

CYTOMEGALOVIRUS

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



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AND PHILIP M. PARKER, PH.D., EDITORS

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The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on cytomegalovirus. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.

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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 cytomegalovirus 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 cytomegalovirus, 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 cytomegalovirus, 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 cytomegalovirus. 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 cytomegalovirus, 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 cytomegalovirus.

The Editors

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

CHAPTER 1. STUDIES ON CYTOMEGALOVIRUS

Overview

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

The Combined Health Information Database

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

- **Congenital Cytomegalovirus and Deafness**

Source: American Journal of Audiology. 3(2): 27-38. July 1994.

Summary: After a brief discussion of the medical aspects of CMV infection and of the Annual Survey of Hearing Impaired Children and Youth, this paper presents data on children with cytomegalovirus (CMV)-induced hearing loss reported to the 1991-92 Annual Survey. The author includes demographic and audiological information and also data related to school achievement and to other factors affecting performance in the classroom (e.g., disabilities in addition to hearing impairment). Although the disease occurs at all stages of life, the focus of this report is on congenital CMV infection. Data reviewed in this study resemble those reported for children with impaired hearing from the 1964-65 maternal rubella epidemic: hearing loss in the severe to profound range, often accompanied by serious additional disabilities, especially mental retardation and

cerebral palsy. Depressed achievement test results of children with CMV-induced hearing loss are further indications of the serious nature of this disease. 1 appendix. 2 tables. 56 references. (AA-M).

- **Cytomegalovirus in Renal Transplantation**

Source: JASN. Journal of the American Society of Nephrology. 12(4): 848-855. April 2001.

Contact: Available from Lippincott Williams and Wilkins. 12107 Insurance Way, Hagerstown, MD 21740. (800) 638-6423.

Summary: Cytomegalovirus (CMV) continues to be a common cause of morbidity (illness) and mortality (death), occurring in 20 to 60 percent of all transplant recipients. This article reviews the role of CMV in renal transplantation. The author notes that CMV has shifted from being overtly lethal to a more insidious presentation. CMV has been associated with both atherosclerosis and chronic rejection, and the two most common causes of late graft loss are cardiovascular death and chronic rejection. Until fairly recently, the available techniques for diagnosing CMV were limited to histologic identification of CMV inclusion bodies, viral culture, and serology. These techniques are labor intensive and not completely sensitive, and the time to diagnosis is protracted, allowing for undetected and untreated disease progression. Newer techniques include shell vial culture, pp65 antigenemia assay, PCR, and the hybrid capture RNA DNA hybridization assay, which has recently received FDA (Food and Drug Administration) clearance. The wide incidence of reported CMV infection and disease probably reflects differing transplantation programs' immunosuppressive strategies, ability to monitor for CMV, ability to perform the most appropriate diagnostic tests, and ability to recognize the more subtle presentations of CMV. Therapeutic treatment of established CMV disease is primarily with the antiviral agent ganciclovir. Even with effective preventive, preemptive, and treatment strategies for CMV, the disease continues to be the most concerning viral agent for transplant recipients. The author concludes that the best approach to solving the problem of CMV is to work to develop effective vaccination programs rather than developing safer and more convenient drugs to battle CMV and the emerging problem of resistance to the current antiviral agents. 1 figure. 2 tables. 63 references.

- **Cytomegalovirus Gastrointestinal Disease in Acquired Immune Deficiency Syndrome**

Source: European Journal of Gastroenterology and Hepatology. 4(6): 443-448. June 1992.

Summary: Cytomegalovirus (CMV) is a very common opportunistic pathogen in acquired immune deficiency syndrome (AIDS), not only because of the profound immunodepression of the disease, but also because of the specific epidemiology of CMV infection, which has a frequency of nearly 100 percent in homosexual men. This review article covers the prevalence, clinical manifestations, diagnosis, and treatment of CMV gastrointestinal disease in AIDS. Manifestations discussed include esophagitis, gastritis and duodenitis, colitis, anal ulceration, and appendicitis. Treatment consists of ganciclovir 5 mg/kg twice daily or foscarnet 100 mg/kg twice daily. (AA-M).

- **Prevention of Cytomegalovirus Infection and Disease in High-Risk Renal Transplant Recipients with Polyvalent Intravenous Immunoglobulins**

Source: Transplantation Proceedings. 34(3): 812-813. May 2002.

Contact: Available from Elsevier Science Inc. 655 Avenue of the Americas, New York, NY 10010. (212) 633-3730. Website: www.elsevier.com.

Summary: Cytomegalovirus (CMV) is the most frequent cause of infectious complications after renal (kidney) transplantation (post-TxR) and is associated with increased morbidity (illness) and mortality (death). CMV infection has been implicated as a cause of graft rejection, and in contrast may also enhance immunodepression, thereby facilitating the occurrence of bacterial, fungal, or other opportunistic superinfections. In this article, the authors retrospectively evaluate the incidence of CMV infection in high risk renal transplant recipients in whom intravenous (IV) immunoglobulin (Ig) preparations were used as the primary preventive strategy (prophylaxis). Among the 177 graft recipients in the study, 23 (19.7 percent) were CMV seronegative and at high risk for CMV infection. None of the patients treated with IV Ig developed CMV disease; the infection only occurred in patients not treated because of false-negative blood testing on the donor. The CMV syndrome occurred in less than 50 percent of patients treated with IV Ig; the other members of the treatment group either remained asymptomatic from or free of CMV infection. Patient tolerance of IV Ig was excellent: no renal or systemic side effects were noted. 2 tables. 3 references.

- **Role of Immunosuppressive Drugs in the Development of Tissue-Invasive Cytomegalovirus Infection in Renal Transplant Recipients**

Source: Transplantation Proceedings. 34(4): 1164-1170. June 2002.

Contact: Available from Elsevier Science Inc. 655 Avenue of the Americas, New York, NY 10010. (212) 633-3730. Website: www.elsevier.com.

Summary: Cytomegalovirus disease occurring after renal (kidney) transplantation still represents an important cause of morbidity (related illness or complications) and even mortality (death), increasing hospital expenses. This article reports on a study that considered the role of various immunosuppressive drugs (and combined drug regimens) on the occurrence and the characteristics of cytomegalovirus (CMV) disease in kidney transplant recipients. The study included 741 patients who received cadaveric kidney transplants, of whom the majority (91.2 percent) did not receive CMV prophylaxis (oral ganciclovir or valganciclovir). The 101 patients (13.6 percent) who developed CMV disease during the study period were designated as the study group; 82 percent of these (83 patients of 101 patients) experienced a single episode of CMV disease. Recurrent CMV disease happened in 18 patients (18 percent), usually within weeks after the first episode. The control group consisted of all transplant patients who did not develop CMV disease during the same period (n = 640). Total cumulative CMV related mortality was 3 percent (3 patients of 101 patients). The use of tacrolimus, together with MMF (mycophenolate mofetil) and steroids, was identified as an independent risk factor for CMV disease. These observations have to be taken into account when evaluating the cost-effectiveness of oral CMV prophylaxis, especially in the elderly renal transplant patients who are at risk for CMV infection. 5 tables. 17 references.

- **Hearing Loss and Cytomegalovirus**

Source: Volta Review. 9(5): 71-74. November 1999.

Contact: Available from Alexander Graham Bell Association for the Deaf and Hard of Hearing. Subscription Department, 3417 Volta Place, NW, Washington, DC 20007-2778. Voice/TTY (202) 337-5220. Website: www.agbell.org. Also available as individual copies from Publication Sales Department, 3417 Volta Place, NW, Washington, DC 20007-2778.

Voice/TTY (202) 337-5220. Website: www.agbell.org. PRICE: \$22.95 plus shipping and handling.

Summary: Cytomegalovirus is the most common cause of congenital viral induced hearing loss. Maternal infection is most often asymptomatic as is the infection in the newborn. Hearing loss occurs in both clinically apparent infection and in the asymptomatic infection as well, although to a lesser degree. This chapter on hearing loss and cytomegalovirus is from a monograph that was written by assembling the leading experts from all over the country to present to both the consumer and the professional the latest information on the diagnosis and management of hearing loss in children and adults. In this chapter, the author outlines the current methods of detection, treatment, and prevention and research efforts related to this disorder. The author cautions that no effective therapy is available to prevent or halt the progression of a CMV inner ear infection once it has begun. Early detection, habilitation, and long term audiologic follow up are recommended. The author concludes that major progress in the prevention and therapy of this disease will come from knowledge gained using animal models of CMV inner ear infection.

- **Oral Manifestations of Cytomegalovirus Infection**

Source: Oral Surgery, Oral Medicine, Oral Pathology. Volume 75: 443-451. April 1993.

Summary: The most common manifestation of cytomegalovirus (CMV) infection of the gastrointestinal tract, including the oral mucosa, is ulceration. This article discusses the oral manifestations of CMV, including gingivitis, xerostomia, Sjogren's syndrome, and Kaposi's sarcoma. Two case reports of patients with CMV and HIV are also presented. The authors stress that it is vital for physicians to be aware of CMV-induced oral disease and to use the recent advances in the technology of CMV detection to make a specific diagnosis. 5 figures. 55 references. (AA-M).

- **Cytomegalovirus Ulcer of the Tongue**

Source: American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc. 110(4): 463-464. April 1994.

Summary: This article presents the case report of a 63-year-old man who was referred for evaluation of a painful ulcer on the right lateral surface of the tongue. The patient had a history of diabetes and had recently been diagnosed as having polymyositis. He was taking high doses of prednisone, as well as weekly methotrexate and glucotrol for diabetes. A biopsy revealed vascular proliferation with scattered atypical cells exhibiting intranuclear and cytoplasmic inclusions. Immunoperoxidase staining confirmed the presence of cytomegalovirus (CMV). The lesion slowly healed over a 7-week period as the patient was weaned from the immunosuppressive medications. The author discusses this case and other CMV-associated oral ulcerations. A final section discusses the medications for treatment of CMV. 1 figure. 3 references.

- **Prevention of Cytomegalovirus Disease in Renal Transplantation**

Source: American Journal of Kidney Diseases. 16(3): 175-188. September 1990.

Summary: This in-depth review article considers the prevention of cytomegalovirus disease (CMV) in renal transplantation. CMV can be prevented in renal transplant recipients with the use of either CMV hyperimmune globulin (CMVig) or acyclovir. Started within 72 hours of transplantation and continued for 16 weeks posttransplant, CMVig decreases the incidence of primary CMV disease from 60 percent to 21 percent.

Acyclovir administered preoperatively and for 3 months thereafter decreases the incidence of CMV disease from 29 percent to 8 percent, and is the most cost-effective therapy. The author notes that the effectiveness of these preparations in preventing CMV reinfection or reactivation has not been established. The author also discusses other therapies, including vaccination, polyvalent immunoglobulins, and interferon alpha. 5 tables. 194 references. (AA-M).

- **Cytomegalovirus Infection and Disease after Liver Transplantation: An Overview**

Source: Digestive Diseases and Sciences. 37(5): 673-688. May 1992.

Summary: This review article covers cytomegalovirus (CMV) infection and disease after liver transplantation, the single most important pathogen in clinical transplantation. Topics discussed include the characteristics of CMV, a definition of SMV infection versus disease, the epidemiology of CMV, clinical presentations and manifestations, factors affecting the severity of CMV infection, risk factors for CMV disease, the clinical effects of CMV, and the prophylaxis and treatment of CMV infection and disease. Results obtained using intravenous ganciclovir, intravenous immunoglobulin, and oral acyclovir for treating CMV are presented. The authors note that although CMV remains a major cause of morbidity, it is no longer a major cause of mortality after liver transplantation. 9 figures. 2 tables. 97 references. (AA-M).

- **Cytomegalovirus: A Virus of Increasing Relevance to Oral Medicine and Pathology**

Source: Journal of Oral Pathology and Medicine. 22(8): 348-353. September 1993.

Contact: Available from Munksgaard International Publishers Ltd. Commerce Place, 350 Main Street, Malden, MA 02148-5018. (781) 388-8273. Fax (781) 388-8274.

Summary: This review article focuses on cytomegalovirus, a virus of increasing relevance to oral medicine and pathology. Topics covered include epidemiology; immunopathogenesis; the clinical features of primary human cytomegalovirus (HCMV); HCMV infections in pregnancy; HCMV in immunocompromised patients, including those with bone marrow transplantation, organ transplantation, or HIV disease; the diagnosis of HCMV infection; oral lesions related to HCMV, including gastrointestinal ulceration, oral ulcers, gingival lesions, and sialadenitis; the possible association of HCMV with other conditions, including Kaposi's sarcoma, oral squamous cell carcinoma, salivary gland disease, and Behcet's syndrome and aphthae; prophylaxis and treatment of HCMV infections; and the aspects of the transmission of HCMV that are relevant to dentistry. 107 references.

- **Cytomegalovirus DNA Identified in Skin Biopsy Specimens of Patients with Vitiligo**

Source: Journal of the American Academy of Dermatology. 35:21-26; July 1996.

Summary: This study determined the presence or absence of viral genomes in the depigmented and uninvolved skin of patients with vitiligo. Researchers used a polymerase chain reaction assay to detect viral genomes in paraffinembedded skin biopsy specimens. Twenty-nine patients with vitiligo and 22 control subjects participated. Biopsy specimens were screened in a blinded fashion for a panel of DNA and RNA viruses included herpes simplex, varicella-zoster, cytomegalovirus (CMV), Epstein-Barr, HIV, and human T-cell lymphotropic virus. Results show that CMV DNA was identified in 38 percent of the patients studied. Twenty-one percent had indeterminate results. Results in all control subjects were negative. Polymerase chain reaction screening for identification of other viral genomes was negative. Although not

statistically significant, data trends suggested a correlation between the presence of CMV DNA in biopsy specimens and active vitiligo of relatively brief duration. In addition, CMV-positive patients had a statistically significant increased frequency of other concurrent autoimmune diseases. The results suggest that vitiligo may indeed be triggered by a viral infection in select patients. 3 tables, 52 references. (AA-M).

Federally Funded Research on Cytomegalovirus

The U.S. Government supports a variety of research studies relating to cytomegalovirus. 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 cytomegalovirus.

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

- **Project Title: A MOLECULAR BASIS FOR THE RHESUS CYTOMEGALOVIRUS MODEL**

Principal Investigator & Institution: Anders, David G.; Associate Professor; Wadsworth Center Empire State Plaza Albany, Ny 12237

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

Summary: Human **cytomegalovirus** remains a significant health problem. Great strides have been made in understanding the basic molecular biology of HCMV lytic infection of cells in culture and, although much is yet to be learned, many tools to study HCMV lytic infection are available. However, comprehensive studies of the latent phase and pathogenesis are difficult or impossible in tissue culture, and these aspects of HCMV biology are less well understood. Small animal models, most notably murine CMV, have been developed to study pathogenesis and latency, and have proven invaluable. These models are nevertheless significantly divergent from the human system in several respects. Many genes have diverged beyond ready recognition. Regulatory elements are not always conserved. Aspects of pathogenesis differ. For these reasons, they are not adequate to address some questions. In contrast, the rhesus CMV (RhCMV) is very similar to HCMV. The limited sequence data available show that the overall genome is roughly colinear with the human virus, with a few notable differences. Even genes encoding regulatory proteins that are quite divergent in small animal models are relatively well conserved in RhCMV. Most importantly, infection in rhesus macaques appears to recapitulate in many important details infection by HCMV of the human host. Therefore, RhCMV is hypothesized to be an ideal model for the study of those

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).

aspects of CMV pathogenesis that cannot be addressed in the small animal models. Unfortunately, the basic molecular information required to confirm this hypothesis and efficiently exploit this system is not yet available. The specific aims are to: 1) establish an ordered set or sets of cosmid clones containing the entire RhCMV genome, 2) determine and analyze the complete nucleotide sequence of the RhCMV genome, and 3) develop systems for generating recombinants that will enable efficient construction of mutant viruses whose biological properties can then be assessed in vivo. These aims will be addressed using standard molecular cloning and sequencing methods, and methods already applied to other herpesviruses to construct mutants. The long-term goal of the work proposed here is to build the knowledge base that will enable efficient application of the RhCMV system to otherwise intractable problems in studies of CMV pathogenesis and latency.

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

- **Project Title: A POTENT ORAL THERAPY FOR CYTOMEGALOVIRUS INFECTION**

Principal Investigator & Institution: Bowlin, Terry L.; Microbiotix, Inc. 1 Innovation Dr Worcester, Ma 01605

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

Summary: (provided by applicant): **Cytomegalovirus** infection represents a major health concern in the immunocompromised population, causing a variety of serious and even life threatening disorders. The current standard of care for CMV infection, ganciclovir, suffers from complications of low oral bioavailability, bone marrow toxicity and emerging resistance in the clinic. Although two alternatives to ganciclovir exist, foscarnet and cidofovir, their own issues of severe renal toxicity limit them to use only in situations of ganciclovir failure. A new series of purine nucleoside analogues, the MP analogs, have been shown to be more potent and less toxic than ganciclovir. In addition, the MP analogs also exhibit increased activity against all ganciclovir resistant strains tested to date. Microbiotix, Inc. has exclusive license to the MP analogs and proposes to develop this class of compounds for the treatment of CMV disease. The focus of this Phase I Small Business Innovation Research (SBIR) application is the identification of a lead compound through a thorough investigation of in vitro efficacy and cytotoxicity. The applicants intend to advance this lead compound into pre-Investigational New Drug (IND) studies in the Phase II application.

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

- **Project Title: A PRIMATE MODEL OF MATERNAL FETAL IMMUNE TOLERANCE**

Principal Investigator & Institution: Golos, Thaddeus G.; Associate Professor; Primate Research Center; University of Wisconsin Madison 750 University Ave Madison, Wi 53706

Timing: Fiscal Year 2002; Project Start 03-AUG-1995; Project End 31-MAR-2007

Summary: The primate placenta is unique in its selective expression of nonclassical MHC class I molecules (in the human HLA-G and HLA-E). Recent work has strongly suggested that HLA-E may play an important role in its coexpression with HLA-G on human trophoblasts in establishing maternal-fetal immune tolerance. However, the functional relevance of the unusual expression of MHC molecules in the human placenta remains undefined. A lack of appropriate nonprimate animal models has significantly restrained progress in this area. Our central hypothesis is that nonclassical placental MHC class I molecules play a role in the modulation of the maternal response to pregnancy, both locally within the maternal endometrium as well as in the maternal

peripheral serum. To functionally address the role(s) of MHC class I molecule expression in the placenta, we propose 4 specific aims, using a nonhuman primate model for maternal-fetal immune tolerance developed in the previous funding period. Specific Aim 1. To define the ontogeny of Mamu-E expression within the rhesus placenta and localize sites of mRNA and protein expression. Specific Aim 2. To evaluate maternal-fetal immune interactions and placental development in pregnancies with transgenic modification of rhesus placental MHC class I expression. Specific Aim 3. To determine MHC class I expression in rhesus monkey trophoblasts exposed to simian **cytomegalovirus**, with relevance for maternal-fetal viral transmission. Specific Aim 4. To define the expression of a soluble isoform of Mamu-AG. Although there has been remarkable progress in defining the biochemical and molecular characteristics of MHC class I molecules expressed in the human placenta, a significant gap remains in our appreciation of either the function of these molecules in normal pregnancy, or the role(s) they may play in pathological situations. With these 4 specific aims we proceed beyond defining placental nonclassical MHC class I expression in the nonhuman primate, to investigating function at the maternal-fetal interface. The successful implementation of our recent adaptation of transgenic technology to the primate placenta will provide unprecedented opportunity for novel models of primate placental biology.

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- **Project Title: ACCESSORY CELL ACTIVATION OF THE IMMUNE RESPONSE**

Principal Investigator & Institution: Auron, Philip E.; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

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

Summary: Monocytes express at least two different classes of cell-type specific genes. One class, exemplified by the M-CSF receptor gene, *c-fms*, is constitutively expressed and dependent upon the differentiated state. Another class, represented by the IL-1 β gene (*il1b*), is also generally monocyte-specific, but is only expressed immediately in response to a stimulation event that parallels the conversion of the resting monocyte to the activated monocyte/macrophage. Investigation of the *il1b* regulation mechanisms have revealed two distinct and separable regions of the gene that correspond to each of the two criteria, a cell type specific 143bp basal promoter and a signal-responsive upstream enhancer. The enhancer function depends upon the cooperative function of several broadly expressed signal-responsive transcription factors (e.g., C/EBP β , CREB, c-Jun, and NF- κ B), including a novel STAT-like factor, whereas the 71 bp basal promoter appears to depend upon binding of one molecule of the mono-myeloid factor Spi-1/PU.1 (Spi-1), a factor that plays a central key role in monocyte development and cell type-specific gene expression. The functional interaction between the basal promoter and an enhancer requires a critical additional 73bp element that requires the binding of an additional Spi-1 molecule. This element is not required for enhancer-independent activity in the presence of IE2, a **cytomegalovirus** protein. IE2 appears to interact directly with the Spi-1 ETS domain. This region is found in all ETS proteins and mediates associations with a broad range of other proteins, modulating function in both partners. The object of this proposal is to elucidate the mechanism by which Spi-1 interacts with other proteins and integrates enhancer function into the core promoter and to attempt to clone the novel STAT-like factor that is activated in response to LPS, IL-1, and IL-6.

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- **Project Title: ACTIVATION OF INTERFERON REGULATED GENES**

Principal Investigator & Institution: David, Michael; Associate Professor; Biology; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 920930934

Timing: Fiscal Year 2002; Project Start 01-APR-2000; Project End 31-MAR-2005

Summary: (adapted from investigator's abstract): Conservative estimates hold that in the United States alone, more than 20,000 people die each year as a result of septic shock brought on by Gram-negative infection. The lethality is linked to the biological effects of the bacterial cell wall component lipopolysaccharide (LPS), which prompts the production and release of proinflammatory cytokines such as TNF-alpha, and IL-1. LPS binds to the Toll-like receptors (TLRs), a receptor family which also includes the IL-1 receptor and is part of the evolutionary conserved innate immune system. We have identified a novel signaling pathway that is initiated by LPS or IL-1, and leads through the activation of Interferon Regulatory Factor 3 (IRF-3) to the induction of Interferon Stimulated Genes (ISGs). We had previously found this pathway to be activated upon viral infection, indicating that IRF-3 plays a crucial role in the host defense against either viral or bacterial pathogens. Furthermore, IRF-3 activation by IL-1 suggests that this signaling cascade might also contribute to inflammatory processes such as rheumatoid arthritis. The three aims of Part I are focused on identifying the activation mechanism of IRF-3. In Aim 1 we will identify the phosphorylation sites in IRF-3 after LPS or IL-1 stimulation, In Aim 2 we will generate phosphospecific antisera against IRF-3. Aim 3 proposes experiments to isolate and identify the kinase(s), which phosphorylates IRF-3 in response to LPS or IL-1. Part II of the proposal contains two aims that investigate the biological role of IRF-3. In Aim 4 we will examine the crosstalk between IL-1- and LPS-induced activation of IRF-3 and ISGs. We will further explore whether IL-1 and/or LPS treatment interfere with viral infection. In Aim 5 we propose to generate transgenic mice that express a dominant-negative mutant of IRF-3 either ubiquitously or in a myeloid restricted manner. We will investigate the susceptibility of these animals to septic shock and collagen-induced arthritis as well as viral and bacterial infection. Results from these proposed studies will not only facilitate our understanding of the mechanism of IRF-3 activation, but will also shed light on the role of IRF-3 in physiological and pathological processes.

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- **Project Title: ADAPTATIONS OF HUMAN HERPESVIRUS-7 TO SALIVARY GLANDS**

Principal Investigator & Institution: Dewhurst, Stephen; Professor; Microbiology and Immunology; University of Rochester Orpa - Rc Box 270140 Rochester, Ny 14627

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

Summary: Human herpesvirus (HHV)-7 infection is associated with persistence of viral genomes in salivary gland (SG) tissues, and chronic expression of viral antigens in these sites. The virus is generally thought to be spread by a salivary route, and there is lifelong shedding of large amounts of infectious virions in saliva. These observations suggest the following hypothesis: that HHV-7 has evolved specific mechanisms to gain entry to SG cells and to evade host immune responses in SG tissues. In this proposal, we will examine the role of specific viral proteins in virus attachment and entry to SG epithelial cells. In the first two specific aims, the unique viral glycoprotein, gp65, will be studied. Gp65 is a component of the virus particle, and polyclonal antisera directed against gp65 neutralize virus infectivity; HHV-7 gp65 also binds to heparan sulfate proteoglycans (HSPGs). These data strongly suggest that gp65 plays a role in cellular attachment and

entry by HHV-7; this hypothesis will be tested experimentally. First, we will examine the interaction of purified recombinant HHV-7 gp65 with cell surface HSPGs found on cultured human SG cells. Second, a gp65- deleted recombinant virus will be constructed, and its ability to attach to and enter cultured SG cells will be examined. Third, the molecular architecture of gp65, and its interaction with host macromolecules will be studied. In the third aim, we will study two putative 7-transmembrane (7- tm) receptors encoded by HHV-7, U12 and U51. Homologous genes encoded by rat and mouse **cytomegalovirus** (CMV) are essential for efficient viral replication in salivary glands, and a related gene in human CMV has been shown to contribute to membrane fusion events that may be involved in virus entry or spread. Experiments will therefore be conducted, to determine whether HHV-7 U12 and U51 can enhance membrane fusion events mediated by different viral proteins in cultured SG cells. It is expected that a greater understanding of the molecular pathways exploited by HHV-7 will contribute to the future design of enhanced gene delivery vehicles for SG gene therapy; such vector systems may incorporate components of HHV-7.

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- **Project Title: ADULT AIDS CLINICAL TRIALS GROUP**

Principal Investigator & Institution: Saag, Michael S.; Professor of Medicine; Medicine; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

Timing: Fiscal Year 2002; Project Start 01-APR-1992; Project End 31-DEC-2004

Summary: (adapted from the application's abstract): This is a competitive renewal of the UAB ACTU, established in 1992 at the UAB AIDS Outpatient (1917) Clinic, and is submitted in conjunction with the ACTG Group application led by Robert T. Schooley, M.D. (Principal Investigator). The UAB ACTU has developed and implemented clinical trials that link therapeutics and pathogenesis, a priority of the ACTG recompetition. With the last competitive renewal, investigators from Emory University were added to the UAB ACTU site through the establishment of a subunit at the Ponce de Leon Clinic in Atlanta. Since that time, investigators from the UAB/Emory ACTU have continued to assume leadership positions within the ACTG and have played a role in the establishment and performance of the Group's Scientific Agenda. The UAB/Emory ACTU has the primary foci: (1) establish collaborative studies within the ACTG that focus on the clinical significance and therapeutic implications of recent insights into human immunodeficiency virus (HIV) viral- and immuno- pathogenesis; (2) further develop improved therapeutic approaches in the treatment of **cytomegalovirus**, mycobacterial, human papillomavirus, herpes- related viruses, mycoplasma, and fungal disease, areas where UAB/Emory investigators have made contributions and have expertise; (3) continue to improve access of women and minorities to ACTG-related clinical trials through the 1917 Women's Clinic and the Women's Clinic at the Ponce de Leon Center and through targeted outreach programs to HIV-infected African Americans; and (4) continue to contribute to the overall mission and Scientific Agenda of the ACTG through active participation in Group activities and provision of leadership within key administrative committees.

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- **Project Title: ADULT AIDS CLINICAL TRIALS UNIT**

Principal Investigator & Institution: Collier, Ann C.; Assistant Professor; Medicine; University of Washington Grant & Contract Services Seattle, Wa 98105

Timing: Fiscal Year 2002; Project Start 30-JUN-1986; Project End 31-DEC-2004

Summary: (adapted from application's abstract): This application responds to NIH RFA NIAID-98-013. It describes the renewal application of the University of Washington (UW) Adult AIDS Clinical Trials Unit (AACTU). The purpose of the UW AACTU is to perform exemplary HIV/AIDS treatment research in support of the Adult AIDS Clinical Trials Group (AACTG) scientific agenda. UW AACTU was one of 14 original centers funded in 1986 to study therapies for HIV infection. The UW AACTU has made contributions to the AACTG through leadership and participation of its faculty in AACTG committees and protocols, accrual of 1758 patients into AACTG studies, and generation of high quality data. Since 1996, UW AACTU investigators have been members of 38 committees, subcommittees, and focus groups; Chair or Vice-chair for seven of these; Protocol Chair or Co-chair of 23 studies and substudies; and the UW AACTU has enrolled 419 patients in AACTG protocols. The UW AACTU application describes three specific aims: (1) contribute to the pathogenesis-based scientific agenda of the AACTG by providing scientific expertise and leadership in HIV disease, complications of HIV, neurology, immunology, women's health and outcomes; and provide technical expertise to support protocol-mandated procedures; (2) participate in AACTG clinical trials by maintaining the UW AACTUs infrastructure and its experienced staff; enroll 90 patients in main studies and 50 in substudies per year and follow them with a <5 percent loss-to-follow-up rate; and maintain high data quality, quality assurance programs, and a high standard of regulatory compliance; and (3) support special issues of relevance to the AACTG by enrolling patients representative of local demographics; continue an outreach program and partnerships with People of Color Against AIDS Network and Northwest Family Center to maximize enrollment of people of color and women; maintain links with the HIV-infected community, community-based organizations and their network of referring physicians; continue the UW AACTU Community Advisory Board, and provide opportunities for research training of women and minority investigators.

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- **Project Title: ADULT AIDS CLINICAL TRIALS UNIT**

Principal Investigator & Institution: Balfour, Henry H.; Professor of Laboratory Medicine, Pathol; Lab Medicine and Pathology; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

Timing: Fiscal Year 2002; Project Start 01-MAR-1992; Project End 31-DEC-2004

Summary: (adapted from the application's abstract): The Minnesota AIDS Clinical Trials Unit (ACTU) requests to continue to be a unit of the Adult AIDS Clinical Trials Group (AACTG). The Minnesota ACTU is committed to the Scientific Agenda of the AACTG, in which they have participated continuously since January 1, 1987. In addition to recruiting and retaining a cohort of new HIV-infected patients in clinical trials (estimated to be 85 patients in main studies and 54 patients in substudies annually), the Minnesota ACTU plans to contribute to the Group Scientific agenda with the following specific aims: (1) to correlate the quantity and replication competence of HIV at the cellular level in lymphoid tissue (LT), peripheral blood fractions and other compartments; (2) to develop more sensitive methods to detect HIV and apply these to selection of more effective therapies; (3) to define the natural history of **cytomegalovirus** (CMV) disease in the era of potent antiretroviral therapy and determine the best assays (virologic and immunologic) to monitor its clinical course (AACTG 360); (4) to identify and properly manage the patients who are at risk for complications of the dyslipidemias associated with potent antiretroviral therapy; (5) to identify resistant CMV strains and assess their pathogenicity; (6) to study relationships between the production of

neurotoxins in plasma and cerebrospinal fluid of HIV-infected patients, neuronal loss as measured by proton magnetic resonance spectroscopy and the development or progression of HIV-associated dementia (HAD); and (7) to understand and characterize pharmacokinetic behavior, including drug-drug interactions, of antiretrovirals and other HIV-related drugs in biologic fluids. To help achieve these specific aims, the Minnesota ACTU has both Virology and Pharmacology Advanced Technology Laboratories (ATL). The Virology ATL is focusing on quantitation and characterization of HIV in lymphoid tissue and other body compartments. This laboratory also has expertise in HIV and CMV resistance. The Pharmacology ATL is developing assays for simultaneous determination of levels of protease inhibitors and measurement of intracellular antiretroviral anabolites. The Nebraska subunit has a special interest in neuroAIDS and has identified neurotoxins putatively responsible for pathology in HAD. The Iowa subunit has expertise in the detection of hepatitis C and will be collaborating in studies of the pathogenesis of coinfection with HIV and hepatitis C.

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- **Project Title: ADULT THERAPEUTIC CLINICAL TRIALS PROGRAM FOR AIDS**

Principal Investigator & Institution: Eron, Joseph J.; Associate Professor; Medicine; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

Timing: Fiscal Year 2002; Project Start 30-SEP-1987; Project End 31-DEC-2004

Summary: (adapted from the application's abstract): The applicants propose to continue their multidisciplinary multi-year research program, that will integrate institutional expertise in infectious diseases, neurology, ophthalmology, gynecology, pharmacology, immunology, retrovirology, herpes viruses, and numerous clinical resources in North Carolina. The main focus is the evaluation of novel therapies for HIV-infected persons. Clinical investigators at the UNC and two satellite units, Greensboro, and Charlotte will study new compounds active against HIV and associated infections, malignancies, and neurologic disorders in new patients and follow previously enrolled patients. This proposes to continue a high rate of accrual among minorities, women, and intravenous (I.V.) drug users. The trials will be of all Phases (I, II, and III) and types. Patients will be followed for in vivo evidence of study drug effects on HIV, Mycobacterium avium intracellular complex (MAC), **cytomegalovirus** (CMV), herpes simplex virus (HSV), and other opportunistic infections using the ACTG-certified retrovirology and immunology virus laboratory, as well as UNC hospital laboratories. Pharmacokinetics (PK) will be monitored in the General Clinical Research Center (GCRC) and Microbiology and Pharmacology Laboratories. Concepts for new protocols will originate by participation in the Executive, Neurology, and Complications of HIV, HIV Pharmacology and Immunology ACTG committees. The established scientific advisory board (SAB) also will be involved in concept development. The UNC group application has new proposals for many trials including the eradication of HIV, simplification of regimens, novel therapies, improving adherence and immune restoration. Outreach to the community may be accomplished through the community advisory boards (CAB) at each site, the website and through a statewide newsletter. Finally, low protocol costs may be maintained by cost sharing with NIH grants (GCRC, Pediatric ACTU, Center for AIDS Research (CFAR), as well as with UNC Hospitals, and the Departments of Medicine, Neurology, Ophthalmology, Microbiology and School of Pharmacy.

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- **Project Title: AIDS CLINICAL TRIALS GROUP - ACTU**

Principal Investigator & Institution: Feinberg, Judith T.; Internal Medicine; University of Cincinnati 2624 Clifton Ave Cincinnati, Oh 45221

Timing: Fiscal Year 2002; Project Start 30-SEP-1987; Project End 31-DEC-2004

Summary: (adapted from the application's abstract): Since its inception in 1987, the University of Cincinnati (UC) ACTU has made contributions to the overall mission of the ACTG in a number of key areas. The UC ACTU has provided both scientific and administrative leadership especially in opportunistic infections, and more recently, in antiretroviral studies, HIV- associated neurologic diseases, research nursing, and study design. In the current cycle, the UC ACTU proposes to continue to perform a broad range of clinical trials and substudies to assure maximum UC ACTU contribution to the objectives of the ACTG research agenda. These include to translate the findings of basic research conducted at UC on immunopathogenesis of *Pneumocystis carinii* and other opportunistic pathogens that may help determine when and if prophylaxis can be discontinued safely in antiretroviral therapy responders. Also, to explore microbial and immunologic measures which define risk for the protection against *Pneumocystis* as a basis for adjunctive immune- based therapy and prophylaxis. In addition to study the pathogenesis and clinical significance of hepatitis C/HIV co-infection in the HARRT era, and use this knowledge to develop improved treatments. Another Aim is to continue to elucidate the underlying mechanisms in the neuropathogenesis of HIV infection, and exploit these mechanisms in the development of new therapeutic modalities for central nervous system HIV infection, including HIV dementia and multifocal leukoencephalopathy. The UC ACTU will also work to develop treatment strategies for the management of patients with discordant responses to current antiretroviral therapy and to develop simplified, potent treatment strategies, including the use of novel agents, to enhance antiretroviral adherence and therefore improve clinical outcome. The short and longer-term incremental cost of quality-adjusted life expectancy associated with various treatment strategies using utility assessment will also be studied. Finally, the UC ACTU proposes to evaluate whether an intensive educational intervention that is paced by the patient yields improved short and long-term virologic suppression in naive patients.

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- **Project Title: AIDS CLINICAL TRIALS UNIT**

Principal Investigator & Institution: Currier, Judith Silverstein.; Medicine; University of California Los Angeles 10920 Wilshire Blvd., Suite 1200 Los Angeles, Ca 90024

Timing: Fiscal Year 2004; Project Start 30-JUN-1986; Project End 31-DEC-2004

Summary: (adapted from the application's abstract): The ACTU has been an active participant in clinical trials for the treatment of human immunodeficiency virus (HIV) and related diseases of the ACTG since 1986. Metropolitan Los Angeles is culturally diverse and its residents are significantly affected by the AIDS epidemic. The UCLA ACTU, located on the west side of Los Angeles, with its subunits in various areas of greater Los Angeles is applying for competitive renewal as part of the ACTG under the group leadership of Robert T. Schooley, M.D. The goal of the UCLA ACTU is to fully participate in the scientific and operational activities of the Group. This would include involvement in the Group scientific and administrative leadership via participation in ACTG research agenda committees, working groups and protocol teams, accruing patients to studies, and providing laboratory expertise in specific areas in which this ACTU has expertise such as immunology. Both the UCLA main site and the Harbor-

UCLA subunit will enroll patients in high priority Phase I, II and III clinical trials of antiretroviral drugs, immune-based therapies and treatments for opportunistic infections, neurologic disorders and complications of HIV treatment. Patients also will be enrolled and maintained in the longitudinal assessment study (ALLRT protocol) to help answer important questions about the pathogenesis and clinical management of HIV, as well as in other studies designed to address the specific aims of the ACTG. Administrative oversight, specimen storage and shipping, performance of protocol mandated laboratory assays, data quality assurance, maintenance of a CAB and outreach activities to stimulate greater participation of women and racial/ethnic minorities in ACTG clinical trials will be the responsibility of the UCLA main site.

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- **Project Title: ANTI-HERPESVIRUS SIGNALING BY CYTOKINES**

Principal Investigator & Institution: Ware, Carl F.; Head Division Molecular Immunology; La Jolla Institute for Allergy/Immunology 10355 Science Center Dr San Diego, Ca 921211118

Timing: Fiscal Year 2002; Project Start 15-FEB-2001; Project End 31-JAN-2006

Summary: (provided by applicant): The Tumor Necrosis Factor (TNF) superfamily of cytokines and receptors play critical roles in development of the immune system, and in innate and acquired immune defenses to pathogens. LIGHT, an integral member of the lymphotoxin (LT)-alpha, LT beta, and TNF cytokine superfamily, signals through the Herpesvirus entry mediator (HVEM) and the LT betaR, a receptor that also binds membrane Lt alpha beta complex. Membrane Lt alpha beta is required for the development of the progenitors of natural killer (NK) and NK-T cell lineage. Ligands that engage the LT betaR, including LIGHT and LTalpha1 beta2, activate a potent non-apoptotic, antiviral response that suppresses spread of human **cytomegalovirus** (HCMV) in cell culture. Furthermore, LTalpha deficient mice exhibit a profound and specific susceptibility to acute infection with mouse CMV (MCMV), implicating the LT betaR as a key signaling element for host defense. The developmental connection between NKJNK-T cells and LT alpha beta provides compelling evidence that the antiviral activity of LT alpha beta/LIGHT is mediated by NK or NK-T cells and suggests that lymphotoxins are intimately linked to viral defenses. The antiviral signaling by the LTBR is hypothesized to provide a key checkpoint in limiting virus spread. The three specific aims are proposed to address this hypothesis. The first aim will use defined mutants of the LT betaR to identify receptor signaling complex, which leads to the anti-viral response observed in primary fibroblasts. Dominant negative mutants of TRAFs and death domain adaptors, known to bifurcate the signaling pathways at the receptor level, will be used in tissue culture models to determine the role that NFkappaB, JNK, and IRF signaling pathways contribute to the anti-HCMV activity. The second aim is directed at delineating the signaling pathways leading to LT alpha beta/LIGHT induction of interferon (IFN)beta in HCMV infected cells. Additionally, in order to dissect the mechanism of cytokine anti-viral effects, DNA microarray technology will be used to analyze differences in HCMV gene expression in the presence of Ltalpha beta/LIGHT and IFNB. The third aim will address the physiologic role of LT alpha beta and LIGHT in regulating innate and immune defense to MCMV using: genetically defined mice deficient in LTcx/13 and LIGHT systems, transgenic mice expressing decoy receptors, and pharmacological modulation by receptor specific monoclonal antibodies and purified soluble decoy receptors. MCMV models of acute infection and reactivation will be investigated. Together these studies will provide a comprehensive investigation into anti-CMV actions of the LT alpha beta/LIGHT cytokine systems in

human and mouse models that will elucidate molecular mechanisms of host-pathogen interactions that occur during acute and persistent infections.

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- **Project Title: ANTIVIRAL DRUG KINETICS IN VITREOUS USING MICRODIALYSIS**

Principal Investigator & Institution: Mitra, Ashim K.; Professor and Chairman; Pharmaceutical Sciences; University of Missouri Kansas City Kansas City, Mo 64110

Timing: Fiscal Year 2002; Project Start 01-APR-1996; Project End 31-JUL-2003

Summary: (Adapted from Applicant's Abstract) In this competing renewal application, the Principal Investigator proposes to study the vitreal pharmacokinetics of ganciclovir, foscarnet, and cidofovir, three antiviral agents used to treat **cytomegalovirus**. A relatively new procedure, microdialysis, will be used which has the advantage of measuring drug levels in a continuous manner. By using this approach and from the experiments that are planned in pigmented rabbit eyes, it will be possible to more thoroughly determine each drug's ocular kinetics than from using previously methods in which each time interval represented a different group of animals. In addition, the investigator proposes to determine physico-chemical and biological determinants that help to explain ganciclovir's distribution and elimination profile. From this information, the investigator plans to develop approximately eighteen prodrugs that in theory could optimize antiviral therapy by prolonging drug levels in the vitreous.

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- **Project Title: CD8+ T CELL IMMUNITY TO CYTOMEGALOVIRUS**

Principal Investigator & Institution: Riddell, Stanley R.; Professor; Fred Hutchinson Cancer Research Center Box 19024, 1100 Fairview Ave N Seattle, Wa 98109

Timing: Fiscal Year 2003; Project Start 21-JAN-2003; Project End 31-DEC-2007

Summary: (provided by applicant): Advances in cellular and molecular immunology have provided new opportunities for defining the mechanisms operative in the control of persistent virus infections, for developing immune-based therapies for progressive infection in immunocompromised hosts, and for the rational design and testing of vaccines to prevent or modulate infection. **Cytomegalovirus** (CMV) is an important cause of prenatal infection and infection in immunocompromised hosts. CD8+ class I MHC-restricted cytotoxic T cells are thought to have a decisive role in controlling CMV infection and deficiencies permit progressive infection. However, CMV is endowed with genes that function to interfere with class I antigen presentation and eliciting T cell responses of the desired specificity and magnitude pose a significant challenge for CMV vaccine development. Recent studies using a strain of CMV that is deleted in the genes that interfere with class I presentation and can display all potentially relevant epitopes from the viral proteome, demonstrate that the CD8+ T cell response to CMV in immunocompetent CMV individuals is more complex than previously appreciated. The results suggest there are additional immunodominant CMV antigens that may be essential to consider in the development of cell therapy or vaccination for CMV. The proposed experiments are designed to identify novel CMV antigens recognized by CD8+ CTL, elucidate their role in controlling CMV infection in normal CMV+ individuals, and determine if adoptive transfer of CMV-specific T cell clones can restore protective immunity in haploidentical stem cell transplant recipients. The specific aims are: 1. To identify **cytomegalovirus** genes encoding novel antigens recognized by CD8+ CMV-specific cytotoxic T cells. 2. To determine the frequency and function of CD8+ T

cells specific for individual CMV antigens in healthy CMV+ individuals with protective immunity. 3. To determine if adoptively transferring CMV-specific T cell clones to recipients of T cell depleted haploidentical stem cell transplant (SCT) is safe, restores CMV-specific immunity, and mediates antiviral activity.

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

- **Project Title: CHARACTERIZATION OF HCMV UL84**

Principal Investigator & Institution: Pari, Gregory S.; Microbiology and Immunology; University of Nevada Reno 204 Ross Hall Mailstop 325 Reno, Nv 89557

Timing: Fiscal Year 2002; Project Start 15-JAN-2000; Project End 31-DEC-2004

Summary: Human **cytomegalovirus** (HCMV) is a ubiquitous herpes virus causing mild or subclinical disease in immunocompetent adults. However, severe complications may be encountered in immunocompromised individuals. HCMV is a systemic infection that may infect several sites in the body, including the retina, gastrointestinal tract, lungs, liver and central nervous system. Initially it was shown that human **cytomegalovirus** (HCMV) required eleven distinct loci for origin-dependent DNA replication. In later studies it was demonstrated that, of the eleven loci originally described, UL84 appeared to be the only non-core replication protein required for oriLyt-dependent replication. This fact, coupled with the observation that RNA-DNA hybrid structures are present within HCMV oriLyt, suggests the possibility that HCMV may have a mode of initiation of DNA replication unlike that of other herpesviruses. UL84 may be the key factor involved in initiation of HCMV DNA replication and, therefore, an ideal target for chemotherapeutic agents needed to control infection. To this end, this proposal will define the role of UL84 in the initiation of HCMV DNA replication and effects on cellular processes. The UL84 protein is required for HCMV DNA replication as demonstrated in transient assays and with a viral mutant. The elucidation of a function for UL84 will allow for the development of anti-HCMV drugs. Our hypothesis is that UL84 is involved in the initiation of HCMV DNA replication by a direct interaction with the origin of replication, oriLyt, and participates in the regulation of host cell RNA processing.

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- **Project Title: CHARACTERIZATION OF HUMAN CYTOMEGALOVIRUS VIRION RNA**

Principal Investigator & Institution: Bresnahan, Wade A.; Microbiology; University of Texas Sw Med Ctr/Dallas Dallas, Tx 753909105

Timing: Fiscal Year 2002; Project Start 01-APR-2002; Project End 31-MAR-2004

Summary: (provided by applicant): Human **cytomegalovirus** is a ubiquitous herpesvirus that infects greater than 80% of the human population. Like all herpesviruses, HCMV is capable of establishing a life-long infection following primary exposure to the virus. Although HCMV infection is usually sub-clinical in healthy individuals, it is a major health problem for newborns and immunocompromised individuals. HCMV is the most common cause of congenital viral infection in the United States occurring in approximately 1% of all newborn infants. These congenital infections often result in severe mental and motor abnormalities. The other groups of individuals frequently affected by HCMV are immunocompromised individuals, such as AIDS patients and transplant recipients. For example, HCMV has been reported to be the primary cause of death in over 25% of AIDS patients, and is the single most important infectious agent affecting organ recipients. At least two-thirds of organ recipients

develop a HCMV infection after transplantation, which often results in organ rejection. The increasing use of therapeutic immunosuppression, organ transplantation, and the incidence of AIDS, has focused attention upon the HCMV life cycle. The goal of the research in this proposal is to provide a better understanding of HCMV replication and specifically, characterize viral transcripts that are packaged within HCMV virions. This proposal is designed to investigate two of these virion RNAs, the 5kb immediate- early (IE) and 1.2kb early transcripts. Two objectives have been outlined; 1) determine if the 5kb IE and 1.2kb early virion RNA transcripts are required during the HCMV life cycle, and 2) identify the mechanism by which virion RNAs are targeted to the HCMV particle. By understanding why and how HCMV packages viral transcripts within virions, novel approaches or therapeutics may be identified to help combat HCMV infection.

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

- **Project Title: CHEMISTRY AND DEVELOPMENT OF TRANSPLANTATION ANTIGENS**

Principal Investigator & Institution: Edidin, Michael A.; Professor; Biology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

Timing: Fiscal Year 2003; Project Start 01-JAN-1978; Project End 31-DEC-2007

Summary: (provided by applicant): Assembly and intracellular trafficking of MHC I molecules is the crucial to their display and antigen presentation to T cells. All of the steps of assembly and peptide loading of MHC I molecules occur in the membrane of one cell organelle, the endoplasmic reticulum, ER. However, the distribution of assembly and quality control regions of the ER remains largely unknown. Biochemistry defines the molecules involved and the temporal dimensions of assembly and quality control, but does not yield their spatial dimensions. It also does not address the steps of ER export after MHC I is peptide loaded. We will ask 3 questions about the ER assembly, quality control and export of MHC I molecules. I. How are MHC I assembly, quality control and carrier-mediated ER export organized over the large area of the ER membrane? Are the individual steps in these processes confined to ER membrane domains or do they occur at random throughout the ER? II. How does BAP31, an ER export and quality control protein, function in the export and quality control of MHC I molecules? Does it function solely as an export carrier, or is it also an MHC I quality control protein? III. Do viral proteins that interfere with ER exit aggregate MHC I molecules and direct them to domains that are isolated from ER exit sites, or do they compete with export carriers for MHC I binding? These questions will be first addressed by a combination of FRAP and FLIP measurements to measure molecular mobility and formation of domains in the ER. Immunoprecipitation and resonance energy transfer, FRET, measurements will detect molecular clustering and molecular associations for ER export and quality control. These techniques will be used to study wild-type and mutant MHC I molecules tagged with GFP and other fluorescent proteins, FP. Chaperones and export carriers, tapasin and BAP31 will also be tagged with FP as will viral proteins, the US3 protein of HCMV, and the MCMV proteins m4(p34) and m152.

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

- **Project Title: CMV DISRUPTION OF CONSTITUTIVE MHC CLASS II**

Principal Investigator & Institution: Sedmak, Daniel D.; Professor and Chair; Pathology; Ohio State University 1960 Kenny Road Columbus, Oh 43210

Timing: Fiscal Year 2002; Project Start 01-JAN-2001; Project End 31-DEC-2004

Summary: (Verbatim from the applicant's abstract) Human **cytomegalovirus** (CMV) is a significant viral cause of morbidity and mortality in transplant recipients. In these patients CMV disease often results from reactivation of latent and persistent virus. A central mechanism of persistence is the ability of CMV to escape detection by host T lymphocyte-mediated immuno-surveillance, which is mediated by both CD8+ T lymphocytes and CD4+ T lymphocytes. In an analogous fashion to CMV encoding multiple genes which disrupt MHC class I, it now appears that CMV has developed mechanisms to evade CD4+ T lymphocyte mediated immuno-surveillance through disruption of MHC class II molecule expression. Within infected cells, CMV inhibits IFN-g induced MHC class II expression by mechanisms that disrupt the IFN-g signaling pathway. Recently the effect of CMV on MHC class II expression has been expanded to include inhibition of constitutively expressed class II, by its gene US2. Using a constitutive HLA class II expressing cell line, we have found a major CMV-mediated decrease in surface class II expression that is independent of US2 or proteasomal degradation. Our Northern, Western and confocal microscopy studies suggest that the mechanism is a defect in trafficking of mature class II to the cell surface. Moreover, this mechanism specifically targets class II, since studies with mutant CMV lacking the genes that alter class I demonstrate normal to increased class I expression, but decreased class II surface expression. Based on our preliminary data, we will test the hypothesis that CMV specifically blocks class II trafficking by altering the intracellular vesicle trafficking machinery. In Specific Aim I, we will further characterize the effect of CMV infection on MHC class II expression. The transport and assembly of MHC class II molecules in infected cells will be examined using co-immunoprecipitation, Western blot analyses, and confocal microscopy. In Specific Aim II, the mechanism(s) of the CMV-mediated decrease in constitutive MHC class II expression will be investigated, specifically examining the role of CMV-mediated disruption of the actin and microtubule networks in this inhibition. We will quantify the effect of CMV on the polymerization, cleavage and integrity of these structures and determine the mechanism(s) CMV uses to inhibit their ability to traffic class II positive vesicles. In Specific Aim III, stable transfections of the U373-CIITA line with CMV Towne strain cosmid clones will be used, in conjunction with a CMV cDNA library, to identify and isolate the CMV genes responsible for the decrease in constitutive MHC class II surface expression.

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- **Project Title: CMV DISRUPTION OF IFN SIGNAL TRANSDUCTION**

Principal Investigator & Institution: Trgovcich, Joanne; Pathology; Ohio State University
1960 Kenny Road Columbus, Oh 43210

Timing: Fiscal Year 2003; Project Start 01-APR-2002; Project End 31-MAR-2006

Summary: Human **cytomegalovirus** (HCMV) is a significant cause of morbidity and mortality in transplant recipients. The majority of HCMV- associated morbidity and mortality is the result of the spread of persistent virus. The long term goal of our laboratory is to understand at the host, cellular, and molecular level the mechanisms by which HCMV persists, to develop novel strategies for blocking HCMV persistence, and ultimately reduce the incidence of HCMV disease in transplantation. A critical means by which HCMV establishes a persistent infection is to evade host innate and adaptive immune responses. Recently, we have discovered that one of these key immunoevasion strategies is the blockade of interferon (IFN) stimulated responses in HCMV infected fibroblasts and endothelial cells. HCMV blocks IFN-gamma and IFN-alpha/beta stimulated signal transduction, IFN-stimulated transcription factor activation, and IFN-stimulated gene expression in infected cells. Analyses of the JAK/STAT signal

transduction pathway reveals that protein levels of JAK1, a tyrosine kinase required for activation of IFN-gamma and IFN- alpha/beta signal transduction, are decreased in HCMV infected cells. The focus of this proposal is to determine the molecular mechanism for the HCMV-mediated decrease in JAK1 expression, identify the HCMV gene that decreases JAK1 expression and disrupts IFN signal transduction, and investigate the significance of IFN-blocking activity in mutant HCMV strains lacking this capability. In Specific Aim I, we will test the hypothesis that JAK1 protein levels are decreased by a proteasome-dependent process in HCMV infected cells. We will analyze the mechanism for the degradation of JAK1 proteins in infected cells and the upstream events prior to JAK1 degradation including phosphorylation, ubiquitination, and IFN-receptor binding. Moreover, the role of suppressors of cytokine signaling (SOCS) proteins in blocking the kinase activity of JAK1 and mediating JAK1 degradation will be investigated. In Aim II, we test the hypothesis that HCMV encodes a gene product that mediates the decrease of JAK1 levels thereby blocking IFN signal transduction in infected cells. 2C4 cells, which are stably transfected with an IFN-responsive promoter linked to the cell surface CD2 glycoprotein, will be utilized to expression clone the HCMV gene with IFN signal transduction blocking activity. In Aim III, we will test the hypothesis that HCMV-mediated IFN-blocking activity is critical for HCMV gene expression, replication, and reducing MHC-based antigen presentation. To test this hypothesis, we will generate a mutant HCMV strain lacking IFN-blocking activity and investigate HCMV gene expression, replication, and MHC based antigen presentation in the presence of IFNs.

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- **Project Title: CYTOMEGALOVIRUS IN THE BRAIN**

Principal Investigator & Institution: Van Den Pol, Anthony N.; Professor; Neurosurgery; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

Timing: Fiscal Year 2002; Project Start 01-JUL-2001; Project End 31-MAY-2006

Summary: (provided by applicant): **Cytomegalovirus** is the leading viral cause of congenital disease, often producing serious neurological deficits. CMV attacks the developing central nervous system (CNS) resulting in serious brain disorders that include microencephaly, epilepsy, deafness, microgyria, mental retardation, sensory loss, motor problems, and psychiatric disturbances. In addition, CMV is a clinically important opportunistic virus that can lead to serious neurological disease in AIDS patients. Despite the clinical importance of CMV infections of the brain, relatively little experimental work has been done in this area, and many basic questions remained unanswered. The present application addresses basic mechanisms of viral spread into the brain, and once in the brain, spread by intracellular transport or extracellular diffusion to other brain cells. The hypothesis that CMV can be spread through axonal transport will be studied with in vitro and in vivo models. Although CMV appears to have no absolute host cell preference in the brain, the hypothesis that CMV shows relative cellular preferences will be tested in living brain slices at different developmental ages. A recombinant mouse CMV expressing green fluorescent protein will be used to identify infected cells. Neurons in vitro are all killed by CMV, whereas mature neurons in vivo are protected against CMV. Using a mouse model of immunosuppression, parallel to AIDS, we will test the hypothesis that cell-mediated immunity protects neurons in vivo from CMV proliferation. Neuronal activity plays an important role in establishing the correct circuitry during brain development. The hypothesis that early infection by CMV can generate disturbances in the electrophysiological activity of developing neurons will be tested with whole cell patch

clamp recording using current and voltage clamp electrophysiology, and with calcium digital imaging, using primary mouse neuron cultures and brain slices. Virus mediated changes in intracellular ion levels, ion currents, transmitter responses, and membrane properties will be compared in CMV infected and control cells.

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

- **Project Title: CYTOTOXIC T CELL TRANSFER FOR THERAPY OF EBV LYMPHOMA**

Principal Investigator & Institution: Rooney, Cliona M.; Professor; Pediatrics; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

Timing: Fiscal Year 2002; Project Start 01-SEP-1993; Project End 31-JAN-2004

Summary: (Adapted from Applicant's Abstract): Adenovirus, **cytomegalovirus** (CMV) and Epstein-Barr virus (EBV) are the three commonest causes of lethal viral disease in patients immunocompromised by allogeneic stem cell transplantation (SCT). No drugs are available to treat adenovirus or EBV infections, and conventional agents for CMV have many limitations. Hence there is considerable interest in the use of T-cell based therapies to restore immunity to these pathogens. The current application builds on this group's earlier work, showing that EBV specific CTL generated by culture of donor T cells with donor EBV-transformed lymphoblastoid cell lines (LCL) can be safely administered to SCT recipients and act as effective EBV prophylaxis. Moreover, gene marking the CTL before infusion showed that these cells persisted long term and infiltrated and destroyed sites of active EBV lymphoma. This grant now proposes to use the excellent antigen presenting properties of EBV-LCL to present additional antigens, derived from adenovirus and CMV, ultimately generating a CTL line from a single culture that has specificity for all three viruses. The three Specific Aims are based on substantial pre-clinical feasibility data. In Aim 1, patients will continue to receive EBV-specific CTL but will receive in addition gene marked adenovirus specific CTL in a dose escalation study, to establish their safety and persistence. In Aim 2, EBV-LCL themselves will be pulsed with adenovirus and used to generate bi-specific lines recognizing both EBV and CMV. These will be infused into patients and their persistence and anti-viral immune activity measured. In Aim 3, EBV-LCL will be pulsed with both adenovirus and CMV, and tri-specific CTL lines prepared. Following infusion, their safety, persistence and anti-viral immune activity will be determined. This plan to develop a cell based anti-viral therapeutic that derives from a single culture system, will offer a practical and cost-effective means of preventing these three lethal infections after SCT.

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- **Project Title: DEVELOPMENT OF A CYTOMEGALOVIRUS DNA VACCINE**

Principal Investigator & Institution: Evans, Thomas G.; Executive Director, Clinical Research; Vical, Inc. 10390 Pacific Center Ct San Diego, Ca 921214340

Timing: Fiscal Year 2004; Project Start 01-FEB-2004; Project End 31-JUL-2004

Summary: (provided by applicant): The specific AIM of this Phase I SBIR proposal from Vical Incorporated is to move forward an immunotherapeutic vaccine for **cytomegalovirus** (CMV) from preclinical to clinical development. Vical has undertaken a program that focuses on the prevention of CMV viremia, disease, and associated complications in patients undergoing either hematopoietic or solid organ transplantation. The vaccine is a bivalent construct that encodes modified genes for the proteins gB and pp65, and is formulated in the poloxamer CRL 1005 in order to enhance

B and T cell responses. This SBIR proposal will support that development through the final phases of pre-clinical safety studies, assay development, manufacturing, and planning for a Phase I clinical trial in humans. The specific milestone to be reached for moving to Phase II of the SBIR program will be to have the IND allowed in preparation to enroll the first patient by the end of 2003. The work plan takes the development process from the point of this project in March 03 forward to the IND allowance, estimated to occur on approximately 10/30/03. The specific goals to be achieved during that time, and financed in part by this Phase I SBIR application, include 1) the conduct of the pre-clinical safety and toxicology studies, 2) clinical protocol and site development, 3) the manufacture of GMP products, 4) the preclinical analytic testing plan and assay development, and 5) development of the clinical immunogenicity assays needed to support the clinical trials.

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

- **Project Title: EFFECT OF ETHANOL CONSUMPTION ON VACCINE RESPONSES**

Principal Investigator & Institution: Shanley, John D.; Professor; Medicine; University of Connecticut Sch of Med/Dnt Bb20, Mc 2806 Farmington, Ct 060302806

Timing: Fiscal Year 2002; Project Start 01-AUG-2001; Project End 31-JUL-2004

Summary: (provided by applicant): Alcohol abuse is a major health problem in the US. This is especially true among certain populations, such as those affected by HIV infection. Previous studies demonstrated that ethanol use among HIV infected homosexual and bisexual men is significantly more common than those not infected. As the HIV epidemic in this country evolves, HIV is increasingly affecting populations who abuse a number of substances, including alcohol. Ethanol consumption is known to alter host immunity and suppress host defenses to a number of infectious agents. Many of these infectious diseases are amenable to prevention through vaccination. Surprisingly, the impact of acute and chronic ethanol consumption on the ability of vaccines to alter host immunity has not been systematically studied. Infections due to **cytomegalovirus** (CMV) are common worldwide. CMV is also a serious cause of human disease in congenital infection and in infection of individuals with abnormal immunity. For example, CMV is a common and serious cause of disease in individuals with HIV infection. Because of its ability to cause disease in these situations, there is currently intense interest in the ability of vaccines to prevent or modify the course of CMV infection. We have developed a murine model of vaccination to modify immunity to CMV infection. We will utilize this model to determine if acute or chronic ethanol consumption alters either the course of CMV infection or the host response to vaccination. The broad objective of this proposal is to test the hypothesis that ethanol consumption will alter the host response to vaccination. With this in mind, the specific aims of the proposal are the following: Specific Aim 1: To determine whether acute or chronic ethanol consumption alters the course of acute CMV infection. Specific Aim 2: To determine if acute or chronic ethanol consumption alters the ability vaccination to alter the host response for CMV. The proposed experiments are designed to explore the effects of ethanol consumption on acute viral infection and response to vaccination in a highly defined and reproducible system. These studies will set the stage for a systematic analysis of the mechanisms by which ethanol alters the host responses to viral infection and viral vaccine administration.

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- **Project Title: ENHANCEMENT OF POST-BMT IMMUNE RECONSTITUTION BY IL-7**

Principal Investigator & Institution: Weinberg, Kenneth I.; Professor of Pediatrics; Children's Hospital Los Angeles 4650 Sunset Blvd Los Angeles, Ca 90027

Timing: Fiscal Year 2002; Project Start 15-JUL-1996; Project End 31-MAR-2007

Summary: (PROVIDED BY APPLICANT): Immune reconstitution after hematopoietic stem cell transplantation (HSCT), high dose chemotherapy or highly active anti-retroviral therapy (HAART) for HIV infection has emerged as a major problem, which limits the success of the therapies. When the mature T lymphocyte compartment is ablated or significantly decreased, as in the above conditions, immune reconstitution depends on production of mature T lymphocytes from immature progenitors in the thymus. Failure to regenerate a full repertoire and normal numbers of T lymphocytes results in morbidity and mortality from opportunistic infections or viral-associated malignancies. Factors contributing to defective thymopoiesis include age, intensive chemo- or radiotherapy, and graft versus host disease. Previous work by others and us has demonstrated that a major cause of post-BMT immune deficiency is the loss of thymopoietic capacity. The ability of the thymus to generate new T lymphocytes depends on two cytokines, IL-7 and c-kit ligand (KL), which are produced by thymic epithelial cells (TEC) and interact with their cognate receptors on immature thymocytes. IL-7 mediates proliferative, anti-apoptotic and differentiative effects on prothymocytes and immature thymocytes. Destruction or inhibition of the IL-7 producing TEC by irradiation or chemotherapy results in an inability to produce thymocytes normally. Recent data on aging mice also indicates that loss of intrathymic IL-7 production underlies the age-related decline in thymopoietic capacity. The general model that underlies our work is that the loss of IL-7 producing TEC underlies many forms of thymic insufficiency. We have shown that administration of either recombinant IL-7 or retrovirally transduced marrow stroma which expresses the IL-7 gene (IL-7 stroma) to mice after HSCT can restore thymopoiesis, mature T lymphocyte numbers and antigen-specific immune function. The experiments in the present grant will determine whether IL-7 or IL-7 stroma can be used to enhance thymopoiesis in murine models that simulate clinical situations. Because IL-7 is a survival and proliferation factor for mature T lymphocytes, it is necessary to determine whether IL-7 treatment will exacerbate graft-versus-host disease (GVHD) after HSCT. Increasingly, transplantation is being performed with purified progenitor populations; the effects of IL-7 administration after transplantation of either purified HSC or of common lymphoid progenitors (CLP) will be determined. Previous studies have demonstrated that IL-7 treatment enhances responses to neo-antigen after HSCT; the present grant will test whether IL-7 confers protection after experimental challenge with murine **cytomegalovirus** infection. The durability of the thymopoietic improvements induced by IL-7 or IL-7 stroma will be examined. Together, the studies will elucidate mechanisms by which IL-7 replacement can be used to treat thymic insufficiency.

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

- **Project Title: ENVELOPE ASSEMBLY OF HUMAN CYTOMEGALOVIRUS**

Principal Investigator & Institution: Britt, William J.; Professor; Pediatrics; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

Timing: Fiscal Year 2002; Project Start 01-JUL-1995; Project End 31-MAY-2005

Summary: The assembly of human herpesviruses, specifically the envelopment of the virion, has remained an active by contentious area of investigation. Two different

pathways of assembly have been proposed for alpha-herpesviruses based on studies in HSV, VSV, and PRV. Although considerable evidence has suggested that envelopment occurs at the nuclear membrane, more recent findings have argued for cytoplasmic envelopment following an envelopment/deenvelopment step at the nuclear envelope. The assembly of beta-herpesviruses, specifically human **cytomegalovirus** (HCMV), appears to differ from that of alpha-herpesviruses in that the final tegumentation and compartment in which both tegument and envelope proteins accumulate and have suggested this is a cytoplasmic site of assembly. Furthermore, the PI and others have shown that tegument coated particles bud into cytoplasmic vacuoles whose limiting membranes contain viral envelope glycoproteins. More recently, the PI has described biochemical and imaging findings which indicate that the cytoplasmic tail of the major envelope glycoprotein of HCMV, gB, interacted with an abundant, myristylated tegument protein, pp28. Together these findings have argued for an assembly pathway which is similar to that described for RNA viruses. This pathway included accumulation of structural proteins in an cytoplasmic compartment, specific interactions between matrix (tegument) proteins and envelope glycoprotein, deformation of host membranes and exclusion of host proteins, and finally, budding of the particle. In this proposal, the PI will investigate this model by initially characterizing the interaction between gB and pp28 and between other viral proteins, which interact with these two structural proteins. They will then define targeting signals, which direct these proteins to cytoplasmic sites of assembly. In the final section of the proposal, they will generate recombinant viruses with mutations in gB, pp28 and interacting proteins which based on earlier finding, will interrupt or interfere with the assembly program. Analysis of the phenotypes of these viruses will all them to directly address their hypothesis and determine the specific protein interactions between tegument proteins and envelope glycoproteins which are crucial to the assembly of HCMV.

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- **Project Title: EPIDEMIOLOGY OF CAROTID ARTERY ATHEROSCLEROSIS IN YOUTH**

Principal Investigator & Institution: Davis, Patricia H.; Neurology; University of Iowa Iowa City, Ia 52242

Timing: Fiscal Year 2002; Project Start 30-SEP-1995; Project End 31-MAR-2004

Summary: (Adapted from Investigator's Abstract) The atherosclerotic process begins in childhood and progresses through adult life resulting in coronary heart disease (CHD), stroke, and peripheral vascular disease. There is a need to identify young people at risk for premature atherosclerosis so that preventive measures can be instituted before occlusive vascular disease occurs. The ultrasonic measurement of carotid intimal-medial thickness (IMT) allows detection of early atherosclerosis and is related to incident CHD and stroke in older adults. In 1970, a population of school age children and adolescents was first examined in Muscatine, Iowa. A sample of 776 members of this longitudinal cohort, who are representative of the initial childhood population, is now aged 37 to 45 years. Their risk factors were measured in childhood, young adulthood and twice in later adult life, and they have undergone measurement of carotid IMT as well as electron beam computed tomography to identify coronary artery calcification (CAC). In this cohort, carotid IMT is significantly associated with CAC as well as current LDL cholesterol and systolic blood pressure, but only 14 percent of carotid IMT variability can be explained by these risk factors. Parents of the cohort have been assessed for cardiovascular morbidity and mortality. In this application the investigators propose to do the following: (1) examine the third generation to determine whether the offspring of

cohort members with premature atherosclerosis and/or a familial history of cardiovascular disease have increased carotid IMT or elevated risk factors; (2) identify risk factors for progression of carotid IMT over four years in this cohort; and (3) measure putative risk factors for increased IMT (serologic evidence of *Chlamydia pneumoniae* or **cytomegalovirus** infection, high sensitivity C-reactive protein, fibrinogen, plasminogen activator inhibitor-1 and glycosylated hemoglobin). The investigators state that the study has the potential of providing information which would allow identification of subjects at risk for atherosclerosis at an early age and may lead the way to interventions to halt or slow progression of atherosclerosis prior to the development of clinical disease.

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

- **Project Title: GENE THERAPY FOR CHRONIC NEURODEGENERATIVE DISORDERS**

Principal Investigator & Institution: Castro, Maria G.; Professor; Cedars-Sinai Medical Center Box 48750, 8700 Beverly Blvd Los Angeles, Ca 900481804

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

Summary: (provided by applicant): Parkinson's disease (PD) is a chronic neurodegenerative disorder. Although we do not yet understand its cause, there is extensive degeneration of nigro-striatal DA neurons. Powerful neurotrophic factors which could be used for the treatment of PD, like GDNF, have been described recently. The ultimate goal of this proposal is to develop novel high-capacity adenoviral systems for cell-type specific, inducible, long term, stable, and non-immunogenic delivery of neuroprotective genes to the brain for both experimental transgene expression in adult animals, and for the future treatment of chronic neurodegenerative diseases such as PD and Alzheimer's disease by gene therapy. Currently the use of adenovirus vectors has been limited by the low efficiency of transcriptional promoter elements currently used, which directly leads to the need to use higher doses of vectors, and the cytotoxicity and immunogenicity of viral proteins expressed from the genomes of first generation adenoviral vectors. We now wish to develop novel cell-type specific and inducible vectors, that will allow efficient, safe, and long-term gene delivery vectors for neurological gene therapy. We will construct high-capacity helper-dependent adenoviral vectors that express no adenoviral genes. We will utilize the powerful, astrocyte specific major immediate early murine **Cytomegalovirus** promoter, driving novel tetracycline-dependent transcriptional activators to achieve cell-type specific and regulatable expression of GDNF. The efficacy, cell-type specificity, and inducibility of these vectors will be tested stringently to assess their capacity to deliver cell-type specific and regulatable GDNF, and also to determine any potential side effects caused either by the vectors or the long term expression of powerful neurotrophic agents. The reagents and principles established by this work will be of substantial value to those with interests in the basic and clinical neurosciences, and will lead to the development of novel, efficient, and safe approaches for the treatment of human chronic neurodegenerative diseases. This research will facilitate the development of the tools needed to achieve long-lived, safe, cell-type specific, regulatable, non-cytotoxic transgene expression, and, ultimately, for the treatment of patients suffering from chronic neurodegenerative diseases.

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- **Project Title: GENERATION OF HERPES VIRUSES FOR IN VIVO OBSERVATION**

Principal Investigator & Institution: Maul, Gerd G.; Professor; Wistar Institute Philadelphia, Pa 191044268

Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 31-MAR-2005

Summary: (provided by applicant): The effect of viruses on the host can be observed at different levels of complexity and resolution depending on the technique used. The single-cell observation combined with various labeling techniques has provided great insight into host-virus interactions; however, the observations are made on fixed (dead) infected cells. We propose to develop an in vivo virus genome labeling system that will allow observation of virus genomes in live cells. Visualization of a viral genome in vivo requires tagging its DNA sequence. The construction of a "green" genome is possible by labeling a DNA tag in the viral genome as it enters the nucleus or before packaging with green fluorescent protein (GFP). Cells inducibly producing the GFP-fusion protein to bind to the DNA tag will be generated to assemble a system where upon virus entry into the nucleus or during packaging the viral genome is rendered "green" through very tight binding of the DNA tag and the reporter protein. These genomes can be visualized by confocal microscopy and documented in a time-resolved fashion by time-lapse microscopy. We propose to produce DNA-tagged recombinant herpes simplex virus and mouse **cytomegalovirus**. To complete the system, we will develop cell lines that inducibly produce GFP-labeled DNA-binding protein, where HSV-1 and MCMV can replicate and which are useful as quiescent ("latent") virus containing cultured cell model systems. Such a new system would recognize single viral genomes directly in the live cells and obviate in situ hybridization. The "green" viral genomes will open up new lines of inquiry into the dynamics of virus entry into the nucleus, the sequence of degradation by endonucleases and/or retention in a nuclease-resistant episome, replication and segregation by multiple observation of single cells or populations during quiescence, affinity immune separation of quiescent viral genomes and identification of viral genomes by immunoelectron microscopy.

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

- **Project Title: GLOBAL GENETIC ANALYSIS OF THE HUMAN CYTOMEGALOVIRUS**

Principal Investigator & Institution: Yu, Dong; Molecular Biology; Princeton University 4 New South Building Princeton, Nj 085440036

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

Summary: (provided by applicant): Human **cytomegalovirus** (HCMV) encodes more than 200 putative genes. The function of a substantial number of the viral genes remains unknown. My long-term goal is to understand how the viral genes function during infection and how they regulate the host-virus interactions to facilitate infection. The knowledge obtained from these studies will lead to a better understanding of the molecular mechanism of HCMV pathogenesis. An infectious bacterial artificial chromosome (BAC), pAD/Cre, has been constructed that carries the complete genome of the HCMV strain AD169. In this proposal, transposon random mutagenesis will be carried out on pAD/Cre to systematically introduce insertions into the viral genome. The transposon insertion mutants will be characterized and the viral genes will be classified as being (i) essential, (ii) dispensable, and (iii) non-essential but required for optimal growth in human fibroblasts. A set of complementing cell lines will be constructed to propagate the mutant viruses defective in essential genes. In addition, a protocol will be established to confirm that the growth defect is a direct result of loss of

the presumed gene. Finally, a subset of growth-defective mutant viruses will be fully characterized to delineate the function of the underlying genes that have not been previously studied. The work will be initiated in Dr. Thomas Shenk's lab at Princeton University. The lab is fully equipped for carrying out research in molecular biology and virology. The Shenk lab, the department and the university provide a vibrant intellectually stimulating and interdisciplinary research environment for the candidate's professional development. The department also provides all core facilities required for the success of this proposal. The graduate work as well as the former postdoctoral training of the candidate has well prepared him to perform the proposed studies. At completion of the mentored phase of the award, the candidate will establish his own lab at a research-oriented academic institution to pursue research on HCMV replication and pathogenesis.

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

- **Project Title: GROWTH OF RHEUSUS CYTOMEGALOVIRUS IN MACROPHAGES**

Principal Investigator & Institution: Hansen, Scott G.; Vaccine and Gene Therapy Institute; Oregon Health & Science University Portland, or 972393098

Timing: Fiscal Year 2003; Project Start 01-SEP-2003; Project End 31-AUG-2005

Summary: (provided by applicant): The purpose of this proposal is to develop rhesus **cytomegalovirus** (RhCMV) as model system for studying human **cytomegalovirus** pathogenesis. Specifically, we will be studying the growth determinants of RhCMV in monocyte-derived macrophages (also infected by human immunodeficiency virus or simian immunodeficiency virus), by using a transposon mutagenesis system and bacterial artificial chromosome (BAC) technology.

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

- **Project Title: HCMV IN HUMAN MALIGNANT GLIOMA PATHOGENESIS**

Principal Investigator & Institution: Cobbs, Charles S.; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

Timing: Fiscal Year 2002; Project Start 05-SEP-2002; Project End 31-MAY-2007

Summary: Malignant gliomas are the most common primary central nervous system tumors in humans. Our laboratory has obtained evidence indicating that human **cytomegalovirus** (HCMV), a ubiquitous herpesvirus, is strongly associated with malignant gliomas in vivo. HCMV can promote oncogenic transformation and can dysregulate key cellular pathways such as those affecting angiogenesis, invasion and cell cycle. Multiple strains of HCMV exist in the wild that have different genotypes and phenotypes. Cell mediated immune mechanisms, which can vary from individual to individual, are essential in preventing HCMV disease. Based on these observations, we hypothesize that HCMV infection of glioma cells promotes malignant glioma tumor progression. Further, we hypothesize that HCMV strains with increased oncogenic phenotypes may occur in the wild and may be able to promote glioma progression in individuals with relatively impaired cell mediated immune systems, and that this could explain why a common virus is associated with a rare disease. To test this hypothesis, we have designed experiments with three aims: 1) to determine the role of HCMV infection on the angiogenic, invasive and cell cycle properties astrocyte-derived cells, 2) to determine whether glioma-derived HCMV strains possess distinct genotypes and/or gene expression patterns, and 3) to determine if patients with gliomas possess immunogenetic markers associated with an increased risk of HCMV related disease.

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

- **Project Title: HCMV UL78 EXPRESSION AND FUNCTION**

Principal Investigator & Institution: Brown, David M.; Molecular Biology; Princeton University 4 New South Building Princeton, NJ 085440036

Timing: Fiscal Year 2003; Project Start 01-SEP-2003; Project End 31-AUG-2006

Summary: (provided by applicant): Human **Cytomegalovirus** (HCMV) causes morbidity and mortality in neonates and in immunocompromised individuals. HCMV encodes at least four genes (UL33, UL78, US27, and US28) with homology to G-protein coupled receptors (GPCRs). Studies of M78, the murine homologue of UL78, have shown that M78 is an integral protein in the envelope of virions. Mutations in this gene result in a viral growth defect and reduced expression of an immediate early gene, m123. Interestingly, the de novo expression of M78 is not required to mediate this effect suggesting that the M78 protein present in the virion envelope is sufficient for the efficient expression of m123. This research proposal will: 1.) Determine the expression pattern of UL78 mRNA and protein, 2.) Determine the growth properties of a UL78 deleted mutant virus and 3.) Determine whether the presence of UL78 protein by itself, or in the presence of a CC chemokine (RANTES, MCP-1, MIP-1alpha and MIP-1beta), influences the expression of HCMV and/or cellular genes. Protein expression and localization will be determined by Western blot analysis and/or epitope tagging of the C-terminal domain of UL78. Mutant virus will be generated in an infectious HCMV bacterial artificial chromosome (BAC) and, if necessary, utilizing a complementing cell-line. Growth properties will be determined at a high and low multiplicity of infection in several primary or life-extended cell types. Effects on HCMV or cellular gene expression patterns can be monitored using a viral gene array or cellular affymetrix array respectively, and confirmed by Northern blot analysis.

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

- **Project Title: HCMV-SPECIFIC CELL-MEDIATED IMMUNITY IN INFANTS/CHILDREN**

Principal Investigator & Institution: Luzuriaga, Katherine F.; Professor; Pediatrics; Univ of Massachusetts Med Sch Worcester Office of Research Funding Worcester, Ma 01655

Timing: Fiscal Year 2003; Project Start 01-FEB-2003; Project End 31-JAN-2006

Summary: (provided by applicant): **Cytomegalovirus** (HCMV) is the most common human congenital infection worldwide and frequently causes multi-organ disease in immunocompromised hosts. In adults, the importance of HCMV-specific cell-mediated immune responses has been established for control of HCMV viremia and protection against disease development. However, the capability of young human infants to generate virus-specific cell-mediated immunity has not been well defined. We therefore propose to study the development of HCMV-specific:CD4+ and CD8+ T lymphocyte responses in infants experiencing primary infection. We hypothesize that virus-specific T lymphocyte responses will demonstrate qualitative and quantitative changes over time following primary infection. To address this hypothesis, we will characterize the magnitude and breadth of HCMV-specific CD8+ T cell responses in infants and children from acute through chronic infection. We will first use ELISPOT assays to identify the hierarchy of recognition of HCMV proteins. Epitopes within the most commonly recognized HCMV proteins and their HLA Class I-restricting elements will be defined. Tetramers representing commonly recognized epitopes will be made and used to characterize changes in HCMV epitope-specific CD8+ T cell frequencies over time. We will then characterize the cell surface phenotypes cellular turnover, and activation state of HCMV epitope-specific T cells using tetramer-staining, along with monoclonal

antibodies to cell-surface antigens; functional properties (lytic function, chemokine/cytokine secretion) of HCMV epitope-specific CD8⁺ T cells will be evaluated. The frequencies and specificities of HCMV-specific CD4⁺ T cells will also be examined over time and correlated with HCMV-specific CD8⁺ T cell frequencies. Concurrent measurement of blood HCMV load will allow us to examine the relationship between HCMV-specific cell-mediated immune responses and blood HCMV load. Data from these studies will contribute to our understanding of age-related susceptibility to viral infections and will complement ongoing NIH-funded projects in our laboratory focused on examining the ability of young human infants to generate HIV-1 specific cell-mediated immune responses. The characterization of HCMV-specific cell-mediated immune responses and HCMV viral load over time following infection should help us to better understand virus-host interactions that contribute to the establishment of persistent viral infections and should aid in the development of improved prophylactic and therapeutic interventions for pediatric HCMV infection.

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- **Project Title: HEALTH IMPACT OF CONGENITAL CYTOMEGALOVIRUS INFECTION**

Principal Investigator & Institution: Dekker, Cornelia L.; Associate Professor of Pediatrics; Pediatrics; Stanford University Stanford, Ca 94305

Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-DEC-2007

Summary: (provided by applicant) Human HCMV infection is the leading infectious cause of congenital birth defects and causes important morbidity and mortality in immunocompromised patients of all ages. Humans are the only reservoir for this infection and many unique strains circulate in the general population throughout the world. Rates of congenital HCMV infection in the U.S. range from 0.2 percent to 2.2 percent of all live births, affecting approximately 10,000 to 80,000 infants born each year. The Institute of Medicine study of vaccine objectives has therefore identified congenital HCMV prevention by vaccines as a Level I priority. The overall objective of this application is to define the epidemiology and disease burden of congenital infection caused by HCMV in a diverse, Northern California population by virologically screening 20,000 newborns from three area hospitals over a two-year period. In Specific Aim 1, screening will be done using a direct early antigen detection of fluorescent foci (DEAFF) method to identify HCMV in saliva samples of newborns. We hypothesize that incidence in white infants will be different than that for Hispanic and Asian/Pacific Islander infants born in this area. Virus isolates obtained from infected infants will be tested to determine genetic relatedness and whether specific subtypes are associated with the occurrence of symptomatic vs. asymptomatic infection of the infant. To assess disease burden, we will describe clinical features in infected infants and determine the distribution of symptomatic vs. asymptomatic presentation among demographic groups. In Specific Aim 2, we will describe the incidence, severity and timing of sensorineural hearing loss (SNHL) over three years in infected infants, and determine whether universal newborn hearing screening identifies SNHL caused by congenital HCMV. The pattern of hearing loss will be described for the cohort, and affected infants will be offered remedial treatment. In Specific Aim 3, we will describe the HCMV-specific CD4 and CD8 T cell responses of the infected cohort over three years and determine whether there are differences in immune response pattern between symptomatically and asymptotically infected infants, and between infants and adults. Data from this study will help to define target populations for immunization and clinically relevant immune responses for vaccine researchers.

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- **Project Title: HEMATOPOIETIC CELL TRANSPLANTATION FOR MALIGNANCY**

Principal Investigator & Institution: Forman, Stephen J.; Director; City of Hope National Medical Center Duarte, Ca 91010

Timing: Fiscal Year 2002; Project Start 01-JUL-1981; Project End 31-MAR-2003

Summary: This Program Project Grant application seeks support for clinical and experimental studies concerning the major obstacles to successful allogeneic and autologous stem cell transplantation for the treatment of hematologic malignancies. These problems include recurrence of the underlying disease, graft-versus-host disease and infectious with **cytomegalovirus**. The program consists of two clinical and four experimental projects that are supported by six cores. The two clinical projects propose studies designed to eradicate leukemia and lymphoma utilization innovations in the preparatory regimen as well as in the treatment of minimal residual disease following either allogeneic and lymphoma antigens in the preparatory regimen of patients undergoing allogeneic for leukemia and myelodysplasia or autologous transplantation for lymphoma. It is also the goal of our studies to use antigen-specific cytolytic T cells in the treatment of minimal residual disease in patients undergoing autologous transplantation for B cell lymphoma and allogeneic transport for Ph+ ALL. Two transplant studies involve genetic manipulation of hematopoietic cells to convey resistance to HIV in patients with HIV-related lymphoma utilizing adeno-associated virus and lentiviruses. Studies will also continue on the prevention of graft-versus-host disease and will develop novel immunologic strategies to prevent **cytomegalovirus** disease after allogeneic transplantation. The two clinical projects in allogeneic and autologous transplantation serve as a resource for the experimental projects in the program. The four experimental projects address biologically important questions related to transplantation including acquisition of immunity to CMV, the development of antigen-specific cytolytic T cells, treatment of minimal residual disease after autologous and allogeneic transplantation, and genetic modification of stem cells to induce HIV resistant immune reconstitution. These projects attempt to bring laboratory based innovative concepts to clinical use in the treatment of Administration for the coordination of research, Biostatistics, Cellular and Molecular Correlative studies, radioimmunotherapy, Long-Term Follow-Up and a new Biomedicine Production Facility for the production of antibodies, antigen specific cells and viral vectors to be used in the experimental studies proposed in this grant.

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- **Project Title: HERPESVIRUS PROTEIN SYNTHESIS AND VIRION ASSEMBLY**

Principal Investigator & Institution: Gibson, Wade; Professor; Pharmacol & Molecular Sciences; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

Timing: Fiscal Year 2002; Project Start 01-SEP-1977; Project End 31-MAY-2006

Summary: (provided by applicant): The long-term goal of this research is to learn more about the structure and function of herpesvirus proteins, and translate that information to new diagnostic, preventive, and therapeutic strategies for dealing with CMV-related diseases of man. We use **cytomegalovirus** (CMV) as our model system because of its medical relevance to immunosuppression resulting from AIDS, organ transplantation, and cancer chemotherapy, and to sexually transmitted diseases and birth defects. Additionally, there is a need to determine the molecular similarities and differences between herpes group viruses in order to understand their biological differences. Our

more immediate objectives are to study the synthesis, structure, and function of specific viral proteins that are essential for virus replication, with a concentration on those involved in virus assembly. Our rationale for studying virus structure and assembly is that most aspects of virus replication are directly or indirectly coupled to the assembly process; therefore, it ultimately represents a major and largely untapped source of new targets for antivirals. The specific aims of the work proposed here are to uncover processes that modulate the very early and intermediate stages of CMV assembly. We will continue our studies of how the proteins of the capsid interact and why, and what modifications they undergo and how these govern the process of capsid formation and maturation. Our plans also include studying three of the tegument proteins that appear to be most closely associated with the capsid and which may anchor other tegument or envelope proteins to the capsid, or perhaps help the capsid negotiate the nuclear membrane as it exits or target it after entry. We will apply a combination of biochemical, cryo-EM/imaging, and genetic experiments to bear on these questions, including (i) use of a recently developed in vitro binding system to study capsid/tegument interactions, and (ii) use of the HCMV-bacterial artificial chromosome system to produce mutant viruses.

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- **Project Title: HIV AND KAPOSI'S SARCOMA PROTEASES**

Principal Investigator & Institution: Craik, Charles S.; Professor; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

Timing: Fiscal Year 2002; Project Start 01-SEP-1997; Project End 31-AUG-2007

Summary: HIV Drotease (HIV PR) is an important drug target due to its crucial role in the maturation of HIV virions. The emergence of drug-resistant strains of the virus has prompted increased study into the nature of the resistance, with the goal of designing more effective drugs. Examination of public and private sequence databases of drug experienced HIV strains may yield proteases with the unique resistance mechanism of altered substrate specificity. These proteases will then be cloned, expressed and biophysically characterized with respect to their kinetic parameters, substrate specificity and inhibitor profiles. This will provide a molecular image of what the enzyme recognizes and help identify the determinants of resistance. Reversion mutagenesis will then be used to evaluate the contribution of specific amino acids to resistance. Selected variants will be pursued at a structural level using both X-ray crystallography and NMR spectroscopy. This will provide an atomic level understanding of the role of specific amino acids to altered conformational flexibility, a key mechanism of resistance. Significant progress has been made on variants of HIV PR that exhibit altered substrate specificity and are resistant to current protease inhibitors. The results of these studies will enable us to understand the mechanism by which HIV PR becomes resistant to small-molecule inhibitors. This, in turn, may lead to the design of more effective anti-proteolytic drugs that continue to reduce viremia in HIV-positive individuals. In a closely related project we will study the serine protease encoded by the Kaposi's sarcoma-associated herpesvirus (KSHV) as a potential target for KS, the most common neoplasm of patients with AIDS. Demonstrating the role of KSHV protease in cell culture has proven difficult because of a lack of potent, specific inhibitors. We will determine the basis of substrate recognition of KSHV PR. This information will assist us in developing a selective chemical probe targeting the active site of the protease. We will also target the interface of this unique dimeric serine protease with dimerization disrupters. Our efforts will be guided by X-ray and NMR structural analysis on the dimeric and monomeric forms of the protease where we have already made significant

progress. Herpesvirus protease inhibition will reveal the importance of protease activity on viral replication. The reagents obtained should be easily adaptable to all of the herpesviruses, including the herpes simplex viruses (HHV1 & HHV-2), Varicella-Zoster virus (HHV-3), Epstein-Barr virus (HHV-4), and human **cytomegalovirus** (HHV-5).

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- **Project Title: HIV REPLICATION AND THYMOPOIESIS IN ADOLESCENTS**

Principal Investigator & Institution: Krogstad, Paul A.; Associate Professor; Pediatrics; University of California Los Angeles 10920 Wilshire Blvd., Suite 1200 Los Angeles, Ca 90024

Timing: Fiscal Year 2003; Project Start 01-FEB-2003; Project End 31-JAN-2008

Summary: (provided by applicant): A large number of children with perinatally-acquired HIV infection are now surviving into adolescence and adulthood. For many of these, HIV infection was not diagnosed and treated until significant immunological abnormalities were already present. In addition, nearly all had poor suppression of HIV replication with the less potent treatment regimens available during their pre-adolescent years. We hypothesize that prolonged and poorly controlled HIV infection throughout childhood in these individuals will lead to premature immunological senescence in early to mid-adulthood, perhaps by accelerating the physiological thymic involution that occurs in childhood and adolescence. The general goal of the studies proposed is to better understand the immunological status and prognosis of long-term survivors of perinatal HIV infection, and to identify possible therapeutic strategies to promote a normal, healthy lifespan for this growing population of infected youths. Taking scientific advantage of the availability of a large local cohort of perinatally infected adolescents, we are proposing studies to examine the balance between the pathogenic properties of HIV, the suppressive and selective power of antiretroviral therapy, and the regenerative capacity of the immune system that exists in these individuals. The specific aims are: 1) To use in vivo labeling methods and other approaches to compare quantitative parameters of thymopoiesis from adolescents/young adults with perinatal HIV infection with those from two age-matched control groups: seronegative subjects, and youths with HIV infection acquired via recent adult behaviors; 2) To evaluate the relationship between these parameters of thymopoiesis, and the pol and nef genotypes and the replication properties of patient HIV isolates, and 3) To examine the magnitude and breadth of cellular immune responses of perinatally infected adolescents to HIV and common infectious agents (including **cytomegalovirus**, influenza, and Epstein-Barr Virus) compared to the age matched controls.

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- **Project Title: HIV-1 SHEDDING FROM FEMALE GENITAL TRACT**

Principal Investigator & Institution: Coombs, Robert W.; Associate Professor; Laboratory Medicine; University of Washington Grant & Contract Services Seattle, Wa 98105

Timing: Fiscal Year 2002; Project Start 23-APR-2001; Project End 31-MAR-2006

Summary: This is a new Program Project application in response to RFA-HD-00- 006 to establish a Women's HIV Pathogenesis program at the University of Washington in collaboration the University of Rochester and the University of Nairobi, Kenya. The central Program these is to explore the hypothesis that the female genital tract is a separate virological compartment from blood. As such, viral application in the genital compartment may be influenced by several factors including the host's hormonal status (i.e., menses), and both viral and microbiological cofactors that could have an important

influence on the evolution of HIV-1 (i.e., generation of viral diversity), re-seeding of the blood compartment with potentially drug-resistant, and disease pathogenesis both within the genital tract (changes from favorable to unfavorable microbiological flora) and systemically (HIV-1 disease progression). Understanding these gender-specific HIV-1 factors may provide additional insight into the control of both vertical and horizontal transmission of HIV-1. To accomplish the central Program theme, we will use three different cohorts of HIV-1-infected women recruited at the three collaborating institutions. The research activities of the Program Project will be accomplished through three Cores and three Research Projects. The infrastructure will reside within an Administrative Core (Core A) located at the University of Washington, a Clinical Core (Core B) and a Laboratory Core (Core C). Both internal and external advisory committees will review the Program's research progress and report to the Principal Investigator, Dr. Coombs. Since our hypothesis is that genital tract inflammation represents a continuum as defined by local vaginitis (bacterial vaginosis), to cervicitis (cytomegalovirus), to endometritis (microbial) and ultimately to pelvic inflammatory disease, each of the three research Projects are designed to capture this continuum. In Project I (HIV-1 shedding and evolution), we will characterize subjects for shedding of HIV-1, CMV and HSV-2, and definitively establish, through viral phylogenetic typing that HIV-1- re-emerges from the genital tract to re-infect the blood compartment in subjects that receive stable anti- retroviral therapy. In Project II (CMV co-shedding) we will show that CMV is an independent viral co-factor for HIV-1 shedding, whether CMV shedding from the cervix represents reactivation or re-infection, and that the suppression of CMV using valganciclovir can decrease HIV-1 genital shedding. In Project III(Bacterial Vaginosis), we will show the effect of bacterial vaginosis as a local co-factor for HIV-1 shedding, how this local abnormal microbiological flora contributes to HIV-1 shedding through local cytokine-mediated mechanisms, and that anti-microbial treatment of bacterial vaginosis in both anti-retroviral treated and untreated women results in decreased HIV-1 genital shedding. Taken together, these studies will provide important comparative data to the male genital tract shedding of HIV-1 and may have implications for both the vertical and horizontal transmission of HIV-1.

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- **Project Title: HUMAN CYTOMEGALOVIRUS DNA CLEAVAGE AND PACKAGING**

Principal Investigator & Institution: Mcvoy, Michael A.; Pediatrics; Virginia Commonwealth University Richmond, Va 232980568

Timing: Fiscal Year 2002; Project Start 15-MAY-2001; Project End 31-MAR-2006

Summary: (Adapted from applicant's abstract): The Herpesviridae family of viruses includes several significant human pathogens, including herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, Kaposi's sarcoma associated herpesvirus, and human **cytomegalovirus** (HCMV). DNA replication in these viruses produces large concatemeric intermediates, from which unit genomes are cleaved at specific sequences and packaged into viral particles. The halogenated benzimidazole ribonucleosides are a new class of antiviral drugs which block this process. Unfortunately, our understanding of herpesvirus cleavage and packing is scant and the mechanism of action of these drugs remains unknown. Using murine **cytomegalovirus** (MCMV), we have begun to define the cis elements that are recognized at the cleavage site. Using guinea pig **cytomegalovirus** (GPCMV), we have demonstrated that the mechanism of cleavage duplicates sequences at the viral termini. Recent findings in GPCMV and HCMV suggest that the benzimidazoles induce a premature cleavage to produce truncated

genomes. In aim 1 of this proposal, we will more accurately define the cis cleavage/packaging signals of MCMV and initiate efforts to analyze cis elements in HCMV. In aim 2, experiments to elucidate the mechanisms of cleavage and packaging will define the phenotypes of cis mutations in MCMV with respect to formation of intracellular replicative DNAs and extracellular viral genomes. The benzimidazole-induced accumulation of truncated genomes will be investigated by further analysis of the novel ends formed, characterization of capsid composition and structure, and by electron microscopy. A model proposed for the mechanism of repeat duplication will be tested both by analysis of replicative intermediates and by construction of genetic mutations in cleavage/packaging cis elements. In aim 3, viral cleavage/packaging proteins will be characterized both in vitro and in vivo using recombinant expression and their functions studied using either in vitro or permeabilized cell cleavage assays. As cleavage and packaging are highly conserved among herpesviruses, this information should be directly applicable to pathogenic human herpesviruses and may reveal the mechanism of action of the benzimidazoles or facilitate the discovery of novel compounds that target the cleavage and packaging processes.

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- **Project Title: HUMAN CYTOMEGALOVIRUS ENVELOPE GLYCOPROTEINS**

Principal Investigator & Institution: Compton, Teresa G.; Professor; Medical Microbiol & Immunology; University of Wisconsin Madison 750 University Ave Madison, WI 53706

Timing: Fiscal Year 2002; Project Start 01-JUN-1999; Project End 31-MAY-2004

Summary: Viral envelope glycoproteins expressed on cellular membranes and/or incorporated into the envelope, mediate critical steps in the lifecycle such as entry, egress and cell to cell spread of infection. A hallmark and defining feature of human **cytomegalovirus** (HCMV) infection, is its capacity to enter and spread cell to cell between cell types of distinct and divergent developmental lineages. Since few cell surface molecules are distributed on all of these cell types, it is likely that multiple viral glycoproteins participate in HCMV pathogenesis. Sequence analysis predicts 67 possible glycoproteins reflecting the potential to utilize multiple viral ligand/cellular interactions. Biochemical analysis of HCMV envelope revealed the presence of at least 10 glycoproteins, many of which are organized into large disulfide-linked complexes. However, only 5 of these proteins are mapped to the viral genome. Before the mechanism of viral entry, egress and spread can be delineated, the composition of the envelope must be defined and the genes encoding the envelope proteins identified. This outlines an experimental plan that will define the composition of two major HCMV envelop complexes, gCII and gCIII. Both of these complexes are implicated in virus-cell interactions and both contain identified (gM and gH/gL respectively) as well as unidentified components. The availability of monoclonal antibodies to the known constituents of these complexes will allow purification of gCII and gCIII. Further purification and separation of individual complex proteins will precede microsequence analysis and genetic identification of the unmapped glycoproteins. The feasibility of this approach is bolstered by significant preliminary data regarding the identification of a previously unmapped component of gCIII. Once reagents to the newly mapped proteins are produced, the composition of the complexes will be verified. Biophysical parameters such as the molecular mass and stoichiometry of gCII and gCIII will be determined using a variety of biochemical techniques. The biosynthetic pathway and cellular localization within infected cells will be characterized. These studies will facilitate our understanding of virion maturation and egress, an area of the HCMV lifecycle with enormous gaps in knowledge. In studies aimed at future functional analysis of the gCII

and gCIII, the complexes will be reconstituted by co-expression of the individual components. The information learned in the course of the studies is critical for future advances in the understanding of the HCMV lifecycle and pathogenesis and may also serve as the basis for future antiviral drug design.

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- **Project Title: IMMUNE CONTROL AND EVASION IN MURINE CMV INFECTION**

Principal Investigator & Institution: Hill, Ann B.; Assistant Professor; Molecular Microbiology and Immunology; Oregon Health & Science University Portland, or 972393098

Timing: Fiscal Year 2002; Project Start 15-APR-2002; Project End 31-MAR-2006

Summary: (provided by applicant): **Cytomegaloviruses** (CMVs) encode multiple genes that function to impair MHC class 1-restricted antigen 1 presentation to cytotoxic T lymphocytes (CTL). It has been assumed that these genes are necessary to enable CMV to persist in the host in the presence of a primed immune response, but this has not been demonstrated. This application uses the murine **cytomegalovirus** model of infection of its natural host (the mouse) to ask what effect the immune evasion genes have on the course of MCMV infection, and how they achieve this effect. A panel of mutant viruses lacking each of the immune evasion genes of MCMV- m4, m6 and m152-alone and in combination, has been generated using bacterial artificial chromosomes technology. These will be used to analyze the effect of the immune evasion genes on the CTL response, and the consequent effect on virus persistence and replication. In order to be able to study the CTL response, the immunodominant MCMV antigens recognized by H-2b mice will first be identified. An expression library containing the entire MCMV genome expressed in short DNA fragments has been generated and will be screened using MCMV-specific CTL clones to identify the antigens they recognize. MCMV infects macrophages and dendritic cells as well as epithelial and other somatic cells in vivo. Antigen presentation by professional antigen presenting cells is likely to be the major determinant of the size of the CTL response, and it has been reported that the immune evasion genes do not function effectively in macrophages. However, data suggesting that the immune evasion genes may function in some macrophages is presented here. A comprehensive analysis of the function of the immune evasion genes on antigen presentation by Kb and Db in primary macrophages and dendritic cells will be carried out and contrasted with the effect seen in mouse embryo fibroblasts. This information will be used to interpret experiments measuring the CTL response and virus load in mice infected with wildtype virus and viruses lacking immune evasion genes.

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- **Project Title: IMMUNOTHERAPY WITH PEPTIDE MHC TETRAMER ISOLATED T CELLS**

Principal Investigator & Institution: Lyerly, Herbert K.; Director; Surgery; Duke University Durham, Nc 27706

Timing: Fiscal Year 2002; Project Start 16-SEP-2002; Project End 31-JUL-2006

Summary: (provided by applicant): Recent advances in T cell phenotyping and high speed sorting have coalesced to allow the direct testing of an important basic tenet in immunotherapy-specifically that adoptive immunotherapy with antigen specific T cells will eradicate antigen expressing cells in vivo. Although immunotherapy with T cells activated and expanded in vitro have shown promise, an alternative broadly applicable strategy may allow therapy with antigen specific T cells prior to significant activation.

Specifically, peptide major histocompatibility complex (MHC)-tetramers allow the identification of T cells that specifically bind to unique nanopeptides in the context of a specific human leukocyte antigen (HLA) allele. This technology allows for the sorting and isolation of highly purified populations of antigens specific T cells from peripheral blood mononuclear cells (PBMC). We have hypothesized that the adoptive immunotherapy with purified populations of antigen specific T cells will have clinical benefits in patients immunosuppressed following bone marrow/peripheral blood stem cell transplant. A relevant model system to test this hypothesis exists in immunocompromised patients with **cytomegalovirus** (CMV) infection or Epstein Barr virus (EBV) associated LPD (LPD). Clinical benefit has been achieved with administration CMV specific clones expanded in vitro and as few as 10(7) cells/M2PBMC activated in vitro with autologous EBV transformed B cells. While these strategies are clinically effective, they cannot be widely applied because they are complex and time-consuming, taking as long as to 3 to 4 months to generate the appropriate cells for administration. An exciting alternative to this laborious process would be to directly isolate CMV or EBV specific T cells from peripheral blood samples by high speed sorting with CMV or EBV peptide MHC tetramers. This strategy would allow for the rapid isolation of up to 10-40 x 10(6) antigen specific T cells. These cells could then be directly administered, or administered after a brief period of ex vivo activation and expansion. This application proposes pre-clinical studies and pilot clinical trials of adoptive immunotherapy with peptide MHC tetramer sorted T cells. It is anticipated that these studies would provide an important proof of principle for this general concept which would have wide application for antigen specific adoptive immunotherapy of viral disorders and cancer.

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- **Project Title: INFLAMMATION AND INFECTION AS RISK FACTORS IN STROKE**

Principal Investigator & Institution: Elkind, Mitchell S.; Gertrude H Sergievsky Center; Columbia University Health Sciences New York, Ny 10032

Timing: Fiscal Year 2002; Project Start 15-JAN-2002; Project End 31-DEC-2006

Summary: (provided by applicant): Serum markers of infection and inflammation have been associated with both incident myocardial infarction (MI) and prognosis after MI, but very little data about the relationship of these markers to stroke incidence or prognosis is available. Preliminary studies by the applicant have shown that chronic infection with *Chlamydia pneumoniae* (*C. pneumoniae*) is associated with stroke risk, and that elevated white blood cell count and soluble tumor necrosis factor receptor levels are associated with carotid atherosclerosis. The applicant has training in epidemiology, but no advanced training in laboratory techniques or in the basic biology of inflammation or infection. This career development award will train the applicant in the pathobiology of inflammation and infection, in basic techniques of molecular biology, and in advanced epidemiologic and biostatistical analysis. The proposed study will test the following hypotheses: 1) Elevated levels of markers of inflammation (CRP, interleukin 6, tumor necrosis factor receptor levels) and specific infections (*C. pneumoniae*, CMV) are independent predictors of first ischemic stroke, and 2) elevated levels of these markers of inflammation and infection are associated with worse prognosis after stroke. Two concurrent prospective study designs are proposed to test these hypotheses. For hypothesis 1, levels of these markers will be compared in 125 stroke cases and 250 controls, all of whom are drawn from the 3300 initially strokefree subjects in the Northern Manhattan Stroke Study (NOMASS, NINDS 2RO1-29993). ELISA will be used to measure marker levels. The blood samples analyzed will be those drawn at baseline, prior to stroke occurrence, using a strong design, the nested

casecontrol study. Multiple conditional logistic regression analysis will be used to assess the significance of the main exposure variables after matching for age, gender, and race/ethnicity, and after adjustment for other risk factors. For hypothesis 2, 300 prospectively enrolled stroke patients in the Aortic Plaque and Risk of Ischemic Stroke Study (APRIS, NINDS R01-36286) will be followed up annually for 3 years for the occurrence of stroke, death, or MI, and the levels of these markers in blood samples will be analyzed by ELISA. Cox proportional hazards modeling will be used to assess survival based on baseline inflammatory marker status after adjustment for other risk factors and stroke severity. The applicant will pursue coursework in infectious diseases and pathobiology of inflammation, as well as in advanced epidemiologic and biostatistical analysis. He will participate in laboratory practicums at Columbia and the CDC to gain hands-on knowledge of laboratory techniques, including ELISA and PCR, necessary for the present and future studies. It is anticipated that these experiences and the successful completion of the proposed project will allow him to compete for independent investigator awards. Nationally recognized experts in stroke epidemiology and basic vascular biology will serve as mentors for these studies.

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- **Project Title: INFLAMMATION IN SICKLE DISEASE**

Principal Investigator & Institution: Vercellotti, Gregory M.; Senior Associate Dean for Education; Medicine; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

Timing: Fiscal Year 2002; Project Start 01-APR-2001; Project End 31-MAR-2005

Summary: (Investigator's abstract) Sickle cell anemia patients suffer end organ damage due to vaso-occlusion. Over the past two decades investigations of red blood cell/vessel wall interactions have led to a revised paradigm for the understanding of vaso-occlusive phenomena in sickle cell disease. Clinical conditions associated with inflammation such as infections, surgery and others exacerbate crises in sickle cell anemia patients. Preliminary data demonstrate that patients with sickle cell disease have markers of inflammation including elevated C-reactive protein levels and activated monocytes. In vitro these monocytes activate human endothelial cell NF- κ B and adhesion molecule expression. Transgenic mouse models of human sickle cell disease also have markers of inflammation, including elevated white blood cell counts and activated monocytes. This proposal posits that an inflammatory phenotype augments tissue injury through worsened vasoocclusion. Thus, inflammation augments vaso-occlusion while anti-inflammatory agents may minimize vaso-occlusion. The project will examine these hypotheses in transgenic mouse models of human sickle cell disease: (1) Anti-inflammatory agents decrease vascular inflammation and improve blood flow. (2) Pro-inflammatory agents such as murine **cytomegalovirus**, lipopolysaccharide and hypoxia/reoxygenation, increase vascular inflammation and worsen vaso-occlusion. (3) TNF- α , IL-1 β and CD18 transgenic knockout mice that express human betaS hemoglobin have decreased vascular inflammation and improved blood flow parameters. These studies will provide information for understanding the role of the inflammatory response and its relationship to vaso-occlusion in sickle cell disease and serve as an important foundation for developing new and novel therapies to prevent organ dysfunction.

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

- **Project Title: LYMPHOMA THERAPY USING MIXED PROGENITOR TRANSPLANTS**

Principal Investigator & Institution: Strober, Samuel; Professor of Medicine; Medicine; Stanford University Stanford, Ca 94305

Timing: Fiscal Year 2002; Project Start 08-JUN-2001; Project End 31-MAY-2005

Summary: The goal of the proposed research is to effectively treat the BCL1, B cell lymphoma, in mice using an in allogeneic bone marrow transportation regimen that will not only eliminate tumor cells without graft versus host disease (GVHD), but also allow for satisfactory immune reconstitution of hosts lacking a thymus. Immune reconstitution of MHC-haplotype matched humans given bone marrow or hematopoietic progenitor transplants for treatment of malignancy remains a major problem. In order to facilitate immune reconstitution of CD4+ and CD8* T cells in lethally irradiated BALB/c x C57BL/6 hosts, we will add a newly identified committed T cell progenitor (CTP) to allogeneic C57BL/6 transplants that include purified hematopoietic stem cells (HSC) for hematopoietic reconstitution and purified marrow CD8' T cells for tumor cell killing without GVHD. Hosts will be euthymic or thymectomized. The CTP have been shown to rapidly reconstitute the CD4+ and CD8' T cells of irradiated athymic nude mice via an extrathymic pathway. Hosts will be monitored for survival, tumor cell elimination chimerism, GVHD, and reconstitution of mature CD4' and CD8' T cells. The function of the latter cells will be determined by assaying protection against murine **cytomegalovirus** infection, antibody responses to sheep red blood cells, and delayed type hypersensitivity responses to ovalbumin. In addition, donor-type chimeric cells will be studied for tolerance to host alloantigens. Purified populations of donor cells will be obtained by cytometry to identify and sort HSC, CTP, and CDS' T cells. Chimerism and presence of tumor cells will be measured by immunofluorescent staining and flow cytometric analysis such that chimeric cells derived from each of the three injected donor cells can be identified. GVHD will be monitored by clinical signs, survival, and histopathology.

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

- **Project Title: MECHANISMS OF VASCULAR INJURY BY HCMV**

Principal Investigator & Institution: Crumpacker, Clyde S.; Associate Professor; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2006

Summary: (provided by applicant): This proposal will address possible mechanisms for human CMV to cause atherosclerosis. The goal of this study is to examine the interaction of HCMV with host cells mediating vascular atherosclerosis. The ability of HCMV clinical isolates to cause infection in endothelial cells and induce cellular genes early in infection will be studied. The use of DNA array technology to study induction of human genes in vascular smooth muscle cells and infected endothelial cells will be employed. The hypothesis to be tested is that endothelial derived HCMV infection of vascular smooth muscle and endothelial cells can upregulate cellular gene expression. Cellular genes which enhance apoptosis or death ligands and enhance cellular proliferation will be initially measured. A murine model of atherosclerosis employing a strain of atherosclerosis prone mice infected with murine CMV will be developed. A pathological examination of the atherosclerosis induced in these mice will be performed. The CMV DNA copy number in atherosclerosis lesions will be correlated with the pathology of atherosclerosis. A trial of anti-CMV drugs will be employed to test that anti-CMV treatment will prevent development of atherosclerosis. The specific aims for this proposal

are :1. To determine the induction of human cellular gene expression by infection of smooth muscle cells by endothelial derived clinical isolates of HCMV. 2. To develop a model of murine CMV infection in mice to study vascular wall injury and the development of atherosclerosis. 3. To evaluate the role of specific treatment with anti CMV drugs in the development of endothelial damage in a murine model of atherosclerosis. This trial will include a novel inhibitor of HCMV primase. The overall goal of these studies is to identify the specific molecular interaction between HCMV gene products and human genes induced by HCMV which trigger the development of atherosclerosis.

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

- **Project Title: MIAMI ADULT AIDS CLINICAL TRIALS GROUP, AACTG**

Principal Investigator & Institution: Fischl, Margaret A.; Associate Professor; Medicine; University of Miami-Medical Box 248293 Coral Gables, FL 33124

Timing: Fiscal Year 2002; Project Start 01-APR-1992; Project End 31-DEC-2004

Summary: (adapted from application's abstract): The Miami ACTU has been a member of the AACTG since its inception and has contributed to a number of AACTG studies that led to the approval of seven antiretroviral drugs and numerous HIV treatment strategies including lower and alternative dosing schedules for all three classes of antiretroviral agents, early treatment intervention, combination therapies with dual NRTIs and triple-drug therapy. The Miami ACTU has also actively participated in the Virology Laboratory Subcommittee working groups with an active role in the standardization of a PBMC culture assay for determining drug susceptibility, the assessment of interlaboratory concordance of DNA sequencing analysis of HIV RT, and the development of a consensus sequencing protocol to detect drug resistant mutations. This unit has also been involved with the Surrogate Markers Subcommittee with an active role in the assessment of plasma cytokines and soluble markers, cytotoxic T-lymphocyte activity, lymphocyte proliferation and advanced flow cytometry, and defining and validating immunologic markers as surrogate markers independent of CD4 and HIV RNA. Finally, this unit has contributed to the Pharmacology Committee with the evaluation of targeted- concentration control studies and the correlation of drug exposure with treatment response and failure parameters. The Miami ACTU will actively participate in HIV Disease RAC efforts and provide expertise to address study treatment strategies for initial therapy, treatment options for virologic failure and utilization of phenotypic and genotypic assessments to direct subsequent therapy and treatment intensification. The Miami ACTU will also bring expertise in the areas of hepatitis B and C pathogenesis and treatment, metabolic complications of HIV-1 protease inhibitor pathogenesis and treatment, HIV dementia pathogenesis and treatment and peripheral neuropathy pain assessment, Kaposi sarcoma (KS) pathogenesis, intensive immunologic monitoring and definition, and validation of immunologic determinants of treatment response. The Miami ACTU plans to enroll 100 subjects per year across AACTG studies and 70 patients into AACTG substudies, including but limited to Compartmental, Virology, Viral Dynamics, Pharmaceuticals, Metabolic, Neurologic, Women's Health and Adherence and Outcomes substudies. With a support system in place for the long-term follow-up of patients, the Miami ACTU anticipates to enroll approximately 80 patients into the ALLRT study (ACTG 5001) over a 2-year period.

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

- **Project Title: MOLECULAR GENETICS OF HSV DNA POLYMERASE GENE**

Principal Investigator & Institution: Coen, Donald M.; Professor; Biological Chem & Molecular Pharm; Harvard University (Medical School) Medical School Campus Boston, Ma 02115

Timing: Fiscal Year 2002; Project Start 01-APR-1983; Project End 31-MAR-2007

Summary: (provided by applicant): The long-term objective of this research is a detailed understanding of herpesvirus DNA polymerases. These enzymes, which include a catalytic subunit (Pol) and an accessory subunit that stimulates long-chain DNA synthesis, are prototype alpha-like DNA polymerases and excellent targets for antiviral drugs. New drugs are needed for treatment of herpesvirus infections, especially those caused by human **cytomegalovirus** (CMV) in immunosuppressed patients such as those with AIDS. Specific aim 1 is to determine mechanisms that regulate translation of HSV Pol and their importance to the virus. Mutational, RNA-binding, and translational analyses will test the hypotheses that a virion protein, US11, stimulates Pol translation early in infection, while inefficient translation later is beneficial to the virus. Specific aim 2 is to analyze the interaction of the accessory subunit, HSV UL42, with DNA that permits sliding despite high affinity binding and the implications of this interaction for processive DNA synthesis. The UL42-DNA interaction will be explored using mutational approaches, protein-DNA crosslinking, measurements of affinity, on, off, and sliding rates, and single molecule studies and will be correlated with effects on processivity. Specific aim 3 is to determine mechanisms by which mutant CMV Pols, especially those altered in exonuclease motifs, resist ganciclovir (GCV) action, by analyzing Pol interactions with GCV-TP and GCV-containing DNA. Specific aim 4 is to investigate CMV Pol's interaction with its accessory subunit, UL44. Interacting residues will be defined genetically and tested for their importance in CMV DNA and viral replication to determine if this interaction is a valid drug target. If so, a high throughput screening assay will be used to discover new antiviral drugs. Specific aim 5 is to use X-ray crystallography and, if necessary, nuclear magnetic resonance, to solve the three dimensional structures of domains of HSV US11, and HSV and CMV DNA polymerase and/or domains thereof to gain basic information regarding polymerase functions and as a starting point for drug discovery.

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

- **Project Title: MOLECULAR PHYSIOLOGY OF NKG2D LIGAND EXPRESSION**

Principal Investigator & Institution: Carayannopoulos, Leondias N.; Internal Medicine; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

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

Summary: (provided by applicant): To withstand assaults by viral pathogens, animals mount two types of immune responses following infection. An initial innate response acts both to limit pathogen growth and to prime the later adaptive response that generates cells and antibodies highly specific for a given pathogen. Innate effector cells such as natural killer (NK) cells recognize infection using germline-encoded receptors that detect molecular patterns common to subgroups of pathogens. These cells can also recognize infection or injury indirectly through receptors that detect "distress signals" displayed by damaged tissue. Understanding these receptors and their ligands would aid the production of agents that mimic or block those signals in the clinical setting. NKG2D is such a receptor expressed by all NK cells. It can trigger NK cell function in response to cells injured by viruses and other insults. In preliminary work, the applicant with his mentor and others have shown that NKG2D recognizes multiple ligands

possessing very different gene expression patterns and binding kinetics. Herein, the applicant proposes to investigate the biological function of NKG2D ligands in relation to these differences in binding. This work is part of a career development plan. The specific aims of the investigation are: 1) to characterize the relationship between the binding kinetics of these ligands and their abilities to signal through NKG2D; 2) to determine whether viral infection preferentially induces cell surface expression of the high-affinity and/or slowly-dissociating ligands; and 3) to demonstrate the role of NKG2D and its binding partners in viral infection *in vivo*. This career development program will provide the applicant with a transition to research independence. The applicant is a physician with a Ph.D. in immunology and biophysics. He is completing his fellowship training in pulmonary and critical care medicine at Washington University School of Medicine under the supervision of Dr. Wayne Yokoyama.

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

- **Project Title: MOLECULAR STUDIES OF HUMAN CYTOMEGALOVIRUS PROTEASE**

Principal Investigator & Institution: Tong, Liang; Biological Sciences; Columbia Univ New York Morningside 1210 Amsterdam Ave, Mc 2205 New York, Ny 10027

Timing: Fiscal Year 2002; Project Start 01-JUN-1999; Project End 31-MAY-2004

Summary: (Adapted from Applicant's Abstract) Human **cytomegalovirus** (HCMV), a herpesvirus, is a major opportunistic infectious agent in individuals suffering from AIDS, as well as individuals with suppressed immune systems (for example, organ and bone marrow transplant recipients). Both primary and reactivated latent HCMV infections can cause severe acute diseases in these individuals, such as retinitis, pneumonitis, hepatitis and gastroenteritis. Current therapies against HCMV infections are mostly targeted at the DNA polymerase of the virus, and are limited in their usefulness by their toxic side effects. In addition, viral resistance to anti-herpes agents is becoming an increasingly more significant problem. Therefore, new and efficacious treatments for HCMV infections, and herpesvirus infections in general, are highly desirable. The protease of herpesviruses is essential for their life cycle, and represents a novel target for the design and development of anti-herpes chemotherapeutic agents. Several classes of inhibitors against HCMV protease have been reported, but none of these have sufficient potency and/or pharmacokinetic properties. Breakthroughs are needed to develop a new generation of inhibitors against the protease, with higher potency, metabolic stability, and oral bioavailability. Structure-based drug design can play an important role in this process, as it has in the development of AIDS therapeutic agents targeted at the HIV protease. Such design efforts require a detailed structural and biochemical knowledge of the protein target, which are currently still lacking for HCMV protease. Despite being a serine protease, HCMV protease has many unique biochemical and structural features and belongs to a new class of serine protease, distinct from the classical serine proteases such as chymotrypsin and subtilisin. Therefore, a new body of knowledge is needed on this new class of enzymes. The proposed research will use structural, biochemical and biophysical techniques to achieve a greater understanding of the molecular basis for the inhibition and the catalytic mechanism of HCMV protease. Special emphasis will be placed on studying the unique features of the protease, such as the Ser-His-His catalytic triad, the requirement for dimerization for activity, the activation by antichaperone agents, the conformational flexibility and the induced fit behavior, and the inhibition of the protease by non-peptidic and peptidomimetic compounds. The crystal structure of HCMV protease free enzyme and the recently determined structure of the protease inhibitor complex represent an excellent starting

point for the performance and completion of the proposed research. A long-term goal of the research is to expand the studies to include the proteases of other herpesviruses, many of which (herpes simplex virus and Kaposi's sarcoma associated herpesvirus) are also targets for the development of anti-herpes agents.

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

- **Project Title: MOLECULAR STUDY OF MOUSE VIRAL RESISTANCE MECHANISMS.**

Principal Investigator & Institution: Brown, Michael D.; Assistant Professor; Internal Medicine; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

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

Summary: The long-term objective of our laboratory is to understand how the innate immune system recognizes and responds to pathogen invasion at the molecular level, especially since such defenses may be controlled by genomic elements. In particular, this study will focus on NK cell-mediated viral immunity to murine **cytomegalovirus** (MCMV) as it is controlled by the NKO linked Cm1 locus. Notably NK cells are important contributors of host innate immune defenses to a range of pathogens including, viruses, bacteria, and protozoan parasites, through cytokines released (e.g. IFN-gamma) and direct cell-mediated cytotoxicity mechanisms. Moreover, NK cells directly limit viral replication in mice during murine **cytomegalovirus** (MCMV) infection, this capacity directly correlates with host survival during MCMV challenge, and NK cell-mediated immunity is directly regulated by the Cm1 locus. Cm1 was recently mapped within the distal NKC, however Cm1 candidate sequences were not reported. In preliminary data, we report that an additional NKC encoded NK receptor (Ly- 49H) may be involved in MCMV resistance, but this NKC gene is physically and genetically separate from the Cm1 locus. Hence, we will determine whether more than one NKC locus is required MCMV resistance by assessing MCMV resistance in novel intra-NKC recombinant mice and Cm1 minus/minus mice (Specific Aim 1). Novel Cm1 coding sequences will be selected from C57BL/6 mice and from MCMV susceptible strains of mice. These sequences will be compared structurally and biochemically to identify a best Cm1 candidate sequence. Confirmation of Cm1 candidate sequences will be performed using a transgenic approach (Specific Aim 2). Finally, should genetic data be obtained implicating Ly49h in MCMV resistance immunity using a transgenic approach. Furthermore, this gene will be thoroughly characterized in C57BL/6 and several MCMV susceptible mouse strains (Specific Aim 3). Thus, these studies should clarify our understanding of NK cell recognition of viral infection and Cm1-regulated immunity, as these are not currently understood mechanistically.

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

- **Project Title: MOLECULAR THERAPEUTICS FOR ANAPLASTIC GLIOMAS**

Principal Investigator & Institution: Rosenfeld, Steven S.; Associate Professor; Neurology; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

Timing: Fiscal Year 2002; Project Start 05-SEP-2002; Project End 31-MAY-2007

Summary: In spite of over thirty years of effort, the prognosis for patients afflicted with malignant gliomas remains dismal. It is the purpose of this Brain Cancer SPORE to have a positive impact on this unacceptable situation by translating the laboratory-based efforts of five groups of scientists into clinical protocols that address the needs for more effective treatments. The themes that will be investigated in this SPORE include:

Pathogenesis, Anti-Invasion Strategies, Glioma-Host Interactions, Viral and Gene Therapy, and Anti-Angiogenesis Strategies. Five research projects are proposed, each of which has a translational component that has or is expected to lead to a clinical research protocol. These include: 1) "The role of Human **Cytomegalovirus** in Human Malignant Glioma Pathogenesis" which will examine an intriguing finding that suggests that **cytomegalovirus** promotes the development and progression of gliomas; 2) "Interferon-Mediated Suppression of MMP-9 Gene Expression and Function in Gliomas" which will examine the role of cytokines and signal transduction pathways in regulating secretion of a pro-invasive enzyme; 3) "Ion Channels and Transporters as Novel, Glioma-specific Targets", which will examine how abnormal functioning of glioma ion channels can be potentially manipulated to develop new treatment modalities, 4) "Viral and Molecular Chemotherapy of Malignant CNS Tumors", which will utilize the extensive expertise in virology available at UAB to development new gene and viral vector therapies for gliomas, and 5) "The Role of TSP-1 and -2 in the Biology of Gliomas", which will investigate how to utilize fragments of the protein thrombospondin as anti-angiogenic agents. These projects will be supported by Four Cores: 1) Human Brain Tumor Tissue, 2) Clinical Trials; 3) Brain Tumor Animal Core Facility; and 4) Biostatistics. In addition, the SPORC will have a Career Development Program directed at developing the careers of young investigators in brain tumor translational research and a Developmental/Pilot Research Program. This SPORC has strong institutional commitments from both the University and its Cancer Center, and we fully expect to develop active collaborative interactions with both our institutional SPORCs as well as with other SPORCs nationally.

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

- **Project Title: NATURAL KILLER CELL GROWTH AND DEVELOPMENT**

Principal Investigator & Institution: Biron, Christine A.; Professor & Chair; Molecular Microbiol and Immun; Brown University Providence, Ri 02912

Timing: Fiscal Year 2002; Project Start 01-DEC-1987; Project End 31-JAN-2004

Summary: (Adapted from Investigator's Abstract): The overall goal of this application is to characterize physiologically relevant factors controlling NK and T cell responses in vivo. The work is based on the investigator's previous analyses of cytokine responses and of NK and T cell activation and proliferation during infections in mice with LCMV or MCMV, and after treatments with the chemical analog of viral nucleic acids, polyinosinic:polycytidylic acid (poly I:C), IFN-alpha/beta, or IL-12. The experiments proposed here will expand characterization by examining the hypothesis that: (I) particular cellular interactions with virus-type stimuli determine composition of innate cytokine, and resulting NK cell, responses; (II) IL-15 is induced by IFN-alpha/beta in vivo to promote NK cell proliferation as well as support conditions preferentially activating CD8 T cell responses; (III) pathways are in place limiting systemic NK cell IFN-gamma production to protect against damaging consequences of this response; (IV) alternative pathways sustain local IFN-gamma production to access beneficial effects; and (V) NK cells can limit CD4 T cell responses through an IFN-alpha/beta- induced pathway. These will be examined in four specific aims to: 1) further characterize regulation of NK cell responses under conditions of challenges with viruses, viral analogs, and IFN-alpha/beta to include potential roles of IL-15, events in the bone marrow, and conditions promoting IL-12 refractory states; 2) define mechanisms for the different pathways of cytokine induction and NK cell activation by examining ranges of cytokines induced in particular cell types as well as initial targets of the in vivo challenge conditions; 3) identify mechanisms regulating NK cell responses in livers

during MCMV infections, including defining roles for IGIF (interferon gamma inducing factor), and characterizing responses of NK1+ T cells in this compartment; and 4) determine mechanisms by which innate responses regulate T cell responses, including characterizing IFN-alpha/beta- induced and NK cell-mediated effects. The information resulting from this work will generate basic immunological knowledge as well as significant new insights for developing anti-viral and/or anti-cancer treatment protocols.

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

- **Project Title: NEUROTROPIC CYTOMEGALOVIRUS DURING IMMUNOSUPPRESSION**

Principal Investigator & Institution: Reuter, Jon; Comparative Medicine; Yale University
47 College Street, Suite 203 New Haven, Ct 065208047

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

Summary: Cytomegalovirus (CMV) is an important opportunistic pathogen with an estimated prevalence in the human population of 50-90%. While most immunocompetent individuals do not develop clinical infection, immunosuppressed patients such as those with AIDS or undergoing immunosuppressive therapy open develop debilitating neurological deficits, mental disorders, cognitive impairment, and potentially fatal infection. CMV also may further suppress the immune system and has been suggested as a co-factor in AIDS dementia syndrome. Lack of an appropriate animal model of natural neurotropic CMV infection has limited understanding of virus entry mechanisms and dissemination in brain. The central hypothesis of this proposal is that systemic CMV infection in immunosuppressed patients disseminates to the brain through specific mechanisms in a predictable, localized pattern and is strongly influenced by the competency of host immune disease. The research described below will define the relationship of systemic CMV infection, host immunity and CNS disease. A novel murine model of parenteral CMV inoculation resulting in neurotropic CMV infection will be used to test this hypothesis through 4 primary strategies: 1) determine whether severity of mouse immunodeficiency alters susceptibility to neurotropic CMV dissemination, 2) determine if CMV infection of the CNS can occur through hematogenous dissemination through free virus, infected leukocytes, or directly through intra-axonal transport to brain, 3) determine if mice are protected from neurotropic MCMV by adoptive transfer of specific immune lymphoid cell populations, 4.) determine whether adoptive transfer of immune or non-specific immune T cells can reduce or clear established CMV encephalitis. This proposal elucidates the significance of neurotropic CMV as a principal opportunistic CNS pathogen without confounding variables such as co-incident HIV replication and may help to advance the diagnosis and therapy of CMV related encephalitis and AIDS dementia syndrome. Training inherent to the proposal will extend, broaden, and deepen my knowledge of infectious disease pathogenesis and develop intellectual and technical competency in immune modulation crucial to my scientific independence. Training will be performed at Yale University School of Medicine under the mentorship of Anthony van den Pol, PhD, Professor of Neurosurgery, and a senior neuroscientist, Nancy Ruddle, PhD, Professor of Epidemiology and Public Health/Immunobiology and Epidemiology of Microbial Diseases, and world-class immunologist in collaboration with Akiko Iwasaki, PhD, Assistant Professor of Epidemiology/Public Health who has strong research credentials in the mechanism of host immunity to infectious microorganisms.

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

- **Project Title: NEWBORN SCREENING FOR HEARING IMPAIRMENT**

Principal Investigator & Institution: Naylor, Edwin W.; Neo Gen Screening, Inc. Box 219, Abele Business Park Bridgeville, Pa 15017

Timing: Fiscal Year 2002; Project Start 01-JUL-2001; Project End 31-MAR-2004

Summary: (Adapted from applicant's abstract): The feasibility of screening borns for hearing impairment in an assay paralleling routine metabolic screening will be demonstrated. Hearing loss owing to heredity factors and **cytomegalovirus** are analyzed. DNA from the universally collected newborn filter paper blood card serves as the source of nucleic acids to perform the assay. Several target sequences in the **cytomegalovirus** genome will be evaluated for their utility to identify viral DNA in the newborn specimen. The following mutations in connexin 26, Pendrin, and connexin 31 genes serve as model systems for hereditary hearing loss: (1) connexin 26 35 del G, 167 del T, Usher2A 231delG; (2) Pendrin L236S, T416P; Mitochondrial A1555G. Amplicons that are diagnostic for CMV DNA and the described mutations are analyzed using a low-density oligonucleotide microarray in a multiplex format. The microarray will clearly distinguish homozygous wild type, heterozygotes, and homozygous mutants for the described mutations. Screening for hearing impairment in a laboratory-based program, parallel to auditory screening, will provide an overall superior screening service. The lab assay will identify many newborns that would be missed where auditory screening is not available. PROPOSED COMMERCIAL APPLICATION: NOT AVAILABLE

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

- **Project Title: NK RECEPTORS AND CD1 ROLES IN NK AND NK T CELL FUNCTION**

Principal Investigator & Institution: Brossay, Laurent; Assistant Professor; Molecular Microbiol and Immun; Brown University Providence, Ri 02912

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

Summary: (Adapted from applicant's abstract) Murine CD1 molecules have the ability to present glycolipids to NK T cell. NK T cells are a lymphocyte subset that is characterized by the expression of an invariant TCR, autoreactivity to CD1 molecules, and the ability to rapidly produce large amounts of IFN γ and/or IL-4 following stimulation. NK T cells have been implicated in a variety of immune responses, including the response to tumors, infectious agents and the regulation of autoimmune disease progression. We hypothesize that CD1 mediated NK T cell responses may be regulated by the inhibitory and activating NK receptors expressed by NK T cells. We propose to characterize the pattern of expression of inhibiting and activating NK receptors on mouse NK T cells and NK T cell hybridomas. In addition, a series of NK receptors will be tested for their ability to regulate the NK T cell activation induced by CD1 molecules, by transfecting them into NK T cell hybridomas. The specificity of the hybridomas is well characterized, and the strength of the stimulating antigen signal can be regulated by manipulating the amount of CD1 expressed on the APC, the amount of lipoglycan antigen used. Experiments also will be carried out with primary NK T cells to study how these NK receptors act in the context of immune responses in vivo and in vitro. While NK receptors are known to react with MHC encoded class I molecules, we have made the surprising finding that a subset of NK cells are inhibited by interaction with CD1, although CD1 is only very distantly related to the MHC class I molecules. Therefore, several strategies will be undertaken to identify the CD1 binding NK receptor(s), and we will determine if these act as co-receptors for the NKT cell. The dual

role of CD1 molecule as an activating molecule through the TCR on NK T cells and as an inhibitory molecule through an inhibitory receptor on NK cells will be studied in the context of the murine **cytomegalovirus** infection of mice. This virus replicates in murine liver, an organ particularly rich in NK cell and NK T cells and with high amount of CD1 molecules on hepatocytes. These novel studies will provide insights into the: specificity and immunoregulatory role of NK receptors on both CD1 reactive NK T cells and NK cells, and provide strategies for the regulation of this important category of immune cell responses.

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

- **Project Title: OCULAR COMPLICATION OF AIDS**

Principal Investigator & Institution: Meinert, Curtis L.; Professor; Epidemiology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

Timing: Fiscal Year 2002; Project Start 15-AUG-1988; Project End 31-JUL-2003

Summary: (Applicant's Abstract) Ocular complications of AIDS, particularly **cytomegalovirus** (CMV) retinitis are associated with poor visual outcomes, impaired quality of life, and high treatment costs. Secular trends in HIV disease management, such as the use of highly active antiretroviral therapy, are altering the epidemiology of these ocular complications, but have not eliminated them. Accordingly, the primary goals of the Studies of Ocular Complications of AIDS (SOCA) Research Group, organized in response to a request for application from the National Eye Institute, are: 1) to evaluate strategies for the treatment of and, when indicated, the prevention of CMV retinitis via randomized, controlled clinical trials; and 2) to investigate the changing epidemiology of the ocular complications of AIDS, in particular, to identify subpopulations at high risk for CMV retinitis and other ocular complications. related goal of the SOCA Research Group is to investigate the pathogenesis of CMV retinitis, including the relationship between HIV and CMV. Current and proposed studies include: 1) the ongoing Ganciclovir-Cidofovir **Cytomegalovirus** Retinitis Trial, a randomized controlled clinical trial comparing cidofovir to a regimen of the ganciclovir implant and oral ganciclovir for the treatment of CMV retinitis; and 2) a longitudinal observational study of the ocular complications of AIDS to assess the impact of secular trends in AIDS management on the incidence and clinical course of these ocular complications over time. Outcomes of interest include visual acuity, visual field, photographic assessments, quality of life, cost effectiveness, and virologic outcomes such as CMV viral load and HIV viral load. This application is for the Chairman's Office of the Studies of Ocular Complications of AIDS.

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

- **Project Title: OCULAR COMPLICATIONS OF AIDS**

Principal Investigator & Institution: Jabs, Douglas A.; Professor; Ophthalmology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

Timing: Fiscal Year 2002; Project Start 15-AUG-1988; Project End 31-JUL-2003

Summary: (Applicant's Abstract) Ocular complications of AIDS, particularly **cytomegalovirus** (CMV) retinitis are associated with poor visual outcomes, impaired quality of life, and high treatment costs. Secular trends in HIV disease management, such as the use of highly active anti-retroviral therapy, are altering the epidemiology of these ocular complications, but have not eliminated them. Accordingly, the primary goals of the Studies of Ocular Complications of AIDS (SOCA) Research Group, organized in response to a request for application from the National Eye Institute, are: 1)

to evaluate strategies for the treatment of and, when indicated, the prevention of CMV retinitis via randomized, controlled clinical trials; and 2) to investigate the changing epidemiology of the ocular complications of AIDS, in particular, to identify subpopulations at high risk for CMV retinitis and other ocular complications. A related goal of the SOCA Research Group is to investigate the pathogenesis of CMV retinitis, including the relationship between HIV and CMV. Current and proposed studies include: 1) the ongoing Ganciclovir-Cidofovir **Cytomegalovirus** Retinitis Trial, a randomized controlled clinical trial comparing cidofovir to a regimen of the ganciclovir implant and oral ganciclovir for the treatment of CMV retinitis; and 2) a longitudinal observational study of the ocular complications of AIDS to assess the impact of secular trends in AIDS management on the incidence and clinical course of these ocular complications over time. Outcomes of interest include visual acuity, visual field, photographic assessments, quality of life, cost effectiveness, and virologic outcomes such as CMV viral load and HIV viral load. This application is for the Chairman's Office of the Studies of Ocular Complications of AIDS.

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

- **Project Title: OCULAR COMPLICATIONS OF AIDS--PHOTOGRAPH READING CENTER**

Principal Investigator & Institution: Davis, Matthew D.; Professor; Ophthalmology and Visual Sci; University of Wisconsin Madison 750 University Ave Madison, WI 53706

Timing: Fiscal Year 2002; Project Start 15-AUG-1988; Project End 31-JUL-2003

Summary: Ocular complications of AIDS, particularly **cytomegalovirus** (CMV) retinitis are associated with poor visual outcomes, impaired quality of life, and high treatment costs. Secular trends in HIV disease management, such as the use of highly active antiretroviral therapy, are altering the epidemiology of these ocular complications, but have not eliminated them. Accordingly, the primary goals of the Studies of Ocular Complications of AIDS (SOCA) Research Group, organized in response to a request for application from the National Eye Institute, are: 1) to evaluate strategies for the treatment of and, when indicated, the prevention of CMV retinitis via randomized, controlled clinical trials; and 2) to investigate the changing epidemiology of the ocular complications of AIDS, in particular, to identify subpopulations at high risk for CMV retinitis and other ocular complications. A related goal of the SOCA Research Group is to investigate the pathogenesis of CMV retinitis, including the relationship between HIV and CMV. Current and proposed studies include: 1) the ongoing Ganciclovir- Cidofovir **Cytomegalovirus** Retinitis Trial, a randomized controlled clinical trial comparing cidofovir to a regimen of the ganciclovir implant and the oral ganciclovir for the treatment of CMV retinitis; and 2) a longitudinal observational study of the ocular complications of AIDS to assess the impact of secular trends in AIDS management on the incidence and clinical course of these ocular complications over time. Outcomes of interest include visual acuity, visual field, photographic assessments, quality of life, cost effectiveness, and virologic outcomes such as CMV viral load and HIV viral load. This application is for the Fundus Photograph Reading Center of the Studies of Ocular Complications of AIDS.

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

- **Project Title: POLYNUCLEOTIDES AS ANTI-AIDS AGENTS**

Principal Investigator & Institution: Broom, Arthur D.; Professor; Medicinal Chemistry; University of Utah Salt Lake City, UT 84102

Timing: Fiscal Year 2002; Project Start 01-JAN-1989; Project End 31-DEC-2003

Summary: (Adapted from Applicant's Abstract). The objectives of the present proposal have been expanded to enable a clearer definition of structure-activity relationships, mechanism of action, binding affinity, and kinetics for HIV reverse transcriptase, and cell uptake for the oligo- and polynucleotides synthesized to date and proposed herein. Emphasis will be placed on identifying one or more potential clinical candidates, then adding sufficient value to them by the types of studies noted above to interest a major industrial partner in further development. The specific aims are as follows: 1. Continue the design and synthesis of novel purine-derived bases to enable the refinement of structure-activity relationships and test the hypotheses which have been developed during the course of this work. 2. Prepare modified oligonucleotide backbones, particularly phosphorothioate and PNA analogues, and compare their biological properties with the corresponding phosphodiester derivatives. 3. Utilize sugar modifications, especially 2'-O-methyl and 2'-O-methoxyethyl, to confer nuclease stability and facilitate oligonucleotide synthesis. 4. Utilizing UV and circular dichroism spectroscopy, MALDI-TOF, and electrospray MS and, as appropriate, NMR, characterize the physico-chemical properties of the newly synthesized compounds. 5. Append fluorescein derivatives to oligo- and polynucleotides, and examine the possibility that some of the bases used will exhibit useful fluorescence in their own right. 6. In collaboration with Dr. Jindrich Kopecek, study the cell uptake and localization of the polymers using fluorescent confocal microscopy. 7. In collaboration with Dr. Robert Fisher, examine the binding affinity and kinetics of selected oligos and polymers with HIV reverse transcriptase using surface plasmon resonance (BIAcore). 8. In continuing collaboration with Dr. Robert Buckheit, examine the anti-HIV activity, ability to produce resistance and mechanism of action of the synthetic oligos and polymers. 9. In continuing collaboration with Drs. Robert Sidwell and John Huffman, evaluate the anti-HCMV activity of these compounds.

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

- **Project Title: PRE-DIAGNOSTIC MARKERS OF INFECTION AND RISK OF MS**

Principal Investigator & Institution: Ascherio, Alberto; Associate Professor; Nutrition; Harvard University (Sch of Public Hlth) Public Health Campus Boston, Ma 02115

Timing: Fiscal Year 2002; Project Start 15-AUG-2001; Project End 31-JUL-2004

Summary: We propose to conduct a prospective investigation to assess whether infection with the Epstein-Barr Virus or Chlamydia pneumoniae increases the risk of multiple sclerosis (MS). For this purpose we have identified two large populations of individuals whose blood samples were collected and stored several years ago and are available for analyses, and we are in the process of documenting cases of MS that occurred in these populations after the date of blood collection. One population comprises over 3 million US Army personnel whose blood samples are stored in the Department of Defense (DOD) Serum Repository; the other comprises 125,000 participants in the Kaiser Permanente Health Plan (KPHP), whose blood samples were collected over 20 years ago. The identification and diagnostic confirmation of the cases of MS occurring in these populations has already been funded in part by a pilot grant from the National Multiple Sclerosis Foundation. Based on our preliminary work, we estimate that we will be able to document 216 cases of MS with onset after the date of collection of the stored serum samples. Main hypotheses to be addressed are that risk of MS is increased among individuals infected with EBV or C pneumoniae, as determined by the presence of specific serum antibodies, and that elevated antibody titers against EBV or C pneumoniae antigens predate the onset of MS.

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

- **Project Title: PREVENTION OF CYTOMEGALOVIRUS INFECTION**

Principal Investigator & Institution: Adler, Stuart P.; Professor and Chairman; Pediatrics; Virginia Commonwealth University Richmond, Va 232980568

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

Summary: (provided by applicant): Infection of the fetus with **cytomegalovirus** (CMV) results in approximately 8,000 infants born each year who will be mentally retarded and/or deaf. These effects are mainly due to primary maternal CMV infection during pregnancy. We and others have found that between 25% and 80% of children acquire CMV infections in daycare and shed the virus for between 3 and 41 months (mean of 18 months). At least half of seronegative mothers with infected children under age 2 years acquire CMV from their children within one year compared to an annual rate of < 5% among other seronegative women. CMV vaccines with the potential to control this infection are available for evaluation. An effective national vaccination strategy to prevent primary maternal infection during pregnancy should include childhood immunization. In adults we found that natural seropositivity protects against reinfections. To determine neutralizing antibodies are effect the natural history of CMV infection in toddlers, we will evaluate a purified protein vaccine, CMV gB/MF59, in an expanded placebo controlled double blinded phase I-II safety and immunogenicity trial. Because the infants in this study will be enrolled in daycare and will have a high rate of primary CMV infections we will be testing the hypothesis that immunized children less than two years of age are protected against infection or have a reduced duration of viral excretion and one or the other of these will be associated with high levels of neutralizing antibodies. We will compare the infection rate or the duration of viral excretion of infants under two years of age enrolled in daycare and immunized with CMV gB/MF59 vaccine to the infection rate and duration of viral excretion of matched seronegative infants receiving a placebo. We will also determine if infection or the duration of viral shedding are associated with an infant's immune response or age. The parameters of the immune response to be measured will include IgG, IgG to CMV gB, neutralizing titers, IgG responses characterized by immunoblotting, CD4+ responder cell frequencies, and mucosal immunity. The results of this study will establish if prevention of CMV infections is possible.

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

- **Project Title: REDIRECTING SPECIFICITY OF VIRAL SPECIFIC T CELLS**

Principal Investigator & Institution: Clay, Tim; Surgery; Duke University Durham, Nc 27706

Timing: Fiscal Year 2003; Project Start 01-JUN-2003; Project End 31-MAY-2007

Summary: (provided by applicant): This project addresses the hypothesis that we can retarget potent anti-viral immune responses to also become potent anti-tumor immune responses by genetically engineering antiviral T cells to over express T cell receptors (TCR) specific for tumor associated antigens. We propose to specifically engineer **cytomegalovirus** (CMV) pp65(495-503) peptide specific T cells to also recognize the E75 T cell epitope of the tumor antigen HER2/neu. We have found that high levels of CMV specific T cells are present in CMV seropositive patients and know that recovery of circulating CMV specific T cells provides protection against CMV disease. Although passive administration of HER2/neu specific antibodies have clinical effects on HER2/neu specific tumors, attempts to immunize patients against HER2/neu to achieve

high levels of circulating anti-HER2/neu specific T cells have had limited success. We have demonstrated the feasibility of cloning T cell receptors to melanoma antigens into human T cells, demonstrating our ability to retarget the antigen specificity of human T cells. Therefore, we propose to produce dual specificity T cells by over expressing a high affinity T cell receptor specific for HER2/neu E75 in T cells with existing antigen specificity against CMV pp65 (495-503) peptide. This application proposes to support the pre-clinical studies to test this hypothesis. The construction of the reagents proposed in this application will allow us to test fundamental questions about TCR affinity and avidity by comparing high and low affinity TCR in these dual specificity T cells. These studies will lead to a better understanding about the role of antigen specific T cells in eradicating CMV and HER2/neu expressing cells in breast cancer patients. They will also provide the preclinical data for a subsequent clinical trial to address a fundamental question in clinical cancer immunotherapy: "In the presence of a highly effective cellular response, defined as being of a magnitude sufficient to eradicate CMV expressing cells, will a HER2/neu directed immune response mediated by the same T cells be sufficient to delay recurrence of HER2/neu expressing tumor"?

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

- **Project Title: REGULATION OF CMV IMMEDIATE EARLY GENE EXPRESSION**

Principal Investigator & Institution: Colberg-Poley, Anamaris M.; Professor of Pediatrics; Children's Research Institute Washington, D.C., Dc 20010

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

Summary: (prepared by the applicant): Viruses provide valuable systems to study gene regulation since they exploit the cellular machinery in unconventional ways and can identify novel mechanisms. DNA replication of human **cytomegalovirus** (HCMV), a medically important herpesvirus, requires its UL36-38 gene products. Differential processing of UL36-38 RNAs generates four immediate early (IE) RNAs, which share sequences and an early RNA. The UL37 and UL37M spliced IE RNAs are expressed at very low abundance at IE times of HCMV infection, while the others are abundant throughout the viral life cycle. Our overall aim is to determine the mechanistic basis for this differential regulation. We hypothesize that the targets for differential regulation lie within UL37 RNA unique sequences and result from inefficient splicing, inhibition of transcription elongation, and/or RNA instability. In Aim 1, we will determine if UL37 RNA splicing is reduced by efficient polyadenylation (PA). Intriguingly, UL37 Introns 1 and 2 have juxtaposed PA signals, branch points, and 3' splice sites. We hypothesize that abundance of UL37x1 unspliced RNA results from inhibition of RNA splicing by competition of factors for juxtaposed cis-elements. To test this, we will mutate the PA signals in UL37 Introns 1 and 2 and examine their effects on UL37 RNA splicing. We will characterize UL37 RNA splicing by defining the cis-elements controlling RNA processing and studying the effects of mutant cis-elements on splicing in cells and in vitro. As the abundance of UL37 spliced RNAs changes temporally, we will define how HCMV infection alters splicing and/or PA machineries at IE, early, or late times using in vitro extracts and gel shift assays. In Aim 2, we will test whether transcription of the UL3 7 IE gene is blocked. We will test if thymidine (T)-rich regions in the UL3 7 Intron 1/Exon 2 boundary inhibit transcript elongation by measuring transcription through the UL37 gene using nuclear run-ons. We will identify and mutate the sequences responsible for inhibition of RNA elongation. In Aim 3, we will test whether UL37 RNA sequences are selectively targeted for degradation. We will examine the stability of UL37 RNA in HCMVinfected cells and define its instability elements by selectively deleting UL37 sequences and measuring the stability of the encoded RNAs. A thorough

understanding of how the UL36-38 essential gene locus is regulated in HCMV infected HFF cells is of fundamental importance to understanding the modulation of HCMV gene expression, ultimately understanding the viral life cycle and potentially identifying novel mechanisms of cellular gene regulation.

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

- **Project Title: REGULATION OF HCMV EARLY GENE EXPRESSION**

Principal Investigator & Institution: Kerry, Julie A.; Assistant Professor; Microbiol/Molec Cell Biology; Eastern Virginia Medical School Norfolk, Va 23507

Timing: Fiscal Year 2003; Project Start 01-JUN-1996; Project End 31-DEC-2007

Summary: (provided by applicant): Human **cytomegalovirus** (HCMV) is a significant opportunistic pathogen causing severe disease in newborns infected in utero and the immunocompromised. HCMV replication requires a cascade of gene expression, consisting of immediate early (IE), early and late phases. As products of the early genes play key roles in both pathogenesis and DNA replication, transition into this phase is critical in determining the outcome of viral infection. The objective of this application is to determine how viral and cellular proteins control transcription of viral genes during this transition. Our hypothesis is that two viral proteins, pp71 and IE86, play key roles in this process via direct interaction and/or alteration of the nuclear environment. This hypothesis will be tested in four aims: (1) Characterize the role of cellular factors in US6 regulation in the viral genome. We will determine the role of ATF and Sp1 in the activation of the US6 early gene in the natural genomic environment. (2) Determine the role of IE86 interactions with cellular proteins in the activation of viral early promoters. We hypothesize that co-activator functions of IE86 play a critical role in the activation of viral early genes. To assess this, mutants within a key region from amino acids 535 to 545 will be used to define the properties of IE86 that are essential for transcriptional regulation of viral early promoters. (3) Determine the mechanism of transactivation by the viral tegument protein pp71. Our hypothesis is that pp71 regulates viral gene expression via direct interaction with cellular transcription factors. This hypothesis will be tested by identifying domains of pp71 required for both protein-protein interactions and transcriptional regulation. (4) Determine the mechanism of transcriptional cooperation between IE86 and pp71. We hypothesize that direct and/or functional interaction between IE86 and pp71 is important in regulating viral gene expression during the transition from the IE to early phase. This hypothesis will be tested by determining the domains required for functional association between these two proteins and assessing the effects on transcriptional activation. The studies that we describe in this proposal will therefore enhance our understanding of the mechanisms of transcriptional activation of viral early genes and may lead to the development of novel antiviral therapies.

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- **Project Title: REGULATION OF HUMAN CYTOMEGALOVIRUS GENE EXPRESSION**

Principal Investigator & Institution: Stinski, Mark F.; Professor; Microbiology; University of Iowa Iowa City, Ia 52242

Timing: Fiscal Year 2002; Project Start 01-SEP-1976; Project End 31-MAY-2006

Summary: (provided by applicant): Human **cytomegalovirus** (HCMV) can cause congenital neurological damage and disseminated infections resulting in pneumonitis, retinitis, hepatitis, and gastroenteritis. HCMV infections have been associated with

accelerated atherosclerosis and with coronary restenosis following angioplasty. HCMV infections in solid organ and bone marrow transplant recipients are a significant cause of morbidity. Both hematopoietic cells of the bone marrow and monocytes of the blood can be latently infected with HCMV. Productive infection occurs in a variety of terminally differentiated cells including fibroblast, cytotrophoblast, smooth muscle, endothelial, epithelial, and microglial cells and in macrophages. Abortive infection occurs in polymorphonuclear cells. Our laboratory is interested in viral DNA regulatory elements and in viral and cellular proteins that regulate latency, persistent infection, and productive infection. In Specific Aim I, we propose to determine the role of specific regulatory elements in the proximal 3'-end of the major immediate early (MIE) enhancer on viral gene expression in undifferentiated cells relevant to HCMV latency. Regulatory elements that function to repress transcription from the MIE promoter upon binding a regulator protein in undifferentiated cells of the myeloid lineage will be mutated in the context of the viral genome, and recombinant viruses will be analyzed. In Specific Aim II, we propose to characterize a repressor-boundary region 5' to the MIE enhancer that prevents the MIE enhancer from affecting transcription from the flanking UL1 27 promoter. We have identified a repressor-boundary region between the UL127 promoter and the MIE enhancer that is unique to HCMV and to date, not found in other herpesviruses or DNA viruses. Due to its location, the repressor-boundary region has a role in the temporal expression of the immediate early (IE) and early HCMV genes that flank the MIE enhancer. Downstream of the MIE promoter are the MIE genes, IE1 and IE2, which encode for proteins of 72 (IE72) and 86 kDa (IE86), respectively. These viral proteins are key regulatory proteins for efficient productive infection. In Specific Aim III, we propose to determine early gene regulation in recombinant viruses with both the IE1 and IE2 genes deleted and to determine the effects of HCMV IE1 and IE2 gene products on viral and host cell gene expression relevant to the viral life cycle. We will investigate the functions of this replication defective HCMV in activation of viral or cellular gene expression and compare these functions to those of the IE72 and IE86 proteins.

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- **Project Title: RISK FACTORS FOR CV DISEASE IN A DIALYSIS COHORT**

Principal Investigator & Institution: Coresh, Josef; Associate Professor; Epidemiology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

Timing: Fiscal Year 2002; Project Start 01-SEP-2000; Project End 31-JUL-2004

Summary: (Adapted from Investigator's Abstract) Atherosclerotic cardiovascular disease (ASCVD) is a leading contributor to the high morbidity and mortality among end-stage renal disease (ESRD) patients, accounting for 36 percent of ESRD deaths (total annual mortality of 23 percent). This application tests the hypothesis that higher levels of several novel risk factors (Lp(a) levels and apo(a) isoforms; homocysteine and related vitamins; Chlamydia pneumoniae and **cytomegalovirus**; and C-reactive protein and fibrinogen) and traditional risk factors predict higher risk of ASCVD in a prospective study of 925 incident dialysis patients recruited within three months of starting dialysis. Although these factors have been implicated in the etiology of ASCVD in ESRD patients, little prospective data exist. Cross-sectional studies are susceptible to large survival bias because of the high mortality of patients with renal disease. This cohort has already been recruited through a collaboration between Johns Hopkins and 80 Dialysis Clinics Incorporated (DCI) clinics; many of the important predictors and possible confounders have been measured. This application proposes to obtain long term followup (extending mean followup of 2.4 years by four more years) and conduct laboratory assays. The investigators will: 1) extend specimen collection, and follow-up, and institute

standardized review of ASCVD events; 2) characterize baseline associations of novel and traditional factors with each other, dialysis modality and dose, nutritional status, and ASCVD prevalence in the full cohort using a cross-sectional design; 3) determine whether baseline levels of risk factors predict subsequent incidence of ASCVD events, and total mortality using a prospective cohort study design and test a priori hypothesized interactions between risk factors and the risk of ASCVD; 4) study the variability of risk factors over time using annual measurements in a random subset of 180 patients (subcohort) using a longitudinal design; and lastly, 5) use a case-cohort design, utilizing the subcohort, to test whether the most recent level before an ASCVD event, the baseline level, or the mean level of each risk factor is most predictive of ASCVD risk. Baseline data collection will include a patient health questionnaire and a standardized review of comorbidity using dialysis chart records. Serum, plasma and DNA will be stored at -80 degrees C. from patient visits at recruitment (month 0), and followup (months 1,2,3,6,12,8,24, etc.). ASCVD will be assessed by review of hospital charts, patients and care providers questionnaires, and HCFA death forms. The investigators state that this study will use state-of-the-art epidemiologic and laboratory methods to identify modifiable risk factors, answer the call of an NKF task force for prospective studies of risk factors for ASCVD in the dialysis population, and lay the essential groundwork for future preventive interventions to reduce the burden of ASCVD in persons with ESRD.

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- **Project Title: ROLE OF HCMV GLYCOPROTEIN IN VIRAL BIOGENESIS**

Principal Investigator & Institution: Thomas, Gary; Scientist/Professor; None; Oregon Health & Science University Portland, or 972393098

Timing: Fiscal Year 2002; Project Start 15-JUL-2001; Project End 31-MAY-2006

Summary: (provided by applicant): Human **cytomegalovirus** (HCMV) is a ubiquitous pathogen that is a major cause of disease in immunocompromised individuals, such as AIDS and bone marrow transplantation patients. HCMV is also the most common congenital viral infection and is the leading cause of infectious CNS maldevelopment in children. Despite the clinical importance of this viral pathogen, little is known regarding the molecular and cellular basis of HCMV assembly in infected cells. Current models of HCMV suggest that following transport of viral capsids to the cytoplasm, they are enveloped at the trans-Golgi Network (TGN) and associated endosomal compartments by membranes studded with envelope glycoproteins. Correct localization and processing of the envelope glycoproteins is required for the production of infectious virus. Key to understanding HCMV biogenesis is a determination of the cellular and molecular mechanisms that localize the mature glycoproteins to the compartment(s) of viral assembly. Recent studies of the cell biology of the major HCMV envelope glycoprotein gB, an essential herpes virus glycoprotein, show that: 1) HCMV gB is localized to the TGN and sorts to the apical surface in polarized cells (the surface of HCMV release), 2) TGN localization is mediated by interaction of gB with the cellular connector, PACS- 1, and 3) inhibition of furin-dependent cleavage of gB causes missorting of the unprocessed glycoprotein and is coupled with a dramatic block in the production of infectious virus. The goal of this application is to determine the role of gB in HCMV assembly. To achieve this goal, we will address four specific aims: 1) identify the cis-acting sorting signals that direct binding of gB to PACS-1 and the gB motifs and domains necessary and sufficient to direct the TGN localization and sorting, 2) determine the mechanism(s) of PACS-1-mediated localization of gB to the TGN, and the requirement of this interaction for the production of infectious HCMV, 3) investigate the

role of the furin-dependent processing of gB in both TGN localization of the viral glycoprotein and in virus assembly, 4) determine the role of gB TGN localization, endosome sorting, and furin-dependent proteolysis in virus assembly by analysis of HCMV recombinants expressing gB genes defective in these processes. Together, these studies will increase our knowledge of the cell biology of HCMV gB and provide insight into the molecular mechanisms of viral assembly that will enable development of novel therapeutics to treat viral disease.

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- **Project Title: SAN DIEGO AIDS CLINICAL TRIAL UNIT**

Principal Investigator & Institution: Richman, Douglas D.; Associate Professor; Medicine; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 920930934

Timing: Fiscal Year 2002; Project Start 30-JUN-1986; Project End 31-DEC-2004

Summary: (adapted from the application's abstract): The University of California, San Diego AIDS Clinical Trials Unit (UCSD ACTU) proposes to continue participation in the Adult AIDS Clinical Trials Group (AACTG). Members of the UCSD ACTU have contributed to the leadership and development of the AACTG scientific agenda. They have designed, implemented and analyzed AACTG trials in antiretroviral therapy, opportunistic infections and outcomes. Laboratory studies conducted by the investigators have increased the understanding of the pathogenesis of HIV disease and complications, particularly in the areas of drug resistance, mycobacteria and **cytomegalovirus** disease. This group has established a record of patient accrual and retention by creating a program that is recognized by the community as being devoted to improving the lives of HIV-infected individuals. The ACTU has and will continue to make efforts to recruit as study participants women, minorities, and intravenous drug users. UCSD has a good relationship with the community advisory board that ensures community representation and enhances the overall effectiveness of the unit. The scientific contributions of the unit will focus on three aims: First, it will address the development of novel approaches to antiretroviral therapy and the incorporation of nested studies into clinical trials. The nested studies may provide insight into viral dynamics, resistance and reservoirs of HIV infection. Second, complications of HIV infection, which will provide leadership, innovative ideas and laboratory expertise for studies designed to increase understanding of the pathogenesis, prevention and treatment of opportunistic infections and the neurologic complications of HIV disease. Finally, attention will be given to outcomes and adherence, which will contribute expertise to the AACTG effort to evaluate outcome measures across clinical trials and to develop and test interventions, which may improve patient adherence.

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- **Project Title: SHORT TANDEM REPEAT POLYMORPHISMS IN CYTOMEGALOVIRUS**

Principal Investigator & Institution: Bale, James F.; Professor and Vice-Chair; Pediatrics; University of Utah Salt Lake City, Ut 84102

Timing: Fiscal Year 2002; Project Start 15-MAY-2002; Project End 31-MAR-2004

Summary: (Provided by Applicant): Strains of human **cytomegalovirus** (HCMV), a member of the human herpesvirus family, display genetic variations, and these polymorphisms can be analyzed to study viral transmission, pathogenesis, and evolution. Our laboratory has used restriction fragment polymorphism (RFLP) and

polymerase chain reaction (PCR)- based analysis to conduct detailed studies of HCMV transmission among young children. Recently, short tandem repeat (STR) length polymorphisms were identified in the HCMV genome. Davis and colleagues found at least 24 regions that exhibited length or sequence STR polymorphisms. In a study of 44 wild-type isolates and two laboratory strains of HCMV, we subsequently confirmed the presence of STR length polymorphisms and showed that a multiplexed PCR based on 10 STR regions may allow accurate comparisons of HCMV strains. This application requests support to validate this methodology. We intend to study at least 300 HCMV isolates from Iowa and Texas to determine the precise nature of the STR polymorphisms and their role in analyzing HCMV strains. We will examine three hypotheses regarding STR polymorphisms in HCMV: 1) Many STR polymorphisms exist for HCMV; 2) HCMV STR polymorphisms remain stable during prolonged excretion by individual children and after horizontal transmission among children; and 3) STF polymorphisms provide novel information regarding HCMV evolution. These aims will be accomplished by analyzing HCMV strains using a multiplexed PCR analysis. STR data regarding HCMV strains will be compared against the "gold standard" of nucleotide sequence and RFLP analysis. Characterizing HCMV strains by STR analysis will facilitate future studies of HCMV evolution and will provide a novel means to fingerprint HCMV strains.

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- **Project Title: SURGICAL STUDIES OF CMV REACTIVATION IN TRANSPLANTATION**

Principal Investigator & Institution: Abecassis, Michael; Associate Professor of Surgery; Surgery; Northwestern University Office of Sponsored Research Chicago, IL 60611

Timing: Fiscal Year 2004; Project Start 05-JAN-1999; Project End 31-DEC-2008

Summary: (provided by applicant): Reactivation of **cytomegalovirus** (CMV) from latency results in significant morbidity and mortality in immunocompromised solid organ and bone marrow recipients. Despite the ongoing development of effective antiviral agents, and the advent of preemptive therapy, drug-related toxicity and viral gene mutations leading to resistant virus present new clinical challenges, highlighting the need for alternative therapies, potentially aimed at early events in the process of reactivation. This project will focus on the molecular mechanisms of reactivation of CMV from latency, emphasizing the requirement for early triggers of Immediate Early (IE) gene expression, a necessary first step in the viral lytic cycle. The first aim will continue our current investigations into the requirement for TNF signal transduction and downstream activation of NFkB in both HCMV and MCMV IE gene expression in allogeneic grafts transplanted into immunocompetent hosts and investigate other factors likely to contribute to induction of IE gene expression, in an attempt to expand our current knowledge of the molecular mechanisms underlying CMV IE gene expression in vivo. The second aim will be to assemble a molecular definition of the events leading to reactivation of infectious virus from latency in vitro, by characterizing and investigating the molecular requirements for reactivation inferred from the in vivo model. In the third aim, we will test the requirement for the same mechanisms in the production of infectious virus in reactivation from latency in selectively immunocompromised hosts, in an effort to examine the role of the allogeneic immune response in host control of CMV reactivation to infectious virus, to test the hypothesis that TNF induced NFkB activation produced by allogeneic transplantation is required for reactivation of infectious virus in an immunocompromised allograft recipient. In the aggregate, the proposed studies form a logical extension of studies performed in the current grant

period and will provide a comprehensive paradigm of central importance to the immunocompromised recipient of an allograft. A better understanding of the viral and cellular factors responsible for the initial events required for CMV reactivation from latency to productive infection is essential to the development of novel strategies in the prevention of CMV infection and disease.

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- **Project Title: T-CELL RECEPTOR BASED THERAPEUTICS FOR CYTOMEGALOVIRUS**

Principal Investigator & Institution: Wong, Hing C.; Altor Bioscience Corporation 2810 N Commerce Pky Miramar, Fl 330253958

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

Summary: (provided by investigator): The goal of these studies is to evaluate the feasibility of using a T-cell receptor based fusion protein as a targeting agent for therapies for CMV, which remains a major cause of morbidity and mortality in immunocompromised patients. For these studies a TCR recognizing a distinct, naturally processed, highly immunogenic peptide fragment from the human **cytomegalovirus** tegument protein pp65 presented on the cell surface in the context of HLA-A2 was cloned. This TCR was isolated from CMV peptide specific CD8+ T-cells that were generated by CMV peptide stimulation of HLA-A2 positive human PBMC. A CMV specific single chain TCR/IgG1 fusion protein, CMVscTCR/IgG1, was prepared and will be expressed at high levels in mammalian cells and purified for characterization. The fusion protein will be characterized in vitro for MHC restricted peptide specific binding, stability, affinity, ability to target antigen positive cells, and ability to conjugate target and effector cells. Finally, the CMVscTCR/IgG1 fusion protein will be evaluated in vivo for pharmacokinetics and toxicity. Successful completion of these studies will lead to in vivo efficacy studies in a novel mouse model of human CMV infection and to eventual production of TCR-based targeted CMV therapeutics for commercialization.

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

- **Project Title: TRANSFUSION TRANSMISSION OF CELL-ASSOCIATED INFECTIONS**

Principal Investigator & Institution: Hillyer, Christopher D.; Professor; Pathology and Lab Medicine; Emory University 1784 North Decatur Road Atlanta, Ga 30322

Timing: Fiscal Year 2002; Project Start 01-SEP-2000; Project End 31-JUL-2004

Summary: The focus of this resubmitted application is to determine the cellular site and mechanisms of reactivation of **cytomegalovirus** (CMV). Human CMV (HCMV) infections are life-long and the virus persists in a latent state in monocytes, although other cellular sites are also thought to exist. During blood transfusion and organ transplantation, HCMV reactivation can cause severe disease in immunocompromised individuals. Therefore, determination of the parameters (including types and numbers of cells, and immune responses) that permit HCMV transmission during blood transfusions (TT) and organ transplantation is clinically important. The transfer of latently infected monocytes is hypothesized to be the mechanism of HCMV transmission and reactivation during blood transfusions. However, the exact cell number or type of infected cells required for transmission during blood transfusions or organ transplantation is unclear. In addition, the processes involved in cellular activation that result in CMV reactivation from latency are also unknown. The

applicants propose two specific aims to analyze these aspects of CMV transfusion/reactivation using a MCMV/mouse model. In the first specific aim, the investigator will identify the cellular sites of infection and latency in MCMV infected donor mice. For these studies, serial dilutions of purified leukocyte subsets will be made and the viral burden quantitated prior to transfusion into syngeneic and allogeneic recipients. Through the removal of specific leukocyte subpopulations prior to transfusion he will test the hypotheses that a) only latently infected monocytes are able to transmit MCMV, b) transmission of MCMV by transfusion is inefficient, and c) MCMV-infected blood depleted monocytes is CMV safe. The second specific aim has been refocused from the original proposal. In this part of the project, the investigator will utilize the optimized MCMV transfusion model described in the first specific aim to evaluate recipient factors that modulate the efficiency of MCMV reactivation. These factors include allogeneic leukocyte interactions mediated by CD4 and CD8 T-lymphocytes, NK cells, and the effects of g IFN. He predicts that allogeneic leukocyte interactions mediate reactivation of MCMV in the recipient and that g IFN inhibits this process.

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

- **Project Title: TRANSLATIONAL CONTROL OF CYTOMEGALOVIRUS GENE EXPRESSION**

Principal Investigator & Institution: Geballe, Adam P.; Member; Fred Hutchinson Cancer Research Center Box 19024, 1100 Fairview Ave N Seattle, Wa 98109

Timing: Fiscal Year 2003; Project Start 01-AUG-1988; Project End 31-MAR-2008

Summary: (provided by applicant): The long-range goals of this research are to elucidate mechanisms that regulate human **cytomegalovirus** (HCMV) gene expression at the translational level. Cells infected by HCMV continue to synthesize proteins, despite activation of host mechanisms designed to shut off translation and thereby prevent viral replication. These studies will clarify the biochemical and genetic basis for the preservation of the robust protein synthetic capacity in HCMV-infected cells. HCMV rescues replication of a vaccinia virus mutant lacking the double-stranded RNA binding protein gene E3L (VVdeltaE3L). In the absence of HCMV, cells infected with the VVdeltaE3L contain high levels of phosphorylated eIF2-alpha and RNaseL activity, and low levels of protein synthesis, viral late gene expression and viral production. HCMV infection reverses each of these properties. Using VVdeltaE3L as a means to activate the host cell antiviral responses, experiments will delineate the steps in the pathways leading to eIF2-alpha phosphorylation and RNaseL activation that are blocked by HCMV infection. The HCMV gene(s) responsible for the rescue of late gene expression and replication of VVdeltaE3L will be identified and its functional domains will be delineated. The mechanism of action of the complementing gene(s) will be elucidated and its expression properties, conservation among HCMV isolates and role in the replicative cycle will be determined. These studies will reveal new insights into the host-virus interactions that are likely to be critical determinants of the pathogenesis of HCMV disease.

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

- **Project Title: VACCINES FOR PREVENTION OF EXPERIMENTAL CONGENITAL CMV**

Principal Investigator & Institution: Schleiss, Mark R.; Associate Professor; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 45229

Timing: Fiscal Year 2002; Project Start 01-APR-2000; Project End 31-MAR-2004

Summary: Human **cytomegalovirus** (HCMV) is an important pathogen which causes severe morbidity in immunocompromised individuals, including newborn infants. In particular, infants born with congenital CMV infection are at high risk for poor neurodevelopmental outcome. Since pre-existing maternal immunity protects against severe disease caused by HCMV, there is considerable interest in developing vaccines designed to prevent the substantial morbidity associated with congenital infection. Vaccines for CMV have been difficult to evaluate in the preclinical setting, however, because of the strict species specificity of **cytomegaloviruses**. Since the guinea pig **cytomegalovirus** (GPCMV) crosses the placenta, causing infection in utero, the guinea pig provides a model system in which to test vaccines for the prevention of CMV disease. Unfortunately, this system has not to date been exploited to its fullest potential, largely because so little is known about the molecular biology of GPCMV. However, recently the GPCMV genes encoding the major humoral immune target glycoprotein B (gB) and the cell-mediated immune target pp65 (UL83) have been cloned, characterized and expressed. Subunit vaccine studies are thus now feasible in this model. Therefore, these studies propose three major aims. First, the immunogenicity and protective efficacy of a recombinant form of envelope glycoprotein gB will be evaluated in our congenital infection model. The hypothesis we will test is that recombinant gB will provide protection against congenital CMV, but in an adjuvant-dependent fashion. We will directly evaluate whether a more potent immunomodulatory agent, monophosphoryl lipid A (MPL), provides a better adjuvant effect than alum-based adjuvants alone. These will be the first assessments of adjuvants relevant to human clinical use in the GPCMV model. In the second specific aim, we will test the role of a cytotoxic-T-lymphocyte (CTL) target, UL83, as a vectored vaccine expressed in vaccinia. We hypothesize that vaccination against this CTL target will provide protection against congenital CMV disease. This will be the first assessment of a vaccine which elicits only cell-mediated responses in a model of congenital infection. Finally, in the third specific aim we will conduct the first studies to test the protective efficacy of DNA vaccines for protection against congenital CMV infection. We hypothesize that DNA vaccines which target both gB and UL83 will provide efficacy against disease in our model. Information obtained from these studies will be relevant to ongoing studies of HCMV vaccines, and will help to prioritize which vaccine strategies should be pursued in further clinical trials for the prevention of congenital **cytomegalovirus** infection.

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

- **Project Title: VIRAL CHEMOKINE RECEPTORS: TRANSPLANT VASCULAR SCLEROSIS**

Principal Investigator & Institution: Orloff, Susan L.; Surgery; Oregon Health & Science University Portland, or 972393098

Timing: Fiscal Year 2002; Project Start 01-FEB-2001; Project End 31-JAN-2004

Summary: The long term goal of this project is to identify mechanisms involved with human **cytomegalovirus** (HCMV) acceleration of transplant vascular sclerosis. The primary cause of graft loss of all vascularized organ transplants is due to a vascular lesion associated with chronic rejection. This form of vasculopathy referred to as TVS is characterized by concentric neointimal smooth muscle cell proliferation that results in vessel occlusion and ultimately graft failure. To date the only therapy available to treat severe TVS is retransplantation. Clinical studies in transplant recipients have demonstrated a direct link between HCMV and the acceleration of TVS. Based on these findings, we have developed a rat model of heart and small bowel transplantation in

which CMV infection accelerates the time and severity of TVS. While the exact mechanism through which CMV mediates this process is unknown, recent work from our group suggests that CMV may contribute to TVS through induction of smooth muscle cell (SMC) migration towards sites of chemokine production through expression of a virally encoded chemokine receptor (US28). We have also observed that Rat and Murine CMV also induce SMC migration through their respective viral chemokine receptors R33 and M33, which are functional homologues of HCMV US28. We hypothesize that the mechanism of CMV-accelerated TVS involves the expression of virally encoded chemokine receptors leading to intimal SMC migration, which results in the characteristic vascular lesions of TVS. Therefore, we will utilize our in vitro and in vivo models to extend our observations and determine the role of virally encoded chemokine receptors in the development of TVS in three specific aims. First, using a rat cardiac transplant model of chronic rejection, we will determine the effects of virus on the kinetics of disease progression of TVS and the extent of viral expression in tissues as well as the cell types involved in the process. We will also determine the host factors such as chemokines and cytokines, and the contribution of R33 involved at various stages of the development of RCMV-induced TVS. Secondly, we will characterize the R33 domains involved in signaling which induce SMC migration and the ligands, which serve as agonists or antagonists to induced cellular movement. In the last specific, we will generate recombinant RCMV which contain mutations in domains involved in signaling to understand their contribution to TVS in the rat cardiac transplant model. Lastly, antagonists of R33 induced SMC migration in vitro will be tested for their ability to block TVS in the in vivo rat model. These studies will provide a valuable animal model to understand the role of CMV in the acceleration of TVS. In addition completion of these studies will form the basis for novel and rational design of therapeutic strategies to enhance long-term graft survival in HCMV infected transplant recipients.

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- **Project Title: VIRAL EVASION STRATEGIES: ANALYSIS OF HERPES VIRUSES**

Principal Investigator & Institution: Ploegh, Hidde L.; Professor; Pathology; Harvard University (Medical School) Medical School Campus Boston, Ma 02115

Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 31-MAR-2008

Summary: Human Herpesviruses cause a life-long latent infection, from which reactivation can occur in the face of a fully primed immune system. This viral strategy necessitates evasion of host immune reactions. For human **cytomegalovirus** (HCMV), a set of genes in the unique short (US) region encode a collection of in all likelihood structurally similar-type I membrane glycoproteins. Several of these genes, notably US2, US3, US6 and US 11, are known to interfere with MHC class I restricted antigen presentation when analyzed in tissue culture systems. To complement the recent determination of the Class I-US2 structure we have initiated structural studies of the HCMV US3 product. We shall further analyze the mode of action and structure of U21, an HHV7-encoded immunoevasin that also down-regulates MHC class I molecules. Because there is no animal model for HCMV infection, the suggestions for the biological role of the immunoevasins encoded in the HCMV US cluster remain conjectural. Murine CMV recombinants equipped with the US genes, alone or in combination, will be generated, along with the flu matrix protein, which will serve as the "passenger" antigen to allow enumeration of antigen-specific T cells. With these viruses we shall infect HLA-A2 and I-ILA-B7 transgenic mice in which the endogenous H-2K and H-2D genes have been disrupted through gene targeting. These animals must rely on the human restriction elements for the generation of CD8 T cells, the presence and frequency of

which will be determined with the appropriate HLA-Class I peptide tetramers. In view of the intimate connection between the US gene products and MHC class I antigens, the nucleotide sequence of the US2, US3, US6 and US 11 genes will be determined for a number of clinical HCMV isolates, to be obtained preferably from different ethnic groups with different sets and distributions of MHC class I alleles. This analysis should reveal if and to what extent the MHC alleles in the human population help shape the "repertoire" of immunoevasins.

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- **Project Title: VIROLOGIC AND IMMUNOLOGIC STUDIES MURINE CMV RETINITIS**

Principal Investigator & Institution: Atherton, Sally S.; Professor and Chair; Cellular Biology and Anatomy; Medical College of Georgia 1120 15Th St Augusta, Ga 30912

Timing: Fiscal Year 2002; Project Start 30-SEP-2000; Project End 31-AUG-2005

Summary: (Applicant's Description): Even though much known about the course and treatment of CMV retinitis in immunosuppressed human patients, many aspects of the pathogenesis of CMV retinitis remain to be deciphered. Understanding the pathogenesis of CMV retinitis continues to be an important area of investigation since even though the incidence of new cases of CMV retinitis decreased in patients on highly active antiretroviral therapy (HAART) and several antivirals with anti-CMV activity are widely available, the number of new cases of CMV retinitis has begun to slowly increase again at many centers. The studies proposed in this application will use the BALB/c mouse model of MCMV retinitis and will focus on those aspects of retinitis in the mouse that appear to be relevant to understanding the pathogenesis of CMV retinitis in human patients - latency and reactivation in the eye, the role of the blood-retinal barrier (BRB) and whether intravenously injected virus-infected cells enter and infect the retina, and finally, the role of infected RPE in causing apoptosis of apparently uninfected retinal cells. The first Specific Aim is to define the site(s) of latency in the eye and whether the route that is used for ocular injection plays a role in determining the sites at which MCMV becomes latent. The second Specific Aim is to determine if MCMV can spread to and replicate in the retina of immunosuppressed mice following disruption of the BRB and intravenous injection of MCMV-infected mononuclear cells or MCMV. The third Specific Aim is to determine the mechanism by which infection of the RPE results in apoptosis of the overlying retina. By using the mouse model to provide new information about how MCMV causes infection of the retina, the results of these studies may provide new insight into the mechanisms of CMV infection of the retina in human patients, which, in turn, might lead to new therapies for preventing infection or reducing its harmful effects.

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

- **Project Title: VISUAL OUTCOMES & QUALITY OF LIFE IN CMV RETINITIS**

Principal Investigator & Institution: Thorne, Jennifer E.; Ophthalmology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

Timing: Fiscal Year 2002; Project Start 01-FEB-2002; Project End 31-JAN-2007

Summary: This application proposes a training plan to develop Jennifer E. Thorne, MD, into a independent clinical scientists , and expert in epidemiologic research methods and clinical trial design. As of December 2001, Dr. Thorne will be a board-certified ophthalmologist with subspecialty training in uveitis and ocular immunology. The Johns Hopkins University is well-suited to serve as her training site. The

training program will consist of mentored research experience, multi-disciplinary conferences, and courses leading to a PhD in Epidemiology. Mentored research will be conducted as a member of the Studies of Ocular Complications of AIDS (SOCA) Research Group under primary mentor Curtis Meinert, Ph.D., Director of the SOCA Coordinating Center, and co-mentor Douglas A. Jabs, M.D., SOCA Chair. Dr. Thorne will take part in the full spectrum of SOCA Coordinating Center activities, as well as assuming a leading role on the visual outcomes and quality of life (QOL) and Sheila West, Ph.D., a senior ophthalmic epidemiologist, will serve as consultants for this project. **Cytomegalovirus (CMV)** retinitis complicating AIDS is associated with reduced visual acuity, visual field and quality of life (QOL). LSOCA is a multi-centered prospective cohort study designed to follow patients with AIDS and CMV retinitis over a five year period. Since the advent of highly active anti-retroviral therapy (HAART), the epidemiology of AIDS and CMV retinitis is rapidly evolving. LSOCA seeks to define the incidence of CMV retinitis, the factors that place patients at increased risk for developing CMV retinitis and the sequelae of AIDS-related eye disease in the HAART era. Since therapy for CMV retinitis is driven by maintaining and/or improving visual function and QOL, assessment of these outcomes will play a major role in interpreting the study's results. The primary goals of these sections of the study are to quantify visual loss over time in patients with CMV retinitis, to determine the characteristics that put these patients at high risk for poor visual outcomes, and to evaluate how HAART may affect visual function and QOL outcomes in these patients.

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

E-Journals: PubMed Central³

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 "cytomegalovirus" (or synonyms) into the search box. This search gives you access to full-text articles. The following is a sample of items found for cytomegalovirus in the PubMed Central database:

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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.

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

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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 CYTOMEGALOVIRUS

Overview

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

Finding Nutrition Studies on Cytomegalovirus

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 "cytomegalovirus" (or synonyms) into the search box, and click "Go." To narrow the search, you can also select the "Title" field.

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 "cytomegalovirus" (or a synonym):

- **Affinity-based collection of amplified viral DNA: application to the detection of human immunodeficiency virus type 1, human cytomegalovirus and human papillomavirus type 16.**
 Author(s): Orion Pharmaceutica, Biotechnology, Helsinki, Finland.
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- **Antiviral activity of artesunate towards wild-type, recombinant, and ganciclovir-resistant human cytomegaloviruses.**
 Author(s): Virtual Campus Rhineland-Palatinate, P.O. Box 4380, 55033 Mainz, Germany. efferth@vcrp.de
 Source: Efferth, T Marschall, M Wang, X Huong, S M Hauber, I Olbrich, A Kronschnabl, M Stamminger, T Huang, E S J-Mol-Med. 2002 April; 80(4): 233-42 0946-2716
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 Author(s): Department of Medical Microbiology, University of Cape Town Medical School, South Africa.
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- **Cell activation signals and the pathogenesis of human cytomegalovirus.**
 Author(s): Department of Microbiology, University of Texas Medical Branch, Galveston 77550.
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 Author(s): Institut fur Klinische und Molekulare Virologie, Universitat Erlangen-Nurnberg, F.R.G.
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 Author(s): Pathology and Laboratory Medicine Department, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.
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 Author(s): Department of Anatomical Pathology, Nelson R Mandela School of Medicine and King Edward VIII Hospital, Private Bag 7, Congella, 4013, Kwazulu Natal, South Africa. ramdial@nu.ac.za
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- **Detection of cytomegalovirus-infected cells by flow cytometry and fluorescence in suspension hybridisation (FLASH) using DNA probes labeled with biotin by polymerase chain reaction.**
 Author(s): Department of Haematology and Oncology, Hannover Medical School, Germany.
 Source: Link, H Battmer, K Kleine, H D J-Med-Virol. 1992 June; 37(2): 143-8 0146-6615
- **Differences in cell-type-specific blocks to immediate early gene expression and DNA replication of human, simian and murine cytomegalovirus.**
 Author(s): Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.
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 Author(s): Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania 19104, USA.
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- **Effect of the complexation with cyclodextrins on the in vitro antiviral activity of ganciclovir against human cytomegalovirus.**
 Author(s): Unite Mixte de Recherche Universite-CNRS 7565, Structure et Reactivite des Systemes Moleculaires Complexes, UHP, Nancy, France.
 Source: Nicolazzi, C Abdou, S Collomb, J Marsura, A Finance, C Bioorg-Med-Chem. 2001 February; 9(2): 275-82 0968-0896
- **Effects of changing immunosuppressive regimen on the incidence, duration, and viral load of cytomegalovirus infection in renal transplantation: a single center report.**
 Author(s): Renal Transplantation Unit and Division of Clinical Immunology, department of Internal Medicine, University Hospital, Groningen, The Netherlands. e.f.de.maar@int.azg.nl
 Source: de Maar, E F Verschuuren, E A Homan vd Heide, J J Kas Deelen, D M Jagernath, D The, T H Ploeg, R J van Son, W J Transpl-Infect-Dis. 2002 March; 4(1): 17-24 1398-2273
- **Effects of oral ciclosporin on acute and chronic murine cytomegalovirus infection.**
 Author(s): Department of Infectious Diseases and Microbiology, Graduate School of Public Health, University of Pittsburgh, Pa. 15261.
 Source: Zhang, X Q Zhang, J T Ho, M Intervirology. 1987; 27(3): 130-7 0300-5526
- **Etoposide as a virocidal anticytomegalovirus therapy: intravitreal toxicology and pharmacology in rabbits.**
 Author(s): Department of Ophthalmology, Prince of Wales Hospital, Sydney, New South Wales, Australia.
 Source: Morlet, N Stayt, J Vaegan Salonikas, C Naidoo, D Crouch, R Graham, G Coroneo, M Aust-N-Z-J-Ophthalmol. 1999 October; 27(5): 342-9 0814-9763

- **Evaluation of the antiviral activity of kaempferol and its glycosides against human cytomegalovirus.**
Source: Mitrocotsa, D. Mitaku, S. Axarlis, S. Harvala, C. Malamas, M. Planta-med. Stuttgart : Georg Thieme Verlag,. May 2000. volume 66 (4) page 377-379. 0032-0943
- **Expression of oncogenic ras in human teratocarcinoma cells induces partial differentiation and permissiveness for human cytomegalovirus infection.**
Author(s): Department of Medicine, Addenbrooke's Hospital, Cambridge, U.K.
Source: Shelbourn, S L Sissons, J G Sinclair, J H J-Gen-Virol. 1989 February; 70 (Pt 2)367-74 0022-1317
- **Factors affecting human cytomegalovirus gene expression in human monocyte cell lines.**
Author(s): Division of Life Sciences, Chungbuk National University, Cheongju, Korea. chlee@cbucc.chungbuk.ac.kr
Source: Lee, C H Lee, G C Chan, Y J Chiou, C J Ahn, J H Hayward, G S Mol-Cells. 1999 February 28; 9(1): 37-44 1016-8478
- **Fatal cytomegalovirus disease in a high-risk renal transplant recipient.**
Author(s): Department of Pediatrics, Division of Pediatric Nephrology, Louisiana State University Health Sciences Center at Shreveport, 1501 Kings Highway, Shreveport, LA 71130, USA.
Source: Tenney, F Sakarcn, A Pediatr-Nephrol. 2001 January; 16(1): 8-10 0931-041X
- **Functional changes in murine macrophages infected with cytomegalovirus relate to H-2-determined sensitivity to infection.**
Author(s): Department of Microbiology, University of Western Australia.
Source: Price, P Winter, J G Nikoletti, S Hudson, J B Shellam, G R J-Virol. 1987 November; 61(11): 3602-6 0022-538X
- **Genetically determined resistance to murine cytomegalovirus: a role for lymphocytostatic macrophages.**
Author(s): Department of Microbiology, University of Western Australia, Nedlands.
Source: Price, P Winter, J G Shellam, G R J-Gen-Virol. 1987 December; 68 (Pt 12)2997-3008 0022-1317
- **Growth of human cytomegalovirus in primary macrophages.**
Author(s): Department of Molecular Microbiology and Immunology, Oregon Health Sciences University, Portland, Oregon, 97201, USA.
Source: Soderberg Naucner, C Fish, K N Nelson, J A Methods. 1998 September; 16(1): 126-38 1046-2023
- **Human cytomegalovirus. Stimulation of [3H] release from [3H]-arachidonic acid prelabelled cells.**
Author(s): Department of Microbiology, University of Texas Medical Branch, Galveston.
Source: AbuBakar, S Boldogh, I Albrecht, T Arch-Virol. 1990; 113(3-4): 255-66 0304-8608
- **Hydrolysis of inositol lipids: an early signal of human cytomegalovirus infection.**
Author(s): Department of Microbiology, University of Texas Medical Branch, Galveston.
Source: Valyi Nagy, T Bandi, Z Boldogh, I Albrecht, T Arch-Virol. 1988; 101(3-4): 199-207 0304-8608
- **Improving permissive infection of human cytomegalovirus in cell culture.**
Author(s): Department of Microbiology, SEALS, Prince of Wales Hospital, Randwick, NSW, Australia.
Source: Scott, G M Ratnamohan, V M Rawlinson, W D Arch-Virol. 2000; 145(11): 2431-8 0304-8608

- **Inactivation of cytomegalovirus in platelet concentrates using Helinx technology.**
Author(s): Biological Research Division, Cerus Corporation, Concord, CA 94520, USA.
Source: Lin, L Semin-Hematol. 2001 October; 38(4 Suppl 11): 27-33 0037-1963
- **Induction by sodium butyrate of cytomegalovirus replication in human endothelial cells.**
Author(s): Institute of Virology, Philipps University, Marburg, Federal Republic of Germany.
Source: Radsak, K Fuhrmann, R Franke, R P Schneider, D Kollert, A Brucher, K H Drenckhahn, D Arch-Virol. 1989; 107(1-2): 151-8 0304-8608
- **Induction of gene expression under human cytomegalovirus immediate early enhancer-promoter control by inhibition of protein synthesis is cell cycle-dependent.**
Author(s): Department of Virology, University of Amsterdam, The Netherlands.
Source: Boom, R Sol, C J Minnaar, R P Geelen, J L Raap, A K van der Noordaa, J J-Gen-Virol. 1988 June; 69 (Pt 6)1179-93 0022-1317
- **Influence of 2-substituent on the activity of imidazo[1,2-a] pyridine derivatives against human cytomegalovirus.**
Author(s): Laboratoire de Chimie Therapeutique, Faculte de Pharmacie, 31 Av. Monge, 37200, Tours, France.
Source: Mavel, S Renou, J L Galtier, C Allouchi, H Snoeck, R Andrei, G De Clercq, E Balzarini, J Gueffier, A Bioorg-Med-Chem. 2002 April; 10(4): 941-6 0968-0896
- **Ligand induction of retinoic acid receptors alters an acute infection by murine cytomegalovirus.**
Author(s): Departments of Immunology and Molecular Biology, Division of Virology, The Scripps Research Institute, La Jolla, California 92037, USA.
Source: Angulo, A Chandraratna, R A LeBlanc, J F Ghazal, P J-Virol. 1998 June; 72(6): 4589-600 0022-538X
- **Modulation of immunocompetence by cyclosporin A, cyclophosphamide or protein malnutrition potentiates murine cytomegalovirus pneumonitis.**
Author(s): Department of Microbiology, University of Western Australia, School of Veterinary Studies.
Source: Price, P Hopkins, R M Teo, H K Papadimitriou, J M Shellam, G R Pathol-Res-Pract. 1991 December; 187(8): 993-1000 0344-0338
- **Modulation of T-cell activation through protein kinase C- or A-dependent signalling pathways synergistically increases human immunodeficiency virus long terminal repeat induction by cytomegalovirus immediate-early proteins.**
Author(s): Departement des Retrovirus, Institut Pasteur, Paris, France.
Source: Paya, C V Virelizier, J L Michelson, S J-Virol. 1991 October; 65(10): 5477-84 0022-538X
- **Molecular characterization of the guinea-pig cytomegalovirus glycoprotein L gene.**
Source: Paglino, J.C. Brady, R.C. Schleiss, M.R. Arch-virol. Wien, Austria : Springer-Verlag. 1999. volume 144 (3) page 447-462. 0304-8608
- **Morphological and functional changes during cytomegalovirus replication in murine macrophages.**
Author(s): Department of Pathology, University of Western Australia, Nedlands.
Source: van Bruggen, I Price, P Robertson, T A Papadimitriou, J M J-Leukoc-Biol. 1989 December; 46(6): 508-20 0741-5400

- **Morphology and distribution of gp52 on extracellular human cytomegalovirus (HCMV) supports biochemical evidence that it represents the HCMV glycoprotein B.**
 Author(s): Department of Medical Microbiology, University of Cape Town Medical School, South Africa.
 Source: Stannard, L M Rider, J R Farrar, G H J-Gen-Virol. 1989 June; 70 (Pt 6)1553-60 0022-1317
- **Patterns of cytomegalovirus infection in simultaneous kidney-pancreas transplant recipients receiving tacrolimus, mycophenolate mofetil, and prednisone with ganciclovir prophylaxis.**
 Author(s): Department of Pharmacy, University of Tennessee-Memphis, Tennessee 38163, USA.
 Source: Lo, A Stratta, R J Egidi, M F Shokouh Amiri, M H Grewal, H P Kisilisik, A T Trofe, J Alloway, R R Gaber, L W Gaber, A O Transpl-Infect-Dis. 2001 March; 3(1): 8-15 1398-2273
- **Phytohemagglutinin-induced activity of cyclic AMP (cAMP) response elements from cytomegalovirus is reduced by cyclosporine and synergistically enhanced by cAMP.**
 Author(s): Laboratory of Biochemistry and Metabolism, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland 20892.
 Source: Niller, H H Hennighausen, L J-Virol. 1990 May; 64(5): 2388-91 0022-538X
- **Potential of murine cytomegalovirus pneumonitis by antibiotics in clinical use.**
 Author(s): Department of Microbiology, University of Western Australia, Nedlands.
 Source: Olver, S D Price, P Karthigasu, K T J-Antimicrob-Chemother. 1991 January; 27(1): 81-94 0305-7453
- **Prevention of cytomegalovirus disease in hematopoietic stem cell transplantation.**
 Author(s): Division of Virology, Beckman Research Institute of the City of Hope, Duarte, CA 91010, USA. jzaia@bricoh.edu
 Source: Zaia, J A Clin-Infect-Dis. 2002 October 15; 35(8): 999-1004 1537-6591
- **Proinflammatory potential of cytomegalovirus infection. specific inhibition of cytomegalovirus immediate-early expression in combination with antioxidants as a novel treatment strategy?**
 Author(s): Institut fur Medizinische Virologie, Johann-Wolfgang-Goethe-Universitat, Frankfurt am Main, Deutschland. cinatl@em.uni-frankfurt.de
 Source: Cinatl, J Vogel, J U Kotchetkov, R Scholz, M Doerr, H W Intervirology. 1999; 42(5-6): 419-24 0300-5526
- **Properties of the immunosuppressive factor induced by murine cytomegalovirus.**
 Author(s): Division of Medical Microbiology, University of British Columbia, Vancouver, Canada.
 Source: Hudson, J B Whyte, P F Subramaniam, R Comp-Immunol-Microbiol-Infect-Dis. 1989; 12(1-2): 39-46 0147-9571
- **Randomized comparison of oral valgacyclovir and intravenous ganciclovir for prevention of cytomegalovirus disease after allogeneic bone marrow transplantation.**
 Author(s): University of California, Center for the Health Sciences, Los Angeles, USA. dwinston@mednet.ucla.edu
 Source: Winston, D J Yeager, A M Chandrasekar, P H Snyderman, D R Petersen, F B Territo, M C Clin-Infect-Dis. 2003 March 15; 36(6): 749-58 1537-6591

- **Rapid detection of cytomegalovirus infections by a tissue culture-centrifugation-monoclonal antibody-biotin/avidin immunofluorescence technique.**
Author(s): Division of Infectious Diseases, Children's Hospital of Philadelphia, PA 19104.
Source: Ho, W Z Plotkin, S A Mol-Cell-Probes. 1987 March; 1(1): 83-93 0890-8508
- **Receptor-binding properties of a soluble form of human cytomegalovirus glycoprotein B.**
Author(s): Department of Medical Microbiology and Immunology, University of Wisconsin-Madison, 53706-1532, USA.
Source: Boyle, K A Compton, T J-Virol. 1998 March; 72(3): 1826-33 0022-538X
- **Relationship between HOX2 homeobox gene expression and the human cytomegalovirus immediate early genes.**
Author(s): Institute for Developmental Research, Aichi Prefectural Colony, Japan.
Source: Kadota, C Nagahama, M Tsutsui, Y J-Gen-Virol. 1992 April; 73 (Pt 4)975-81 0022-1317
- **Stable expression of functional human cytomegalovirus immediate-early proteins IE1 and IE2 in HeLa cells.**
Author(s): Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, Republic of China.
Source: Yuo, C Y Wu, G J Huang, E S Wu, F Y Wu, C W Intervirology. 1992; 34(2): 94-104 0300-5526
- **Studies of depressed interleukin-2 production by spleen cells from mice following infection with cytomegalovirus.**
Author(s): Department of Microbiology, United Medical and Dental School, Guy's Hospital, London, U.K.
Source: Blackett, S Mims, C A Arch-Virol. 1988; 99(1-2): 1-8 0304-8608
- **Surfactant protein A binding to cytomegalovirus proteins enhances virus entry into rat lung cells.**
Author(s): Departments of Virology, Medical Immunology, and Neonatology, Humboldt University, Medical School (Charite), Berlin, Germany.
Source: Weyer, C Sabat, R Wissel, H Kruger, D H Stevens, P A Prosch, S Am-J-Respir-Cell-Mol-Biol. 2000 July; 23(1): 71-8 1044-1549
- **Synergistic activation of the human cytomegalovirus major immediate early promoter by prostaglandin E2 and cytokines.**
Author(s): Department of Medicine, University of Iowa College of Medicine, Iowa City, USA.
Source: Kline, J N Hunninghake, G M He, B Monick, M M Hunninghake, G W Exp-Lung-Res. 1998 Jan-February; 24(1): 3-14 0190-2148
- **The inflammatory macrophage response to murine cytomegalovirus in genetically susceptible mice.**
Author(s): Department of Microbiology, University of Western Australia, Nedlands.
Source: Price, P Winter, J G Shellam, G R Arch-Virol. 1989; 106(1-2): 35-50 0304-8608
- **The procoagulant response of cytomegalovirus infected endothelial cells.**
Author(s): Open University of The Netherlands, Dept. Natural Sciences, Heerlen.
Source: van Dam Mieras, M C Muller, A D van Hinsbergh, V W Mullers, W J Bomans, P H Bruggeman, C A Thromb-Haemost. 1992 September 7; 68(3): 364-70 0340-6245

- **Transcriptional activation of the major immediate early transcription unit of human cytomegalovirus by heat-shock, arsenite and protein synthesis inhibitors.**
Author(s): Department of Virology, Academic Medical Center, University of Amsterdam, The Netherlands.
Source: Geelen, J L Boom, R Klaver, G P Minnaar, R P Feltkamp, M C van Milligen, F J Sol, C J van der Noordaa, J J-Gen-Virol. 1987 November; 68 (Pt 11)2925-31 0022-1317
- **Valacyclovir for the prevention of cytomegalovirus infection after allogeneic stem cell transplantation: a single institution retrospective cohort analysis.**
Author(s): Division of Hematology and Oncology, Department of Medicine, Vanderbilt University School of Medicine and VA Medical Center, Nashville, TN 37212, USA.
Source: Vusirikala, M Wolff, S N Stein, R S Brandt, S J Morgan, D S Greer, J P Schuening, F G Dummer, J S Goodman, S A Bone-Marrow-Transplant. 2001 August; 28(3): 265-70 0268-3369
- **Viral replication in HeLa/fibroblast hybrid cells infected with human cytomegalovirus.**
Source: Tsutsui, Y Sonta, S Kashiwai, A Nogami, T Furukawa, T Arch-Virol. 1987; 95(1-2): 29-40 0304-8608

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 cytomegalovirus; 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:

- **Minerals**

Stinging Nettle

Alternative names: *Urtica dioica*, *Urtica urens*, Nettle

Source: Integrative Medicine Communications; www.drkoop.com

CHAPTER 3. ALTERNATIVE MEDICINE AND CYTOMEGALOVIRUS

Overview

In this chapter, we will begin by introducing you to official information sources on complementary and alternative medicine (CAM) relating to cytomegalovirus. 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 cytomegalovirus 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 "cytomegalovirus" (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 cytomegalovirus:

- **Activation of protein kinase C enhances the infection of endothelial cells by human cytomegalovirus.**
 Author(s): Slobbe-van Drunen ME, Vossen RC, Couwenberg FM, Hulsbosch MM, Heemskerk JW, van Dam-Mieras MC, Bruggeman CA.
 Source: Virus Research. 1997 May; 48(2): 207-13.
http://www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9175259&dopt=Abstract
- **Application of intensified (+) Qi Gong energy, (-) electrical field, (S) magnetic field, electrical pulses (1-2 pulses/sec), strong Shiatsu massage or acupuncture on the accurate organ representation areas of the hands to improve circulation and enhance drug uptake in pathological organs: clinical applications with special emphasis on the "Chlamydia-(Lyme)-uric acid syndrome" and "Chlamydia-(cytomegalovirus)-uric acid syndrome".**
 Author(s): Omura Y, Beckman SL.

Source: Acupuncture & Electro-Therapeutics Research. 1995 January-March; 20(1): 21-72.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7572329&dopt=Abstract

- **Bilateral cytomegalovirus panuveitis after high-dose corticosteroid therapy.**
 Author(s): Berger BB, Weinberg RS, Tessler HH, Wyhinny GJ, Vygantas CM.
 Source: American Journal of Ophthalmology. 1979 December; 88(6): 1020-5.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=229732&dopt=Abstract
- **CD8+ cytotoxic T cell therapy of cytomegalovirus and HIV infection.**
 Author(s): Riddell SR, Gilbert MJ, Greenberg PD.
 Source: Current Opinion in Immunology. 1993 August; 5(4): 484-91. Review.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8216922&dopt=Abstract
- **Cells infected with human cytomegalovirus release a factor(s) that stimulates cell DNA synthesis.**
 Author(s): Gonczol E, Plotkin SA.
 Source: The Journal of General Virology. 1984 October; 65 (Pt 10): 1833-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6149254&dopt=Abstract
- **Characterization of a human cytomegalovirus glycoprotein complex (gCI).**
 Author(s): Gretsch DR, Gehrz RC, Stinski MF.
 Source: The Journal of General Virology. 1988 June; 69 (Pt 6): 1205-15.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2838571&dopt=Abstract
- **Combination of antiviral immunotoxin and ganciclovir or cidofovir for the treatment of murine cytomegalovirus infections.**
 Author(s): Smee DF, Sidwell RW, Barnett BB.
 Source: Antiviral Research. 1996 November; 32(3): 165-71.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8955511&dopt=Abstract
- **Comparison of EDTA and acid-citrate-dextrose collection tubes for detection of cytomegalovirus antigenemia and infectivity in leukocytes before and after storage.**
 Author(s): Landry ML, Cohen S, Huber K.
 Source: Journal of Clinical Microbiology. 1997 January; 35(1): 305-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8968934&dopt=Abstract
- **Comparison of heparin and EDTA transport tubes for detection of cytomegalovirus in leukocytes by shell vial assay, pp65 antigenemia assay, and PCR.**
 Author(s): Storch GA, Gaudreault-Keener M, Welby PC.
 Source: Journal of Clinical Microbiology. 1994 October; 32(10): 2581-3.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7814504&dopt=Abstract

- **Cytomegalovirus (CMV) DNA amplification from plasma compared with CMV pp65 antigen (ppUL83) detection in leukocytes for early diagnosis of symptomatic CMV infection in kidney transplant patients.**
 Author(s): Wirgart BZ, Claesson K, Eriksson BM, Brundin M, Tufveson G, Totterman T, Grillner L.
 Source: Clinical and Diagnostic Virology. 1996 November; 7(2): 99-110.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9137866&dopt=Abstract
- **Cytomegalovirus activates interferon immediate-early response gene expression and an interferon regulatory factor 3-containing interferon-stimulated response element-binding complex.**
 Author(s): Navarro L, Mowen K, Rodems S, Weaver B, Reich N, Spector D, David M.
 Source: Molecular and Cellular Biology. 1998 July; 18(7): 3796-802.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9632763&dopt=Abstract
- **Cytomegalovirus colitis after administration of docetaxel-5-fluorouracil-cisplatin chemotherapy for locally advanced hypopharyngeal cancer.**
 Author(s): Van den Brande J, Schrijvers D, Colpaert C, Vermorken JB.
 Source: Annals of Oncology : Official Journal of the European Society for Medical Oncology / Esmo. 1999 November; 10(11): 1369-72.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10631467&dopt=Abstract
- **Cytomegalovirus colitis--a severe complication after standard chemotherapy.**
 Author(s): Matthes T, Kaiser L, Weber D, Kurt AM, Dietrich PY.
 Source: Acta Oncologica (Stockholm, Sweden). 2002; 41(7-8): 704-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14651217&dopt=Abstract
- **Cytomegalovirus glycoprotein B sequence variation in Chinese liver transplant recipients.**
 Author(s): Zheng SS, Zhou L, Qian J, Cai T, Fan J, Ma WH.
 Source: Hepatobiliary Pancreat Dis Int. 2002 February; 1(1): 26-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14607617&dopt=Abstract
- **Cytomegalovirus infection in children with blood diseases.**
 Author(s): Rokicka-Milewska R, Pacholska J, Lukowska K, Paciorkiewicz W, Jastrzebska M.
 Source: Acta Haematol Pol. 1992; 23(3): 191-5.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1283481&dopt=Abstract
- **Cytomegalovirus infection in infants: an example of a chronopharmacological approach.**
 Author(s): Stefanov R, Dimitrov BD.

Source: Folia Med (Plovdiv). 1999; 41(1): 20-4.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10462914&dopt=Abstract

- **Demonstration of the anti-viral activity of garlic extract against human cytomegalovirus in vitro.**
 Author(s): Guo NL, Lu DP, Woods GL, Reed E, Zhou GZ, Zhang LB, Waldman RH.
 Source: Chinese Medical Journal. 1993 February; 106(2): 93-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8389276&dopt=Abstract
- **Detection of cytomegalovirus antibody with latex agglutination.**
 Author(s): Adler SP, McVoy M, Biro VG, Britt WJ, Hider P, Marshall D.
 Source: Journal of Clinical Microbiology. 1985 July; 22(1): 68-70.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2991330&dopt=Abstract
- **Detection of cytomegalovirus from blood leukocytes separated by sepracell-MN and Ficoll-Paque/Macrodex methods.**
 Author(s): Paya CV, Wold AD, Smith TF.
 Source: Journal of Clinical Microbiology. 1988 October; 26(10): 2031-3.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2846635&dopt=Abstract
- **Determination of cytomegalovirus DNA load for monitoring of cytomegalovirus disease and antiviral treatment in solid organ transplant patients, comparing limiting-dilution PCR and hybrid capture assay with cytomegalovirus isolation.**
 Author(s): Barkholt L, Lore K, Tyden G, Lewensohn-Fuchs I, Andersson J, Ericzon BG, Lundgren G, Ehrnst A.
 Source: Clinical Microbiology and Infection : the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases. 1999 February; 5(2): 78-87.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11856222&dopt=Abstract
- **Development and evaluation of an internally controlled semiautomated PCR assay for quantification of cell-free cytomegalovirus.**
 Author(s): Tedder RS, Ayliffe U, Preiser W, Brink NS, Grant PR, Peggs KS, Mackinnon S, Kreig-Schneider F, Kirk S, Garson JA.
 Source: Journal of Medical Virology. 2002 April; 66(4): 518-23.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11857531&dopt=Abstract
- **Direct interaction between human cytomegalovirus glycoprotein B and cellular annexin II.**
 Author(s): Pietropaolo RL, Compton T.
 Source: Journal of Virology. 1997 December; 71(12): 9803-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9371650&dopt=Abstract

- **Etoposide as a virocidal anticytomegalovirus therapy: intravitreal toxicology and pharmacology in rabbits.**
 Author(s): Morlet N, Stayt J, Vaegan, Salonikas C, Naidoo D, Crouch R, Graham G, Coroneo M.
 Source: Australian and New Zealand Journal of Ophthalmology. 1999 October; 27(5): 342-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10571395&dopt=Abstract
- **Evaluation of the antiviral activity of kaempferol and its glycosides against human cytomegalovirus.**
 Author(s): Mitrocotsa D, Mitaku S, Axarlis S, Harvala C, Malamas M.
 Source: Planta Medica. 2000 May; 66(4): 377-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10865462&dopt=Abstract
- **Ex vivo stimulation of cytomegalovirus (CMV)-specific T cells using CMV pp65-modified dendritic cells as stimulators.**
 Author(s): Carlsson B, Cheng WS, Totterman TH, Essand M.
 Source: British Journal of Haematology. 2003 May; 121(3): 428-38.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12716365&dopt=Abstract
- **Experimental and clinical study on the antiviral activity of jinyebaidu granule against human cytomegalovirus.**
 Author(s): Wen LZ, Xing W.
 Source: International Journal of Gynaecology and Obstetrics: the Official Organ of the International Federation of Gynaecology and Obstetrics. 2002 May; 77(2): 149-50.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12031566&dopt=Abstract
- **Experimental study on the prevention and treatment of murine cytomegalovirus hepatitis by using allitridin.**
 Author(s): Liu ZF, Fang F, Dong YS, Li G, Zhen H.
 Source: Antiviral Research. 2004 February; 61(2): 125-8.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14670586&dopt=Abstract
- **Ganciclovir prophylaxis for cochlear pathophysiology during experimental guinea pig cytomegalovirus labyrinthitis.**
 Author(s): Woolf NK, Ochi JW, Silva EJ, Sharp PA, Harris JP, Richman DD.
 Source: Antimicrobial Agents and Chemotherapy. 1988 June; 32(6): 865-72.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2843084&dopt=Abstract
- **High-dose (2000-microgram) intravitreal ganciclovir in the treatment of cytomegalovirus retinitis.**
 Author(s): Young S, Morlet N, Besen G, Wiley CA, Jones P, Gold J, Li Y, Freeman WR, Coroneo MT.

Source: Ophthalmology. 1998 August; 105(8): 1404-10.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9709750&dopt=Abstract

- **High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis.**
 Author(s): Velez G, Roy CE, Whitcup SM, Chan CC, Robinson MR.
 Source: American Journal of Ophthalmology. 2001 March; 131(3): 396-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11239885&dopt=Abstract
- **Host cellular annexin II is associated with cytomegalovirus particles isolated from cultured human fibroblasts.**
 Author(s): Wright JF, Kurosky A, Pryzdial EL, Wasi S.
 Source: Journal of Virology. 1995 August; 69(8): 4784-91.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7609045&dopt=Abstract
- **Human cytomegalovirus DNA in plasma and serum specimens of renal transplant recipients is highly fragmented.**
 Author(s): Boom R, Sol CJ, Schuurman T, Van Breda A, Weel JF, Beld M, Ten Berge IJ, Wertheim-Van Dillen PM, De Jong MD.
 Source: Journal of Clinical Microbiology. 2002 November; 40(11): 4105-13.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12409382&dopt=Abstract
- **Human cytomegalovirus nuclear and cytoplasmic dense bodies.**
 Author(s): Severi B, Landini MP, Cenacchi G, Zini N, Maraldi NM.
 Source: Archives of Virology. 1992; 123(1-2): 193-207.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1372496&dopt=Abstract
- **In situ hybridization at the ultrastructural level: localization of cytomegalovirus DNA using digoxigenin labelled probes.**
 Author(s): Cenacchi G, Musiani M, Gentilomi G, Righi S, Zerbini M, Chandler JG, Scala C, La Placa M, Martinelli GN.
 Source: J Submicrosc Cytol Pathol. 1993 July; 25(3): 341-5.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8402533&dopt=Abstract
- **Inhibitory effects of various anticoagulants on the infectivity of human cytomegalovirus.**
 Author(s): Kimpton CP, Morris DJ, Corbitt G.
 Source: Journal of Virological Methods. 1989 June; 24(3): 301-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2547823&dopt=Abstract
- **Irreversible inhibition of human cytomegalovirus replication by topoisomerase II inhibitor, etoposide: a new strategy for the treatment of human cytomegalovirus infection.**
 Author(s): Huang ES, Benson JD, Huong SM, Wilson B, van der Horst C.

Source: Antiviral Research. 1992 January; 17(1): 17-32.

http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1310581&dopt=Abstract

- **Modulation of the frequency of human cytomegalovirus-induced chromosome aberrations by camptothecin.**
 Author(s): Deng CZ, AbuBakar S, Fons MP, Boldogh I, Albrecht T.
 Source: Virology. 1992 July; 189(1): 397-401.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1318615&dopt=Abstract
- **Multiple transforming regions of human cytomegalovirus DNA.**
 Author(s): el-Beik T, Razzaque A, Jariwalla R, Cihlar RL, Rosenthal LJ.
 Source: Journal of Virology. 1986 November; 60(2): 645-52.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3021997&dopt=Abstract
- **Neonatal cytomegalovirus exposure decreases prepulse inhibition in adult rats: implications for schizophrenia.**
 Author(s): Rothschild DM, O'Grady M, Wecker L.
 Source: Journal of Neuroscience Research. 1999 August 15; 57(4): 429-34.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10440892&dopt=Abstract
- **Nuclear bodies (sphaeridia) in Sertoli cells of a man with acquired immunodeficiency syndrome (AIDS) and testicular infection by cytomegalovirus.**
 Author(s): Nistal M, Regadera J, Paniagua R, Rodriguez MC.
 Source: Ultrastructural Pathology. 1990 January-February; 14(1): 21-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2153322&dopt=Abstract
- **Persistent human cytomegalovirus infection induces drug resistance and alteration of programmed cell death in human neuroblastoma cells.**
 Author(s): Cinatl J Jr, Cinatl J, Vogel JU, Kotchetkov R, Driever PH, Kabickova H, Kornhuber B, Schwabe D, Doerr HW.
 Source: Cancer Research. 1998 January 15; 58(2): 367-72.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9443419&dopt=Abstract
- **Processing of human cytomegalovirus glycoprotein B in recombinant adenovirus-infected cells.**
 Author(s): Marshall GS, Fenger DP, Stout GG, Knights ME, Hunt LA.
 Source: The Journal of General Virology. 1996 July; 77 (Pt 7): 1549-57.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8757998&dopt=Abstract
- **Prophylactic treatment of cytomegalovirus infection with traditional herbs.**
 Author(s): Yukawa TA, Kurokawa M, Sato H, Yoshida Y, Kageyama S, Hasegawa T, Namba T, Imakita M, Hozumi T, Shiraki K.

Source: Antiviral Research. 1996 October; 32(2): 63-70.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8891165&dopt=Abstract

- **Protective effect of black seed oil from *Nigella sativa* against murine cytomegalovirus infection.**
 Author(s): Salem ML, Hossain MS.
 Source: International Journal of Immunopharmacology. 2000 September; 22(9): 729-40.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10884593&dopt=Abstract
- **Protective effects of hochu-ekki-to, a Chinese traditional herbal medicine against murine cytomegalovirus infection.**
 Author(s): Hossain MS, Takimoto H, Hamano S, Yoshida H, Ninomiya T, Minamishima Y, Kimura G, Nomoto K.
 Source: Immunopharmacology. 1999 April; 41(3): 169-81.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10428645&dopt=Abstract
- **Pulmonary macrophage function during experimental cytomegalovirus interstitial pneumonia.**
 Author(s): Miller SA, Bia FJ, Coleman DL, Lucia HL, Young KR Jr, Root RK.
 Source: Infection and Immunity. 1985 January; 47(1): 211-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2981196&dopt=Abstract
- **Purification of Ag-specific T lymphocytes after direct peripheral blood mononuclear cell stimulation followed by CD25 selection. I. Application to CD4(+) or CD8(+) cytomegalovirus phosphoprotein pp65 epitope determination.**
 Author(s): Gallot G, Vivien R, Ibisch C, Lule J, Davrinche C, Gaschet J, Vie H.
 Source: Journal of Immunology (Baltimore, Md. : 1950). 2001 October 15; 167(8): 4196-206.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11591740&dopt=Abstract
- **Rapid detection by reverse hybridization of mutations in the UL97 gene of human cytomegalovirus conferring resistance to ganciclovir.**
 Author(s): Zhou L, Harder TC, Ullmann U, Rautenberg P.
 Source: Journal of Clinical Virology : the Official Publication of the Pan American Society for Clinical Virology. 1999 June; 13(1-2): 53-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10405892&dopt=Abstract
- **Rapid, large-scale generation of highly pure cytomegalovirus-specific cytotoxic T cells for adoptive immunotherapy.**
 Author(s): Foster AE, Gottlieb DJ, Marangolo M, Bartlett A, Li YC, Barton GW, Romagnoli JA, Bradstock KF.

Source: Journal of Hematotherapy & Stem Cell Research. 2003 February; 12(1): 93-105.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12662440&dopt=Abstract

- **Selective cytotoxicity towards cytomegalovirus-infected cells by immunotoxins consisting of gelonin linked to anti-cytomegalovirus antibody.**
 Author(s): Barnett BB, Smee DF, Malek SM, Sidwell RW.
 Source: Antiviral Research. 1995 September; 28(1): 93-100.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8585763&dopt=Abstract
- **Seroepidemiology of cytomegalovirus infection among children between the ages of 4 and 12 years in Taiwan.**
 Author(s): Shen CY, Chang WW, Chang SF, Chao MF, Huang ES, Wu CW.
 Source: Journal of Medical Virology. 1992 May; 37(1): 72-5.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1320100&dopt=Abstract
- **Taxol inhibits stimulation of cell DNA synthesis by human cytomegalovirus.**
 Author(s): Ball RL, Carney DH, Albrecht T.
 Source: Experimental Cell Research. 1990 November; 191(1): 37-44.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1977604&dopt=Abstract
- **The mannose-specific plant lectins from Cymbidium hybrid and Epipactis helleborine and the (N-acetylglucosamine)n-specific plant lectin from Urtica dioica are potent and selective inhibitors of human immunodeficiency virus and cytomegalovirus replication in vitro.**
 Author(s): Balzarini J, Neyts J, Schols D, Hosoya M, Van Damme E, Peumans W, De Clercq E.
 Source: Antiviral Research. 1992 June; 18(2): 191-207.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1329650&dopt=Abstract
- **The RGD sequence in the cytomegalovirus DNA polymerase accessory protein can mediate cell adhesion.**
 Author(s): Loh LC, Locke D, Melnychuk R, Lafert.
 Source: Virology. 2000 July 5; 272(2): 302-14.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10873773&dopt=Abstract
- **Time course analysis of semi-quantitative PCR and antigenaemia assay for prevention of cytomegalovirus disease after bone marrow transplantation.**
 Author(s): Kanda Y, Chiba S, Suzuki T, Kami M, Yazaki Y, Hirai H.
 Source: British Journal of Haematology. 1998 January; 100(1): 222-5.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9450815&dopt=Abstract

- **Treatment of hepatitis caused by cytomegalovirus with allitridin injection--an experimental study.**

Author(s): Fang F, Li H, Cui W, Dong Y.

Source: J Tongji Med Univ. 1999; 19(4): 271-4.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12938515&dopt=Abstract

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 cytomegalovirus; 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**

- **Immune Function**

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

- **Pancreatitis**

- Source: Integrative Medicine Communications; www.drkoop.com

- **Uveitis**

- Source: Integrative Medicine Communications; www.drkoop.com

- **Herbs and Supplements**

Aloe

Alternative names: Aloe vera, Aloe barbadensis, Aloe ferox , Aloe Vera

Source: Integrative Medicine Communications; www.drkoop.com

Aloe Vera

Source: Integrative Medicine Communications; www.drkoop.com

Glycyrrhiza

Alternative names: Licorice; Glycyrrhiza glabra L.

Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Nettle

Source: Integrative Medicine Communications; www.drkoop.com

Syzygium Clove

Alternative names: Clove, Jamun; Syzygium sp.

Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Terminalia

Alternative names: Myrobalans; Terminalia arjuna

Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Urtica Dioica

Source: Integrative Medicine Communications; www.drkoop.com

Urtica Urens

Source: Integrative Medicine Communications; www.drkoop.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 CYTOMEGALOVIRUS

Overview

In this chapter, we will give you a bibliography on recent dissertations relating to cytomegalovirus. 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 “cytomegalovirus” (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on cytomegalovirus, we have not necessarily excluded non-medical dissertations in this bibliography.

Dissertations on Cytomegalovirus

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 cytomegalovirus. 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:

- **A Nested Case-Control Study of the Association between Chlamydia Pneumoniae and Cytomegalovirus and Coronary Heart Disease** by Arcari, Christine Marie, PhD from The Johns Hopkins University, 2003, 185 pages
<http://wwwlib.umi.com/dissertations/fullcit/3068112>
- **Cellular Immune Responses to Allografts and Cytomegalovirus** by Engstrand, Mats, PhD from Uppsala Universitet (Sweden), 2003, 50 pages
<http://wwwlib.umi.com/dissertations/fullcit/f279921>
- **Characterization of Immediate-Early and Early Proteins of Murine Cytomegalovirus Synthesized in Permissive and Nonpermissive Cells** by Walker, Douglas Gordon; PhD from The University of British Columbia (Canada), 1985
<http://wwwlib.umi.com/dissertations/fullcit/NK24193>
- **Detection of RNA in Highly Purified Human Cytomegalovirus Virions** by Sarcinella, Elizabeth, MSC from University of Toronto (Canada), 2003, 90 pages
<http://wwwlib.umi.com/dissertations/fullcit/MQ78209>

- **Human Cytomegalovirus Assembly Functions: UI38 and UI99** by da Silva, Maria Cristina Carlan, PhD from Princeton University, 2003, 157 pages
<http://wwwlib.umi.com/dissertations/fullcit/3103048>
- **Immune Modulation by Guinea Pig Cytomegalovirus** by Lacayo, Juan Carlos, PhD from Virginia Commonwealth University, 2003, 156 pages
<http://wwwlib.umi.com/dissertations/fullcit/3101579>
- **Multiple Interactions between Murine Cytomegalovirus and Mouse Lymphoid Cells in Vitro** by Loh, Lambert C; PhD from The University of British Columbia (Canada), 1979
<http://wwwlib.umi.com/dissertations/fullcit/NK42685>
- **Peromyscus Maniculatus Cytomegalovirus As an Expression Vector in Deer Mice** by Rizvanov, Albert A., PhD from University of Nevada, Reno, 2003, 66 pages
<http://wwwlib.umi.com/dissertations/fullcit/3090886>
- **Porcine Cytomegalovirus: Diagnosis, Pathogenesis and Control** by Guedes, Maria Isabel Maldonado Coelho, PhD from University of Minnesota, 2003, 227 pages
<http://wwwlib.umi.com/dissertations/fullcit/3095462>
- **Structure of the Murine Cytomegalovirus Genome and Its Expression in Productive and Non-productive Infections** by Misra, Vikram; PhD from The University of British Columbia (Canada), 1977
<http://wwwlib.umi.com/dissertations/fullcit/NK34897>
- **Suppression of Antiviral Gene Expression by Human Cytomegalovirus** by Browne, Edward Patrick, PhD from Princeton University, 2003, 112 pages
<http://wwwlib.umi.com/dissertations/fullcit/3103022>
- **Symptomatic Congenital Cytomegalovirus Infection and Hearing Impairment** by Mccollister, Faye Perry, EDD from The University of Alabama, 1987, 113 pages
<http://wwwlib.umi.com/dissertations/fullcit/8720700>

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. CLINICAL TRIALS AND CYTOMEGALOVIRUS

Overview

In this chapter, we will show you how to keep informed of the latest clinical trials concerning cytomegalovirus.

Recent Trials on Cytomegalovirus

The following is a list of recent trials dedicated to cytomegalovirus.⁸ Further information on a trial is available at the Web site indicated.

- **Valganciclovir Prevention of Cytomegalovirus (CMV) Organ Damage**

Condition(s): Cytomegalovirus Infections; HIV Infections

Study Status: This study is currently recruiting patients.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: The purpose of this study is to find out whether treatment with valganciclovir is safe and effective in preventing CMV organ damage. Some patients with weakened immune systems have a high risk of developing CMV disease, an opportunistic (AIDS-related) infection. Doctors want to see if giving valganciclovir will help prevent the disease in patients who are at high risk for it, and if it is an effective treatment for CMV disease, especially CMV retinitis (eye disease). This study has been changed to include new information: Valganciclovir has been approved by the FDA for the treatment of CMV retinitis.

Phase(s): Phase III

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00006145>

⁸ These are listed at www.ClinicalTrials.gov.

- **A Pharmacokinetic and Tolerance Study of Oral Ganciclovir in HIV-Infected Children With Asymptomatic Cytomegalovirus Infection and Low CD4 Cell Counts or Quiescent Cytomegalovirus Disease**

Condition(s): Cytomegalovirus Infections; HIV Infections

Study Status: This study is no longer recruiting patients.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: PRIMARY: To determine the pharmacokinetics, MTD, and long-term safety and tolerance of oral ganciclovir in HIV-infected infants, children, and adolescents. SECONDARY: To evaluate the effect of oral ganciclovir on the virologic parameters of CMV. Maintenance treatment with intravenous (IV) ganciclovir for cytomegalovirus retinitis in AIDS patients is now standard therapy, but daily IV therapy can be complicated by catheter infections and thrombosis. An oral regimen of ganciclovir has been administered safely in adult AIDS patients and may be of significant benefit to children and infants as well.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000805>

- **A Phase III Study to Evaluate the Safety and Efficacy of Ganciclovir (Dihydroxypropoxymethyl Guanine [DHPG]) Treatment of Symptomatic Central Nervous System (CNS) Congenital Cytomegalovirus (CMV) Infections.**

Condition(s): Cytomegalovirus Infections

Study Status: This study is no longer recruiting patients.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: The purpose of this study is to evaluate the benefits and safety of the antiviral drug ganciclovir (DHPG) given intravenously to treat newborn infants who are born infected with cytomegalovirus (CMV). CMV is a herpes virus that can infect most organs of the body, resulting in death in 10-30% of babies with symptoms of CMV. It can cause severe brain damage in a large percentage of surviving babies. Children in this study have a CMV infection of the central nervous system (CNS).

Phase(s): Phase III

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00001100>

- **A Study of Cidofovir in the Treatment of Cytomegalovirus (CMV) of the Eyes in Patients with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is no longer recruiting patients.

Sponsor(s): Gilead Sciences; Anderson Clinical Research

Purpose - Excerpt: Incomplete Closed Protocol

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002384>

- **A Study of Foscarnet in the Treatment of Cytomegalovirus (CMV) of the Eyes in Patients with AIDS Who Have Not Had Success with Ganciclovir**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is no longer recruiting patients.

Sponsor(s): Astra USA

Purpose - Excerpt: To evaluate the safety and efficacy of foscarnet induction treatment of cytomegalovirus (CMV) retinitis in AIDS patients who have previously suffered severe dose-limiting ganciclovir-related myelosuppression, who are ineligible for ganciclovir treatment due to myelosuppression or who have clearly failed to have a therapeutic response to ganciclovir therapy. To assess the duration of clinical response. To evaluate the effect on quantitative CMV cultures of blood and urine. To determine the effect on recovery of HIV p24 antigen capture direct from plasma.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002301>

- **Kinetics of response of cytomegalovirus with ganciclovir treatment using quantitative real-time PCR**

Condition(s): Cytomegalovirus Infections

Study Status: This study is no longer recruiting patients.

Sponsor(s): National Center for Research Resources (NCRR)

Purpose - Excerpt: The overall purpose of this research is to develop and use a blood test to better understand how quickly the viral drug ganciclovir works to clear infection with the CMV virus (Cytomegalovirus) when it occurs. This test will potentially let doctors know early in the course of therapy when a virus is not responding well to the therapy and could therefore be resistant to the drug. The target population of this study will be primarily kidney and lung transplant patients with CMV detected in the blood, although other patients may also be included if they meet criteria. The study will be divided into two phases. Phase I will evaluate a small number of exploratory patients initiating ganciclovir therapy and will require frequent blood sampling to obtain detailed information regarding the kinetic response of the virus to therapy. This information will be analyzed to help guide decisions regarding the number and frequency of blood samples needed in the larger phase II portion of the study. Strains will be characterized using phenotypic and genotypic methods to determine the presence or absence of mutations potentially responsible for the resistance.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00004573>

- **The Safety and Effectiveness of Ganciclovir in the Prevention of Cytomegalovirus (CMV) of the Eyes and Disease of the Stomach and Intestines in Patients with HIV**

Condition(s): Cytomegalovirus Retinitis; HIV Infections; Gastrointestinal Diseases

Study Status: This study is no longer recruiting patients.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID); Hoffmann-La Roche

Purpose - Excerpt: To evaluate the safety and efficacy of oral ganciclovir for prophylaxis against cytomegalovirus (CMV) retinal and gastrointestinal mucosal disease in HIV-infected patients with severe immunosuppression. The most recent treatments against CMV disease have been ganciclovir and foscarnet. Until recently, both drugs required intravenous administration. An oral form of ganciclovir, if shown to be effective therapy against CMV, would be a more suitable method of administration for prophylaxis.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00001034>

- **A Comparison of ISIS 2922 Used Immediately or Later in Patients with Cytomegalovirus (CMV) of the Eyes**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Isis Pharmaceuticals

Purpose - Excerpt: To determine a clinically safe and effective dose of intravitreally injected ISIS 2922 and to compare the safety and efficacy of immediate versus delayed treatment in AIDS patients with previously untreated, peripheral cytomegalovirus (CMV) retinitis.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002355>

- **A Comparison of Valganciclovir and Ganciclovir in the Treatment of Cytomegalovirus (CMV) of the Eyes**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Roche Global Development

Purpose - Excerpt: To investigate the efficacy and safety of RS-79070 when used as induction therapy in patients with newly diagnosed peripheral retinitis. To assess the effects of induction and maintenance level dosing of RS-79070 on CMV viral load, estimated by plasma CMV PCR. To assess the pharmacokinetics of ganciclovir following administration of RS-79070 in the target population.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002377>

- **A Phase I/II Trial to Assess the Safety and Tolerance of Escalating Doses of a Human Anti-Cytomegalovirus Monoclonal Antibody (SDZ MSL-109) in Patients With the Acquired Immunodeficiency Syndrome and CMV Retinitis**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Sandoz Pharmaceuticals

Purpose - Excerpt: To determine the safety and tolerance of 3 dosage levels of human anti-cytomegalovirus (CMV) monoclonal antibody (SDZ MSL-109) when administered once every 2 weeks for a total of 8 doses during the maintenance phase of ganciclovir (DHPG) therapy to patients with AIDS and documented evidence of CMV retinitis. In addition for those patients with positive CMV cultures upon entry into this trial a preliminary attempt will be made to assess the potential in vivo antiviral effects of the concomitant administration of DHPG and SDZ MSL-109.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002016>

- **A Randomized Comparison of Intravitreal ISIS 2922 Plus Ganciclovir Versus Ganciclovir as Treatment for Patients With Cytomegalovirus Retinitis (CMVR)**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Isis Pharmaceuticals

Purpose - Excerpt: To determine the clinically safe and effective dose of intravitreal ISIS 2922 alone and as an additive antiviral therapy to ganciclovir in AIDS patients with cytomegalovirus (CMV) retinitis.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002156>

- **A Randomized Controlled Study of the Efficacy and Safety of Maintenance Treatment with Oral Ganciclovir for Newly Diagnosed Cytomegalovirus Retinitis in People with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Hoffmann-La Roche

Purpose - Excerpt: To compare the time to progression of CMV retinitis between oral ganciclovir and IV ganciclovir during 20 weeks of maintenance treatment. To compare the safety and tolerance of oral ganciclovir with IV ganciclovir therapy during 20 weeks of maintenance treatment. To describe the safety and tolerance of oral ganciclovir treatment when given concurrently with anti-retroviral treatment, e.g. zidovudine or ddI. To describe the survival of people with AIDS and CMV retinitis.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002257>

- **A Randomized Study Comparing the Safety and Efficacy of Two Regimens of Oral Ganciclovir to Intravenous Ganciclovir Maintenance Therapy for Cytomegalovirus Retinitis in People with AIDS Who Have Received Prior Ganciclovir Therapy**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Hoffmann-La Roche

Purpose - Excerpt: To compare the safety and tolerance of oral ganciclovir at a double dose 3 times/day or a single dose 6 times/day to IV ganciclovir given for 20 weeks of maintenance therapy. To compare the time to progression of cytomegalovirus (CMV) retinitis between two regimens of oral ganciclovir and IV ganciclovir therapy given for 20 weeks of maintenance therapy. To describe the efficacy and safety of double dose versus single dose oral ganciclovir in patients who have a progression of retinitis while on the originally assigned maintenance treatment. To describe the safety, tolerance, and time to progression of retinitis during the 52 weeks of oral ganciclovir maintenance therapy in people with AIDS. To describe the safety and tolerance of oral ganciclovir maintenance therapy when given concurrently with antiretroviral treatment (e.g., zidovudine, ddI, or ddC). To describe survival of people with AIDS and CMV retinitis.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002247>

- **A Randomized, Controlled Study of Intravenous Ganciclovir Therapy for Peripheral Cytomegalovirus Retinitis in Patients With AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID); Hoffmann-La Roche

Purpose - Excerpt: To provide information about the usefulness and safety of giving injections of ganciclovir (DHPG) for treating peripheral cytomegalovirus (CMV) retinitis. CMV retinitis is an important sight-threatening opportunistic infection which affects 1 to 2 out of every 10 patients with AIDS. Results from an earlier study suggest that about 80 percent of patients with CMV retinitis will be helped by receiving intravenous doses of DHPG.

Phase(s): Phase III

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000688>

- **A Randomized, Controlled Study of the Safety and Preventive Efficacy of Oral Ganciclovir When Used in Conjunction With An Intravitreal Ganciclovir Implant in the Treatment of Cytomegalovirus Retinitis**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Roche Global Development

Purpose - Excerpt: To demonstrate the efficacy of oral ganciclovir in preventing new cytomegalovirus (CMV) disease in AIDS patients with unilateral CMV retinitis treated with an intravitreal ganciclovir implant. To compare safety and tolerance, time to progression, quality of life, and survival among patients treated with an intravitreal ganciclovir implant, with and without oral ganciclovir, versus standard intravenous (IV) ganciclovir therapy.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002134>

- **A Randomized, Phase I/II Trial to Assess the Safety and Antiviral Effects of Escalating Doses of A Human Anti-Cytomegalovirus Monoclonal Antibody (SDZ MSL-109) in Patients With the Acquired Immunodeficiency Syndrome and CMV Viremia and/or Viruria**

Condition(s): Cytomegalovirus Infections; HIV Infections

Study Status: This study is completed.

Sponsor(s): Sandoz Pharmaceuticals

Purpose - Excerpt: To determine the safety, tolerance, and potential in vivo antiviral effects of five dosage levels and a dose to be determined of human anti-cytomegalovirus (CMV) monoclonal antibody (SDZ MSL-109; formerly SDZ 89-109) when administered once every 2 weeks for a total of 12 doses to patients with either AIDS or eligible AIDS-related complex (ARC) and with culture proven evidence of CMV viremia and/or viruria. Sandoglobulin will be employed as a comparative control.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002268>

- **A Study of AZT Plus Ganciclovir in Patients with AIDS and Cytomegalovirus (CMV) Infection**

Condition(s): Cytomegalovirus Infections; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: To evaluate the clinical and laboratory toxicity of ganciclovir (GCV) and zidovudine (AZT) when given in combination. Because recent information has shown AZT to be useful in treating AIDS, it is assumed that most patients with AIDS, and probably with AIDS related complex (ARC), will be receiving AZT. Because AZT is reported not to be active against cytomegalovirus (CMV), it is important to see if it is useful to give GCV along with AZT.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000995>

- **A Study of Cidofovir in HIV-Infected Children with Cytomegalovirus (CMV) Disease**

Condition(s): Cytomegalovirus Infections; Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is terminated.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: Part A: To determine the safety and pharmacokinetics of sequential single doses of cidofovir in HIV-infected children with end-organ cytomegalovirus (CMV) disease. Part B: To determine the safety (including time to progression of CMV retinitis by retinal exam), pharmacokinetics, and long-term (6 months) tolerance of multiple-dose cidofovir in HIV-infected children with CMV retinitis. Part B: To determine the effect of multiple-dose cidofovir on the virologic parameters of CMV retinitis (viral load, shedding, and resistance to antiviral agents). [AS PER AMENDMENT 1/7/98: To determine the safety, tolerance and pharmacokinetics of sequential single doses of cidofovir in HIV-infected children with CMV retinitis. To determine the safety (including time to progression of CMV retinitis by retinal exam), pharmacokinetics, and long-term (6-month) tolerance of multiple doses of cidofovir in HIV-infected children with CMV retinitis.] While the intravenous formulation of cidofovir has been approved for the treatment of CMV retinitis in HIV-infected individuals, information is limited regarding its safety and tolerance in HIV-infected children. Intravenous cidofovir requires less frequent administration for both induction and maintenance therapy of CMV retinitis than other currently available therapies. If found to be safe and well tolerated in HIV-infected children with CMV retinitis, intravenous cidofovir would add significantly to agents available to treat this debilitating opportunistic infection.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000881>

- **A Study of Foscarnet in the Treatment of Cytomegalovirus (CMV) of the Eyes in Patients with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Astra USA

Purpose - Excerpt: To evaluate the safety and efficacy of foscarnet induction therapy for treatment of AIDS patients experiencing their first episode of cytomegalovirus (CMV) retinitis. To evaluate the safety and efficacy of foscarnet maintenance therapy for treatment of AIDS patients experiencing CMV retinitis.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002432>

- **A Study of Foscarnet in the Treatment of Cytomegalovirus (CMV) of the Eyes in Patients with AIDS Who Cannot Use Ganciclovir**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is terminated.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: To study the safety and effectiveness of foscarnet in the treatment of AIDS patients who have active infection with cytomegalovirus (CMV) that is causing inflammation of the retina (retinitis). In addition, these patients cannot be treated with ganciclovir (DHPG) because of its toxic effect on the body's blood-forming cells or because white blood cell or platelet counts were too low. CMV is a common virus, which can cause blindness and death in AIDS patients. Previous studies demonstrate that foscarnet has been effective in both AIDS and non-AIDS patients with CMV infection. Although treatment with ganciclovir (DHPG) is also effective, a significant toxicity leading to dose-limiting neutropenia (low white blood cell count) in one third of treated patients has been associated with the drug. Based on the serious nature of CMV retinitis and the lack of alternative drug therapies for DHPG-sensitive patients, the present study will evaluate the safety and efficacy of intravenous (IV) foscarnet in AIDS patients with CMV retinitis.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000697>

- **A Study of Foscarnet Plus Ganciclovir in the Treatment of Cytomegalovirus of the Eye in Patients with AIDS Who Have Already Been Treated with Ganciclovir**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID); Astra USA; Hoffmann-La Roche

Purpose - Excerpt: To examine the safety and tolerance of the administration of ganciclovir and foscarnet given together or alternately; to determine the interactive pharmacokinetics (blood level) profile of long-term combined and alternating therapy with these two drugs. Additional objectives are to examine the effect of these treatments in controlling time to cytomegalovirus (CMV) retinitis progression and to examine the antiviral activity of combined and alternating ganciclovir/foscarnet treatment and development of antiviral resistance. Sight-threatening CMV retinitis occurs in at least 6 percent of AIDS patients. By 1991 (US), there may be 6000 to 10000 patients with CMV retinitis. Many clinical reports suggest that both ganciclovir (DHPG) and foscarnet have an antiviral effect against CMV that is often associated with clinical stabilization. Effectiveness of ganciclovir and foscarnet is correlated with weekly maintenance and since toxicity is dose-limiting in up to 20 percent of patients receiving either drug for long periods, it may be beneficial in long-term maintenance treatment to combine or alternate these two drugs at a lower total weekly dose of each drug. This strategy may result in a greater net antiviral effect with less toxicity than is seen with either drug alone, because the toxicities of each drug are quite different.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000970>

- **A Study of Ganciclovir in the Treatment of Cytomegalovirus of the Eyes**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: To determine whether alternating oral ganciclovir with intravenous (IV) ganciclovir can prevent relapse of Cytomegalovirus (CMV) retinitis and improve quality of life in AIDS patients. A systemic treatment strategy for CMV retinitis is needed that will be effective yet convenient to administer, without the need for a permanent indwelling IV catheter. Although oral ganciclovir has been used as maintenance following induction with IV ganciclovir, patients with reactivation of disease must be reinduced IV. A fixed-schedule regimen in which oral and IV ganciclovir are alternated may prevent reactivation and progression of disease, as opposed to the current therapeutic strategy in which changes in therapy are event-driven. Also, the duration of intermittent IV therapy required to control disease may be short enough to eliminate the need for an indwelling catheter.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00001062>

- **A Study of HIV and Cytomegalovirus (CMV) in HIV-Infected Patients**

Condition(s): Cytomegalovirus Infections; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: To define relationships between 1) HIV load and risk of CMV disease, 2) CMV load and the risk of developing CMV disease, and 3) CMV load and HIV load. To establish threshold CMV and HIV load values in peripheral blood fractions that are associated with development of CMV end-organ disease. To define the natural history of CMV diseases in the context of highly active antiretroviral therapy (HAART). Establishment of threshold CMV and HIV load values associated with CMV disease would facilitate identification of HIV-infected individuals truly at risk for CMV disease in whom targeted prophylactic interventions to prevent CMV disease would be indicated. These studies would also further the understanding of the natural history of CMV disease within the context of AIDS. Natural history studies conducted prior to the advent of highly active antiretroviral therapy (HAART; i.e., 3-drug regimens that include HIV reverse transcriptase and protease inhibitors) have demonstrated that the risk for developing CMV disease increases with progression of HIV disease and with declining CD4 counts. Presently the need exists to define the natural history of CMV disease in patients with AIDS within the context of HAART.

Study Type: Observational

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00001089>

- **A Study of ISIS 2922 in the Treatment of Advanced Cytomegalovirus Retinitis**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Isis Pharmaceuticals

Purpose - Excerpt: The purpose of this study is to compare the safety and effectiveness of two dosage schedules for ISIS 2922 in the treatment of advanced cytomegalovirus (CMV) retinitis

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002187>

- **A Study of the Safety and Tolerance of Long-Term Therapy with Intravenous Cytovene (Ganciclovir Sodium) for Cytomegalovirus Retinitis in Persons with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Hoffmann-La Roche

Purpose - Excerpt: To evaluate the safety and tolerance of long-term ganciclovir (DHPG) therapy for newly diagnosed macular threatening Cytomegalovirus (CMV) retinitis in AIDS patients. To evaluate the clinical response to a 52 week course of intravenous DHPG therapy. To evaluate the safety and tolerance of long-term DHPG with concurrent treatment with zidovudine (AZT). (Patients utilizing treatment with other anti-retroviral drugs will be considered for study entry on a case by case basis.) To determine survival in this group of patients with AIDS and CMV retinitis.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002034>

- **A Study of Two Forms of Ganciclovir in the Treatment of Cytomegalovirus (CMV) of the Eyes in Patients with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Roche Global Development

Purpose - Excerpt: To compare the time to progression of Cytomegalovirus (CMV) retinitis among each of three doses of oral ganciclovir, as well as to intravenous therapy, when given as maintenance for 26 weeks. To compare the safety and tolerance among oral doses of ganciclovir at the study doses, as well as to intravenous therapy, when administered as maintenance for 26 weeks.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002330>

- **A Study of Valacyclovir Hydrochloride in the Prevention of Life-Threatening Cytomegalovirus Disease in HIV-Infected Patients**

Condition(s): Cytomegalovirus Infections; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID); Glaxo Wellcome

Purpose - Excerpt: PRIMARY: To evaluate the efficacy of valacyclovir hydrochloride (BW 256U87) in the prevention of cytomegalovirus (CMV) end-organ disease in HIV/CMV co-infected patients with CD4+ lymphocytes < 100 cells/mm³. To assess the impact of BW 256U87, high-dose oral acyclovir and low-dose oral acyclovir on survival. SECONDARY: To evaluate the effect of BW 256U87 on quality of life, the safety of the drug administered concurrently with standard antiretroviral agents and other essential therapies for the treatment and prevention of opportunistic diseases, and the efficacy of BW 256U87 in suppressing activation of other herpesviruses. To evaluate serologic and virologic risk factors for the development of CMV disease, including assessment of HIV activation, and the risk of developing drug-resistant CMV, HSV, and VZV. Gastrointestinal absorption of acyclovir is not high enough to prevent CMV disease in patients with advanced HIV disease, although there is evidence that high doses of the drug may extend survival. Valacyclovir, a prodrug that is rapidly converted to acyclovir after oral administration, has a higher absorption rate and may therefore provide inhibitory activity against CMV.

Phase(s): Phase III

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00001038>

- **A Study of Valganciclovir in the Treatment of Cytomegalovirus (CMV) Retinitis in Patients with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Hoffmann-La Roche

Purpose - Excerpt: The purpose of this study is to see if valganciclovir is a safe treatment for CMV retinitis in patients who have been treated for this condition in the past. This study also examines the effectiveness of valganciclovir in preventing the recurrence of CMV retinitis.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002222>

- **A Study of Viracept in AIDS Patients with Cytomegalovirus Retinitis**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Agouron Pharmaceuticals

Purpose - Excerpt: The purpose of this study is to see if it is safe and effective to give Viracept to AIDS patients who are already being treated for cytomegalovirus (CMV) retinitis.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002169>

- **A Study to Evaluate the Effects of Stopping Maintenance Therapy for Cytomegalovirus (CMV) Retinitis after Effective Anti-HIV Therapy**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: The purpose of this study is to see if it is safe to stop maintenance therapy in HIV-positive patients with treated and healed CMV retinitis (eye disease) who have responded well to anti-HIV (antiretroviral) therapy. The current therapies available to treat CMV retinitis are long-term therapies. However, it may be safe to stop long-term anti-CMV therapy in patients with healed CMV retinitis and stable CD4 counts resulting from taking a combination of at least 2 antiretroviral drugs.

Study Type: Observational

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000905>

- **An Open-Label Study of the Safety and Efficacy of Cidofovir for the Treatment of Relapsing Cytomegalovirus Retinitis in Patients With AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Gilead Sciences

Purpose - Excerpt: To evaluate the safety and tolerance of cidofovir (HPMPC) infusions in AIDS patients with relapsing cytomegalovirus (CMV) retinitis. To determine the time to retinitis progression in this patient population. To evaluate the impact of cidofovir therapy on visual acuity.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002142>

- **Assessment of Valganciclovir in Neonates with CMV**

Condition(s): Cytomegalovirus Infections

Study Status: This study is suspended.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: To determine the pharmacokinetics and pharmacodynamics of ganciclovir following administration of oral valganciclovir syrup in patients with symptomatic congenital **cytomegalovirus** (CMV) disease involving the central nervous system (CNS). To evaluate the short-term tolerability of valganciclovir syrup in the neonatal and infantile populations.

Phase(s): Phase I; Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00031434>

- **Comparison of Two Methods in the Treatment of Cytomegalovirus of the Eyes in Patients with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID); Protein Design Labs

Purpose - Excerpt: To evaluate the effect of MSL 109, human monoclonal anti-cytomegalovirus (CMV) antibody, on time to progression of CMV retinitis. To determine the safety and pharmacokinetic profile of MS 109. To evaluate the relationship between pharmacokinetic measurements of MSL 109 and efficacy and virologic markers. Therapeutic agents currently available for CMV retinitis are limited by their inherent toxicities and short half-lives which require frequent intravenous dosing. Alternatively, MSL 109 has demonstrated safety and effectiveness in neutralizing CMV isolates at concentrations easily maintained in AIDS patients.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00001061>

- **Comparison of Two Test Methods-NASBA and Antigenemia-for Detecting Cytomegalovirus Infection**

Condition(s): Cytomegalovirus Infection; Infection

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: This study will evaluate the reliability of a new test called Real-Time Polymerase chain reaction (RT PCR) in detecting cytomegalovirus (CMV) in the blood and predicting the course of CMV disease in patients who have recently had a bone marrow transplant. The test's effectiveness will be compared with that of the "pp65 antigenemia assay" now routinely used for this purpose. CMV is a common virus that is transmitted from person to person by close personal contact. In most healthy people, CVM can remain in the body indefinitely without causing any harm. But, in people with weakened immune systems-including those who have just undergone bone marrow transplant-CMV infection can cause serious, and possibly fatal, complications. Drugs are available to treat this infection, however. Optimum treatment depends on early and accurate detection. Patients aged 10 to 80 years who are scheduled to undergo bone marrow transplant at the NIH Clinical Center as part of an NIH protocol may be eligible for this 2-phase study. In phase 1, patients will have blood drawn for both RT PCR and antigenemia testing once before the bone marrow transplantation and then weekly for the first 100 days after the transplant. During Phase 2-which begins immediately after the end of phase 1 and continues for one year after the transplant-blood samples for both tests will be drawn up to once a week. The samples for both tests will be collected at the same time and will be taken through a catheter (a thin flexible tube inserted into a vein) that has already been placed for the transplant study. RT PCR testing will require an extra 5 milliliters (1 teaspoon) above what is needed for antigenemia testing, amounting to a maximum of about one-half pint extra over the course of the 1-year

study. It is hoped that the new RT PCR test will prove to be more accurate in detecting CMV infection and predicting disease development, thus enabling doctors to plan early and effective treatment.

Study Type: Observational

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00001976>

- **Cytotoxic T-Lymphocytes for the Prophylaxis of Cytomegalovirus after Allogeneic Stem Cell Transplant**

Condition(s): Stem Cell Transplantation; Cytomegalovirus Infections

Study Status: This study is not yet open for patient recruitment.

Sponsor(s): Baylor College of Medicine; The Methodist Hospital; Texas Children's Hospital

Purpose - Excerpt: Patients enrolled on this study have a type of blood cell cancer, other blood disease or a genetic disease for which they will receive a stem cell transplant. The donor of the stem cells will be either a brother or sister or another relative or a closely matched unrelated donor. This study tests if blood cells from the donor, that have been grown in a special way, can prevent patients from getting an infection with a virus called Cytomegalovirus or CMV. CMV is a virus that can cause serious infections in patients with suppressed immune systems. It usually affects the lungs and can cause a very serious pneumonia, but it can also affect the intestinal tract, the liver and the eyes. Approximately 2/3 of normal people harbor this virus in their body. In healthy people CMV rarely causes any problems because the immune system can keep it under control. If the donor is positive for CMV, patients are at risk of developing CMV disease while their immune system is weak post transplant. Usually, this risk is highest during the first 3-4 months after the transplant. CMV disease can be prevented during this time in most people by using drugs that can kill the virus such as Ganciclovir or Foscarnet. However, these medications have many side effects and have to be given daily by vein for approximately 4-5 months after transplant. One of the side effects is that it takes the new immune system much longer to develop an effective defense against the virus. Therefore, once the medicines are stopped, patients still have a chance to develop CMV disease. We want to see if we can use a kind of white blood cell called T cells that we have grown from the patients stem cell donor instead of the regular treatment with Ganciclovir or Foscarnet to prevent CMV from "flaring up". These cells have been trained to attack CMV virus infected cells. We will grow these T cells from blood taken from the donor before the transplant. These cells are called CMV-specific cytotoxic T-lymphocytes or CMV CTL and they will be given to the patient around 30 days after their transplant. We have used this sort of therapy to treat a different virus which can cause problems after transplant called Epstein Barr Virus (EBV).

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00078533>

- **Effects of Hormone Therapy on the Immune Systems of Postmenopausal Women with Chronic Infections**

Condition(s): Atherosclerosis; Chlamydia Infections; Cytomegalovirus Infections; Pneumonia, Bacterial; Postmenopause

Study Status: This study is completed.

Sponsor(s): National Heart, Lung, and Blood Institute (NHLBI)

Purpose - Excerpt: Hardening of the arteries (atherosclerosis) and heart disease are much more common in men than in women. However, as women grow older, especially after menopause the incidence of atherosclerosis and heart disease increases. These findings suggest that estrogen may be protective and help in preventing heart disease. Studies of large groups of post-menopausal women suggest that hormone replacement therapy (therapy that includes estrogen) reduces the risk of heart disease. Estrogen causes favorable changes in particles that carry cholesterol in the blood stream and improves function of blood vessels. Estrogen may also stimulate the immune system's ability to fight off infections that may lead to or contribute to atherosclerosis. Researchers believe two specific infectious agents (Chlamydia pneumoniae and human cytomegalovirus) may cause damage to the lining of blood vessels resulting in inflammation and the development of atherosclerosis. The purpose of this study is to determine if estrogen treatment can change how the immune system responds to chronic infections, by Chlamydia pneumoniae and human **cytomegalovirus**, in postmenopausal women.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00001890>

- **Ganciclovir Implant Study for Cytomegalovirus Retinitis**

Condition(s): HIV Infections; Acquired Immunodeficiency Syndrome; Cytomegalovirus Retinitis

Study Status: This study is completed.

Sponsor(s): National Eye Institute (NEI)

Purpose - Excerpt: To determine the therapeutic efficacy of a sustained-release intraocular drug delivery system for ganciclovir therapy of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

Phase(s): Phase III

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000118>

- **Ganciclovir: Compassionate Use in Patients With Serious or Life-Threatening Cytomegalovirus Infections**

Condition(s): Cytomegalovirus Infections; HIV Infections

Study Status: This study is completed.

Sponsor(s): Hoffmann-La Roche

Purpose - Excerpt: To provide ganciclovir on a compassionate use basis to immunocompromised patients with serious cytomegalovirus (CMV) infections and to study safety and efficacy in this patient population.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002024>

- **Immune Response to Cytomegalovirus**

Condition(s): Cytomegalovirus Infections

Study Status: This study is completed.

Sponsor(s): National Heart, Lung, and Blood Institute (NHLBI)

Purpose - Excerpt: This study will evaluate immune responses against cytomegalovirus (CMV). About 80 percent of adults have been exposed to this virus. CMV typically remains dormant (inactive) in the body, causing no problems. In people with immune suppression, however, the virus can become reactivated and cause life-threatening pneumonia. The knowledge gained from this study may be useful in developing ways to improve immune responses to CMV in stem cell transplant recipients. Healthy normal volunteers between 18 and 65 years of age who have been exposed to cytomegalovirus are eligible for this study. Candidates will be screened with a medical history and blood tests. Those enrolled will provide a 30-milliliter (6-tablespoon) blood sample once a week for 4 weeks and a final sample 2 months later. The blood will be used to design a test to detect immune responses against CMV and determine the differences in these responses among healthy individuals.

Study Type: Observational

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00034437>

- **Open Label Ganciclovir Therapy for Sight- or Life-Threatening Cytomegalovirus Disease in the Immunocompromised Patient**

Condition(s): Cytomegalovirus Infections; Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Hoffmann-La Roche

Purpose - Excerpt: To make intravenous (IV) ganciclovir available to immunocompromised patients with life-threatening or sight-threatening Cytomegalovirus (CMV) infection, where the symptoms of the disease are too severe to allow admission to a controlled clinical study of ganciclovir therapy. To determine the safety and tolerance of 2 - 3 weeks induction course of ganciclovir IV followed by a maintenance course of ganciclovir IV for an indefinite duration. To tabulate the patient's clinical response.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002025>

- **Phase I/II Study of Human Anti-Cytomegalovirus (CMV) Monoclonal Antibody MSL-109 in Newborns with Symptomatic Congenital CMV Infection without Central Nervous System Disease**

Condition(s): Cytomegalovirus Infections

Study Status: This study is completed.

Sponsor(s): National Center for Research Resources (NCRR); National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: Objectives: I. Evaluate the safety, tolerance, and potential efficacy of 3 doses of human anti-cytomegalovirus (CMV) monoclonal antibody SDZ MSL-109 (MOAB MSL-109) in the treatment of newborns with congenital CMV infection and no central nervous system disease. II. Determine the relationship between plasma concentrations of MOAB MSL-109 and therapeutic outcome. III. Determine whether MOAB MSL-109 influences the antibody response and clearance of virus from the urine.

Phase(s): Phase I; Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00004642>

- **Phase II Randomized Study of Cidofovir for Peripheral Cytomegalovirus Retinitis**

Condition(s): Cytomegalovirus Retinitis; Acquired Immunodeficiency Syndrome

Study Status: This study is completed.

Sponsor(s): National Center for Research Resources (NCRR); Northwestern University

Purpose - Excerpt: Objectives: I. Evaluate the safety and efficacy of intravenous cidofovir in patients with small peripheral cytomegalovirus retinitis. II. Obtain safety and efficacy data related to different dosages of cidofovir.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00004794>

- **Phase III Randomized, Controlled Study of Ganciclovir for Symptomatic Congenital Cytomegalovirus Infection**

Condition(s): Cytomegalovirus Infections

Study Status: This study is completed.

Sponsor(s): National Center for Research Resources (NCRR); National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: Objectives: I. Evaluate the efficacy of ganciclovir (12 mg/kg per day) versus no treatment in neonates with symptomatic congenital cytomegalovirus infection with central nervous system disease.

Phase(s): Phase III

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00004278>

- **Suppression of Cytomegalovirus Retinitis Utilizing High Dose Intravenous Acyclovir and Oral Zidovudine in Patients With AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID)

Purpose - Excerpt: To study the use of acyclovir (ACV) and zidovudine (AZT) in the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS who would otherwise be treated with ganciclovir (DHPG) alone. CMV retinitis is one of the most common opportunistic infections in patients with AIDS. DHPG is at present the only drug available for widespread compassionate use in the United States. Although most patients respond to treatment with DHPG, the medication does not cure the infection. Most patients will have a relapse and will require retreatment with DHPG. Because of the large relapse rate, most people treated for CMV retinitis are placed on continuous treatment with DHPG. There are two major problems associated with ongoing use of DHPG: 1) The development of a low white blood cell (WBC) count (leukopenia) which is a known side effect of the drug; and 2) the increased risk for leukopenia when DHPG is given together with AZT, the only antiviral drug currently available for the treatment of HIV infection. Therefore, patients cannot take both AZT and DHPG at the same time because the bone marrow toxicity is made much more severe when the drugs are given together. This has resulted in the difficult decision as to whether to forgo potential life-extending therapy with AZT in order to preserve sight. An effective treatment for CMV retinitis is needed that will allow the patient to also take AZT. ACV is presently the drug of choice for severe herpes virus infections. It has been shown to be effective in suppressing severe CMV disease in patients who have received bone marrow transplants.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000693>

- **The Safety and Effectiveness of Cidofovir in the Treatment of Cytomegalovirus (CMV) of the Eyes in Patients with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Gilead Sciences

Purpose - Excerpt: To determine whether cidofovir (HPMPC) therapy administered by intravenous infusion can extend the time to progression of peripheral cytomegalovirus (CMV) retinitis in AIDS patients. To evaluate the safety and tolerance of HPMPC therapy when administered by intravenous infusion in AIDS patients with CMV retinitis that is not immediately sight-threatening. To evaluate the virologic effects of intravenous HPMPC therapy on CMV shedding in urine, blood, and/or semen. To evaluate the impact of HPMPC therapy on visual acuity.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002437>

- **The Safety and Effectiveness of Different Dose Levels of 1263W94 in the Treatment of Cytomegalovirus (CMV) of the Eyes in HIV-Infected Patients**

Condition(s): Cytomegalovirus Infections; HIV Infections

Study Status: This study is completed.

Sponsor(s): Glaxo Wellcome

Purpose - Excerpt: To evaluate the safety and tolerability of multiple escalating doses of 1263W94 administered orally for 28 days in HIV infected patients with asymptomatic CMV shedding. To obtain preliminary evidence of the in vivo anti CMV activity of different doses of 1263W94 in humans based on quantitative reduction of CMV load in semen and if possible in other biological fluids and to explore the dose response relationship in the anti-CMV activity of 1263W94.

Phase(s): Phase I

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002373>

- **The Safety and Effectiveness of FIAC in the Treatment of Cytomegalovirus (CMV) in Patients with AIDS**

Condition(s): Cytomegalovirus Infections; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID); Oclassen Pharmaceuticals

Purpose - Excerpt: To find oral doses of FIAC (a pyrimidine nucleoside analog) that are effective in treating cytomegalovirus (CMV) viremia in HIV-infected immunocompromised patients; to determine tolerance and safety of FIAC in this patient population; and to determine pharmacokinetics following multiple doses of FIAC. (An example of another nucleoside analog effective against retroviruses such as HIV is zidovudine (AZT).) CMV infection is a medically significant opportunistic disease in patients with HIV-related infection. The purine nucleoside ganciclovir has been used to treat AIDS patients with CMV disease. Although ganciclovir is useful in treating CMV disease, such treatment is frequently complicated by hematologic (blood) toxicity. Also, treatment is difficult because it requires daily intravenous dosing. Test tube studies show that FIAC and its primary breakdown product FIAU are highly and specifically active against several viruses including CMV. A single-dose, pharmacokinetic (blood level) study showed that FIAC, when taken orally, is readily absorbed into the bloodstream, and most of it is converted to FIAU.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000981>

- **The Safety and Effectiveness of Ganciclovir Plus Interferon Beta in Preventing the Return of Cytomegalovirus (CMV) of the Eyes in Patients with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Hoffmann-La Roche

Purpose - Excerpt: The use of ganciclovir (DHPG) in combination with interferon beta to prevent relapse of cytomegalovirus retinitis in patients with AIDS. While early clinical trials have shown that 30 mg/kg/week of DHPG is usually sufficient to delay or prevent relapse, neutropenia is a common dose-limiting problem in about 50 percent of patients. Since in vitro data have suggested that there is synergism between DHPG and interferon beta against cytomegalovirus, a reduced dose of DHPG in combination with a low dose of interferon beta may prevent relapse without causing neutropenia. If remission can be maintained with low-dose DHPG and interferon beta, maintenance therapy with a moderate dose of interferon beta alone will be evaluated in a subsequent protocol.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002299>

- **The Safety and Effectiveness of Ganciclovir Used Alone or in Combination with Granulocyte-Macrophage Colony Stimulating Factor in the Treatment of Cytomegalovirus (CMV) of the Eye in Patients with AIDS**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): National Institute of Allergy and Infectious Diseases (NIAID); Schering-Plough; Hoffmann-La Roche

Purpose - Excerpt: AMENDED: To evaluate the effect of sargramostim (GM-CSF) on modulating the granulocytopenia associated with concomitant DHPG and AZT therapy (Phase B), in terms of time to development of granulocytopenia as defined by an absolute neutrophil count (ANC) less than or equal to 750 cells/mm³. Original design: To determine if granulocyte-macrophage colony-stimulating factor (GM-CSF) is helpful in preventing the decreased numbers of white blood cells (infection-fighting cells) associated with ganciclovir (DHPG) therapy and to determine if GM-CSF can be safely used in AIDS patients with cytomegalovirus (CMV) retinitis. AMENDED: In ACTG 004, among 11 AIDS patients with CMV infection receiving DHPG maintenance therapy (5 mg/kg, 5x/week) with stable white blood cells (WBC)/absolute neutrophil counts (ANC) 7 (64 percent) required dose reduction or discontinuation of both antiviral medications due to granulocytopenia when AZT (600 mg/day) was added. A mean nadir ANC of 717 cells/ml was reached at a mean of 5 weeks of concomitant DHPG/AZT therapy in these patients. While recovery of depressed ANC occurred following discontinuation of study medications, progressive CMV infection (most commonly retinitis) occurred in 19 of 40 patients and seemed to be associated with DHPG therapy interruption. Only 3 of 40 patients were able to tolerate the complete 16 week study duration of DHPG/AZT. Pharmacokinetic studies of co-administration of DHPG and AZT revealed no significant drug-drug interactions. The study investigators concluded that the main, treatment limiting toxicity of combination DHPG/AZT therapy is granulocytopenia and that many patients treated on this study developed intercurrent OIs or staphylococcal septicemia. In order to determine whether patients receiving maintenance DHPG therapy with or without GM-CSF can tolerate concomitant AZT therapy, extended maintenance therapy with the assigned study regimen in combination with AZT will be incorporated into this protocol. Original design: CMV infection causes inflammation of the retina and can lead to permanent blindness. Treatment for CMV retinitis with DHPG has been shown to be effective in

halting the progression of retinal disease. During DHPG treatment, however, about 30 to 55 percent of patients develop decreased white blood cell counts. GM-CSF, a naturally occurring human hormone, stimulates the body's bone marrow to produce more white blood cells. Studies with GM-CSF in AIDS patients have shown that it can significantly increase depressed white blood cell counts in these patients.

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00000989>

- **The Safety and Effectiveness of ISIS 2922 in Patients with AIDS Who Have Cytomegalovirus (CMV) of the Eyes**

Condition(s): Cytomegalovirus Retinitis; HIV Infections

Study Status: This study is completed.

Sponsor(s): Isis Pharmaceuticals

Purpose - Excerpt: To evaluate the efficacy and safety of ISIS 2922 in AIDS patients with Cytomegalovirus (CMV) retinitis who are unresponsive or intolerant to ganciclovir and/or foscarnet but are otherwise ineligible for ISIS Pharmaceuticals' controlled trials OR who have failed ISIS 2922 therapy on another controlled clinical trial. PER 2/8/96 AMENDMENT: Patients must rollover from another ISIS 2922 controlled trial.

Phase(s): Phase II

Study Type: Interventional

Contact(s): see Web site below

Web Site: <http://clinicaltrials.gov/ct/show/NCT00002356>

Keeping Current on Clinical Trials

The U.S. National Institutes of Health, through the National Library of Medicine, has developed ClinicalTrials.gov to provide current information about clinical research across the broadest number of diseases and conditions.

The site was launched in February 2000 and currently contains approximately 5,700 clinical studies in over 59,000 locations worldwide, with most studies being conducted in the United States. ClinicalTrials.gov receives about 2 million hits per month and hosts approximately 5,400 visitors daily. To access this database, simply go to the Web site at <http://www.clinicaltrials.gov/> and search by "cytomegalovirus" (or synonyms).

While ClinicalTrials.gov is the most comprehensive listing of NIH-supported clinical trials available, not all trials are in the database. The database is updated regularly, so clinical trials are continually being added. The following is a list of specialty databases affiliated with the National Institutes of Health that offer additional information on trials:

- For clinical studies at the Warren Grant Magnuson Clinical Center located in Bethesda, Maryland, visit their Web site: <http://clinicalstudies.info.nih.gov/>
- For clinical studies conducted at the Bayview Campus in Baltimore, Maryland, visit their Web site: <http://www.jhbm.jhu.edu/studies/index.html>

- For cancer trials, visit the National Cancer Institute: <http://cancertrials.nci.nih.gov/>
- For eye-related trials, visit and search the Web page of the National Eye Institute: <http://www.nei.nih.gov/neitrials/index.htm>
- For heart, lung and blood trials, visit the Web page of the National Heart, Lung and Blood Institute: <http://www.nhlbi.nih.gov/studies/index.htm>
- For trials on aging, visit and search the Web site of the National Institute on Aging: <http://www.grc.nia.nih.gov/studies/index.htm>
- For rare diseases, visit and search the Web site sponsored by the Office of Rare Diseases: http://ord.aspensys.com/asp/resources/rsch_trials.asp
- For alcoholism, visit the National Institute on Alcohol Abuse and Alcoholism: http://www.niaaa.nih.gov/intramural/Web_dicbr_hp/particip.htm
- For trials on infectious, immune, and allergic diseases, visit the site of the National Institute of Allergy and Infectious Diseases: <http://www.niaid.nih.gov/clintrials/>
- For trials on arthritis, musculoskeletal and skin diseases, visit newly revised site of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health: <http://www.niams.nih.gov/hi/studies/index.htm>
- For hearing-related trials, visit the National Institute on Deafness and Other Communication Disorders: <http://www.nidcd.nih.gov/health/clinical/index.htm>
- For trials on diseases of the digestive system and kidneys, and diabetes, visit the National Institute of Diabetes and Digestive and Kidney Diseases: <http://www.niddk.nih.gov/patient/patient.htm>
- For drug abuse trials, visit and search the Web site sponsored by the National Institute on Drug Abuse: <http://www.nida.nih.gov/CTN/Index.htm>
- For trials on mental disorders, visit and search the Web site of the National Institute of Mental Health: <http://www.nimh.nih.gov/studies/index.cfm>
- For trials on neurological disorders and stroke, visit and search the Web site sponsored by the National Institute of Neurological Disorders and Stroke of the NIH: http://www.ninds.nih.gov/funding/funding_opportunities.htm#Clinical_Trials

CHAPTER 6. PATENTS ON CYTOMEGALOVIRUS

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.⁹ 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 "cytomegalovirus" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on cytomegalovirus, we have not necessarily excluded non-medical patents in this bibliography.

Patents on Cytomegalovirus

By performing a patent search focusing on cytomegalovirus, 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.

⁹Adapted 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 cytomegalovirus:

- **Alphavirus vectors for paramyxovirus vaccines**

Inventor(s): Klein; Michel H. (Toronto, CA), Li; Xiaomao (Toronto, CA), Parrington; Mark (Bradford, CA)

Assignee(s): Aventis Pasteur Limited (toronto, Ca)

Patent Number: 6,475,780

Date filed: October 20, 2000

Abstract: A DNA vector comprises a first DNA sequence which is complementary to at least part of an alphavirus RNA genome and having the complement of complete alphavirus DNA genome replication regions, and a second DNA sequence encoding a paramyxovirus protein, particularly a respiratory syncytial virus fusion (RSV F) protein or a RSV F protein fragment that generates antibodies that specifically react with RSV F protein, the first and second DNA sequences being under the transcriptional control of a promoter, preferably a **cytomegalovirus** promoter, which may include Intron A. Such vectors also contain a further nucleotide sequence located between the promoter sequence and the alphavirus sequence to enhance the immunoprotective ability of the RSV F protein when expressed in vivo. Such DNA vectors may be used to immunize a host against disease caused by infection with RSV or other paramyxovirus, including a human host, by administration thereto, and may be formulated as immunogenic compositions with pharmaceutically-acceptable carriers for such purposes. Such vectors also may be used to produce antibodies for detection of RSV or other paramyxovirus infection in a sample.

Excerpt(s): The present invention relates to the field of paramyxoviridae vaccines and is particularly concerned with vaccines comprising DNA encoding the fusion (F) protein of respiratory syncytial virus (RSV) in an alphavirus vector. Formalin-inactivated (FI-RSV) and live attenuated RSV vaccines have failed to demonstrate efficacy in clinical trials (refs. 7, 8, 9, 10). Moreover, the formalin-inactivated RSV vaccine caused enhanced disease in some children following exposure to wild-type RSV (refs. 7, 8, 9, 10). Elucidation of the mechanism(s) involved in the potentiation of RSV disease is important for the design of safe RSV vaccines, especially for the seronegative population. Recent experimental evidence suggests that an imbalance in cell-mediated responses may contribute to immunopotential. Enhanced histopathology observed in mice that were immunized with the FI-RSV and challenged with virus could be abrogated by depletion of CD4⁺ cells or both interleukin-4 (IL-4) and IL-10. The RSV fusion (F) glycoprotein is one of the major immunogenic proteins of the virus. This envelope glycoprotein mediates both fusion of the virus to the host cell membrane and cell-to-cell spread of the virus (ref. 1). The F protein is synthesized as a precursor (F.sub.0) molecule which is proteolytically cleaved to form a disulphide-linked dimer composed of the N-terminal F.sub.2 and C-terminal F.sub.1 moieties (ref. 11). The amino acid sequence of the F protein is highly conserved among RSV subgroups A and B and is a cross-protective antigen (refs. 6, 12). In the baculovirus expression system, a truncated secreted version of the RSV F protein has been expressed in *Trichoplusia ni* insect cells (ref. 13). The recombinant protein was demonstrated to be protective in the cotton rats (ref. 13).

Web site: http://www.delphion.com/details?pn=US06475780__

- **Antiretroviral compounds and compositions**

Inventor(s): Brewer; Arthur D. (Puslinch, CA), Cantor; Stephen E. (Cheshire, CT), Dekeyser; Mark A. (Waterloo, CA), Doweiko; Arthur M. P. (Long Valley, NJ), Harris; John W. (Sugar Land, TX), Harrison; William A. (Guelph, CA), Lacadie; John A. (Woodbury, CT), Pierce; James B. (Southbury, CT), Plant; Howard L. (late of Milford, CT)

Assignee(s): Uniroyal Chemical Company, Inc. (middlebury, Ct)

Patent Number: 6,498,254

Date filed: October 29, 2001

Abstract: Certain pyridine and quinoline derivatives' which inhibit replication of the retroviruses HIV-1, HIV-2 and human **cytomegalovirus** (HCMV) are provided. Pharmaceutical compositions useful in methods of treating or inhibiting certain retrovirus infections are described.

Excerpt(s): This invention relates to compounds useful as antiretroviral agents. More particularly, this invention relates to pyridine and quinoline derivatives which inhibit replication of the retroviruses HIV-1, HIV-2 and human **cytomegalovirus** (HCMV). There are currently about seven nucleoside reverse transcriptase (RT) inhibitors (NRTIs), about three nonnucleoside RT inhibitors (NNRTI) and about six protease inhibitors (PI) officially approved for the treatment of HIV-infected individuals. Reverse transcriptase and protease are virus-encoded enzymes. The clinical efficacy of the individual drugs varies depending on the nature and the molecular target of the drugs. U.S. Pat. No. 5,268,389 describes certain thiocarboxylate ester compounds that are said to inhibit replication of HIV. It is alleged that the selectivity of these compounds for HIV-1 is due to a highly specific interaction with HIV-1 RT.

Web site: http://www.delphion.com/details?pn=US06498254__

- **Controlling immune response to specific antigens**

Inventor(s): Curiel; David T. (Birmingham, AL), Mountz; John D. (Birmingham, AL), Zhang; Huang-Ge (Birmingham, AL)

Assignee(s): Uab Research Foundation (birmingham, Al)

Patent Number: 6,689,605

Date filed: January 2, 2000

Abstract: One major problem with adenovirus gene therapy has been the T-cell mediated immune response elicited by inoculation of adenovirus, which leads to rapid clearance of the virus and loss of transgene expression. In the instant invention, the immune response to a virus is prevented by pre-treatment with adenovirus, adenoassociated virus or herpes virus infected antigen-presenting cell (APC) expressing Fas ligand with induced T-cell tolerance. Administration of AdCMVLacZ after tolerance resulted in prolonged expression of LacZ in tolerized animals compared to control treated animals. In control, but not tolerized animals, there was proliferation of CD3.sup.+ T-cell in the spleen in response to AdCMVLacZ treatment. Tolerance induction is also indicated by decreased production of interferon-.gamma. and IL-2 by peripheral T-cells isolated from treated animals after stimulation with the adenovirus infected APCs. T-cell tolerance is specific for the virus as the T-cell responses to an irrelative virus, mouse **cytomegalovirus** (MCMV) remained unimpaired. The instant

invention utilizes virus specific T-cell tolerance, which is induced by APCs that co-express Fas ligand and virus antigens. The instant invention involves novel vectors and methods to induce tolerance to a viral vector gene therapy and prolong expression of a transgene in a viral host.

Excerpt(s): This invention relates generally to gene therapy. More specifically, the invention relates to suppressing immune system response to antigens expressed on an infected host cell. The proper function of the immune system of an organism is to attack and neutralize materials which are perceived as being foreign to that organism. T-cells are one component of the immune system. T-cells can become activated to specific antigens, and function to directly destroy materials which display that antigen, and they also function to sensitize other components of the immune system to the presence of that antigen. While a properly functioning immune system is vital to the health of an organism, in some instances there is a need for the selective inhibition of an immune response to particular materials. For example, viral vectors, such as adenovirus, are employed in genetic therapies to introduce genetic material and products into an organism. One problem encountered with the use of such viral vectors is that they can provoke an immune response in the organism. This immune response can destroy the viral vector, and those host cells which are intentionally infected by the vector, as well as therapeutic gene products produced by the action of the vector. Furthermore, immune system "memory" provides a lasting response to this vector; hence, readministration of the material will be ineffective. Therefore, there is a need for a method whereby the immune response to a selected viral vector may be blocked or destroyed. Suppression of immune response is also desirable in the instances of autoimmune disease. As is known, such disease results when the immune system of an organism inappropriately recognizes an organ or tissue of that organism as being foreign, and commences an immune response against it. If this immune response can be blocked, the autoimmune disease can be controlled. Immune suppression is also needed in those instances where organs are transplanted. Immune system suppressing drugs are sometimes employed in the foregoing situations; however, such drugs produce a generalized suppression of the immune system, which leaves a patient open to a number of infections. It would therefore be advantageous if immune response to a specific antigen could be suppressed and/or an immune suppressed zone of tissue created within an organism.

Web site: http://www.delphion.com/details?pn=US06689605__

- **Detection of nucleic acids by multiple sequential invasive cleavages 02**

Inventor(s): Brow; Mary Ann D. (Madison, WI), Hall; Jeff G. (Madison, WI), Lyamichev; Victor I. (Madison, WI), Mast; Andrea L. (Madison, WI)

Assignee(s): Third Wave Technologies, Inc (madison, Wi)

Patent Number: 6,458,535

Date filed: July 9, 1999

Abstract: The present invention relates to means for the detection and characterization of nucleic acid sequences, as well as variations in nucleic acid sequences. The present invention also relates to methods for forming a nucleic acid cleavage structure on a target sequence and cleaving the nucleic acid cleavage structure in a site-specific manner. The structure-specific nuclease activity of a variety of enzymes is used to cleave the target-dependent cleavage structure, thereby indicating the presence of specific nucleic acid sequences or specific variations thereof. The present invention further relates to methods and devices for the separation of nucleic acid molecules based on

charge. The present invention also provides methods for the detection of non-target cleavage products via the formation of a complete and activated protein binding region. The invention further provides sensitive and specific methods for the detection of human **cytomegalovirus** nucleic acid in a sample.

Excerpt(s): The present invention relates to means for the detection and characterization of nucleic acid sequences and variations in nucleic acid sequences. The present invention relates to methods for forming a nucleic acid cleavage structure on a target sequence and cleaving the nucleic acid cleavage structure in a site-specific manner. The 5' nuclease activity of a variety of enzymes is used to cleave the target-dependent cleavage structure, thereby indicating the presence of specific nucleic acid sequences or specific variations thereof. The present invention further provides novel methods and devices for the separation of nucleic acid molecules based by charge. The present invention further provides methods for the detection of non-target cleavage products via the formation of a complete and activated protein binding region. The detection and characterization of specific nucleic acid sequences and sequence variations has been utilized to detect the presence of viral or bacterial nucleic acid sequences indicative of an infection, the presence of variants or alleles of mammalian genes associated with disease and cancers and the identification of the source of nucleic acids found in forensic samples, as well as in paternity determinations. Various methods are known to the art which may be used to detect and characterize specific nucleic acid sequences and sequence variants. Nonetheless, as nucleic acid sequence data of the human genome, as well as the genomes of pathogenic organisms accumulates, the demand for fast, reliable, cost-effective and user-friendly tests for the detection of specific nucleic acid sequences continues to grow. Importantly, these tests must be able to create a detectable signal from samples which contain very few copies of the sequence of interest. The following discussion examines two levels of nucleic acid detection assays currently in use: I. Signal Amplification Technology for detection of rare sequences; and II. Direct Detection Technology for quantitative detection of sequences.

Web site: http://www.delphion.com/details?pn=US06458535__

- **Generation of human cytomegalovirus yeast artificial chromosome recombinants**

Inventor(s): Ghazal; Peter (Edinburgh, GB), Huang; Huang (Chicago, IL)

Assignee(s): The Scripps Research Institute (La Jolla, Ca)

Patent Number: 6,692,954

Date filed: November 3, 2000

Abstract: The present invention relates to a recombinant DNA construct comprising a YAC vector and at least a portion of the HCMV genome. The vector is useful as a basic research tool with which to study CMV biology, or as a vaccine with which to immunize a mammalian host against infection by CMV.

Excerpt(s): Human **cytomegalovirus** (HCMV) is the leading cause of viral congenital infections worldwide, involving about 1% of newborns. In children, the consequences may be severe, especially in case of maternal primary infection during pregnancy. In the United States, about 30,000 to 40,000 newborns are affected each year; more than 9,000 of these children are left with permanent neurological sequelae. Demmler, G. J., 1994, Congenital **cytomegalovirus** infection, Semin. Pediatr. Neurol. 1(1):36-42. The annual cost of treating **cytomegalovirus** infection complications in the United States is about two billion dollars. Daniel Y. et al., 1995, Congenital **cytomegalovirus** infection, Eur. J.

Obstet. Gynecol. Reprod. Biol., 63(1):7-16. Infection in adults is frequently asymptomatic, but may manifest as mononucleosis, hepatitis, pneumonitis, or retinitis. HCMV infection is particularly significant in immunocompromised patients such as AIDS sufferers, chemotherapy patients, and organ transplant patients undergoing tissue rejection therapy. The mechanisms of HCMV pathogenesis are not fully understood. It is believed that host factors, such as cellular and/or humoral immune responses might be involved. See, Alford and Britt, "The Human Herpesviruses", Eds. Roizman, B., R. J. Whitley and C. Lopez, Raven Press, N.Y., 1993, pp 227-55. It has also been speculated that genetic variability (either structural or antigenic or both) among different strains of HCMV could be responsible for the variability in clinical manifestations observed. See, Pritchett, R. F., 1980, DNA nucleotide sequence heterogeneity between the Towne and AD169 strains of **cytomegalovirus**, J. Virol. 36(1):152-61; Lehner, R. et al., 1991, Comparative sequence analysis of human **cytomegalovirus** strains, J. Clin. Microbiol. 29(11):2494-502; Fries, B. C., 1994, Frequency distribution of **cytomegalovirus** envelope glycoprotein genotypes in bone marrow transplant recipients, J. Infect. Dis. 169(4):769-74.

Web site: http://www.delphion.com/details?pn=US06692954__

- **Herpes virus proteinase and methods of assaying**

Inventor(s): Gibson; D. Wade (Baltimore, MD), Welch; Anthony R. (Sunnyvale, CA)

Assignee(s): Johns Hopkins University (baltimore, Md)

Patent Number: 6,406,902

Date filed: June 2, 2000

Abstract: A herpes virus proteinase has been found to be encoded by a member of a family of four nested genes in simian **cytomegalovirus**. Another member of the nested genes encodes the assembly protein precursor, which is a substrate for the proteinase. Homologous genes are found in other herpes viruses. Cleavage sites recognized by the proteinase are identified in **cytomegalovirus** and are found to be highly conserved in other herpes viruses. Substrates, inhibitors, assay kits, and methods of assaying are provided which rely on the proteinase and its activity.

Excerpt(s): This invention relates to the area of herpes virology. More particularly, it relates to a new enzyme and the use of that enzyme as a target for anti-viral therapy. Herpes viruses are large double stranded DNA viruses that are responsible for a number of human diseases including chicken pox, shingles, fever blisters, salivary gland virus disease, and infectious mononucleosis. The seven human herpes viruses that have been described thus far are HSV-1, HSV-2, **cytomegalovirus** (CMV), Epstein-Barr Virus (EBV), varicella zoster virus (VZV), HHV-6, and HHV-7. Maturation of herpes virus particles is believed to occur through the formation of a procapsid structure, which acquires DNA and an envelope to become an infectious virion. A herpes virus group-common protein referred to as the assembly protein in CMV, and as p40, VP22a, NCP-3, and ICP35e in HSV-1, is an abundant constituent of the herpes virus procapsid. The assembly protein is phosphorylated and proteolytically processed from a precursor molecule. It is absent from the mature virion, although its fate is unknown. These characteristics of the assembly protein have suggested an analogy between it and the bacteriophage scaffolding protein, which is an essential component for phage assembly but is not found in mature virus particles (Gibson et al. (1991) J. Virol. 64:1241-1249).

Web site: http://www.delphion.com/details?pn=US06406902__

- **Human cytomegalovirus DNA sequences**

Inventor(s): Cha; Tai-An (San Ramon, CA), Spaete; Richard (Belmont, CA)

Assignee(s): Aviron (mountain View, Ca)

Patent Number: 6,291,236

Date filed: March 17, 2000

Abstract: Provided are novel Toledo and Towne Human **cytomegalovirus** DNA sequences (HCMV) and proteins encoded thereby. The sequences are useful in methods and compositions for detecting HCMV infections and in immunogenic compositions for preventing HCMV infections.

Excerpt(s): This invention pertains to the field of virology, specifically to the diagnosis, treatment and prevention of viral infections in humans. More specifically, this invention relates to the diagnosis, treatment and prevention of human **cytomegalovirus** infections. Human **cytomegalovirus** (HCMV) is a ubiquitous agent in human populations. Infections are generally asymptomatic, but there can be serious medical sequelae in immunocompromised individuals and in congenitally infected newborns. In immunocompromised individuals, HCMV infection can result in interstitial pneumonia, retinitis progressing to blindness and disseminated infection. Infections in newborns can be severely damaging, with multiple organ involvement including the central nervous system and may also result in auditory damage. The mechanisms of pathogenesis are not understood, although it is believed that host factors, such as cellular and/or humoral immune responses might be involved. See, Alford and Britt, "The Human Herpesviruses", eds Roizman, B., R. J. Whitley and C. Lopez, Raven Press, New York, 1993, pp 227-55. It has also been speculated that genetic variability (either structural or antigenic or both) among different strains of HCMV could be responsible for the variance in clinical manifestations observed. Pritchett, J. Virol. 26:152-61 (1980); Lehner, J. Clin. Microbiol. 29:2492-2502(1991); Fries, J. Infect. Dis. 169:769-74 (1994). Considerable attention has been focused recently on the analysis of strain variation among HCMV isolates. Some twenty different HCMV strains have been isolated and differentiated by restriction analysis of PCR amplified DNA fragments. Chou, J. Infect. Dis. 162:738-42(1990).

Web site: http://www.delphion.com/details?pn=US06291236__

- **Immuno-reactive peptide CTL epitopes of human cytomegalovirus**

Inventor(s): Diamond; Don J. (Glendora, CA)

Assignee(s): City of Hope (duarte, Ca)

Patent Number: 6,562,345

Date filed: October 20, 2000

Abstract: The invention provides a plurality of peptides (and immunologically functional variants thereof) which are immunogenic epitopes recognized by CD8.sup.+ class I MHC restricted cytotoxic T-lymphocytes of patients harboring latent human **cytomegalovirus** (HCMV) infection. The peptides are capable of activating CTLs and CTLps in the absence of active viral replication, and thus are useful for eliciting a cellular immune response against HCMV by normal and immunodeficient subjects. Peptide and lipopeptide vaccines, with and without adjuvants, also are disclosed. Cellular vaccines comprising the peptides form a further embodiment of this invention.

Excerpt(s): This invention relates to human **cytomegalovirus** (HCMV), and in particular to peptide fragments from one or more subunit proteins that function as T-cell epitopes of HCMV in human beings. The peptides of this invention are capable of directing human cytotoxic T lymphocytes (CTL) to recognize and lyse human cells equivalently to infection with HCMV. Vaccines formulated using those peptides also are provided by this invention. The HCMV genome is relatively large (about 235 k base pairs) and has the capacity to encode more than two hundred proteins. HCMV is composed of a nuclear complex of double-stranded DNA surrounded by capsid proteins having structural or enzymatic functions, and an external glycopeptide- and glycolipid-containing membrane envelope. HCMV is a member of the herpes virus family and has been associated with a number of clinical syndromes. Several studies have begun to question whether persistent and apparently asymptomatic HCMV infection in an otherwise healthy adult poses health risks in certain individuals. For example, individuals who have undergone coronary angioplasty sometimes subsequently develop restenosis as a result of arterial remodeling. In one study, about one third of such patients with restenosis had detectable HCMV DNA in their arterial lesions (E. Speir et al., *Science* 265:391-394 (1994)). In another study, CMV seropositive patients were five times more likely to develop restenosis than their seronegative counterparts (Y. F. Zhou et al., *New England J. Med.* 335:624-630 (1996)). These studies suggest that decreasing the number of HCMV infected host cells can benefit certain individuals.

Web site: http://www.delphion.com/details?pn=US06562345__

- **Immunoreactive peptide CTL epitopes of human cytomegalovirus pp150**

Inventor(s): Diamond; Don J. (Glendora, CA)

Assignee(s): City of Hope (duarte, Ca)

Patent Number: 6,544,521

Date filed: October 22, 2001

Abstract: The invention provides peptides which are immunogenic epitopes recognized by CD8.sup.+ class I MHC restricted cytotoxic T-lymphocytes of patients harboring latent **cytomegalovirus** (HCMV) infection. The peptides are capable of activating CTL in the absence of active viral replication, and thus are useful for eliciting a cellular immune response against HCMV by normal and immunodeficient subjects. Vaccines against HCMV, with and without adjuvants, and immunological and diagnostic reagents are disclosed.

Excerpt(s): This invention relates to human **cytomegalovirus** (HCMV), and in particular to peptide fragments from a protein that produces T-cell epitopes of HCMV in human beings. The peptide fragment epitopes are capable of directing human cytotoxic T lymphocytes (CTL) to recognize and lyse human cells infected with HCMV. The HCMV genome is relatively large (about 235,000 base pairs) and can encode more than two hundred proteins. HCMV comprises a nuclear complex of double-stranded DNA surrounded by capsid proteins having structural or enzymatic functions, and an external glycopeptide- and glycolipid-containing membrane envelope. Patients with an active HCMV infection often suffer impairment of at least some of their vital organs, including salivary glands, brain, kidney, liver and lungs. Furthermore, HCMV is associated with a wide spectrum of classical syndromes including mononucleosis and interstitial pneumonia. HCMV also has an oncogenic potential and a possible association with certain types of malignancies, including Kaposi's sarcoma.

Web site: http://www.delphion.com/details?pn=US06544521__

- **Methods and compositions for retarding the development of atherosclerotic lesions**

Inventor(s): Berencsi; Klara (Rosemont, PA), Gonczol; Eva (Rosemont, PA)

Assignee(s): The Wistar Institute of Anatomy and Biology (philadelphia, Pa)

Patent Number: 6,291,437

Date filed: August 14, 1997

Abstract: A method for preventing or retarding the development atherosclerotic lesions or restenosis involves administering to a subject, preferably a human, an effective amount of an anti-viral composition directed against CMV, and optionally an anti-microbial composition directed against *C. pneumoniae*. These compositions may be conventional chemical anti-microbial pharmaceuticals. Alternatively, the compositions may contain a **cytomegalovirus** (CMV) protein or fragment thereof (or nucleic acid containing compositions expressing such protein or fragment). Such compositions may contain an immunogenic *C. pneumoniae* protein or fragment thereof (or nucleic acid containing compositions expressing such protein or fragment). The protein/nucleic acid compositions are administered in an amount capable of inducing cell mediated immunity and/or antibody response in the subject.

Excerpt(s): The present invention relates generally to pharmaceutical compositions and methods of use thereof in treating or preventing atherosclerosis. Atherosclerosis (AT) results from an excessive inflammatory and fibroproliferative response to vascular insult and has been noted to be a principal cause of heart attack and stroke, accounting for up to half of all mortalities in the industrialized world including about 13 million Americans. Atherogenesis is theorized to follow a response to injury, but the agent(s) of injury have yet to be identified fully. Viral and/or bacterial infection(s) have been found to be associated in some way with the complex process of the development of AT. Particles, antigens and DNA sequences of human **cytomegalovirus** (HCMV), a member of the herpesvirus group, have been described in AT plaques of biopsy or autopsy material [M. G. Hendrix et al, *Am. J. Pathol.*, 136:23-28 (1990); J. L. Melnick et al., *BioEssays*, 17(10): 899 (October 1995)]. However, Melnick, cited above, states that the "observations do not demonstrate a viral role in the pathogenesis of atherosclerosis". The possible involvement of reactivated HCMV in restenosis of coronary arteries, an accelerated form of AT, following angioplastic surgery has been suggested [S. E. Epstein et al, *Lancet*, 348:13-17 (1996); E. Speir et al, *Science*, 265:391-394 (1994); Y. F. Zhou et al, *N. Engl. J. Med.*, 335: 624-630 (1996)]. Seroepidemiologic data show that HCMV infection usually occurs in childhood, paralleling the pattern of the appearance of early AT lesions; by young adulthood, 50-100% of individuals are HCMV-seropositive. In some individuals, the virus is apparently reactivated in artery walls, where it may initiate abnormal cell growth that can lead to blocked blood flow and, ultimately, heart attack.

Web site: http://www.delphion.com/details?pn=US06291437__

- **Methods and reagents for regulating obesity**

Inventor(s): Bernfield; Merton (Boston, MA), Reizes; Ofer (Newton, MA)

Assignee(s): Children's Medical Center Corporation (boston, Ma)

Patent Number: 6,284,729

Date filed: May 6, 1998

Abstract: It has now been demonstrated that syndecan binds to and interacts with MC4-R, and thereby modulates neuropeptide regulation of body weight, via the agouti/MC4-R signaling pathway. Transgenic animals were made initially using a construct including a **cytomegalovirus** promoter and the 3' untranslated region, including the polyadenylation site, of the bovine growth hormone gene, as well as cDNA encoding syndecan-1. The mice express the syndecan-1 transgene in many tissues, with expression in the brain occurring preferentially in their hypothalamus. These mice are characterized by elevated levels of circulating syndecan-1 ectodomain and exhibit enormous weight gain after reaching sexual maturity, but have a relatively normal distribution of fat, are completely healthy and heterozygotes reproduce, and show other indicators associated with obesity in humans. Agouti mice which are transgenic for syndecan-1 ectodomain demonstrate that syndecan-1 and agouti interact, potentiating obesity. The double heterozygote shows both an earlier onset, and greater extent, of obesity than either normal agouti or the original transgenic syndecan-1 mice. Based on these studies and animal models, one can design and test compounds regulating obesity. These mice are also useful in understanding the factors involved in weight regulation and in designing and screening for drugs which are involved in weight regulation and that can either enhance or reduce appetite and activity.

Excerpt(s): Obesity is a well established risk factor for a number of potentially life-threatening diseases such as atherosclerosis, hypertension, diabetes, stroke, pulmonary embolism, and cancer. Furthermore, it complicates numerous chronic conditions such as respiratory diseases, osteoarthritis, osteoporosis, gall bladder disease, and dyslipidemias. The enormity of this problem is best reflected in the fact that death rates escalate with increasing body weight. More than 50% of all-cause mortality is attributable to obesity-related conditions once the body mass index (BMI) exceeds 30 kg/m², as seen in 35 million Americans. (Lee 1992. JAMA. 268:2045-2049). By contributing to greater than 300,000 deaths per year, obesity ranks second only to tobacco smoking as the most common cause of potentially preventable death. (McGinnis 1993 MA.270:2207-2212). Accompanying the devastating medical consequences of this problem is the severe financial burden placed on the health care system in the United States. The estimated economic impact of obesity and its associated illnesses from medical expenses and loss of income are reported to be in excess of \$68 billion/year. (Colditz G. 1992. Am J Clin Nutr. 55:503S-507S). This does not include the greater than \$30 billion per year spent on weight loss foods, products, and programs. (Wolf 1994. Pharmacoeconomics. 5:34-37). A major reason for the long-term failure of established approaches is their basis on misconceptions and a poor understanding of the mechanisms of obesity. Conventional wisdom maintained that obesity is a self-inflicted disease of gluttony. Comprehensive treatment programs, therefore, focused on behavior modifications to reduce caloric intake and increase physical activity using a myriad of systems. These methods have limited efficacy and are associated with recidivism rates exceeding 95%. (NIH Technology Assessment Conference Panel. 1993. Ann Intern Med. 119:764-770). Failure of short-term approaches, together with the recent progress made in elucidating the pathophysiology of obesity, have lead to a reappraisal of pharmacotherapy as a potential long-term, adjuvant treatment. (National Task Force on

Obesity. 1996. JAMA. 276:1907-1915). The premise is that body weight is a physiologically controlled parameter similar to blood pressure and obesity is a chronic disease similar to hypertension. The goal of long-term (perhaps life long) medical therapy would be to facilitate both weight loss and subsequent weight maintenance in conjunction with a healthy diet and exercise. To assess this approach, the long-term efficacy of currently available drugs must be judged against that of non-pharmacological interventions alone. Currently, no single drug regimen emerges as superior in either promoting or sustaining weight loss. Although promising, the success of this approach is limited by the efficacy of currently available anorexiants. Surgical interventions, such as gastric partitioning procedures, jejunoileal bypass, and vagotomy, have also been developed to treat severe obesity. (Greenway 1996. *Endo Metab Clin N Amer.* 25:1005-1027). Although these procedures induce similar rates of early weight loss as nonsurgical interventions, they have been shown to maintain a weight loss of up to 33% for more than 10 years. (Long 1994. *Diabetes Care.* 17:372-375). While still far from optimal, this is a substantial improvement over that achieved with behavioral and medical management alone. The superior long-term outcome with surgical procedures is attributed to the inherent permanence of the intervention which addresses the chronic nature of the disease. Although advantageous in the long run, the acute risk benefit ratio has reserved these invasive procedures for morbidly obese patients according to the NIH consensus conference on obesity surgery (BMI>40 kg/m²). (NIH Conference. 1991. *Ann Intern Med.* 115:956-961). Therefore, this is not an alternative for the majority of overweight patients unless and until they become profoundly obese and are suffering the attendant complications. No one knows all of the mechanisms involved in regulation of weight gain, although it is believed that many genetic as well as environmental factors, including diet and exercise, play major, interrelated roles. A number of publications have reported the discovery of genes that have been "knocked out" or overexpressed in transgenic mice, resulting in affected animals becoming incredibly obese, or vice versa. See, for example, Ezzell, "Fat Times for Obesity Research: Tons of New Information, but How Does It All Fit Together" *J. NIH Res.* 7, 39-43 (October 1995). Researchers have reported the cloning of at least two distinct genes, *Ob* which encodes a protein "leptin" believed to cause weight reduction in obese animals, and *Db*, which is believed to cause weight gain in animals. Other genes which have been reported include the *fat*, *tub*, *agouti*, and *melanocortin 4 receptor* genes. Recent reviews relating to the insights regarding the mechanisms involved in obesity help to understand these complex pathways. See, for example, Trish Gura, *Science* 275, 752-753 (Feb. 7, 1997) and Jeffrey S. Flier, *Proc. Natl. Acad. Sci. USA* 94, 4242-4245 (April 1997). Leptin, discovered in 1994 by Jeffrey Friedman's team at Rockefeller University, NY, is a 16 kD protein produced by the obesity (*ob*) gene of mice. Homozygotes with defective *ob* genes are unable to reproduce, stay warm, or grow normally, and become grossly overweight. The receptor for leptin has now been identified and cloned. Defects in the receptor also result in grossly obese animals. The receptor is expressed in the brain primarily in four regions, including the arcuate nucleus. In humans, however, the linkage between obesity and overexpression of leptin does not seem to be closely correlated, and no individuals have been identified that have a mutated *Ob* receptor or gene. Another molecule which appears to be important in weight control is the appetite-stimulating neurotransmitter referred to as neuropeptide Y or "NPY". NPY levels are elevated in animals with decreased levels of leptin. Genetic studies with knockout NPY and *ob/ob* animals indicate that NPY plays a role in, but is not a controlling factor, in obesity. Another line of research has implicated a role in obesity for the melanocortin receptor ("MCR"). Two MCRs, MCR3 and MCR4, are produced in the arcuate nucleus of the hypothalamus, a prime target of leptin action as well as of NPY production. Synthetic peptides mimicking melanocortins which bind to

MCR-4 suppress feeding. Animals in which the gene encoding MCR-4 has been knocked out show the opposite behavior, exhibiting high weight gain and high NPY expression.

Web site: http://www.delphion.com/details?pn=US06284729__

- **Methods for treating subjects infected with a herpes virus**

Inventor(s): Docherty; John (Kent, OH), Tsai; Chun-che (Kent, OH)

Assignee(s): Kent State University (kent, Oh), Northeastern Ohio Universities College of Medicine (rootstown, Oh)

Patent Number: 6,599,945

Date filed: August 15, 2001

Abstract: The present invention provides a method of inhibiting the formation of infectious herpes virus particles, particularly infectious herpes simplex virus (HSV) particles, in a host cell. The method involves administering an effective amount of a hydroxylated tolan, particularly a polyhydroxylated tolan, to a herpes virus infected host cell. The present invention also provides a method of treating a herpes virus infection, particularly an HSV infection. The method comprises administering a topical composition comprising a therapeutically effective amount of a hydroxylated tolan to a herpes virus-infected site. The present invention also relates to a topical composition for treating a herpes virus infection selected from the group consisting of an HSV infection, a **cytomegalovirus** infection, and a varicella zoster virus infection. The present invention also provides a method of treating a subject infected with *Neisseria gonorrhea*.

Excerpt(s): The present invention relates to compositions which inhibit replication of herpes virus and the bacterium *Neisseria gonorrhoeae*, and methods of using such compositions to treat subjects infected with these microorganisms. Human herpes viruses can infect host cells in virtually any organ of the human body. Replication of a herpes virus within an infected host cell leads to lysis of the infected cell and the release of large numbers of infectious virus. The infectious particles released from the lysed cell can infect and destroy other cells at or near the site of the initial infection. These infectious particles can also be transmitted to a non-infected individual. Human herpes viruses can also enter and remain latent, i.e., in the non-replicative state, in other cells of the afflicted individual for life. This life-long infection serves as a reservoir of infectious virus for recurrent infections in the afflicted individual and as a source of infection for an unwitting contact. At least four of the human herpes viruses, including herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), **cytomegalovirus** (CMV), and varicella zoster virus (VZV) are known to infect and cause lesions in the eye of certain infected individuals. Together, these four viruses are the leading cause of infectious blindness in the developed world.

Web site: http://www.delphion.com/details?pn=US06599945__

- **Nucleic acid respiratory syncytial virus vaccines**

Inventor(s): Ewasysbyn; Mary E. (Willowdale, CA), Klein; Michel H. (Willowdale, CA), Li; Xiaomao (Thornhill, CA), Sambhara; Suryaprakash (Markham, CA)

Assignee(s): Aventis Pasteur Limited (toronto, Ca)

Patent Number: 6,677,127

Date filed: September 13, 1999

Abstract: Vectors containing a nucleotide sequence coding for an F protein of respiratory syncytial virus (RSV) and a promoter for such sequence, preferably a **cytomegalovirus** promoter, are described. Such vectors also may contain a further nucleotide sequence located adjacent to the RSV F protein encoding sequence to enhance the immunoprotective ability of the RSV F protein when expressed in vivo. Such vectors may be used to immunize a host, including a human host, by administration thereto. Such vectors also may be used to produce antibodies for detection of RSV infection in a sample.

Excerpt(s): The present invention is related to the field of Respiratory Syncytial Virus (RSV) vaccines and is particularly concerned with vaccines comprising nucleic acid sequences encoding the fusion (F) protein of RSV. Respiratory syncytial virus (RSV), a negative-strand RNA virus belonging to the Paramyxoviridae family of viruses, is the major viral pathogen responsible for bronchiolitis and pneumonia in infants and young children (ref. 1--Throughout this application, various references are referred to in parenthesis to more fully describe the state of the art to which this invention pertains. Full bibliographic information for each citation is found at the end of the specification, immediately preceding the claims. The disclosures of these references are hereby incorporated by reference into the present disclosure). Acute respiratory tract infections caused by RSV result in approximately 90,000 hospitalizations and 4,500 deaths per year in the United States (ref. 2). Medical care costs due to RSV infection are greater than \$340 M annually in the United States alone (ref. 3). There is currently no licensed vaccine against RSV. The main approaches for developing an RSV vaccine have included inactivated virus, live-attenuated viruses and subunit vaccines. The F protein of RSV is considered to be one of the most important protective antigens of the virus. There is a significant similarity (89% identity) in the amino acid sequences of the F proteins from RSV subgroups A and B (ref. 3) and anti-F antibodies can cross-neutralize viruses of both subgroups as well as protect immunized animals against infection with viruses from both subgroups (ref. 4). Furthermore, the F protein has been identified as a major target for RSV-specific cytotoxic T-lymphocytes in mice and humans (ref. 3 and ref. 5).

Web site: http://www.delphion.com/details?pn=US06677127__

- **Oligonucleotide therapies for modulating the effects of herpesviruses**

Inventor(s): Crooke; Stanley T. (Carlsbad, CA), Draper; Kenneth G. (San Marcos, CA), Ecker; David J. (Carlsbad, CA), Mirabelli; Christopher K. (Encinitas, CA)

Assignee(s): Isis Pharmaceuticals, Inc. (carlsbad, Ca)

Patent Number: 6,310,044

Date filed: April 28, 1992

Abstract: Compositions and methods are provided for the treatment and diagnosis of herpesvirus infections. In accordance with preferred embodiments, oligonucleotides are

provided which are specifically hybridizable with RNA or DNA deriving from a gene corresponding to one of the open reading frames UL5, UL8, UL9, UL13, UL29, UL30, UL39, UL40, UL42 AND UL52 of herpes simplex virus type 1. The oligonucleotide comprises nucleotide units sufficient in identity and number to effect said specific hybridization. In other preferred embodiments, the oligonucleotides are specifically hybridizable with a translation initiation site; it is also preferred that they comprise the sequence CAT. Methods of treating animals suspected of being infected with herpesvirus comprising contacting the animal with an oligonucleotide specifically hybridizable with RNA or DNA deriving from one of the foregoing genes of the herpesvirus are disclosed. Methods for treatment of infections caused by herpes simplex virus type 1, herpes simplex virus type 2, **cytomegalovirus**, human herpes virus 6, Epstein Barr virus or varicella zoster virus are disclosed.

Excerpt(s): This invention relates to therapies and diagnostics for herpesvirus infections. In particular, this invention relates to antisense oligonucleotide interactions with certain portions of herpesvirus RNA which have been found to lead to modulation of the activity of the RNA and, thus, to modulation of the effects of the viruses themselves. Approximately 500,000 new cases of genital herpes are reported each year, and it is estimated that 30 million Americans are affected by this currently incurable disease. Similarly, it is estimated that there is an annual incidence of 500,000 new cases of herpes simplex gingivostomatitis and at least 100 million Americans suffer from recurrent herpes labialis. Overall the prevalence of seropositive individuals in the general population is approximately 70-80%. Although recurrent herpes simplex virus infections are the most prevalent of all herpesvirus infections, there is a need to develop more specific forms of therapy for diseases such as herpes simplex encephalitis, keratoconjunctivitis, herpetic whitlow and disseminated herpes infections of neonates and immunocompromised hosts. The incidence of encephalitis is low (one case in 250,000 individuals per year), yet with existing therapy, the mortality rate is as high as 40% and approximately 50% of the survivors are left with severe neurological sequelae. Ocular infections are neither rare nor trivial. They are usually caused by HSV-1 and are a leading cause of blindness in many countries of the world. Herpetic whitlow is an occupational hazard of nurses, dentists and physicians which begins with erythema and tenderness of the distal segments of the fingers and is followed by coalescence and enlargement of the vesicles. An accompanying lymphangitis and lymphadenopathy of the draining lymphatics is a common feature. Neonatal HSV infection is usually encountered as a consequence of a child being born through an infected birth canal. The incidence of the disease is approximately 1 in 10,000 births. Mortality in babies with limited infection can be as high as 20% while mortality of neonates from disseminated infection, even with current therapy, can approach 75% and many survivors have significant neurological impairment.

Web site: http://www.delphion.com/details?pn=US06310044__

- **Oligonucleotides that can be used in the amplification and detection of CMV nucleic acid**

Inventor(s): Clasina Timmermans; Eveline Catharina Anna (Diessen, NL), Sillekens; Peter Theodorus Gerardus (Gemonde, NL)

Assignee(s): Akzo Nobel N.v. (arnhem, NL)

Patent Number: 6,306,602

Date filed: December 17, 1999

Abstract: The sensitivity and reliability (robustness) of CMV mRNA detection is greatly dependent on the selection of suitable oligonucleotides for amplification, since there is sequence variation among strains of CMV potentially in every region of the genome. The present invention is concerned with oligonucleotides that can be used in the amplification and detection of human **Cytomegalovirus** (HCMV) mRNA. These novel oligonucleotides show an improved sensitivity and robustness of CMV mRNA detection if compared with known sequences when used in amplification and detection. Furthermore a method for the diagnosis of HCMV disease is provided.

Excerpt(s): The present invention is concerned with oligonucleotides that can be used in the amplification detection of human **Cytomegalovirus** (HCMV) mRNA. Furthermore a method for the diagnosis of HCMV disease is provided. Human **Cytomegalovirus** is an ubiquitous Herpes-type virus, having a double stranded DNA genome of about 240,000 nucleotides in length that infects 40-80% of humans before puberty. A prominent feature common to all herpesviruses is their establishment of lifelong persistence after infection and their ability to cause recurrent infection after reactivation (Stevens, J. G. Microbiol. Rev. 53, 318-332., 1989). HCMV also becomes latent after primary infection which often occurs without clinical symptoms. Even recurrent infection in most cases goes asymptomatic or leads to only mild disease in the immunocompetent host. However, in congenitally infected infants and immunocompromised patients, such as allograft recipients (Meyers, J. D., et al., J. Infect. Dis. 153, 478-488., 1986) or AIDS patients (Drew, W. L. J Infect. Dis 158, 449-456., 1988; Drew, W. L. Clin. Infect. Dis 14, 608-615., 1992), where the fine balance between the immune system and the latently existing virus is disturbed, HCMV may cause severe and sometimes life-threatening disease, including retinitis, gastrointestinal disorders, and encephalitis (Drew, 1992). Early administration of antiviral drugs like ganciclovir and foscarnet can have significant beneficial effects on the prognosis of a patient (Jahn, G. et al., Intervirology 35, 60-72., 1993; Schmidt, G. M. et al., N. Engl. J Med. 324, 1005-1011., 1991). Therefore, with the availability of clinically effective antiviral therapy, early and sensitive diagnosis is of significant importance. At the moment, the method of choice for the early diagnosis of acute symptomatic HCMV infection is the antigenemia assay based on immunological detection of the structural protein pp65 by using specific antibodies (Storch, G. A., et al., J. Clin. Microbiol. 32, 997-1003., 1994; Gerna, G. et al., J. Infect. Dis. 164, 488-498., 1991; Gerna, G., et al., J Clin. Microbiol. 30, 1232-1237.98., 1992). However, a matter of concern employing this method is its sensitivity. The number of pp65-positive cells in the early course of infection may be very low. Furthermore, in expressing cells stability of the pp65 antigen appeared to be limited (Chou, S., Curr. Opin. Infect. Dis. 5, 427-432., 1991) and sensitivity can be reduced due to the application of monoclonal antibodies rather than a pool of anti-pp65 antibodies that would recognize different epitopes of the protein.

Web site: http://www.delphion.com/details?pn=US06306602__

- **Phototherapeutic inactivation of ocular viruses**

Inventor(s): Crean; David H. (Santa Barbara, CA), Kupperman; Baruch D. (Laguna Beach, CA)

Assignee(s): Pdt Systems, Inc. (santa Barbara, Ca), The Regents of the University of California (oakland, Ca)

Patent Number: 6,586,419

Date filed: April 16, 1997

Abstract: A method for inactivating ocular viral pathogens and for treating associated lesions on tissue by means of selectively activating a tissue-associated photosensitizing agent with light. The photosensitizing agent, preferably tin ethyl etiopurpurin, is administered to a patient to concentrate within the lesionous target tissue of the eye. The photosensitizer-laden target tissue is irradiated with photoactivating light. In pre-clinical in vitro studies, the photoactivated photosensitizer drug within the lesionous target tissue inactivates both cell free Herpes simplex virus (HSV) and cell-associated HSV and **cytomegalovirus** (CMV). The use of PDT for treating ocular viral diseases reduces the toxicity to the biological system when compared with prior art therapeutic procedures.

Excerpt(s): This invention describes a method for treating ocular viral diseases using photodynamic therapy. In order to give a clinical perspective to the significance of viral ocular infections, for example, **cytomegalovirus** (CMV) retinitis is the most common ocular opportunistic infection and the leading cause of blindness in patients having Acquired Immune Deficiency Syndrome (AIDS) 30,000 new case being each year in the United States alone. CMV related retinitis has been found in 30% of AIDS patients, typically late in their disease processes. The drugs, ganciclovir, and foscarnet, are effective in the treatment of CMV retinitis. With 82%-100% of patients exhibit an initial response to therapy with either drug. All three drugs are virostatic and require daily systemic intravenous administration for the remainder of the patient's life. Such systemic intravenous administration requires the use of an indwelling catheter which has been associated with high rates of infection. In addition all three drugs exhibit various systemic toxicity; with ganciclovir suppressing the bone marrow and both anywhere and foscarnet causing renal toxicity. The use of these compounds for treating ocular retinitis discussed by Kupparmann, et al. in *Ann I Ophthalmol*, 1993; 115:575-582; and by Holland et al. in *Ophthalmol* 1987; 94:815-823, and by Caleri et al in *Ann. Intern. Med.* 1977 126:257-263, A further discussion of the use of these drugs for treating a retinitis of viral etiology is presented by various AIDS research groups in the *New England journal of medicine*, 1992; 326; 213-220. Prior to the advent of antiviral therapy (both anti-CMV and anti-HIV) AIDS patients with CMV retinitis typically survived only 6 weeks after developing the latter infection. In the current setting of anti-HIV therapy and anti-CMV therapy, median survival has recently been shown to be 8.5 months for patients receiving ganciclovir and 12.6 months for patients receiving foscarnet and more recent studies suggest that median survival is now approaching two years. Longer survival has been associated with greater difficulty related to the continuous suppression of the retinitis over this extended period. Recurrence of the retinitis while on therapy has been reported to occur in 50% of patients within 3 months. (Gross, et al. *Ophthalmol.* 1990; 97:681-686.) Because of the high incidence of reactivation following the initial favorable response to therapy, the current measure of anti-CMV drug efficacy is based on the length of time to recurrence in addition to the initial therapeutic response to the drug. The fact that the efficacy of anti-CMV agents is, in part, measured by the agents' ability to prolong the interval for viral reactivation rather than by its ability to effect permanent suppression of viral activity emphasizes the marginal clinical effectiveness of current regimens wherein ganciclovir, acyclovir and foscarnet are administered intravenously. While these three drugs are preventing blindness in most AIDS patients, many patients are still losing their sight. A therapeutic procedure for controlling viral retinitis which reduces systemic toxicity over the current therapies is needed.

Web site: http://www.delphion.com/details?pn=US06586419__

- **Polynucleotide decoys that inhibit MHC-II expression and uses thereof**

Inventor(s): Garovoy; Marvin R. (San Anselmo, CA), Hunt; C. Anthony (San Francisco, CA), Lim; Carol (San Francisco, CA)

Assignee(s): The Regents of the University of California (oakland, Ca)

Patent Number: 6,410,721

Date filed: January 5, 1999

Abstract: The invention is directed to a newly discovered class of polynucleotide decoys that is capable of competitively inhibiting the binding of transcription factors to the X-box sequence. This binding is necessary for the expression of MHC-II genes. The invention is also directed to methods of preparing these polynucleotide decoys, and methods of use thereof. In particular, we have identified a class of polynucleotide decoys that mimic the X-Box of MHC-II and competitively bind the MHC-II transcription factor RF-X, resulting in the modulation of MHC-II antigen expression. Thus, the invention can be used to inhibit the expression of HLA molecules on the surface of donor cells or organs, in order to render them invisible to the host's immune system, or in methods of treating an individual with an autoimmune disease characterized by dysfunctional expression of an MHC class II antigen. Further, because of the role of RF-X in the expression of several viral proteins, the polynucleotide decoys of the invention can be used in methods of treating an individual infected with hepatitis B virus, or **cytomegalovirus**.

Excerpt(s): This invention relates to nucleotide therapeutics, transplantation and immunology. More specifically, it relates to a newly discovered class of polynucleotide decoy molecules and methods for making cells and organs that are less likely to be rejected when transplanted into a recipient host using these polynucleotide decoys, which are capable of binding to a specific gene regulatory factor and reducing the expression of MHC class II transplantation antigens. Among gene products that relate to transplantation antigens are the products of the Human Leukocyte Antigen (HLA) complex, also known as the major histocompatibility complex (MHC), located on the short arm of chromosome 6. The HLA antigens are divided into two classes depending on their structure. The genetic loci denoted HLA-A -B, and -C code for the HLA Class I antigens, and HLA-DP, -DQ and -DR code for the HLA Class II antigens. Regulation of HLA class II antigen expression occurs in part through a series of promoter regions such as the J, W, X (including X.sub.1 and X.sub.2), and Y boxes, and the gamma interferon response element. The X (including X.sub.1 and X.sub.2) and Y boxes are known to be required in the transcriptional regulation of all class II promoters. Ono, S. J. et al., Proc. Natl. Acad. Sci. (USA) (1991) 88:4304-4308.

Web site: http://www.delphion.com/details?pn=US06410721__

- **Recombinant poxvirus--cytomegalovirus compositions and uses**

Inventor(s): Cox; William I. (Troy, NY), Kauffman; Elizabeth K. (Averill Park, NY), Paoletti; Enzo (Delmar, NY), Pincus; Steven E. (East Greenbush, NY)

Assignee(s): Virogenetics Corporation (troy, Ny)

Patent Number: 6,267,965

Date filed: May 26, 1998

Abstract: Attenuated recombinant viruses containing DNA encoding an HCMV antigen, as well as methods and compositions employing the viruses, expression products therefrom, and antibodies generated from the viruses or expression products, are disclosed and claimed. The recombinant viruses can be NYVAC or ALVAC recombinant viruses. The recombinant viruses and gene products therefrom and antibodies generated by the viruses and gene products have several preventive, therapeutic and diagnostic uses. The DNA of the recombinant viruses can be used as probes or for generating PCR primers.

Excerpt(s): The present invention relates to a modified poxvirus and to methods of making and using the same; for instance, a vaccinia virus or avipox (e.g. canarypox or fowlpox), e.g., modified recombinant poxvirus-cytomegalovirus (CMV), e.g. human **cytomegalovirus** (HCMV) such as an attenuated recombinant, especially a NYVAC or ALVAC CMV or HCMV recombinant. More in particular, the invention relates to improved vectors for the insertion and expression of foreign genes for use as safe immunization vehicles to elicit an immune response against CMV or HCMV virus. Thus, the invention relates to a recombinant poxvirus, which virus expresses gene products of CMV or HCMV and to immunogenic compositions which induce an immunological response against CMV or HCMV infections when administered to a host, or in vitro (e.g., ex vivo modalities) as well as to the products of expression of the poxvirus which by themselves are useful for eliciting an immune response e.g., raising antibodies, which antibodies are useful against CMV or HCMV infection, in either seropositive or seronegative individuals, or which expression products or antibodies elicited thereby, isolated from an animal or human or cell culture as the case may be, are useful for preparing a diagnostic kit, test or assay for the detection of the virus, or of infected cells, or, of the expression of the antigens or products in other systems. The isolated expression products are especially useful in kits, tests or assays for detection of antibodies in a system, host, serum or sample, or for generation of antibodies. The poxvirus recombinants preferably contain DNA coding for any or all of CMV or HCMVgB, gH, gL, pp105, pp65 and IE1, including recombinants expressing truncated versions of IE1; and, the recombinant poxvirus DNA is useful for probes for CMV or HCMV or for preparing PCR primers for detecting the presence or absence of CMV or HCMV or antigens thereof. Several publications are referenced in this application. Full citation to these references is found at the end of the specification immediately preceding the claims or where the publication is mentioned; and each of these publications is hereby incorporated herein by reference. Vaccinia virus and more recently other poxviruses have been used for the insertion and expression of foreign genes. The basic technique of inserting foreign genes into live infectious poxvirus involves recombination between pox DNA sequences flanking a foreign genetic element in a donor plasmid and homologous sequences present in the rescuing poxvirus (Piccini et al., 1987).

Web site: http://www.delphion.com/details?pn=US06267965__

- **Ring-expanded nucleosides and nucleotides**

Inventor(s): Hosmane; Ramachandra S. (Columbia, MD), Sood; Ramesh K. (Rockville, MD)

Assignee(s): Nabi (rockville, Md), University of Maryland Baltimore County (baltimore, Md)

Patent Number: 6,677,310

Date filed: April 21, 1999

Abstract: The present invention relates to compositions comprising analogues of purine nucleosides containing a ring-expanded ("fat") heterocyclic ring, in place of purine, and an unmodified or modified sugar residue, pharmaceutically acceptable derivatives of such compositions, as well as methods of use thereof. In particular, these compositions may be utilized in the treatment of certain cancers, bacterial, fungal, parasitic, and viral infections, including, but not limited to, Acquired Immunodeficiency Syndrome (AIDS), hepatitis, Epstein-Barr and **cytomegalovirus**.

Excerpt(s): The present invention relates to compositions comprising analogues of purine nucleosides containing a ring-expanded ("fat" or "REN", used interchangeably) heterocyclic ring, in place of purine, and an unmodified or modified sugar residue, pharmaceutically acceptable derivatives of such compositions, as well as methods of use thereof. In particular, these compositions can be utilized in the treatment of certain cancers, bacterial, fungal, parasitic, and viral infections, including, but not limited to, Acquired Immunodeficiency Syndrome (AIDS) and hepatitis. The concept of the present invention can be extended to include pyrimidine nucleosides and pharmaceutically acceptable derivatives thereof. Acquired Immunodeficiency Syndrome (AIDS) has become the deadliest epidemic of the closing years of the 20th century (Benditt, J., Ed., "AIDS, The Unanswered Questions," Science 260:1253-93 (1993); Mitsuya, et al., Science 249:1533-44 (1990); Fauci, Proc. Natl. Acad. Sci. USA 83:9278 (1986); Chemical and Engineering News Jan. 19, 1987, p. 30, Jan. 26, 1987, p. 18, Jun. 8, 1987, p. 6, Jun. 29, 1987, p. 25; Nov. 23, 1989, pp. 12-70; Jun. 26, 1989, pp. 7-16; and Jul. 5, 1993, pp.20-27). It is caused by a retrovirus called the human immunodeficiency virus (HIV). Retroviruses contain ribonucleic acid (RNA) in their genomes instead of deoxyribonucleic acid (DNA) as is the case with mammals, including humans, and many other bacteria and viruses.

Web site: http://www.delphion.com/details?pn=US06677310__

- **Suppression of cyclin kinase 2 activity for prevention and treatment of DNA viral infections**

Inventor(s): Albrecht; Thomas (Galveston, TX), Bresnahan; Wade (Plainsboro, NJ), Meijer; Laurent (Roscoff, FR), Thompson; Aubrey E. (Dickinson, TX)

Assignee(s): Board of Regents, the University of Texas (austin, Tx)

Patent Number: 6,486,166

Date filed: September 3, 1999

Abstract: An important aspect of the present invention is a method for inhibiting proliferation of a DNA virus dependent upon events associated with cell proliferation for replication. The DNA virus includes any of the herpesvirus family, and most particularly human **cytomegalovirus**. The method involves administering

prophylactically or therapeutically effective amount of a cyclin-dependent kinase inhibitor to a patient or animal.

Excerpt(s): The entire text of the above-referenced disclosure is specifically incorporated by reference herein without disclaimer. The present invention relates generally to the fields of prophylaxis and treatment for viral infections. More particularly, it concerns the use of cyclin dependent kinase inhibitors for blocking replication of any DNA virus dependent on Cdk activity for proliferation, an example being herpesvirus and, more particularly, **cytomegalovirus**. Marek's disease represents a chicken-CMV, equine abortion virus represents a horse variety and cattle have several specific CMV's, to name but a few species-specific CMV's. Human **cytomegalovirus** (HCMV) is a ubiquitous herpesvirus that infects greater than 80% of the human population. HCMV is capable of establishing a life-long infection following primary infection. Reactivation of HCMV often results during pregnancy, perfusion, and in immunocompromised states (Huang and Kowalik, 1993). HCMV rarely causes symptomatic disease in healthy immunocompetent individuals. However, HCMV can result in severe clinical manifestations in congenitally infected newborns and in immunocompromised individuals, such as those undergoing organ transplantation or those infected with HIV (Alford et al., 1990; Schooley, 1990; Rubin, 1990). Most animal species may be infected with species-specific **cytomegalovirus**.

Web site: http://www.delphion.com/details?pn=US06486166__

- **Therapeutic treatment for cytomegalovirus infection**

Inventor(s): Ways; Douglas Kirk (Indianapolis, IN)

Assignee(s): Eli Lilly and Company (Indianapolis, IN)

Patent Number: 6,291,446

Date filed: February 22, 1999

Abstract: A method for treating CMV infection and disease conditions associated therewith is disclosed, particularly using the isozyme selective PKC inhibitor, (S)-3,4-[N,N'-1,1'-((2"-ethoxy)-3'''(O)-4'''-(N,N-dimethylamino)-butane)-bis -(3,3'-indolyl)]-1(H)-pyrrole-2,5-dione hydrochloride salt.

Excerpt(s): The present invention is broadly directed to a method for inhibiting activation of **cytomegalovirus** (CMV), especially reactivation of latent CMV. The present invention is particularly directed to the use of a particular class of isozyme selective Protein Kinase C (PKC) inhibitors for treating CMV infection and disease conditions associated with CMV infection, e.g., CMV mononucleosis and CMV syndromes in immunocompromised hosts. No specific and/or effective therapy is available for CMV infections. Treatment of ongoing CMV syndromes has been largely unsuccessful to date in transplant recipients and in patients with AIDS. Interferons, vidarabine, and acyclovir have failed, whether used alone or in combination. Newer nucleoside derivatives, such as 9-(1,3-dihydroxy-2-propoxymethyl) guanine (DHPG), have shown considerable activity against CMV in vitro. DHPG also shows promise in early clinical trials against CMV retinitis, colitis, and pneumonitis. As one can appreciate, the presently available treatments for CMV infection and syndromes are scarce and not yet completely effective. There remains a need in the art to develop more ways to treat CMV infection and syndromes.

Web site: http://www.delphion.com/details?pn=US06291446__

- **Treatment of cytomegalovirus using aminopeptidase N**

Inventor(s): Giugni; Terrence D. (Alta Loma, CA), Moller; Erna (Morabergsv 14, 13333 Saltsjobaden, SE), Soderberg; Cecilia (Hagersten, SE), Zaia; John A. (Arcadia, CA)

Assignee(s): Moller; Erna (saltsjobaden, Se), Soderberg-nauciler; Cecilia (hagersten, Se)

Patent Number: 6,511,662

Date filed: November 28, 2000

Abstract: A method for the prevention or treatment of human **cytomegalovirus** is described. Aminopeptidases, preferably in soluble form is administered exogenously to the patient. The invention involves the discovery that aminopeptidases are a CMV surface protein involved in post-binding events in the CMV infection process. The invention includes the discovery that AP, including specifically APN, on the surface of the virion and on the surface of the cell is involved in the CMV infection process.

Excerpt(s): This invention relates to the use of aminopeptidases (AP), preferably human aminopeptidase N (APN), for the prevention and treatment of human **cytomegalovirus** (CMV). Human **cytomegalovirus** is responsible for significant morbidity and mortality in the immunocompromised groups, i.e., neonates, organ transplant recipients, AIDS patients (1-3).^{*} Treatment is limited because the early events of CMV infection, involving cell binding and penetration, are largely unknown (4). At least four different cell surface proteins, a 30-34 K protein(s) (5-7), a 92.5 K protein (8), a heparin-binding protein (9), and class I human leukocyte antigen (10), have been suggested as important in virus binding. ^{*} A bibliography precedes the claims.

Web site: http://www.delphion.com/details?pn=US06511662__

- **Vaccine containing whole killed herpes viruses to prevent development of atherosclerotic plaque**

Inventor(s): Chaihorsky; Alexander (Garfield, NJ), Golubev; Daniel (New York, NY)

Assignee(s): Bio-virus Research Incorporated (san Matteo, Ca)

Patent Number: 6,471,965

Date filed: July 27, 1994

Abstract: A vaccine is disclosed for the prophylaxis against pathogenic development of atherosclerotic plaque in a mammalian subject susceptible thereto which consists essentially of a multiplicity of killed whole-virus strains, selected from the group consisting of: Herpes Simplex Virus 1; Herpes Simplex Virus 2; Herpes Simplex Virus 6; Human **Cytomegalovirus**; and Epstein-Barr Virus; in combination with a pharmaceutically acceptable inert vaccine carrier or diluent.

Excerpt(s): This invention relates to a vaccine containing herpes virus for the prevention of atherosclerosis. More particularly the invention relates to a herpes vaccine containing several types of whole killed herpes viruses that affect humans and that acts as a prophylaxis against pathogenic development of atherosclerotic plaque in a mammalian subjected susceptible thereto. It is generally accepted that atherogenesis is triggered by primary injury to the endothelial lining of the arterial walls. This injury is believed to be the result of exposure of the underlying smooth muscle to several factors of non-infectious origin (hormones, low density lipoproteins, growth factors, among others). The prevailing view is that human atherosclerosis (AS) is a pleiotropic process with various causes. See Ross, R., The Pathogenesis of Atherosclerosis: An Update, New

England J. Med., 314, 488 to 500 (1986). A fundamentally new etiological factor: herpes virus infection-was reported by Fabricant et al, who demonstrated that chickens infected with Marek Disease Virus (MDV), have an unusually high incidence of atherosclerotic plaque-(ASP) in the arteries. See Fabricant, C. G. et al, Virus-Induced Cholesterol Crystals, *Science*, 181, 566 to 567 (1973); and Fabricant, C. G. et al, Virus-Induced Atherosclerosis, *J. Exp. Med.*, 148, 335 to 340 (1978). Since that time data have been accumulated suggesting the role of herpes virus in AS in humans. It was shown that different herpes viruses can alter smooth muscle cells lipid metabolism and induce cholesterol and cholesterol ester accumulation in these cells. See Fabricant, C. G. et al, Herpes Virus Infection Enhances Cholesterol and Cholesterol Ester Accumulation in Cultured Arterial Smooth Muscle Cells, *Am. J. Pathol.*, 105, 176 to 184 (1981); Fabricant, C. G. et al, Herpes Virus-Induced Atherosclerosis in Chickens, *Fed. Proc.*, 42, 2476 to 2479 (1983); Melnick, J. L. et al, **Cytomegalovirus** Antigen within Human Arterial Smooth Muscle Cells, *Lancet*, ii, 644 to 647 (1983); Gyorkey, F. et al, Herpesviridae in the Endothelial and Smooth Muscle Cells of Proximal Aorta in Atherosclerotic Patients, *Exp. Mol. Pathol.*, 40, 328 to 339 (1984); Hajjar et al, Virus-Induced Atherosclerosis: Herpes Virus Infection Alters Aortic Cholesterol Metabolism and Accumulation, *Am. J. Pathol.*, 122, 62 to 70 (1986); Adam et al, High Levels of **Cytomegalovirus** Antibody in Patients Requiring Vascular Surgery for Atherosclerosis, *Lancet*, 2, 291 to 293 (1987); Petrie, Association of Herpesvirus/Cytomegalovirus Infections with Human Atherosclerosis, *Prog. Med. Virol.*, 35, 21 to 42 (1988); Grattan, M. T. et al, **Cytomegalovirus** Infection is Associated with Cardiac Allograft Rejection and Atherosclerosis, *J. A. Med. Assoc.*, 261, 3561 to 3566 (1989); Mc Donald, K. et al, Association of Coronary Artery Disease in Cardiac Transplant Recipients with **Cytomegalovirus** Infection, *Am. J. Cardiol.*, 64, 359 to 362 (1989); Visser et al, Granulocyte-Mediated Injury in Herpes Simplex Virus-Infected Human Endothelium, *Lab. Invest.*, 60, 296 to 304 (1989); Melnick, J. L. et al, Possible Role of **Cytomegalovirus** in Atherogenesis, *J. Am. Assoc.*, 263, 2204 to 2207 (1990); Bruggeman, C. A. et al, The Possible Role of **Cytomegalovirus** in Atherogenesis, *Prog. Med. Virol.*, 38, 1 to 26 (1991); Melnick, J. L. et al, Accelerated Graft Atherosclerosis Following Cardiac Transplantation; Do Viruses Play a Role?, *Clin. Cardiol.*, 14 (Supp. II), 21 to 26 (1991); and Hajjar, D. P., Viral Pathogenesis of Atherosclerosis, *Am. J. Pathol.*, 133, 1195 to 1211 (1991).

Web site: http://www.delphion.com/details?pn=US06471965__

Patent Applications on Cytomegalovirus

As of December 2000, U.S. patent applications are open to public viewing.¹⁰ 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 cytomegalovirus:

¹⁰ This has been a common practice outside the United States prior to December 2000.

- **4-hydroxycinnoline-3-carboxyamides as antiviral agents**

Inventor(s): Larsen, Scott D.; (Kalamazoo, MI), Nair, Sajiv K.; (Kalamazoo, MI), Vaillancourt, Valerie A.; (Kalamazoo, MI)

Correspondence: Andrew M. Solomon; Pharmacia & Upjohn Company; Global Intellectual Property; 301 Henrietta Street; Kalamazoo; MI; 49001; US

Patent Application Number: 20020042397

Date filed: March 15, 2001

Abstract: Certain novel 4-hydroxycinnoline-3-carboxyamides. The compounds are particularly effective in the treatment or prevention of viral infections, particularly infections caused by herpes viruses including herpes simplex virus types 1 and 2, human herpes virus types 6, 7 and 8, varicello zoster virus, human **cytomegalovirus** or Epstein-Barr virus.

Excerpt(s): This application claims the benefit of the following provisional application: U.S. Ser. No. 60/190976, filed Mar. 21, 2000. The present invention provides novel cinnolines, which are useful as antiviral agents (e.g. as agents against viruses of the herpes family). The herpesviruses comprise a large family of double stranded DNA viruses. They are also a source of the most common viral illnesses in man. Eight of the herpes viruses, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), human **cytomegalovirus** (HCMV), epstein-Barr virus (EBV), and human herpes viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), have been shown to infect humans.

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

- **Advancing the detection of hearing loss in newborns through parallel genetic analysis**

Inventor(s): Dobrowolski, Steven F.; (Park City, UT), Lin, Zhili; (Pittsburgh, PA)

Correspondence: Mckay & Associates, PC.; 801 Mcneilly Road; Pittsburg; PA; 15226; US

Patent Application Number: 20040038266

Date filed: May 22, 2003

Abstract: A newborn screening method is provided for detecting the causes of hereditary hearing loss. Patient specimen amplicons are synthesized, wherein the amplicon is an oligonucleotide specific to a gene selected from the group consisting of **cytomegalovirus** (CMV), mitochondria, and connexin 26 (Cx26). They are then spotted on a substrate and immobilized as a target for microarray production as wild type and mutated alleles are allowed to hybridize thereto and undergo image analysis.

Excerpt(s): This application hereby claims benefit of provisional application serial No. 60/370,762, having a filing date of May 28, 2002. Profound sensorineural hearing loss affects at least 0.1% of the general newborn population, while an equal number are found to have lesser, but clinically significant degrees of hearing loss. This frequency is far higher than observed in disorders, such as PKU and congenital hypothyroidism, that are routinely screened for in the United States and other countries. It is now clearly established that auditory stimulation in the first six months of life is required to drive the development of normal speech and language. Sensory deprivation, due to hearing impairment, inhibits this development resulting in learning dysfunction, along with impaired social and emotional development. Screening newborns for hearing loss using

auditory methods is generally performed using a two tiered approach. In the first tier, newborns are screened using transient evoked otoacoustic emission (TEOAC). TEOAC measures sounds generated by the hair cells in the cochlea in response to acoustic stimulation. The sounds generated are indicative of the integrity of the inner ear. Those who fail TEOAC are referred for second tier audiometric testing using the more sensitive auditory brainstem response (ABR) assay. ABR is considered the standard for assessment of hearing in neonates and infants by measuring electroencephalographic waveforms in response to clicks. ABR assesses the outer, middle, and inner ear but also lower auditory pathways. The 2-tiered approach (TEOAC followed by ABR) to screening newborns for hearing loss via audiometric means is effective, however major caveats exist that reduce its overall sensitivity and specificity.

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

- **Aminopyridine-containing thiourea inhibitors of herpes viruses**

Inventor(s): Bloom, Jonathan; (Nyack, NY), DiGrandi, Martin; (Piermont, NY), Dushin, Russell; (Garrison, NY), Lang, Stanley; (Carlsbad, CA), O'Hara, Bryan; (Norwood, NJ)

Correspondence: American Home Products Corporation; Patent Law Department; Five Giralda Farms; Madison; NJ; 07940; US

Patent Application Number: 20020026055

Date filed: March 12, 2001

Abstract: Compounds of the formula 1 wherein A is heteroaryl; R.sub.9-R.sub.12 are independently hydrogen, alkyl of 1 to 4 carbon atoms, perhaloalkyl of 1 to 4 carbon atoms, halogen, alkoxy of 1 to 4 carbon atoms, or cyano, or R, and R.sub.10 or R.sub.11 and R.sub.12 may be taken together to form aryl of 5 to 7 carbon atoms; W is O, NR, or is absent; G is aryl or heteroaryl; and X is a bond X is a bond, --NH, alkyl of 1 to 6 carbon atoms, alkenyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, thioalkyl of 1 to 6 carbon atoms, alkylamino of 1 to 6 carbon atoms, or (CH)₂; and J is alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl or benzyl; and n is an integer from 1 to 6; or a pharmaceutical salt thereof, useful in the treatment of diseases associated with herpes viruses including human **cytomegalovirus**, herpes simplex viruses, Epstein-Barr virus, varicella-zoster virus, human herpesviruses-6 and -7, and Kaposi herpesvirus.

Excerpt(s): This application claims the benefit of U.S. Provisional Application Nos. 60/150,698, 60/155,240, 60/155,192, and 60/150,692, and U.S. Application Nos. 09/208,540, 09/208,164, 09/208,561 each of which was filed Dec. 9, 1998. These applications are herein incorporated by reference in their entireties. Eight viruses have been identified which are members of the family Herpesviridae (reviewed in Roizman, B. 1996. Herpesviridae, p. 2221-2230. In B. N. Fields, D. M. Knipe, and P. M. Howley (ed.), Fields Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, Pa.). Each member of this family is characterized by an enveloped virus containing proteinaceous tegument and nucleocapsid, the latter of which houses the viruses' relatively large double-stranded DNA genome (i.e. approximately 80-250 kilobases). Members of the human alphaherpesvirus subfamily are neurotropic and include herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), and varicella-zoster virus (VZV). The human betaherpesviruses are **cytomegalovirus** (HCMV), human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7). The gammaherpesviruses are lymphotropic and include Epstein-Barr virus (EBV) and Kaposi's herpesvirus (HHV-8). Each of these herpesviruses is causally-related to human disease, including herpes labialis and herpes genitalis (HSV-1 and HSV-2 [Whitley, R. J. 1996. Herpes Simplex Viruses, p. 2297-2342. In B. N.

Fields, D. M. Knipe, and P. M. Howley (ed.), Fields Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, Pa.); chicken pox and shingles (VZV [Arvin, A. 1996. Varicella-Zoster Virus, p. 2547-2585. In B. N. Fields, D. M. Knipe, and P. M. Howley (ed.), Fields Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, Pa.]); infectious mononucleosis (EBV [Rickinson, A. B. and Kieff, E. 1996. Epstein-Barr Virus, p. 2397-2446. In B. N. Fields, D. M. Knipe, and P. M. Howley (ed.), Fields Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, Pa.]); pneumonia and retinitis (HCMV [(Britt, W. J., and Alford, C. A. 1996. **Cytomegalovirus**, p. 2493-2523. In B. N. Fields, D. M. Knipe, and P. M. Howley (ed.), Fields Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, Pa.]); exanthem subitum (HHV-6 [(Pellet, P. E, and Black, J. B. 1996. Human Herpesvirus 6, p. 2587-2608. In B. N. Fields, D. M. Knipe, and P. M. Howley (ed.), Fields Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, Pa.] and HHV-7 [Frenkel, N., and Roffman, E. 1996. Human Herpesvirus 7, p. 2609-2622. In B. N. Fields, D. M. Knipe, and P. M. Howley (ed.), Fields Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, Pa.]); and Kaposi's sarcoma (HHV-8 [Neipel, F., Albrecht, J.C., and Fleckenstein, B. 1997. Cell-homologous genes in the Kaposi's sarcoma-associated rhadinovirus human herpesvirus 8: determinants of its pathogenicity? J. Virol. 71:4187-92, 1997]). HCMV is considered in more detail below. Following the primary infection, herpesviruses establish latency within the infected individual and remain there for the remainder of his/her life. Periodic reactivation of latent virus is clinically relevant. In the case of HSV, reactivated virus can be transmitted to infants during birth, causing either skin or eye infection, central nervous system infection, or disseminated infection (i.e. multiple organs or systems). Shingles is the clinical manifestation of VZV reactivation. Treatment of HSV and VZV is generally with antiviral drugs such as acyclovir (Glaxo Wellcome), ganciclovir (Roche) and foscarnet (Asta) which target viral encoded DNA polymerase. HCMV is a ubiquitous opportunistic pathogen infecting 50-90% of the adult population (Britt, W. J., and Alford, C. A. 1996. **Cytomegalovirus**, p. 2493-2523. In B. N. Fields, D. M. Knipe, and P. M. Howley (ed.), Fields Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, Pa.). Primary infection with HCMV is usually asymptomatic, although heterophile negative mononucleosis has been observed. The virus is horizontally transmitted by sexual contact, breast milk, and saliva. Intrauterine transmission of HCMV from the pregnant mother to the fetus occurs and is often the cause of serious clinical consequences. HCMV remains in a latent state within the infected person for the remainder of his/her life. Cell-mediated immunity plays a central role in controlling reactivation from latency. Impaired cellular immunity leads to reactivation of latent HCMV in seropositive persons.

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- **Anticytomegalovirus monoclonal antibodies and processes for the in vitro diagnosis of infections by human cytomegaloviruses and a protein-kinase inducible by cytomegaloviruses and recognisable by aforesaid monoclonal antibodies**

Inventor(s): Amadei, Claire; (Courbevoie, FR), Barzu, Octavian; (Massy, FR), Boue, Andre; (Saint-Cyr L'Ecole, FR), Horaud, Florian; (Meudon, FR), Michelson, Susan; (Noisy Le Roi, FR)

Correspondence: R. Danny Huntington; Burns, Doane, Swecker & Mathis, L.L.P.; P.O. Box 1404; Alexandria; VA; 22313-1404; US

Patent Application Number: 20010039008

Date filed: November 29, 2000

Abstract: The invention relates to a process for in vitro diagnosis of an infection by human **cytomegaloviruses**. The process consists of contacting cells, possibly carrying the infection, with a monoclonal antibody reacting with a polypeptide of molecular weight 68,000, induced by human **cytomegalovirus** and which possesses a protein-kinase activity. The detection of the reaction is preferably carried out by immunofluorescence.

Excerpt(s): The invention relates to human anticytomegalovirus monoclonal antibodies (HCMV) and to a process for the in vitro diagnosis of infections induced by human **cytomegaloviruses**. It relates more particularly to antibodies of this type which are capable of simultaneously detecting human **cytomegaloviruses** (CMV), human cells infected by CMV and a polypeptide, particularly a protein induced by HCMV and having protein-kinase activity. The invention relates also to the aforesaid polypeptide having the aforesaid protein-kinase activity. It is known that CMV is the cause of numerous clinical infections, ranging between benign infectious manifestations, and congenital manifestations, for example, particularly severe malformations.

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

- **Cellular kinases involved in Cytomegalovirus infection and their inhibition**

Inventor(s): Bevec, Dorian; (Germering, DE), Habenberger, Peter; (Munchen, DE), Schubart, Daniel; (Weil am Rhein, DE), Stein-Gerlach, Matthias; (Munchen, DE)

Correspondence: Leon R. Yankwich, ESQ.; Yankwich & Associates; 130 Bishop Allen Drive; Cambridge; MA; 02139; US

Patent Application Number: 20030082519

Date filed: October 16, 2001

Abstract: The role of certain cellular kinases active during Human **Cytomegalovirus** infection is disclosed. These cellular kinases are useful to detect HCMV infection, and can be used to screen for cellular kinase inhibitors. Cellular kinases inhibitors, which effectively downregulate these key cellular components, serve as effective therapeutics against HCMV infection.

Excerpt(s): The present invention is in the fields of molecular biology and virology. The present invention is directed to novel methods for treating **Cytomegalovirus** using kinase inhibitors. Human **Cytomegalovirus** (HCMV) is a highly specific beta-herpesvirus. Primary infection of healthy children and adults is usually asymptomatic, with a minority of cases developing a mononucleose-like syndrome. In contrast, congenital infection (U.S. 0.2%-2.2% per live birth; aprox. 40,000 per year) leads to several neurological defects in 10-15% of infected neonates. Immunocompromised patients represent another host group facing serious disease complications caused by HCMV infection or reactivation of a persistent infection. Up to 40% of the AIDS patients, for example, develop retinitis, pneumonitis, gastroenteritis or disseminated HCMV disease. In addition, allograft recipients (20,000 allograft transplantations per year in the U.S.) are often infected (or superinfected) by virus from the transplanted organ. Clinical symptoms in the posttransplant period include prolonged fever, leukopenia, thrombocytopenia, atypical lymphocytosis, elevated hepatic transaminases and decreased graft survival. In bone marrow transplantations, HCMV infection is associated with high mortality rates (80-90% for untreated HCMV pneumonia).

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- **COMPOSITIONS AND METHODS FOR THE TREATMENT OF HUMAN CYTOMEGALOVIRUS INFECTION**

Inventor(s): BARBOSA, MIGUEL S.; (SAN DIEGO, CA), WU, JUN; (SAN DIEGO, CA)

Correspondence: Pennie & Edmonds LLP; 1155 Avenue OF The Americas; New York, N.Y.; NY; 10036; US

Patent Application Number: 20020010143

Date filed: May 6, 1999

Abstract: Compositions and methods are provided for identifying proteins and other agents that modulate transactivation of HCMV early genes. In particular, agents that inhibit the cell-type specific transactivation of HCMV DNA polymerase are provided. Such agents may be used, for example, in the treatment of patients infected with HCMV.

Excerpt(s): This application is a continuation-in-part of U.S. patent application Ser. No. 08/720,543, filed Sep. 30, 1996. The present invention relates generally to human **cytomegalovirus** infection. The invention is more particularly related to the identification of proteins and other agents that modulate gene expression necessary for HCMV replication and to the use of such agents in antiviral therapies. Human **cytomegalovirus** (HCMV) is a ubiquitous member of the herpesvirus family that can induce a wide range of diseases, typically in newborns and immunocompromised adults. Nearly one percent of all live births in the United States are associated with congenital HCMV infection, with approximately 5 to 10 percent of infections resulting in significant neurological defects. In bone marrow transplant recipients, mortality due to HCMV pneumonia can be as high as forty percent. In addition, disseminated HCMV infection is common in AIDS patients and is frequently associated with conditions such as gastroenteritis and sight-threatening chorioretinitis.

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- **CYTOKINE RESISTANT CYTOMEGALOVIRUS PROMOTER MUTANTS AND RELATED PRODUCTS AND METHODS**

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Patent Application Number: 20020106635

Date filed: May 26, 1999

Abstract: The present invention relates generally to gene expression and regulation, and more particularly to cytokine resistant **cytomegalovirus** promoter mutants useful in gene therapy.

Excerpt(s): The following discussion of the background of the invention is merely provided to aid the reader in understanding the invention and is not admitted to describe or constitute prior art to the present invention. The use of strong constitutive viral promoters, such as the CMV immediate early (i.e.,) promoter, have been widely used in mammalian gene expression vectors for gene therapy. A major limitation of current plasmids used for in vivo transfections is short-term low level transgene expression. Several studies have demonstrated that the in vivo administration of DNA from bacterial and viral origin, which is commonly found in gene therapy expression vectors, stimulates the immune response to produce a variety of cytokines including

IFN.γ, TNF.α and IL-12, Pisetsky, D. S., et al., Ann. N. Y. Acad. Sci. 772:152, 1995; Klinman, D., G. et al., J. Immunol. 158:3635, 1997; Raz, E., et al., Proc. Natl. Acad. Sci. U. S. A. 93:5141, 1996; Ghazizadeh, S., et al., J. Virology 71:9163, 1997.

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

- **Expression monitoring for human cytomegalovirus (HCMV) infection**

Inventor(s): Gingeras, Thomas R.; (Encinitas, CA), Shenk, Thomas; (Princeton, NJ), Zhu, Hua; (Newark, NJ)

Correspondence: Banner & Witcoff; 1001 G Street N W; Suite 1100; Washington; DC; 20001; US

Patent Application Number: 20040014027

Date filed: September 12, 2001

Abstract: Certain human genes have been found to be induced or repressed in host cells infected with HCMV. A large set of such genes has been identified. These have diagnostic use in determining the extent of tissue damage caused by the infection as well as in determining the stage of disease progression of the HCMV infection. Such genes are likely those involved in mediating the pathology of the infected tissues. Thus by identifying agents which are able to reverse the induction or repression of such genes, one can find candidate therapeutic agents for use in treating and or preventing HCMV-caused disease pathologies.

Excerpt(s): Many biological functions are accomplished by altering the expression of various genes through transcriptional (e.g. through control of initiation, provision of RNA precursors, RNA processing, etc.) and/or translational control. For example, fundamental biological processes such as cell cycle, cell differentiation and cell death, are often characterized by the variations in the expression levels of groups of genes. Gene expression is also associated with pathogenesis. For example, the lack of sufficient expression of functional tumor suppressor genes and/or the over expression of oncogene/protooncogenes could lead to tumorigenesis (Marshall, Cell, 64: 313-326 (1991); Weinberg, Science, 254: 1138-1146 (1991), incorporated herein by reference for all purposes). Thus, changes in the expression levels of particular genes (e.g. oncogenes or tumor suppressors) serve as signposts for the presence and progression of various diseases. The study of gene expression in the art has been generally concentrated on the regulatory regions of the gene of interest and on the relationships among a few genes. A number of transcriptional factors/DNA binding proteins have been identified and a limited number of regulatory pathways have been discovered. However, the expression of a particular gene is frequently regulated by the expression of a large number of other genes. The expression of those regulatory genes may also be under the control of additional genes. This complex regulatory relationship among genes constitutes a genetic network. The function and regulation of a particular gene can be best understood in the context of this genetic network. As the Human Genome Project and commercial genome research progress at a great rate, most, if not all, of the expressed genes will be partially sequenced in the near future. Understanding the functions and regulatory relationships among the large number of genes is becoming a difficult task with traditional tools. Therefore, there is a need in the art to develop a systematic approach to understand the complex regulatory relationships among large numbers of genes.

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- **Expression vectors containing hybrid ubiquitin promoters**

Inventor(s): Yew, Nelson; (West Upton, MA)

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Patent Application Number: 20020090719

Date filed: September 13, 2001

Abstract: Sustained transgene expression will be required for the vast majority of genetic diseases being considered for gene therapy. The initially high levels of expression attained with plasmid DNA (pDNA) vectors containing viral promoters, such as that from **cytomegalovirus** (CMV), decline precipitously to near background levels within 2 to 3 weeks. We have constructed pDNA vectors containing the human cellular ubiquitin B (Ub) promoter and evaluated their expression in the mouse lung. Cationic lipid-pDNA complexes were instilled intranasally (IN) or injected intravenously (IV) into immunodeficient BALB/c mice. Chloramphenicol acetyltransferase (CAT) reporter gene expression from the Ub promoter was initially very low at day 2 post-administration but by day 35 exceeded the level of expression attained from a CMV promoter vector by 4- to 9-fold. Appending a portion of the CMV enhancer 5' of the Ub promoter (CMV-Ub) increased CAT expression to nearly that of the CMV promoter and expression persisted in the lung for at least three months, with 50% of day 2 levels remaining at day 84. In the liver, expression from the CMV-Ub hybrid promoter was sustained for 42 days. Since previous studies have shown that eliminating immunostimulatory CpG motifs in pDNA vectors reduces their toxicity, we constructed a CpG deficient version of the CMV-Ub vector expressing alpha-galactosidase A, the enzyme that is deficient in Fabry disease, a lysosomal storage disorder. After IN or IV administration, levels of alpha-galactosidase A from this vector were not only undiminished but increased 500% to 1500% by day 35. These results suggest that CpG-reduced plasmid vectors containing a CMV-Ub hybrid promoter may provide the long-term expression and efficacy required for a practical gene therapeutic.

Excerpt(s): The present invention relates to expression vectors that contain hybrid ubiquitin promoters. The promoters are useful, among other uses, for high and sustained transgene expression in in vivo and ex vivo gene therapy and for recombinant protein expression in vitro. Ubiquitin is an abundant, small, 76 amino acid protein that is expressed in all eukaryotic cells (Ciechanover et al. 2000; Wilkinson et al, 2000). The protein covalently attaches to abnormal, misfolded or short-lived proteins, marking them for destruction in proteasomes (Ciechanover, supra). Ubiquitin also associates with histones and may play a role in the regulation of gene expression (Spencer and Davie, 1999). The coding sequence is remarkably conserved evolutionarily, being identical from insect to man. There are at least three known ubiquitin genes in humans, named UbA, UbB, and UbC, which appear to contain one, three or nine precise direct repeats of the 76 amino acid coding unit, respectively (Baker and Board, Nucleic Acids Research, 15:443-463 (1987); Lund et al. 1985; Neno, et al 1996; and Wiborg et al., EMBO J., 4:755-759 (1985). The human UbB and UbC genes have been sequenced and shown to contain no introns within their coding regions, but each contain an intron in the 5' flanking region (Baker and Board, supra; Neno supra). The UbC promoter has been shown to provide high level, ubiquitous expression when inserted into transgenic mice and when incorporated into plasmid DNA vectors (Johansen et al., FEBS 267:289-294 (1990); Schorpp et al., Nucleic Acids Research, 24:1787-1788 (1996); Wulff et al., 1990). The promoter from human **cytomegalovirus** (CMV) (see U.S. Pat. Nos. 5,849,522; 5,168,062) is known to provide strong constitutive expression of transgenes at high

levels. However, in gene therapy applications, expression levels achieved using the CMV promoter have been shown to be significantly reduced over time.

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- **FUSION PROTEIN COMPRISING THE WHOLE OR PART OF THE PP65 PROTEIN OF HUMAN CMV, USEABLE IN PARTICULAR FOR PREPARING A VACCINE**

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Patent Application Number: 20020156251

Date filed: July 6, 1999

Abstract: The invention concerns a fusion protein characterised in that it comprises at least part of the pp65 protein of the **cytomegalovirus** (or CMV), or a protein having at least 80% homology with the pp65 protein, in combination with at least a second peptide fragment derived from CMV. The invention also concerns a nucleotide sequence coding for such a protein, or a pharmaceutical composition containing them. It further concerns its use as medicine and a method for preparing the protein.

Excerpt(s): The present invention relates to novel combinations of proteins and to their use as medicament. More particularly, it relates to the preparation of vaccines against CMV. Human **cytomegalovirus** (CMV), an enveloped virus with a 230 kbp DNA double strand, is the largest virus of the herpesvirus family. Like the other members of this virus family, it exists in latent form and can undergo repeated reactivation steps which lead to a viremia several years after the initial infection. CMV is widely distributed throughout the world and, while being well tolerated by healthy individuals, it is associated with pathologies which frequently have drastic consequences for the fetus and for immuno-depressed patients (transplant, AIDS and cancer patients) (see Review (1)). Following a primary infection during pregnancy, the vertical transmission of the virus to the fetus via the placenta leads to complications in the newborn. These are, in particular, sensorial disorders (vision, hearing) and significant mental backwardness which arise during the first few years of the child's life. Infection with CMV is associated with graft rejection in transplant patients (foreign transplants of marrow, kidneys, heart, liver). It constitutes one of the most drastic opportunistic infections in HIV+ patients which, despite antiviral chemotherapy, fall victim to--frequently lethal--pathologies. All these reasons mean that CMV infection raises a substantial public health problem.

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- **HCMV-reactive T cells and uses therefor**

Inventor(s): Diamond, Don J.; (Glendora, CA)

Correspondence: Rothwell, Figg, Ernst & Manbeck, P.C.; 1425 K Street, N.W.; Suite 800; Washington; DC; 20005; US

Patent Application Number: 20030118602

Date filed: September 11, 2002

Abstract: The invention provides a plurality of peptides (and immunologically functional variants thereof) which are immunogenic epitopes recognized by CD8.sup.+ class I MHC restricted cytotoxic T-lymphocytes of patients harboring latent human **cytomegalovirus** (HCMV) infection. The peptides are capable of activating CTLs and CTLps in the absence of active viral replication, and thus are useful for eliciting a cellular immune response against HCMV by normal and immunodeficient subjects. Peptide and lipopeptide vaccines, with and without adjuvants, also are disclosed. Cellular vaccines comprising the peptides form a further embodiment of this invention.

Excerpt(s): This application is a continuation-in-part of prior copending application Ser. No. 09/534,639, filed Mar. 27, 2000, which is a divisional of Ser. No. 09/075,257, filed May 11, 1998 (U.S. Pat. No. 6,074,645), which is a continuation-in-part of co-pending application Ser. No. 09/021,298, filed Feb. 10, 1998, which is a continuation-in-part of application Ser. No. 08/950,064, filed Oct. 14, 1997, now abandoned, which is a continuation-in-part of application Ser. No. 08/747,488, filed Nov. 12, 1996, now abandoned. This invention relates to human **cytomegalovirus** (HCMV), and in particular to peptide fragments from one or more subunit proteins that function as T-cell epitopes of HCMV in human beings. The peptides of this invention are capable of directing human cytotoxic T lymphocytes (CTL) to recognize and lyse human cells equivalently to infection with HCMV. Vaccines formulated using those peptides also are provided by this invention. The HCMV genome is relatively large (about 235k base pairs) and has the capacity to encode more than two hundred proteins. HCMV is composed of a nuclear complex of double-stranded DNA surrounded by capsid proteins having structural or enzymatic functions, and an external glycopeptide- and glycolipid-containing membrane envelope. HCMV is a member of the herpes virus family and has been associated with a number of clinical syndromes.

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• **HSV VIRAL VECTOR**

Inventor(s): ECOB-PRINCE, MARION S.; (NEWCASTLE-UPON-TYNE, GB), PRESTON, CHRISTOPHER; (GLASGOW, GB)

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Patent Application Number: 20020028925

Date filed: January 28, 1997

Abstract: The present invention relates to a recombinant herpes simplex virus (HSV) viral vector genome which has substantially lost its transducing properties as a result of a DNA sequence change in the gene coding for Vmw65 protein and also comprises an expressible heterologous gene inserted into a region of the HSV genome which is non-essential for the culture of the virus, the gene being under the control of the immediate early (IE1) gene enhancer of **cytomegalovirus** (CMV) and to the use of the recombinant HSV genome in therapy and vaccination.

Excerpt(s): The present invention relates to a recombinant herpes simplex virus (HSV), especially type 1 (HSV-1) or type 2 (HSV-2) having a good ability to continuously express an inserted heterologous gene whilst the virus is at the same time maintained in its latent non-replicative state. A distinguishing feature of herpes virus infections is the ability to persist in the host for long periods in a non-replicative or latent state. Herpes simplex virus type 1 (HSV-1) establishes latent infection in human peripheral sensory

ganglia and can reactivate to produce recurrent mucocutaneous lesions. Operationally, the pathogenesis of herpes virus infections can be divided into several distinct stages which can be studied individually in experimental animal models: acute viral replication, establishment of latency, maintenance, and reactivation. Following inoculation, HSV-1 replicates at the site of inoculation and is transported to sensory ganglia. Replication at the periphery or in sensory ganglia may increase the amount of virus that can establish latent infection. During latent infection, HSV-1 DNA can be detected in infected tissues but infectious virus cannot be detected. This latent state is often maintained for the life of the host. A variety of stimulæ (such as fibrile illness and exposure to ultraviolet irradiation) can interrupt the latent state and cause the reappearance of infectious virus or reactivation. Transcription of the HSV-1 immediate early (IE) genes is not detectable during latency. However, in tissue culture, IE gene expression is a pre-requisite for viral replication. Transcription of the IE genes is transinduced by a virion protein Vmw65 (transinducing factor) that is a component of the HSV-1 virion. Vmw65 does not bind directly to HSV-1 DNA but mediates transinduction by association with cellular proteins to form a complex which interacts with the IE regulatory element.

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- **Human cytomegalovirus DNA constructs and uses therefor**

Inventor(s): Girerd, Yves; (Francheville, FR), Gonczol, Eva; (Rosemont, PA), Haensler, Jean; (Saint Genis les Ollieres, FR), Kari, Csaba; (Rosemont, PA), Berencsi, Klara; (Rosemont, PA)

Correspondence: Mary E. Bak; Howson And Howson; Spring House Corporate Center, Box 457; Spring House; PA; 19477; US

Patent Application Number: 20030120060

Date filed: August 19, 2002

Abstract: Novel DNA molecules for in vitro and in vivo expression of HCMV gB, gB transmembrane-deleted derivatives, pp65, pp150, and IE-exon-4 proteins are described. Preferably, the molecules are plasmids. Also described are methods of using these DNA molecules to induce immune responses to HCMV, and the use of a plasmid of the invention to prime immune responses to HCMV vaccines.

Excerpt(s): This application is a divisional of U.S. patent application Ser. No. 09/171,699, filed Jan. 19, 1999, which is a.sctn.371 of International Patent Application No. PCT/US97/06866, filed Apr. 22, 1997, which claims the benefit of the priority of U.S. Provisional Patent Application No. 60,015,717, filed Apr. 23, 1996. Cytomegalovirus (CMV) is one of a group of highly host specific herpes viruses that produce unique large cells bearing intranuclear inclusions. The envelope of the human **cytomegalovirus** (HCMV) is characterized by a major glycoprotein complex termed gB or gCI, which was previously referred to as gA. Infection with HCMV is common and usually asymptomatic. However, the incidence and spectrum of disease in newborns and immunocompromised hosts establishes this virus as an important human pathogen. HCMV has also been suggested to be an important co-factor in the development of atherosclerosis and restenosis after angioplastic surgery.

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- **Human cytomegalovirus glycoprotein O as a new drug target and subunit vaccine candidate**

Inventor(s): Compton, Teresa; (Madison, WI), Huber, Mary T.; (Portland, OR)

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Patent Application Number: 20040013682

Date filed: June 26, 2002

Abstract: A method of designing a new anti-CMV drug is disclosed. In one embodiment, the invention comprises (a) analyzing the binding of glycoprotein O to a glycoprotein O receptor and (b) designing a candidate drug that would competitively interfere with glycoprotein O binding to glycoprotein O receptor and (c) showing that the candidate drug competitively inhibits glycoprotein O binding to glycoprotein O receptor. A method of screening anti-CMV drugs, a vaccine effective to diminish CMV infection, and a method of diminishing CMV infection are also disclosed.

Excerpt(s): This application claims priority to U.S. provisional application Serial No. 60/146,180, filed Jul. 29, 1999. Serial No. 60/146,180 is incorporated by reference herein. For viruses such as the herpes viruses, which contain a cell-derived lipid envelope, the virally-encoded envelope proteins are the primary determinants of tissue tropism and the mediators of virus entry, cell to cell spread and maturation of virus particles. Human **cytomegalovirus** (CMV), a member of the Herpesviridae family, is a significant opportunistic pathogen responsible for serious clinical consequences in a variety of immunosuppressed patient groups such as neonate and infants, persons with AIDS and individuals undergoing immunosuppressive regimes for the purpose of organ or bone marrow transplantation. As is true for other human herpes viruses, CMV establishes a life-long latent infection with its human host and is ubiquitous in the population with upwards of 75% infectivity rate found in the United States. At present there is no protective vaccine. Currently available antiviral drugs which target viral DNA replication are efficacious but exhibit significant host toxicity and a high spontaneous resistance rate. Thus, there is a tremendous need to identify alternative drug targets and immunogens that elicit protective immunity. In one embodiment, the present invention is a method of designing a new anti-CMV drug comprising (a) analyzing the binding of glycoprotein O to a glycoprotein O receptor and (b) designing a candidate drug that would competitively interfere with glycoprotein O binding to glycoprotein O receptor and (c) showing that the candidate drug competitively inhibits glycoprotein O binding to glycoprotein O receptor.

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- **Human tissue urokinase type plasminogen activator production**

Inventor(s): Hung, Paul Porwen; (Bryn Mawr, PA), Wu, Bryan T. H.; (Taipei, TW)

Correspondence: Fish & Richardson PC; 225 Franklin ST; Boston; MA; 02110; US

Patent Application Number: 20040002137

Date filed: March 27, 2003

Abstract: This invention features a nucleic acid expression vector that includes a bicistronic coding unit that comprises a first segment that encodes a human tissue urokinase plasminogen activator protein and a second segment that encodes an

amplifiable dominant selectable marker (e.g., dihydrofolate reductase); and a promoter (e.g., a **cytomegalovirus** promoter) operably linked to the bicistronic coding unit.

Excerpt(s): This application claims priority to U.S. Provisional Application Serial No. 60/371,013 filed Apr. 9, 2002, the contents of which are incorporated herein by reference. Plasminogen activators are a class of serine proteases that convert plasminogen into plasmin. Plasmin degrades the fibrin matrix of blood clots, thereby restoring the hemodynamic condition of an open vascular system after an internal vascular accident has produced thrombosis or thromboembolism. Vascular disease states, which involve partial or total blockage of blood vessels and are amenable to treatment with plasminogen activators, include stroke, pulmonary embolism, myocardial infarction, as well as deep vein and peripheral artery obstructions. There are two immunologically distinct types of plasminogen activators found in human plasma and other body fluids: the urokinase-type plasminogen activator (UPA; Mr, 55,000) and the tissue-type plasminogen activator (TPA; Mr, 68,000). The activity of the tissue-type plasminogen activator is potentiated by fibrin. This enzyme acts at the site of a thrombus and demonstrates a higher affinity for fibrin than does the urokinase-type plasminogen activator (Haylaeris et al. (1982) J. Biol. Chem. 257: 2912). In fact, a recombinant form of the tissue-type plasminogen activator, brought to market by Genentech (European Patent No. 93,619), has been in use for medicine for many years. But this recombinant form is short-lived (half life.apprxeq.4 min) in plasma. Although a second generation of the recombinant tissue-type plasminogen activator has been engineered, it still falls short of the need for new generation of the tissue-type plasminogen activator with a longer half life.

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

- **Hybrid vector having a cytomegalovirus enhancer and myeloproliferative sarcoma virus promoter**

Inventor(s): Moore, Margaret Dow; (Seattle, WA)

Correspondence: Michelle L. Johnson; Zymogenetics, INC.; 1201 Eastlake Avenue East; Seattle; WA; 98102; US

Patent Application Number: 20030232414

Date filed: June 18, 2003

Abstract: An expression vector capable of expressing high levels of heterologous proteins having a **cytomegalovirus** (CMV) enhancer 5' upstream from a myeloproliferative sarcoma virus (MPSV) promoter.

Excerpt(s): This application claims the benefit under 35 U.S.C. 119(e) of provisional application No. 60/389,612, filed Jun. 18, 2002. The present invention is related to the construction and utilization of a DNA plasmid vector, in particular, those hybrid non-retroviral vectors that comprise the **cytomegalovirus** (CMV) enhancer and the myeloproliferative sarcoma virus (MPSV) promoter minus its negative control region. This hybrid sequence promotes the high expression of cloned genes under its transcriptional control when the vector is transfected into mammalian cell lines. Preferably, the vector also comprises other functional sequences to increase expression of the cloned sequence such as the Ig intron sequence, a viral internal ribosome entry site (IRES), a leader sequence to allow for secreted protein expression, and polyadenylation signals. The vector can also comprise selectable markers and other features that facilitate the replication of the vector in mammalian, yeast, and prokaryotic

host cells, thus increasing the stability of the vector in whatever expression system is being used. The expression of foreign proteins by bacteria, yeast or mammalian cell lines has become routine. One type of commonly used means involves the construction of virion-plasmid hybrid vectors that possess the capacity to express cloned inserts in mammalian cells. The expression of the cloned gene with such hybrid vectors can occur in a transient, extrachromosomal manner, but higher production is usually obtained through random insertion of the vector into the host cell genome. The typical mammalian expression vector will contain regulatory elements, usually in the form of viral promoter or enhancer sequences and characterized by a broad host and tissue range, a polylinker sequence facilitating the insertion of a DNA fragment within the plasmid vector, and the sequences responsible for intron splicing and polyadenylation of mRNA transcripts. This contiguous region of promoter-polylinker-polyadenylation site is commonly referred to as the transcription unit. Viral promoter and enhancer regions have long been utilized as regulatory elements for use in mammalian host cells. For example, the strength of the CMV enhancer caused it to be a suggested component in eukaryotic expression vectors upon its discovery (Boshart et al., *Cell*, 41 (2):521-30 (1985)) and it has been utilized as a universal cell control element in transgenic mice (Schmidt et al. *Mol. Cell. Biol.* 10: 4406-4411 (1990)). The MPSV promoter conveys a wide host cell specificity to the virus including fibroblasts and hematopoietic stem cells (Stocking et al. *Proc. Natl. Acad. Sci. USA*, 82: 5746-5750 (1985)). Accordingly, this promoter has been used to express heterologous genes in a number of cell types, including skin fibroblasts (Pamer et al., *Blood*, 73: 438-445 (1989), primary hepatocytes (Ponder et al., *Hum. Gene Ther.* 2:41-52 (1991), and rodent cells lines and human fibroblast cell lines (van den Wollenberg, *Gene* 144: 237-241 (1994)).

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

- **Immunologic activities of rhesus cytomegalovirus encoded IL-10 and human cytomegalovirus encoded IL-10**

Inventor(s): Penfold, Mark; (Mountain View, CA), Schall, Thomas J.; (Menlo Park, CA), Spencer, Juliet; (Foster City, CA)

Correspondence: Townsend And Townsend And Crew, LLP; Two Embarcadero Center; Eighth Floor; San Francisco; CA; 94111-3834; US

Patent Application Number: 20020197234

Date filed: July 30, 2001

Abstract: The present invention is provides pharmaceutical compositions and prophylactic and therapeutic methods of treatment for immune disorders using rhesus or human CMV IL-10. The invention is useful for inhibiting lymphocyte proliferation and underlying cellular events both in vitro and in vivo.

Excerpt(s): This application is a nonprovisional of U.S. application No. 60/221,831, filed Jul. 28, 2000, which is incorporated herein by reference in its entirety for all purposes. Cytomegaloviruses (CMVs) are members of the beta subgroup of the herpesvirus family. CMV is a slow replicating, species-specific complex DNA virus found in most mammals. The CMV phenotype is distinguished by slow replication in a limited number of cell types and a typical cytopathology. Human CMV has a 230-kb double stranded DNA genome encoding at least 200 open reading frames (ORFs), giving CMV the highest potential coding capacity within the herpesvirus family. A viral IL-10-like protein encoded by ORF UL111A has been identified within the human CMV genome. The ORF corresponding to the UL111A ORF of human CMV has been identified in

rhesus CMV genome and encodes for a viral IL-10-like protein. The term "allergen" means noninfectious antigens that induce hypersensitivity reactions, most commonly IgE-mediated type I reaction.

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

- **Invasion assays**

Inventor(s): Brow, Mary Ann D.; (Madison, WI), Hall, Jeff G.; (Madison, WI), Lyamichev, Victor I.; (Madison, WI), Mast, Andrea L.; (Madison, WI)

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Patent Application Number: 20020187486

Date filed: November 2, 2001

Abstract: The present invention relates to means for the detection and characterization of nucleic acid sequences, as well as variations in nucleic acid sequences. The present invention also relates to methods for forming a nucleic acid cleavage structure on a target sequence and cleaving the nucleic acid cleavage structure in a site-specific manner. The structure-specific nuclease activity of a variety of enzymes is used to cleave the target-dependent cleavage structure, thereby indicating the presence of specific nucleic acid sequences or specific variations thereof. The present invention further relates to methods and devices for the separation of nucleic acid molecules based on charge. The present invention also provides methods for the detection of non-target cleavage products via the formation of a complete and activated protein binding region. The invention further provides sensitive and specific methods for the detection of human **cytomegalovirus** nucleic acid in a sample.

Excerpt(s): The present invention relates to means for the detection and characterization of nucleic acid sequences and variations in nucleic acid sequences. The present invention relates to methods for forming a nucleic acid cleavage structure on a target sequence and cleaving the nucleic acid cleavage structure in a site-specific manner. The 5' nuclease activity of a variety of enzymes is used to cleave the target-dependent cleavage structure, thereby indicating the presence of specific nucleic acid sequences or specific variations thereof. The present invention further provides novel methods and devices for the separation of nucleic acid molecules based by charge. The present invention further provides methods for the detection of non-target cleavage products via the formation of a complete and activated protein binding region. The detection and characterization of specific nucleic acid sequences and sequence variations has been utilized to detect the presence of viral or bacterial nucleic acid sequences indicative of an infection, the presence of variants or alleles of mammalian genes associated with disease and cancers and the identification of the source of nucleic acids found in forensic samples, as well as in paternity determinations. Various methods are known to the art which may be used to detect and characterize specific nucleic acid sequences and sequence variants. Nonetheless, as nucleic acid sequence data of the human genome, as well as the genomes of pathogenic organisms accumulates, the demand for fast, reliable, cost-effective and user-friendly tests for the detection of specific nucleic acid sequences continues to grow. Importantly, these tests must be able to create a detectable signal from samples which contain very few copies of the sequence of interest. The following discussion examines two levels of nucleic acid detection assays currently in use: I. Signal Amplification Technology for detection of rare sequences; and II. Direct Detection Technology for quantitative detection of sequences.

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

- **Method and device for the rapid clinical diagnosis of human cytomegalovirus (hCMV) infection in biological samples**

Inventor(s): Kondiboyina, Venkata Ramana; (Mumbai, IN), Sharma, Vijay; (Mumbai, IN)

Correspondence: Lackenbach Siegel; One Chase Road; Scarsdale; NY; 10583; US

Patent Application Number: 20030104354

Date filed: November 30, 2001

Abstract: The present invention is a method and kit for rapid clinical diagnosis of hCMV in which the amplimers are transcripts of a glycoprotein B neutralization-related epitope gene of hCMV. The amplicons are hybridized to a specific oligonucleotide probe, which allows the amplicons to be detected.

Excerpt(s): The present invention relates to methods and devices for the diagnosis of infections. In particular, the present invention relates to methods and kits for detection of Human **Cytomegalovirus** Veremia (hCMV). Human **Cytomegalovirus** (hCMV) is a significant pathogen in immuno-compromised patients. hCMV is a member of beta-herpesvirinae, a subfamily of the herpesvirinae, which includes herpes simplex virus type I and II, varicella-zoster virus (the virus that causes chicken pox), and Epstein-Barr virus (the virus that causes mononucleosis). These viruses share a characteristic ability to remain dormant within the body over a long period of time. The initial infection, which is usually without symptoms, is always followed by a prolonged infection, during which the virus resides in cells without causing detectable damage or biochemical illness. Although the factors controlling latency and re-activation are not completely understood, impairment of the body's immune system by medication or disease can consistently re-activate the virus. hCMV is a DNA virus and is approximately 200 nm in diameter. hCMV infection is usually subclinical in the healthy host. However, hCMV infection in a immuno-compromised host or a developing fetus may result in localized and/or disseminated disease. Clinical manifestations of hCMV include pneumonia, retinitis, hepatitis, enteritis, and neurological disease. Despite improved treatment modalities, hCMV infection may result in significant morbidity and mortality in transplant patients, AIDS patients, and cancer patients, particularly those with leukemia or lymphoma. Patients are at risk from both primary hCMV infection and reactivation of latent infection.

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

- **Method for the treatment or prevention of viral infection using nucleoside analogues**

Inventor(s): Bedard, Jean; (Quebec, CA), Giles, Francis J.; (Houston, TX), Rando, Robert F.; (Annandale, NJ)

Correspondence: Millen, White, Zelano & Branigan, PC; 2200 Clarendon Blvd; Suite 1400; Arlington; VA; 22201; US

Patent Application Number: 20040014757

Date filed: March 31, 2003

Abstract: The present invention relates to uses and methods for treating or preventing a viral infection selected from the group consisting of herpes simple virus, varicella zoster

virus, respiratory syncytial virus and **cytomegalovirus** in a host comprising using a therapeutically effective amount of a compound having the formula I or a pharmaceutically acceptable salt thereof. The present invention also includes pharmaceutical compositions and combinations.

Excerpt(s): The present invention relates to a method for the treatment or prevention of viral infection using nucleoside analogues. The herpes group of viruses which include **cytomegalovirus** (CMV), a member of Epstein-Barr virus (EBV), Varicella Zoster virus (VZV), herpes simplex viruses (HSV-1, HSV-2) and human herpes viruses HHV6, HHV7, and HHV8, is recognized as an important pathogen in patients with AIDS. The virus often contributes to the immunosuppression observed in such patients and may cause disseminated disease involving the lungs, gastrointestinal tract, central nervous system, or eyes. CMV retinitis is recognized as a major cause of blindness in patients with AIDS. Also, human **cytomegalovirus** (HCMV) infection is a major cause of death in AIDS patients. Currently, there are only two approved drugs, ganciclovir, an acyclic guanine nucleoside, and foscarnet, for its treatment. Ganciclovir has exhibited bone marrow suppression as a serious side effect and resistant strains have also been isolated. Foscarnet presents side effects that are associated with its administration such as reversible renal dysfunction, thrombophlebitis at the infusion site, headaches and anemia. Also, foscarnet is not orally bioavailable, limiting its utility in clinical treatment. It is poorly soluble, and large doses are required because of its relatively low potency. Thus, the development of patent and non-toxic anti-CMV agents is therefore highly desirable. Unfortunately, in general these compounds present problems in cytotoxicity, particularly, PMEG which is very cytotoxic.

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

- **Methods and compositions for preventing or retarding the development of atherosclerotic lesions**

Inventor(s): Berencsi, Klara; (Rosemont, PA), Gonczol, Eva; (Rosemont, PA)

Correspondence: Howson And Howson; One Spring House Corporation Center; Box 457; 321 Norristown Road; Spring House; PA; 19477; US

Patent Application Number: 20010029251

Date filed: May 17, 2001

Abstract: A method for preventing or retarding the development atherosclerotic lesions or restenosis involves administering to a subject, preferably a human, an effective amount of an anti-viral composition directed against CMV, and optionally an anti-microbial composition directed against *C. pneumoniae*. These compositions may be conventional chemical anti-microbial pharmaceuticals. Alternatively, the compositions may contain a **cytomegalovirus** (CMV) protein or fragment thereof (or nucleic acid containing compositions expressing such protein or fragment). Such compositions may contain an immunogenic *C. pneumoniae* protein or fragment thereof (or nucleic acid containing compositions expressing such protein or fragment). The protein/nucleic acid compositions are administered in an amount capable of inducing cell mediated immunity and/or antibody response in the subject.

Excerpt(s): This application is a continuation-in-part of pending provisional United States patent application Ser. No. 60/023,404 filed Aug. 14, 1996. The present invention relates generally to pharmaceutical compositions and methods-of use thereof in treating or preventing atherosclerosis. Atherosclerosis (AT) results from an excessive

inflammatory and fibroproliferative response to vascular insult and has been noted to be a principal cause of heart attack and stroke, accounting for up to half of all mortalities in the industrialized world including about 13 million Americans. Atherogenesis is theorized to follow a response to injury, but the agent(s) of injury have yet to be identified fully.

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

- **Methods and compositions useful for stimulating an immune response**

Inventor(s): Penfold, Mark E.T.; (Mountain View, CA), Schall, Thomas J.; (Menlo Park, CA)

Correspondence: Townsend And Townsend And Crew, LLP; Two Embarcadero Center; Eighth Floor; San Francisco; CA; 94111-3834; US

Patent Application Number: 20020176870

Date filed: February 1, 2002

Abstract: The invention provides compositions containing modified **cytomegalovirus**, and methods of using the compositions. In various embodiments, the modifications include adding a heterologous sequence encoding a non-viral chemokine element and/or immunogenic polypeptide, and/or disabling a viral dissemination gene.

Excerpt(s): This application claims the benefit of U.S. Provisional Application No. 60/265,925, filed Feb. 2, 2001, which is incorporated herein by reference in its entirety for all purposes. Cytomegaloviruses (CMVs) are common pathogens and are members of the beta subgroup of the herpesvirus family. CMV is a slow replicating, species-specific complex DNA virus found in most mammals. CMV has adopted subtle evolutionary strategies for evading the immune system of an infected host, while disseminating through the host tissues. The genome (230 kb) of human CMV (HCMV) includes a long and short unique region (UL and US, respectively), each of which is flanked by inverted repetitions. The entire HCMV genome has been sequenced (Chee, M. S., et al. (1990) Curr. Top. Microbiol. Immunol. 154:125-169) and appears to contain over 200 open reading frames.

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

- **Methods for treating subjects infected with a herpes virus or neisseria gonorrhoeae**

Inventor(s): Docherty, John; (Kent, OH), Tsai, Chun-che; (Kent, OH)

Correspondence: Calfee Halter & Griswold, LLP; 800 Superior Avenue; Suite 1400; Cleveland; OH; 44114; US

Patent Application Number: 20020103262

Date filed: August 15, 2001

Abstract: The present invention provides a method of inhibiting the formation of infectious herpes virus particles, particularly infectious herpes simplex virus (HSV) particles, in a host cell. The method involves administering an effective amount of a hydroxylated tolan, particularly a polyhydroxylated tolan, to a herpes virus infected host cell. The present invention also provides a method of treating a herpes virus infection, particularly an HSV infection. The method comprises administering a topical composition comprising a therapeutically effective amount of a hydroxylated tolan to a

herpes virus-infected site. The present invention also relates to a topical composition for treating a herpes virus infection selected from the group consisting of an HSV infection, a **cytomegalovirus** infection, and a varicella zoster virus infection. The present invention also provides a method of treating a subject infected with *Neisseria gonorrhea*.

Excerpt(s): This application claims priority to U.S. Provisional Application No. 60/225,609, filed Aug. 15, 2000. The present invention relates to compositions which inhibit replication of herpes virus and the bacterium *Neisseria gonorrhoeae*, and methods of using such compositions to treat subjects infected with these microorganisms. Human herpes viruses can infect host cells in virtually any organ of the human body. Replication of a herpes virus within an infected host cell leads to lysis of the infected cell and the release of large numbers of infectious virus. The infectious particles released from the lysed cell can infect and destroy other cells at or near the site of the initial infection. These infectious particles can also be transmitted to a non-infected individual. Human herpes viruses can also enter and remain latent, i.e., in the non-replicative state, in other cells of the afflicted individual for life. This life-long infection serves as a reservoir of infectious virus for recurrent infections in the afflicted individual and as a source of infection for an unwitting contact.

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

- **Novel human cytomegalovirus DNA sequences**

Inventor(s): Cha, Tai-An; (San Ramon, CA), Spaete, Richard; (Emerald Hills, CA)

Correspondence: Quine Intellectual Property Law Group, P.C.; P O Box 458; Alameda; CA; 94501; US

Patent Application Number: 20040001850

Date filed: March 21, 2003

Abstract: Provided are novel Toledo and Towne human **cytomegalovirus** DNA sequences (HCMV) and proteins encoded thereby. The sequences are useful in methods and compositions for detecting HCMV infections and in immunogenic compositions for preventing HCMV infections.

Excerpt(s): This invention pertains to the field of virology, specifically to the diagnosis, treatment and prevention of viral infections in humans. More specifically, this invention relates to the diagnosis, treatment and prevention of human **cytomegalovirus** infections. Human **cytomegalovirus** (HCMV) is a ubiquitous agent in human populations. Infections are generally asymptomatic, but there can be serious medical sequelae in immunocompromised individuals and in congenitally infected newborns. In immunocompromised individuals, HCMV infection can result in interstitial pneumonia, retinitis progressing to blindness and disseminated infection. Infections in newborns can be severely damaging, with multiple organ involvement including the central nervous system and may also result in auditory damage. The mechanisms of pathogenesis are not understood, although it is believed that host factors, such as cellular and/or humoral immune responses might be involved. See, Alford and Britt, "The Human Herpesviruses", eds Roizman, B., R. J. Whitley and C. Lopez, Raven Press, New York, 1993, pp 227-55. It has also been speculated that genetic variability (either structural or antigenic or both) among different strains of HCMV could be responsible for the variance in clinical manifestations observed. Pritchett, J. Virol. 36:152-61(1980); Lehner, J. Clin. Microbiol. 29:2494-2502(1991); Fries, J. Infect. Dis. 169:769-74(1994). Considerable attention has been focused recently on the analysis of strain variation among HCMV

isolates. Some twenty different HCMV strains have been isolated and differentiated by restriction analysis of PCR amplified DNA fragments. Chou, J. Infect. Dis. 162:738-42(1990).

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

- **Oligonucleotide sequence formula for labeling oligonucleotide probes and proteins for in-situ analysis**

Inventor(s): Connaughton, John F.; (Laytonsville, MD), Utermohlen, Joseph G.; (Tucson, AZ)

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Patent Application Number: 20040014088

Date filed: July 21, 2003

Abstract: The present invention provides oligonucleotide probes and oligonucleotide probe collections and protein labeling for detecting or localizing a plurality nucleic acid target genes or antigens within a cell or tissue sample. Specifically, the provides collections of oligonucleotide probe for use in in situ hybridization analyses in which each probe has a label-domain with the sequence formulas of (CTATTTT).sub.n, (AAAATAG).sub.n or (TTTTATC).sub.n or (GATAAAA).sub.n in which all cases "n" would equal 1 or greater. The present invention provides collections or "cocktails" of oligonucleotide probes for detecting or localizing specific nucleic acid target genes within a cell or tissue sample. The cocktails are useful for detecting the following: the Kappa gene (SEQ ID NOS: 1-16 inclusive); the Lambda gene (SEQ ID NOS: 501-509, 511-513, and 515); the CMV (cytomegalovirus) gene (SEQ ID NOS: 221-241 inclusive); EBER (Epstein-Barr RNA) gene (SEQ IN NOS: 51-54 inclusive); Alu (SEQ IN NOS: 55-56); PolyA (SEQ ID NO: 57); and the detection tail (SEQ ID NO: 330).

Excerpt(s): This invention relates to oligonucleotide probes and collections of oligonucleotide probes for detecting or localizing nucleic acid genes targets within a cell or tissue sample. In particular, the invention relates to collections of oligoprobes. In situ analysis includes in situ hybridization and immunohistochemistry. In situ hybridization (ISH) employs labeled DNA or RNA probe molecules that are anti-sense to a target gene sequence or transcript to detect or localize targeted nucleic acid target genes within a cell or tissue sample. ISH has proven to be a useful tool in a number of biomedical fields, including developmental biology, cell biology, and molecular biology. ISH has been used, for example, to diagnose genetic disorders, map genes, study gene expression, and localize sites of target gene expression. Typically, ISH is performed by exposing a cell or tissue sample immobilized on a glass slide to a labeled nucleic acid probe which is capable of specifically hybridizing to a given target gene in the cell or tissue sample (In Situ Hybridization: Medical Applications (G. R. Coulton and J. de Belleruche, eds., Kluwer Academic Publishers, 1992); In Situ Hybridization: In Neurobiology; Advances in Methodology (J. H. Eberwine, K. L. Valentino, and J. D. Barchas, eds., Oxford University Press, 1994); In Situ Hybridization: A Practical Approach (D. G. Wilkinson, ed., Oxford University Press, 1992)). The hybridization of labeled probe molecules to nucleic acids in the cell or tissue sample can then be detected using, for example, radioactive-based direct detection methods, fluorescence-based direct detection methods, or indirect detection methods based on the binding of a fluorescence-labeled protein binding to a hapten such as BrdU, digoxigenin-labeled or biotin-labeled nucleotides incorporated into probes. Hapten-based methods have been further extended

to include those molecules to be bonded by binding protein-enzyme conjugates such as antibody-enzyme-conjugates and colorimetric based detection chemistry. In addition, several target genes can be simultaneously analyzed by exposing a cell or tissue sample to a plurality of nucleic acid probes that have been labeled with a plurality of different nucleic acid tags. For example, a plurality of nucleic acid probes can be labeled with a plurality of fluorescent compounds having different emission wavelengths, thereby permitting simultaneous multicolored analysis to be performed in a single step on a single target cell or tissue sample.

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

- **Peptide reagent for the detection of human cytomegalovirus (CMV)**

Inventor(s): Middeldorp, Jaap Michiel; (Oss, NL), Van De Crommert, Johannes Martinus Gerardus; (Veghel, NL)

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Patent Application Number: 20030119039

Date filed: November 5, 2002

Abstract: The invention relates to a peptide reagent comprising peptides immunochemically reactive with antibodies to the human **cytomegalovirus** (CMV). New antibodies directed to said peptides or fragments thereof are also part of the invention. Also cell lines capable of producing monoclonal antibodies are part of the invention. The invention also relates to a method for the detection of CMV or antibodies directed against CMV in a test fluid and a test kit to be used when applying the said detection methods. Detection of CMV in a test fluid or tissue specimen using antibodies, monoclonal and polyclonal, directed to said peptide, which have the characteristics of detecting both native and denatured DMV proteins are also part of said invention.

Excerpt(s): The present invention relates to a peptide reagent comprising peptides immunochemically reactive with antibodies to the human **cytomegalovirus** (CMV), (monoclonal) antibodies directed against said peptides, and cell lines capable of producing monoclonal antibodies. The invention is further concerned with methods for (direct) detection of CMV or (indirect) detection of antibodies directed against CMV. Cytomegalovirus (CMV) is a world-wide spread member of the human herpesvirus family, infecting between 50-100% of all individuals depending on age and socio-economic status. CMV is naturally transmitted via saliva, urine or breast-milk but can also be recovered from other body secretions. In addition, CMV can be transmitted transplacentally to the foetus, by geno-urinary contact during birth or sexual intercourse, by blood transfusion (esp. white cells) and bone marrow cq. organ transplantation.

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

- **Production of therapeutic proteins in transgenic cereal crops**

Inventor(s): Altosaar, Illimar; (Ottawa, CA), Dudani, Anil; (Ottawa, CA), Ganz, Peter; (Orleans, CA), Sardana, Ravinder; (Ottawa, CA), Tackaberry, Eilleen; (Ottawa, CA)

Correspondence: MR. W. Charles Kent; Ridout & Maybee Llp; 19th Floor; 150 Metcalfe ST.; Ottawa; ON; K2p 1p1; CA

Patent Application Number: 20030159182

Date filed: August 29, 2002

Abstract: There is provided a herpes virus vaccine produced in in the seeds of a cereal crop and a method of producing the vaccine. The method comprises: a) obtaining a nucleic acid sequence encoding a herpes virus antigen; b) introducing the nucleic acid sequence into cereal plant tissue competent to form seeds; c) permitting said cereal plant tissue to develop; and, d) directing preferential expression of the antigen encoded by the nucleic acid sequence in seeds formed by the cereal plant tissue. Herpes viruses antigens of particular interest include all or antigenic portions of gB (from human **cytomegalovirus** ("HCMV")), gH (from HCMV), and gD (from herpes simplex virus 1 or 2), as well as antigens from Epstein Barr virus and varicello-zoster virus-8. Envelope glycoproteins from herpes viruses are antigens of interest. Cereal crops of particular interest include rice, wheat, oats, barley, and corn. Vaccines produced according to the invention are very stable and may be administered by a variety of routes, including injection and contact with mucosal membranes, such as by oral administration in purified or unpurified form.

Excerpt(s): Human **cytomegalovirus** ("HCMV") is a widely distributed member of the herpes virus family that is transmitted by blood and other body secretions. In immunocompromised individuals such as AIDS patients, organ transplant recipients and low weight pre-term infants, the virus can cause severe and/or lethal disease, while congenital infection may result in damage to the central nervous system. The HCMV encoded glycoprotein B complex ("gB") is a transmembrane protein of 907 amino acids (for the prototype Towne strain) which is initially synthesized in infected cells as a 105 kDa non-glycosylated polypeptide. In normal infected mammalian host cells, the gB polypeptide undergoes post-translational glycosylation, cleavage of the N-terminal 24 amino acid signal peptide, oligomerization and folding which take place in the endoplasmic reticulum of the cell, where it is transiently associated with a membrane-bound chaperonin. This results in transport of a 150 kDa gB precursor to the Golgi complex where further carbohydrate modifications occur and the polypeptide is proteolytically cleaved to yield products of 116 kDa and 58 kDa which are disulfide linked. Both species are targets for neutralizing and non-neutralizing antibodies, each representing both continuous and discontinuous epitopes. A phosphorylation site is located in the cytoplasmic tail and may be important for correct intracellular trafficking. The sequence of gB (Towne) is reported in Spaete et al., Virology 167(1), 207 (1988), Pub. Med. Acc. No. M22343. Mammalian immune responses are highly specific and sensitive to even minor differences between potential antigenic sites. Thus, changes to the post-translational modification of an antigen such as gB will have the potential to render it unsuitable for use as a vaccine against infection by the native organism. Plant seeds are an ideal organ for the targeted synthesis of heterologous proteins. However, where the proteins of interest are of non-plant origin, numerous technical challenges arise in the production and recovery of useful transgenic proteins. In particular, differences in post-translational modification and transport may render plant-produced proteins unsuitable for some uses in mammals.

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

- **Pyrimidine derivatives**

Inventor(s): Chen, Xiaoqi; (San Mateo, CA), Cushing, Timothy D.; (Pacifica, CA), Flygare, John A.; (Burlingame, CA), Jaen, Juan C.; (Burlingame, CA), Mellon, Heather L.; (Limerick, PA), Miao, Shi-Chang; (Foster City, CA), Powers, Jay P.; (Pacifica, CA)

Correspondence: Townsend And Townsend And Crew; Two Embarcadero Center; Eighth Floor; San Francisco; CA; 94111-3834; US

Patent Application Number: 20010018436

Date filed: December 15, 2000

Abstract: Compounds and compositions are provided which are useful for the treatment of viral infections, particularly human **Cytomegalovirus** infection. The compounds include novel pyrimidine-based derivatives.

Excerpt(s): This application is a continuation in part of U.S. Ser. No. 60/075,005, filed Feb. 17, 1998, the disclosure of which is incorporated herein by reference in its entirety. The invention described herein was not made with the aid of any federally sponsored grants. The field of the invention is in novel substituted pyrimidine compounds and their use as pharmacologically active agents capable of suppressing and inhibiting viruses (e.g., herpes viruses). The subject compounds and compositions are particularly useful in treating and suppressing human **Cytomegalovirus**.

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

- **Reagents and methods for the diagnosis of CMV dissemination**

Inventor(s): Dairaghi, Daniel J.; (Palo Alto, CA), McMaster, Brian E.; (Mountain View, CA), Schall, Thomas J.; (Palo Alto, CA)

Correspondence: Townsend And Townsend And Crew, Llp; Two Embarcadero Center; Eighth Floor; San Francisco; CA; 94111-3834; US

Patent Application Number: 20020193374

Date filed: August 30, 2001

Abstract: Methods are provided for detecting the spread of **cytomegalovirus** in a host infected with CMV, by administering to the host a detectable and labeled amount of a non-endogenous compound which binds to US28 or a US28 fragment. Typically, the methods use a labeled form of IBZM.

Excerpt(s): This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/229,191, filed Aug. 30, 2000, the disclosure of which is incorporated herein by reference. Cytomegalovirus (CMV) is an important human pathogen and a major opportunist which emerges to cause disease in the immuno-compromised such as AIDS patients, neonates, and individuals who have been given immunosuppressive drugs as part of a transplantation regimen. In these individuals, the consequences of CMV in acute or re-emerging infections can be dire, including retinitis, encephalitis, and pneumocystis, among other pathologies. Furthermore, in immuno-competent hosts, CMV establishes a persistent lifelong infection through which it has been linked to a variety of inflammatory conditions including coronary artery occlusion following heart transplant and arthrectomy and restenosis following angioplasty. CMV interacts with

leukocytes during acute infection of the host as well as during lifelong latency. As such, leukocytes are important players in CMV-induced disease and have been implicated in the acute phase of infection as vehicles for dissemination of virus and as sites of residence during lifelong latency. or a pharmaceutically acceptable salt thereof; wherein Ar represents a substituted aryl group; R^{sup.11} represents H or (C_{sub.1}-C_{sub.4})alkyl; and N^{sup.Het} is a substituted or unsubstituted 4-, 5-, 6-, or 7-membered nitrogen heterocycle.

Web site: <http://appft1.uspto.gov/netathtml/PTO/search-bool.html>

- **Recombinant AAV packaging systems**

Inventor(s): Hardy, Stephen F.; (San Francisco, CA)

Correspondence: Chiron Corporation; Intellectual Property - R 440; P. O. Box 8097; Emeryville; CA; 94662-8097; US

Patent Application Number: 20020058325

Date filed: January 26, 2001

Abstract: Methods and compositions are provided for producing recombinant AAV vector particles; comprising the general steps of (a) introducing into a host cell (i) pfloxAAV, (ii) a recombinant viral vector encoding plasmid, and (iii) a plasmid encoding herpesvirus, **cytomegalovirus**, or adenoviral functions, or a herpesvirus, **cytomegalovirus**, or, adenovirus itself, in order to produce flox AAV particles and recombinant AAV particles; and (b) introducing into a second host cell (i) the recombinant AAV particles and flox AAV particles of (a), (ii) a vector which directs the expression of Cre, and (iii) a vector which directs the expression of herpesvirus, CMV, or adenovirus helper functions, such that said recombinant AAV vector particles are produced.

Excerpt(s): This application claims the benefit of United States Provisional Application No. 60/178,536, filed Jan. 26, 2000, which is herein incorporated by reference in its entirety. The present invention relates generally to compositions and methods for producing recombinant adeno-associated virus (rAAV) vectors. More specifically, the present invention relates to packaging cell lines and methods for making and using them. Moreover, the rAAV packaging cell lines of the present invention are used to produce high-titer rAAV, that is free of replication-competent AAV and that are suitable for a wide range of applications including ex vivo and in vivo gene therapy as well as in vitro recombinant protein production. Adeno-associated virus (AAV) is a ubiquitous single stranded DNA parvovirus capable of infecting a wide range of cell types from a variety of different species. Under normal physiological conditions, AAV enters the host cell where it is transported to the cell nucleus. Once inside the cell nucleus, the viral capsid is removed and the viral DNA is stably integrated into the host chromosome. After integration, AAV remains dormant and is generally incapable of self-replication. However, AAV replication can be induced when the cell containing the latent AAV DNA is co-infected with either an adenovirus or a member of the herpesviridae, including herpes simplex virus (HSV), **cytomegalovirus** (CMV), Epstein Barr virus (EBV) or Vaccinia Virus and pseudorabies virus (Berns, K. I. Parvoviridae: The Viruses and Their Replication. In: Fields, B. N. ed. Virology. Philadelphia. Lippincott-Raven 1996 Third Edition Vol. 2 2181-2192.) These so-called "helper viruses" provide AAV the necessary helper functions required to rescue and activate the AAV genome and initiate transcription.

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

- **Recombinant poxvirus cytomegalovirus, compositions, and uses**

Inventor(s): Cox, William I.; (Troy, NY), Kauffman, Elizabeth K.; (Averill Park, NY), Paoletti, Enzo; (Delmar, NY), Pincus, Steven E.; (East Greenbush, NY)

Correspondence: Michael S. Greenfield; McDonnell Boehnen Hulbert & Berghoff; 32nd Floor; 300 S. Wacker Drive; Chicago; IL; 60606; US

Patent Application Number: 20030064077

Date filed: July 26, 2001

Abstract: Attenuated recombinant viruses containing DNA encoding an HCMV antigen, as well as methods and compositions employing the viruses, expression products therefrom, and antibodies generated from the viruses or expression products, are disclosed and claimed. The recombinant viruses can be NYVAC or ALVAC recombinant viruses. The recombinant viruses and gene products therefrom and antibodies generated by the viruses and gene products have several preventive, therapeutic and diagnostic uses. The DNA of the recombinant viruses can be used as probes or for generating PCR primers.

Excerpt(s): This application is a continuation-in-part of application Ser. No. 08/105,483, filed Aug. 13, 1993, which in turn is a continuation of application Ser. No. 07/847,951, filed Mar. 6, 1992, which in turn is a continuation-in-part of application Ser. No. 07/713,967, filed Jun. 11, 1991, which in turn is a continuation-in-part of application Ser. No. 07/666,056, filed Mar. 7, 1991; application Ser. No. 08/036,217, filed Mar. 24, 1993, was a continuation of application Ser. No. 07/666,056 and issued Nov. 15, 1994 as U.S. Pat. No. 5,364,773. This application is also a continuation-in-part of U.S. application Ser. No. 08/124,668, filed Sep. 21, 1993, as a divisional of application Ser. No. 07/502,834, filed Apr. 4, 1990, now U.S. Pat. No. 5,338,683; application Ser. No. 07/502,834 was a continuation-in-part of application Ser. No. 07/394,488, filed Aug. 16, 1989, which was a continuation-in-part of application Ser. No. 07/339,004, filed Apr. 17, 1989; and, a continuation-in-part of application Ser. No. 07/090,209, filed Aug. 27, which was a division of application Ser. No. 622,135, filed Jun. 19, 1984, now U.S. Pat. No. 4,722,848, which was a continuation-in-part of application Ser. No. 446,824, filed Dec. 8, 1982, now U.S. Pat. No. 4,603,112, which was a continuation-in-part of U.S. application Ser. No. 334,456, filed Dec. 24, 1981, now U.S. Pat. No. 4,769,330. Each of the aforementioned and above-referenced application and patents are hereby incorporated herein by reference. The present invention relates to a modified poxvirus and to methods of making and using the same; for instance, a vaccinia virus or avipox (e.g. canarypox or fowlpox), e.g., modified recombinant poxvirus-cytomegalovirus (CMV), e.g. human **cytomegalovirus** (HCMV) such as an attenuated recombinant, especially a NYVAC or ALVAC CMV or HCMV recombinant. More in particular, the invention relates to improved vectors for the insertion and expression of foreign genes for use as safe immunization vehicles to elicit an immune response against CMV or HCMV virus. Thus, the invention relates to a recombinant poxvirus, which virus expresses gene products of CMV or HCMV and to immunogenic compositions which induce an immunological response against CMV or HCMV infections when administered to a host, or in vitro (e.g., ex vivo modalities) as well as to the products of expression of the poxvirus which by themselves are useful for eliciting an immune response e.g., raising antibodies, which antibodies are useful against CMV or HCMV infection, in either seropositive or seronegative individuals, or which expression products or antibodies elicited thereby, isolated from an animal or

human or cell culture as the case may be, are useful for preparing a diagnostic kit, test or assay for the detection of the virus, or of infected cells, or, of the expression of the antigens or products in other systems. The isolated expression products are especially useful in kits, tests or assays for detection of antibodies in a system, host, serum or sample, or for generation of antibodies. The poxvirus recombinants preferably contain DNA coding for any or all of CMV or HCMVgB, gH, gL, pp150, pp65 and IE1, including recombinants expressing truncated versions of IE1; and, the recombinant poxvirus DNA is useful for probes for CMV or HCMV or for preparing PCR primers for detecting the presence or absence of CMV or HCMV or antigens thereof. Several publications are referenced in this application. Full citation to these references is found at the end of the specification immediately preceding the claims or where the publication is mentioned; and each of these publications is hereby incorporated herein by reference.

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

- **Regulatory elements for delivery to the liver**

Inventor(s): Armentano, Donna; (Belmont, MA), Souza, David W.; (Waltham, MA), Wadsworth, Samuel C.; (Shrewsbury, MA)

Correspondence: Genzyme Corporation; Legal Department; 15 Pleasant ST Connector; Framingham; MA; 01701-9322; US

Patent Application Number: 20030017139

Date filed: May 6, 2002

Abstract: The invention is directed to novel combinations of liver specific enhancers and promoter elements for achieving persistent transgene expression in the liver. The liver specific enhancer elements may be derived from either the human serum albumin, prothrombin, alpha-1microglobulin or aldolase genes in single copies or in multimerized form linked to elements derived from the **cytomegalovirus** intermediate early (CMV), alpha-1-antitrypsin or albumin promoters. In a preferred embodiment of the invention, an adenoviral vector comprising a liver specific enhancer/promoter combination operably linked to a transgene is administered to recipient cells. In other embodiments of the invention, adeno-associated viral vectors, retroviral vectors, lentiviral vectors or a plasmid comprising the liver specific enhancer/promoter combination linked to a transgene is administered to recipient cells. Also within the scope of the invention are promoter elements derived from the human prothrombin gene and the beta-fibrinogen gene.

Excerpt(s): This invention relates to nucleic acid delivery vehicle constructs that have an enhanced capability of expression in target cells, namely to hepatocytes and other liver cells. The ability to deliver nucleic acids carried by delivery vehicles, e.g., recombinant viruses (adenovirus, adeno-associated virus, herpesvirus, retrovirus) which are used with nucleic acid molecules, such as a plasmid, comprising a transgene, to transfect a target cell; molecular conjugate vectors; and modified viral vectors are important for the potential treatment of genetic diseases through gene delivery. Adenovirus is a non-enveloped, nuclear DNA virus with a genome of about 36 kb. See generally, Horwitz, M. S., "Adenoviridae and Their Replication," in Virology, 2nd edition, Fields et al., eds., Raven Press, New York, 1990. Recombinant (adenovirus dodecahedron and recombinant adenovirus conglomerates) to specific cell types is useful for various applications in oncology, developmental biology and gene therapy. Adenoviruses have advantages for use as expression systems for nucleic acid molecules coding for, inter alia, proteins, ribozymes, RNAs, antisense RNA that are foreign to the adenovirus

carrier (i.e. a transgene), including tropism for both dividing and non-dividing cells, minimal pathogenic potential, ability to replicate to high titer for preparation of vector stocks, and the potential to carry large inserts. See Berkner, K. L., 1992, *Curr. Top. Micro Immunol*, 158:39-66; Jolly D., 1994, *Cancer Gene Therapy*, 1:51-64.

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

- **Therapeutic anti-cytomegalovirus compounds**

Inventor(s): Nicolette, Charles A.; (Framingham, MA)

Correspondence: Antoinette F. Konski; Mccutchen Doyle, Brown & Enersen, L.L.P.; Suite 1800; 3 Embarcadero Center; San Francisco; CA; 94111; US

Patent Application Number: 20020058038

Date filed: March 19, 2001

Abstract: The present invention provides synthetic compounds, antibodies that recognize and bind to these compounds, polynucleotides that encode these compounds, and immune effector cells raised in response to presentation of these epitopes. The invention further provides methods for inducing an immune response and administering immunotherapy to a subject by delivering the compositions of the invention.

Excerpt(s): This application claims priority under 35 U.S.C.sctn. 119(e) to U.S. Provisional Patent Application Ser. Nos. 60/191,050 and 60/254,989, filed Mar. 21, 2000 and Dec. 12, 2000, respectively. The contents of these applications are hereby incorporated by reference into the present disclosure. The invention relates to the field of therapeutic compounds useful against **Cytomegalovirus** ("CMV") infections. The recognition of antigenic epitopes presented by molecules of the Major Histocompatibility Complex (MHC) plays a central role in the establishment, maintenance and execution of mammalian immune responses. T cell surveillance and recognition of peptide antigens presented by cell surface MHC molecules expressed by somatic cells and antigen presenting leukocytes functions to control invasion by infectious organisms such as viruses, bacteria, and parasites. In addition it has now been demonstrated that antigen-specific cytotoxic T lymphocytes (CTLs) can recognize certain cancer cell antigens and attack cells expressing these antigens. This T cell activity provides a basis for developing novel strategies for anti-cancer vaccines. Furthermore, inappropriate T cell activation plays a central role in certain debilitating autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and asthma. Thus presentation and recognition of antigenic epitopes presented by MHC molecules play a central role in mediating immune responses in multiple pathological conditions.

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 cytomegalovirus, 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

“cytomegalovirus” (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 cytomegalovirus.

You can also use this procedure to view pending patent applications concerning cytomegalovirus. 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 7. BOOKS ON CYTOMEGALOVIRUS

Overview

This chapter provides bibliographic book references relating to cytomegalovirus. In addition to online booksellers such as **www.amazon.com** and **www.bn.com**, excellent sources for book titles on cytomegalovirus include the Combined Health Information Database and the National Library of Medicine. Your local medical library also may have these titles available for loan.

Book Summaries: Federal Agencies

The Combined Health Information Database collects various book abstracts from a variety of healthcare institutions and federal agencies. To access these summaries, go directly to the following hyperlink: <http://chid.nih.gov/detail/detail.html>. You will need to use the "Detailed Search" option. To find book summaries, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer. For the format option, select "Monograph/Book." Now type "cytomegalovirus" (or synonyms) into the "For these words:" box. You should check back periodically with this database which is updated every three months. The following is a typical result when searching for books on cytomegalovirus:

- **Self - Treatment for AIDS; Oxygen Therapies, etc**

Contact: Aurora Books, PO Box 5852, Denver, CO, 80217.

Summary: In this monograph, Persons with AIDS (PWA's), or those who are infected with Human immunodeficiency virus (HIV), are presented with the full spectrum of alternative therapies and self-care strategies for treating Acquired immunodeficiency syndrome (AIDS). The monograph is based on the premise that HIV may lead to infection if a person's immune system is weakened and unable to resist poisonous pathological microorganisms. Testimonials from PWA's, research reports, studies, and articles describe oxygen therapies, tests for Epstein-Barr virus, **cytomegalovirus**, herpes, food or chemical hypersensitivity, fungal hypersensitivity, immuno-nutritional profiles, safe water and nutrition strategies, chemicals, allergies, detoxification centers, colon health, parasites, acidophilus, electromagnetic health hazards and healing, silver (mercury) fillings, and stress management. Although the therapies, remedies, and

treatments are deemed valid, the monograph recommends that they be incorporated with other avenues of healing. These include colon cleansing; bathing to release toxins; stress reduction; elimination of smoking, drinking, drug use, or poor nutrition; avoidance of low-energy people; maintenance of peace, forgiveness, positive thought, music, laughter, and joy; massage, osteopathic, acupuncture, chiropractic, and dental treatments; exercise; and avoidance of TV, computers, and other machines which emit low-level radiation. These measures may bring the body back into alignment and homeostasis. The patient is encouraged to engage a holistic-health practitioner to help raise the body's resistance level. Because oxygen starvation is the single greatest cause of disease, full oxygenation plays a critical role in the immune system.

- **AIDS and Vision Loss**

Contact: American Foundation for the Blind, Eastern Regional Center, Brooklyn Navy Yard Building No 3, Brooklyn, NY, 11205, (718) 935-0683.

Summary: In this monograph, the challenges presented to those who deliver services to the visually impaired due to Acquired immunodeficiency syndrome (AIDS), caused by Human immunodeficiency virus (HIV), are described. Vision impairment is often a late complication of AIDS and is becoming more common as Persons with AIDS (PWA's) live longer through improved treatment programs. The monograph describes the characteristic symptoms and infections of AIDS and details visual complications including Kaposi sarcoma, **cytomegalovirus** infection, cotton-wool spots, and infections of the central nervous system. The monograph outlines the epidemiology of AIDS, risk-related behaviors, and treatment programs. Eye involvement therapies include ganciclovir and foscarnet. Psychological factors are described in terms of reactions to the disease and specifically to vision loss. The monograph discusses policy development for agencies providing services to the visually impaired. Policy statements should consider waiting lists, types of services, confidentiality, allocation of services, roles of other organizations, staff training, and communication. Staff training programs should focus on attitudes toward AIDS, knowledge about the disease, people at risk, infection control, HIV transmission, death and dying, burnout, and continuing education. Rehabilitation for visually impaired PWA's rests on several principles: Cooperating with other agencies, going to the clients, spreading the message to the community, and organizing a team. Individual services are comprised of assessment, goal setting, training, using remaining vision, coping with everyday life, and counseling. The monograph contains a list of resource materials relating to AIDS and visual impairment including organizations, newsletters, State agencies, libraries, and selected readings.

- **Oral Manifestations of AIDS**

Source: Torrance, CA: Homestead Schools, Inc. 2000. [37 p.].

Contact: Available from Homestead Schools, Inc. 23844 Hawthorne Boulevard, Suite 200, Torrance, CA 90505. (310) 791-9975. Fax (310) 791-0135. E-mail: Education@homesteadschools.com. Website: www.homesteadschools.com. PRICE: \$36.00 plus shipping and handling. Course No. 6215.

Summary: Knowledge of HIV infection has become a critically important requirement for professionals responsible for oral health care delivery. This continuing education program for dentists focuses on the oral manifestations of AIDS. Topics covered include the nature of HIV infection, including demographics, pathogenesis, transmission, progression, survival and treatment strategies; the oral manifestations of HIV infection,

including the role of clinicians and dental professionals, transmission risks, saliva, other transmissible diseases, differential diagnosis, and patient approach; fungal infections, including candidiasis, histoplasmosis, and other oral fungal infections; viral infections, including herpes family viruses, Epstein-Barr virus (EBV) and oral hairy leukoplakia, varicella virus reactivation, **cytomegalovirus** (CMV), human papillomavirus (HPV) and condyloma acuminatum, molluscum contagiosum (MC), and hepatitis viruses; bacterial infections, including necrotizing ulcerative gingivitis and periodontitis, non-oral-flora opportunists, and tuberculosis (TB); HIV associated malignancies, including Kaposi's sarcoma (KS), non-Hodgkin's lymphoma, and squamous carcinoma; and other HIV-associated lesions, including recurrent aphthous-like stomatitis, hypersensitivity and lichenoid reaction, sialadenitis (inflamed salivary glands) and xerostomia (dry mouth), thrombocytopenia, and ulcerative stomatitis and unclassified lesions. The program includes a posttest with which readers can qualify for continuing education credit.

- **50 Things You Should Know About the Chronic Fatigue Syndrome Epidemic**

Contact: TNM, Incorporated, PO Box 1475, New York, NY, 10008, (212) 627-2120.

Summary: The author of this book discusses Chronic Fatigue Syndrome (CFS), which he views as an AIDS-like illness that is of epidemic, and even pandemic, proportions. CFS is an illness of immune dysfunction that is contagious and has been overlooked by health authorities, says the author. He discusses symptoms that can develop in CFS, including blindness, skin problems, brain lesions, and loss of fingerprints. He says that CFS shares many characteristics with AIDS, such as immune dysfunction, nervous system problems, and high antibodies against **cytomegalovirus** (CMV), Epstein-Barr Virus, and Human Herpes Virus 6 (HHV-6). The author urges people to write their Congressional representatives to voice their concerns about this growing public health problem.

- **Screening for Transmissible Diseases**

Source: Guidelines for the Organization of a Blood Transfusion Service.

Contact: World Health Organization, Health Laboratory Technology and Blood Safety Unit, 20 Avenue Appia, 1211 Geneva 27.

Summary: This book chapter discusses screening to prevent transmission of infectious diseases through blood and blood products. Topics covered are donor screening for viral hepatitis B, non-A non-B hepatitis, viral hepatitis C; delta agent; Human immunodeficiency virus (HIV), HIV variants such as HIV-2; syphilis and yaws; malaria; Chagas disease (American trypanosomiasis); **cytomegalovirus** (CMV); antigen testing; and "look-back" programs that trace seropositive donors to determine if they have previously given blood. It is also noted that microfilariae are not transmitted by blood transfusion, and that donors who have had diseases such as dengue fever, schistosomiasis, leptospirosis, yellow fever, or encephalitis are not permanently debarred from donating blood after their diseases have been cured.

- **Guidelines for Perinatal Care**

Source: Guidelines for Perinatal Care; 3rd edition, 1992.

Contact: American College of Obstetricians and Gynecologists, PO Box 96920, Washington, DC, 20090-6920, (202) 638-5577, <http://www.acog.com>. American Academy of Pediatrics, Department of Maternal Child and Adolescent Health,

Committee on Pediatric AIDS, 141 NW Point Blvd, Elk Grove Village, IL, 60007-1098, (847) 434-4000, <http://www.aap.org>.

Summary: This book chapter focuses on the clinical management of viral and bacterial perinatal infections. These include **cytomegalovirus**, herpes simplex, the human immunodeficiency virus (HIV), human papillomavirus, human parvovirus, rubella, varicella-zoster, group B streptococcal, listeriosis, syphilis, lyme disease, and chlamydia infection. For each of these infections, guidelines are provided on treatment and counseling during pregnancy, obstetric management, management of exposed newborns, nursery management, and early diagnosis. The section on HIV focuses on diagnostic criteria for adults, children, and infants; prevention; and management after delivery.

- **Directory of Chicago HIV/AIDS Clinical Trials. Translated title**

Contact: AIDS Foundation of Chicago, 411 S Wells Ste 300, Chicago, IL, 60607-3924, (312) 922-2322, <http://www.aidschicago.org>. Test Positive Aware Network, 5537 N Broadway, Chicago, IL, 60640, (773) 989-9400, <http://www.tpan.com>. African American AIDS Network, 1307 S Wabash Ave 2nd Fl, Chicago, IL, 60605, (773) 371-0032.

Summary: This directory provides access to clinical trials related to Acquired immunodeficiency syndrome (AIDS) in the Chicago area. It explains what clinical trials are and the Food and Drug Administration (FDA) approval process, and answers questions about drug studies. The entries include information on anemia, anorexia, **cytomegalovirus** (CMV) retinitis, meningitis, herpes simplex, histoplasmosis, Human immunodeficiency virus (HIV) infection, Kaposi's sarcoma, lymphoma, mycobacterial prophylaxis, *Pneumocystis carinii* pneumonia (PCP), and toxoplasma, and studies on women and children.

- **Compilation of Selected Abstracts on CMV Retinitis**

Contact: XI International Conference on AIDS, 595 Burrard St, Vancouver, (604) 878-9995.

Summary: This is a collection of abstracts from an international AIDS conference. The abstracts summarize research on **cytomegalovirus** (CMV) retinitis, a major opportunistic infection in individuals with HIV/AIDS. The articles summarize the state of the art in the management of CMV and recent advances in therapy. Several papers focus on the results of pharmaceutical research with ganciclovir, foscarnet, and cidofovir.

- **Kidney Transplant Rejection: Diagnosis and Treatment. 2nd ed**

Source: New York, NY: Marcel Dekker, Inc. 1992. 773 p.

Contact: Available from Marcel Dekker, Inc. P.O. Box 5005, Monticello, NY 12701. (800) 228-1160 or (212) 696-9000. Fax (914) 796-1772. E-mail: bookorders@dekker.com. PRICE: \$275.00. ISBN: 0824784871.

Summary: This medical text on the diagnosis and treatment of kidney transplant rejection presents 26 chapters in 4 sections: the biology of the allograft response; the diagnosis of rejection; new immunosuppressive agents; and systemic problems with immunosuppression. Specific topics include the mechanisms of cell-mediated rejection; the role of cytokines; suppressor cell regulation; antibody-mediated rejection; the pathology of acute tubular necrosis and acute rejection; fine needle aspiration biopsy; monitoring the components of the immune system; radionuclides in the evaluation of

kidney transplant rejection; magnetic resonance imaging; antilymphocyte antibody therapy; cyclosporine; nephrotoxicity; **cytomegalovirus** infection; cancer in recipients of organ allografts; HIV infection and kidney transplantation; and molecular biology of transplant rejection. Each chapter, written by international experts in the field, includes numerous charts and diagrams, as well as extensive references. A detailed subject index concludes the volume.

- **AIDS and Infections of Homosexual Men**

Contact: Butterworth Heinemann Publishers, 225 Wild Wood Ave, Woburn, MA, 01801, (800) 366-2665.

Summary: This monograph details clinical information on infections related to Acquired immunodeficiency syndrome (AIDS) that occur in homosexual men. The first section examines nondiarrheal Sexually transmitted disease (STD's), such as syphilis and proctitis due to *Chlamydia trachomatis*, and also examines the relationship of Human immunodeficiency virus (HIV) infection to infections with pathogenic neisseria. In the second section, authors turn to diarrheal STD's, including gay bowel syndrome, bacterial diarrhea, parasitic infectious diseases, cryptosporidiosis, isosporiasis, and microsporidiosis. The third section studies other STD's, beginning with Hepatitis B transmission as a model for AIDS. It also studies herpes simplex virus infection, **cytomegalovirus** infection in both healthy and immune deficient homosexual men, and laboratory diagnosis of STD's and opportunistic infections. The fourth section looks at infectious and neoplastic complications. It opens with a chapter on HIV as the etiologic agent of AIDS, then gives a revision of the Centers for Disease Control and Prevention (CDC) surveillance case definition for AIDS. The section also includes chapters on surveillance and epidemiology in the U.S between 1981 and 1985; clinical manifestations of Kaposi's Sarcoma and its treatment; neurology in AIDS; AIDS in prostitutes, children, and prisoners; AIDS in Europe; and opportunistic infections and their treatment. The fifth section turns to immunologic evaluation methods and controls, such as analysis of mechanisms of immune suppression. It also deals with immunologic responses, epidemiologic observations of immunologic abnormalities, immunogenetic findings in patients with Kaposi's Sarcoma, the significance of endogenous interferon and interferon-induced enzymes in patients with AIDS, and approaches to AIDS therapy. The sixth and final section provides a diagnostic perspective.

- **Sexually Transmitted Diseases: Problems in Primary Care**

Contact: Practice Management Information Corporation, 4727 Wilshire Blvd Ste 300, Los Angeles, CA, 90010, (800) 633-7467.

Summary: This monograph provides basic and practical information on sexually transmitted diseases (STDs). It is designed for physicians, particularly those practicing family and emergency medicine. The monograph describes how various STDs are spread and exactly what is meant by safe sexual practices. It covers the many types of venereal disease (VD) currently prevalent, as well as non-VD infections that can be spread by sexual contact. Each chapter deals with one type of disease, or groups of closely related diseases or infections. Methods of recognizing, treating, and preventing each disease are covered. The effectiveness and outcome statistics for treatments are discussed, with effectiveness based on current sensitivities of the infecting organism. The type of the organism and its life cycle are described. Chapters on the "classic" STDs include: gonorrhea, syphilis, lymphogranuloma venereum, and chancroid. Other chapters discuss: HIV infection, herpes simplex, **cytomegalovirus** (CMV), human papilloma virus (HPV), hepatitis, and chlamydia. The monograph also contains

information concerning related topics such as management of rape victims and contraception.

- **Herd Immunity and the HIV Epidemic**

Contact: HIVE Foundation, PO Box 808, Vacaville, CA, 95696.

Summary: This monograph suggests that persons with HIV infection are more susceptible to infection by a number of other viruses, and because they carry these viruses in their bodies for longer periods of time than normal, they are a potential source of epidemics among the general population. It looks at the rising incidence of a number of illnesses, including syphilis, salmonella, tuberculosis, hepatitis, **cytomegalovirus**, and influenza. The monograph advocates increased reporting, tracking, and screening of HIV-infected persons in order to prevent epidemics.

- **Medical Aspects of Hearing Loss for the Consumer and the Professional**

Source: Volta Review. 9(5): 1-203. November 1999.

Contact: Available from Alexander Graham Bell Association for the Deaf and Hard of Hearing, Subscription Department, 3417 Volta Place, NW, Washington, DC 20007-2778. Voice/TTY (202) 337-5220. Website: www.agbell.org. Also available as individual copies from Publication Sales Department, 3417 Volta Place, NW, Washington, DC 20007-2778. Voice/TTY (202) 337-5220. Website: www.agbell.org. PRICE: \$22.95 plus shipping and handling.

Summary: This monograph was written by assembling the leading experts from all over the country to present to both the consumer and the professional the latest information on the diagnosis and management of hearing loss in children and adults. Seventeen articles are included, on how the ear works, research on hearing and balance, screening for hearing loss in infants, hereditary hearing loss, hearing loss and **cytomegalovirus**, the emotional aspects of hearing loss, genetic counseling for hearing loss, otitis media (middle ear infections) in children, the diagnosis and management of tinnitus (ringing or buzzing in the ears), the evaluation and treatment of the patient with vertigo, immunologic disorders of the inner ear, sudden sensorineural hearing loss (the role of perilymph fistula), hearing loss in adults, otosclerosis, sudden hearing loss, Meniere's disease, and medications and characteristics of drugs causing ototoxicity. Each article includes a brief summary and references.

- **A Holistic Protocol for the Immune System**

Contact: Tree of Life Publications, PO Box 126, Joshua Tree, CA, 92252.

Summary: This self-help manual presents a holistic approach, or natural healing process, for patients with a compromised immune system. The author outlines a four-stage protocol to treat AIDS and HIV, kill the body's parasites, rebuild the adrenal and thyroid glands, rid the body of bacteria and fungi, and repair the immune system. Each phase of this protocol will last approximately four to six weeks. Following the introduction, the author provides detailed descriptions of the holistic protocols and products, and an overview of AIDS, HIV, herpes, hepatitis, chronic fatigue syndrome, candidiasis, Kaposi's sarcoma, **cytomegalovirus**, Pneumocystis carinii pneumonia (PCP), and staphylococcus and streptococcus infections.

- **Kidney Transplant Rejection: Diagnosis and Treatment. 3rd ed**

Source: New York, NY: Marcel Dekker, Inc. 1998. 680 p.

Contact: Available from Marcel Dekker, Inc. Cimarron Road, P.O. Box 5005, Monticello, NY 12701. (800) 228-1160 or (845) 796-1919. Fax (845) 796-1772. E-mail: custserv@dekker.com. International E-mail: intlcustserv@dekker.com. Website: www.dekker.com. PRICE: \$225.00 plus shipping and handling. ISBN: 0824701399.

Summary: This text on kidney transplant rejection is focused on basic immunological principles, mechanisms of rejection, diagnostic modalities, infections in the transplant setting, and clinical treatment of renal allograft rejection. All chapters have been contributed by recognized experts in the field of renal transplantation. Twenty-two chapters cover the molecular basis for transplantation immunity, the mechanisms of cell mediated rejection, cytokines (regulators and effectors of the immune response), regulation of allograft rejection by anti-idiotypic responses, clinical syndromes associated with antibody in allografts, renal injury and preservation in transplantation, mechanism of chronic rejection, xenotransplantation, histocompatibility and organ allocation, immunological tolerance and its relationship to clinical transplantation, pathology of kidney transplantation, fine needle aspiration cytology, the sonographic evaluation of acute renal transplant rejection, the history and prospects for antilymphocyte antibody therapy for tolerance induction, mechanisms of action of immunosuppressive agents (cyclosporine, FK506, rapamycin), the clinical use of cyclosporine in kidney transplantation, tacrolimus and mycophenolate mofetil as primary immunosuppression for renal allograft recipients, newer immunosuppressive agents and combination therapy, immune monitoring for transplant recipients, cancer in recipients of organ allografts, the impact of **cytomegalovirus** infection on renal transplantation, and hepatitis in the renal allograft recipient. Each chapter, written by experts in the field, includes lengthy references; a subject index concludes the text.

Book Summaries: Online Booksellers

Commercial Internet-based booksellers, such as Amazon.com and Barnes&Noble.com, offer summaries which have been supplied by each title's publisher. Some summaries also include customer reviews. Your local bookseller may have access to in-house and commercial databases that index all published books (e.g. Books in Print®). **IMPORTANT NOTE:** Online booksellers typically produce search results for medical and non-medical books. When searching for "cytomegalovirus" at online booksellers' Web sites, you may discover non-medical books that use the generic term "cytomegalovirus" (or a synonym) in their titles. The following is indicative of the results you might find when searching for "cytomegalovirus" (sorted alphabetically by title; follow the hyperlink to view more details at Amazon.com):

- **Controversies in Transfusion Medicine: Immune Complications and Cytomegalovirus Transmission** by Sanford R. Kurtz, et al; ISBN: 0915355876; <http://www.amazon.com/exec/obidos/ASIN/0915355876/icongroupinterna>
- **Cytomegalovirus** by Herve Guibert, Clara Orban (Translator); ISBN: 076180305X; <http://www.amazon.com/exec/obidos/ASIN/076180305X/icongroupinterna>
- **Cytomegalovirus**; ISBN: 9067670987; <http://www.amazon.com/exec/obidos/ASIN/9067670987/icongroupinterna>
- **Cytomegalovirus (CMV) infection and your child (SuDoc HE 20.3002:IN 3/3)** by U.S. Dept of Health and Human Services; ISBN: B00010L57Q; <http://www.amazon.com/exec/obidos/ASIN/B00010L57Q/icongroupinterna>

- **Cytomegalovirus and Immunity** by John D. Hamilton; ISBN: 3805534957;
<http://www.amazon.com/exec/obidos/ASIN/3805534957/icongroupinterna>
- **Cytomegalovirus Protocols** by John Sinclair (Editor); ISBN: 0896037495;
<http://www.amazon.com/exec/obidos/ASIN/0896037495/icongroupinterna>
- **Cytomegalovirus: Biology and Infection** by Monto Ho; ISBN: 0306408449;
<http://www.amazon.com/exec/obidos/ASIN/0306408449/icongroupinterna>
- **Ganciclovir Therapy for Cytomegalovirus Infection** by Stephen A. Spector (Editor); ISBN: 082478572X;
<http://www.amazon.com/exec/obidos/ASIN/082478572X/icongroupinterna>
- **Human cytomegalovirus infection; journal articles, a collection of selected papers** by James Barry Hanshaw; ISBN: 0874885221;
<http://www.amazon.com/exec/obidos/ASIN/0874885221/icongroupinterna>
- **Molecular Aspects of Human Cytomegalovirus Diseases (Frontiers of Virology, 2)** by G. Darai, et al; ISBN: 0387559485;
<http://www.amazon.com/exec/obidos/ASIN/0387559485/icongroupinterna>
- **Multidisciplinary Approach to Understanding Cytomegalovirus Disease: Proceedings of the Fourth International Cytomegalovirus Workshop: Multidisciplina** by Stanley A. Plotkin (Editor), Susan Michelson (Editor); ISBN: 0444816992;
<http://www.amazon.com/exec/obidos/ASIN/0444816992/icongroupinterna>
- **Progress in Cytomegalovirus Research: Proceedings of the Third International Cytomegalovirus Workshop, Bologna, 11-14 June, 1991** by Italy)/ Landini, Maria Paola International Cytomegalovirus Workshop 1991 Bologna (Editor); ISBN: 0444893377;
<http://www.amazon.com/exec/obidos/ASIN/0444893377/icongroupinterna>

Chapters on Cytomegalovirus

In order to find chapters that specifically relate to cytomegalovirus, an excellent source of abstracts is the Combined Health Information Database. You will need to limit your search to book chapters and cytomegalovirus using the "Detailed Search" option. Go to the following hyperlink: <http://chid.nih.gov/detail/detail.html>. To find book chapters, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Book Chapter." Type "cytomegalovirus" (or synonyms) into the "For these words:" box. The following is a typical result when searching for book chapters on cytomegalovirus:

- **AIDS and Related Conditions**

Source: in Little, J.W., et al. Dental Management of the Medically Compromised Patient. 5th ed. St. Louis, MO: Mosby, Inc. 1997. p. 325-356.

Contact: Available from Harcourt Health Sciences. 11830 Westline Industrial Drive, St. Louis, MO 63146. (800) 325-4177. Fax (800) 874-6418. Website: www.harcourthealth.com. PRICE: \$48.00 plus shipping and handling. ISBN: 0815156340.

Summary: A working knowledge of the multitude of compromised health states is essential for dental professionals, as the majority of medically compromised patients need or want oral health care. This chapter on AIDS and related conditions is from a text that provides the dental practitioner with an up to date reference work describing the dental management of patients with selected medical problems. After an introductory

section that covers definitions, morbidity and mortality statistics, and geographic factors, the authors discuss incidence and prevalence, etiology, pathophysiology and complications, signs and symptoms (clinical presentation and laboratory findings), the medical management of patients with AIDS, managing opportunistic infections (cytomegalovirus, herpes viruses, Epstein Barr virus, human papillomavirus), and the dental management of this population. Dental considerations include the prevention of medical complications, patient evaluation, treatment planning considerations, and common oral complications in patients with AIDS, including candidiasis, Kaposi's sarcoma, hairy leukoplakia, aphthous lesions (canker sores), HIV periodontal disease, salivary gland disease, and lymphadenopathy. 18 figures. 16 tables. 108 references.

- **Gastritis and Peptic Ulcer Disease in Children**

Source: in Brandt, L., et al., eds. *Clinical Practice of Gastroenterology*. Volume Two. Philadelphia, PA: Current Medicine. 1999. p. 1294-1300.

Contact: Available from W.B. Saunders Company. Order Fulfillment, 6277 Sea Harbor Drive, Orlando, FL 32887. (800) 545-2522. Fax (800) 874-6418 or (407) 352-3445. Website: www.wbsaunders.com. PRICE: \$235.00 plus shipping and handling. ISBN: 0443065209 (two volume set); 0443065217 (volume 1); 0443065225 (volume 2).

Summary: Gastritis in children remains underrecognized and poorly characterized. This chapter on gastritis and peptic ulcer disease in children is from a lengthy textbook that brings practitioners up to date on the complexities of gastroenterology practice, focusing on the essentials of patient care. This chapter covers anatomy and physiology; etiology, pathology and clinical features; nonerosive, nonspecific gastritis or chronic active gastritis; specific and distinctive types of gastritis; peptic ulcer disease (PUD), and duodenitis. Specific types of gastritis covered include Crohn's disease, chronic granulomatous disease, eosinophilic gastropathy, allergic gastropathy, Menetrier's disease, chronic varioliform gastritis, graft versus host disease, and **cytomegalovirus**. The author notes that in children with chronic peptic ulcer disease, duodenal ulcers are far more prevalent than are gastric ulcers. Secondary PUD usually occurs in association with an identifiable ulcerogenic agent or circumstance, including ulcers caused by physiologic stress, drugs, and those associated with other diseases. The ulcers are more often acute and are more prevalent in the stomach than in the duodenum. The treatment of specific disorders in children is similar to that in adults. The difference in treatment results from the issues specific to children: the management of fluid and electrolyte balance in resuscitation; dosage, palatability and appropriate form of medications; and the potential adverse effects of medications. 3 tables. 34 references.

- **Infection-Associated Glomerulonephritis**

Source: in Catto, G.R.D. *New Clinical Applications-Nephrology: Glomerulonephritis*. Hingham, MA: Kluwer Academic Publishers. p. 69-95. 1990.

Contact: Available from Kluwer Academic Publishers. P.O. Box 358, Accord Station, Hingham, MA 02018-0358. (617) 871-6600. PRICE: \$54. ISBN: 0746201095.

Summary: Infections with many organisms may produce glomerular lesions. This review concentrates on the glomerular consequences of infection with specific organisms. Separate detailed attention is given to each specific source of infection, covering viral (hepatitis B, **cytomegalovirus**, HIV), bacterial (*Streptococcus*, *Staphylococcus*, *Treponema pallidum*, *Mycobacterium leprae*), and parasitic (*Plasmodium malariae*, *Schistosoma mansoni*) infections. Rarer types of infection also are discussed. It is concluded that, in most patients, the glomerular changes are induced

by an immune mechanism as a consequence of exposure to a foreign antigen or by modification of a host protein, making it antigenic with a subsequent autologous response. Since organisms (even of the same species) vary with respect to their nephritogenic potential and the response obtained is governed by a wide variety of patient characteristics (including genetic and nutritional), it not surprising that a uniform glomerular response is seldom obtained following a specific infection. 72 references.

- **Kidney Transplantation**

Source: in Schena, F.P., ed. *Nephrology*. New York, NY: McGraw-Hill, Inc. 2001. p. 451-462.

Contact: Available from McGraw-Hill, Inc. Shoppenhangers Road, Maidenhead, Berkshire SL6 2QL. 44 (0)1628 502700. Fax: +44 (0)1628 635895 E-mail: emea_orders@mcgraw-hill.com. Website: www.mcgraw-hill.co.uk. PRICE: \$79.95; plus shipping and handling. ISBN: 0077095251.

Summary: Kidney (renal) transplantation is now accepted all over the world as the treatment for patients in end stage renal failure that not only restores life, but also gives an acceptable quality of life to such patients. This chapter on kidney transplantation is from a book on nephrology (the study of the kidney and kidney diseases) designed for general practitioners and family care providers that offers strategies for the management of patients with renal (kidney) damage. The author notes that the transplantability of patients with renal disease can be screened with pretransplantation checklists. The HLA system is important in kidney transplantation for two reasons: anti donor HLA antibodies may lead to hyperacute rejection, and better matching for donor and recipient HLA leads to better results posttransplantation. This is true for both postmortal (cadaver) and living donor kidney transplantation. Immunosuppression is a necessity after kidney transplantation and can never be stopped completely. Most transplant centers start patients with a combination of corticosteroids and a calcineurin inhibitor (such as cyclosporine A or FK506). Other immunosuppressive agents can be added. The most frequent infection incurred after kidney transplantation is **cytomegalovirus**. For optimal treatment of transplanted patients, transplant physicians with special knowledge of opportunistic infections and immunosuppressive drugs have to be part of the therapeutic team. Chronic graft loss is still the major problem after kidney transplantation. 4 figures. 7 tables. 12 references.

- **Hearing Loss Associated With Perinatal Infections**

Source: in Pappas, D.G. *Diagnosis and Treatment of Hearing Impairment in Children*. 2nd ed. San Diego, CA: Singular Publishing Group, Inc. 1998. p. 97-114.

Contact: Available from Singular Publishing Group, Inc. 401 West 'A' Street, Suite 325, San Diego, CA 92101-7904. (800) 521-8545. Fax (800) 774-8398. E-mail: singpub@mail.cerfnet.com. Website: www.singpub.com. PRICE: \$55.00 plus shipping and handling. ISBN: 1565938658.

Summary: Of all known causes of hearing loss in neonates and children, perhaps the most difficult to confirm are those resulting from infectious agents. This chapter on hearing loss associated with perinatal infections is from a text that discusses the prevention, diagnosis, and treatment of hearing impairment in children. The chapter covers the classifications of infections, screening for causes of hearing loss, **cytomegalovirus** (CMV), rubella, and syphilis. For each of the infections, the authors describe incidence, the impact of the infection on sensorineural hearing loss (SNHL),

pathophysiology, diagnosis, and treatment options. The authors also note that although congenital hearing loss induced by viral infection has been proved, a viral cause is difficult to ascertain in cases of acquired hearing impairment. 1 figure. 2 tables. 56 references.

- **Management of Severe Ulcerative Colitis**

Source: in Bayless, T.M. and Hanauer, S.B. *Advanced Therapy of Inflammatory Bowel Disease*. Hamilton, Ontario: B.C. Decker Inc. 2001. p. 143-147.

Contact: Available from B.C. Decker Inc. 20 Hughson Street South, P.O. Box 620, L.C.D. 1 Hamilton, Ontario L8N 3K7. (905) 522-7017 or (800) 568-7281. Fax (905) 522-7839.

Email: info@bcdecker.com. Website: www.bcdecker.com. PRICE: \$129.00 plus shipping and handling. ISBN: 1550091220.

Summary: Severe or fulminant ulcerative colitis (UC) is a potentially fatal disease that was associated with a 30 percent mortality rate prior to the introduction of corticosteroids and, in steroid-refractory cases, early surgery. During recent years, the trend has changed from saving lives to improving the quality of life of patients by saving colons or using modern surgical methods. This chapter on the management of severe UC is from the second edition of a book devoted to the details of medical, surgical, and supportive management of patients with Crohn's disease (CD) and UC, together known as inflammatory bowel disease (IBD). The author discusses the etiology, differential diagnosis, and definition of severe UC. Patients with definite or strongly suspected severe colitis must be admitted to the hospital for intensive treatment. The mainstay of the medical treatment is corticosteroids, taken orally with nothing except small sips of water, and total parenteral nutrition (TPN, outside the gastrointestinal tract). Usually, corticosteroids are administered intravenously in severe colitis, but even in acute colitis, corticosteroids given orally are absorbed completely but somewhat more slowly than those administered intravenously. Colonoscopy, rather than food challenge, is relied on to improve decision making in patients with incomplete or poor response to treatment. The author discusses the indications for using antibiotics, 5 aminosalicylic acid (5 ASA), and immunosuppressives. Beyond the drug therapy, the patient must be monitored carefully. Three or 4 days after initiating therapy, a sigmoidoscopy is of further help in monitoring the response and a biopsy helps to rule out **cytomegalovirus**. Assessment of response is made mainly on clinical and laboratory grounds, although repeat plain abdominal radiography during ongoing treatment can show signs of impending perforation or definite toxic dilatation that requires surgery. 1 table. 10 references.

- **Viral Arthritis**

Source: in Maddison, P.J.; et al., Eds. *Oxford Textbook of Rheumatology*. Volume 2. New York, NY: Oxford University Press, Inc. 1993. p. 552-560.

Contact: Available from Oxford University Press, Inc., New York, NY.

Summary: This chapter for health professionals focuses on viral causes of arthritis. Virus-host interactions are examined. The viral pathogenesis of arthritis is explained. The structure, epidemiology, clinical and rheumatic manifestations, pathogenesis, diagnosis, treatment, and outcome of various viruses or virus vaccines are discussed. These viruses or vaccines include rubella and the rubella vaccine, human parvovirus B19, hepatitis B and hepatitis B vaccine, mumps, and arboviruses. In addition, enteroviruses, variola and vaccinia viruses, adenovirus, varicella-zoster, Epstein-Barr virus, herpes simplex virus, and **cytomegalovirus** are described. 45 references.

- **Oral Manifestations of HIV Infection and AIDS**

Source: in Merigan, T.C., Jr.; Bartlett, J.G.; Bolognesi, D., eds. Textbook of AIDS Medicine. 2nd ed. Baltimore, MD: Williams and Wilkins. 1999. p. 521-535.

Contact: Available from Williams and Wilkins. 351 West Camden Street, Baltimore, MD 21201-2436. (800) 638-0672. Fax (800) 447-8438. E-mail: custserv@wwilkins.com. Website: www.wwilkins.com. PRICE: \$155.00. ISBN: 0683302167.

Summary: This chapter from a textbook of AIDS medicine focuses on the oral manifestations of HIV infection and AIDS. Topics include epidemiology, including the significance of oral manifestations, the prevalence, incidence, and classification of these findings; neoplasms, including Kaposi's sarcoma, lymphoma, and oral cancer; fungal lesions, including oral candidiasis, erythematous candidiasis, pseudomembranous candidiasis, and angular cheilitis; viral lesions, including herpes simplex, varicella zoster virus (VZV), **cytomegalovirus**, hairy leukoplakia, and papillomavirus lesions; bacterial infections, including periodontal diseases such as gingivitis and necrotizing ulcerative periodontitis; idiopathic or autoimmune lesions, including recurrent aphthous ulcers, HIV-associated salivary gland disease, immune thrombocytopenic purpura, and abnormal pigmentation; the oral complications associated with pediatric HIV infection; and other oral problems associated with HIV infection. For each condition discussed, the authors report symptoms, diagnosis, and basic management strategies, including drug therapy where appropriate. The authors conclude that initial clinical impressions concerning the frequency of oral lesions and their place in the natural history and progression of HIV disease and AIDS have been supported by a substantial number of studies. However, standardized classification schemes, definitions, and diagnostic criteria are far from being applied universally. 12 figures. 1 table. 191 references.

- **Acquired Hearing Impairment**

Source: in Mencher, G.T.; Gerber, S.E.; McCombe, A. Audiology and Auditory Dysfunction. Needham Heights, MA: Allyn and Bacon. 1997. p. 143-165.

Contact: Available from Allyn and Bacon. 160 Gould Street, Needham Heights, MA 02194-2310. (800) 278-3525; Fax (617) 455-7024; E-mail: AandBpub@aol.com; http://www.abacon.com. PRICE: \$46.95 plus shipping and handling. ISBN: 0205161014.

Summary: This chapter on acquired hearing impairment is from an audiology textbook on auditory dysfunction. The author notes that, from a clinical perspective, the auditory behavior of an acquired loss is not very different from that of a congenital loss, and the audiological treatment thus may be similar. The overt results of systemic disturbances, diseases, and hereditary degenerative disorders, all acquired, are often quite similar and difficult to tell apart, and therefore lend themselves to combined study. On the other hand, ototoxicity, noise trauma, and presbycusis (hearing loss due to aging) each has its own special effect on hearing and thus are discussed in separate chapters. This chapter covers tinnitus and recruitment; acquired disease, including **cytomegalovirus**, mumps, AIDS, herpes, meningitis, and syphilis; sudden onset and degenerative disorders; trauma; and hearing loss associated with systemic disease, including thyroid disease, diabetes mellitus, kidney disease, multiple sclerosis, connective tissue disease, and Meniere's disease. Hearing impairment after viral or bacterial disease is usually unchanging, that is, the hearing loss should not get worse. Metabolic disorders often display fluctuating hearing losses. Except for Meniere's disease, there is little that can be done surgically specifically for acquired sensory hearing impairments. They are not subject to surgical intervention, nor are they usually amenable to medical otologic

treatment. Of course, the underlying disease is a medical problem that needs to be treated, and that treatment may have a beneficial effect on the hearing impairment. 6 figures. 1 table.

- **Congenital Hearing Impairment**

Source: in Mencher, G.T.; Gerber, S.E.; McCombe, A. *Audiology and Auditory Dysfunction*. Needham Heights, MA: Allyn and Bacon. 1997. p. 117-142.

Contact: Available from Allyn and Bacon. 160 Gould Street, Needham Heights, MA 02194-2310. (800) 278-3525; Fax (617) 455-7024; E-mail: AandBpub@aol.com; <http://www.abacon.com>. PRICE: \$46.95 plus shipping and handling. ISBN: 0205161014.

Summary: This chapter on congenital hearing impairment is from an audiology textbook on auditory dysfunction. After a brief discussion delineating the differences between congenital and genetic, the author discusses the etiology and pathology of congenital genetic deafness, forms of pathology, and associated anomalies, including integumentary, skeletal, ocular, and other anomalies. The second section of the chapter addresses congenital nongenetic deafness, including viral deafness due to rubella or **cytomegalovirus**, protozoal infections, and the remaining causes of the TORCHS (Toxoplasmosis, Rubella, **Cytomegalovirus**, Herpes, and Syphilis) syndrome, i.e., congenital syphilis and herpes simplex virus. The chapter concludes with a discussion of the medical and audiological considerations for patients with congenital hearing impairment. The author notes that audiometric data should not lead to the assumption that a profoundly hearing impaired patient should not be provided with amplification. When examining and when providing rehabilitative programming, the audiologist must consider all the special problems of someone who has never had any hearing or never had sufficient hearing to communicate aurally. 2 tables. 11 figures.

- **Eyes**

Source: in Daugirdas, J.T. and Ing, T.S., eds. *Handbook of Dialysis*. 2nd ed. Boston, MA: Little, Brown and Company. 1994. p. 590-597.

Contact: Available from Lippincott-Raven Publishers. 12107 Insurance Way, Hagerstown, MD 21740. (800) 777-2295. Fax (301) 824-7390. E-mail: lrorders@phl.lrpublish.com. Website: <http://www.lrpublish.com>. PRICE: \$37.95. ISBN: 0316173835.

Summary: This chapter on eye diseases is from a handbook that outlines all aspects of dialysis therapy, emphasizing the management of dialysis patients. The author notes that, with infrequent exceptions, kidney disorders do not directly affect vision or change the morphology of the eyes. Ophthalmic complications of diabetes mellitus, the first-ranked cause of irreversible renal failure, are the most prevalent eye disorders noted in dialysis patients. Two sections cover anterior eye disease, including conjunctivitis, corneal-conjunctival calcification, ocular pressure and glaucoma, and cataracts; and posterior eye disease, including complications of hypertension, complications of diabetes, retinal toxicity associated with deferoxamine (DFO) administration, retinal findings with selected systemic infections, including bacterial endocarditis, **cytomegalovirus** infection, systemic candidiasis, and HIV, and retinal oxalosis. The author presents information in outline form, for easy reference. 1 table. 13 references.

- **Infections, Intoxication, and Iatrogens**

Source: in Gerber, S.E. *Etiology and Prevention of Communicative Disorders*. 2nd ed. San Diego, CA: Singular Publishing Group, Inc. 1998. p. 83-127.

Contact: Available from Singular Publishing Group, Inc. 401 West 'A' Street, Suite 325, San Diego, CA 92101-7904. (800) 521-8545 or (619) 238-6777. Fax (800) 774-8398 or (619) 238-6789. E-mail: singpub@singpub.com. Website: www.singpub.com. PRICE: \$65.00 plus shipping and handling. ISBN: 1565939476.

Summary: This chapter on infection, intoxication, and iatrogens is from a textbook that focuses on the primary and secondary prevention of communicative disorders. In this chapter, the author focuses on exogenous factors for communication disorders, that is, factors that come from outside the organism. The author discusses viral diseases, including rubella, **cytomegalovirus**, and AIDS; protozoal diseases, including syphilis, and toxoplasmosis; bacterial diseases; maternal diseases, including diabetes, thyroid disorders, and hyperbilirubinemia; acquired diseases; intoxication, including environmental toxins, lead and other metals, radiation, petroleum and petroleum products, pesticides and other chemicals, foods and food additives, social toxins, fetal alcohol syndrome, drugs, and smoking; and iatrogens, including teratogens, neurotoxins, ototoxicity, antibiotics, loop diuretics, antimalarial agents, and antineoplastic or chemotherapeutic agents. The author concludes with a brief discussion of the preventive efforts appropriate in these areas. The chapter concludes with a glossary of terms and a reference list. 13 figures. 6 tables. 183 references.

- **Infections**

Source: in Daugirdas, J.T. and Ing, T.S., eds. *Handbook of Dialysis*. 2nd ed. Boston, MA: Little, Brown and Company. 1994. p. 469-490.

Contact: Available from Lippincott-Raven Publishers. 12107 Insurance Way, Hagerstown, MD 21740. (800) 777-2295. Fax (301) 824-7390. E-mail: lrorders@phl.lrpublish.com. Website: <http://www.lrpublish.com>. PRICE: \$37.95. ISBN: 0316173835.

Summary: This chapter on infections is from a handbook that outlines all aspects of dialysis therapy, emphasizing the management of dialysis patients. Topics include the derangement of immune function in uremia, including etiology and the increased susceptibility to infection; the derangement of temperature control in uremia; the incidence and management of bacterial infections in hemodialysis and peritoneal dialysis patients; infections unrelated to the access site, including urinary tract infection, pneumonia, intraabdominal infections, tuberculosis, listeriosis, *Salmonella* septicemia, *Yersinia* septicemia, and mucormycosis; viral infections, including hepatitis A, hepatitis B, hepatitis C, **cytomegalovirus** and mononucleosis, influenza, AIDS, routine screening, and dialysis in patients who are HIV positive; vaccination in dialysis patients; and antimicrobial usage in dialysis patients. The authors present information in outline form, for easy reference. The chapter features a lengthy chart outlining the usual nonuremic dosage, dialysis patient dosage, post-hemodialysis supplements, and dosage for CAPD for each antimicrobial agent in common use. 3 tables. 21 references.

- **Infectious Agents as Aggravating Factors in Inflammatory Bowel Disease**

Source: in Bayless, T.M. and Hanauer, S.B. *Advanced Therapy of Inflammatory Bowel Disease*. Hamilton, Ontario: B.C. Decker Inc. 2001. p. 95-98.

Contact: Available from B.C. Decker Inc. 20 Hughson Street South, P.O. Box 620, L.C.D. 1 Hamilton, Ontario L8N 3K7. (905) 522-7017 or (800) 568-7281. Fax (905) 522-7839. Email: info@bcdecker.com. Website: www.bcdecker.com. PRICE: \$129.00 plus shipping and handling. ISBN: 1550091220.

Summary: This chapter on infectious agents as aggravating factors is from the second edition of a book devoted to the details of medical, surgical, and supportive management of patients with Crohn's disease (CD) and ulcerative colitis (UC), together known as inflammatory bowel disease (IBD). When patients present with diarrhea, one of the first questions is whether it is an infection or an attack of IBD. Initial symptoms may be very similar, including diarrhea (with or without blood), abdominal pain or cramps, fever, and even arthralgias (pain in the joints). Clinical features that favor infection are acute onset of diarrhea (often greater than 10 bowel movements per day) and fever early in the course. Conversely, IBD usually has a more insidious onset, fewer than 6 bowel movements daily, and early fever is uncommon. Colonoscopic features can suggest infection or UC, but are rarely diagnostic. Mucosal biopsy, however, can be useful in distinguishing acute self-limited colitis or infectious-type colitis from IBD. However, to further complicate matters, infections sometimes can precipitate IBD, and intercurrent (happening at the same time) infections can mimic or induce flares of IBD. This chapter considers infections that mimic IBD, including amebic colitis and chronic infectious colitides (including *Entamoeba histolytica* and *Yersinia*); and infections that aggravate IBD, including *Campylobacter jejuni*, *Salmonella*, *Shigella*, *Escherichia coli*, *Clostridium difficile*, **Cytomegalovirus**, Herpes simplex virus, parasites, and mycobacterium. 1 table. 22 references.

- **Viral Infections**

Source: in Greenspan, D., et al. AIDS and the Mouth. Copenhagen, Denmark: Munksgaard. 1992. p. 113-134.

Contact: Available from Munksgaard. 35 Norre Sogade, P.O. Box 2148, DK-1016, Copenhagen K, Denmark. Telephone +45 33 12 70 30; Fax +45 33 12 93 87; E-mail: bookservice@mail.munksgaard.dk; <http://www.munksgaard.dk/publishers/>. PRICE: DKK 516 plus postage; contact directly for current price in US dollars. ISBN: 8716103211.

Summary: This chapter on oral viral infections related to HIV is from a medical textbook on the diagnosis and management of oral lesions related to AIDS. The authors cover herpes simplex, varicella zoster virus (chickenpox and herpes zoster), **cytomegalovirus**, human papillomavirus, and hairy leukoplakia. The section on hairy leukoplakia is the most extensive, considering clinical features, histopathology, etiology and pathogenesis, transformation to AIDS, differential diagnosis, definitive diagnosis, and management of the condition. Full-color photographs illustrate each of the lesions described; some depict lesions before and after treatment. 23 figures. 2 tables. 58 references.

- **Other Colitides**

Source: in Kirsner, J.B., ed. Inflammatory Bowel Disease. 5th ed. Saint Louis, MO: W.B. Saunders Company. 1999. p. 410-423.

Contact: Available from W.B. Saunders Company. Book Order Fulfillment Department, 11830 Westline Industrial Drive, Saint Louis, MO 63146-9988. (800) 545-2522. Fax (800) 568-5136. E-mail: wbsbcs@harcourt.com. Website: www.wbsaunders.com. PRICE: \$145.00 plus shipping and handling. ISBN: 0721676162.

Summary: This chapter on other colitides in inflammatory bowel disease (IBD) is from a comprehensive textbook that describes all the latest scientific and clinical advances in the field of IBD, including etiology and pathogenesis, evaluation and classification, medical and surgical therapies, and patient care management. The other colitides include collagenous and lymphocytic colitis, and infectious colitis, including colitis due to bacteria (such as *Clostridium difficile* or *Escherichia coli*), mycobacteria (tuberculosis, *Salmonella*, *Shigella*, or *Yersinia*), viral infection (including **cytomegalovirus** or HIV), protozoa (including *cryptosporidium*), other parasites, and fungal infection (including with *Candida* and *Aspergillus*). In each section the author discusses symptoms, diagnosis, associations with other gastrointestinal diseases, and treatment options. The author notes that the mimicry of ulcerative colitis and Crohn's disease by other forms of colitis and by many bacterial, viral, and protozoan infections reflects the well known limitation of the intestine's clinical and morphologic responsiveness to disease. This restriction emphasizes the importance of the careful evaluation of all patients with intestinal symptoms (diarrhea, rectal bleeding, and associated symptoms), not only to recognize treatable (curable) diseases but also to identify clues as to the nature and treatment of IBD. 4 figures. 8 tables. 101 references.

- **Auditory System and Related Disorders**

Source: in Gelfand, S.A. *Essentials of Audiology*. 2nd ed. New York, NY: Thieme Medical Publishers, Inc. 2001. p. 173-218.

Contact: Available from Thieme Medical Publishers, Inc. 333 Seventh Avenue, New York, NY 10001. (800) 782-3488. Fax (212) 947-0108. E-mail: custserv@thieme.com. PRICE: \$49.00 plus shipping and handling. ISBN: 1588900177.

Summary: This chapter on the auditory (hearing) system and related disorders is from an undergraduate textbook that deals with audiology and related topics in speech language pathology. The author addresses the nature of various pathologies (problems or diseases), where and when they occur, their major signs and symptoms, how hearing is affected, and the ways they are treated. The author first explains the importance of the case history in diagnosis and patient care. The chapter then covers conductive, sensorineural, and mixed hearing impairments; tinnitus (ringing or buzzing sounds in the ears); congenital and hereditary disorders; maternal infections, including syphilis, toxoplasmosis, rubella, **cytomegalovirus** (CMV); other influences in the maternal environment; congenital anomalies of the ear, including dysplasia (abnormal development in the anatomical structure); syndromes involving the ear and hearing; acquired disorders, including head trauma; outer ear disorders, including impacted cerumen (earwax), foreign bodies, growths and tumors, and infections; middle ear disorders, including bullous myringitis, tympanosclerosis, perforations of the tympanic membrane (eardrum), otitis media (middle ear infection), and otosclerosis (bone disease); surgery to improve or restore hearing, including otosclerosis surgery, tympanoplasty (repair and reconstruction of the eardrum), and surgery for growths and tumors; cochlear disorders, including noise induced hearing loss (NIHL), Meniere's disease, ototoxicity (chemical damage to the ear), infections, perilymphatic fistulas; retrocochlear disorders; auditory neuropathy; central disorders; sudden hearing loss; presbycusis (hearing loss related to aging); Paget's disease (osteitis deformans, a progressive bone disease); obscure auditory dysfunction; and nonorganic hearing loss. 19 figures. 2 tables. 138 references.

- **Oral Manifestations: Classification**

Source: in Greenspan, D., et al. *AIDS and the Mouth*. Copenhagen, Denmark: Munksgaard. 1992. p. 85-90.

Contact: Available from Munksgaard. 35 Norre Sogade, P.O. Box 2148, DK-1016, Copenhagen K, Denmark. Telephone +45 33 12 70 30; Fax +45 33 12 93 87; E-mail: bookservice@mail.munksgaard.dk; <http://www.munksgaard.dk/publishers/>. PRICE: DKK 516 plus postage; contact directly for current price in US dollars. ISBN: 8716103211.

Summary: This chapter on the classification of oral manifestations of HIV infection is from a medical textbook on the diagnosis and management of oral lesions related to AIDS. The authors define and classify fungal infections including candidiasis, histoplasmosis, cryptococcoses, and geotrichosis; bacterial infections including necrotizing gingivitis and progressive periodontitis, mycobacterium avium intracellular, actinomycosis, cat-scratch disease, Klebsiella pneumoniae infection, Enterobacter cloacae, Escherichia coli, exacerbation of apical periodontitis, sinusitis, and submandibular cellulitis; viral infections including herpetic stomatitis, **cytomegalovirus**, Epstein-Barr virus, varicella zoster virus, and papillomavirus lesions; neoplasms including Kaposi's sarcoma, non-Hodgkin's lymphoma, and squamous cell carcinoma; neurologic disturbances including trigeminal neuropathy and facial palsy; and oral manifestations of unknown cause, including recurrent aphthous ulceration (RAU), progressive necrotizing ulceration, toxic epidermolysis (Lyell's syndrome), delayed wound healing, idiopathic thrombocytopenia, salivary gland enlargement, xerostomia, and oral mucosal hyperpigmentation. The authors note that this classification system is designed to be used in epidemiologic studies. 2 tables. 6 references.

- **Diagnosis and Management of Soft-Tissue Lesions**

Source: in *Oral Health Care for Adults, Adolescents, and Children with HIV Infection*. New York, NY: AIDS Institute, New York State Department of Health. 1998. p. 6-1 to 6-17.

Contact: Available from New York State Department of Health. AIDS Institute, Director, HIV Educational Materials, 5 Penn Plaza, First Floor, New York, NY 10001. Fax (212) 613-4996. PRICE: Single copy free. Order number 9290.

Summary: This chapter on the diagnosis and management of soft tissue lesions is from a handbook that assists dentists, dental hygienists, dental assistants, and primary care providers in providing patients with HIV infection with the most up to date care. The authors emphasize that oral health care is an important component of the overall management of patients with HIV infection. The chapter opens by noting that oral manifestations of HIV infection include candidiasis, hairy leukoplakia, Kaposi's sarcoma, and several different types of oral ulcers, such as atypical herpes simplex ulceration, major aphthous-like ulcers, **cytomegalovirus** (CMV) related oral ulceration, and ulcers due to histoplasmosis and lymphoma. The chapter then offers specific recommendations and discusses their implementation. Topics discussed include oral lesions, oral candidiasis (diagnosis, treatment, and medications), topical medications for angular cheilitis, special considerations for systemic antifungal medications, hairy leukoplakia (diagnosis and treatment), herpes simplex ulceration (diagnosis, treatment, managing acyclovir-resistant herpes simplex), aphthous ulcers, **cytomegalovirus** infection, Kaposi's sarcoma, salivary gland disease associated with HIV infection (including xerostomia, or dry mouth), human papillomavirus infection, and mucosal melanin pigmentation. 8 references.

- **Sensorineural Hearing Loss in Children: Etiology and Pathology**

Source: in Martin, F.N.; Greer Clark, J., eds. *Hearing Care for Children*. Needham Heights, MA: Allyn and Bacon. 1996. p. 73-91.

Contact: Available from Allyn and Bacon. 160 Gould Street, Needham Heights, MA 02194-2310. (800) 278-3525; Fax (617) 455-7024; E-mail: AandBpub@aol.com; <http://www.abacon.com>. PRICE: \$59.00 plus shipping and handling. ISBN: 0131247026.

Summary: This chapter on the etiology and pathology of sensorineural hearing loss is from a textbook that focuses on the provision of hearing care for children with hearing loss. Topics covered include the etiologies of congenital hearing loss, including ototoxic drugs, teratogenic drugs, viral infections (maternal rubella, **cytomegalovirus**, herpes simplex, HIV), toxoplasmosis, erythroblastosis fetalis, and prematurity and birth trauma; the etiologies of acquired hearing loss, including bacterial infections, syphilis, viral diseases, neoplastic disorders (cancer), traumatic injury, acoustic trauma, metabolic disorders, and sudden deafness; monitoring dynamic sensorineural hearing loss in children; and medical diagnosis and treatment strategies. The authors emphasize that health care cost containment and the medical and legal implications of missed or delayed diagnosis of sensorineural hearing loss in children are critical issues for the pediatric otolaryngologist. 3 tables. 134 references. (AA-M).

- **Medical and Surgical Treatment of Cochlear Hearing Loss**

Source: in Valente, M.; Hosford-Dunn, H.; Roeser, R.J., eds. *Audiology: Treatment*. New York, NY: Thieme. 2000. p. 377-396.

Contact: Available from Thieme. 333 Seventh Avenue, New York, NY 10001. (800) 782-3488. Fax (212) 947-0108. E-mail: custserv@thieme.com. PRICE: \$69.00 plus shipping and handling. ISBN: 0865778590.

Summary: This chapter on the medical and surgical management of cochlear hearing loss is from a textbook that provides a comprehensive overview of the numerous treatment options available to help patients relieve the clinical symptoms seen in an audiology practice. Cochlear hearing loss may be caused by a wide variety of medical problems; it is the responsibility of the practitioner to identify the cause of hearing loss and to evaluate the other potential associated medical ramifications to treat the patient as a whole. Topics covered include metabolic disorders, including Meniere's disease, diabetes mellitus, renal disease, hypothyroidism, and cochlear otosclerosis; immunologic disorders, including autoimmune inner ear disease, Cogan's syndrome, polyarteritis nodosa, Vogt Koyanagi Harada syndrome, Wegener's granulomatosis, sarcoidosis, and postapedectomy granuloma; ototoxicity, including that from aminoglycoside antibiotics, erythromycin, vancomycin, other antibiotics, loop diuretics, antineoplastic (chemotherapy) agents, antiinflammatory agents, and antimalarials; trauma, including temporal bone fractures, noise trauma, and barotrauma (from barometric pressure changes); infections, including **cytomegalovirus**, toxoplasmosis, congenital rubella, mumps, measles, Varicella Zoster virus, HIV, other viruses and Mycoplasma, meningitis, labyrinthitis, fungal infections, and syphilis; malignancy; presbycusis; sudden idiopathic sensorineural hearing loss; and hereditary or development causes. The authors stress that complete audiological assessments are crucial in the initial evaluation and subsequent therapeutic monitoring of sensorineural hearing losses. The chapter includes an outline of the topic covered, a list of references, a summary outline of the related preferred practice guidelines, and various 'pearls and pitfalls' offering practical advice to the reader. 11 figures. 1 table. 67 references.

- **Otolaryngologic Manifestations of AIDS**

Source: in Jafek, B.W.; Stark, A.K., eds. *ENT Secrets: Questions You Will Be Asked On Rounds, In the Clinic, In the OR, On Exams*. Philadelphia, PA: Hanley and Belfus. 1996. p. 153-158.

Contact: Available from Hanley and Belfus. Medical Publishers, 210 South 13th Street, Philadelphia, PA 19107. (800) 962-1892 or (215) 546-7293; Fax (215) 790-9330; <http://www.hanleyandbelfus.com>. PRICE: \$35.95 plus shipping and handling. ISBN: 1560531592.

Summary: This chapter on the otolaryngologic manifestations of AIDS is from a book that utilizes a question and answer format to review details of the specialty of otorhinolaryngology (ear, nose and throat, or ENT). Topics discussed include the transmission of HIV, risk factors of acquiring HIV infection from blood transfusion or from mother to child, the percentage of HIV positive patients who develop AIDS, AIDS indicator diseases (including pneumocystis carinii pneumonia, most common index disease for the diagnosis of AIDS), CD4 counts and how they classify HIV infection, toxoplasmosis, problems with **cytomegalovirus** (CMV), common dermatologic manifestations of HIV infection, Kaposi's sarcoma, chronic otitis externa, serous and acute otitis media (the most common otologic condition seen in HIV infected patients), problems with pneumococcus as a middle ear pathogen, Ramsay Hunt syndrome (herpes zoster oticus), sinusitis and its treatment, oral candidiasis, hairy leukoplakia, salivary gland disease, risks of seroconversion after needlestick exposure from an HIV positive patient, non-Hodgkin's lymphoma, indications for lymph node biopsy, infection control measures for nasopharyngoscopy, and management of benign lymphoepithelial cysts. The chapter focuses on helping readers acquire the vocabulary required to discuss the otolaryngologic care of patients with AIDS. 1 figure. 1 table. 13 references.

- **Viral Hepatitis: General Features, Hepatitis A, Hepatitis E and Other Viruses**

Source: in Sherlock, S.; Dooley, J. *Diseases of the Liver and Biliary System*. Malden, MA: Blackwell Science, Inc. 2002. p.267-283.

Contact: Available from Blackwell Science, Inc. 350 Main Street, Commerce Place, Malden, MA 02148. (800) 215-1000 or (617) 388-8250. Fax (617) 388-8270. E-mail: books@blacksci.com. Website: www.blackwell-science.com. PRICE: \$178.95. ISBN: 0632055820.

Summary: This chapter on viral hepatitis (liver inflammation) is from a textbook that presents a comprehensive and up-to-date account of diseases of the liver and biliary system. The chapter covers general features of viral hepatitis and then focuses on hepatitis A and hepatitis E (other variants are covered in later chapters) and other viruses that have an impact on the liver. Topics include pathology, clinical types, investigations, differential diagnosis, prognosis, treatment, and follow-up; and specific viruses, including hepatitis A virus, hepatitis E virus, hepatitis G virus, hepatitis TT virus, yellow fever, infectious mononucleosis (Epstein-Barr virus), other viruses (cytomegalovirus, herpes simplex) and hepatitis due to exotic viruses. For each type of virus, the authors review epidemiology, clinical features, diagnostic tests, prevention, and treatment. Each section offers a list of references for additional reading. 15 figures. 4 tables. 89 references.

- **Esophageal Infections**

Source: in Snape, W.J., ed. *Consultations in Gastroenterology*. Philadelphia, PA: W.B. Saunders Company. 1996. p. 237-243.

Contact: Available from W.B. Saunders Company. Order Fulfillment, 6277 Sea Harbor Drive, Orlando, FL 32887. (800) 545-2522. Fax (800) 874-6418 or (407) 352-3445. PRICE: \$125.00. ISBN: 0721646700.

Summary: This chapter, from a gastroenterology text, covers esophageal infections. The authors note that infectious esophagitis was previously regarded to be rather uncommon; however, the AIDS epidemic has dramatically changed this perception and is probably the single most important factor accounting for the increasing incidence of infectious esophagitis. Growing numbers of immunosuppressed organ transplant patients also provide an at-risk population. These infections are responsible for serious morbidity and mortality in compromised patients. Most patients with esophageal infections present with odynophagia or dysphagia. Although reflux esophagitis is generally not a predisposing factor, other causes of esophagitis such as radiation therapy or cytotoxic chemotherapy may be responsible for symptoms in this group of patients or may provide a portal of entry for infection to occur. Still, gastroesophageal reflux disease, pill-induced esophageal injury, pericardial disease, and myocardial ischemia must be considered in the differential diagnosis of acute odynophagia and dysphagia. The authors discuss the infections by cause (fungi, viruses, and bacteria) and review the clinical presentation, diagnosis, and therapeutic options for each. They note that *Candida albicans* and herpes simplex virus are the most commonly encountered pathogens, although a number of other agents including **cytomegalovirus** (CMV), *Aspergillus*, and tuberculosis may infect the esophagus. 2 tables. 26 references. (AA-M).

- **Role of Viruses in the Pathogenesis of Insulin-Dependent Diabetes Mellitus**

Source: in LeRoith, D.; Taylor, S.I.; Olefsky, J.M., eds. *Diabetes Mellitus: A Fundamental and Clinical Text*. Philadelphia, PA: Lippincott-Raven Publishers. 1996. p. 339-349.

Contact: Available from Lippincott-Raven Publishers. 12107 Insurance Way, Hagerstown, MD 21740-5184. (800) 777-2295. Fax (301) 824-7390. PRICE: \$199.00. ISBN: 0397514565.

Summary: This chapter, from a medical textbook on diabetes, considers the role of viruses in the pathogenesis of insulin-dependent diabetes mellitus (IDDM or Type 1). The author briefly reviews viruses as one environmental factor, as well as the various pathogenic mechanisms by which viruses may act either to induce or to prevent diabetes. The first section describes virus-induced diabetes in animals, including encephalomyocarditis virus-induced diabetes in mice, Coxsackie B virus-induced diabetes in mice, Coxsackie B4-induced diabetes in nonhuman primates, retrovirus and autoimmune diabetes in nonobese diabetic mice, Kilham's rat virus-induced diabetes in diabetes-resistant BB rats, bovine viral diarrhea mucosal disease virus and diabetes in cattle, and rubella virus and diabetes in rabbits and hamsters. The next section considers virus-induced diabetes in humans, including the role of Coxsackie B viruses, rubella virus, **cytomegalovirus**, mumps virus, Epstein-Barr virus, and retrovirus. A final section describes the prevention of IDDM by viruses. The author concludes that, although a genetic predisposition appears to be necessary for the development of IDDM, nongenetic environmental factors play a critical role in the expression of the disease. Viruses, as one environmental factor, may directly infect and destroy pancreatic beta cells or trigger beta cell specific autoimmunity. 6 figures. 95 references.

- **Infection**

Source: Cambridge, MA: Harvard University Press. 1991. 13 p.

Contact: Available from Harvard University Press. 79 Garden Street, Cambridge, MA 02138-9983. (617) 495-2577 or (617) 495-2480. PRICE: \$24.95 plus shipping and handling. ISBN: 067464235X.

Summary: This chapter, from a patient education book about organ transplantation, discusses the task of preventing infection in patients who have received donor organs. Topics include the role of good tissue typing and matching in prevention of infection; reducing the risks of infection; preoperative, perioperative and postoperative measures taken to reduce the risk of infection; a timetable used to divide the times when the recipient is susceptible; urinary tract infection; pneumonia; special viral infections including general infections like influenza and those infections for which the transplant recipient faces a higher-than-average risk; the herpes group of viruses, including **cytomegalovirus**, Epstein-Barr virus, herpes simplex virus, and varicella-zoster virus; hepatitis; and suggestions for reducing the risks of acquiring a contagious disease. The chapter presents detailed medical information about these topics in clear, easy-to-understand language designed for the layperson.

CHAPTER 8. MULTIMEDIA ON CYTOMEGALOVIRUS

Overview

In this chapter, we show you how to keep current on multimedia sources of information on cytomegalovirus. We start with sources that have been summarized by federal agencies, and then show you how to find bibliographic information catalogued by the National Library of Medicine.

Video Recordings

An excellent source of multimedia information on cytomegalovirus is the Combined Health Information Database. You will need to limit your search to "Videorecording" and "cytomegalovirus" using the "Detailed Search" option. Go directly to the following hyperlink: <http://chid.nih.gov/detail/detail.html>. To find video productions, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Videorecording (videotape, videocassette, etc.)." Type "cytomegalovirus" (or synonyms) into the "For these words:" box. The following is a typical result when searching for video recordings on cytomegalovirus:

- **Nutritional Findings and Interventions in the AIDS Patient**

Source: Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, 1992, 60 minutes.

Contact: WIN, 1 WIN WAY, Bethesda, MD 20892-3665.

Summary: Dr. Kotler begins his lecture by listing potential adverse effects of malnutrition in AIDS patients. Malnutrition may be an independent risk factor for mortality and may affect immune dysfunction, disease progression, quality of life, response to therapies, and use of health care resources. He notes that although these problems appear self-evident, none have actually been proven. Body weight is a reliable measure of nutritional status in healthy individuals but not in those acutely ill. Dr. Kotler prefers to measure body cell mass (the chief constituent of muscle, organs, and nonadipose tissue) in the laboratory, calculated from a person's potassium levels. He cites his 1985 study showing that a group of men with AIDS had a mean body weight

that was 82 percent of ideal body weight (or low-normal), but a mean body cell mass 68 percent of normal. Thus, someone with AIDS may be normal weight but extremely malnourished. Loss of body cell mass limits patients' performance. Studies of patients with wasting illnesses reveal that death occurs when a patient's body cell mass reaches 54 percent of normal. Treating AIDS patients is not simply a matter of prescribing nutritional supplementation, because not every AIDS patient is malnourished. In addition, malnutrition may be caused by a variety of conditions that require different nutritional strategies. Sometimes the answer is to treat the complication, and the patient will recover on his or her own, as Dr. Kotler found in a study of AIDS patients who suffered from CMV (cytomegalovirus) colitis. Another study of AIDS patients with gastrointestinal disease and AIDS patients with systemic infections found that the patients with GI infections responded to nutritional supplementation, but those with systemic infections did not. Strategies to be tested, in addition to nutritional supplementation, include appetite stimulants, enteral or parenteral nutrition, and anabolic agents such as growth hormone.

- **Lost Hope in Hopewell**

Contact: Free Teens, U.S.A., Center for Educational Media, PO Box 97, Westwood, NJ, 07675, (201) 358-1504.

Summary: This video illustrates the impact of the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) on an individual's life through the true story of one woman, Beth Severn. The video consists of a series of interviews with Beth about how HIV has affected her physically, emotionally, and financially. Beth explains that she contracted HIV through injection drug use by sharing needles and as a result developed **cytomegalovirus** (CMV) and AIDS-related dementia and wasting syndrome, and came to terms with death. The video shows Beth in the early and progressive stages of HIV and AIDS.

- **Visual Field Testing to Detect CMV Retinitis**

Contact: David M. Bachman MD, 1133 20th St NW Ste B-150, Washington, DC, 20036, (202) 296-4900.

Summary: This videocassette recording presents Dr. David Bachman, MD, describing the procedure for visual field testing to detect **cytomegalovirus** (CMV) retinitis. Dr. Bachman, an ophthalmologist, discusses the CMV infection and its symptoms. He demonstrates how to test visual fields, emphasizes the need for early detection, and explains that early detection is important in controlling infection and preventing further eye damage.

- **Living With AIDS - Prevention & Beyond: A National Conference on HIV Infection and AIDS Among Racial and Ethnic Populations**

Summary: This videorecording features speakers presenting different perspectives on living with HIV/AIDS, recorded at a plenary session of a congress on HIV/AIDS among racial and ethnic populations. Phil Wilson, Project Director of HMWT LA, states that AIDS is about courage: to live with the illness, to die with dignity, or to care for someone who is ill. He shows a tape on Mildred Pearson, an elderly African American woman who cared for her son in his last months before his death from AIDS. She then became an activist in the African American community, speaking in churches, and urging others not to abandon their adult children with AIDS. Mrs. Pearson herself is the next speaker, recalling her son's life with AIDS and claiming the legacy of strength that

those who die from AIDS leave behind. Loren Laureano, Co-chair of the National Latino AIDS Caucus, identifies himself as an "irate Puerto Rican" living with HIV. He angrily denounces homophobia in the Latino community, rails about the injustices facing those with HIV/AIDS, and challenges Latinos to get over their denial concerning the epidemic. Other speakers, infected or affected by HIV/AIDS, also relate their stories: a Black female, recovering injecting drug user and crack addict sees HIV as yet another challenge; an Asian activist urges inclusion of Asians and Pacific Islanders in the fight against AIDS; and a Native American recounts his difficulties in finding care. The final speaker, who lost his sight overnight from **cytomegalovirus** (CMV), good-humoredly discusses discrimination he has faced as a blind bisexual Black man with AIDS.

- **Now That You Know: Living Healthy With HIV; Part 4 - Understanding Treatment**

Contact: Kaiser Permanente, National Video Communications, 825 Colorado Blvd Ste 301, Los Angeles, CA, 90041, (323) 259-4776,
<http://www.kaiserpermanente.org/locations/index.html>.

Summary: This videorecording tells persons with Human immunodeficiency virus (HIV) infection about symptoms, opportunistic infections, and available treatment. Narrators Bob Goen and Susan Campos introduce the material by saying that infected persons need to take control of their own health, become educated, and become informed. The main portion of the videorecording opens with a segment on azidothymidine (AZT). It discusses early intervention and when it is appropriate to begin treatment. A model demonstrates how antiviral treatment, such as AZT intervention, slows the rate of growth. Viewers are warned that being on antiviral therapy does not prevent them from being infectious. Possible side effects of the medication are discussed. After turning to general background information on opportunistic infections, that videorecording takes a detailed look at some of the most common. It classifies symptoms into infections that do not lead to an AIDS diagnosis, such as candida, shingles, and weight loss; nonspecific symptoms, such as fatigue, fever, and night sweats; and opportunistic infections that lead to an AIDS diagnosis. Of those, it takes the most detailed looks at *Pneumocystis carinii* pneumonia (PCP), **cytomegalovirus** retinitis (CMV) infection, toxoplasmosis, and *Mycobacterium avium* intracellulare (MAI). Holistic therapies are considered briefly at the conclusion of the videorecording.

Audio Recordings

The Combined Health Information Database contains abstracts on audio productions. To search CHID, go directly to the following hyperlink: <http://chid.nih.gov/detail/detail.html>. To find audio productions, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Sound Recordings." Type "cytomegalovirus" (or synonyms) into the "For these words:" box. The following is a typical result when searching for sound recordings on cytomegalovirus:

- **Patient Management and Treatment**

Contact: Health Impact, PO Box 9443, Seattle, WA, 98109-9443, (206) 284-3865,
<http://www.healthimpact.org/>.

Summary: This sound recording deals with the management and treatment of persons with Human immunodeficiency virus (HIV) infection or Acquired immunodeficiency virus (AIDS). Various opportunistic infections, including pneumocystis carinii pneumonia, **cytomegalovirus**, and certain neurological disorders are described, along with the treatment programs recommended for each at the time the recording was made. Since diagnosis of some opportunistic infections is difficult, various options for laboratory tests are also listed. Review questions and visuals are included in the booklet that accompanies this recording.

- **AIDS and Other Transmissible Diseases: Protecting Yourself in the Operating Room**

Contact: California Medical Association, Audio Digest Foundation, 1577 E Chevy Chase Dr, Glendale, CA, 91206, (213) 245-8505.

Summary: This sound recording, along with accompanying pre-test and post-test questions, is part of an ongoing series of educational activities. The first speaker, Elizabeth A. Donegan, Assistant Professor of Clinical Laboratory Medicine, University of California, San Francisco, School of Medicine, discusses the major infections transmitted by blood transfusions which include **cytomegalovirus** (CMV), Human immunodeficiency virus (HIV) infection, and HTLV-1. Nancy B. Bjerke, Major, United States Air Force, in North Carolina, and course supervisor/instructor of Sheppard Air Force Base in Texas, talks about the mechanisms for health care worker protection. Her presentation deals with the most frequent occupational injuries to health-care workers, disease transmission, safety precautions and hepatitis B immunization for health-care workers. The third speaker, Arnold J. Berry, Associate Professor of Anesthesiology, Emory University School of Medicine in Atlanta, looks at disease transmission in the operating room. His presentation deals with the implementation of universal precautions, risks to anesthesiologists other than Acquired immunodeficiency syndrome (AIDS) and Hepatitis B, specific recommendations for anesthesia equipment, handwashing, and infections from intravenous lines. The final speaker, C. Daniel Sooy, Assistant Professor of Otolaryngology, University of California in San Francisco, School of Medicine; and Director of Otolaryngology Clinic, San Francisco General Hospital, discusses policies for protecting the anesthesiologist. This presentation includes universal precautions, preoperative testing for HIV, and exposed health care workers.

- **AIDS: Counseling Patient and Family**

Contact: California Medical Association, Audio Digest Foundation, 1577 E Chevy Chase Dr, Glendale, CA, 91206, (213) 245-8505.

Summary: This sound recording, along with an accompanying pre-test and post-test, is part of an ongoing series of educational activities. It opens with a presentation on Acquired immunodeficiency syndrome (AIDS) and the primary-care physician given by Thomas C. Cesario, professor of medicine at the University of California, Irvine, College of Medicine. He describes the Human immunodeficiency virus (HIV) and its effects on the immune system, then discusses routes of HIV transmission. The HIV-antibody test and its reliability is explained, and criteria for clinical AIDS and for AIDS-related complex (ARC) are given. He goes on to discuss various opportunistic infections, such as Pneumocystis carinii pneumonia (PCP), cryptosporidium, toxoplasmosis, **cytomegalovirus**, atypical tuberculosis, candidal infections, Kaposi's sarcoma, and hairy leukoplakia. Treatment with azidothymidine (AZT) is explained. The second presentation comes from Sherman N. Williamson, Department of Family Medicine at the University of California, Irvine, College of Medicine. He discusses managing the families of AIDS patients. He looks at specific risk groups and which members needed

to be tested, then goes on to list specific goals in family management, other precautionary measures to take, and other considerations.

CHAPTER 9. PERIODICALS AND NEWS ON CYTOMEGALOVIRUS

Overview

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

News Services and Press Releases

One of the simplest ways of tracking press releases on cytomegalovirus 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 "cytomegalovirus" (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 cytomegalovirus. 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 "cytomegalovirus" (or synonyms). The following was recently listed in this archive for cytomegalovirus:

- **Treatment with anti-cytomegalovirus agent may improve schizophrenia symptoms**
Source: Reuters Medical News
Date: December 25, 2003

- **Cytomegalovirus reduces survival in patients with advanced HIV disease**
Source: Reuters Medical News
Date: September 03, 2003
- **EGF receptor mediates cytomegalovirus cell entry**
Source: Reuters Medical News
Date: July 23, 2003
- **Maternal immunity reduces risk of congenital cytomegalovirus infection**
Source: Reuters Medical News
Date: February 26, 2003
- **Novel compound effective against cytomegalovirus infection**
Source: Reuters Medical News
Date: September 20, 2002
- **Oral valganciclovir safe for AIDS-related cytomegalovirus retinitis**
Source: Reuters Industry Breifing
Date: August 14, 2002
- **Resistant cytomegalovirus leads to retinitis progression in AIDS patients**
Source: Reuters Industry Breifing
Date: November 19, 2001
- **Cytomegalovirus susceptibility gene identified in mice**
Source: Reuters Medical News
Date: May 08, 2001
- **Anti-CMV IgM titer predicts cytomegalovirus disease after liver transplantation**
Source: Reuters Medical News
Date: December 08, 2000
- **Cytomegalovirus role in CAD may vary by sex**
Source: Reuters Medical News
Date: November 13, 2000

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 "cytomegalovirus" (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 "cytomegalovirus" (or synonyms). If you know the name of a company that is relevant to cytomegalovirus, 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 "cytomegalovirus" (or synonyms).

Newsletter Articles

Use the Combined Health Information Database, and limit your search criteria to "newsletter articles." Again, you will need to use the "Detailed Search" option. Go directly to the following hyperlink: <http://chid.nih.gov/detail/detail.html>. Go to the bottom of the search page where "You may refine your search by." Select the dates and language that you prefer. For the format option, select "Newsletter Article." Type "cytomegalovirus" (or synonyms) into the "For these words:" box. You should check back periodically with this database as it is updated every three months. The following is a typical result when searching for newsletter articles on cytomegalovirus:

- **Spotlight On: Ten Syndromes Most Commonly Associated with Hearing Impairment**

Source: *Advances in the Genetics of Deafness*. 2(1): 1-4. Autumn 1995.

Contact: Available from National Institute on Deafness and Other Communication Disorders (NIDCD). Hereditary Hearing Impairment Resource Registry (HHIRR), 555 North 30th Street, Omaha, NE 68131. Voice/TTY (800) 320-1171; Fax (402) 498-6331.

Summary: In this article, the author familiarizes readers with ten syndromes most commonly associated with hearing impairment. The author has chosen to look at all patients in a national registry who carry the diagnosis of hearing loss, and who also have another associated clinical congenital anomaly or genetic feature, and look at the

most common recurring diagnoses. The syndromes discussed are: hemifacial microsomia; Stickler syndrome; congenital **cytomegalovirus**; Usher syndrome; branchio-oto-renal syndrome; Pendred syndrome; CHARGE association; neurofibromatosis type II; mitochondrial disorders; and Waardenburg syndrome. For each syndrome, the author discusses the incidence and prevalence, common features, and hearing loss, and provides comments.

- **Oral Infections in HIV Patients Can Be Destructive**

Source: Skin and Allergy News. 31(2): 45. February 2000.

Contact: Available from Skin and Allergy News. 12230 Wilkins Avenue, Rockville, MD 20852. (301) 816-8796.

Summary: This article from a newsletter for dermatologists reports on a presentation on common oral infections in patients with HIV disease. The author stresses that extra diligence is required in diagnosing and treating the oral manifestations of bacterial, viral, and fungal infections in patients with HIV, as the lesions of these infections tend to be widely distributed, persistent, and destructive to tissue in this patient population. The author discusses specific infections, including necrotizing stomatitis, bacillary angiomatosis, hairy leukoplakia, herpes simplex, oral candidiasis, and **cytomegalovirus**. The author briefly reviews the treatment strategies to undertake for each of these infections. 4 figures.

Academic Periodicals covering Cytomegalovirus

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to cytomegalovirus. In addition to these sources, you can search for articles covering cytomegalovirus 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."

CHAPTER 10. RESEARCHING MEDICATIONS

Overview

While a number of hard copy or CD-ROM resources are available for researching medications, a more flexible method is to use Internet-based databases. Broadly speaking, there are two sources of information on approved medications: public sources and private sources. We will emphasize free-to-use public sources.

U.S. Pharmacopeia

Because of historical investments by various organizations and the emergence of the Internet, it has become rather simple to learn about the medications recommended for cytomegalovirus. One such source is the United States Pharmacopeia. In 1820, eleven physicians met in Washington, D.C. to establish the first compendium of standard drugs for the United States. They called this compendium the U.S. Pharmacopeia (USP). Today, the USP is a non-profit organization consisting of 800 volunteer scientists, eleven elected officials, and 400 representatives of state associations and colleges of medicine and pharmacy. The USP is located in Rockville, Maryland, and its home page is located at <http://www.usp.org/>. The USP currently provides standards for over 3,700 medications. The resulting USP DI® Advice for the Patient® can be accessed through the National Library of Medicine of the National Institutes of Health. The database is partially derived from lists of federally approved medications in the Food and Drug Administration's (FDA) Drug Approvals database, located at <http://www.fda.gov/cder/da/da.htm>.

While the FDA database is rather large and difficult to navigate, the Pharmacopeia is both user-friendly and free to use. It covers more than 9,000 prescription and over-the-counter medications. To access this database, simply type the following hyperlink into your Web browser: <http://www.nlm.nih.gov/medlineplus/druginformation.html>. To view examples of a given medication (brand names, category, description, preparation, proper use, precautions, side effects, etc.), simply follow the hyperlinks indicated within the United States Pharmacopeia (USP).

Below, we have compiled a list of medications associated with cytomegalovirus. If you would like more information on a particular medication, the provided hyperlinks will direct you to ample documentation (e.g. typical dosage, side effects, drug-interaction risks, etc.).

The following drugs have been mentioned in the Pharmacopeia and other sources as being potentially applicable to cytomegalovirus:

Cidofovir

- **Systemic - U.S. Brands:** Vistide
<http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203520.html>

Fomivirsen

- **Parenteral-Local - U.S. Brands:** Vitravene
<http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203675.html>

Foscarnet

- **Systemic - U.S. Brands:** Foscavir
<http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202617.html>

Ganciclovir

- **Implantation-Ophthalmic - U.S. Brands:** Vitrasert
<http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203488.html>
- **Systemic - U.S. Brands:** Cytovene; Cytovene-IV
<http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202255.html>

Valganciclovir

- **Systemic - U.S. Brands:** Valcyte
<http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/500289.html>

Commercial Databases

In addition to the medications listed in the USP above, a number of commercial sites are available by subscription to physicians and their institutions. Or, you may be able to access these sources from your local medical library.

Mosby's Drug Consult™

Mosby's Drug Consult™ database (also available on CD-ROM and book format) covers 45,000 drug products including generics and international brands. It provides prescribing information, drug interactions, and patient information. Subscription information is available at the following hyperlink: <http://www.mosbysdrugconsult.com/>.

PDRhealth

The PDRhealth database is a free-to-use, drug information search engine that has been written for the public in layman's terms. It contains FDA-approved drug information adapted from the Physicians' Desk Reference (PDR) database. PDRhealth can be searched by brand name, generic name, or indication. It features multiple drug interactions reports. Search PDRhealth at http://www.pdrhealth.com/drug_info/index.html.

Other Web Sites

Drugs.com (www.drugs.com) reproduces the information in the Pharmacopeia as well as commercial information. You may also want to consider the Web site of the Medical Letter, Inc. (<http://www.medletter.com/>) which allows users to download articles on various drugs and therapeutics for a nominal fee.

Researching Orphan Drugs

Although the list of orphan drugs is revised on a daily basis, you can quickly research orphan drugs that might be applicable to cytomegalovirus by using the database managed by the National Organization for Rare Disorders, Inc. (NORD), at <http://www.rarediseases.org/>. Scroll down the page, and on the left toolbar, click on "Orphan Drug Designation Database." On this page (<http://www.rarediseases.org/search/noddsearch.html>), type "cytomegalovirus" (or synonyms) into the search box, and click "Submit Query." When you receive your results, note that not all of the drugs may be relevant, as some may have been withdrawn from orphan status. Write down or print out the name of each drug and the relevant contact information. From there, visit the Pharmacopeia Web site and type the name of each orphan drug into the search box at <http://www.nlm.nih.gov/medlineplus/druginformation.html>. You may need to contact the sponsor or NORD for further information.

NORD conducts "early access programs for investigational new drugs (IND) under the Food and Drug Administration's (FDA's) approval 'Treatment INDs' programs which allow for a limited number of individuals to receive investigational drugs before FDA marketing approval." If the orphan product about which you are seeking information is approved for marketing, information on side effects can be found on the product's label. If the product is not approved, you may need to contact the sponsor.

The following is a list of orphan drugs currently listed in the NORD Orphan Drug Designation Database for cytomegalovirus:

- **Monoclonal antibody to cytomegalovirus (human)**
http://www.rarediseases.org/nord/search/nodd_full?code=142
- **Monoclonal antibody to cytomegalovirus (human)**
http://www.rarediseases.org/nord/search/nodd_full?code=145
- **Cytomegalovirus immune globulin (human) (trade name: CytoGam)**
http://www.rarediseases.org/nord/search/nodd_full?code=421
- **Cytomegalovirus immune globulin intravenous (human)**
http://www.rarediseases.org/nord/search/nodd_full?code=434
- **Ganciclovir intravitreal implant (trade name: Vitrsert Implant)**
http://www.rarediseases.org/nord/search/nodd_full?code=718
- **Ganciclovir intravitreal implant (trade name: Vitrasert Implant)**
http://www.rarediseases.org/nord/search/nodd_full?code=807
- **Filgrastim (trade name: Neupogen)**
http://www.rarediseases.org/nord/search/nodd_full?code=701

If you have any questions about a medical treatment, the FDA may have an office near you. Look for their number in the blue pages of the phone book. You can also contact the FDA through its toll-free number, 1-888-INFO-FDA (1-888-463-6332), or on the World Wide Web at **www.fda.gov**.

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 Institute¹¹:

- 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/>

¹¹ 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.¹² 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:¹³

- **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/aidsinfo.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

¹² Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINEplus (<http://medlineplus.gov/> or <http://www.nlm.nih.gov/medlineplus/databases.html>).

¹³ 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 Gateway¹⁴

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.¹⁵ To use the NLM Gateway, simply go to the search site at <http://gateway.nlm.nih.gov/gw/Cmd>. Type "cytomegalovirus" (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	26143
Books / Periodicals / Audio Visual	131
Consumer Health	856
Meeting Abstracts	1611
Other Collections	64
Total	28805

HSTAT¹⁶

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.¹⁷ 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.¹⁸ Simply search by "cytomegalovirus" (or synonyms) at the following Web site: <http://text.nlm.nih.gov>.

¹⁴ Adapted from NLM: <http://gateway.nlm.nih.gov/gw/Cmd?Overview.x>.

¹⁵ 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).

¹⁶ Adapted from HSTAT: <http://www.nlm.nih.gov/pubs/factsheets/hstat.html>.

¹⁷ The HSTAT URL is <http://hstat.nlm.nih.gov/>.

¹⁸ 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 Biologists¹⁹

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.²⁰ 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.²¹ 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/clinweb/>.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see <http://www.mwsearch.com/>.

¹⁹ Adapted from <http://www.ncbi.nlm.nih.gov/Coffeebreak/Archive/FAQ.html>.

²⁰ 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.

²¹ 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 cytomegalovirus 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 cytomegalovirus. 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 cytomegalovirus. 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 “cytomegalovirus”:

- Other guides

- Hearing Disorders and Deafness**

- <http://www.nlm.nih.gov/medlineplus/hearingdisordersanddeafness.html>

- Hemorrhagic Fevers**

- <http://www.nlm.nih.gov/medlineplus/hemorrhagicfevers.html>

- High Risk Pregnancy**

- <http://www.nlm.nih.gov/medlineplus/highriskpregnancy.html>

- Infections and Pregnancy**

- <http://www.nlm.nih.gov/medlineplus/infectionsandpregnancy.html>

- Infectious Mononucleosis**

- <http://www.nlm.nih.gov/medlineplus/infectiousmononucleosis.html>

- Influenza**

- <http://www.nlm.nih.gov/medlineplus/influenza.html>

- Viral Infections**

- <http://www.nlm.nih.gov/medlineplus/viralinfections.html>

- West Nile Virus**

- <http://www.nlm.nih.gov/medlineplus/westnilevirus.html>

Within the health topic page dedicated to cytomegalovirus, the following was listed:

- General/Overviews

- Viral Infections**

- Source: Merck & Co., Inc.

- http://www.merck.com/mrkshared/mmanual_home2/sec17/ch198/ch198a.jsp

- Virus or Bacterium?**

- Source: American Society for Microbiology

- http://www.microbe.org/microbes/virus_or_bacterium.asp

- Viruses and Some Virus-Like Agents**

- Source: American Society for Microbiology

- <http://www.microbeworld.org/htm/aboutmicro/microbes/types/virus.htm>

- Treatment

- Antibiotics: Why Don't They Work on Viral Infections?**

- Source: Mayo Foundation for Medical Education and Research

- <http://www.mayoclinic.com/invoke.cfm?id=HQ01610>

- Specific Conditions/Aspects

- Adenoviruses**

- Source: National Center for Infectious Diseases

- <http://www.cdc.gov/ncidod/dvrd/revb/respiratory/eadfeat.htm>

- Cytomegalic Inclusion Body Disease (CIBD)**

- Source: National Institute of Neurological Disorders and Stroke

- http://www.ninds.nih.gov/health_and_medical/disorders/cytomegalic.htm

Do You Know What Role Microbes Play in These Products?

Source: American Society for Microbiology

<http://www.microbeworld.org/htm/aboutmicro/microbes/uses.htm>**Molluscum Contagiosum**

Source: American Academy of Dermatology

<http://www.aad.org/pamphlets/molluscum.html>**Non-Polio Enterovirus Infections**

Source: National Center for Infectious Diseases

http://www.cdc.gov/ncidod/dvrd/revb/enterovirus/non-polio_entero.htm**Viral Gastroenteritis**

Source: National Digestive Diseases Information Clearinghouse

<http://digestive.niddk.nih.gov/ddiseases/pubs/viralgastroenteritis/index.htm>**Yellow Fever**

Source: World Health Organization

<http://www.who.int/inf-fs/en/fact100.html>**Yellow Fever: Health Information for International Travel**

Source: National Center for Infectious Diseases

<http://www.cdc.gov/travel/diseases/yellowfever.htm>

- Children

Adenovirus

Source: Nemours Foundation

<http://kidshealth.org/parent/infections/lung/adenovirus.html>**Coxsackie Viruses**

Source: Nemours Foundation

http://kidshealth.org/parent/infections/bacterial_viral/coxsackie.html**Cytomegalovirus (CMV)**

Source: Nemours Foundation

http://kidshealth.org/parent/infections/bacterial_viral/cytomegalovirus.html**Hand, Foot, & Mouth Disease**

Source: National Center for Infectious Diseases

<http://www.cdc.gov/ncidod/dvrd/hfmd.htm>**Human Parainfluenza Viruses**

Source: National Center for Infectious Diseases

<http://www.cdc.gov/ncidod/dvrd/revb/respiratory/hpivfeat.htm>**Roseola**

Source: Mayo Foundation for Medical Education and Research

<http://www.mayoclinic.com/invoke.cfm?id=DS00452>

- From the National Institutes of Health

Microbes in Sickness and in Health

Source: National Institute of Allergy and Infectious Diseases

<http://www.niaid.nih.gov/publications/microbes.htm>

- Latest News

- Antibacterial Soap Doesn't Prevent Viral Infection**

- Source: 03/01/2004, Reuters Health

- http://www.nlm.nih.gov/www.nlm.nih.gov/medlineplus/news/fullstory_16333.html

- 'Drink Lots of Fluids': Unproven, Perhaps Dangerous**

- Source: 02/27/2004, Reuters Health

- http://www.nlm.nih.gov/www.nlm.nih.gov/medlineplus/news/fullstory_16311.html

- Women More at Risk from Infections**

- Source: 03/01/2004, United Press International

- http://www.nlm.nih.gov/www.nlm.nih.gov/medlineplus/news/fullstory_16322.html

- Organizations

- National Center for Infectious Diseases**

- <http://www.cdc.gov/ncidod/index.htm>

- National Foundation for Infectious Diseases**

- <http://www.nfid.org/>

- National Institute of Allergy and Infectious Diseases**

- <http://www.niaid.nih.gov/>

- Prevention/Screening

- 10 Tips for Preventing the Spread of Infection**

- Source: Association for Professionals in Infection Control and Epidemiology

- <http://www.apic.org/cons/tentips.cfm>

- You Can Prevent CMV (Cytomegalovirus): A Guide for People with HIV Infection**

- Source: National Center for HIV, STD, and TB Prevention

- http://www.cdc.gov/hiv/pubs/brochure/Oi_cmv.htm

- Research

- Single Protein Is Key in Response to Bacterial, Viral Infections**

- Source: National Institute of Allergy and Infectious Diseases

- <http://www.nih.gov/news/pr/jul2003/niid-20.htm>

- Women

- Cytomegalovirus Infection in Pregnancy**

- Source: March of Dimes Birth Defects Foundation

- http://www.marchofdimes.com/professionals/681_1195.asp

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 Combined Health Information Database (CHID)

CHID Online is a reference tool that maintains a database directory of thousands of journal articles and patient education guidelines on cytomegalovirus. CHID offers summaries that describe the guidelines available, including contact information and pricing. CHID's general Web site is <http://chid.nih.gov/>. To search this database, go to <http://chid.nih.gov/detail/detail.html>. In particular, you can use the advanced search options to look up pamphlets, reports, brochures, and information kits. The following was recently posted in this archive:

- **Cytomegalovirus Retinitis: Optimizing Your Treatment With Foscavir (Foscarnet Sodium) Injection**

Contact: Astra USA Incorporated, 50 Otis St, Westborough, MA, 01581-4500, (800) 388-4148.

Summary: The use of Foscavir to treat cytomegalovirus (CMV) retinitis, a possible opportunistic infection in HIV disease, is explained in this brochure. What CMV retinitis is and how it threatens one's eyesight is described as well what Foscavir is and how it can halt CMV retinitis. Side effects and ways to reduce them are explained. Active participation by the health care team and the patient are urged to optimize treatment with Foscavir.

- **Cytomegalovirus Translated title**

Contact: Project Inform, HIV Treatment Hotline, 205 13th St Ste 2001, San Francisco, CA, 94103, (415) 558-8669, <http://www.projectinform.org>.

Summary: This fact sheet provides information for persons with the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) about cytomegalovirus (CMV). The fact sheet identifies the three types of CMV and their symptoms. It explains how CMV is diagnosed and its prevention for persons with HIV/AIDS through prophylaxis treatment. It outlines the various therapies that can be used for the treatment of CMV. The fact sheet provides information concerning the different drugs used to treat CMV such as ganciclovir, foscarnet, cidofovir, and formivirsen. It differentiates between systemic and localized therapy, and discusses the possible drug interactions between HIV/AIDS and CMV medications. The fact sheet promotes the use of formivirsen in the care of HIV-positive persons with CMV.

- **CMV (Cytomegalovirus)**

Contact: University of New Mexico School of Medicine, Infectious Diseases Division, New Mexico AIDS Education and Training Center, New Mexico AIDS InfoNet, PO Box 810, Arroyo Seco, NM, 87514-0810, (505) 776-8032, <http://www.aidsinonet.org>.

Summary: This information sheet discusses cytomegalovirus (CMV), an opportunistic infection (OI) that attacks people with weakened immune systems, such as people with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). CMV causes retinitis, which can quickly cause blindness unless treated. The information sheet explains symptoms of CMV, treatment, and prevention. Physicians often

recommend that HIV-positive individuals get regular eye exams to encourage early detection of CMV. CMV can be treated with medications given in pill form, intravenously, or as an implant. Issues to consider when deciding on treatment include how effective it is, how it is administered, whether it is a local therapy or systemic, and its side effects.

- **You Can Prevent CMV (Cytomegalovirus): A Guide for People With HIV Infection**

Contact: CDC National Prevention Information Network, PO Box 6003, Rockville, MD, 20849-6003, (800) 458-5231, <http://www.cdcnpin.org>.

Summary: This pamphlet, for persons with the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), provides information on the cytomegalovirus (CMV). It discusses the consequences of CMV infection for people with HIV/AIDS including blurred vision and blindness, painful swallowing, diarrhea, pain, weakness, and numbness in the legs; how CMV is transmitted from person to person through saliva, semen, vaginal secretions, blood, urine, and breast milk, during sexual contact, breastfeeding, blood transfusions, and organ transplants; how it may be prevented by frequent hand washing, using condoms, talking to a doctor before undergoing a blood transfusion; and its symptoms including fatigue, swollen glands, fever, and sore throat; testing; and treatment. The pamphlet makes recommendations for individuals who work in day care centers including frequent hand washing after contact with urine or saliva, avoiding oral contact with saliva or objects covered with saliva, and talking to a doctor about whether to continue working in a day care center. Sources for locating referrals, materials, and information on HIV/AIDS treatment, clinical trials, and social security benefits are provided.

Healthfinder™

Healthfinder™ is sponsored by the U.S. Department of Health and Human Services and offers links to hundreds of other sites that contain healthcare information. This Web site is located at <http://www.healthfinder.gov>. Again, keyword searches can be used to find guidelines. The following was recently found in this database:

- **Cytomegalovirus (CMV) Infection**

Summary:

Source: National Center for Infectious Diseases, Centers for Disease Control and Prevention

<http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=6998>

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 cytomegalovirus. 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 cytomegalovirus. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with cytomegalovirus.

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 cytomegalovirus. 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 "cytomegalovirus" (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 "cytomegalovirus". 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 "cytomegalovirus" (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 "cytomegalovirus" (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.²²

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

²² 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)²³:

- **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/>

²³ 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.lsuhscc.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, Worcester), <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 Resource 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.lvcld.org/special_collections/medical/index.htm
- **New Hampshire:** Dartmouth Biomedical Libraries (Dartmouth College Library, Hanover), <http://www.dartmouth.edu/~biomed/resources.html#conshealth.html#d/>
- **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/commmlib.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.shscare.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).

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>

CYTOMEGALOVIRUS DICTIONARY

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

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]

Abdominal Pain: Sensation of discomfort, distress, or agony in the abdominal region. [NIH]

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

Abortion: 1. The premature expulsion from the uterus of the products of conception - of the embryo, or of a nonviable fetus. The four classic symptoms, usually present in each type of abortion, are uterine contractions, uterine haemorrhage, softening and dilatation of the cervix, and presentation or expulsion of all or part of the products of conception. 2. Premature stoppage of a natural or a pathological process. [EU]

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]

Acetylglucosamine: The N-acetyl derivative of glucosamine. [NIH]

Acoustic: Having to do with sound or hearing. [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]

Actinomycosis: Infections with bacteria of the genus *Actinomyces*. [NIH]

Acute Disease: Disease having a short and relatively severe course. [NIH]

Acute renal: A condition in which the kidneys suddenly stop working. In most cases, kidneys can recover from almost complete loss of function. [NIH]

Acyclovir: Functional analog of the nucleoside guanosine. It acts as an antimetabolite, especially in viruses. It is used as an antiviral agent, especially in herpes infections. [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]

Adenocarcinoma: A malignant epithelial tumor with a glandular organization. [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]

Adipocytes: Fat-storing cells found mostly in the abdominal cavity and subcutaneous tissue. Fat is usually stored in the form of triglycerides. [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]

Adolescence: The period of life beginning with the appearance of secondary sex characteristics and terminating with the cessation of somatic growth. The years usually referred to as adolescence lie between 13 and 18 years of age. [NIH]

Adoptive Transfer: Form of passive immunization where previously sensitized immunologic agents (cells or serum) are transferred to non-immune recipients. When transfer of cells is used as a therapy for the treatment of neoplasms, it is called adoptive immunotherapy (immunotherapy, adoptive). [NIH]

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

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]

Afferent: Concerned with the transmission of neural impulse toward the central part of the nervous system. [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]

Agar: A complex sulfated polymer of galactose units, extracted from *Gelidium cartilagineum*, *Gracilaria confervoides*, and related red algae. It is used as a gel in the preparation of solid culture media for microorganisms, as a bulk laxative, in making

emulsions, and as a supporting medium for immunodiffusion and immunoelectrophoresis. [NIH]

Agonists: Drugs that trigger an action from a cell or another drug. [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]

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]

Alkylating Agents: Highly reactive chemicals that introduce alkyl radicals into biologically active molecules and thereby prevent their proper functioning. Many are used as antineoplastic agents, but most are very toxic, with carcinogenic, mutagenic, teratogenic, and immunosuppressant actions. They have also been used as components in poison gases. [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]

Allergen: An antigenic substance capable of producing immediate-type hypersensitivity (allergy). [EU]

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]

Alopecia: Absence of hair from areas where it is normally present. [NIH]

Alpha Particles: Positively charged particles composed of two protons and two neutrons, i.e., helium nuclei, emitted during disintegration of very heavy isotopes; a beam of alpha particles or an alpha ray has very strong ionizing power, but weak penetrability. [NIH]

Alpha-1: A protein with the property of inactivating proteolytic enzymes such as leucocyte collagenase and elastase. [NIH]

Alpha-Galactosidase: An enzyme that catalyzes the hydrolysis of terminal, non-reducing alpha-D-galactose residues in alpha-galactosides including galactose oligosaccharides, galactomannans, and galactolipids. EC 3.2.1.22. [NIH]

Alpha-Thalassemia: A disorder characterized by reduced synthesis of the alpha chains of hemoglobin. The severity of this condition can vary from mild anemia to death, depending on the number of genes deleted. [NIH]

Alphavirus: A genus of Togaviridae, also known as Group A arboviruses, serologically related to each other but not to other Togaviridae. The viruses are transmitted by

mosquitoes. The type species is the sindbis virus. [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]

Alum: A type of immune adjuvant (a substance used to help boost the immune response to a vaccine). Also called aluminum sulfate. [NIH]

Aluminum: A metallic element that has the atomic number 13, atomic symbol Al, and atomic weight 26.98. [NIH]

Amino acid: Any organic compound containing an amino (-NH₂) and a carboxyl (-COOH) group. The 20 α-amino acids listed in the accompanying table are the amino acids from which proteins are synthesized by formation of peptide bonds during ribosomal translation of messenger RNA; all except glycine, which is not optically active, have the L configuration. Other amino acids occurring in proteins, such as hydroxyproline in collagen, are formed by posttranslational enzymatic modification of amino acid residues in polypeptide chains. There are also several important amino acids, such as the neurotransmitter γ-aminobutyric acid, that have no relation to proteins. Abbreviated AA. [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]

Aminopeptidases: A subclass of exopeptidases that act on the free N terminus end of a polypeptide liberating a single amino acid residue. EC 3.4.11. [NIH]

Amnion: The extraembryonic membrane which contains the embryo and amniotic fluid. [NIH]

Amniotic Fluid: Amniotic cavity fluid which is produced by the amnion and fetal lungs and kidneys. [NIH]

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

Amputation: Surgery to remove part or all of a limb or appendage. [NIH]

Anabolic: Relating to, characterized by, or promoting anabolism. [EU]

Anaerobic: 1. Lacking molecular oxygen. 2. Growing, living, or occurring in the absence of molecular oxygen; pertaining to an anaerobe. [EU]

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]

Analytes: A component of a test sample the presence of which has to be demonstrated. The

term "analyte" includes where appropriate formed from the analyte during the analyses. [NIH]

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]

Anaplasia: Loss of structural differentiation and useful function of neoplastic cells. [NIH]

Anastomosis: A procedure to connect healthy sections of tubular structures in the body after the diseased portion has been surgically removed. [NIH]

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

Androgens: A class of sex hormones associated with the development and maintenance of the secondary male sex characteristics, sperm induction, and sexual differentiation. In addition to increasing virility and libido, they also increase nitrogen and water retention and stimulate skeletal growth. [NIH]

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]

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]

Angiogenesis: Blood vessel formation. Tumor angiogenesis is the growth of blood vessels from surrounding tissue to a solid tumor. This is caused by the release of chemicals by the tumor. [NIH]

Angioplasty: Endovascular reconstruction of an artery, which may include the removal of atheromatous plaque and/or the endothelial lining as well as simple dilatation. These are procedures performed by catheterization. When reconstruction of an artery is performed surgically, it is called endarterectomy. [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]

Annealing: The spontaneous alignment of two single DNA strands to form a double helix. [NIH]

Anomalies: Birth defects; abnormalities. [NIH]

Anorexia: Lack or loss of appetite for food. Appetite is psychologic, dependent on memory and associations. Anorexia can be brought about by unattractive food, surroundings, or company. [NIH]

Anorexiant: A drug, process, or event that leads to anorexia. [NIH]

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]

Antibodies, Anticardiolipin: Antiphospholipid antibodies found in association with systemic lupus erythematosus (lupus erythematosus, systemic), antiphospholipid syndrome, and in a variety of other diseases as well as in healthy individuals. The antibodies are detected by solid-phase immunoassay employing the purified phospholipid antigen cardiolipin. [NIH]

Antibodies, Antiphospholipid: Autoantibodies directed against phospholipids. These antibodies are characteristically found in patients with systemic lupus erythematosus, antiphospholipid syndrome, related autoimmune diseases, some non-autoimmune diseases, and also in healthy individuals. [NIH]

Antibodies, Monoclonal: Antibodies produced by clones of cells such as those isolated after hybridization of activated B lymphocytes with neoplastic cells. These hybrids are often referred to as hybridomas. [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]

Antibody therapy: Treatment with an antibody, a substance that can directly kill specific tumor cells or stimulate the immune system to kill tumor cells. [NIH]

Anticoagulant: A drug that helps prevent blood clots from forming. Also called a blood thinner. [NIH]

Antifungal: Destructive to fungi, or suppressing their reproduction or growth; effective against fungal infections. [EU]

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]

Antigen-presenting cell: APC. A cell that shows antigen on its surface to other cells of the immune system. This is an important part of an immune response. [NIH]

Anti-infective: An agent that so acts. [EU]

Anti-Infective Agents: Substances that prevent infectious agents or organisms from spreading or kill infectious agents in order to prevent the spread of infection. [NIH]

Anti-inflammatory: Having to do with reducing inflammation. [NIH]

Anti-Inflammatory Agents: Substances that reduce or suppress 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]

Antimicrobial: Killing microorganisms, or suppressing their multiplication or growth. [EU]

Antineoplastic: Inhibiting or preventing the development of neoplasms, checking the maturation and proliferation of malignant cells. [EU]

Antioxidants: Naturally occurring or synthetic substances that inhibit or retard the oxidation of a substance to which it is added. They counteract the harmful and damaging effects of oxidation in animal tissues. [NIH]

Antiphospholipid Syndrome: The presence of antibodies directed against phospholipids (antibodies, antiphospholipid). The condition is associated with a variety of diseases, notably systemic lupus erythematosus and other connective tissue diseases, thrombopenia, and arterial or venous thromboses. In pregnancy it can cause abortion. Of the phospholipids, the cardiolipins show markedly elevated levels of anticardiolipin antibodies (antibodies, anticardiolipin). Present also are high levels of lupus anticoagulant (lupus coagulation inhibitor). [NIH]

Antiserum: The blood serum obtained from an animal after it has been immunized with a particular antigen. It will contain antibodies which are specific for that antigen as well as antibodies specific for any other antigen with which the animal has previously been immunized. [NIH]

Antiviral: Destroying viruses or suppressing their replication. [EU]

Antiviral Agents: Agents used in the prophylaxis or therapy of virus diseases. Some of the ways they may act include preventing viral replication by inhibiting viral DNA polymerase; binding to specific cell-surface receptors and inhibiting viral penetration or uncoating; inhibiting viral protein synthesis; or blocking late stages of virus assembly. [NIH]

Anus: The opening of the rectum to the outside of the body. [NIH]

Aorta: The main trunk of the systemic arteries. [NIH]

Aphakia: Absence of crystalline lens totally or partially from field of vision, from any cause except after cataract extraction. Aphakia is mainly congenital or as result of lens dislocation and subluxation. [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]

Appendicitis: Acute inflammation of the vermiform appendix. [NIH]

Appetite Stimulants: Agents that are used to stimulate appetite. These drugs are frequently used to treat anorexia associated with cancer and AIDS. [NIH]

Aqueous: Having to do with water. [NIH]

Aqueous humor: Clear, watery fluid that flows between and nourishes the lens and the cornea; secreted by the ciliary processes. [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]

Arcuate Nucleus: A nucleus located in the middle hypothalamus in the most ventral part of the third ventricle near the entrance of the infundibular recess. Its small cells are in close contact with the ependyma. [NIH]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Aromatic: Having a spicy odour. [EU]

Arrestin: A 48-Kd protein of the outer segment of the retinal rods and a component of the phototransduction cascade. Arrestin quenches G-protein activation by binding to phosphorylated photolyzed rhodopsin. Arrestin causes experimental autoimmune uveitis when injected into laboratory animals. [NIH]

Arterial: Pertaining to an artery or to the arteries. [EU]

Arteries: The vessels carrying blood away from the heart. [NIH]

Arterioles: The smallest divisions of the arteries located between the muscular arteries and the capillaries. [NIH]

Artery: Vessel-carrying blood from the heart to various parts of the body. [NIH]

Articular: Of or pertaining to a joint. [EU]

Artifacts: Any visible result of a procedure which is caused by the procedure itself and not by the entity being analyzed. Common examples include histological structures introduced by tissue processing, radiographic images of structures that are not naturally present in living tissue, and products of chemical reactions that occur during analysis. [NIH]

Aspergillus: A genus of mitosporic fungi containing about 100 species and eleven different teleomorphs in the family Trichocomaceae. [NIH]

Aspiration: The act of inhaling. [NIH]

Assay: Determination of the amount of a particular constituent of a mixture, or of the biological or pharmacological potency of a drug. [EU]

Astringents: Agents, usually topical, that cause the contraction of tissues for the control of bleeding or secretions. [NIH]

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]

Astrocytoma: A tumor that begins in the brain or spinal cord in small, star-shaped cells called astrocytes. [NIH]

Asymptomatic: Having no signs or symptoms of disease. [NIH]

Atopic: Pertaining to an atopen or to atopy; allergic. [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]

Atypical: Irregular; not conformable to the type; in microbiology, applied specifically to strains of unusual type. [EU]

Audiologist: Study of hearing including treatment of persons with hearing defects. [NIH]

Audiology: The study of hearing and hearing impairment. [NIH]

Auditory: Pertaining to the sense of hearing. [EU]

Autoimmune disease: A condition in which the body recognizes its own tissues as foreign and directs an immune response against them. [NIH]

Autoimmune Hepatitis: A liver disease caused when the body's immune system destroys liver cells for no known reason. [NIH]

Autoimmunity: Process whereby the immune system reacts against the body's own tissues. Autoimmunity may produce or be caused by autoimmune diseases. [NIH]

Autologous: Taken from an individual's own tissues, cells, or DNA. [NIH]

Autologous bone marrow transplantation: A procedure in which bone marrow is removed from a person, stored, and then given back to the person after intensive treatment. [NIH]

Autopsy: Postmortem examination of the body. [NIH]

Avidin: A specific protein in egg albumin that interacts with biotin to render it unavailable to mammals, thereby producing biotin deficiency. [NIH]

Avidity: The strength of the interaction of an antiserum with a multivalent antigen. [NIH]

Axonal: Condition associated with metabolic derangement of the entire neuron and is manifest by degeneration of the distal portion of the nerve fiber. [NIH]

Bacteremia: The presence of viable bacteria circulating in the blood. Fever, chills, tachycardia, and tachypnea are common acute manifestations of bacteremia. The majority of cases are seen in already hospitalized patients, most of whom have underlying diseases or procedures which render their bloodstreams susceptible to invasion. [NIH]

Bacteria: Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccil, rodlike or bacillary, and spiral or spirochetal. [NIH]

Bacterial Infections: Infections by bacteria, general or unspecified. [NIH]

Bacterial Physiology: Physiological processes and activities of bacteria. [NIH]

Bactericidal: Substance lethal to bacteria; substance capable of killing bacteria. [NIH]

Bacteriophage: A virus whose host is a bacterial cell; A virus that exclusively infects bacteria. It generally has a protein coat surrounding the genome (DNA or RNA). One of the coliphages most extensively studied is the lambda phage, which is also one of the most important. [NIH]

Bacteriostatic: 1. Inhibiting the growth or multiplication of bacteria. 2. An agent that inhibits the growth or multiplication of bacteria. [EU]

Bacterium: Microscopic organism which may have a spherical, rod-like, or spiral unicellular or non-cellular body. Bacteria usually reproduce through asexual processes. [NIH]

Barotrauma: Injury following pressure changes; includes injury to the eustachian tube, ear drum, lung and stomach. [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]

Basophils: Granular leukocytes characterized by a relatively pale-staining, lobate nucleus and cytoplasm containing coarse dark-staining granules of variable size and stainable by basic dyes. [NIH]

Benign: Not cancerous; does not invade nearby tissue or spread to other parts of the body.

[NIH]

Bilateral: Affecting both the right and left side of body. [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]

Bile duct: A tube through which bile passes in and out of the liver. [NIH]

Biliary: Having to do with the liver, bile ducts, and/or gallbladder. [NIH]

Bilirubin: A bile pigment that is a degradation product of heme. [NIH]

Binding Sites: The reactive parts of a macromolecule that directly participate in its specific combination with another molecule. [NIH]

Bioavailability: The degree to which a drug or other substance becomes available to the target tissue after administration. [EU]

Bioavailable: The ability of a drug or other substance to be absorbed and used by the body. Orally bioavailable means that a drug or other substance that is taken by mouth can be absorbed and used by the body. [NIH]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

Biogenesis: The origin of life. It includes studies of the potential basis for life in organic compounds but excludes studies of the development of altered forms of life through mutation and natural selection, which is evolution. [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]

Biomolecular: A scientific field at the interface between advanced computing and biotechnology. [NIH]

Biophysics: The science of physical phenomena and processes in living organisms. [NIH]

Biopsy: Removal and pathologic examination of specimens in the form of small pieces of tissue from the living body. [NIH]

Biopsy specimen: Tissue removed from the body and examined under a microscope to determine whether disease is present. [NIH]

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]

Biotin: Hexahydro-2-oxo-1H-thieno(3,4-d)imidazole-4-pentanoic acid. Growth factor present in minute amounts in every living cell. It occurs mainly bound to proteins or polypeptides and is abundant in liver, kidney, pancreas, yeast, and milk. The biotin content of cancerous tissue is higher than that of normal tissue. [NIH]

Bivalent: Pertaining to a group of 2 homologous or partly homologous chromosomes during

the zygotene stage of prophase to the first metaphase in meiosis. [NIH]

Bladder: The organ that stores urine. [NIH]

Blastocyst: The mammalian embryo in the post-morula stage in which a fluid-filled cavity, enclosed primarily by trophoblast, contains an inner cell mass which becomes the embryonic disc. [NIH]

Blood Cell Count: A count of the number of leukocytes and erythrocytes per unit volume in a sample of venous blood. A complete blood count (CBC) also includes measurement of the hemoglobin, hematocrit, and erythrocyte indices. [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 Platelets: Non-nucleated disk-shaped cells formed in the megakaryocyte and found in the blood of all mammals. They are mainly involved in blood coagulation. [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 transfusion: The administration of blood or blood products into a blood vessel. [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]

Blood-Retinal Barrier: Specialized nonfenestrated tightly-joined endothelial cells that form a transport barrier for certain substances between the retinal capillaries and the retinal tissue. [NIH]

Blot: To transfer DNA, RNA, or proteins to an immobilizing matrix such as nitrocellulose. [NIH]

Body Fluids: Liquid components of living organisms. [NIH]

Body Mass Index: One of the anthropometric measures of body mass; it has the highest correlation with skinfold thickness or body density. [NIH]

Bone Conduction: Sound transmission through the bones of the skull to the inner ear. [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 Cells: Cells contained in the bone marrow including fat cells, stromal cells, megakaryocytes, and the immediate precursors of most blood cells. [NIH]

Bone Marrow Transplantation: The transference of bone marrow from one human or animal to another. [NIH]

Bone Resorption: Bone loss due to osteoclastic activity. [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]

Bowel Movement: Body wastes passed through the rectum and anus. [NIH]

Brachytherapy: A collective term for interstitial, intracavity, and surface radiotherapy. It uses small sealed or partly-sealed sources that may be placed on or near the body surface or

within a natural body cavity or implanted directly into the tissues. [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]

Branch: Most commonly used for branches of nerves, but applied also to other structures. [NIH]

Breakdown: A physical, metal, or nervous collapse. [NIH]

Bronchioles: The tiny branches of air tubes in the lungs. [NIH]

Bronchiolitis: Inflammation of the bronchioles. [NIH]

Bronchoalveolar Lavage: Washing out of the lungs with saline or mucolytic agents for diagnostic or therapeutic purposes. It is very useful in the diagnosis of diffuse pulmonary infiltrates in immunosuppressed patients. [NIH]

Bronchoalveolar Lavage Fluid: Fluid obtained by washout of the alveolar compartment of the lung. It is used to assess biochemical and inflammatory changes in and effects of therapy on the interstitial lung tissue. [NIH]

Buccal: Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

Bullous: Pertaining to or characterized by bullae. [EU]

Bypass: A surgical procedure in which the doctor creates a new pathway for the flow of body fluids. [NIH]

Cadaver: A dead body, usually a human body. [NIH]

Calcification: Deposits of calcium in the tissues of the breast. Calcification in the breast can be seen on a mammogram, but cannot be detected by touch. There are two types of breast calcification, macrocalcification and microcalcification. Macrocalcifications are large deposits and are usually not related to cancer. Microcalcifications are specks of calcium that may be found in an area of rapidly dividing cells. Many microcalcifications clustered together may be a sign of cancer. [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 adenylyl cyclase with subsequent activation. Thereby this protein modulates cyclic AMP and cyclic GMP levels. [NIH]

Caloric intake: Refers to the number of calories (energy content) consumed. [NIH]

Camptothecin: An alkaloid isolated from the stem wood of the Chinese tree, *Camptotheca acuminata*. This compound selectively inhibits the nuclear enzyme DNA topoisomerase. Several semisynthetic analogs of camptothecin have demonstrated antitumor activity. [NIH]

Cancer vaccine: A vaccine designed to prevent or treat cancer. [NIH]

Candidiasis: Infection with a fungus of the genus *Candida*. It is usually a superficial infection of the moist cutaneous areas of the body, and is generally caused by *C. albicans*; it most commonly involves the skin (dermatocandidiasis), oral mucous membranes (thrush, def. 1), respiratory tract (bronchocandidiasis), and vagina (vaginitis). Rarely there is a systemic infection or endocarditis. Called also moniliasis, candidosis, oidiomycosis, and formerly blastodendriosis. [EU]

Candidosis: An infection caused by an opportunistic yeasts that tends to proliferate and become pathologic when the environment is favorable and the host resistance is weakened. [NIH]

Canonical: A particular nucleotide sequence in which each position represents the base more often found when many actual sequences of a given class of genetic elements are compared. [NIH]

Capsid: The outer protein protective shell of a virus, which protects the viral nucleic acid. [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, $(CH_2O)_n$. 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]

Carcinogen: Any substance that causes cancer. [NIH]

Carcinogenic: Producing carcinoma. [EU]

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]

Cardiolipins: Acidic phospholipids composed of two molecules of phosphatidic acid covalently linked to a molecule of glycerol. They occur primarily in mitochondrial inner membranes and in bacterial plasma membranes. They are the main antigenic components of the Wassermann-type antigen that is used in nontreponemal syphilis serodiagnosis. [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]

Cardiovirus: A genus of the family Picornaviridae causing encephalitis and myocarditis in rodents. Encephalomyocarditis virus is the type species. [NIH]

Carotene: The general name for a group of pigments found in green, yellow, and leafy vegetables, and yellow fruits. The pigments are fat-soluble, unsaturated aliphatic

hydrocarbons functioning as provitamins and are converted to vitamin A through enzymatic processes in the intestinal wall. [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]

Case series: A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. [NIH]

Caspase: Enzyme released by the cell at a crucial stage in apoptosis in order to shred all cellular proteins. [NIH]

Cataract: An opacity, partial or complete, of one or both eyes, on or in the lens or capsule, especially an opacity impairing vision or causing blindness. The many kinds of cataract are classified by their morphology (size, shape, location) or etiology (cause and time of occurrence). [EU]

Catecholamine: A group of chemical substances manufactured by the adrenal medulla and secreted during physiological stress. [NIH]

Catheter: A flexible tube used to deliver fluids into or withdraw fluids from the body. [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]

Cat-Scratch Disease: A self-limiting bacterial infection of the regional lymph nodes caused by *Afipia felis*, a gram-negative bacterium recently identified by the Centers for Disease Control and Prevention and by *Bartonella henselae*. It usually arises one or more weeks following a feline scratch, with raised inflammatory nodules at the site of the scratch being the primary symptom. [NIH]

Caudal: Denoting a position more toward the cauda, or tail, than some specified point of reference; same as inferior, in human anatomy. [EU]

Causal: Pertaining to a cause; directed against a cause. [EU]

Cause of Death: Factors which produce cessation of all vital bodily functions. They can be analyzed from an epidemiologic viewpoint. [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 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 Fusion: Fusion of somatic cells in vitro or in vivo, which results in somatic cell hybridization. [NIH]

Cell Lineage: The developmental history of cells as traced from the first division of the original cell or cells in the embryo. [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 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 Size: The physical dimensions of a cell. It refers mainly to changes in dimensions correlated with physiological or pathological changes in cells. [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]

Cell Transplantation: Transference of cells within an individual, between individuals of the same species, or between individuals of different species. [NIH]

Cellulitis: An acute, diffuse, and suppurative inflammation of loose connective tissue, particularly the deep subcutaneous tissues, and sometimes muscle, which is most commonly seen as a result of infection of a wound, ulcer, or other skin lesions. [NIH]

Central Nervous System: The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [NIH]

Centrifugation: A method of separating organelles or large molecules that relies upon differential sedimentation through a preformed density gradient under the influence of a gravitational field generated in a centrifuge. [NIH]

Cerebral: Of or pertaining of the cerebrum or the brain. [EU]

Cerebral Palsy: Refers to a motor disability caused by a brain dysfunction. [NIH]

Cerebrospinal: Pertaining to the brain and spinal cord. [EU]

Cerebrospinal fluid: CSF. The fluid flowing around the brain and spinal cord. Cerebrospinal fluid is produced in the ventricles in the brain. [NIH]

Cerebrovascular: Pertaining to the blood vessels of the cerebrum, or brain. [EU]

Cerebrum: The largest part of the brain. It is divided into two hemispheres, or halves, called the cerebral hemispheres. The cerebrum controls muscle functions of the body and also controls speech, emotions, reading, writing, and learning. [NIH]

Cerumen: The yellow or brown waxy secretions produced by vestigial apocrine sweat glands in the external ear canal. [NIH]

Cervical: Relating to the neck, or to the neck of any organ or structure. Cervical lymph nodes are located in the neck; cervical cancer refers to cancer of the uterine cervix, which is the lower, narrow end (the "neck") of the uterus. [NIH]

Cervix: The lower, narrow end of the uterus that forms a canal between the uterus and vagina. [NIH]

Chancroid: Acute, localized autoinoculable infectious disease usually acquired through sexual contact. Caused by *Haemophilus ducreyi*, it occurs endemically almost worldwide, especially in tropical and subtropical countries and more commonly in seaports and urban areas than in rural areas. [NIH]

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]

Cheilitis: Inflammation of the lips. It is of various etiologies and degrees of pathology. [NIH]

Chemokines: Class of pro-inflammatory cytokines that have the ability to attract and activate leukocytes. They can be divided into at least three structural branches: C (chemokines, C), CC (chemokines, CC), and CXC (chemokines, CXC), according to variations in a shared cysteine motif. [NIH]

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]

Chickenpox: A mild, highly contagious virus characterized by itchy blisters all over the body. [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]

Chiropractic: A system of treating bodily disorders by manipulation of the spine and other parts, based on the belief that the cause is the abnormal functioning of a nerve. [NIH]

Cholecystitis: Inflammation of the gallbladder. [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]

Chorioretinitis: Inflammation of the choroid in which the sensory retina becomes edematous and opaque. The inflammatory cells and exudate may burst through the sensory retina to cloud the vitreous body. [NIH]

Choroid: The thin, highly vascular membrane covering most of the posterior of the eye between the retina and sclera. [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]

Chromosome Aberrations: Deviations from the normal number or structure of chromosomes, not necessarily associated with disease. [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]

Chymotrypsin: A serine endopeptidase secreted by the pancreas as its zymogen, chymotrypsinogen and carried in the pancreatic juice to the duodenum where it is activated by trypsin. It selectively cleaves aromatic amino acids on the carboxyl side. [NIH]

Cidofovir: A drug used to treat infection caused by viruses. [NIH]

Ciliary: Inflammation or infection of the glands of the margins of the eyelids. [NIH]

Ciliary processes: The extensions or projections of the ciliary body that secrete aqueous

humor. [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]

Cisplatin: An inorganic and water-soluble platinum complex. After undergoing hydrolysis, it reacts with DNA to produce both intra and interstrand crosslinks. These crosslinks appear to impair replication and transcription of DNA. The cytotoxicity of cisplatin correlates with cellular arrest in the G2 phase of the cell cycle. [NIH]

Clamp: A u-shaped steel rod used with a pin or wire for skeletal traction in the treatment of certain fractures. [NIH]

Clear cell carcinoma: A rare type of tumor of the female genital tract in which the inside of the cells looks clear when viewed under a microscope. [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 Protocols: Precise and detailed plans for the study of a medical or biomedical problem and/or plans for a regimen of therapy. [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]

Clone: The term "clone" has acquired a new meaning. It is applied specifically to the bits of inserted foreign DNA in the hybrid molecules of the population. Each inserted segment originally resided in the DNA of a complex genome amid millions of other DNA segment. [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]

Clot Retraction: Retraction of a clot resulting from contraction of platelet pseudopods attached to fibrin strands that is dependent on the contractile protein thrombosthenin. Used as a measure of platelet function. [NIH]

CMV: A virus that belongs to the herpes virus group. [NIH]

Coagulation: 1. The process of clot formation. 2. In colloid chemistry, the solidification of a sol into a gelatinous mass; an alteration of a disperse phase or of a dissolved solid which causes the separation of the system into a liquid phase and an insoluble mass called the clot or curd. Coagulation is usually irreversible. 3. In surgery, the disruption of tissue by physical means to form an amorphous residuum, as in electrocoagulation and photocoagulation. [EU]

Cochlea: The part of the internal ear that is concerned with hearing. It forms the anterior part of the labyrinth, is conical, and is placed almost horizontally anterior to the vestibule. [NIH]

Cochlear: Of or pertaining to the cochlea. [EU]

Cochlear Diseases: Diseases of the cochlea, the part of the inner ear that is concerned with hearing. [NIH]

Codons: Any triplet of nucleotides (coding unit) in DNA or RNA (if RNA is the carrier of primary genetic information as in some viruses) that codes for particular amino acid or signals the beginning or end of the message. [NIH]

Cofactor: A substance, microorganism or environmental factor that activates or enhances the action of another entity such as a disease-causing agent. [NIH]

Cognitive restructuring: A method of identifying and replacing fear-promoting, irrational beliefs with more realistic and functional ones. [NIH]

Cohort Studies: Studies in which subsets of a defined population are identified. These groups may or may not be exposed to factors hypothesized to influence the probability of the occurrence of a particular disease or other outcome. Cohorts are defined populations which, as a whole, are followed in an attempt to determine distinguishing subgroup characteristics. [NIH]

Coliphages: Viruses whose host is *Escherichia coli*. [NIH]

Colitis: Inflammation of the colon. [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]

Collagen disease: A term previously used to describe chronic diseases of the connective tissue (e.g., rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis), but now is thought to be more appropriate for diseases associated with defects in collagen, which is a component of the connective tissue. [NIH]

Collapse: 1. A state of extreme prostration and depression, with failure of circulation. 2. Abnormal falling in of the walls of any part of organ. [EU]

Colloidal: Of the nature of a colloid. [EU]

Colon: The long, coiled, tubelike organ that removes water from digested food. The remaining material, solid waste called stool, moves through the colon to the rectum and leaves the body through the anus. [NIH]

Combination Therapy: Association of 3 drugs to treat AIDS (AZT + DDC or DDI + protease inhibitor). [NIH]

Common Variable Immunodeficiency: Heterogeneous group of immunodeficiency syndromes characterized by hypogammaglobulinemia of most isotypes, variable B-cell defects, and the presence of recurrent bacterial infections. [NIH]

Communicable disease: A disease that can be transmitted by contact between persons. [NIH]

Communication Disorders: Disorders of verbal and nonverbal communication caused by receptive or expressive language disorders, cognitive dysfunction (e.g., mental retardation), psychiatric conditions, and hearing disorders. [NIH]

Comorbidity: The presence of co-existing or additional diseases with reference to an initial diagnosis or with reference to the index condition that is the subject of study. Comorbidity may affect the ability of affected individuals to function and also their survival; it may be used as a prognostic indicator for length of hospital stay, cost factors, and outcome or survival. [NIH]

Compassionate: A process for providing experimental drugs to very sick patients who have

no treatment options. [NIH]

Competency: The capacity of the bacterium to take up DNA from its surroundings. [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]

Complete remission: The disappearance of all signs of cancer. Also called a complete response. [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 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 computerized axial tomography (CAT) scan and computed tomography (CT scan). [NIH]

Concentric: Having a common center of curvature or symmetry. [NIH]

Conception: The onset of pregnancy, marked by implantation of the blastocyst; the formation of a viable zygote. [EU]

Concomitant: Accompanying; accessory; joined with another. [EU]

Condoms: A sheath that is worn over the penis during sexual behavior in order to prevent pregnancy or spread of sexually transmitted disease. [NIH]

Conduction: The transfer of sound waves, heat, nervous impulses, or electricity. [EU]

Condyloma: *C. acuminatum*; a papilloma with a central core of connective tissue in a treelike structure covered with epithelium, usually occurring on the mucous membrane or skin of the external genitals or in the perianal region. [EU]

Cones: One type of specialized light-sensitive cells (photoreceptors) in the retina that provide sharp central vision and color vision. [NIH]

Confounding: Extraneous variables resulting in outcome effects that obscure or exaggerate the "true" effect of an intervention. [NIH]

Congestion: Excessive or abnormal accumulation of blood in a part. [EU]

Conjunctiva: The mucous membrane that lines the inner surface of the eyelids and the anterior part of the sclera. [NIH]

Conjunctivitis: Inflammation of the conjunctiva, generally consisting of conjunctival hyperaemia associated with a discharge. [EU]

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]

Connective Tissue Cells: A group of cells that includes fibroblasts, cartilage cells, adipocytes, smooth muscle cells, and bone cells. [NIH]

Connective Tissue Diseases: A heterogeneous group of disorders, some hereditary, others acquired, characterized by abnormal structure or function of one or more of the elements of connective tissue, i.e., collagen, elastin, or the mucopolysaccharides. [NIH]

Consciousness: Sense of awareness of self and of the environment. [NIH]

Constitutional: 1. Affecting the whole constitution of the body; not local. 2. Pertaining to the constitution. [EU]

Constriction: The act of constricting. [NIH]

Consumption: Pulmonary tuberculosis. [NIH]

Contamination: The soiling or pollution by inferior material, as by the introduction of organisms into a wound, or sewage into a stream. [EU]

Continuum: An area over which the vegetation or animal population is of constantly changing composition so that homogeneous, separate communities cannot be distinguished. [NIH]

Contraception: Use of agents, devices, methods, or procedures which diminish the likelihood of or prevent conception. [NIH]

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]

Control group: In a clinical trial, the group that does not receive the new treatment being studied. This group is compared to the group that receives the new treatment, to see if the new treatment works. [NIH]

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]

Coordination: Muscular or motor regulation or the harmonious cooperation of muscles or groups of muscles, in a complex action or series of actions. [NIH]

Cornea: The transparent part of the eye that covers the iris and the pupil and allows light to enter the inside. [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 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]

Cortex: The outer layer of an organ or other body structure, as distinguished from the internal substance. [EU]

Cortical: Pertaining to or of the nature of a cortex or bark. [EU]

Corticosteroid: Any of the steroids elaborated by the adrenal cortex (excluding the sex hormones of adrenal origin) in response to the release of corticotrophin (adrenocorticotrophic hormone) by the pituitary gland, to any of the synthetic equivalents of these steroids, or to angiotensin II. They are divided, according to their predominant biological activity, into three major groups: glucocorticoids, chiefly influencing carbohydrate, fat, and protein metabolism; mineralocorticoids, affecting the regulation of electrolyte and water balance; and C19 androgens. Some corticosteroids exhibit both types of activity in varying degrees, and others exert only one type of effect. The corticosteroids are used clinically for hormonal replacement therapy, for suppression of ACTH secretion by the anterior pituitary, as antineoplastic, antiallergic, and anti-inflammatory agents, and to suppress the immune response. Called also adrenocortical hormone and corticoid. [EU]

Cortisol: A steroid hormone secreted by the adrenal cortex as part of the body's response to stress. [NIH]

Cortisone: A natural steroid hormone produced in the adrenal gland. It can also be made in the laboratory. Cortisone reduces swelling and can suppress immune responses. [NIH]

Cosmids: Plasmids containing at least one cos (cohesive-end site) of phage lambda. They are used as cloning vehicles for the study of aberrant eukaryotic structural genes and also as genetic vectors for introducing the nucleic acid of transforming viruses into cultured cells. [NIH]

Cowpox: A mild, eruptive skin disease of milk cows caused by cowpox virus, with lesions occurring principally on the udder and teats. Human infection may occur while milking an infected animal. [NIH]

Cowpox Virus: A species of orthopoxvirus that is the etiologic agent of cowpox. It is closely related to but antigenically different from vaccinia virus. [NIH]

Cranial: Pertaining to the cranium, or to the anterior (in animals) or superior (in humans) end of the body. [EU]

Craniocerebral Trauma: Traumatic injuries involving the cranium and intracranial structures (i.e., brain; cranial nerves; meninges; and other structures). Injuries may be classified by whether or not the skull is penetrated (i.e., penetrating vs. nonpenetrating) or whether there is an associated hemorrhage. [NIH]

Critical Care: Health care provided to a critically ill patient during a medical emergency or crisis. [NIH]

Crossing-over: The exchange of corresponding segments between chromatids of homologous chromosomes during meiosis, forming a chiasma. [NIH]

Cross-Sectional Studies: Studies in which the presence or absence of disease or other health-related variables are determined in each member of the study population or in a representative sample at one particular time. This contrasts with longitudinal studies which are followed over a period of time. [NIH]

Cryptosporidiosis: Parasitic intestinal infection with severe diarrhea caused by a protozoan, *Cryptosporidium*. It occurs in both animals and humans. [NIH]

Cryptosporidium: A genus of coccidian parasites of the family *Cryptosporidiidae*, found in the intestinal epithelium of many vertebrates including humans. [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]

Cyclodextrins: A homologous group of cyclic glucans consisting of alpha-1,4 bound glucose units obtained by the action of cyclodextrin glucanotransferase on starch or similar substrates. The enzyme is produced by certain species of *Bacillus*. Cyclodextrins form inclusion complexes with a wide variety of substances. [NIH]

Cycloheximide: Antibiotic substance isolated from streptomycin-producing strains of *Streptomyces griseus*. It acts by inhibiting elongation during protein synthesis. [NIH]

Cyclophosphamide: Precursor of an alkylating nitrogen mustard antineoplastic and immunosuppressive agent that must be activated in the liver to form the active aldophosphamide. It is used in the treatment of lymphomas, leukemias, etc. Its side effect, alopecia, has been made use of in defleecing sheep. Cyclophosphamide may also cause sterility, birth defects, mutations, and cancer. [NIH]

Cyclosporine: A drug used to help reduce the risk of rejection of organ and bone marrow transplants by the body. It is also used in clinical trials to make cancer cells more sensitive to

anticancer drugs. [NIH]

Cystine: A covalently linked dimeric nonessential amino acid formed by the oxidation of cysteine. Two molecules of cysteine are joined together by a disulfide bridge to form cystine. [NIH]

Cystitis: Inflammation of the urinary bladder. [EU]

Cytogenetics: A branch of genetics which deals with the cytological and molecular behavior of genes and chromosomes during cell division. [NIH]

Cytokine: Small but highly potent protein that modulates the activity of many cell types, including T and B cells. [NIH]

Cytomegalovirus: A genus of the family Herpesviridae, subfamily Betaherpesvirinae, infecting the salivary glands, liver, spleen, lungs, eyes, and other organs, in which they produce characteristically enlarged cells with intranuclear inclusions. Infection with Cytomegalovirus is also seen as an opportunistic infection in AIDS. [NIH]

Cytomegalovirus Infections: Infection with Cytomegalovirus, characterized by enlarged cells bearing intranuclear inclusions. Infection may be in almost any organ, but the salivary glands are the most common site in children, as are the lungs in adults. [NIH]

Cytomegalovirus Retinitis: Infection of the retina by cytomegalovirus characterized by retinal necrosis, hemorrhage, vessel sheathing, and retinal edema. Cytomegalovirus retinitis is a major opportunistic infection in AIDS patients and can cause blindness. [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]

Cytosine: A pyrimidine base that is a fundamental unit of nucleic acids. [NIH]

Cytotoxic: Cell-killing. [NIH]

Cytotoxic chemotherapy: Anticancer drugs that kill cells, especially cancer cells. [NIH]

Cytotoxicity: Quality of being capable of producing a specific toxic action upon cells of special organs. [NIH]

Data Collection: Systematic gathering of data for a particular purpose from various sources, including questionnaires, interviews, observation, existing records, and electronic devices. The process is usually preliminary to statistical analysis of the data. [NIH]

Day Care: Institutional health care of patients during the day. The patients return home at night. [NIH]

De novo: In cancer, the first occurrence of cancer in the body. [NIH]

Decidua: The epithelial lining of the endometrium that is formed before the fertilized ovum reaches the uterus. The fertilized ovum embeds in the decidua. If the ovum is not fertilized, the decidua is shed during menstruation. [NIH]

Decision Making: The process of making a selective intellectual judgment when presented with several complex alternatives consisting of several variables, and usually defining a course of action or an idea. [NIH]

Deferoxamine: Natural product isolated from *Streptomyces pilosus*. It forms iron complexes and is used as a chelating agent, particularly in the form of its mesylate. [NIH]

Degenerative: Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

Delavirdine: A potent, non-nucleoside reverse transcriptase inhibitor with activity specific for HIV-1. [NIH]

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]

Denaturation: Rupture of the hydrogen bonds by heating a DNA solution and then cooling it rapidly causes the two complementary strands to separate. [NIH]

Dendrites: Extensions of the nerve cell body. They are short and branched and receive stimuli from other neurons. [NIH]

Dendritic: 1. Branched like a tree. 2. Pertaining to or possessing dendrites. [EU]

Dendritic cell: A special type of antigen-presenting cell (APC) that activates T lymphocytes. [NIH]

Density: The logarithm to the base 10 of the opacity of an exposed and processed film. [NIH]

Dental Assistants: Individuals who assist the dentist or the dental hygienist. [NIH]

Dental Hygienists: Persons trained in an accredited school or dental college and licensed by the state in which they reside to provide dental prophylaxis under the direction of a licensed dentist. [NIH]

Dentists: Individuals licensed to practice dentistry. [NIH]

Deoxyribonucleic: A polymer of subunits called deoxyribonucleotides which is the primary genetic material of a cell, the material equivalent to genetic information. [NIH]

Deoxyribonucleic acid: A polymer of subunits called deoxyribonucleotides which is the primary genetic material of a cell, the material equivalent to genetic information. [NIH]

Deoxyribonucleotides: A purine or pyrimidine base bonded to a deoxyribose containing a bond to a phosphate group. [NIH]

Depigmentation: Removal or loss of pigment, especially melanin. [EU]

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]

Deprivation: Loss or absence of parts, organs, powers, or things that are needed. [EU]

Dermatitis: Any inflammation of the skin. [NIH]

DES: Diethylstilbestrol. A synthetic hormone that was prescribed from the early 1940s until 1971 to help women with complications of pregnancy. DES has been linked to an increased risk of clear cell carcinoma of the vagina in daughters of women who used DES. DES may also increase the risk of breast cancer in women who used DES. [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]

Developing Countries: Countries in the process of change directed toward economic growth, that is, an increase in production, per capita consumption, and income. The process of economic growth involves better utilization of natural and human resources, which

results in a change in the social, political, and economic structures. [NIH]

Developmental Biology: The field of biology which deals with the process of the growth and differentiation of an organism. [NIH]

Dexamethasone: (11 beta,16 alpha)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione. An anti-inflammatory glucocorticoid used either in the free alcohol or esterified form in treatment of conditions that respond generally to cortisone. [NIH]

Diabetes Mellitus: A heterogeneous group of disorders that share glucose intolerance in common. [NIH]

Diagnostic procedure: A method used to identify a disease. [NIH]

Dialyzer: A part of the hemodialysis machine. (See hemodialysis under dialysis.) The dialyzer has two sections separated by a membrane. One section holds dialysate. The other holds the patient's blood. [NIH]

Diarrhea: Passage of excessively liquid or excessively frequent stools. [NIH]

Diarrhoea: Abnormal frequency and liquidity of faecal discharges. [EU]

Diastolic: Of or pertaining to the diastole. [EU]

Diencephalon: The paired caudal parts of the prosencephalon from which the thalamus, hypothalamus, epithalamus, and subthalamus are derived. [NIH]

Difluoromethylornithine: DFMO. An anticancer drug that has been shown to reduce the risk of cancer in animals. [NIH]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Digestive system: The organs that take in food and turn it into products that the body can use to stay healthy. Waste products the body cannot use leave the body through bowel movements. The digestive system includes the salivary glands, mouth, esophagus, stomach, liver, pancreas, gallbladder, small and large intestines, and rectum. [NIH]

Digestive tract: The organs through which food passes when food is eaten. These organs are the mouth, esophagus, stomach, small and large intestines, and rectum. [NIH]

Digoxigenin: 3 beta,12 beta,14-Trihydroxy-5 beta-card-20(22)-enolide. A cardenolide which is the aglycon of digoxin. Can be obtained by hydrolysis of digoxin or from *Digitalis orientalis* L. and *Digitalis lanata* Ehrh. [NIH]

Dihydrotestosterone: Anabolic agent. [NIH]

Dihydroxy: AMPA/Kainate antagonist. [NIH]

Dilatation: The act of dilating. [NIH]

Dilution: A diluted or attenuated medicine; in homeopathy, the diffusion of a given quantity of a medicinal agent in ten or one hundred times the same quantity of water. [NIH]

Dimerization: The process by which two molecules of the same chemical composition form a condensation product or polymer. [NIH]

Dimethyl: A volatile metabolite of the amino acid methionine. [NIH]

Dimethyl Sulfoxide: A highly polar organic liquid, that is used widely as a chemical solvent. Because of its ability to penetrate biological membranes, it is used as a vehicle for topical application of pharmaceuticals. It is also used to protect tissue during cryopreservation. Dimethyl sulfoxide shows a range of pharmacological activity including analgesia and anti-inflammation. [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]

Discrimination: The act of qualitative and/or quantitative differentiation between two or more stimuli. [NIH]

Disease Progression: The worsening of a disease over time. This concept is most often used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis. [NIH]

Disease Transmission: The transmission of infectious disease or pathogens. When transmission is within the same species, the mode can be horizontal (disease transmission, horizontal) or vertical (disease transmission, vertical). [NIH]

Disease Transmission, Horizontal: The transmission of infectious disease or pathogens from one individual to another in the same generation. [NIH]

Disease Transmission, Vertical: The transmission of infectious disease or pathogens from one generation to another. It includes transmission in utero or intrapartum by exposure to blood and secretions, and postpartum exposure via breastfeeding. [NIH]

Disinfectant: An agent that disinfects; applied particularly to agents used on inanimate objects. [EU]

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]

Dissociative Disorders: Sudden temporary alterations in the normally integrative functions of consciousness. [NIH]

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]

Disulphide: A covalent bridge formed by the oxidation of two cysteine residues to a cystine residue. The-S-S-bond is very strong and its presence confers additional stability. [NIH]

Dizziness: An imprecise term which may refer to a sense of spatial disorientation, motion of the environment, or lightheadedness. [NIH]

Docetaxel: An anticancer drug that belongs to the family of drugs called mitotic inhibitors. [NIH]

Domesticated: Species in which the evolutionary process has been influenced by humans to meet their needs. [NIH]

Dopamine: An endogenous catecholamine and prominent neurotransmitter in several systems of the brain. In the synthesis of catecholamines from tyrosine, it is the immediate precursor to norepinephrine and epinephrine. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. A family of dopaminergic receptor subtypes mediate its action. Dopamine is used pharmacologically for its direct (beta adrenergic agonist) and indirect (adrenergic releasing) sympathomimetic effects including its actions as an inotropic agent and as a renal vasodilator. [NIH]

Dorsal: 1. Pertaining to the back or to any dorsum. 2. Denoting a position more toward the back surface than some other object of reference; same as posterior in human anatomy;

superior in the anatomy of quadrupeds. [EU]

Dosage schedule: A scheme set up to determine and regulate size, frequency and number of doses. [EU]

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]

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 Design: The molecular designing of drugs for specific purposes (such as DNA-binding, enzyme inhibition, anti-cancer efficacy, etc.) based on knowledge of molecular properties such as activity of functional groups, molecular geometry, and electronic structure, and also on information cataloged on analogous molecules. Drug design is generally computer-assisted molecular modeling and does not include pharmacokinetics, dosage analysis, or drug administration analysis. [NIH]

Drug Interactions: The action of a drug that may affect the activity, metabolism, or toxicity of another drug. [NIH]

Drug Resistance: Diminished or failed response of an organism, disease or tissue to the intended effectiveness of a chemical or drug. It should be differentiated from drug tolerance which is the progressive diminution of the susceptibility of a human or animal to the effects of a drug, as a result of continued administration. [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]

Duodenal Ulcer: An ulcer in the lining of the first part of the small intestine (duodenum). [NIH]

Duodenitis: An irritation of the first part of the small intestine (duodenum). [NIH]

Duodenum: The first part of the small intestine. [NIH]

Dura mater: The outermost, toughest, and most fibrous of the three membranes (meninges) covering the brain and spinal cord; called also pachymeninx. [EU]

Dysphagia: Difficulty in swallowing. [EU]

Dysplasia: Cells that look abnormal under a microscope but are not cancer. [NIH]

Eardrum: A thin, tense membrane forming the greater part of the outer wall of the tympanic cavity and separating it from the external auditory meatus; it constitutes the boundary between the external and middle ear. [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]

Effector cell: A cell that performs a specific function in response to a stimulus; usually used to describe cells in the immune system. [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]

Effusion: The escape of fluid into a part or tissue, as an exudation or a transudation. [EU]

Ejaculation: The release of semen through the penis during orgasm. [NIH]

Elastin: The protein that gives flexibility to tissues. [NIH]

Elective: Subject to the choice or decision of the patient or physician; applied to procedures that are advantageous to the patient but not urgent. [EU]

Electrolyte: A substance that dissociates into ions when fused or in solution, and thus becomes capable of conducting electricity; an ionic solute. [EU]

Electrophysiological: Pertaining to electrophysiology, that is a branch of physiology that is concerned with the electric phenomena associated with living bodies and involved in their functional activity. [EU]

Elementary Particles: Individual components of atoms, usually subatomic; subnuclear particles are usually detected only when the atomic nucleus decays and then only transiently, as most of them are unstable, often yielding pure energy without substance, i.e., radiation. [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 embryo). [NIH]

Embryology: The study of the development of an organism during the embryonic and fetal stages of life. [NIH]

Emergency Medicine: A branch of medicine concerned with an individual's resuscitation, transportation and care from the point of injury or beginning of illness through the hospital or other emergency treatment facility. [NIH]

Emergency Treatment: First aid or other immediate intervention for accidents or medical conditions requiring immediate care and treatment before definitive medical and surgical management can be procured. [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]

Encephalomyocarditis Virus: The type species of cardiovirus causing encephalomyelitis

and myocarditis in rodents, pigs, and monkeys. Infection in man has been reported with CNS involvement but without myocarditis. [NIH]

Endarterectomy: Surgical excision, performed under general anesthesia, of the atheromatous tunica intima of an artery. When reconstruction of an artery is performed as an endovascular procedure through a catheter, it is called atherectomy. [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]

Endocarditis: Exudative and proliferative inflammatory alterations of the endocardium, characterized by the presence of vegetations on the surface of the endocardium or in the endocardium itself, and most commonly involving a heart valve, but sometimes affecting the inner lining of the cardiac chambers or the endocardium elsewhere. It may occur as a primary disorder or as a complication of or in association with another disease. [EU]

Endocardium: The innermost layer of the heart, comprised of endothelial cells. [NIH]

Endocrinology: A subspecialty of internal medicine concerned with the metabolism, physiology, and disorders of the endocrine system. [NIH]

Endogenous: Produced inside an organism or cell. The opposite is external (exogenous) production. [NIH]

Endometrium: The layer of tissue that lines the uterus. [NIH]

Endonucleases: Enzymes that catalyze the hydrolysis of the internal bonds and thereby the formation of polynucleotides or oligonucleotides from ribo- or deoxyribonucleotide chains. EC 3.1.-. [NIH]

Endopeptidases: A subclass of peptide hydrolases. They are classified primarily by their catalytic mechanism. Specificity is used only for identification of individual enzymes. They comprise the serine endopeptidases, EC 3.4.21; cysteine endopeptidases, EC 3.4.22; aspartic endopeptidases, EC 3.4.23, metalloendopeptidases, EC 3.4.24; and a group of enzymes yet to be assigned to any of the above sub-classes, EC 3.4.99. EC 3.4.-. [NIH]

Endorphins: One of the three major groups of endogenous opioid peptides. They are large peptides derived from the pro-opiomelanocortin precursor. The known members of this group are alpha-, beta-, and gamma-endorphin. The term endorphin is also sometimes used to refer to all opioid peptides, but the narrower sense is used here; opioid peptides is used for the broader group. [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-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes it. [NIH]

Endotoxin: Toxin from cell walls of bacteria. [NIH]

End-stage renal: Total chronic kidney failure. When the kidneys fail, the body retains fluid and harmful wastes build up. A person with ESRD needs treatment to replace the work of the failed kidneys. [NIH]

Energy balance: Energy is the capacity of a body or a physical system for doing work. Energy balance is the state in which the total energy intake equals total energy needs. [NIH]

Enhancer: Transcriptional element in the virus genome. [NIH]

Enkephalins: One of the three major families of endogenous opioid peptides. The enkephalins are pentapeptides that are widespread in the central and peripheral nervous

systems and in the adrenal medulla. [NIH]

Enteritis: Inflammation of the intestine, applied chiefly to inflammation of the small intestine; see also enterocolitis. [EU]

Enterocolitis: Inflammation of the intestinal mucosa of the small and large bowel. [NIH]

Enterovirus: A genus of the family Picornaviridae whose members preferentially inhabit the intestinal tract of a variety of hosts. The genus contains many species. Newly described members of human enteroviruses are assigned continuous numbers with the species designated "human enterovirus". [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]

Enzymatic: Phase where enzyme cuts the precursor protein. [NIH]

Enzyme: A protein that speeds up chemical reactions in the body. [NIH]

Enzyme-Linked Immunosorbent Assay: An immunoassay utilizing an antibody labeled with an enzyme marker such as horseradish peroxidase. While either the enzyme or the antibody is bound to an immunosorbent substrate, they both retain their biologic activity; the change in enzyme activity as a result of the enzyme-antibody-antigen reaction is proportional to the concentration of the antigen and can be measured spectrophotometrically or with the naked eye. Many variations of the method have been developed. [NIH]

Eosinophil: A polymorphonuclear leucocyte with large eosinophilic granules in its cytoplasm, which plays a role in hypersensitivity reactions. [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]

Ependyma: A thin membrane that lines the ventricles of the brain and the central canal of the spinal cord. [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]

Epidemiologic Studies: Studies designed to examine associations, commonly, hypothesized causal relations. They are usually concerned with identifying or measuring the effects of risk factors or exposures. The common types of analytic study are case-control studies, cohort studies, and cross-sectional studies. [NIH]

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]

Epidermoid carcinoma: A type of cancer in which the cells are flat and look like fish scales. Also called squamous cell carcinoma. [NIH]

Epigastric: Having to do with the upper middle area of the abdomen. [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]

Epstein: Failure of the upper eyelid to move downward on downward movement of the eye, occurring in premature and nervous infants. [NIH]

Epstein-Barr virus: EBV. A common virus that remains dormant in most people. It has been associated with certain cancers, including Burkitt's lymphoma, immunoblastic lymphoma, and nasopharyngeal carcinoma. [NIH]

Erythema: Redness of the skin produced by congestion of the capillaries. This condition may result from a variety of causes. [NIH]

Erythrocyte Indices: Quantification of size and cell hemoglobin content or concentration of the erythrocyte, usually derived from erythrocyte count, blood hemoglobin concentration, and hematocrit. Includes the mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC). Use also for cell diameter and thickness. [NIH]

Erythrocytes: Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [NIH]

Erythromycin: A bacteriostatic antibiotic substance produced by *Streptomyces erythreus*. Erythromycin A is considered its major active component. In sensitive organisms, it inhibits protein synthesis by binding to 50S ribosomal subunits. This binding process inhibits peptidyl transferase activity and interferes with translocation of amino acids during translation and assembly of proteins. [NIH]

Escalation: Progressive use of more harmful drugs. [NIH]

Esophageal: Having to do with the esophagus, the muscular tube through which food passes from the throat to the stomach. [NIH]

Esophagitis: Inflammation, acute or chronic, of the esophagus caused by bacteria, chemicals, or trauma. [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]

Ethnic Groups: A group of people with a common cultural heritage that sets them apart from others in a variety of social relationships. [NIH]

Etoposide: A semisynthetic derivative of podophyllotoxin that exhibits antitumor activity. Etoposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA. This complex induces breaks in double stranded DNA and prevents repair by topoisomerase II binding. Accumulated breaks in DNA prevent entry into the mitotic phase

of cell division, and lead to cell death. Etoposide acts primarily in the G2 and S phases of the cell cycle. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

Eustachian tube: The middle ear cavity is in communication with the back of the nose through the Eustachian tube, which is normally closed, but opens on swallowing, in order to maintain equal air pressure. [NIH]

Excipients: Usually inert substances added to a prescription in order to provide suitable consistency to the dosage form; a binder, matrix, base or diluent in pills, tablets, creams, salves, etc. [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]

Exhaustion: The feeling of weariness of mind and body. [NIH]

Exocrine: Secreting outwardly, via a duct. [EU]

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]

Exopeptidases: A sub-subclass of peptide hydrolases that act only near the ends of polypeptide chains. Exopeptidases are further divided into aminopeptidases, EC 3.4.11; dipeptidases, EC 3.4.13; dipeptidyl peptidases & tripeptidyl peptidases, EC 3.4.14; peptidyl-dipeptidases, EC 3.4.15; carboxypeptidases, EC 3.4.16 - EC 3.4.18, and omega peptidases, EC 3.4.19. EC 3.4.-. [NIH]

Extensor: A muscle whose contraction tends to straighten a limb; the antagonist of a flexor. [NIH]

External-beam radiation: Radiation therapy that uses a machine to aim high-energy rays at the cancer. Also called external radiation. [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 Space: Interstitial space between cells, occupied by fluid as well as amorphous and fibrous substances. [NIH]

Extraction: The process or act of pulling or drawing out. [EU]

Exudate: Material, such as fluid, cells, or cellular debris, which has escaped from blood vessels and has been deposited in tissues or on tissue surfaces, usually as a result of inflammation. An exudate, in contrast to a transudate, is characterized by a high content of protein, cells, or solid materials derived from cells. [EU]

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]

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]

Fermentation: An enzyme-induced chemical change in organic compounds that takes place in the absence of oxygen. The change usually results in the production of ethanol or lactic acid, and the production of energy. [NIH]

Fetal Alcohol Syndrome: A disorder occurring in children born to alcoholic women who continue to drink heavily during pregnancy. Common abnormalities are growth deficiency (prenatal and postnatal), altered morphogenesis, mental deficiency, and characteristic facies - small eyes and flattened nasal bridge. Fine motor dysfunction and tremulousness are observed in the newborn. [NIH]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

Fever of Unknown Origin: Fever in which the etiology cannot be ascertained. [NIH]

Fibrin: A protein derived from fibrinogen in the presence of thrombin, which forms part of the blood clot. [NIH]

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]

Fistula: Abnormal communication most commonly seen between two internal organs, or between an internal organ and the surface of the body. [NIH]

Fixation: 1. The act or operation of holding, suturing, or fastening in a fixed position. 2. The condition of being held in a fixed position. 3. In psychiatry, a term with two related but distinct meanings : (1) arrest of development at a particular stage, which like regression (return to an earlier stage), if temporary is a normal reaction to setbacks and difficulties but if protracted or frequent is a cause of developmental failures and emotional problems, and (2) a close and suffocating attachment to another person, especially a childhood figure, such as one's mother or father. Both meanings are derived from psychoanalytic theory and refer to 'fixation' of libidinal energy either in a specific erogenous zone, hence fixation at the oral, anal, or phallic stage, or in a specific object, hence mother or father fixation. 4. The use of a fixative (q.v.) to preserve histological or cytological specimens. 5. In chemistry, the process whereby a substance is removed from the gaseous or solution phase and localized, as in carbon dioxide fixation or nitrogen fixation. 6. In ophthalmology, direction of the gaze so that the visual image of the object falls on the fovea centralis. 7. In film processing, the chemical removal of all undeveloped salts of the film emulsion, leaving only the developed silver to form a permanent image. [EU]

Flavoring Agents: Substances added to foods and medicine to improve the quality of taste. [NIH]

Flow Cytometry: Technique using an instrument system for making, processing, and displaying one or more measurements on individual cells obtained from a cell suspension.

Cells are usually stained with one or more fluorescent dyes specific to cell components of interest, e.g., DNA, and fluorescence of each cell is measured as it rapidly transverse the excitation beam (laser or mercury arc lamp). Fluorescence provides a quantitative measure of various biochemical and biophysical properties of the cell, as well as a basis for cell sorting. Other measurable optical parameters include light absorption and light scattering, the latter being applicable to the measurement of cell size, shape, density, granularity, and stain uptake. [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]

Fluorescent Dyes: Dyes that emit light when exposed to light. The wave length of the emitted light is usually longer than that of the incident light. Fluorochromes are substances that cause fluorescence in other substances, i.e., dyes used to mark or label other compounds with fluorescent tags. They are used as markers in biochemistry and immunology. [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]

Focus Groups: A method of data collection and a qualitative research tool in which a small group of individuals are brought together and allowed to interact in a discussion of their opinions about topics, issues, or questions. [NIH]

Fold: A plication or doubling of various parts of the body. [NIH]

Food Additives: Substances which are of little or no nutritive value, but are used in the processing or storage of foods or animal feed, especially in the developed countries; includes antioxidants, food preservatives, food coloring agents, flavoring agents, anti-infective agents (both plain and local), vehicles, excipients and other similarly used substances. Many of the same substances are pharmaceutic aids when added to pharmaceuticals rather than to foods. [NIH]

Food Preservatives: Substances capable of inhibiting, retarding or arresting the process of fermentation, acidification or other deterioration of foods. [NIH]

Forearm: The part between the elbow and the wrist. [NIH]

Foscarnet: An antiviral agent used in the treatment of cytomegalovirus retinitis. Foscarnet also shows activity against human herpesviruses and HIV. [NIH]

Fowlpox: A poxvirus infection of poultry and other birds characterized by the formation of wart-like nodules on the skin and diphtheritic necrotic masses (cankers) in the upper digestive and respiratory tracts. [NIH]

Free Radical Scavengers: Substances that influence the course of a chemical reaction by ready combination with free radicals. Among other effects, this combining activity protects pancreatic islets against damage by cytokines and prevents myocardial and pulmonary perfusion injuries. [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]

Fungi: A kingdom of eukaryotic, heterotrophic organisms that live as saprobes or parasites, including mushrooms, yeasts, smuts, molds, etc. They reproduce either sexually or asexually, and have life cycles that range from simple to complex. Filamentous fungi refer to

those that grow as multicellular colonies (mushrooms and molds). [NIH]

Fungus: A general term used to denote a group of eukaryotic protists, including mushrooms, yeasts, rusts, moulds, smuts, etc., which are characterized by the absence of chlorophyll and by the presence of a rigid cell wall composed of chitin, mannans, and sometimes cellulose. They are usually of simple morphological form or show some reversible cellular specialization, such as the formation of pseudoparenchymatous tissue in the fruiting body of a mushroom. The dimorphic fungi grow, according to environmental conditions, as moulds or yeasts. [EU]

Galactosides: Glycosides formed by the reaction of the hydroxyl group on the anomeric carbon atom of galactose with an alcohol to form an acetal. They include both alpha- and beta-galactosides. [NIH]

Gallbladder: The pear-shaped organ that sits below the liver. Bile is concentrated and stored in the gallbladder. [NIH]

Gamma Rays: Very powerful and penetrating, high-energy electromagnetic radiation of shorter wavelength than that of x-rays. They are emitted by a decaying nucleus, usually between 0.01 and 10 MeV. They are also called nuclear x-rays. [NIH]

Gamma-interferon: Interferon produced by T-lymphocytes in response to various mitogens and antigens. Gamma interferon appears to have potent antineoplastic, immunoregulatory and antiviral activity. [NIH]

Ganciclovir: Acyclovir analog that is a potent inhibitor of the Herpesvirus family including cytomegalovirus. Ganciclovir is used to treat complications from AIDS-associated cytomegalovirus infections. [NIH]

Ganglia: Clusters of multipolar neurons surrounded by a capsule of loosely organized connective tissue located outside the central nervous system. [NIH]

Ganglion: 1. A knot, or knotlike mass. 2. A general term for a group of nerve cell bodies located outside the central nervous system; occasionally applied to certain nuclear groups within the brain or spinal cord, e.g. basal ganglia. 3. A benign cystic tumour occurring on a aponeurosis or tendon, as in the wrist or dorsum of the foot; it consists of a thin fibrous capsule enclosing a clear mucinous fluid. [EU]

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]

Gastric: Having to do with the stomach. [NIH]

Gastric Juices: Liquids produced in the stomach to help break down food and kill bacteria. [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]

Gastritis: Inflammation of the stomach. [EU]

Gastroenteritis: An acute inflammation of the lining of the stomach and intestines, characterized by anorexia, nausea, diarrhoea, abdominal pain, and weakness, which has various causes, including food poisoning due to infection with such organisms as *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella* species; consumption of irritating food or drink; or psychological factors such as anger, stress, and fear. Called also enterogastritis. [EU]

Gastroenterology: A subspecialty of internal medicine concerned with the study of the physiology and diseases of the digestive system and related structures (esophagus, liver, gallbladder, and pancreas). [NIH]

Gastroesophageal Reflux: Reflux of gastric juice and/or duodenal contents (bile acids, pancreatic juice) into the distal esophagus, commonly due to incompetence of the lower esophageal sphincter. Gastric regurgitation is an extension of this process with entry of fluid into the pharynx or mouth. [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal Hemorrhage: Bleeding in the gastrointestinal tract. [NIH]

Gastrointestinal tract: The stomach and intestines. [NIH]

Gelatin: A product formed from skin, white connective tissue, or bone collagen. It is used as a protein food adjuvant, plasma substitute, hemostatic, suspending agent in pharmaceutical preparations, and in the manufacturing of capsules and suppositories. [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 Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [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]

General practitioner: A medical practitioner who does not specialize in a particular branch of medicine or limit his practice to a specific class of diseases. [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 Counseling: Advising families of the risks involved pertaining to birth defects, in order that they may make an informed decision on current or future pregnancies. [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 testing: Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder. [NIH]

Genetic Vectors: Any DNA molecule capable of autonomous replication within a host cell and into which other DNA sequences can be inserted and thus amplified. Many are derived from plasmids, bacteriophages or viruses. They are used for transporting foreign genes into recipient cells. Genetic vectors possess a functional replicator site and contain genetic

markers to facilitate their selective recognition. [NIH]

Genital: Pertaining to the genitalia. [EU]

Genitourinary: Pertaining to the genital and urinary organs; urogenital; urinosexual. [EU]

Genotype: The genetic constitution of the individual; the characterization of the genes. [NIH]

Geotrichosis: Infection due to the fungus *Geotrichum*. [NIH]

Gestation: The period of development of the young in viviparous animals, from the time of fertilization of the ovum until birth. [EU]

Giant Cells: Multinucleated masses produced by the fusion of many cells; often associated with viral infections. In AIDS, they are induced when the envelope glycoprotein of the HIV virus binds to the CD4 antigen of uninfected neighboring T4 cells. The resulting syncytium leads to cell death and thus may account for the cytopathic effect of the virus. [NIH]

Gingivitis: Inflammation of the gingivae. Gingivitis associated with bony changes is referred to as periodontitis. Called also *oulitis* and *ulitis*. [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]

Glioma: A cancer of the brain that comes from glial, or supportive, cells. [NIH]

Glomerular: Pertaining to or of the nature of a glomerulus, especially a renal glomerulus. [EU]

Glomerulus: A tiny set of looping blood vessels in the nephron where blood is filtered in the kidney. [NIH]

Glucans: Polysaccharides composed of repeating glucose units. They can consist of branched or unbranched chains in any linkages. [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]

Glucuronic Acid: Derivatives of uronic acid found throughout the plant and animal kingdoms. They detoxify drugs and toxins by conjugating with them to form glucuronides in the liver which are more water-soluble metabolites that can be easily eliminated from the body. [NIH]

Glutamic Acid: A non-essential amino acid naturally occurring in the L-form. Glutamic acid (glutamate) is the most common excitatory neurotransmitter in the central nervous system. [NIH]

Glycine: A non-essential amino acid. It is found primarily in gelatin and silk fibroin and used therapeutically as a nutrient. It is also a fast inhibitory neurotransmitter. [NIH]

Glycoprotein: A protein that has sugar molecules attached to it. [NIH]

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]

Gonadal: Pertaining to a gonad. [EU]

Gonorrhea: Acute infectious disease characterized by primary invasion of the urogenital tract. The etiologic agent, *Neisseria gonorrhoeae*, was isolated by Neisser in 1879. [NIH]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Gp120: 120-kD HIV envelope glycoprotein which is involved in the binding of the virus to its membrane receptor, the CD4 molecule, found on the surface of certain cells in the body. [NIH]

Grade: The grade of a tumor depends on how abnormal the cancer cells look under a microscope and how quickly the tumor is likely to grow and spread. Grading systems are different for each type of cancer. [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]

Graft Survival: The survival of a graft in a host, the factors responsible for the survival and the changes occurring within the graft during growth in the host. [NIH]

Graft-versus-host disease: GVHD. A reaction of donated bone marrow or peripheral stem cells against a person's tissue. [NIH]

Gram-negative: Losing the stain or decolorized by alcohol in Gram's method of staining, a primary characteristic of bacteria having a cell wall composed of a thin layer of peptidoglycan covered by an outer membrane of lipoprotein and lipopolysaccharide. [EU]

Gram-positive: Retaining the stain or resisting decolorization by alcohol in Gram's method of staining, a primary characteristic of bacteria whose cell wall is composed of a thick layer of peptidoglycan with attached teichoic acids. [EU]

Granule: A small pill made from sucrose. [EU]

Granulocyte: A type of white blood cell that fights bacterial infection. Neutrophils, eosinophils, and basophils are granulocytes. [NIH]

Granulocyte-Macrophage Colony-Stimulating Factor: An acidic glycoprotein of MW 23 kDa with internal disulfide bonds. The protein is produced in response to a number of inflammatory mediators by mesenchymal cells present in the hemopoietic environment and at peripheral sites of inflammation. GM-CSF is able to stimulate the production of neutrophilic granulocytes, macrophages, and mixed granulocyte-macrophage colonies from bone marrow cells and can stimulate the formation of eosinophil colonies from fetal liver progenitor cells. GM-CSF can also stimulate some functional activities in mature granulocytes and macrophages. [NIH]

Granulocytopenia: A deficiency in the number of granulocytes, a type of white blood cell. [NIH]

Granuloma: A relatively small nodular inflammatory lesion containing grouped mononuclear phagocytes, caused by infectious and noninfectious agents. [NIH]

Granuloma Inguinale: Anogenital ulcers caused by *Calymmatobacterium granulomatis* as distinguished from lymphogranuloma inguinale (see lymphogranuloma venereum) caused by *Chlamydia trachomatis*. Diagnosis is made by demonstration of typical intracellular Donovan bodies in crushed-tissue smears. [NIH]

Growth: The progressive development of a living being or part of an organism from its earliest stage to maturity. [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]

Guanine: One of the four DNA bases. [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]

Guinea Pigs: A common name used for the family Caviidae. The most common species is *Cavia porcellus* which is the domesticated guinea pig used for pets and biomedical research. [NIH]

Gynecology: A medical-surgical specialty concerned with the physiology and disorders primarily of the female genital tract, as well as female endocrinology and reproductive physiology. [NIH]

Habitat: An area considered in terms of its environment, particularly as this determines the type and quality of the vegetation the area can carry. [NIH]

Haemorrhage: The escape of blood from the vessels; bleeding. Small haemorrhages are classified according to size as petechiae (very small), purpura (up to 1 cm), and ecchymoses (larger). The massive accumulation of blood within a tissue is called a haematoma. [EU]

Hair Cells: Mechanoreceptors located in the organ of Corti that are sensitive to auditory stimuli and in the vestibular apparatus that are sensitive to movement of the head. In each case the accessory sensory structures are arranged so that appropriate stimuli cause movement of the hair-like projections (stereocilia and kinocilia) which relay the information centrally in the nervous system. [NIH]

Handwashing: The act of cleansing the hands with water or other liquid, with or without the inclusion of soap or other detergent, for the purpose of removing soil or microorganisms. [NIH]

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]

Headache: Pain in the cranial region that may occur as an isolated and benign symptom or as a manifestation of a wide variety of conditions including subarachnoid hemorrhage; craniocerebral trauma; central nervous system infections; intracranial hypertension; and other disorders. In general, recurrent headaches that are not associated with a primary disease process are referred to as headache disorders (e.g., migraine). [NIH]

Hearing Disorders: Conditions that impair the transmission or perception of auditory impulses and information from the level of the ear to the temporal cortices, including the sensorineural pathways. [NIH]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Heart Transplantation: The transference of a heart from one human or animal to another. [NIH]

Hematocrit: Measurement of the volume of packed red cells in a blood specimen by centrifugation. The procedure is performed using a tube with graduated markings or with automated blood cell counters. It is used as an indicator of erythrocyte status in disease. For example, anemia shows a low hematocrit, polycythemia, high values. [NIH]

Hematogenous: Originating in the blood or spread through the bloodstream. [NIH]

Hematologic malignancies: Cancers of the blood or bone marrow, including leukemia and lymphoma. Also called hematologic cancers. [NIH]

Hematopoietic Stem Cell Transplantation: The transference of stem cells from one animal or human to another (allogeneic), or within the same individual (autologous). The source for the stem cells may be the bone marrow or peripheral blood. Stem cell transplantation has been used as an alternative to autologous bone marrow transplantation in the treatment of a variety of neoplasms. [NIH]

Hematopoietic Stem Cells: Progenitor cells from which all blood cells derive. [NIH]

Hemodialysis: The use of a machine to clean wastes from the blood after the kidneys have failed. The blood travels through tubes to a dialyzer, which removes wastes and extra fluid. The cleaned blood then flows through another set of tubes back into the body. [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 concentration. 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]

Hemoglobin H: An abnormal hemoglobin composed of four beta chains. It is caused by the reduced synthesis of the alpha chain. This abnormality results in alpha-thalassemia. [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]

Heparan Sulfate Proteoglycan: A substance released by astrocytes, which is critical in stopping nervous fibers in their tracks. [NIH]

Heparin: Heparinic acid. A highly acidic mucopolysaccharide formed of equal parts of sulfated D-glucosamine and D-glucuronic acid with sulfaminic bridges. The molecular weight ranges from six to twenty thousand. Heparin occurs in and is obtained from liver, lung, mast cells, etc., of vertebrates. Its function is unknown, but it is used to prevent blood clotting in vivo and vitro, in the form of many different salts. [NIH]

Heparin-binding: Protein that stimulates the proliferation of endothelial cells. [NIH]

Hepatic: Refers to the liver. [NIH]

Hepatitis: Inflammation of the liver and liver disease involving degenerative or necrotic alterations of hepatocytes. [NIH]

Hepatitis A: Hepatitis caused by hepatovirus. It can be transmitted through fecal contamination of food or water. [NIH]

Hepatitis B: Hepatitis caused by hepatitis B virus. It may be transmitted by transfusion of contaminated blood or blood products. [NIH]

Hepatitis C: A form of hepatitis, similar to type B post-transfusion hepatitis, but caused by a virus which is serologically distinct from the agents of hepatitis A, B, and E, and which may persist in the blood of chronic asymptomatic carriers. Hepatitis C is parenterally transmitted and associated with transfusions and drug abuse. [NIH]

Hepatitis D: Hepatitis caused by the hepatitis delta virus in association with hepatitis B. It is endemic in some European countries and is seen in drug users, hemophiliacs, and

polytransfused persons. [NIH]

Hepatitis Delta Virus: A defective virus, containing particles of RNA nucleoprotein in virion-like form, present in patients with acute hepatitis B and chronic hepatitis. Officially this is classified as a subviral satellite RNA. [NIH]

Hepatitis Viruses: Any of the viruses that cause inflammation of the liver. They include both DNA and RNA viruses as well viruses from humans and animals. [NIH]

Hepatitis, Chronic: A collective term for a clinical and pathological syndrome which has several causes and is characterized by varying degrees of hepatocellular necrosis and inflammation. Specific forms of chronic hepatitis include autoimmune hepatitis, chronic hepatitis B, chronic hepatitis C, chronic hepatitis D, indeterminate chronic viral hepatitis, cryptogenic chronic hepatitis, and drug-related chronic hepatitis. [NIH]

Hepatocellular: Pertaining to or affecting liver cells. [EU]

Hepatocytes: The main structural component of the liver. They are specialized epithelial cells that are organized into interconnected plates called lobules. [NIH]

Hepatomegaly: Enlargement of the liver. [NIH]

Hepatovirus: A genus of Picornaviridae causing infectious hepatitis naturally in humans and experimentally in other primates. It is transmitted through fecal contamination of food or water. [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]

Herpes: Any inflammatory skin disease caused by a herpesvirus and characterized by the formation of clusters of small vesicles. When used alone, the term may refer to herpes simplex or to herpes zoster. [EU]

Herpes Genitalis: Herpes simplex of the genitals. [NIH]

Herpes Simplex Encephalitis: An inflammatory disease of the skin or mucous membrane characterized by the formation of clusters of small vesicles. [NIH]

Herpes virus: A member of the herpes family of viruses. [NIH]

Herpes Zoster: Acute vesicular inflammation. [NIH]

Herpes Zoster Oticus: A virus infection of the Gasserian ganglion and its nerve branches, characterized by discrete areas of vesiculation of the epithelium of the forehead, the nose, the eyelids, and the cornea together with subepithelial infiltration. [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]

Heterotrophic: Pertaining to organisms that are consumers and dependent on other organisms for their source of energy (food). [NIH]

Heterozygote: An individual having different alleles at one or more loci in homologous chromosome segments. [NIH]

Histocompatibility: The degree of antigenic similarity between the tissues of different individuals, which determines the acceptance or rejection of allografts. [NIH]

HIV: Human immunodeficiency virus. Species of lentivirus, subgenus primate lentiviruses, formerly designated T-cell lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV). It is acknowledged to be the agent responsible for the acute infectious

manifestations, neurologic disorders, and immunologic abnormalities linked to the acquired immunodeficiency syndrome. [NIH]

Homeobox: Distinctive sequence of DNA bases. [NIH]

Homodimer: Protein-binding "activation domains" always combine with identical proteins. [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 Replacement Therapy: Therapeutic use of hormones to alleviate the effects of hormone deficiency. [NIH]

Horseradish Peroxidase: An enzyme isolated from horseradish which is able to act as an antigen. It is frequently used as a histochemical tracer for light and electron microscopy. Its antigenicity has permitted its use as a combined antigen and marker in experimental immunology. [NIH]

Host: Any animal that receives a transplanted graft. [NIH]

Host-cell: A cell whose metabolism is used for the growth and reproduction of a virus. [NIH]

Human papillomavirus: HPV. A virus that causes abnormal tissue growth (warts) and is often associated with some types of cancer. [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]

Hydrolysis: The process of cleaving a chemical compound by the addition of a molecule of water. [NIH]

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]

Hyperbilirubinemia: Pathologic process consisting of an abnormal increase in the amount of bilirubin in the circulating blood, which may result in jaundice. [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]

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]

Hypesthesia: Absent or reduced sensitivity to cutaneous stimulation. [NIH]

Hypogammaglobulinemia: The most common primary immunodeficiency in which antibody production is deficient. [NIH]

Hypothalamus: Ventral part of the diencephalon extending from the region of the optic chiasm to the caudal border of the mammillary bodies and forming the inferior and lateral walls of the third ventricle. [NIH]

Hypothyroidism: Deficiency of thyroid activity. In adults, it is most common in women and is characterized by decrease in basal metabolic rate, tiredness and lethargy, sensitivity to cold, and menstrual disturbances. If untreated, it progresses to full-blown myxoedema. In infants, severe hypothyroidism leads to cretinism. In juveniles, the manifestations are intermediate, with less severe mental and developmental retardation and only mild symptoms of the adult form. When due to pituitary deficiency of thyrotropin secretion it is called secondary hypothyroidism. [EU]

Hypoxia: Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood. [EU]

Id: The part of the personality structure which harbors the unconscious instinctive desires and strivings of the individual. [NIH]

Idiopathic: Describes a disease of unknown cause. [NIH]

Ileum: The lower end of the small intestine. [NIH]

Illusion: A false interpretation of a genuine percept. [NIH]

Imidazole: C₃H₄N₂. The ring is present in polybenzimidazoles. [NIH]

Immediate-Early Proteins: Proteins that are coded by immediate-early genes, in the absence of de novo protein synthesis. The term was originally used exclusively for viral regulatory proteins that were synthesized just after viral integration into the host cell. It is also used to describe cellular proteins which are synthesized immediately after the resting cell is stimulated by extracellular signals. [NIH]

Immune adjuvant: A drug that stimulates the immune system to respond to disease. [NIH]

Immune function: Production and action of cells that fight disease or infection. [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]

Immunoassay: Immunochemical assay or detection of a substance by serologic or immunologic methods. Usually the substance being studied serves as antigen both in antibody production and in measurement of antibody by the test substance. [NIH]

Immunocompetence: The ability of lymphoid cells to mount a humoral or cellular immune response when challenged by antigen. [NIH]

Immunocompromised: Having a weakened immune system caused by certain diseases or treatments. [NIH]

Immunocompromised Host: A human or animal whose immunologic mechanism is deficient because of an immunodeficiency disorder or other disease or as the result of the administration of immunosuppressive drugs or radiation. [NIH]

Immunodeficiency: The decreased ability of the body to fight infection and disease. [NIH]

Immunodeficiency syndrome: The inability of the body to produce an immune response. [NIH]

Immunofluorescence: A technique for identifying molecules present on the surfaces of cells or in tissues using a highly fluorescent substance coupled to a specific antibody. [NIH]

Immunogenic: Producing immunity; evoking an immune response. [EU]

Immunoglobulin: A protein that acts as an antibody. [NIH]

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]

Immunosuppressant: An agent capable of suppressing immune responses. [EU]

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]

Immunotoxin: An antibody linked to a toxic substance. Some immunotoxins can bind to cancer cells and kill them. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

Implant radiation: A procedure in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near the tumor. Also called [NIH]

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]

Inclusion Bodies, Viral: An area showing altered staining behavior in the nucleus or cytoplasm of a virus-infected cell. Some inclusion bodies represent "virus factories" in which viral nucleic acid or protein is being synthesized; others are merely artifacts of fixation and staining. One example, Negri bodies, are found in the cytoplasm or processes of nerve cells in animals that have died from rabies. [NIH]

Incompetence: Physical or mental inadequacy or insufficiency. [EU]

Indicative: That indicates; that points out more or less exactly; that reveals fairly clearly. [EU]

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]

Induction therapy: Treatment designed to be used as a first step toward shrinking the cancer and in evaluating response to drugs and other agents. Induction therapy is followed by additional therapy to eliminate whatever cancer remains. [NIH]

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]

Infection Control: Programs of disease surveillance, generally within health care facilities, designed to investigate, prevent, and control the spread of infections and their causative

microorganisms. [NIH]

Infectious Mononucleosis: A common, acute infection usually caused by the Epstein-Barr virus (Human herpesvirus 4). There is an increase in mononuclear white blood cells and other atypical lymphocytes, generalized lymphadenopathy, splenomegaly, and occasionally hepatomegaly with hepatitis. [NIH]

Infertility: The diminished or absent ability to conceive or produce an offspring while sterility is the complete inability to conceive or produce an offspring. [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]

Inflammatory bowel disease: A general term that refers to the inflammation of the colon and rectum. Inflammatory bowel disease includes ulcerative colitis and Crohn's disease. [NIH]

Influenza: An acute viral infection involving the respiratory tract. It is marked by inflammation of the nasal mucosa, the pharynx, and conjunctiva, and by headache and severe, often generalized, myalgia. [NIH]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion. [NIH]

Ingestion: Taking into the body by mouth [NIH]

Inguinal: Pertaining to the inguen, or groin. [EU]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

Inlay: In dentistry, a filling first made to correspond with the form of a dental cavity and then cemented into the cavity. [NIH]

Inner ear: The labyrinth, comprising the vestibule, cochlea, and semicircular canals. [NIH]

Inorganic: Pertaining to substances not of organic origin. [EU]

Inositol: An isomer of glucose that has traditionally been considered to be a B vitamin although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. (From Martindale, The Extra Pharmacopoeia, 30th ed, p1379) Inositol phospholipids are important in signal transduction. [NIH]

Insecticides: Pesticides designed to control insects that are harmful to man. The insects may be directly harmful, as those acting as disease vectors, or indirectly harmful, as destroyers of crops, food products, or textile fabrics. [NIH]

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]

Integumentary: Pertaining to or composed of skin. [EU]

Intercellular Adhesion Molecule-1: A cell-surface ligand with a role in leukocyte adhesion and inflammation. Its production is induced by gamma-interferon and it is required for neutrophil migration into inflamed tissue. [NIH]

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-1: A soluble factor produced by monocytes, macrophages, and other cells which activates T-lymphocytes and potentiates their response to mitogens or antigens. IL-1 consists of two distinct forms, IL-1 alpha and IL-1 beta which perform the same functions but are distinct proteins. The biological effects of IL-1 include the ability to replace macrophage requirements for T-cell activation. The factor is distinct from interleukin-2. [NIH]

Interleukin-10: Factor that is a coregulator of mast cell growth. It is produced by T-cells and B-cells and shows extensive homology with the Epstein-Barr virus BCRF1 gene. [NIH]

Interleukin-2: Chemical mediator produced by activated T lymphocytes and which regulates the proliferation of T cells, as well as playing a role in the regulation of NK cell activity. [NIH]

Interleukin-4: Soluble factor produced by activated T-lymphocytes that causes proliferation and differentiation of B-cells. Interleukin-4 induces the expression of class II major histocompatibility complex and Fc receptors on B-cells. It also acts on T-lymphocytes, mast cell lines, and several other hematopoietic lineage cells including granulocyte, megakaryocyte, and erythroid precursors, as well as macrophages. [NIH]

Interleukins: Soluble factors which stimulate growth-related activities of leukocytes as well as other cell types. They enhance cell proliferation and differentiation, DNA synthesis, secretion of other biologically active molecules and responses to immune and inflammatory stimuli. [NIH]

Intermittent: Occurring at separated intervals; having periods of cessation of activity. [EU]

Internal Medicine: A medical specialty concerned with the diagnosis and treatment of diseases of the internal organ systems of adults. [NIH]

Internal radiation: A procedure in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near the tumor. Also called brachytherapy, implant radiation, or interstitial radiation therapy. [NIH]

Interstitial: Pertaining to or situated between parts or in the interspaces of a tissue. [EU]

Intestinal: Having to do with the intestines. [NIH]

Intestine: A long, tube-shaped organ in the abdomen that completes the process of digestion. There is both a large intestine and a small intestine. Also called the bowel. [NIH]

Intoxication: Poisoning, the state of being poisoned. [EU]

Intracellular: Inside a cell. [NIH]

Intracellular Membranes: Membranes of subcellular structures. [NIH]

Intracranial Hypertension: Increased pressure within the cranial vault. This may result

from several conditions, including hydrocephalus; brain edema; intracranial masses; severe systemic hypertension; pseudotumor cerebri; and other disorders. [NIH]

Intramuscular: IM. Within or into muscle. [NIH]

Intraocular: Within the eye. [EU]

Intravenous: IV. Into a vein. [NIH]

Intrinsic: Situated entirely within or pertaining exclusively to a part. [EU]

Introns: Non-coding, intervening sequences of DNA that are transcribed, but are removed from within the primary gene transcript and rapidly degraded during maturation of messenger RNA. Most genes in the nuclei of eukaryotes contain introns, as do mitochondrial and chloroplast genes. [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]

Involution: 1. A rolling or turning inward. 2. One of the movements involved in the gastrulation of many animals. 3. A retrograde change of the entire body or in a particular organ, as the retrograde changes in the female genital organs that result in normal size after delivery. 4. The progressive degeneration occurring naturally with advancing age, resulting in shrivelling of organs or tissues. [EU]

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]

Ionizing: Radiation comprising charged particles, e. g. electrons, protons, alpha-particles, etc., having sufficient kinetic energy to produce ionization by collision. [NIH]

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]

Irradiation: The use of high-energy radiation from x-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 from materials called radioisotopes. Radioisotopes produce radiation and can be placed in or near the tumor or in the area near cancer cells. This type of radiation treatment is called internal radiation therapy, implant radiation, interstitial radiation, or brachytherapy. Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Irradiation is also called radiation therapy, radiotherapy, and x-ray therapy. [NIH]

Ischemic stroke: A condition in which the blood supply to part of the brain is cut off. Also called "plug-type" strokes. Blocked arteries starve areas of the brain controlling sight, speech, sensation, and movement so that these functions are partially or completely lost. Ischemic stroke is the most common type of stroke, accounting for 80 percent of all strokes. Most ischemic strokes are caused by a blood clot called a thrombus, which blocks blood flow in the arteries feeding the brain, usually the carotid artery in the neck, the major vessel bringing blood to the brain. When it becomes blocked, the risk of stroke is very high. [NIH]

Isosporiasis: Infection with parasitic protozoa of the genus *Isospora*, producing intestinal disease. It is caused by ingestion of oocysts and can produce tissue cysts. [NIH]

Jaundice: A clinical manifestation of hyperbilirubinemia, consisting of deposition of bile pigments in the skin, resulting in a yellowish staining of the skin and mucous membranes. [NIH]

Jejunioileal Bypass: A surgical procedure consisting of the anastomosis of the proximal part of the jejunum to the distal portion of the ileum, so as to bypass the nutrient-absorptive segment of the small intestine, to treat morbid obesity. [NIH]

Jejunum: That portion of the small intestine which extends from the duodenum to the ileum; called also *intestinum jejunum*. [EU]

Joint: The point of contact between elements of an animal skeleton with the parts that surround and support it. [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]

Keratoconjunctivitis: Simultaneous inflammation of the cornea and conjunctiva. [NIH]

Keto: It consists of 8 carbon atoms and within the endotoxins, it connects polysaccharide and lipid A. [NIH]

Kidney Disease: Any one of several chronic conditions that are caused by damage to the cells of the kidney. People who have had diabetes for a long time may have kidney damage. Also called *nephropathy*. [NIH]

Kidney Failure: The inability of a kidney to excrete metabolites at normal plasma levels under conditions of normal loading, or the inability to retain electrolytes under conditions of normal intake. In the acute form (*kidney failure, acute*), it is marked by uremia and usually by oliguria or anuria, with hyperkalemia and pulmonary edema. The chronic form (*kidney failure, chronic*) is irreversible and requires hemodialysis. [NIH]

Kidney stone: A stone that develops from crystals that form in urine and build up on the inner surfaces of the kidney, in the renal pelvis, or in the ureters. [NIH]

Kidney Transplantation: The transference of a kidney from one human or animal to another. [NIH]

Killer Cells: Lymphocyte-like effector cells which mediate antibody-dependent cell cytotoxicity. They kill antibody-coated target cells which they bind with their Fc receptors. [NIH]

Kilobase: 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]

Labyrinth: The internal ear; the essential part of the organ of hearing. It consists of an osseous and a membranous portion. [NIH]

Labyrinthitis: Inflammation of the inner ear. [NIH]

Lactation: The period of the secretion of milk. [EU]

Language Disorders: Conditions characterized by deficiencies of comprehension or expression of written and spoken forms of language. These include acquired and developmental disorders. [NIH]

Large Intestine: The part of the intestine that goes from the cecum to the rectum. The large intestine absorbs water from stool and changes it from a liquid to a solid form. The large intestine is 5 feet long and includes the appendix, cecum, colon, and rectum. Also called *colon*. [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]

Least-Squares Analysis: A principle of estimation in which the estimates of a set of parameters in a statistical model are those quantities minimizing the sum of squared differences between the observed values of a dependent variable and the values predicted by the model. [NIH]

Lectin: A complex molecule that has both protein and sugars. Lectins are able to bind to the outside of a cell and cause biochemical changes in it. Lectins are made by both animals and plants. [NIH]

Lens: The transparent, double convex (outward curve on both sides) structure suspended between the aqueous and vitreous; helps to focus light on the retina. [NIH]

Lentivirus: A genus of the family Retroviridae consisting of non-oncogenic retroviruses that produce multi-organ diseases characterized by long incubation periods and persistent infection. Lentiviruses are unique in that they contain open reading frames (ORFs) between the pol and env genes and in the 3' env region. Five serogroups are recognized, reflecting the mammalian hosts with which they are associated. HIV-1 is the type species. [NIH]

Leptin: A 16-kD peptide hormone secreted from white adipocytes and implicated in the regulation of food intake and energy balance. Leptin provides the key afferent signal from fat cells in the feedback system that controls body fat stores. [NIH]

Leptospirosis: Infections with bacteria of the genus *Leptospira*. [NIH]

Lethal: Deadly, fatal. [EU]

Lethargy: Abnormal drowsiness or stupor; a condition of indifference. [EU]

Leukemia: Cancer of blood-forming tissue. [NIH]

Leukocytes: White blood cells. These include granular leukocytes (basophils, eosinophils, and neutrophils) as well as non-granular leukocytes (lymphocytes and monocytes). [NIH]

Leukoencephalopathy: A condition with spongy holes in the brain's white matter. [NIH]

Leukopenia: A condition in which the number of leukocytes (white blood cells) in the blood is reduced. [NIH]

Leukoplakia: A white patch that may develop on mucous membranes such as the cheek, gums, or tongue and may become cancerous. [NIH]

Leukotrienes: A family of biologically active compounds derived from arachidonic acid by oxidative metabolism through the 5-lipoxygenase pathway. They participate in host defense reactions and pathophysiological conditions such as immediate hypersensitivity and inflammation. They have potent actions on many essential organs and systems, including the cardiovascular, pulmonary, and central nervous system as well as the gastrointestinal tract and the immune system. [NIH]

Library Services: Services offered to the library user. They include reference and circulation. [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]

Life Expectancy: A figure representing the number of years, based on known statistics, to which any person of a given age may reasonably expect to live. [NIH]

Ligaments: Shiny, flexible bands of fibrous tissue connecting together articular extremities of bones. They are pliant, tough, and inextensible. [NIH]

Ligands: A RNA simulation method developed by the MIT. [NIH]

Likelihood Functions: Functions constructed from a statistical model and a set of observed data which give the probability of that data for various values of the unknown model parameters. Those parameter values that maximize the probability are the maximum likelihood estimates of the parameters. [NIH]

Linear Models: Statistical models in which the value of a parameter for a given value of a factor is assumed to be equal to $a + bx$, where a and b are constants. The models predict a linear regression. [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]

Lipopolysaccharide: Substance consisting of polysaccharide and lipid. [NIH]

Lipoprotein: Any of the lipid-protein complexes in which lipids are transported in the blood; lipoprotein particles consist of a spherical hydrophobic core of triglycerides or cholesterol esters surrounded by an amphipathic monolayer of phospholipids, cholesterol, and apolipoproteins; the four principal classes are high-density, low-density, and very-low-density lipoproteins and chylomicrons. [EU]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Liver Transplantation: The transference of a part of or an entire liver from one human or animal to another. [NIH]

Local therapy: Treatment that affects cells in the tumor and the area close to it. [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]

Logistic Models: Statistical models which describe the relationship between a qualitative dependent variable (that is, one which can take only certain discrete values, such as the presence or absence of a disease) and an independent variable. A common application is in epidemiology for estimating an individual's risk (probability of a disease) as a function of a given risk factor. [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]

Lower Esophageal Sphincter: The muscle between the esophagus and stomach. When a person swallows, this muscle relaxes to let food pass from the esophagus to the stomach. It stays closed at other times to keep stomach contents from flowing back into the esophagus. [NIH]

Lubricants: Oily or slippery substances. [NIH]

Lung Transplantation: The transference of either one or both of the lungs from one human or animal to another. [NIH]

Lupus: A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

Lyme Disease: An infectious disease caused by a spirochete, *Borrelia burgdorferi*, which is transmitted chiefly by *Ixodes dammini* and *pacificus* ticks in the United States and *Ixodes ricinus* in Europe. It is a disease with early and late cutaneous manifestations plus involvement of the nervous system, heart, eye, and joints in variable combinations. The

disease was formerly known as Lyme arthritis and first discovered at Old Lyme, Connecticut. [NIH]

Lymph: The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [NIH]

Lymph node: A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Also known as a lymph gland. Lymph nodes are spread out along lymphatic vessels and contain many lymphocytes, which filter the lymphatic fluid (lymph). [NIH]

Lymphadenopathy: Disease or swelling of the lymph nodes. [NIH]

Lymphangitis: Inflammation of a lymphatic vessel or vessels. Acute lymphangitis may result from spread of bacterial infection (most commonly beta-haemolytic streptococci) into the lymphatics, manifested by painful subcutaneous red streaks along the course of the vessels. [EU]

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: A white blood cell. Lymphocytes have a number of roles in the immune system, including the production of antibodies and other substances that fight infection and diseases. [NIH]

Lymphocyte Count: A count of the number of lymphocytes in the blood. [NIH]

Lymphocyte Subsets: A classification of lymphocytes based on structurally or functionally different populations of cells. [NIH]

Lymphocytic: Referring to lymphocytes, a type of white blood cell. [NIH]

Lymphocytosis: Excess of normal lymphocytes in the blood or in any effusion. [NIH]

Lymphogranuloma Venereum: Subacute inflammation of the inguinal lymph glands caused by certain immunotypes of *Chlamydia trachomatis*. It is a sexually transmitted disease in the U.S. but is more widespread in developing countries. It is distinguished from granuloma venereum (granuloma inguinale), which is caused by *Calymmatobacterium granulomatis*. [NIH]

Lymphoid: Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop. [NIH]

Lymphoma: A general term for various neoplastic diseases of the lymphoid tissue. [NIH]

Lymphotoxin: Soluble substance released by lymphocytes activated by antigens or T-cell mitogens, that is cytotoxic to other cells. It is involved in allergies and chronic inflammatory diseases. Lymphotoxin is antigenically distinct from tumor necrosis factor-alpha (tumor necrosis factor), though they both share a common receptor, biological activities, and significant amino acid sequences. [NIH]

Lytic: 1. Pertaining to lysis or to a lysis. 2. Producing lysis. [EU]

Macrophage: A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells. [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]

Magnetic Resonance Spectroscopy: Spectroscopic method of measuring the magnetic moment of elementary particles such as atomic nuclei, protons or electrons. It is employed in clinical applications such as NMR Tomography (magnetic resonance imaging). [NIH]

Maintenance therapy: Treatment that is given to help a primary (original) treatment keep working. Maintenance therapy is often given to help keep cancer in remission. [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]

Malaria: A protozoan disease caused in humans by four species of the genus *Plasmodium* (*P. falciparum* (malaria, falciparum), *P. vivax* (malaria, vivax), *P. ovale*, and *P. malariae*) and transmitted by the bite of an infected female mosquito of the genus *Anopheles*. Malaria is endemic in parts of Asia, Africa, Central and South America, Oceania, and certain Caribbean islands. It is characterized by extreme exhaustion associated with paroxysms of high fever, sweating, shaking chills, and anemia. Malaria in animals is caused by other species of plasmodia. [NIH]

Malaria, Falciparum: Malaria caused by *Plasmodium falciparum*. This is the severest form of malaria and is associated with the highest levels of parasites in the blood. This disease is characterized by irregularly recurring febrile paroxysms that in extreme cases occur with acute cerebral, renal, or gastrointestinal manifestations. [NIH]

Malaria, Vivax: Malaria caused by *Plasmodium vivax*. This form of malaria is less severe than malaria, falciparum, but there is a higher probability for relapses to occur. Febrile paroxysms often occur every other day. [NIH]

Malignancy: A cancerous tumor that can invade and destroy nearby tissue and spread to other parts of the body. [NIH]

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]

Mammogram: An x-ray of the breast. [NIH]

Manifest: Being the part or aspect of a phenomenon that is directly observable : concretely expressed in behaviour. [EU]

Mastication: The act and process of chewing and grinding food in the mouth. [NIH]

Meatus: A canal running from the internal auditory foramen through the petrous portion of the temporal bone. It gives passage to the facial and auditory nerves together with the auditory branch of the basilar artery and the internal auditory veins. [NIH]

Medial: Lying near the midsagittal plane of the body; opposed to lateral. [NIH]

Mediate: Indirect; accomplished by the aid of an intervening medium. [EU]

Mediator: An object or substance by which something is mediated, such as (1) a structure of the nervous system that transmits impulses eliciting a specific response; (2) a chemical substance (transmitter substance) that induces activity in an excitable tissue, such as nerve or muscle; or (3) a substance released from cells as the result of the interaction of antigen with antibody or by the action of antigen with a sensitized lymphocyte. [EU]

Medicament: A medicinal substance or agent. [EU]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

Meiosis: A special method of cell division, occurring in maturation of the germ cells, by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species. [NIH]

Melanin: The substance that gives the skin its color. [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]

Melanoma: A form of skin cancer that arises in melanocytes, the cells that produce pigment. Melanoma usually begins in a mole. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

Membrane Fusion: The adherence of cell membranes, intracellular membranes, or artificial membrane models of either to each other or to viruses, parasites, or interstitial particles through a variety of chemical and physical processes. [NIH]

Membrane Glycoproteins: Glycoproteins found on the membrane or surface of cells. [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]

Meningitis: Inflammation of the meninges. When it affects the dura mater, the disease is termed pachymeningitis; when the arachnoid and pia mater are involved, it is called leptomeningitis, or meningitis proper. [EU]

Menopause: Permanent cessation of menstruation. [NIH]

Menstruation: The normal physiologic discharge through the vagina of blood and mucosal tissues from the nonpregnant uterus. [NIH]

Mental: Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

Mental deficiency: A condition of arrested or incomplete development of mind from inherent causes or induced by disease or injury. [NIH]

Mental Disorders: Psychiatric illness or diseases manifested by breakdowns in the adaptational process expressed primarily as abnormalities of thought, feeling, and behavior producing either distress or impairment of function. [NIH]

Mental Health: The state wherein the person is well adjusted. [NIH]

Mental Processes: Conceptual functions or thinking in all its forms. [NIH]

Mental Retardation: Refers to sub-average general intellectual functioning which originated during the developmental period and is associated with impairment in adaptive behavior. [NIH]

Mentors: Senior professionals who provide guidance, direction and support to those persons desirous of improvement in academic positions, administrative positions or other career development situations. [NIH]

Mercury: A silver metallic element that exists as a liquid at room temperature. It has the atomic symbol Hg (from hydrargyrum, liquid silver), atomic number 80, and atomic weight 200.59. Mercury is used in many industrial applications and its salts have been employed

therapeutically as purgatives, antisyphilitics, disinfectants, and astringents. It can be absorbed through the skin and mucous membranes which leads to mercury poisoning. Because of its toxicity, the clinical use of mercury and mercurials is diminishing. [NIH]

Mesenchymal: Refers to cells that develop into connective tissue, blood vessels, and lymphatic tissue. [NIH]

Metabolic disorder: A condition in which normal metabolic processes are disrupted, usually because of a missing enzyme. [NIH]

Metabolite: Any substance produced by metabolism or by a metabolic process. [EU]

Metaphase: The second phase of cell division, in which the chromosomes line up across the equatorial plane of the spindle prior to separation. [NIH]

Methionine: A sulfur containing essential amino acid that is important in many body functions. It is a chelating agent for heavy metals. [NIH]

Methotrexate: An antineoplastic antimetabolite with immunosuppressant properties. It is an inhibitor of dihydrofolate reductase and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA. [NIH]

MI: 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]

Mice Minute Virus: The type species of parvovirus prevalent in mouse colonies and found as a contaminant of many transplanted tumors or leukemias. [NIH]

Microbe: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microbiological: Pertaining to microbiology : the science that deals with microorganisms, including algae, bacteria, fungi, protozoa and viruses. [EU]

Microbiology: The study of microorganisms such as fungi, bacteria, algae, archaea, and viruses. [NIH]

Microcalcifications: Tiny deposits of calcium in the breast that cannot be felt but can be detected on a mammogram. A cluster of these very small specks of calcium may indicate that cancer is present. [NIH]

Microcirculation: The vascular network lying between the arterioles and venules; includes capillaries, metarterioles and arteriovenous anastomoses. Also, the flow of blood through this network. [NIH]

Microdialysis: A technique for measuring extracellular concentrations of substances in tissues, usually in vivo, by means of a small probe equipped with a semipermeable membrane. Substances may also be introduced into the extracellular space through the membrane. [NIH]

Microgram: A unit of mass (weight) of the metric system, being one-millionth of a gram (10⁻⁶ gm.) or one one-thousandth of a milligram (10⁻³ mg.). [EU]

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]

Microsporidiosis: Infections with protozoa of the phylum Microspora. [NIH]

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [NIH]

Milligram: A measure of weight. A milligram is approximately 450,000-times smaller than a pound and 28,000-times smaller than an ounce. [NIH]

Milliliter: A measure of volume for a liquid. A milliliter is approximately 950-times smaller than a quart and 30-times smaller than a fluid ounce. A milliliter of liquid and a cubic centimeter (cc) of liquid are the same. [NIH]

Mineralocorticoids: A group of corticosteroids primarily associated with the regulation of water and electrolyte balance. This is accomplished through the effect on ion transport in renal tubules, resulting in retention of sodium and loss of potassium. Mineralocorticoid secretion is itself regulated by plasma volume, serum potassium, and angiotensin II. [NIH]

Mitochondria: Parts of a cell where aerobic production (also known as cell respiration) takes place. [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]

Mitosporic Fungi: A large and heterogenous group of fungi whose common characteristic is the absence of a sexual state. Many of the pathogenic fungi in humans belong to this group. [NIH]

Mitotic: Cell resulting from mitosis. [NIH]

Mobility: Capability of movement, of being moved, or of flowing freely. [EU]

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 mass: The sum of the atomic masses of all atoms in a molecule, based on a scale in which the atomic masses of hydrogen, carbon, nitrogen, and oxygen are 1, 12, 14, and 16, respectively. For example, the molecular mass of water, which has two atoms of hydrogen and one atom of oxygen, is 18 (i.e., $2 + 16$). [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]

Monoclonal: An antibody produced by culturing a single type of cell. It therefore consists of a single species of immunoglobulin molecules. [NIH]

Monoclonal antibodies: Laboratory-produced substances that can locate and bind to cancer cells wherever they are in the body. Many monoclonal antibodies are used in cancer detection or therapy; each one recognizes a different protein on certain cancer cells. Monoclonal antibodies can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to a tumor. [NIH]

Monocyte: A type of white blood cell. [NIH]

Mononuclear: A cell with one nucleus. [NIH]

Mononucleosis: The presence of an abnormally large number of mononuclear leucocytes (monocytes) in the blood. The term is often used alone to refer to infectious mononucleosis.

[EU]

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]

Mucins: A secretion containing mucopolysaccharides and protein that is the chief constituent of mucus. [NIH]

Mucociliary: Pertaining to or affecting the mucus membrane and hairs (including eyelashes, nose hair, .): mucociliary clearing: the clearance of mucus by ciliary movement (particularly in the respiratory system). [EU]

Mucocutaneous: Pertaining to or affecting the mucous membrane and the skin. [EU]

Mucolytic: Destroying or dissolving mucin; an agent that so acts : a mucopolysaccharide or glycoprotein, the chief constituent of mucus. [EU]

Mucosa: A mucous membrane, or tunica mucosa. [EU]

Mucositis: A complication of some cancer therapies in which the lining of the digestive system becomes inflamed. Often seen as sores in the mouth. [NIH]

Mucus: The viscous secretion of mucous membranes. It contains mucin, white blood cells, water, inorganic salts, and exfoliated cells. [NIH]

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]

Multivalent: Pertaining to a group of 5 or more homologous or partly homologous chromosomes during the zygotene stage of prophase to first metaphase in meiosis. [NIH]

Mumps Virus: The type species of rubulavirus that causes an acute infectious disease in humans, affecting mainly children. Transmission occurs by droplet infection. [NIH]

Mutate: To change the genetic material of a cell. Then changes (mutations) can be harmful, beneficial, or have no effect. [NIH]

Myalgia: Pain in a muscle or muscles. [EU]

Mycobacterium: A genus of gram-positive, aerobic bacteria. Most species are free-living in soil and water, but the major habitat for some is the diseased tissue of warm-blooded hosts. [NIH]

Mycobacterium avium: A bacterium causing tuberculosis in domestic fowl and other birds. In pigs, it may cause localized and sometimes disseminated disease. The organism occurs occasionally in sheep and cattle. It should be distinguished from the M. avium complex, which infects primarily humans. [NIH]

Mycophenolate mofetil: A drug that is being studied for its effectiveness in preventing graft-versus-host disease and autoimmune disorders. [NIH]

Mycoplasma: A genus of gram-negative, facultatively anaerobic bacteria bounded by a plasma membrane only. Its organisms are parasites and pathogens, found on the mucous membranes of humans, animals, and birds. [NIH]

Myelin: The fatty substance that covers and protects nerves. [NIH]

Myelodysplasia: Abnormal bone marrow cells that may lead to myelogenous leukemia. [NIH]

Myelogenous: Produced by, or originating in, the bone marrow. [NIH]

Myeloid Cells: Cells which include the monocytes and the granulocytes. [NIH]

Myelosuppression: A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. Myelosuppression is a side effect of some cancer treatments. [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]

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]

Myopia: That error of refraction in which rays of light entering the eye parallel to the optic axis are brought to a focus in front of the retina, as a result of the eyeball being too long from front to back (axial m.) or of an increased strength in refractive power of the media of the eye (index m.). Called also nearsightedness, because the near point is less distant than it is in emmetropia with an equal amplitude of accommodation. [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]

Nadir: The lowest point; point of greatest adversity or despair. [EU]

Naive: Used to describe an individual who has never taken a certain drug or class of drugs (e. g., AZT-naive, antiretroviral-naive), or to refer to an undifferentiated immune system cell. [NIH]

Nasal Mucosa: The mucous membrane lining the nasal cavity. [NIH]

Nasopharynx: The nasal part of the pharynx, lying above the level of the soft palate. [NIH]

Natural killer cells: NK cells. A type of white blood cell that contains granules with enzymes that can kill tumor cells or microbial cells. Also called large granular lymphocytes (LGL). [NIH]

Natural selection: A part of the evolutionary process resulting in the survival and reproduction of the best adapted individuals. [NIH]

Nausea: An unpleasant sensation in the stomach usually accompanied by the urge to vomit. Common causes are early pregnancy, sea and motion sickness, emotional stress, intense pain, food poisoning, and various enteroviruses. [NIH]

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]

Need: A state of tension or dissatisfaction felt by an individual that impels him to action

toward a goal he believes will satisfy the impulse. [NIH]

Neisseria: A genus of gram-negative, aerobic, coccoid bacteria whose organisms are part of the normal flora of the oropharynx, nasopharynx, and genitourinary tract. Some species are primary pathogens for humans. [NIH]

Neonatal: Pertaining to the first four weeks after birth. [EU]

Neoplasia: Abnormal and uncontrolled cell growth. [NIH]

Neoplasm: A new growth of benign or malignant tissue. [NIH]

Neoplastic: Pertaining to or like a neoplasm (= any new and abnormal growth); pertaining to neoplasia (= the formation of a neoplasm). [EU]

Nephritis: Inflammation of the kidney; a focal or diffuse proliferative or destructive process which may involve the glomerulus, tubule, or interstitial renal tissue. [EU]

Nephrology: A subspecialty of internal medicine concerned with the anatomy, physiology, and pathology of the kidney. [NIH]

Nephropathy: Disease of the kidneys. [EU]

Nerve: A cordlike structure of nervous tissue that connects parts of the nervous system with other tissues of the body and conveys nervous impulses to, or away from, these tissues. [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 neural arch. [EU]

Neuraminidase: An enzyme that catalyzes the hydrolysis of alpha-2,3, alpha-2,6-, and alpha-2,8-glycosidic linkages (at a decreasing rate, respectively) of terminal sialic residues in oligosaccharides, glycoproteins, glycolipids, colominic acid, and synthetic substrate. (From Enzyme Nomenclature, 1992) EC 3.2.1.18. [NIH]

Neuritis: A general term indicating inflammation of a peripheral or cranial nerve. Clinical manifestation may include pain; paresthesias; paresis; or hypesthesia. [NIH]

Neuroblastoma: Cancer that arises in immature nerve cells and affects mostly infants and children. [NIH]

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]

Neurogenic: Loss of bladder control caused by damage to the nerves controlling the bladder. [NIH]

Neurologic: Having to do with nerves or the nervous system. [NIH]

Neurology: A medical specialty concerned with the study of the structures, functions, and diseases of the nervous system. [NIH]

Neuronal: Pertaining to a neuron or neurons (= conducting cells of the nervous system). [EU]

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]

Neuropeptide: A member of a class of protein-like molecules made in the brain. Neuropeptides consist of short chains of amino acids, with some functioning as neurotransmitters and some functioning as hormones. [NIH]

Neuroretinitis: Inflammation of the optic nerve head and adjacent retina. [NIH]

Neurosciences: The scientific disciplines concerned with the embryology, anatomy, physiology, biochemistry, pharmacology, etc., of the nervous system. [NIH]

Neurotoxic: Poisonous or destructive to nerve tissue. [EU]

Neurotoxins: Toxic substances from microorganisms, plants or animals that interfere with the functions of the nervous system. Most venoms contain neurotoxic substances. Myotoxins are included in this concept. [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, γ -aminobutyrate, glutamic acid, substance P, enkephalins, endorphins, and serotonin. [EU]

Neutralization: An act or process of neutralizing. [EU]

Neutrons: Electrically neutral elementary particles found in all atomic nuclei except light hydrogen; the mass is equal to that of the proton and electron combined and they are unstable when isolated from the nucleus, undergoing beta decay. Slow, thermal, epithermal, and fast neutrons refer to the energy levels with which the neutrons are ejected from heavier nuclei during their decay. [NIH]

Neutrophil: A type of white blood cell. [NIH]

Nevirapine: A potent, non-nucleoside reverse transcriptase inhibitor used in combination with nucleoside analogues for treatment of HIV infection and AIDS. [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]

Non-nucleoside: A member of a class of compounds, including delavirdine, loviride and nevirapine, that acts to directly combine with and block the action of HIV's reverse transcriptase. [NIH]

Nonverbal Communication: Transmission of emotions, ideas, and attitudes between individuals in ways other than the spoken language. [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]

Normal Distribution: Continuous frequency distribution of infinite range. Its properties are

as follows: 1) continuous, symmetrical distribution with both tails extending to infinity; 2) arithmetic mean, mode, and median identical; and 3) shape completely determined by the mean and standard deviation. [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]

Nuclear Envelope: The membrane system of the cell nucleus that surrounds the nucleoplasm. It consists of two concentric membranes separated by the perinuclear space. The structures of the envelope where it opens to the cytoplasm are called the nuclear pores (nuclear pore). [NIH]

Nuclear Localization Signal: Short, predominantly basic amino acid sequences identified as nuclear import signals for some proteins. These sequences are believed to interact with specific receptors at nuclear pores. [NIH]

Nuclear Pore: An opening through the nuclear envelope formed by the nuclear pore complex which transports nuclear proteins or RNA into or out of the cell nucleus and which, under some conditions, acts as an ion channel. [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]

Nucleic Acid Probes: Nucleic acid which complements a specific mRNA or DNA molecule, or fragment thereof; used for hybridization studies in order to identify microorganisms and for genetic studies. [NIH]

Nucleocapsid: A protein-nucleic acid complex which forms part or all of a virion. It consists of a capsid plus enclosed nucleic acid. Depending on the virus, the nucleocapsid may correspond to a naked core or be surrounded by a membranous envelope. [NIH]

Nucleolus: A small dense body (sub organelle) within the nucleus of eukaryotic cells, visible by phase contrast and interference microscopy in live cells throughout interphase. Contains RNA and protein and is the site of synthesis of ribosomal RNA. [NIH]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nursing Care: Care given to patients by nursing service personnel. [NIH]

Nutritional Status: State of the body in relation to the consumption and utilization of nutrients. [NIH]

Nutritive Value: An indication of the contribution of a food to the nutrient content of the diet. This value depends on the quantity of a food which is digested and absorbed and the amounts of the essential nutrients (protein, fat, carbohydrate, minerals, vitamins) which it contains. This value can be affected by soil and growing conditions, handling and storage, and processing. [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]

Ocular: 1. Of, pertaining to, or affecting the eye. 2. Eyepiece. [EU]

Odynophagia: A painful condition of the esophagus. [NIH]

Oligo: Chemical and mineral elements that exist in minimal (oligo) quantities in the body, in foods, in the air, in soil; name applied to any element observed as a microconstituent of plant or animal tissue and of beneficial, harmful, or even doubtful significance. [NIH]

Oligonucleotide Probes: Synthetic or natural oligonucleotides used in hybridization studies in order to identify and study specific nucleic acid fragments, e.g., DNA segments near or within a specific gene locus or gene. The probe hybridizes with a specific mRNA, if present. Conventional techniques used for testing for the hybridization product include dot blot assays, Southern blot assays, and DNA:RNA hybrid-specific antibody tests. Conventional labels for the probe include the radioisotope labels ^{32}P and ^{125}I and the chemical label biotin. [NIH]

Oligosaccharides: Carbohydrates consisting of between two and ten monosaccharides connected by either an alpha- or beta-glycosidic link. They are found throughout nature in both the free and bound form. [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]

Oncology: The study of cancer. [NIH]

Opacity: Degree of density (area most dense taken for reading). [NIH]

Open Reading Frames: Reading frames where successive nucleotide triplets can be read as codons specifying amino acids and where the sequence of these triplets is not interrupted by stop codons. [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]

Ophthalmic: Pertaining to the eye. [EU]

Ophthalmologist: A medical doctor specializing in the diagnosis and medical or surgical treatment of visual disorders and eye disease. [NIH]

Ophthalmology: A surgical specialty concerned with the structure and function of the eye and the medical and surgical treatment of its defects and diseases. [NIH]

Opportunistic Infections: An infection caused by an organism which becomes pathogenic under certain conditions, e.g., during immunosuppression. [NIH]

Opsin: A protein formed, together with retinene, by the chemical breakdown of meta-rhodopsin. [NIH]

Optic Chiasm: The X-shaped structure formed by the meeting of the two optic nerves. At the optic chiasm the fibers from the medial part of each retina cross to project to the other side of the brain while the lateral retinal fibers continue on the same side. As a result each half of the brain receives information about the contralateral visual field from both eyes. [NIH]

Optic Nerve: The 2nd cranial nerve. The optic nerve conveys visual information from the retina to the brain. The nerve carries the axons of the retinal ganglion cells which sort at the optic chiasm and continue via the optic tracts to the brain. The largest projection is to the lateral geniculate nuclei; other important targets include the superior colliculi and the suprachiasmatic nuclei. Though known as the second cranial nerve, it is considered part of the central nervous system. [NIH]

Oral Health: The optimal state of the mouth and normal functioning of the organs of the mouth without evidence of disease. [NIH]

Oral Manifestations: Disorders of the mouth attendant upon non-oral disease or injury. [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]

Organ Transplantation: Transference of an organ between individuals of the same species or between individuals of different species. [NIH]

Organelles: Specific particles of membrane-bound organized living substances present in eukaryotic cells, such as the mitochondria; the golgi apparatus; endoplasmic reticulum; lysosomes; plastids; and vacuoles. [NIH]

Oropharynx: Oral part of the pharynx. [NIH]

Osmotic: Pertaining to or of the nature of osmosis (= the passage of pure solvent from a solution of lesser to one of greater solute concentration when the two solutions are separated by a membrane which selectively prevents the passage of solute molecules, but is permeable to the solvent). [EU]

Ossicles: The hammer, anvil and stirrup, the small bones of the middle ear, which transmit the vibrations from the tympanic membrane to the oval window. [NIH]

Osteitis Deformans: A disease marked by repeated episodes of increased bone resorption followed by excessive attempts at repair, resulting in weakened, deformed bones of increased mass. The resultant architecture of the bone assumes a mosaic pattern in which the fibers take on a haphazard pattern instead of the normal parallel symmetry. [NIH]

Osteoarthritis: A progressive, degenerative joint disease, the most common form of arthritis, especially in older persons. The disease is thought to result not from the aging process but from biochemical changes and biomechanical stresses affecting articular cartilage. In the foreign literature it is often called osteoarthrosis deformans. [NIH]

Osteoporosis: Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis and age-related (or senile) osteoporosis. [NIH]

Otitis: Inflammation of the ear, which may be marked by pain, fever, abnormalities of hearing, hearing loss, tinnitus, and vertigo. [EU]

Otitis Media: Inflammation of the middle ear. [NIH]

Otolaryngologist: A doctor who specializes in treating diseases of the ear, nose, and throat. Also called an ENT doctor. [NIH]

Otorhinolaryngology: That branch of medicine concerned with medical and surgical treatment of the head and neck, including the ears, nose and throat. [EU]

Otosclerosis: The formation of spongy bone in the labyrinth capsule. The ossicles can become fixed and unable to transmit sound vibrations, thereby causing deafness. [NIH]

Ototoxic: Having a deleterious effect upon the eighth nerve, or upon the organs of hearing

and balance. [EU]

Outer ear: The pinna and external meatus of the ear. [NIH]

Outpatient: A patient who is not an inmate of a hospital but receives diagnosis or treatment in a clinic or dispensary connected with the hospital. [NIH]

Ovalbumin: An albumin obtained from the white of eggs. It is a member of the serpin superfamily. [NIH]

Ovary: Either of the paired glands in the female that produce the female germ cells and secrete some of the female sex hormones. [NIH]

Overweight: An excess of body weight but not necessarily body fat; a body mass index of 25 to 29.9 kg/m². [NIH]

Ovum: A female germ cell extruded from the ovary at ovulation. [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]

Oxygenation: The process of supplying, treating, or mixing with oxygen. No:1245 - oxygenation the process of supplying, treating, or mixing with oxygen. [EU]

Pachymeningitis: Inflammation of the dura mater of the brain, the spinal cord or the optic nerve. [NIH]

Palate: The structure that forms the roof of the mouth. It consists of the anterior hard palate and the posterior soft palate. [NIH]

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]

Pancreas Transplant: A surgical procedure that involves replacing the pancreas of a person who has diabetes with a healthy pancreas that can make insulin. The healthy pancreas comes from a donor who has just died or from a living relative. A person can donate half a pancreas and still live normally. [NIH]

Pancreas Transplantation: The transference of a pancreas from one human or animal to another. [NIH]

Pancreatic: Having to do with the pancreas. [NIH]

Pancreatic Juice: The fluid containing digestive enzymes secreted by the pancreas in response to food in the duodenum. [NIH]

Panuveitis: Inflammation in which both the anterior and posterior segments of the uvea are involved and a specific focus is not apparent. It is often severe and extensive and a serious threat to vision. Causes include systemic diseases such as tuberculosis, sarcoidosis, and syphilis, as well as malignancies. The intermediate segment of the eye is not involved. [NIH]

Papilloma: A benign epithelial neoplasm which may arise from the skin, mucous membranes or glandular ducts. [NIH]

Papillomavirus: A genus of Papovaviridae causing proliferation of the epithelium, which may lead to malignancy. A wide range of animals are infected including humans, chimpanzees, cattle, rabbits, dogs, and horses. [NIH]

Paramyxoviridae: A family of spherical viruses, of the order Mononegavirales, somewhat larger than the Orthomyxoviruses, and containing single-stranded RNA. Subfamilies include Paramyxovirinae and Pneumovirinae. [NIH]

Paramyxovirus: A genus of the family Paramyxoviridae (subfamily Paramyxovirinae) where all the virions have both hemagglutinin and neuraminidase activities and encode a C protein. Human parainfluenza virus 1 is the type species. [NIH]

Paranasal Sinuses: Air-filled extensions of the respiratory part of the nasal cavity into the frontal, ethmoid, sphenoid, and maxillary cranial bones. They vary in size and form in different individuals and are lined by the ciliated mucous membranes of the nasal cavity. [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]

Parenteral: Not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc. [EU]

Parenteral Nutrition: The administering of nutrients for assimilation and utilization by a patient who cannot maintain adequate nutrition by enteral feeding alone. Nutrients are administered by a route other than the alimentary canal (e.g., intravenously, subcutaneously). [NIH]

Paresis: A general term referring to a mild to moderate degree of muscular weakness, occasionally used as a synonym for paralysis (severe or complete loss of motor function). In the older literature, paresis often referred specifically to paretic neurosyphilis. "General paresis" and "general paralysis" may still carry that connotation. Bilateral lower extremity paresis is referred to as paraparesis. [NIH]

Paresthesias: Abnormal touch sensations, such as burning or prickling, that occur without an outside stimulus. [NIH]

Parotid: The space that contains the parotid gland, the facial nerve, the external carotid artery, and the retromandibular vein. [NIH]

Paroxysmal: Recurring in paroxysms (= spasms or seizures). [EU]

Partial remission: The shrinking, but not complete disappearance, of a tumor in response to therapy. Also called partial response. [NIH]

Parvovirus: A genus of the family Parvoviridae, subfamily Parvovirinae, infecting a variety of vertebrates including humans. Parvoviruses are responsible for a number of important diseases but also can be non-pathogenic in certain hosts. The type species is mice minute virus. [NIH]

Patch: A piece of material used to cover or protect a wound, an injured part, etc.: a patch over the eye. [NIH]

Paternity: Establishing the father relationship of a man and a child. [NIH]

Pathogen: Any disease-producing microorganism. [EU]

Pathogenesis: The cellular events and reactions that occur in the development of disease. [NIH]

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]

Patient Care Management: Generating, planning, organizing, and administering medical and nursing care and services for patients. [NIH]

Patient Education: The teaching or training of patients concerning their own health needs. [NIH]

Pelvic: Pertaining to the pelvis. [EU]

Pelvic inflammatory disease: A bacteriological disease sometimes associated with intrauterine device (IUD) usage. [NIH]

Pelvis: The lower part of the abdomen, located between the hip bones. [NIH]

Penis: The external reproductive organ of males. It is composed of a mass of erectile tissue enclosed in three cylindrical fibrous compartments. Two of the three compartments, the corpus cavernosa, are placed side-by-side along the upper part of the organ. The third compartment below, the corpus spongiosum, houses the urethra. [NIH]

Pepsin: An enzyme made in the stomach that breaks down proteins. [NIH]

Pepsin A: Formed from pig pepsinogen by cleavage of one peptide bond. The enzyme is a single polypeptide chain and is inhibited by methyl 2-diazoacetamidohexanoate. It cleaves peptides preferentially at the carbonyl linkages of phenylalanine or leucine and acts as the principal digestive enzyme of gastric juice. [NIH]

Peptic: Pertaining to pepsin or to digestion; related to the action of gastric juices. [EU]

Peptic Ulcer: Ulcer that occurs in those portions of the alimentary tract which come into contact with gastric juice containing pepsin and acid. It occurs when the amount of acid and pepsin is sufficient to overcome the gastric mucosal barrier. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Peptide Fragments: Partial proteins formed by partial hydrolysis of complete proteins. [NIH]

Peptide T: N-(N-(N(2)-(N-(N-(N-(N-D-Alanyl L-seryl)-L-threonyl)-L-threonyl) L-threonyl)-L-asparaginy)-L-tyrosyl) L-threonine. Octapeptide sharing sequence homology with HIV envelope protein gp120. It is potentially useful as antiviral agent in AIDS therapy. The core pentapeptide sequence, TTNYT, consisting of amino acids 4-8 in peptide T, is the HIV envelope sequence required for attachment to the CD4 receptor. [NIH]

Perception: The ability quickly and accurately to recognize similarities and differences among presented objects, whether these be pairs of words, pairs of number series, or multiple sets of these or other symbols such as geometric figures. [NIH]

Perforation: 1. The act of boring or piercing through a part. 2. A hole made through a part or substance. [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]

Perianal: Located around the anus. [EU]

Pericardium: The fibroserous sac surrounding the heart and the roots of the great vessels. [NIH]

Perilymph: The fluid contained within the space separating the membranous from the osseous labyrinth of the ear. [NIH]

Perinatal: Pertaining to or occurring in the period shortly before and after birth; variously defined as beginning with completion of the twentieth to twenty-eighth week of gestation and ending 7 to 28 days after birth. [EU]

Perineal: Pertaining to the perineum. [EU]

Perineum: The area between the anus and the sex organs. [NIH]

Periodontal disease: Disease involving the supporting structures of the teeth (as the gums and periodontal membranes). [NIH]

Periodontal disease: Disease involving the supporting structures of the teeth (as the gums and periodontal membranes). [NIH]

Periodontitis: Inflammation of the periodontal membrane; also called periodontitis simplex. [NIH]

Perioperative: Around the time of surgery; usually lasts from the time of going into the hospital or doctor's office for surgery until the time the patient goes home. [NIH]

Peripheral blood: Blood circulating throughout the body. [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]

Peripheral Neuropathy: Nerve damage, usually affecting the feet and legs; causing pain, numbness, or a tingling feeling. Also called "somatic neuropathy" or "distal sensory polyneuropathy." [NIH]

Peripheral stem cells: Immature cells found circulating in the bloodstream. New blood cells develop from peripheral stem cells. [NIH]

Peripheral Vascular Disease: Disease in the large blood vessels of the arms, legs, and feet. People who have had diabetes for a long time may get this because major blood vessels in their arms, legs, and feet are blocked and these limbs do not receive enough blood. The signs of PVD are aching pains in the arms, legs, and feet (especially when walking) and foot sores that heal slowly. Although people with diabetes cannot always avoid PVD, doctors say they have a better chance of avoiding it if they take good care of their feet, do not smoke, and keep both their blood pressure and diabetes under good control. [NIH]

Peripheral vision: Side vision; ability to see objects and movement outside of the direct line of vision. [NIH]

Peritoneal: Having to do with the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). [NIH]

Peritoneal Cavity: The space enclosed by the peritoneum. It is divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the stomach. The two sacs are connected by the foramen of Winslow, or epiploic foramen. [NIH]

Peritoneal Dialysis: Dialysis fluid being introduced into and removed from the peritoneal cavity as either a continuous or an intermittent procedure. [NIH]

Peritoneum: Endothelial lining of the abdominal cavity, the parietal peritoneum covering the inside of the abdominal wall and the visceral peritoneum covering the bowel, the

mesentery, and certain of the organs. The portion that covers the bowel becomes the serosal layer of the bowel wall. [NIH]

Permissiveness: The attitude that grants freedom of expression and activity to another individual, but not necessarily with sanction or approval. [NIH]

Pesticides: Chemicals used to destroy pests of any sort. The concept includes fungicides (industrial fungicides), insecticides, rodenticides, etc. [NIH]

Petroleum: Naturally occurring complex liquid hydrocarbons which, after distillation, yield combustible fuels, petrochemicals, and lubricants. [NIH]

Pharmaceutic Aids: Substances which are of little or no therapeutic value, but are necessary in the manufacture, compounding, storage, etc., of pharmaceutical preparations or drug dosage forms. They include solvents, diluting agents, and suspending agents, and emulsifying agents. Also, antioxidants; preservatives, pharmaceutical; dyes (coloring agents); flavoring agents; vehicles; excipients; ointment bases. [NIH]

Pharmacodynamics: The study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure; also, such effects on the actions of a particular drug or drugs. [EU]

Pharmacokinetic: The mathematical analysis of the time courses of absorption, distribution, and elimination of drugs. [NIH]

Pharmacologic: Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

Pharmacotherapy: A regimen of using appetite suppressant medications to manage obesity by decreasing appetite or increasing the feeling of satiety. These medications decrease appetite by increasing serotonin or catecholamine—two brain chemicals that affect mood and appetite. [NIH]

Pharynx: The hollow tube about 5 inches long that starts behind the nose and ends at the top of the trachea (windpipe) and esophagus (the tube that goes to the stomach). [NIH]

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]

Phenyl: Ingredient used in cold and flu remedies. [NIH]

Phenylalanine: An aromatic amino acid that is essential in the animal diet. It is a precursor of melanin, dopamine, noradrenalin, and thyroxine. [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, nerves, 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]

Phosphorylates: 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]

Photodynamic therapy: Treatment with drugs that become active when exposed to light.

These drugs kill cancer cells. [NIH]

Photosensitizer: A drug used in photodynamic therapy. When absorbed by cancer cells and exposed to light, the drug becomes active and kills the cancer cells. [NIH]

Photosensitizing Agents: Drugs that are pharmacologically inactive but when exposed to ultraviolet radiation or sunlight are converted to their active metabolite to produce a beneficial reaction affecting the diseased tissue. These compounds can be administered topically or systemically and have been used therapeutically to treat psoriasis and various types of neoplasms. [NIH]

Phototransduction: The transducing of light energy to afferent nerve impulses, such as takes place in the retinal rods and cones. After light photons are absorbed by the photopigments, the signal is transmitted to the outer segment membrane by the cyclic GMP second messenger system, where it closes the sodium channels. This channel gating ultimately generates an action potential in the inner retina. [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]

Pigmentation: Coloration or discoloration of a part by a pigment. [NIH]

Pigments: Any normal or abnormal coloring matter in plants, animals, or micro-organisms. [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; absence of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plaque: A clear zone in a bacterial culture grown on an agar plate caused by localized destruction of bacterial cells by a bacteriophage. The concentration of infective virus in a fluid can be estimated by applying the fluid to a culture and counting the number of. [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]

Plasma protein: One of the hundreds of different proteins present in blood plasma, including carrier proteins (such as albumin, transferrin, and haptoglobin), fibrinogen and other coagulation factors, complement components, immunoglobulins, enzyme inhibitors, precursors of substances such as angiotension and bradykinin, and many other types of proteins. [EU]

Plasmid: An autonomously replicating, extra-chromosomal DNA molecule found in many bacteria. Plasmids are widely used as carriers of cloned genes. [NIH]

Plasmin: A product of the lysis of plasminogen (profibrinolysin) by plasminogen activators. It is composed of two polypeptide chains, light (B) and heavy (A), with a molecular weight of 75,000. It is the major proteolytic enzyme involved in blood clot retraction or the lysis of

fibrin and quickly inactivated by antiplasmins. EC 3.4.21.7. [NIH]

Plasminogen: Precursor of fibrinolysin (plasmin). It is a single-chain beta-globulin of molecular weight 80-90,000 found mostly in association with fibrinogen in plasma; plasminogen activators change it to fibrinolysin. It is used in wound debriding and has been investigated as a thrombolytic agent. [NIH]

Plasminogen Activators: A heterogeneous group of proteolytic enzymes that convert plasminogen to plasmin. They are concentrated in the lysosomes of most cells and in the vascular endothelium, particularly in the vessels of the microcirculation. EC 3.4.21.-. [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]

Platelet Count: A count of the number of platelets per unit volume in a sample of venous blood. [NIH]

Platelets: A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

Platinum: Platinum. A heavy, soft, whitish metal, resembling tin, atomic number 78, atomic weight 195.09, symbol Pt. (From Dorland, 28th ed) It is used in manufacturing equipment for laboratory and industrial use. It occurs as a black powder (platinum black) and as a spongy substance (spongy platinum) and may have been known in Pliny's time as "alutiae". [NIH]

Pneumonia: Inflammation of the lungs. [NIH]

Pneumonitis: A disease caused by inhaling a wide variety of substances such as dusts and molds. Also called "farmer's disease". [NIH]

Podophyllotoxin: The main active constituent of the resin from the roots of may apple or mandrake (*Podophyllum peltatum* and *P. emodi*). It is a potent spindle poison, toxic if taken internally, and has been used as a cathartic. It is very irritating to skin and mucous membranes, has keratolytic actions, has been used to treat warts and keratoses, and may have antineoplastic properties, as do some of its congeners and derivatives. [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]

Poisoning: A condition or physical state produced by the ingestion, injection or inhalation of, or exposure to a deleterious agent. [NIH]

Poliomyelitis: An acute viral disease, occurring sporadically and in epidemics, and characterized clinically by fever, sore throat, headache, and vomiting, often with stiffness of the neck and back. In the minor illness these may be the only symptoms. The major illness, which may or may not be preceded by the minor illness, is characterized by involvement of the central nervous system, stiff neck, pleocytosis in the spinal fluid, and perhaps paralysis. There may be subsequent atrophy of groups of muscles, ending in contraction and permanent deformity. The major illness is called acute anterior p., infantile paralysis and Heine-Medin disease. The disease is now largely controlled by vaccines. [EU]

Poliovirus Vaccine, Inactivated: A suspension of formalin-inactivated poliovirus grown in monkey kidney cell tissue culture and used to prevent poliomyelitis. [NIH]

Poliovirus Vaccines: Vaccines used to prevent poliomyelitis. They include inactivated

(poliovirus vaccine, inactivated) and oral vaccines (poliovirus vaccine, oral). [NIH]

Polyarteritis Nodosa: A form of necrotizing vasculitis involving small- and medium-sized arteries. The signs and symptoms result from infarction and scarring of the affected organ system. [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]

Polymerase Chain Reaction: In vitro method for producing large amounts of specific DNA or RNA fragments of defined length and sequence from small amounts of short oligonucleotide flanking sequences (primers). The essential steps include thermal denaturation of the double-stranded target molecules, annealing of the primers to their complementary sequences, and extension of the annealed primers by enzymatic synthesis with DNA polymerase. The reaction is efficient, specific, and extremely sensitive. Uses for the reaction include disease diagnosis, detection of difficult-to-isolate pathogens, mutation analysis, genetic testing, DNA sequencing, and analyzing evolutionary relationships. [NIH]

Polymers: Compounds formed by the joining of smaller, usually repeating, units linked by covalent bonds. These compounds often form large macromolecules (e.g., polypeptides, proteins, plastics). [NIH]

Polymorphism: The occurrence together of two or more distinct forms in the same population. [NIH]

Polysaccharide: A type of carbohydrate. It contains sugar molecules that are linked together chemically. [NIH]

Polyvalent: Having more than one valence. [EU]

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]

Postmenopausal: Refers to the time after menopause. Menopause is the time in a woman's life when menstrual periods stop permanently; also called "change of life." [NIH]

Postnatal: Occurring after birth, with reference to the newborn. [EU]

Postoperative: After surgery. [NIH]

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]

Potentiates: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Potentiating: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Potential: An overall effect of two drugs taken together which is greater than the sum of the effects of each drug taken alone. [NIH]

Practicability: A non-standard characteristic of an analytical procedure. It is dependent on the scope of the method and is determined by requirements such as sample throughput and costs. [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]

Preclinical: Before a disease becomes clinically recognizable. [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]

Predisposition: A latent susceptibility to disease which may be activated under certain conditions, as by stress. [EU]

Prednisolone: A glucocorticoid with the general properties of the corticosteroids. It is the drug of choice for all conditions in which routine systemic corticosteroid therapy is indicated, except adrenal deficiency states. [NIH]

Prednisone: A synthetic anti-inflammatory glucocorticoid derived from cortisone. It is biologically inert and converted to prednisolone in the liver. [NIH]

Pre-Eclampsia: Development of hypertension with proteinuria, edema, or both, due to pregnancy or the influence of a recent pregnancy. It occurs after the 20th week of gestation, but it may develop before this time in the presence of trophoblastic disease. [NIH]

Premalignant: A term used to describe a condition that may (or is likely to) become cancer. Also called precancerous. [NIH]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

Preoperative: Preceding an operation. [EU]

Presbycusis: Progressive bilateral loss of hearing that occurs in the aged. Syn: senile deafness. [NIH]

Presynaptic: Situated proximal to a synapse, or occurring before the synapse is crossed. [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]

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]

Proctitis: Inflammation of the rectum. [EU]

Prodrug: A substance that gives rise to a pharmacologically active metabolite, although not itself active (i. e. an inactive precursor). [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 antiovaratory agent when administered on days 5-25 of the menstrual cycle. [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]

Prophase: The first phase of cell division, in which the chromosomes become visible, the nucleus starts to lose its identity, the spindle appears, and the centrioles migrate toward opposite poles. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Proportional: Being in proportion : corresponding in size, degree, or intensity, having the same or a constant ratio; of, relating to, or used in determining proportions. [EU]

Prospective Studies: Observation of a population for a sufficient number of persons over a sufficient number of years to generate incidence or mortality rates subsequent to the selection of the study group. [NIH]

Prospective study: An epidemiologic study in which a group of individuals (a cohort), all free of a particular disease and varying in their exposure to a possible risk factor, is followed over a specific amount of time to determine the incidence rates of the disease in the exposed and unexposed groups. [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 α or β indicates the configuration at C-9 (α denotes a substituent below the plane of the ring, β , above the plane). The naturally occurring PGF's have the α configuration, e.g., PGF₂ α . 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-oxoprostano-10,13-dien-1-oic acid (PGA(1)); (5Z,13E,15S)-15-hydroxy-9-oxoprostano-5,10,13-trien-1-oic acid (PGA(2)); (5Z,13E,15S,17Z)-15-hydroxy-9-oxoprostano-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]

Prostate: A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]

Prostatic Intraepithelial Neoplasia: A premalignant change arising in the prostatic epithelium, regarded as the most important and most likely precursor of prostatic adenocarcinoma. The neoplasia takes the form of an intra-acinar or ductal proliferation of secretory cells with unequivocal nuclear anaplasia, which corresponds to nuclear grade 2

and 3 invasive prostate cancer. [NIH]

Protease: Proteinase (= any enzyme that catalyses the splitting of interior peptide bonds in a protein). [EU]

Protease Inhibitors: Compounds which inhibit or antagonize biosynthesis or actions of proteases (endopeptidases). [NIH]

Protein Binding: The process in which substances, either endogenous or exogenous, bind to proteins, peptides, enzymes, protein precursors, or allied compounds. Specific protein-binding measures are often used as assays in diagnostic assessments. [NIH]

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 Conformation: The characteristic 3-dimensional shape of a protein, including the secondary, supersecondary (motifs), tertiary (domains) and quaternary structure of the peptide chain. Quaternary protein structure describes the conformation assumed by multimeric proteins (aggregates of more than one polypeptide chain). [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]

Proteinuria: The presence of protein in the urine, indicating that the kidneys are not working properly. [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]

Proteome: The protein complement of an organism coded for by its genome. [NIH]

Prothrombin: A plasma protein that is the inactive precursor of thrombin. It is converted to thrombin by a prothrombin activator complex consisting of factor Xa, factor V, phospholipid, and calcium ions. Deficiency of prothrombin leads to hypoprothrombinemia. [NIH]

Protocol: The detailed plan for a clinical trial that states the trial's rationale, purpose, drug or vaccine dosages, length of study, routes of administration, who may participate, and other aspects of trial design. [NIH]

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, Asctospora, 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]

Protozoan Infections: Infections with unicellular organisms of the subkingdom Protozoa. [NIH]

Proximal: Nearest; closer to any point of reference; opposed to distal. [EU]

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]

Psychology: The science dealing with the study of mental processes and behavior in man and animals. [NIH]

Puberty: The period during which the secondary sex characteristics begin to develop and the capability of sexual reproduction is attained. [EU]

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]

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 Embolism: Embolism in the pulmonary artery or one of its branches. [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]

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]

Purpura: Purplish or brownish red discoloration, easily visible through the epidermis, caused by hemorrhage into the tissues. [NIH]

Purulent: Consisting of or containing pus; associated with the formation of or caused by pus. [EU]

Pustular: Pertaining to or of the nature of a pustule; consisting of pustules (= a visible collection of pus within or beneath the epidermis). [EU]

Pyrimidines: A family of 6-membered heterocyclic compounds occurring in nature in a wide variety of forms. They include several nucleic acid constituents (cytosine, thymine, and uracil) and form the basic structure of the barbiturates. [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]

Quiescent: Marked by a state of inactivity or repose. [EU]

Rabies: A highly fatal viral infection of the nervous system which affects all warm-blooded animal species. It is one of the most important of the zoonoses because of the inevitably fatal outcome for the infected human. [NIH]

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]

Radiography: Examination of any part of the body for diagnostic purposes by means of roentgen rays, recording the image on a sensitized surface (such as photographic film). [NIH]

Radioimmunotherapy: Radiotherapy where cytotoxic radionuclides are linked to antibodies in order to deliver toxins directly to tumor targets. Therapy with targeted radiation rather than antibody-targeted toxins (immunotoxins) has the advantage that adjacent tumor cells, which lack the appropriate antigenic determinants, can be destroyed by radiation cross-fire. Radioimmunotherapy is sometimes called targeted radiotherapy, but this latter term can also refer to radionuclides linked to non-immune molecules (radiotherapy). [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]

Radiolabeled: Any compound that has been joined with a radioactive substance. [NIH]

Radiotherapy: The use of ionizing radiation to treat malignant neoplasms and other benign conditions. The most common forms of ionizing radiation used as therapy are x-rays, gamma rays, and electrons. A special form of radiotherapy, targeted radiotherapy, links a cytotoxic radionuclide to a molecule that targets the tumor. When this molecule is an antibody or other immunologic molecule, the technique is called radioimmunotherapy. [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]

Rape: Unlawful sexual intercourse without consent of the victim. [NIH]

Reactivation: The restoration of activity to something that has been inactivated. [EU]

Reagent: A substance employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances. [EU]

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]

Reconstitution: 1. A type of regeneration in which a new organ forms by the rearrangement of tissues rather than from new formation at an injured surface. 2. The restoration to original form of a substance previously altered for preservation and storage, as the restoration to a liquid state of blood serum or plasma that has been dried and stored. [EU]

Rectal: By or having to do with the rectum. The rectum is the last 8 to 10 inches of the large intestine and ends at the anus. [NIH]

Rectum: The last 8 to 10 inches of the large intestine. [NIH]

Recurrence: The return of a sign, symptom, or disease after a remission. [NIH]

Red blood cells: RBCs. Cells that carry oxygen to all parts of the body. Also called erythrocytes. [NIH]

Reductase: Enzyme converting testosterone to dihydrotestosterone. [NIH]

Refer: To send or direct for treatment, aid, information, de decision. [NIH]

Reflux: The term used when liquid backs up into the esophagus from the stomach. [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]

Regional lymph node: In oncology, a lymph node that drains lymph from the region around a tumor. [NIH]

Regression Analysis: Procedures for finding the mathematical function which best describes the relationship between a dependent variable and one or more independent variables. In linear regression (see linear models) the relationship is constrained to be a straight line and least-squares analysis is used to determine the best fit. In logistic regression (see logistic models) the dependent variable is qualitative rather than continuously variable and likelihood functions are used to find the best relationship. In multiple regression the dependent variable is considered to depend on more than a single independent variable. [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]

Rehabilitative: Instruction of incapacitated individuals or of those affected with some mental disorder, so that some or all of their lost ability may be regained. [NIH]

Reinfection: A second infection by the same pathogenic agent, or a second infection of an organ such as the kidney by a different pathogenic agent. [EU]

Relapse: The return of signs and symptoms of cancer after a period of improvement. [NIH]

Reliability: Used technically, in a statistical sense, of consistency of a test with itself, i. e. the extent to which we can assume that it will yield the same result if repeated a second time. [NIH]

Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although there still may be cancer in the body. [NIH]

Renal failure: Progressive renal insufficiency and uremia, due to irreversible and progressive renal glomerular tubular or interstitial disease. [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]

Residual disease: Cancer cells that remain after attempts have been made to remove the cancer. [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 syncytial virus: RSV. A virus that causes respiratory infections with cold-like symptoms. [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]

Restoration: Broad term applied to any inlay, crown, bridge or complete denture which restores or replaces loss of teeth or oral tissues. [NIH]

Resuscitation: The restoration to life or consciousness of one apparently dead; it includes such measures as artificial respiration and cardiac massage. [EU]

Retina: The ten-layered nervous tissue membrane of the eye. It is continuous with the optic nerve and receives images of external objects and transmits visual impulses to the brain. Its outer surface is in contact with the choroid and the inner surface with the vitreous body. The outer-most layer is pigmented, whereas the inner nine layers are transparent. [NIH]

Retinal: 1. Pertaining to the retina. 2. The aldehyde of retinol, derived by the oxidative enzymatic splitting of absorbed dietary carotene, and having vitamin A activity. In the retina, retinal combines with opsins to form visual pigments. One isomer, 11-cis retinal combines with opsin in the rods (scotopsin) to form rhodopsin, or visual purple. Another, all-trans retinal (trans-r.); visual yellow; xanthopsin) results from the bleaching of rhodopsin by light, in which the 11-cis form is converted to the all-trans form. Retinal also combines with opsins in the cones (photopsins) to form the three pigments responsible for colour vision. Called also retinal, and retinene1. [EU]

Retinal Detachment: Separation of the inner layers of the retina (neural retina) from the pigment epithelium. Retinal detachment occurs more commonly in men than in women, in eyes with degenerative myopia, in aging and in aphakia. It may occur after an uncomplicated cataract extraction, but it is seen more often if vitreous humor has been lost during surgery. (Dorland, 27th ed; Newell, Ophthalmology: Principles and Concepts, 7th ed, p310-12). [NIH]

Retinitis: Inflammation of the retina. It is rarely limited to the retina, but is commonly associated with diseases of the choroid (chorioretinitis) and of the optic nerve (neuroretinitis). The disease may be confined to one eye, but since it is generally dependent on a constitutional factor, it is almost always bilateral. It may be acute in course, but as a rule it lasts many weeks or even several months. [NIH]

Retinoblastoma: An eye cancer that most often occurs in children younger than 5 years. It occurs in hereditary and nonhereditary (sporadic) forms. [NIH]

Retinoblastoma Protein: Product of the retinoblastoma tumor suppressor gene. It is a nuclear phosphoprotein hypothesized to normally act as an inhibitor of cell proliferation. Rb protein is absent in retinoblastoma cell lines. It also has been shown to form complexes with the adenovirus E1A protein, the SV40 T antigen, and the human papilloma virus E7 protein. [NIH]

Retinol: Vitamin A. It is essential for proper vision and healthy skin and mucous membranes. Retinol is being studied for cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Retreatment: The therapy of the same disease in a patient, with the same agent or procedure repeated after initial treatment, or with an additional or alternate measure or follow-up. It

does not include therapy which requires more than one administration of a therapeutic agent or regimen. Retreatment is often used with reference to a different modality when the original one was inadequate, harmful, or unsuccessful. [NIH]

Retrocochlear: Hearing loss in which the air conduction threshold and the bone conduction threshold have risen almost equally with no gap between them. In such cases the defect is usually either in the cochlea of the inner ear or in the central pathways. [NIH]

Retrograde: 1. Moving backward or against the usual direction of flow. 2. Degenerating, deteriorating, or catabolic. [EU]

Retrospective: Looking back at events that have already taken place. [NIH]

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [NIH]

Retrovirus: A member of a group of RNA viruses, the RNA of which is copied during viral replication into DNA by reverse transcriptase. The viral DNA is then able to be integrated into the host chromosomal DNA. [NIH]

Rhadinovirus: A genus of the family Herpesviridae, subfamily Gammaherpesvirinae, infecting New World primates. Herpesvirus 2, Ateline is the type species. [NIH]

Rheumatism: A group of disorders marked by inflammation or pain in the connective tissue structures of the body. These structures include bone, cartilage, and fat. [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]

Rhodopsin: A photoreceptor protein found in retinal rods. It is a complex formed by the binding of retinal, the oxidized form of retinol, to the protein opsin and undergoes a series of complex reactions in response to visible light resulting in the transmission of nerve impulses to the brain. [NIH]

Ribonucleic acid: RNA. One of the two nucleic acids found in all cells. The other is deoxyribonucleic acid (DNA). Ribonucleic acid transfers genetic information from DNA to proteins produced by the cell. [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]

Risk factor: A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

Ristocetin: An antibiotic mixture of two components, A and B, obtained from *Nocardia lurida* (or the same substance produced by any other means). It is no longer used clinically because of its toxicity. It causes platelet agglutination and blood coagulation and is used to assay those functions in vitro. [NIH]

Rod: A reception for vision, located in the retina. [NIH]

Rodenticides: Substances used to destroy or inhibit the action of rats, mice, or other rodents. [NIH]

Rubella Virus: The type (and only) species of Rubivirus causing acute infection in humans, primarily children and young adults. Humans are the only natural host. A live, attenuated vaccine is available for prophylaxis. [NIH]

Rubulavirus: A genus of the family Paramyxoviridae (subfamily Paramyxovirinae) where all the species have hemagglutinin and neuraminidase activities but lack a C protein. Mumps virus is the type species. [NIH]

Safe Sex: Sex behavior that prevents or decreases the spread of sexually transmitted diseases or pregnancy. [NIH]

Saliva: The clear, viscous fluid secreted by the salivary glands and mucous glands of the mouth. It contains mucins, water, organic salts, and ptylin. [NIH]

Salivary: The duct that convey saliva to the mouth. [NIH]

Salivary glands: Glands in the mouth that produce saliva. [NIH]

Salmonella: A genus of gram-negative, facultatively anaerobic, rod-shaped bacteria that utilizes citrate as a sole carbon source. It is pathogenic for humans, causing enteric fevers, gastroenteritis, and bacteremia. Food poisoning is the most common clinical manifestation. Organisms within this genus are separated on the basis of antigenic characteristics, sugar fermentation patterns, and bacteriophage susceptibility. [NIH]

Saponins: Sapogenin glycosides. A type of glycoside widely distributed in plants. Each consists of a sapogenin as the aglycon moiety, and a sugar. The sapogenin may be a steroid or a triterpene and the sugar may be glucose, galactose, a pentose, or a methylpentose. Sapogenins are poisonous towards the lower forms of life and are powerful hemolytics when injected into the blood stream able to dissolve red blood cells at even extreme dilutions. [NIH]

Sarcoidosis: An idiopathic systemic inflammatory granulomatous disorder comprised of epithelioid and multinucleated giant cells with little necrosis. It usually invades the lungs with fibrosis and may also involve lymph nodes, skin, liver, spleen, eyes, phalangeal bones, and parotid glands. [NIH]

Sarcoma: A connective tissue neoplasm formed by proliferation of mesodermal cells; it is usually highly malignant. [NIH]

Sargramostim: A colony-stimulating factor that stimulates the production of blood cells, especially platelets, during chemotherapy. It is a cytokine that belongs to the family of drugs called hematopoietic (blood-forming) agents. Also called GM-CSF. [NIH]

Satellite: Applied to a vein which closely accompanies an artery for some distance; in cytogenetics, a chromosomal agent separated by a secondary constriction from the main body of the chromosome. [NIH]

Schizophrenia: A mental disorder characterized by a special type of disintegration of the personality. [NIH]

Sclera: The tough white outer coat of the eyeball, covering approximately the posterior five-sixths of its surface, and continuous anteriorly with the cornea and posteriorly with the external sheath of the optic nerve. [EU]

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]

Secretory: Secreting; relating to or influencing secretion or the secretions. [NIH]

Secular trends: A relatively long-term trend in a community or country. [NIH]

Sedimentation: The act of causing the deposit of sediment, especially by the use of a centrifugal machine. [EU]

Segregation: The separation in meiotic cell division of homologous chromosome pairs and their contained allelomorphous gene pairs. [NIH]

Semen: The thick, yellowish-white, viscid fluid secretion of male reproductive organs discharged upon ejaculation. In addition to reproductive organ secretions, it contains spermatozoa and their nutrient plasma. [NIH]

Semicircular canal: Three long canals of the bony labyrinth of the ear, forming loops and opening into the vestibule by five openings. [NIH]

Semisynthetic: Produced by chemical manipulation of naturally occurring substances. [EU]

Senescence: The bodily and mental state associated with advancing age. [NIH]

Senile: Relating or belonging to old age; characteristic of old age; resulting from infirmity of old age. [NIH]

Sensory loss: A disease of the nerves whereby the myelin or insulating sheath of myelin on the nerves does not stay intact and the messages from the brain to the muscles through the nerves are not carried properly. [NIH]

Septic: Produced by or due to decomposition by microorganisms; putrefactive. [EU]

Septicemia: Systemic disease associated with the presence and persistence of pathogenic microorganisms or their toxins in the blood. Called also blood poisoning. [EU]

Sequence Analysis: A multistage process that includes the determination of a sequence (protein, carbohydrate, etc.), its fragmentation and analysis, and the interpretation of the resulting sequence information. [NIH]

Sequence Homology: The degree of similarity between sequences. Studies of amino acid and nucleotide sequences provide useful information about the genetic relatedness of certain species. [NIH]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [NIH]

Serine: A non-essential amino acid occurring in natural form as the L-isomer. It is synthesized from glycine or threonine. It is involved in the biosynthesis of purines, pyrimidines, and other amino acids. [NIH]

Seroconversion: The change of a serologic test from negative to positive, indicating the development of antibodies in response to infection or immunization. [EU]

Serologic: Analysis of a person's serum, especially specific immune or lytic serums. [NIH]

Serologic Tests: Diagnostic procedures involving immunoglobulin reactions. [NIH]

Serology: The study of serum, especially of antigen-antibody reactions in vitro. [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]

Serum Albumin: A major plasma protein that serves in maintaining the plasma colloidal osmotic pressure and transporting large organic anions. [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]

Sexually Transmitted Diseases: Diseases due to or propagated by sexual contact. [NIH]

Sharpness: The apparent blurring of the border between two adjacent areas of a radiograph having different optical densities. [NIH]

Shedding: Release of infectious particles (e. g., bacteria, viruses) into the environment, for example by sneezing, by fecal excretion, or from an open lesion. [NIH]

Shock: The general bodily disturbance following a severe injury; an emotional or moral upset occasioned by some disturbing or unexpected experience; disruption of the circulation, which can upset all body functions: sometimes referred to as circulatory shock. [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]

Sigmoid: 1. Shaped like the letter S or the letter C. 2. The sigmoid colon. [EU]

Sigmoidoscopy: Endoscopic examination, therapy or surgery of the sigmoid flexure. [NIH]

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]

Signs and Symptoms: Clinical manifestations that can be either objective when observed by a physician, or subjective when perceived by the patient. [NIH]

Sindbis Virus: The type species of alphavirus normally transmitted to birds by *Culex* mosquitoes in Egypt, South Africa, India, Malaya, the Philippines, and Australia. It may be associated with fever in humans. [NIH]

Sinusitis: An inflammatory process of the mucous membranes of the paranasal sinuses that occurs in three stages: acute, subacute, and chronic. Sinusitis results from any condition causing ostial obstruction or from pathophysiologic changes in the mucociliary transport mechanism. [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]

Smallpox: A generalized virus infection with a vesicular rash. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Sneezing: Sudden, forceful, involuntary expulsion of air from the nose and mouth caused by irritation to the mucous membranes of the upper respiratory tract. [NIH]

Social Environment: The aggregate of social and cultural institutions, forms, patterns, and processes that influence the life of an individual or community. [NIH]

Social Security: Government sponsored social insurance programs. [NIH]

Social Support: Support systems that provide assistance and encouragement to individuals with physical or emotional disabilities in order that they may better cope. Informal social support is usually provided by friends, relatives, or peers, while formal assistance is provided by churches, groups, etc. [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]

Soft tissue: Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. [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]

Somatic cells: All the body cells except the reproductive (germ) cells. [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]

Species Specificity: Restriction of a characteristic or response to the members of one species; it usually refers to that property of the immune response which differentiates one species from another on the basis of antigen recognition, but the concept is not limited to immunology and is used loosely at levels higher than the species. [NIH]

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]

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]

Spirochete: Lyme disease. [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]

Splenomegaly: Enlargement of the spleen. [NIH]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Squamous: Scaly, or platelike. [EU]

Squamous cell carcinoma: Cancer that begins in squamous cells, which are thin, flat cells resembling fish scales. Squamous cells are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts. Also called epidermoid carcinoma. [NIH]

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Squamous cells: Flat cells that look like fish scales under a microscope. These cells cover internal and external surfaces of the body. [NIH]

Stabilization: The creation of a stable state. [EU]

Standard therapy: A currently accepted and widely used treatment for a certain type of cancer, based on the results of past research. [NIH]

Staphylococcus: A genus of gram-positive, facultatively anaerobic, coccoid bacteria. Its organisms occur singly, in pairs, and in tetrads and characteristically divide in more than one plane to form irregular clusters. Natural populations of Staphylococcus are membranes of warm-blooded animals. Some species are opportunistic pathogens of humans and animals. [NIH]

Statistically significant: Describes a mathematical measure of difference between groups. The difference is said to be statistically significant if it is greater than what might be expected to happen by chance alone. [NIH]

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 cell transplantation: A method of replacing immature blood-forming cells that were destroyed by cancer treatment. The stem cells are given to the person after treatment to help the bone marrow recover and continue producing healthy blood cells. [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]

Sterility: 1. The inability to produce offspring, i.e., the inability to conceive (female s.) or to induce conception (male s.). 2. The state of being aseptic, or free from microorganisms. [EU]

Steroid: A group name for lipids that contain a hydrogenated cyclopentanoperhydrophenanthrene ring system. Some of the substances included in this group are progesterone, adrenocortical hormones, the gonadal hormones, cardiac aglycones, bile acids, sterols (such as cholesterol), toad poisons, saponins, and some of the carcinogenic hydrocarbons. [EU]

Steroid therapy: Treatment with corticosteroid drugs to reduce swelling, pain, and other

symptoms of inflammation. [NIH]

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]

Stomatitis: Inflammation of the oral mucosa, due to local or systemic factors which may involve the buccal and labial mucosa, palate, tongue, floor of the mouth, and the gingivae. [EU]

Stool: The waste matter discharged in a bowel movement; feces. [NIH]

Strand: DNA normally exists in the bacterial nucleus in a helix, in which two strands are coiled together. [NIH]

Streptococcal: Caused by infection due to any species of streptococcus. [NIH]

Streptococci: A genus of spherical Gram-positive bacteria occurring in chains or pairs. They are widely distributed in nature, being important pathogens but often found as normal commensals in the mouth, skin, and intestine of humans and other animals. [NIH]

Streptococcus: A genus of gram-positive, coccoid bacteria whose organisms occur in pairs or chains. No endospores are produced. Many species exist as commensals or parasites on man or animals with some being highly pathogenic. A few species are saprophytes and occur in the natural environment. [NIH]

Streptomycin: O-2-Deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1-2)-O-5- deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1-4)-N,N'-bis- (aminoiminomethyl)-D-streptamine. Antibiotic substance produced by the soil actinomycete *Streptomyces griseus*. It acts by inhibiting the initiation and elongation processes during protein synthesis. [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]

Stress management: A set of techniques used to help an individual cope more effectively with difficult situations in order to feel better emotionally, improve behavioral skills, and often to enhance feelings of control. Stress management may include relaxation exercises, assertiveness training, cognitive restructuring, time management, and social support. It can be delivered either on a one-to-one basis or in a group format. [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]

Stroma: The middle, thickest layer of tissue in the cornea. [NIH]

Stromal: Large, veil-like cell in the bone marrow. [NIH]

Stromal Cells: Connective tissue cells of an organ found in the loose connective tissue. These are most often associated with the uterine mucosa and the ovary as well as the hematopoietic system and elsewhere. [NIH]

Structure-Activity Relationship: The relationship between the chemical structure of a compound and its biological or pharmacological activity. Compounds are often classed together because they have structural characteristics in common including shape, size, stereochemical arrangement, and distribution of functional groups. Other factors contributing to structure-activity relationship include chemical reactivity, electronic effects, resonance, and inductive effects. [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]

Submandibular: Four to six lymph glands, located between the lower jaw and the submandibular salivary gland. [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]

Substance P: An eleven-amino acid neurotransmitter that appears in both the central and peripheral nervous systems. It is involved in transmission of pain, causes rapid contractions of the gastrointestinal smooth muscle, and modulates inflammatory and immune responses. [NIH]

Substrate: A substance upon which an enzyme acts. [EU]

Substrate Specificity: A characteristic feature of enzyme activity in relation to the kind of substrate on which the enzyme or catalytic molecule reacts. [NIH]

Subtilisin: A serine endopeptidase isolated from *Bacillus subtilis*. It hydrolyzes proteins with broad specificity for peptide bonds, and a preference for a large uncharged residue in P1. It also hydrolyzes peptide amides. (From Enzyme Nomenclature, 1992) EC 3.4.21.62. [NIH]

Superinfection: A frequent complication of drug therapy for microbial infection. It may result from opportunistic colonization following immunosuppression by the primary pathogen and can be influenced by the time interval between infections, microbial physiology, or host resistance. Experimental challenge and in vitro models are sometimes used in virulence and infectivity studies. [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]

Suppressive: Tending to suppress : effecting suppression; specifically : serving to suppress activity, function, symptoms. [EU]

Surface Plasmon Resonance: A biosensing technique in which biomolecules capable of binding to specific analytes or ligands are first immobilized on one side of a metallic film. Light is then focused on the opposite side of the film to excite the surface plasmons, that is, the oscillations of free electrons propagating along the film's surface. The refractive index of light reflecting off this surface is measured. When the immobilized biomolecules are bound by their ligands, an alteration in surface plasmons on the opposite side of the film is created which is directly proportional to the change in bound, or adsorbed, mass. Binding is measured by changes in the refractive index. The technique is used to study biomolecular interactions, such as antigen-antibody binding. [NIH]

Sweat: The fluid excreted by the sweat glands. It consists of water containing sodium chloride, phosphate, urea, ammonia, and other waste products. [NIH]

Sweat Glands: Sweat-producing structures that are embedded in the dermis. Each gland consists of a single tube, a coiled body, and a superficial duct. [NIH]

Symptomatic: Having to do with symptoms, which are signs of a condition or 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]

Syphilis: A contagious venereal disease caused by the spirochete *Treponema pallidum*. [NIH]

Systemic: Affecting the entire body. [NIH]

Systemic disease: Disease that affects the whole 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]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

Systolic blood pressure: The maximum pressure in the artery produced as the heart contracts and blood begins to flow. [NIH]

Tacrolimus: A macrolide isolated from the culture broth of a strain of *Streptomyces tsukubaensis* that has strong immunosuppressive activity in vivo and prevents the activation of T-lymphocytes in response to antigenic or mitogenic stimulation in vitro. [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]

Teratogens: An agent that causes the production of physical defects in the developing embryo. [NIH]

Terminator: A DNA sequence sited at the end of a transcriptional unit that signals the end of transcription. [NIH]

Testicular: Pertaining to a testis. [EU]

Testis: Either of the paired male reproductive glands that produce the male germ cells and the male hormones. [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]

Therapeutics: The branch of medicine which is concerned with the treatment of diseases, palliative or curative. [NIH]

Thermal: Pertaining to or characterized by heat. [EU]

Thiourea: A photographic fixative used also in the manufacture of resins. According to the Fourth Annual Report on Carcinogens (NTP 85-002, 1985), this substance may reasonably be anticipated to be a carcinogen (Merck Index, 9th ed). Many of its derivatives are antithyroid agents and/or free radical scavengers. [NIH]

Third Ventricle: A narrow cleft inferior to the corpus callosum, within the diencephalon, between the paired thalami. Its floor is formed by the hypothalamus, its anterior wall by the lamina terminalis, and its roof by ependyma. It communicates with the fourth ventricle by the cerebral aqueduct, and with the lateral ventricles by the interventricular foramina. [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]

Thrombolytic: 1. Dissolving or splitting up a thrombus. 2. A thrombolytic agent. [EU]

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]

Thrombopenia: Reduction in the number of platelets in the blood. [NIH]

Thrombophlebitis: Inflammation of a vein associated with thrombus formation. [NIH]

Thromboses: The formation or presence of a blood clot within a blood vessel during life. [NIH]

Thrombosis: The formation or presence of a blood clot inside a blood vessel. [NIH]

Thromboxanes: Physiologically active compounds found in many organs of the body. They are formed in vivo from the prostaglandin endoperoxides and cause platelet aggregation, contraction of arteries, and other biological effects. Thromboxanes are important mediators of the actions of polyunsaturated fatty acids transformed by cyclooxygenase. [NIH]

Thrombus: An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation. Some authorities thus differentiate thrombus formation from simple coagulation or clot formation. [EU]

Thrush: A disease due to infection with species of fungi of the genus *Candida*. [NIH]

Thymidine: A chemical compound found in DNA. Also used as treatment for mucositis. [NIH]

Thymoma: A tumor of the thymus, an organ that is part of the lymphatic system and is located in the chest, behind the breastbone. [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]

Thyroid Hormones: Hormones secreted by the thyroid gland. [NIH]

Thyrotropin: A peptide hormone secreted by the anterior pituitary. It promotes the growth of the thyroid gland and stimulates the synthesis of thyroid hormones and the release of thyroxine by the thyroid gland. [NIH]

Thyroxine: An amino acid of the thyroid gland which exerts a stimulating effect on thyroid metabolism. [NIH]

Ticks: Blood-sucking arachnids of the order Acarina. [NIH]

Time Management: Planning and control of time to improve efficiency and effectiveness. [NIH]

Tin: A trace element that is required in bone formation. It has the atomic symbol Sn, atomic number 50, and atomic weight 118.71. [NIH]

Tin ethyl etiopurpurin: An anticancer drug that is also used in cancer prevention. It belongs to the family of drugs called photosensitizing agents. Also called SnET2. [NIH]

Tinnitus: Sounds that are perceived in the absence of any external noise source which may take the form of buzzing, ringing, clicking, pulsations, and other noises. Objective tinnitus refers to noises generated from within the ear or adjacent structures that can be heard by other individuals. The term subjective tinnitus is used when the sound is audible only to the affected individual. Tinnitus may occur as a manifestation of cochlear diseases; vestibulocochlear nerve diseases; intracranial hypertension; craniocerebral trauma; and other conditions. [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]

Tomography: Imaging methods that result in sharp images of objects located on a chosen plane and blurred images located above or below the plane. [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]

Toxoplasma: A genus of protozoa parasitic to birds and mammals. *T. gondii* is one of the most common infectious pathogenic animal parasites of man. [NIH]

Toxoplasmosis: The acquired form of infection by *Toxoplasma gondii* in animals and man. [NIH]

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]

Transaminases: A subclass of enzymes of the transferase class that catalyze the transfer of an amino group from a donor (generally an amino acid) to an acceptor (generally a 2-keto acid). Most of these enzymes are pyridoxyl phosphate proteins. (Dorland, 28th ed) EC 2.6.1. [NIH]

Transcriptase: An enzyme which catalyses the synthesis of a complementary mRNA molecule from a DNA template in the presence of a mixture of the four ribonucleotides (ATP, UTP, GTP and CTP). [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]

Transforming Growth Factor beta: A factor synthesized in a wide variety of tissues. It acts synergistically with TGF-alpha in inducing phenotypic transformation and can also act as a negative autocrine growth factor. TGF-beta has a potential role in embryonal development, cellular differentiation, hormone secretion, and immune function. TGF-beta is found mostly as homodimer forms of separate gene products TGF-beta1, TGF-beta2 or TGF-beta3. Heterodimers composed of TGF-beta1 and 2 (TGF-beta1.2) or of TGF-beta2 and 3 (TGF-beta2.3) have been isolated. The TGF-beta proteins are synthesized as precursor proteins. [NIH]

Transfusion: The infusion of components of blood or whole blood into the bloodstream. The blood may be donated from another person, or it may have been taken from the person earlier and stored until needed. [NIH]

Transgenes: Genes that are introduced into an organism using gene transfer techniques. [NIH]

Trans-Golgi Network: A network of membrane compartments, located at the cytoplasmic side of the Golgi apparatus, where proteins and lipids are sorted for transport to various locations in the cell or cell membrane. [NIH]

Translating: Conversion from one language to another language. [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]

Trauma: Any injury, wound, or shock, must frequently physical or structural shock, producing a disturbance. [NIH]

Treatment Outcome: Evaluation undertaken to assess the results or consequences of management and procedures used in combating disease in order to determine the efficacy, effectiveness, safety, practicability, etc., of these interventions in individual cases or series. [NIH]

Triad: Trivalent. [NIH]

Trigeminal: Cranial nerve V. It is sensory for the eyeball, the conjunctiva, the eyebrow, the skin of face and scalp, the teeth, the mucous membranes in the mouth and nose, and is motor to the muscles of mastication. [NIH]

Tropism: Directed movements and orientations found in plants, such as the turning of the sunflower to face the sun. [NIH]

Trypanosomiasis: Infection with protozoa of the genus *Trypanosoma*. [NIH]

Trypsin: A serine endopeptidase that is formed from trypsinogen in the pancreas. It is converted into its active form by enteropeptidase in the small intestine. It catalyzes hydrolysis of the carboxyl group of either arginine or lysine. EC 3.4.21.4. [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]

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]

Tumor suppressor gene: Genes in the body that can suppress or block the development of cancer. [NIH]

Tunica: A rather vague term to denote the lining coat of hollow organs, tubes, or cavities. [NIH]

Tympanic membrane: A thin, tense membrane forming the greater part of the outer wall of the tympanic cavity and separating it from the external auditory meatus; it constitutes the boundary between the external and middle ear. [NIH]

Tyrosine: A non-essential amino acid. In animals it is synthesized from phenylalanine. It is also the precursor of epinephrine, thyroid hormones, and melanin. [NIH]

Ubiquitin: A highly conserved 76 amino acid-protein found in all eukaryotic cells. [NIH]

Ulcer: A localized necrotic lesion of the skin or a mucous surface. [NIH]

Ulceration: 1. The formation or development of an ulcer. 2. An ulcer. [EU]

Ulcerative colitis: Chronic inflammation of the colon that produces ulcers in its lining. This condition is marked by abdominal pain, cramps, and loose discharges of pus, blood, and mucus from the bowel. [NIH]

Unconscious: Experience which was once conscious, but was subsequently rejected, as the "personal unconscious". [NIH]

Universal Precautions: Prudent standard preventive measures to be taken by professional and other health personnel in contact with persons afflicted with a communicable disease, to avoid contracting the disease by contagion or infection. Precautions are especially applicable in the diagnosis and care of AIDS patients. [NIH]

Uracil: An anticancer drug that belongs to the family of drugs called alkylating agents. [NIH]

Urea: A compound ($\text{CO}(\text{NH}_2)_2$), formed in the liver from ammonia produced by the deamination of amino acids. It is the principal end product of protein catabolism and constitutes about one half of the total urinary solids. [NIH]

Uremia: The illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion. [NIH]

Ureters: Tubes that carry urine from the kidneys to the bladder. [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]

Urinary tract: The organs of the body that produce and discharge urine. These include the kidneys, ureters, bladder, and urethra. [NIH]

Urinary tract infection: An illness caused by harmful bacteria growing in the urinary tract. [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]

Urogenital: Pertaining to the urinary and genital apparatus; genitourinary. [EU]

Urokinase: A drug that dissolves blood clots or prevents them from forming. [NIH]

Uterine Contraction: Contraction of the uterine muscle. [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]

Uvea: The middle coat of the eyeball, consisting of the choroid in the back of the eye and the ciliary body and iris in the front of the eye. [NIH]

Uveitis: An inflammation of part or all of the uvea, the middle (vascular) tunic of the eye, and commonly involving the other tunics (the sclera and cornea, and the retina). [EU]

Vaccination: Administration of vaccines to stimulate the host's immune response. This includes any preparation intended for active immunological prophylaxis. [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]

Vaccinia: The cutaneous and occasional systemic reactions associated with vaccination using smallpox (variola) vaccine. [NIH]

Vaccinia Virus: The type species of Orthopoxvirus, related to cowpox virus, but whose true origin is unknown. It has been used as a live vaccine against smallpox. It is also used as a vector for inserting foreign DNA into animals. Rabbitpox virus is a subspecies of vaccinia virus. [NIH]

Vacuole: A fluid-filled cavity within the cytoplasm of a cell. [NIH]

Vagina: The muscular canal extending from the uterus to the exterior of the body. Also called the birth canal. [NIH]

Vaginal: Of or having to do with the vagina, the birth canal. [NIH]

Vaginitis: Inflammation of the vagina characterized by pain and a purulent discharge. [NIH]

Vagotomy: The interruption or removal of any part of the vagus (10th cranial) nerve. Vagotomy may be performed for research or for therapeutic purposes. [NIH]

Valganciclovir: An antiviral agent that is being studied as a treatment for AIDS-related cytomegalovirus. It is converted in the body to ganciclovir. [NIH]

Vancomycin: Antibacterial obtained from *Streptomyces orientalis*. It is a glycopeptide related to ristocetin that inhibits bacterial cell wall assembly and is toxic to kidneys and the inner ear. [NIH]

Varicella: Chicken pox. [EU]

Variola: A generalized virus infection with a vesicular rash. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vasculitis: Inflammation of a blood vessel. [NIH]

Vasodilators: Any nerve or agent which induces dilatation of the 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]

Venereal: Pertaining or related to or transmitted by sexual contact. [EU]

Venoms: Poisonous animal secretions forming fluid mixtures of many different enzymes, toxins, and other substances. These substances are produced in specialized glands and secreted through specialized delivery systems (nematocysts, spines, fangs, etc.) for disabling prey or predator. [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]

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]

Venules: The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

Vertigo: An illusion of movement; a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo). The term is sometimes erroneously used to mean any form of dizziness. [EU]

Vesicular: 1. Composed of or relating to small, saclike bodies. 2. Pertaining to or made up of vesicles on the skin. [EU]

Vestibular: Pertaining to or toward a vestibule. In dental anatomy, used to refer to the tooth surface directed toward the vestibule of the mouth. [EU]

Vestibule: A small, oval, bony chamber of the labyrinth. The vestibule contains the utricle and saccule, organs which are part of the balancing apparatus of the ear. [NIH]

Vestibulocochlear Nerve: The 8th cranial nerve. The vestibulocochlear nerve has a cochlear part (cochlear nerve) which is concerned with hearing and a vestibular part (vestibular nerve) which mediates the sense of balance and head position. The fibers of the cochlear nerve originate from neurons of the spiral ganglion and project to the cochlear nuclei (cochlear nucleus). The fibers of the vestibular nerve arise from neurons of Scarpa's ganglion and project to the vestibular nuclei. [NIH]

Vestibulocochlear Nerve Diseases: Diseases of the vestibular and/or cochlear (acoustic)

nerves, which join to form the vestibulocochlear nerve. Vestibular neuritis, cochlear neuritis, and acoustic neuromas are relatively common conditions that affect these nerves. Clinical manifestations vary with which nerve is primarily affected, and include hearing loss, vertigo, and tinnitus. [NIH]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Vial: A small bottle. [EU]

Vidarabine: A nucleoside antibiotic isolated from *Streptomyces antibioticus*. It has some antineoplastic properties and has broad spectrum activity against DNA viruses in cell cultures and significant antiviral activity against infections caused by a variety of viruses such as the herpes viruses, the vaccinia virus and varicella zoster virus. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

Viral Hepatitis: Hepatitis caused by a virus. Five different viruses (A, B, C, D, and E) most commonly cause this form of hepatitis. Other rare viruses may also cause hepatitis. [NIH]

Viral Load: The quantity of measurable virus in the blood. Change in viral load, measured in plasma, is used as a surrogate marker in HIV disease progression. [NIH]

Viral Proteins: Proteins found in any species of virus. [NIH]

Viral Regulatory Proteins: Proteins which regulate the rate of transcription of viral structural genes. [NIH]

Viral vector: A type of virus used in cancer therapy. The virus is changed in the laboratory and cannot cause disease. Viral vectors produce tumor antigens (proteins found on a tumor cell) and can stimulate an antitumor immune response in the body. Viral vectors may also be used to carry genes that can change cancer cells back to normal cells. [NIH]

Viremia: The presence of viruses in the blood. [NIH]

Virion: The infective system of a virus, composed of the viral genome, a protein core, and a protein coat called a capsid, which may be naked or enclosed in a lipoprotein envelope called the peplous. [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]

Virus Diseases: A general term for diseases produced by viruses. [NIH]

Virus Replication: The process of intracellular viral multiplication, consisting of the synthesis of proteins, nucleic acids, and sometimes lipids, and their assembly into a new infectious particle. [NIH]

Visual Acuity: Acuteness or clearness of vision, especially of form vision, which is dependent mainly on the sharpness of the retinal focus. [NIH]

Visual field: The entire area that can be seen when the eye is forward, including peripheral vision. [NIH]

Vitamin A: A substance used in cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Vitiligo: A disorder consisting of areas of macular depigmentation, commonly on extensor aspects of extremities, on the face or neck, and in skin folds. Age of onset is often in young adulthood and the condition tends to progress gradually with lesions enlarging and

extending until a quiescent state is reached. [NIH]

Vitreous: Glasslike or hyaline; often used alone to designate the vitreous body of the eye (corpus vitreum). [EU]

Vitreous Body: The transparent, semigelatinous substance that fills the cavity behind the crystalline lens of the eye and in front of the retina. It is contained in a thin hyoid membrane and forms about four fifths of the optic globe. [NIH]

Vitreous Humor: The transparent, colorless mass of gel that lies behind the lens and in front of the retina and fills the center of the eyeball. [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]

Waiting Lists: Prospective patient listings for appointments. [NIH]

Wart: A raised growth on the surface of the skin or other organ. [NIH]

Weight Gain: Increase in body weight over existing weight. [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]

Womb: A hollow, thick-walled, muscular organ in which the impregnated ovum is developed into a child. [NIH]

Wound Healing: Restoration of integrity to traumatized tissue. [NIH]

Xenograft: The cells of one species transplanted to another species. [NIH]

Xerostomia: Decreased salivary flow. [NIH]

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

X-ray therapy: The use of high-energy radiation from x-rays to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy) or from materials called radioisotopes. Radioisotopes produce radiation and can be placed in or near the tumor or in the area near cancer cells. This type of radiation treatment is called internal radiation therapy, implant radiation, interstitial radiation, or brachytherapy. Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. X-ray therapy is also called radiation therapy, radiotherapy, and irradiation. [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]

Yellow Fever: An acute infectious disease primarily of the tropics, caused by a virus and transmitted to man by mosquitoes of the genera *Aedes* and *Haemagogus*. [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]

Zoster: A virus infection of the Gasserian ganglion and its nerve branches, characterized by discrete areas of vesiculation of the epithelium of the forehead, the nose, the eyelids, and the cornea together with subepithelial infiltration. [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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