. [NIH]

Point Mutation: A mutation caused by the substitution of one nucleotide for another. This results in the DNA molecule having a change in a single base pair. [NIH]

Polymerase: An enzyme which catalyses the synthesis of DNA using a single DNA strand as a template. The polymerase copies the template in the 5'-3'direction provided that sufficient quantities of free nucleotides, dATP and dTTP are present. [NIH]

Polymorphic: Occurring in several or many forms; appearing in different forms at different stages of development. [EU]

Polymorphism: The occurrence together of two or more distinct forms in the same population. [NIH]

Polypeptide: A peptide which on hydrolysis yields more than two amino acids; called tripeptides, tetrapeptides, etc. according to the number of amino acids contained. [EU]

Polysaccharide: A type of carbohydrate. It contains sugar molecules that are linked together chemically. [NIH]

Pons: The part of the central nervous system lying between the medulla oblongata and the mesencephalon, ventral to the cerebellum, and consisting of a pars dorsalis and a pars ventralis. [NIH]

Posterior: Situated in back of, or in the back part of, or affecting the back or dorsal surface of the body. In lower animals, it refers to the caudal end of the body. [EU]

Postsynaptic: Nerve potential generated by an inhibitory hyperpolarizing stimulation. [NIH]

Post-translational: The cleavage of signal sequence that directs the passage of the protein

through a cell or organelle membrane. [NIH]

Potassium: An element that is in the alkali group of metals. It has an atomic symbol K, atomic number 19, and atomic weight 39.10. It is the chief cation in the intracellular fluid of muscle and other cells. Potassium ion is a strong electrolyte and it plays a significant role in the regulation of fluid volume and maintenance of the water-electrolyte balance. [NIH]

Potentiation: An overall effect of two drugs taken together which is greater than the sum of the effects of each drug taken alone. [NIH]

Practice Guidelines: Directions or principles presenting current or future rules of policy for the health care practitioner to assist him in patient care decisions regarding diagnosis, therapy, or related clinical circumstances. The guidelines may be developed by government agencies at any level, institutions, professional societies, governing boards, or by the convening of expert panels. The guidelines form a basis for the evaluation of all aspects of health care and delivery. [NIH]

Precipitating Factors: Factors associated with the definitive onset of a disease, illness, accident, behavioral response, or course of action. Usually one factor is more important or more obviously recognizable than others, if several are involved, and one may often be regarded as "necessary". Examples include exposure to specific disease; amount or level of an infectious organism, drug, or noxious agent, etc. [NIH]

Precipitation: The act or process of precipitating. [EU]

Precursor: Something that precedes. In biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another. [EU]

Preload: The tension in the heart muscle at the end of diastole (before the contraction). [EU]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

Prevalence: The total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time. [NIH]

Prion: Small proteinaceous infectious particles that resist inactivation by procedures modifying nucleic acids and contain an abnormal isoform of a cellular protein which is a major and necessary component. [NIH]

Probe: An instrument used in exploring cavities, or in the detection and dilatation of strictures, or in demonstrating the potency of channels; an elongated instrument for exploring or sounding body cavities. [NIH]

Progesterone: Pregn-4-ene-3,20-dione. The principal progestational hormone of the body, secreted by the corpus luteum, adrenal cortex, and placenta. Its chief function is to prepare the uterus for the reception and development of the fertilized ovum. It acts as an antiovulatory agent when administered on days 5-25 of the menstrual cycle. [NIH]

Prognostic factor: A situation or condition, or a characteristic of a patient, that can be used to estimate the chance of recovery from a disease, or the chance of the disease recurring (coming back). [NIH]

Progression: Increase in the size of a tumor or spread of cancer in the body. [NIH]

Progressive: Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

Proline: A non-essential amino acid that is synthesized from glutamic acid. It is an essential component of collagen and is important for proper functioning of joints and tendons. [NIH]

Promoter: A chemical substance that increases the activity of a carcinogenic process. [NIH]

Promotor: In an operon, a nucleotide sequence located at the operator end which contains all the signals for the correct initiation of genetic transcription by the RNA polymerase holoenzyme and determines the maximal rate of RNA synthesis. [NIH]

Prone: Having the front portion of the body downwards. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Propranolol: A widely used non-cardioselective beta-adrenergic antagonist. Propranolol is used in the treatment or prevention of many disorders including acute myocardial infarction, arrhythmias, angina pectoris, hypertension, hypertensive emergencies, hyperthyroidism, migraine, pheochromocytoma, menopause, and anxiety. [NIH]

Prostaglandin: Any of a group of components derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway that are extremely potent mediators of a diverse group of physiologic processes. The abbreviation for prostaglandin is PG; specific compounds are designated by adding one of the letters A through I to indicate the type of substituents found on the hydrocarbon skeleton and a subscript (1, 2 or 3) to indicate the number of double bonds in the hydrocarbon skeleton e.g., PGE2. The predominant naturally occurring prostaglandins all have two double bonds and are synthesized from arachidonic acid (5,8,11,14-eicosatetraenoic acid) by the pathway shown in the illustration. The 1 series and 3 series are produced by the same pathway with fatty acids having one fewer double bond (8,11,14-eicosatrienoic acid or one more double bond (5,8,11,14,17-eicosapentaenoic acid) than arachidonic acid. The subscript a or ß indicates the configuration at C-9 (a denotes a substituent below the plane of the ring, ß, above the plane). The naturally occurring PGF's have the a configuration, e.g., PGF2a. All of the prostaglandins act by binding to specific cell-surface receptors causing an increase in the level of the intracellular second messenger cyclic AMP (and in some cases cyclic GMP also). The effect produced by the cyclic AMP increase depends on the specific cell type. In some cases there is also a positive feedback effect. Increased cyclic AMP increases prostaglandin synthesis leading to further increases in cyclic AMP. [EU]

Prostaglandins A: (13E,15S)-15-Hydroxy-9-oxoprosta-10,13-dien-1-oic acid (PGA(1)); (5Z,13E,15S)-15-hydroxy-9-oxoprosta-5,10,13-trien-1-oic acid (PGA(2)); (5Z,13E,15S,17Z)-15-hydroxy-9-oxoprosta-5,10,13,17-tetraen-1-oic acid (PGA(3)). A group of naturally occurring secondary prostaglandins derived from PGE. PGA(1) and PGA(2) as well as their 19-hydroxy derivatives are found in many organs and tissues. [NIH]

Prosthesis: An artificial replacement of a part of the body. [NIH]

Protease: Proteinase (= any enzyme that catalyses the splitting of interior peptide bonds in a protein). [EU]

Protein C: A vitamin-K dependent zymogen present in the blood, which, upon activation by thrombin and thrombomodulin exerts anticoagulant properties by inactivating factors Va and VIIIa at the rate-limiting steps of thrombin formation. [NIH]

Protein Folding: A rapid biochemical reaction involved in the formation of proteins. It begins even before a protein has been completely synthesized and proceeds through discrete intermediates (primary, secondary, and tertiary structures) before the final structure (quaternary structure) is developed. [NIH]

Protein S: The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

Proteins: Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

Protein-Tyrosine Kinase: An enzyme that catalyzes the phosphorylation of tyrosine

residues in proteins with ATP or other nucleotides as phosphate donors. EC 2.7.1.112. [NIH]

Proteolytic: 1. Pertaining to, characterized by, or promoting proteolysis. 2. An enzyme that promotes proteolysis (= the splitting of proteins by hydrolysis of the peptide bonds with formation of smaller polypeptides). [EU]

Protons: Stable elementary particles having the smallest known positive charge, found in the nuclei of all elements. The proton mass is less than that of a neutron. A proton is the nucleus of the light hydrogen atom, i.e., the hydrogen ion. [NIH]

Protozoa: A subkingdom consisting of unicellular organisms that are the simplest in the animal kingdom. Most are free living. They range in size from submicroscopic to macroscopic. Protozoa are divided into seven phyla: Sarcomastigophora, Labyrinthomorpha, Apicomplexa, Microspora, Ascetospora, Myxozoa, and Ciliophora. [NIH]

Protozoal: Having to do with the simplest organisms in the animal kingdom. Protozoa are single-cell organisms, such as ameba, and are different from bacteria, which are not members of the animal kingdom. Some protozoa can be seen without a microscope. [NIH]

Protozoan: 1. Any individual of the protozoa; protozoon. 2. Of or pertaining to the protozoa; protozoal. [EU]

Proximal: Nearest; closer to any point of reference; opposed to distal. [EU]

Proxy: A person authorized to decide or act for another person, for example, a person having durable power of attorney. [NIH]

Psychiatric: Pertaining to or within the purview of psychiatry. [EU]

Psychiatry: The medical science that deals with the origin, diagnosis, prevention, and treatment of mental disorders. [NIH]

Psychic: Pertaining to the psyche or to the mind; mental. [EU]

Psychoactive: Those drugs which alter sensation, mood, consciousness or other psychological or behavioral functions. [NIH]

Public Health: Branch of medicine concerned with the prevention and control of disease and disability, and the promotion of physical and mental health of the population on the international, national, state, or municipal level. [NIH]

Public Policy: A course or method of action selected, usually by a government, from among alternatives to guide and determine present and future decisions. [NIH]

Publishing: "The business or profession of the commercial production and issuance of literature" (Webster's 3d). It includes the publisher, publication processes, editing and editors. Production may be by conventional printing methods or by electronic publishing. [NIH]

Pulmonary: Relating to the lungs. [NIH]

Pulmonary Artery: The short wide vessel arising from the conus arteriosus of the right ventricle and conveying unaerated blood to the lungs. [NIH]

Pulmonary hypertension: Abnormally high blood pressure in the arteries of the lungs. [NIH]

Pulse: The rhythmical expansion and contraction of an artery produced by waves of pressure caused by the ejection of blood from the left ventricle of the heart as it contracts. [NIH]

Pupil: The aperture in the iris through which light passes. [NIH]

Purines: A series of heterocyclic compounds that are variously substituted in nature and are known also as purine bases. They include adenine and guanine, constituents of nucleic acids, as well as many alkaloids such as caffeine and theophylline. Uric acid is the metabolic end product of purine metabolism. [NIH]

Quality of Life: A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment. [NIH]

Quaternary: 1. Fourth in order. 2. Containing four elements or groups. [EU]

Race: A population within a species which exhibits general similarities within itself, but is both discontinuous and distinct from other populations of that species, though not sufficiently so as to achieve the status of a taxon. [NIH]

Radiation: Emission or propagation of electromagnetic energy (waves/rays), or the waves/rays themselves; a stream of electromagnetic particles (electrons, neutrons, protons, alpha particles) or a mixture of these. The most common source is the sun. [NIH]

Radiation therapy: The use of high-energy radiation from x-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body in the area near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Also called radiotherapy. [NIH]

Radioactive: Giving off radiation. [NIH]

Radiofrequency ablation: The use of electrical current to destroy tissue. [NIH]

Radioisotope: An unstable element that releases radiation as it breaks down. Radioisotopes can be used in imaging tests or as a treatment for cancer. [NIH]

Radioisotope Renography: Graphic tracing over a time period of radioactivity measured externally over the kidneys following intravenous injection of a radionuclide which is taken up and excreted by the kidneys. [NIH]

Radiological: Pertaining to radiodiagnostic and radiotherapeutic procedures, and interventional radiology or other planning and guiding medical radiology. [NIH]

Radionuclide Angiography: The measurement of visualization by radiation of any organ after a radionuclide has been injected into its blood supply. It is used to diagnose heart, liver, lung, and other diseases and to measure the function of those organs, except renography, for which radioisotope renography is available. [NIH]

Randomized: Describes an experiment or clinical trial in which animal or human subjects are assigned by chance to separate groups that compare different treatments. [NIH]

Randomized clinical trial: A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial. [NIH]

Reactivation: The restoration of activity to something that has been inactivated. [EU]

Reactive Oxygen Species: Reactive intermediate oxygen species including both radicals and non-radicals. These substances are constantly formed in the human body and have been shown to kill bacteria and inactivate proteins, and have been implicated in a number of diseases. Scientific data exist that link the reactive oxygen species produced by inflammatory phagocytes to cancer development. [NIH]

Receptor: A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell. [NIH]

Recombinant: A cell or an individual with a new combination of genes not found together

in either parent; usually applied to linked genes. [EU]

Recombination: The formation of new combinations of genes as a result of segregation in crosses between genetically different parents; also the rearrangement of linked genes due to crossing-over. [NIH]

Rectum: The last 8 to 10 inches of the large intestine. [NIH]

Red Nucleus: A pinkish-yellow portion of the midbrain situated in the rostral mesencephalic tegmentum. It receives a large projection from the contralateral half of the cerebellum via the superior cerebellar peduncle and a projection from the ipsilateral motor cortex. [NIH]

Refer: To send or direct for treatment, aid, information, de decision. [NIH]

Reflective: Capable of throwing back light, images, sound waves : reflecting. [EU]

Reflex: An involuntary movement or exercise of function in a part, excited in response to a stimulus applied to the periphery and transmitted to the brain or spinal cord. [NIH]

Refraction: A test to determine the best eyeglasses or contact lenses to correct a refractive error (myopia, hyperopia, or astigmatism). [NIH]

Refractory: Not readily yielding to treatment. [EU]

Regeneration: The natural renewal of a structure, as of a lost tissue or part. [EU]

Regimen: A treatment plan that specifies the dosage, the schedule, and the duration of treatment. [NIH]

Regurgitation: A backward flowing, as the casting up of undigested food, or the backward flowing of blood into the heart, or between the chambers of the heart when a valve is incompetent. [EU]

Relaxant: 1. Lessening or reducing tension. 2. An agent that lessens tension. [EU]

Renal cell carcinoma: A type of kidney cancer. [NIH]

Renin: An enzyme which is secreted by the kidney and is formed from prorenin in plasma and kidney. The enzyme cleaves the Leu-Leu bond in angiotensinogen to generate angiotensin I. EC 3.4.23.15. (Formerly EC 3.4.99.19). [NIH]

Renin-Angiotensin System: A system consisting of renin, angiotensin-converting enzyme, and angiotensin II. Renin, an enzyme produced in the kidney, acts on angiotensinogen, an alpha-2 globulin produced by the liver, forming angiotensin I. The converting enzyme contained in the lung acts on angiotensin I in the plasma converting it to angiotensin II, the most powerful directly pressor substance known. It causes contraction of the arteriolar smooth muscle and has other indirect actions mediated through the adrenal cortex. [NIH]

Reperfusion: Restoration of blood supply to tissue which is ischemic due to decrease in normal blood supply. The decrease may result from any source including atherosclerotic obstruction, narrowing of the artery, or surgical clamping. It is primarily a procedure for treating infarction or other ischemia, by enabling viable ischemic tissue to recover, thus limiting further necrosis. However, it is thought that reperfusion can itself further damage the ischemic tissue, causing reperfusion injury. [NIH]

Reperfusion Injury: Functional, metabolic, or structural changes, including necrosis, in ischemic tissues thought to result from reperfusion to ischemic areas of the tissue. The most common instance is myocardial reperfusion injury. [NIH]

Repressor: Any of the specific allosteric protein molecules, products of regulator genes, which bind to the operator of operons and prevent RNA polymerase from proceeding into the operon to transcribe messenger RNA. [NIH]

Repressor Proteins: Proteins which are normally bound to the operator locus of an operon,

thereby preventing transcription of the structural genes. In enzyme induction, the substrate of the inducible enzyme binds to the repressor protein, causing its release from the operator and freeing the structural genes for transcription. In enzyme repression, the end product of the enzyme sequence binds to the free repressor protein, the resulting complex then binds to the operator and prevents transcription of the structural genes. [NIH]

Resection: Removal of tissue or part or all of an organ by surgery. [NIH]

Respiration: The act of breathing with the lungs, consisting of inspiration, or the taking into the lungs of the ambient air, and of expiration, or the expelling of the modified air which contains more carbon dioxide than the air taken in (Blakiston's Gould Medical Dictionary, 4th ed.). This does not include tissue respiration (= oxygen consumption) or cell respiration (= cell respiration). [NIH]

Respiratory Muscles: These include the muscles of the diaphragm and the intercostal muscles. [NIH]

Respiratory Physiology: Functions and activities of the respiratory tract as a whole or of any of its parts. [NIH]

Response Elements: Nucleotide sequences, usually upstream, which are recognized by specific regulatory transcription factors, thereby causing gene response to various regulatory agents. These elements may be found in both promotor and enhancer regions. [NIH]

Restrictive cardiomyopathy: Heart muscle disease in which the muscle walls become stiff and lose their flexibility. [NIH]

Retinoid: Vitamin A or a vitamin A-like compound. [NIH]

Retroperitoneal: Having to do with the area outside or behind the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). [NIH]

Retrospective: Looking back at events that have already taken place. [NIH]

Retrospective study: A study that looks backward in time, usually using medical records and interviews with patients who already have or had a disease. [NIH]

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [NIH]

Rhamnose: A methylpentose whose L- isomer is found naturally in many plant glycosides and some gram-negative bacterial lipopolysaccharides. [NIH]

Rheology: The study of the deformation and flow of matter, usually liquids or fluids, and of the plastic flow of solids. The concept covers consistency, dilatancy, liquefaction, resistance to flow, shearing, thixotrophy, and viscosity. [NIH]

Rheumatoid: Resembling rheumatism. [EU]

Rheumatoid arthritis: A form of arthritis, the cause of which is unknown, although infection, hypersensitivity, hormone imbalance and psychologic stress have been suggested as possible causes. [NIH]

Ribose: A pentose active in biological systems usually in its D-form. [NIH]

Ribosome: A granule of protein and RNA, synthesized in the nucleolus and found in the cytoplasm of cells. Ribosomes are the main sites of protein synthesis. Messenger RNA attaches to them and there receives molecules of transfer RNA bearing amino acids. [NIH]

Rickets: A condition caused by deficiency of vitamin D, especially in infancy and childhood, with disturbance of normal ossification. The disease is marked by bending and distortion of the bones under muscular action, by the formation of nodular enlargements on the ends and sides of the bones, by delayed closure of the fontanelles, pain in the muscles, and sweating of the head. Vitamin D and sunlight together with an adequate diet are curative, provided

that the parathyroid glands are functioning properly. [EU]

Rigidity: Stiffness or inflexibility, chiefly that which is abnormal or morbid; rigor. [EU]

Risk factor: A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

Risk patient: Patient who is at risk, because of his/her behaviour or because of the type of person he/she is. [EU]

Rod: A reception for vision, located in the retina. [NIH]

Ryanodine: Insecticidal alkaloid isolated from Ryania speciosa; proposed as a myocardial depressant. [NIH]

Saline: A solution of salt and water. [NIH]

Saphenous: Applied to certain structures in the leg, e. g. nerve vein. [NIH]

Saphenous Vein: The vein which drains the foot and leg. [NIH]

Sarcolemma: The plasma membrane of a smooth, striated, or cardiac muscle fiber. [NIH]

Sarcomere: The repeating structural unit of a striated muscle fiber. [NIH]

Sarcoplasmic Reticulum: A network of tubules and sacs in the cytoplasm of skeletal muscles that assist with muscle contraction and relaxation by releasing and storing calcium ions. [NIH]

Scans: Pictures of structures inside the body. Scans often used in diagnosing, staging, and monitoring disease include liver scans, bone scans, and computed tomography (CT) or computerized axial tomography (CAT) scans and magnetic resonance imaging (MRI) scans. In liver scanning and bone scanning, radioactive substances that are injected into the bloodstream collect in these organs. A scanner that detects the radiation is used to create pictures. In CT scanning, an x-ray machine linked to a computer is used to produce detailed pictures of organs inside the body. MRI scans use a large magnet connected to a computer to create pictures of areas inside the body. [NIH]

Schizoid: Having qualities resembling those found in greater degree in schizophrenics; a person of schizoid personality. [NIH]

Schizophrenia: A mental disorder characterized by a special type of disintegration of the personality. [NIH]

Schizotypal Personality Disorder: A personality disorder in which there are oddities of thought (magical thinking, paranoid ideation, suspiciousness), perception (illusions, depersonalization), speech (digressive, vague, overelaborate), and behavior (inappropriate affect in social interactions, frequently social isolation) that are not severe enough to characterize schizophrenia. [NIH]

Sclerosis: A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Secretion: 1. The process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the elaboration of a new chemical substance. 2. Any substance produced by secretion. [EU]

Segmental: Describing or pertaining to a structure which is repeated in similar form in successive segments of an organism, or which is undergoing segmentation. [NIH]

Segmentation: The process by which muscles in the intestines move food and wastes through the body. [NIH]

Selenium: An element with the atomic symbol Se, atomic number 34, and atomic weight

78.96. It is an essential micronutrient for mammals and other animals but is toxic in large amounts. Selenium protects intracellular structures against oxidative damage. It is an essential component of glutathione peroxidase. [NIH]

Sensor: A device designed to respond to physical stimuli such as temperature, light, magnetism or movement and transmit resulting impulses for interpretation, recording, movement, or operating control. [NIH]

Septal: An abscess occurring at the root of the tooth on the proximal surface. [NIH]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [NIH]

Serotonin: A biochemical messenger and regulator, synthesized from the essential amino acid L-tryptophan. In humans it is found primarily in the central nervous system, gastrointestinal tract, and blood platelets. Serotonin mediates several important physiological functions including neurotransmission, gastrointestinal motility, hemostasis, and cardiovascular integrity. Multiple receptor families (receptors, serotonin) explain the broad physiological actions and distribution of this biochemical mediator. [NIH]

Serous: Having to do with serum, the clear liquid part of blood. [NIH]

Serum: The clear liquid part of the blood that remains after blood cells and clotting proteins have been removed. [NIH]

Sex Characteristics: Those characteristics that distinguish one sex from the other. The primary sex characteristics are the ovaries and testes and their related hormones. Secondary sex characteristics are those which are masculine or feminine but not directly related to reproduction. [NIH]

Side effect: A consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration. [EU]

Signal Transduction: The intercellular or intracellular transfer of information (biological activation/inhibition) through a signal pathway. In each signal transduction system, an activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter) is mediated via the coupling of a receptor/enzyme to a second messenger system or to an ion channel. Signal transduction plays an important role in activating cellular functions, cell differentiation, and cell proliferation. Examples of signal transduction systems are the GABA-postsynaptic receptor-calcium ion channel system, the receptor-mediated T-cell activation pathway, and the receptor-mediated activation of phospholipases. Those coupled to membrane depolarization or intracellular release of calcium include the receptor-mediated activation of cytotoxic functions in granulocytes and the synaptic potentiation of protein kinase activation. Some signal transduction pathways may be part of larger signal transduction pathways; for example, protein kinase activation is part of the platelet activation signal pathway. [NIH]

Skeletal: Having to do with the skeleton (boney part of the body). [NIH]

Skeleton: The framework that supports the soft tissues of vertebrate animals and protects many of their internal organs. The skeletons of vertebrates are made of bone and/or cartilage. [NIH]

Skull: The skeleton of the head including the bones of the face and the bones enclosing the brain. [NIH]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Social Environment: The aggregate of social and cultural institutions, forms, patterns, and processes that influence the life of an individual or community. [NIH]

Sodium: An element that is a member of the alkali group of metals. It has the atomic symbol Na, atomic number 11, and atomic weight 23. With a valence of 1, it has a strong affinity for oxygen and other nonmetallic elements. Sodium provides the chief cation of the extracellular body fluids. Its salts are the most widely used in medicine. (From Dorland, 27th ed) Physiologically the sodium ion plays a major role in blood pressure regulation, maintenance of fluid volume, and electrolyte balance. [NIH]

Solid tumor: Cancer of body tissues other than blood, bone marrow, or the lymphatic system. [NIH]

Solvent: 1. Dissolving; effecting a solution. 2. A liquid that dissolves or that is capable of dissolving; the component of a solution that is present in greater amount. [EU]

Soma: The body as distinct from the mind; all the body tissue except the germ cells; all the axial body. [NIH]

Somatic: 1. Pertaining to or characteristic of the soma or body. 2. Pertaining to the body wall in contrast to the viscera. [EU]

Sound wave: An alteration of properties of an elastic medium, such as pressure, particle displacement, or density, that propagates through the medium, or a superposition of such alterations. [NIH]

Spasm: An involuntary contraction of a muscle or group of muscles. Spasms may involve skeletal muscle or smooth muscle. [NIH]

Specialist: In medicine, one who concentrates on 1 special branch of medical science. [NIH]

Species: A taxonomic category subordinate to a genus (or subgenus) and superior to a subspecies or variety, composed of individuals possessing common characters distinguishing them from other categories of individuals of the same taxonomic level. In taxonomic nomenclature, species are designated by the genus name followed by a Latin or Latinized adjective or noun. [EU]

Specificity: Degree of selectivity shown by an antibody with respect to the number and types of antigens with which the antibody combines, as well as with respect to the rates and the extents of these reactions. [NIH]

Spectrin: A high molecular weight (220-250 kDa) water-soluble protein which can be extracted from erythrocyte ghosts in low ionic strength buffers. The protein contains no lipids or carbohydrates, is the predominant species of peripheral erythrocyte membrane proteins, and exists as a fibrous coating on the inner, cytoplasmic surface of the membrane. [NIH]

Spectrum: A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

Sperm: The fecundating fluid of the male. [NIH]

Spinal cord: The main trunk or bundle of nerves running down the spine through holes in the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]

Spleen: An organ that is part of the lymphatic system. The spleen produces lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach. [NIH]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Staging: Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. [NIH]

Steady state: Dynamic equilibrium. [EU]

Steel: A tough, malleable, iron-based alloy containing up to, but no more than, two percent carbon and often other metals. It is used in medicine and dentistry in implants and instrumentation. [NIH]

Stem Cells: Relatively undifferentiated cells of the same lineage (family type) that retain the ability to divide and cycle throughout postnatal life to provide cells that can become specialized and take the place of those that die or are lost. [NIH]

Steroids: Drugs used to relieve swelling and inflammation. [NIH]

Stimulant: 1. Producing stimulation; especially producing stimulation by causing tension on muscle fibre through the nervous tissue. 2. An agent or remedy that produces stimulation. [EU]

Stimulus: That which can elicit or evoke action (response) in a muscle, nerve, gland or other excitable issue, or cause an augmenting action upon any function or metabolic process. [NIH]

Stomach: An organ of digestion situated in the left upper quadrant of the abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

Stress: Forcibly exerted influence; pressure. Any condition or situation that causes strain or tension. Stress may be either physical or psychologic, or both. [NIH]

Stroke: Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

Stroke Volume: The amount of blood pumped out of the heart per beat not to be confused with cardiac output (volume/time). [NIH]

Subacute: Somewhat acute; between acute and chronic. [EU]

Subclinical: Without clinical manifestations; said of the early stage(s) of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests, or of a very mild form of an infection or other disease or abnormality. [EU]

Subcutaneous: Beneath the skin. [NIH]

Subspecies: A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

Substrate: A substance upon which an enzyme acts. [EU]

Sudden cardiac death: Cardiac arrest caused by an irregular heartbeat. [NIH]

Sudden death: Cardiac arrest caused by an irregular heartbeat. The term "death" is somewhat misleading, because some patients survive. [NIH]

Superior vena cava: Vein which returns blood from the head and neck, upper limbs, and thorax. It is formed by the union of the two brachiocephalic veins. [NIH]

Superoxide: Derivative of molecular oxygen that can damage cells. [NIH]

Superoxide Dismutase: An oxidoreductase that catalyzes the reaction between superoxide anions and hydrogen to yield molecular oxygen and hydrogen peroxide. The enzyme protects the cell against dangerous levels of superoxide. EC 1.15.1.1. [NIH]

Supplementation: Adding nutrients to the diet. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in

which the process of exclusion is not conscious. [NIH]

Supraventricular: Situated or occurring above the ventricles, especially in an atrium or atrioventricular node. [EU]

Sympathetic Nervous System: The thoracolumbar division of the autonomic nervous system. Sympathetic preganglionic fibers originate in neurons of the intermediolateral column of the spinal cord and project to the paravertebral and prevertebral ganglia, which in turn project to target organs. The sympathetic nervous system mediates the body's response to stressful situations, i.e., the fight or flight reactions. It often acts reciprocally to the parasympathetic system. [NIH]

Sympathomimetic: 1. Mimicking the effects of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. 2. An agent that produces effects similar to those of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. Called also adrenergic. [EU]

Symptomatic: Having to do with symptoms, which are signs of a condition or disease. [NIH]

Symptomatic treatment: Therapy that eases symptoms without addressing the cause of disease. [NIH]

Synapse: The region where the processes of two neurons come into close contiguity, and the nervous impulse passes from one to the other; the fibers of the two are intermeshed, but, according to the general view, there is no direct contiguity. [NIH]

Synaptic: Pertaining to or affecting a synapse (= site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means); pertaining to synapsis (= pairing off in point-for-point association of homologous chromosomes from the male and female pronuclei during the early prophase of meiosis). [EU]

Syncope: A temporary suspension of consciousness due to generalized cerebral schemia, a faint or swoon. [EU]

Synergistic: Acting together; enhancing the effect of another force or agent. [EU]

Systemic: Affecting the entire body. [NIH]

Systemic lupus erythematosus: SLE. A chronic inflammatory connective tissue disease marked by skin rashes, joint pain and swelling, inflammation of the kidneys, inflammation of the fibrous tissue surrounding the heart (i.e., the pericardium), as well as other problems. Not all affected individuals display all of these problems. May be referred to as lupus. [NIH]

Systole: Period of contraction of the heart, especially of the ventricles. [NIH]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

Systolic heart failure: Inability of the heart to contract with enough force to pump adequate amounts of blood through the body. [NIH]

Tachycardia: Excessive rapidity in the action of the heart, usually with a heart rate above 100 beats per minute. [NIH]

Taurine: 2-Aminoethanesulfonic acid. A conditionally essential nutrient, important during mammalian development. It is present in milk but is isolated mostly from ox bile and strongly conjugates bile acids. [NIH]

Temporal: One of the two irregular bones forming part of the lateral surfaces and base of the skull, and containing the organs of hearing. [NIH]

Teratogenic: Tending to produce anomalies of formation, or teratism (= anomaly of formation or development : condition of a monster). [EU]

Teratogenicity: The power to cause abnormal development. [NIH]

Terminator: A DNA sequence sited at the end of a transcriptional unit that signals the end of transcription. [NIH]

Testosterone: A hormone that promotes the development and maintenance of male sex characteristics. [NIH]

Tetracycline: An antibiotic originally produced by Streptomyces viridifaciens, but used mostly in synthetic form. It is an inhibitor of aminoacyl-tRNA binding during protein synthesis. [NIH]

Thalamic: Cell that reaches the lateral nucleus of amygdala. [NIH]

Thalamic Diseases: Disorders of the centrally located thalamus, which integrates a wide range of cortical and subcortical information. Manifestations include sensory loss, movement disorders; ataxia, pain syndromes, visual disorders, a variety of neuropsychological conditions, and coma. Relatively common etiologies include cerebrovascular disorders; craniocerebral trauma; brain neoplasms; brain hypoxia; intracranial hemorrhages; and infectious processes. [NIH]

Therapeutics: The branch of medicine which is concerned with the treatment of diseases, palliative or curative. [NIH]

Thoracic: Having to do with the chest. [NIH]

Threonine: An essential amino acid occurring naturally in the L-form, which is the active form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

Threshold: For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [NIH]

Thrombin: An enzyme formed from prothrombin that converts fibrinogen to fibrin. (Dorland, 27th ed) EC 3.4.21.5. [NIH]

Thrombocytopenia: A decrease in the number of blood platelets. [NIH]

Thromboembolism: Obstruction of a vessel by a blood clot that has been transported from a distant site by the blood stream. [NIH]

Thrombomodulin: A cell surface glycoprotein of endothelial cells that binds thrombin and serves as a cofactor in the activation of protein C and its regulation of blood coagulation. [NIH]

Thrombosis: The formation or presence of a blood clot inside a blood vessel. [NIH]

Thymus: An organ that is part of the lymphatic system, in which T lymphocytes grow and multiply. The thymus is in the chest behind the breastbone. [NIH]

Thyroid: A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

Thyroid Gland: A highly vascular endocrine gland consisting of two lobes, one on either side of the trachea, joined by a narrow isthmus; it produces the thyroid hormones which are concerned in regulating the metabolic rate of the body. [NIH]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

Tissue Culture: Maintaining or growing of tissue, organ primordia, or the whole or part of an organ in vitro so as to preserve its architecture and/or function (Dorland, 28th ed). Tissue culture includes both organ culture and cell culture. [NIH]

Tolerance: 1. The ability to endure unusually large doses of a drug or toxin. 2. Acquired

drug tolerance; a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response. [EU]

Tone: 1. The normal degree of vigour and tension; in muscle, the resistance to passive elongation or stretch; tonus. 2. A particular quality of sound or of voice. 3. To make permanent, or to change, the colour of silver stain by chemical treatment, usually with a heavy metal. [EU]

Tonus: A state of slight tension usually present in muscles even when they are not undergoing active contraction. [NIH]

Tooth Preparation: Procedures carried out with regard to the teeth or tooth structures preparatory to specified dental therapeutic and surgical measures. [NIH]

Topical: On the surface of the body. [NIH]

Toxic: Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects. [NIH]

Toxicity: The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. [EU]

Toxicology: The science concerned with the detection, chemical composition, and pharmacologic action of toxic substances or poisons and the treatment and prevention of toxic manifestations. [NIH]

Toxin: A poison; frequently used to refer specifically to a protein produced by some higher plants, certain animals, and pathogenic bacteria, which is highly toxic for other living organisms. Such substances are differentiated from the simple chemical poisons and the vegetable alkaloids by their high molecular weight and antigenicity. [EU]

Trace element: Substance or element essential to plant or animal life, but present in extremely small amounts. [NIH]

Trachea: The cartilaginous and membranous tube descending from the larynx and branching into the right and left main bronchi. [NIH]

Traction: The act of pulling. [NIH]

Transcription Factors: Endogenous substances, usually proteins, which are effective in the initiation, stimulation, or termination of the genetic transcription process. [NIH]

Transduction: The transfer of genes from one cell to another by means of a viral (in the case of bacteria, a bacteriophage) vector or a vector which is similar to a virus particle (pseudovirion). [NIH]

Transfection: The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

Transfer Factor: Factor derived from leukocyte lysates of immune donors which can transfer both local and systemic cellular immunity to nonimmune recipients. [NIH]

Transferases: Transferases are enzymes transferring a group, for example, the methyl group or a glycosyl group, from one compound (generally regarded as donor) to another compound (generally regarded as acceptor). The classification is based on the scheme "donor:acceptor group transferase". (Enzyme Nomenclature, 1992) EC 2. [NIH]

Transgenes: Genes that are introduced into an organism using gene transfer techniques. [NIH]

Translation: The process whereby the genetic information present in the linear sequence of ribonucleotides in mRNA is converted into a corresponding sequence of amino acids in a protein. It occurs on the ribosome and is unidirectional. [NIH]

Translational: The cleavage of signal sequence that directs the passage of the protein

through a cell or organelle membrane. [NIH]

Translocation: The movement of material in solution inside the body of the plant. [NIH]

Transmitter: A chemical substance which effects the passage of nerve impulses from one cell to the other at the synapse. [NIH]

Transplantation: Transference of a tissue or organ, alive or dead, within an individual, between individuals of the same species, or between individuals of different species. [NIH]

Transposition of Great Vessels: A congenital cardiovascular malformation in which the aorta arises entirely from the right ventricle and the pulmonary artery from the left ventricle, so that the venous return from the peripheral circulation is recirculated by the right ventricle via the aorta to the systemic circulation without being oxygenated in the lungs. [NIH]

Trauma: Any injury, wound, or shock, must frequently physical or structural shock, producing a disturbance. [NIH]

Triad: Trivalent. [NIH]

Trigger zone: Dolorogenic zone (= producing or causing pain). [EU]

Tropomyosin: A protein found in the thin filaments of muscle fibers. It inhibits contraction of the muscle unless its position is modified by troponin. [NIH]

Troponin: One of the minor protein components of skeletal muscle. Its function is to serve as the calcium-binding component in the troponin-tropomyosin B-actin-myosin complex by conferring calcium sensitivity to the cross-linked actin and myosin filaments. [NIH]

Troponin C: One of the three polypeptide chains that make up the troponin complex of skeletal muscle. It is a calcium-binding protein. [NIH]

Troponin T: One of the three polypeptide chains that make up the troponin complex. It is a cardiac-specific protein that binds to tropomyosin. It is released from only damaged or injured heart tissue and cells. [NIH]

Tryptophan: An essential amino acid that is necessary for normal growth in infants and for nitrogen balance in adults. It is a precursor serotonin and niacin. [NIH]

Tuberculosis: Any of the infectious diseases of man and other animals caused by species of Mycobacterium. [NIH]

Tumor Necrosis Factor: Serum glycoprotein produced by activated macrophages and other mammalian mononuclear leukocytes which has necrotizing activity against tumor cell lines and increases ability to reject tumor transplants. It mimics the action of endotoxin but differs from it. It has a molecular weight of less than 70,000 kDa. [NIH]

Ubiquitin: A highly conserved 76 amino acid-protein found in all eukaryotic cells. [NIH]

Ultrasonography: The visualization of deep structures of the body by recording the reflections of echoes of pulses of ultrasonic waves directed into the tissues. Use of ultrasound for imaging or diagnostic purposes employs frequencies ranging from 1.6 to 10 megahertz. [NIH]

Urethra: The tube through which urine leaves the body. It empties urine from the bladder. [NIH]

Uric: A kidney stone that may result from a diet high in animal protein. When the body breaks down this protein, uric acid levels rise and can form stones. [NIH]

Urinary: Having to do with urine or the organs of the body that produce and get rid of urine. [NIH]

Urinate: To release urine from the bladder to the outside. [NIH]

Urine: Fluid containing water and waste products. Urine is made by the kidneys, stored in

the bladder, and leaves the body through the urethra. [NIH]

Uterus: The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a fetus develops. Also called the womb. [NIH]

Vaccine: A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. [NIH]

Vacuoles: Any spaces or cavities within a cell. They may function in digestion, storage, secretion, or excretion. [NIH]

Valves: Flap-like structures that control the direction of blood flow through the heart. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vascular endothelial growth factor: VEGF. A substance made by cells that stimulates new blood vessel formation. [NIH]

Vascular Resistance: An expression of the resistance offered by the systemic arterioles, and to a lesser extent by the capillaries, to the flow of blood. [NIH]

Vasoconstriction: Narrowing of the blood vessels without anatomic change, for which constriction, pathologic is used. [NIH]

Vasodilation: Physiological dilation of the blood vessels without anatomic change. For dilation with anatomic change, dilatation, pathologic or aneurysm (or specific aneurysm) is used. [NIH]

Vasodilator: An agent that widens blood vessels. [NIH]

Vector: Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

Vein: Vessel-carrying blood from various parts of the body to the heart. [NIH]

Vena: A vessel conducting blood from the capillary bed to the heart. [NIH]

Venous: Of or pertaining to the veins. [EU]

Venous blood: Blood that has given up its oxygen to the tissues and carries carbon dioxide back for gas exchange. [NIH]

Venter: Belly. [NIH]

Ventilation: 1. In respiratory physiology, the process of exchange of air between the lungs and the ambient air. Pulmonary ventilation (usually measured in litres per minute) refers to the total exchange, whereas alveolar ventilation refers to the effective ventilation of the alveoli, in which gas exchange with the blood takes place. 2. In psychiatry, verbalization of one's emotional problems. [EU]

Ventral: 1. Pertaining to the belly or to any venter. 2. Denoting a position more toward the belly surface than some other object of reference; same as anterior in human anatomy. [EU]

Ventricle: One of the two pumping chambers of the heart. The right ventricle receives oxygen-poor blood from the right atrium and pumps it to the lungs through the pulmonary artery. The left ventricle receives oxygen-rich blood from the left atrium and pumps it to the body through the aorta. [NIH]

Ventricular: Pertaining to a ventricle. [EU]

Ventricular Dysfunction: A condition in which the ventricles of the heart exhibit a decreased functionality. [NIH]

Ventricular fibrillation: Rapid, irregular quivering of the heart's ventricles, with no effective heartbeat. [NIH]

Ventricular Function: The hemodynamic and electrophysiological action of the ventricles.

[NIH]

Ventricular Pressure: The pressure within a cardiac ventricle. Ventricular pressure waveforms can be measured in the beating heart by catheterization or estimated using imaging techniques (e.g., Doppler echocardiography). The information is useful in evaluating the function of the myocardium, cardiac valves, and pericardium, particularly with simultaneous measurement of other (e.g., aortic or atrial) pressures. [NIH]

Ventricular Remodeling: The geometric and structural changes that the ventricle undergoes, usually following myocardial infarction. It comprises expansion of the infarct and dilatation of the healthy ventricle segments. While most prevalent in the left ventricle, it can also occur in the right ventricle. [NIH]

Venules: The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

Vesicular: 1. Composed of or relating to small, saclike bodies. 2. Pertaining to or made up of vesicles on the skin. [EU]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Vinculin: A cytoskeletal protein associated with cell-cell and cell-matrix interactions. The amino acid sequence of human vinculin has been determined. The protein consists of 1066 amino acid residues and its gene has been assigned to chromosome 10. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

Viral Proteins: Proteins found in any species of virus. [NIH]

Virulence: The degree of pathogenicity within a group or species of microorganisms or viruses as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. [NIH]

Virus: Submicroscopic organism that causes infectious disease. In cancer therapy, some viruses may be made into vaccines that help the body build an immune response to, and kill, tumor cells. [NIH]

Viscera: Any of the large interior organs in any one of the three great cavities of the body, especially in the abdomen. [NIH]

Visceral: , from viscus a viscus) pertaining to a viscus. [EU]

Vitamin D: The vitamin that mediates intestinal calcium absorption, bone calcium metabolism, and probably muscle activity. It usually acts as a hormone precursor, requiring 2 stages of metabolism before reaching actual hormonal form. It is isolated from fish liver oils and used in the treatment and prevention of rickets. [NIH]

Vitro: Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

Vivo: Outside of or removed from the body of a living organism. [NIH]

White blood cell: A type of cell in the immune system that helps the body fight infection and disease. White blood cells include lymphocytes, granulocytes, macrophages, and others. [NIH]

Windpipe: A rigid tube, 10 cm long, extending from the cricoid cartilage to the upper border of the fifth thoracic vertebra. [NIH]

Withdrawal: 1. A pathological retreat from interpersonal contact and social involvement, as may occur in schizophrenia, depression, or schizoid avoidant and schizotypal personality disorders. 2. (DSM III-R) A substance-specific organic brain syndrome that follows the

cessation of use or reduction in intake of a psychoactive substance that had been regularly used to induce a state of intoxication. [EU]

Wound Healing: Restoration of integrity to traumatized tissue. [NIH]

Xanthine: An urinary calculus. [NIH]

Xanthine Oxidase: An iron-molybdenum flavoprotein containing FAD that oxidizes hypoxanthine, some other purines and pterins, and aldehydes. Deficiency of the enzyme, an autosomal recessive trait, causes xanthinuria. EC 1.1.3.22. [NIH]

Xenograft: The cells of one species transplanted to another species. [NIH]

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

Yeasts: A general term for single-celled rounded fungi that reproduce by budding. Brewers' and bakers' yeasts are Saccharomyces cerevisiae; therapeutic dried yeast is dried yeast. [NIH]

Zebrafish: A species of North American fishes of the family Cyprinidae. They are used in embryological studies and to study the effects of certain chemicals on development. [NIH]

Zidovudine: A dideoxynucleoside compound in which the 3'-hydroxy group on the sugar moiety has been replaced by an azido group. This modification prevents the formation of phosphodiester linkages which are needed for the completion of nucleic acid chains. The compound is a potent inhibitor of HIV replication, acting as a chain-terminator of viral DNA during reverse transcription. It improves immunologic function, partially reverses the HIV-induced neurological dysfunction, and improves certain other clinical abnormalities associated with AIDS. Its principal toxic effect is dose-dependent suppression of bone marrow, resulting in anemia and leukopenia. [NIH]

Zymogen: Inactive form of an enzyme which can then be converted to the active form, usually by excision of a polypeptide, e. g. trypsinogen is the zymogen of trypsin. [NIH]

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