GLOMERULONEPHRITIS

A 3-IN-1 MEDICAL REFERENCE

Medical Dictionary

Bibliography &

Annotated Research Guide

TO INTERNET REFERENCES

ICON Group International, Inc.

GLOMERULONEPHRITIS

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

JAMES N. PARKER, M.D.
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 glomerulonephritis. 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.

About the Editors

James N. Parker, M.D.

Dr. James N. Parker received his Bachelor of Science degree in Psychobiology from the University of California, Riverside and his M.D. from the University of California, San Diego. In addition to authoring numerous research publications, he has lectured at various academic institutions. Dr. Parker is the medical editor for health books by ICON Health Publications.

Philip M. Parker, Ph.D.

Philip M. Parker is the Eli Lilly Chair Professor of Innovation, Business and Society at INSEAD (Fontainebleau, France and Singapore). Dr. Parker has also been Professor at the University of California, San Diego and has taught courses at Harvard University, the Hong Kong University of Science and Technology, the Massachusetts Institute of Technology, Stanford University, and UCLA. Dr. Parker is the associate editor for ICON Health Publications.

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Fax: 858-546-4341
Web site: **www.icongrouponline.com/health**

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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 glomerulonephritis 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 glomerulonephritis, 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 glomerulonephritis, 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 glomerulonephritis. 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 glomerulonephritis, 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 glomerulonephritis.

The Editors

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

CHAPTER 1. STUDIES ON GLOMERULONEPHRITIS

Overview

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

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and glomerulonephritis, 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 "glomerulonephritis" (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:

- **Glomerulonephritis Recurrence in the Renal Graft**

  Source: JASN. Journal of the American Society of Nephrology. 12(2): 394-402. February 2001.

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

  Summary: Although kidney transplantation may return renal (kidney) function to the recipient, it does not necessarily remove the cause of the recipient's original kidney disease. **Glomerulonephritis** is the cause of renal failure for 20 to 40 percent of those who receive a transplant; for these recipients, the threat of recurrent disease is very real. This article discusses recurrent **glomerulonephritis.** The author first reviews the

epidemiology of recurrence in a general sense, then addresses recurrence of specific forms of the disease. The incidence of recurrence and recurrence leading to graft failure is examined, and risk factors for disease recurrence are assessed. Where available, data on the pathogenesis and management of recurrent **glomerulonephritis** is also presented. The typical features of recurrent **glomerulonephritis** are those of nephritis involving the native kidney, including proteinuria (protein in the urine), hematuria (blood in the urine), and deterioration in renal function. When the diagnosis of recurrence is suspected, renal biopsy is essential. The author discusses IgA nephropathy and Henoch Schonlein purpura; antineutrophil cytoplasmic antibody associated vasculitis, Wegener's granulomatosis, microscopic polyangiitis, and idiopathic necrotizing crescentic **glomerulonephritis;** anti GBM disease; hemolytic uremic syndrome (HUS); focal and segmental glomerulosclerosis; membranous **glomerulonephritis;** mesangiocapillary **glomerulonephritis;** lupus nephritis; systemic sclerosis and scleroderma; and fibrillary **glomerulonephritis** and immunotactoid **glomerulonephritis.** Strong data have emerged on patterns of recurrence, risk factors for recurrence, and the implications for patient and graft outcomes after recurrence of the most common glomerulopathies. However, data available on recurrence of the less common nephropathies are inadequate and make treatment and prevention more difficult. 1 figure. 1 table. 60 references.

- **Idiopathic Glomerulonephritis: Is It IgA Nephropathy?**

  Source: ANNA Journal. 20(2): 127-132, 153. April 1993.

  Summary: Berger's disease or IgA nephropathy is a common form of **glomerulonephritis** that falls under the broad diagnostic category of primary **glomerulonephritis.** This article discusses the differential diagnosis of idiopathic **glomerulonephritis.** Topics include a description and definition of IgA nephropathy, the histology and clinical presentation of IgA nephropathy, the role of humoral immunity plays in immunologic-related **glomerulonephritis,** the pathophysiology of the immune system and glomerular injury in IgA nephropathy, and the treatment and prognosis of IgA nephropathy. The focus throughout is on the role of nephrology nursing in the care of the patient with IgA nephropathy. Continuing education credit is available for this article. 2 figures. 2 tables. 31 references. (AA-M).

- **Outcomes Research in Glomerulonephritis**

  Source: Seminars in Nephrology. 23(4): 340-354. July 2003.

  Summary: Glomerulonephritis remains the second or third most common primary renal (kidney) disease type to progress to end stage renal disease (ESRD). This disease type is particularly important because its focus is limited to the kidney and its reversal or stabilization ensures a return to a normal quality of life for the individual. Also, because its highest incidence rate is in childhood and early adulthood, the implications of effective therapy in terms of preventing ESRD costs benefits not only the individual but also society. In this article, the author describes three of the most common variants that progress to ESRD: membranous nephropathy, focal segmental glomerulosclerosis, and IgA nephropathy. Together, these three diseases represent approximately 80 percent of the primary glomerular diseases known to progress to ESRD. The author discusses the outcome studies published over the past decade in these disorders that permit the best insight into specific immunotherapy. The data is presented in an evidence-based model so the reader can appreciate the strengths or weaknesses of the therapies discussed. A framework for clinical management is also provided. 1 figure. 6 tables. 59 references.

- **Fundamental Concepts and Immunosuppressive Treatment in the Various Forms of Glomerulonephritis**

  Source: Renal Failure. 17(1): 1-11. 1995.

  Contact: Available from Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016. (212) 696-9000.

  Summary: In this article, the authors address the still controversial use of immunosuppressive treatment in **glomerulonephritis** (GN). The authors describe eight histologic expressions of primary GN that can be distinguished and ordered in terms of severity of symptoms and prognosis: endocapillary GN, minimal change GN, mesangioproliferative GN, membranous GM, focal-sclerosing GN, membranoproliferative GN, focal-necrotizing GN, and rapidly progressive GN. The authors note that agreement exists only to the extent that immunosuppression is not required in endocapillary GN, although it is recommended in the other extreme of rapidly progressive GN. They stress that renal biopsy is required to identify the type of GN so as to establish the specific immunosuppressive concept with different intensity and duration of treatment. Immunosuppression can reduce urinary protein excretion and improve deterioration of renal function; however, the proportion of patients responding varies with and depends on the different forms of GN. 1 table. 88 references.

- **Risk of Renal Allograft Loss from Recurrent Glomerulonephritis**

  Source: New England Journal of Medicine. 347(2): 103-109. July 11, 2002.

  Summary: Recurrent **glomerulonephritis** (inflammation of the filtering units of the kidney) is a known cause of renal allograft (a transplanted kidney) loss; however, the incidence of this complication is poorly defined. This article reports on a study that determined the incidence, timing, and relative importance of allograft loss due to the recurrence of **glomerulonephritis.** A total of 1,505 patients with biopsy-proven **glomerulonephritis** received a primary renal transplant in Australia from 1988 through 1997. Allograft loss due to the recurrence of **glomerulonephritis** occurred in 52 recipients, with a 10 year incidence of 8.4 percent. The type of **glomerulonephritis,** the sex of the recipient, and the peak level of panel-reactive antibodies were independent predictors of the risk of recurrence. Recurrence was the third most frequent cause of allograft loss at 10 years, after chronic rejection and death with a functioning allograft. Despite the effect of recurrence the overall 10 year incidence of allograft loss was similar among transplant recipients with **glomerulonephritis** and among those with other causes of renal failure. The authors conclude that no risk factors for recurrence were identified that warrant altering the approach to transplantation. 2 figures. 3 tables. 23 references.

- **Identifying Poststreptococcal Glomerulonephritis**

  Source: Nurse Practitioner. 26(8): 34, 37-38, 40-42, 44, 47. August 2001.

  Contact: Available from Nurse Practitioner. Circulation Department, P.O. Box 5053, Brentwood, TN 37024-5053. (800) 490-6580. Fax (615) 377-0525.

  Summary: Speedy treatment (with antibiotics) of strep throat (group A beta-hemolytic streptococcal, or GAS, tonsillopharyngitis, specifically) prevents suppurative complications and rheumatic fever; however, timely therapy does not prevent acute poststreptococcal **glomerulonephritis** (inflammation of the filtering tubules of the kidneys). Acute poststreptococcal **glomerulonephritis** (APG) is the most common form of postinfectious **glomerulonephritis** and a leading cause of acute and chronic renal

(kidney) failure in childhood. This article discusses the clinical presentation, diagnostic workup, treatment, and prevention of poststreptococcal **glomerulonephritis** in adults and children in the primary care setting. The average risk of developing APG after GAS infection is 15 percent. In 90 percent of cases, the typical symptoms are acute nephritic syndrome: hematuria (blood in the urine), mild proteinuria (protein in the urine), edema (fluid accumulation), and hypertension (high blood pressure). Other symptoms include nausea, vomiting, malaise, anorexia (lack of appetite), back pain, and abdominal discomfort. APG development is probably dependent on host factors and organism characteristics. The bacteria's virulence may increase or decrease with spread. Diagnosis is usually based on clinical presentation and laboratory tests; renal biopsy is rarely necessary for diagnosis. Resolution of this inflammatory process usually occurs spontaneously and completely in children; however, adults may have residual renal impairment. Therapy goals include controlling blood pressure and treating volume overload (the extra fluids); the drug furosemide usually provides prompt diuresis and reduced blood pressure. The clinician should treat infection in carrier patients and close contacts. Prevention may play a role in limiting the spread of nephritogenic (causing kidney disease) streptococcal strains and is valuable during epidemics for at-risk populations. Timely treatment of streptococcal infection may limit the time of antigen availability and immune complex formation and potentially decrease acute **glomerulonephritis** severity. The authors concludes that awareness of this complication of GAS infection is the key to helping streamline diagnosis, resulting in a more timely and cost effective treatment. 2 figures. 27 references.

- **Mesangioproliferative Glomerulonephritis with IgM Deposition: Clinical Characteristics and Outcome**

  Source: Renal Failure. 22(4): 445-457. 2000.

  Contact: Available from Marcel Dekker Journals. P.O. Box 5017, Monticello, NY 12701-5176. (212) 696-9000.

  Summary: The significance of IgM on immunofluorescence in renal biopsy specimens remains unclear. This article reports on a retrospective case study conducted to define the clinical features, response to therapy, and outcome of patients with mesangioproliferative **glomerulonephritis** (MGN) with diffuse IgM deposition. Of 1,919 native renal (kidney) biopsies performed over a 10 year period, 139 (7.2 percent) had light microscopic features of MGN and manifested IgM as the dominant immunoglobulin. When exclusion criteria were applied, 60 patients (3.1 percent) remained. Followup data were available for 54 of these cases, featuring patients with a mean age of 26.5 years (range 1.7 to 63 years). Mean followup period was 7.4 years (range 4.7 to 22.2 years). Patients presented with nephrotic syndrome (41 percent), asymptomatic proteinuria (26 percent), macroscopic hematuria (blood in the urine, 18 percent of the patients), and isolated microscopic hematuria (15 percent). Twenty-one percent of patients were hypertensive (had high blood pressure) at presentation. Creatinine was initially less than 120 (mol per L) in all but one patient. Only four patients (7.4 percent), all nephrotic, suffered a decline in renal function despite treatment; all four developed end stage renal disease (ESRD) after a mean of 5.6 years. Protein excretion rate fell into the normal range in 63 percent of those receiving steroids, with 82 percent becoming steroid dependent. Of those treated with cyclosporine (48 percent) or cyclophosphamide (52 percent), only 9.5 percent and 14.5 percent, respectively, remained in prolonged remission after discontinuing treatment. 4 figures. 3 tables. 24 references.

- **Membranoproliferative Glomerulonephritis in Childhood: Factors Affecting Prognosis**

  Source: International Urology and Nephrology. 29(6): 711-716. 1997.

  Contact: Available from VSP, P.O. Box 346, 3700 AH Zeist, The Netherlands. 31306925790. Fax 31306932081. E-mail: vsppub@compuserve.com.

  Summary: This article describes a study undertaken to identify the factors affecting prognosis in membranoproliferative **glomerulonephritis** (MPGN) in childhood. MPGN is a distinctive form of chronic **glomerulonephritis** with a 15 to 67 percent progression to end stage renal disease (ESRD). The study examined 64 male and 32 female pediatric patients diagnosed with MPGN from 1975 to 1995. Their age range was 2 to 17 years. All patients initially received oral corticosteroid therapy. Remission was achieved in 22.9 percent. The unresponsive 77.1 percent received either cyclophosphamide or pulse methylprednisolone, and 25.4 percent and 50.0 percent of these patients entered complete remission, respectively. The overall 1 year renal survivals of the MPGN patients were 90.1 percent, and 5 year and 10 year survival rates were 81.9 percent and 61 percent, respectively. At multivariate analysis, the factors affecting renal prognosis were hematuria (blood in the urine) at presentation and low hemoglobin values. The article suggests that more aggressive immunosuppressive therapy should in instituted in patients unresponsive to steroids and that the aforementioned risk factors are higher for the development of renal failure. 2 figures. 2 tables. 8 references.

- **Membranous Glomerulonephritis**

  Source: JASN. Journal of the American Society of Nephrology. 8(4): 664-674. April 1997.

  Summary: This article describes membranous **glomerulonephritis** (MGN), the most common primary cause of the nephrotic syndrome, accounting for about 20 percent of cases. It is characterized by basement membrane thickening and subepithelial immune deposits without cellular proliferation or infiltration. MGN is a classic instance of immune complex deposition disease and complement activation. The author explores the etiology and incidence, pathology, pathogenesis, clinical features, diagnosis and differential diagnosis, natural history, and treatment of MGN. The author notes that promising strategies to monitor the progress of MGN have emerged from animal models. Although steroid therapy, at least by the oral route, has been disappointing, a consensus is emerging that cytotoxic therapy has significant benefit in a subset of patients. Risk stratification is proposed as a rational approach to therapy for MGN. However, it remains unknown whether this approach is superior to early treatment of all (or most) patients with nephrotic syndrome. Secondary MGN often resolves after the underlying disease is reversed (malignancy, drug discontinuation, spontaneous or interferon-induced remission of hepatitis B). It is also important to rule out underlying diseases such as cancer and hepatitis before treating apparently idiopathic MGN with immunosuppression. 3 figures. 45 references. (AA-M).

- **Chronic Glomerulonephritis in Childhood: Membranoproliferative Glomerulonephritis, Henoch-Schonlein Purpura Nephritis, and IgA Nephropathy**

  Source: Pediatric Clinics of North America. 42(6): 1487-1503. December 1995.

  Contact: Available from W.B. Saunders Company, Periodicals Fulfillment, 6277 Sea Harbor Drive, Orlando, FL 32887. (800) 654-2452.

  Summary: This article reviews various presentations of common childhood glomerulonephritides and provides an approach to management and potential therapy.

The chronic glomerulonephritides that lead to permanent loss of renal function may present with an acute nephritic syndrome, nephrotic syndrome, or asymptomatic hematuria and proteinuria. The author covers membranoproliferative **glomerulonephritis,** Henoch-Schonlein purpura nephritis, and IgA nephropathy. For each, the clinical, laboratory, and pathologic features are outlined and management and therapeutic strategies proposed. 5 figures. 60 references. (AA-M).

- **Treatment of Glomerulonephritis in the Elderly**

  Source: Seminars in Nephrology. 20(3): 256-264. May 2000.

  Contact: Available from W.B. Saunders Company. Periodicals Department. 6277 Sea Harbor Drive, Orlando, FL 32887-4800. (800) 654-2452.

  Summary: With the increasing use of renal biopsy in the elderly, **glomerulonephritis** (inflammation of the kidney glomerulus) is now known to be a common finding. This article reviews the treatment options for **glomerulonephritis** in the elderly. In general, the elderly present similarly to the younger population, although there are marked changes in the kidney related to aging which may be exaggerated in the patient with concomitant hypertension and more advanced atherosclerotic (cardiovascular) disease. Whereas membranous **glomerulonephritis** and minimal change disease are common in younger and older adults, primary amyloidosis and crescentic **glomerulonephritis** are more common in the elderly. Other glomerulonephritides such as focal segmental glomerulosclerosis or IgA nephropathy are very uncommon in the elderly. Because of the serious consequences of the nephrotic syndrome and acute and chronic renal failure (ARF and CRF, respectively) in the elderly, aggressive treatment with immunosuppression should not be withheld. The authors caution that elderly patients must be monitored carefully, as there is presumed greater morbidity and mortality from such treatment in this population. In all elderly patients with proteinuria, ACE inhibitors should be administered if renal function is not too severely impaired. Diuretics should be given to enhance the antiproteinuric effect of ACE inhibition and to control blood pressure and edema. 57 references.

Federally Funded Research on Glomerulonephritis

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

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

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[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).

animals or simulated models to explore glomerulonephritis. The following is typical of the type of information found when searching the CRISP database for glomerulonephritis:

- **Project Title: AGBD T CELL DEPENDENT MECHANISMS OF GLOMERULONEPHRITIS**

  Principal Investigator & Institution: Mayadas-Norton, Tanya N.; Associate Professor; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 20-AUG-1996; Project End 30-NOV-2006

  Summary: There is compelling evidence that cellular immunity plays a role in the pathogenesis of **glomerulonephritis** (GN). Our recent data indicate that both alpha/beta and the less common gamma/delta T cells, are required for the development of experimental GN in mice. Mice deficient in either of these two T cell subsets developed minimal glomerular injury and interstitial macrophage accumulation in an anti-glomerular basement membrane (GBM) model of GN. This demonstrates that both T cell subsets are required for the progression of disease and is the foundation of our hypothesis that regulatory interactions between alpha/beta and gamma/delta T cells culminates in the production of cytokines, that regulate macrophages, the immune effector cells in GN. The effector phase of specific immunity requires the recruitment of T cells to sites of antigen exposure. Members of the selectin family of leukocyte adhesion receptors are important in alpha/beta and gamma/delta T cell interactions with endothelial cells, in vitro. In vivo, our studies during the current funding period revealed a hitherto unexpected complexity for the role of selectins in GN. Mice deficient in P-selectin, had increased indices of glomerular injury and leukocyte accumulation following experimental GN. This was associated with an absence of endothelial derived soluble P-selectin, which is anti- inflammatory in vitro. On the other hand, L- or E-selectin deficient mice had a significant reduction in disease and in renal alpha/beta T cell and macrophage accumulation suggesting a role for selectins in alpha/beta T cell recruitment/function. We will critically test the hypothesis that L-selectin and the selectin ligands on alpha/beta T cells play a dominant role in T cell recruitment and that soluble P-selectin is a potent stop signal for continued leukocyte influx in GN. Like alpha/beta T cells, gamma/delta T cells may also be recruited into the kidney in GN, although this is not known and will be directly examined in this application. The specific aims are to I) Examine the determinants of alpha/beta and gamma/delta T cell recruitment, and functional cooperation in GN, II) Determine the role of alpha/beta and gamma/delta T cell derived effector cytokines in GN, and III) Examine the contribution of selectins in alpha/beta T cell mediated glomerular injury. The unique advantages of knock-out mice, transgenic mice with green fluorescent protein (GFP) labelled alpha/beta and gamma/delta T cells and adoptive transfer experiments will be emphasized in these studies. The information gained from these studies will help delineate the T cell subpopulations, and mechanisms that downregulate injurious T cell mediated responses in GN and may thus define new targets for therapeutic intervention in the treatment of human glomerulonephritides.

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

- **Project Title: AGE-RELATED MACULOPATHY: COMPLEMENT-MEDIATED EVENTS**

  Principal Investigator & Institution: Johnson, Lincoln V.; Neuroscience Research Institute; University of California Santa Barbara 3227 Cheadle Hall Santa Barbara, Ca 93106

  Timing: Fiscal Year 2002; Project Start 01-AUG-1996; Project End 31-MAR-2006

Summary: (provided by applicant): The objective of the proposed studies is to test the hypothesis that the process of drusen formation is stimulated by complement-mediated inflammatory events involving retinal pigmented epithelial (RPE) cells. Drusen are extracellular deposits that form between the RPE and Bruch's membrane, and are a significant risk factor for age-related macular degeneration (AMD). In AMD, functional compromise and ultimately death of RPE cells as a consequence of drusen formation is thought to lead to secondary degeneration of retinal photoreceptor cells and visual loss. Studies of age-related human diseases that, like AMD, involve cellular degeneration and the formation of insoluble deposits (e.g., Alzheimer's disease, atherosclerosis and kidney glomerulonephritis) now implicate complement activation and inflammatory events as key elements in disease processes. Data that we generated during the prior application period strongly suggest that complement activation also plays an important role in the formation of ocular drusen. We observed that terminal complement complexes and complement regulatory molecules are present in drusen, as are molecules with potential complement-activating properties. Furthermore, our observations show that RPE cells overlying drusen exhibit a compromised molecular phenotype that is consistent with a well-characterized cellular response to complement attack. Thus, these observations suggest an AMD disease process that is consistent with that of other age-related human diseases. A process that involves a primary pathogenic or age-related stimulus, the effects of which are exacerbated by localized, self-perpetuating, complement-mediated tissue destruction and inflammatory sequelae that persist over decades. The studies proposed here will examine the hypothesis that complement-mediated events contribute both to the process of drusen formation, and to the functional compromise of drusen-associated RPE cells. The studies will target the following specific aims: (1) To determine if RPE cell compromise is the result of complement-mediated attack, (2) To characterize the nature of the complement-mediated processes involved in drusen formation, and (3) To examine RPE cell responses to complement attack utilizing an in vitro model system.

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

- **Project Title: ANCA GLOMERULONEPHRITIS: FROM MOLECULES TO MAN**

  Principal Investigator & Institution: Falk, Ronald J.; Chief of Nephrology and Hypertension; Medicine; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

  Timing: Fiscal Year 2002; Project Start 01-SEP-2000; Project End 31-AUG-2005

  Summary: Our program project consists of 5 projects and two cores focusing on anti-neutrophil cytoplasmic autoantibody (ANCA) necrotizing and crescentic **glomerulonephritis** (GN) and small vessel vasculitis (SVV). The scope of the investigation and the diversity of the investigators allow for an integrated evaluation of basic molecular and clinical immunological and epidemiological studies pertaining to both anti-myeloperoxidase (MPO) and proteinase 3 (PR3) autoimmune response. Project 1 considers the derivation of murine anti-MPO autoantibodies with respect to relative contributions of antibody heavy and light chains and somatic mutations within them using basic molecular immunologic techniques and transgenic mice. In parallel, Project 2 investigates the human ANCA autoimmune response with respect to the contribution of light and heavy chains and somatic mutations within them, and the fine specificity of specific epitopes responsible for the generation of ANCA during disease onset or relapse. A novel paradigm of autoimmune response with respect to the contribution of light and heavy chains and somatic mutations within them, and the fine specificity of specific epitopes considered; that is, that the ANCA immune response is directed not only to MPO or PR3, but also to peptides complimentary in translation to MPO or PR3.

Project 3 tests the hypothesis that ANCA directly participate in the pathogenesis of the ANCA immune response, determines the mechanism by which ANCA activate neutrophils and monocytes, delineates the mechanism by which the ANCA antigens MPO and PR3 directly induce vascular damage. Project 4 studies in vitro development of ANCA GN using animal models in which circulating anti-myeloperoxidase antibodies conspire to produce to GN. Project 5 uses state of t he art epidemiological techniques in a large population of ANCA GN patients to ascertain those environmental factors that predispose to the development and exacerbation of the ANCA immune response. In particular the role of silica exposure in the induction of ANCA GN will be tested in animal studies as well as in man. These investigations are tightly interwoven using state of the art techniques. Together, these sharpy focused and integrated projects will shed light on the central question of the overall project. What causes ANCA GN? If we knew the causes of this most aggressive form of glomerular injury targeted therapy would be in the offing. The program involves investigators from the Department of Medicine, Pathology, Microbiology and Immunology in the School of Medicine, the Department of Epidemiology in the School of Public Health, the Department of Medicinal Chemistry in the School of Pharmacy, and the National Institute of Environmental Health Sciences.

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

- **Project Title: ANTIBODY MEDIATED GLOMERULAR INJURY**

  Principal Investigator & Institution: Salant, David J.; Professor; Boston Medical Center Gambro Bldg, 2Nd Fl, 660 Harrison Ave, Ste a Boston, Ma 02118

  Timing: Fiscal Year 2002; Project Start 01-JUL-1982; Project End 31-MAR-2005

  Summary: The primary goals of this proposal are to define the structural biology of the podocyte and determine its role in glomerular permselectivity by an analysis of models of antibody- mediated glomerular injury. There are three aims. 1. Determine if and how nephrin, a major component of the podocyte slit diaphragm, is linked to the podocyte cytoskeleton. Preliminary findings suggest that nephrin may be anchored to the actin cytoskeleton, either directly or through various "nephrin- associated proteins". Extracts of isolated rat glomerular cells will be prepared under defined conditions. High molecular weight complexes of nephrin will be isolated by co-immunoprecipitation or sucrose density ultracentrifugation and analyzed for interacting proteins using tandem mass spectroscopy. If putative nephrin-associated proteins are identified, heterologous expression, co-immunoprecipitation and blot overlay techniques will be used to confirm that they are able to bind the cytoplasmic tail of nephrin. An in vitro actin co-sedimentation system will be used to determine if nephrin or its partners are able to bind to actin. 2. Investigate how the slit diaphragm and its link to the cytoskeleton might be altered in models of antibody-mediated proteinuria. This aim derives from observations that monoclonal antibody (mAb) 5-1-6 directly targets an extracellular epitope of nephrin in the slit diaphragm and causes severe proteinuria. Simultaneously, nephrin redistributes after cross-linking by mAb 5-1-6 and appears to be targeted to a lysosomal compartment and degraded. Nephrin also redistributes after complement-mediated podocyte injury in the passive Heymann nephritis (PHN) model of membranous nephropathy, in which the onset of proteinuria is associated with foot process effacement, collapse of the actin cytoskeleton and dislocation of the slit diaphragm. These two models will be compared and contrasted to determine if there is an alteration in nephrin association with the cytoskeleton and/or putative nephrin-associated proteins, and disruption of slit diaphragm architecture. Immunochemistry, immunohistology and electron microscopy will be used to analyze glomeruli from rats

during the development of, and where relevant, during recovery of proteinuria. 3. Define the effect of mAb 5-1-6 on the fate of nephrin and putative nephrin associated proteins and their link to actin. Standard cell biological techniques will be employed to study the effect of mAb 5-1-6 on nephrin synthesis, cell surface expression, shedding, endocytosis and degradation. In the absence of a well-differentiated podocyte cell line, studies will be done with freshly dispersed glomerular cells using metabolic and cell surface labeling techniques combined with immunoprecipitation and western blotting. The normal state of phosphorylation of soluble and actin-bound fractions of nephrin and associated proteins, as well as the effect of mAb 5-1-6 will also be determined.

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- **Project Title: ANTIGEN DRIVEN SELECTION/TOLERANCE: AUTOIMMUNITY TO DNA**

  Principal Investigator & Institution: Marion, Tony N.; Professor; Molecular Sciences; University of Tennessee Health Sci Ctr Memphis, Tn 38163

  Timing: Fiscal Year 2002; Project Start 01-JUL-1988; Project End 31-MAY-2005

  Summary: (Adapted from the Investigator's abstract): Systemic lupus erythematosus is a systemic autoimmune disease in humans and genetically predisposed mice. Antibodies to a variety of cellular antigens, mostly nuclear in origin, have been detected in lupus sera from mice and humans; however, the autoantibody for which there is the most compelling evidence for pathological relevance is antibody to DNA. Anti-DNA antibodies deposit in kidneys either as immune complexes or by binding directly to glomerular structures and initiate **glomerulonephritis.** The immunological basis for the generation of anti-DNA autoantibody in mice and humans has been difficult to elucidate. The goal of the applicant's research on "Antigen Driven Selection and Tolerance in Autoimmunity to DNA" continues to be directed toward understanding how autoimmunity to DNA is initiated and sustained at the level of individual DNA-specific B cells in autoimmune (NZB x NZW) F1 mice. The applicant's research efforts since the last competitive review of this project have continued to support the hypothesis that autoimmunity to DNA is both initiated and sustained as a clonally selective, antigenic-specific immune response to DNA most likely in the form of DNA-protein complexes. The research has continued to focus on experiments to understand how the specificity and specificity maturation of the autoimmune anti-DNA antibody response within individual (NZB x NZW) F1 mice and the DNA-peptide induced immune anti-DNA antibody response in normal mice proceed. The results have provided new information about B cell selection in the autoimmune response to DNA and the V region structures necessary for that selection to occur. In the applicant's continuing research efforts to understand how autoimmunity to DNA is initiated, they will test the hypothesis that autoimmunity to DNA is initiated by antigen-specific B cell stimulation in the absence of peripheral B cell tolerance induced by extracellular DNA or nucleosomes. The specific experimental aims to be pursued in the research proposed will be to determine what role, if any, germinal centers play in the specificity maturation that generates high avidity autoantibodies to native DNA. Proposed experiments will also determine the role of soluble DNA or nucleosomes in maintaining immunological tolerance to DNA. The experimental systems designed to complete the proposed research will include the use of (NZB x NZW) F1 mice transgenic for expression of anti-DNA antibodies. These mice have an interesting autoimmune phenotype that make them highly suited for experiments to test the hypothesis that autoimmunity to DNA in (NZB x NZW) F1 mice derives from antigen-selective B cell stimulation in the absence of effective peripheral tolerance.

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

- **Project Title: ANTI-MYELOPEROXIDASE AUTOANTIBODY RESPONSE**

  Principal Investigator & Institution: Nachman, Patrick H.; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

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

  Summary: An anti-neutrophil cytoplasmic antibodies (ANCA), directed toward myeloperoxidase (MPO) and proteinase 3 (PR3), are detected in the majority of patients with pauci-immune necrotizing **glomerulonephritis** and small vessel vasculitis. The factors involved in the generation of these autoantibodies remain unknown. We hypothesize that the low incidence of ANCA and their associated diseases is in part due to requirements for particular V region gene recombinations, specific somatic mutations, or both and that the expression of anti-MP antibodies in mice is the result of a breakdown in tolerance. The study of anti-MPO antibodies derived from unimmunized SCG/KJ mice revealed a restriction in Vk gene use, and provides evidence that MPO is a driving antigen in the anti-MPO response. The two specific aims of this project are to (1) assess the affinity of murine anti-MPO autoantibodies, and (2) study the regulation of the anti-MPO response in mice. Aim 1 will be pursued by co-expressing anti-MPO derived H or L chains with a variety of non-anti-MPO-derived chains, and by introducing of removing specific somatic mutations using site-directed mutagenesis. The specificity and avidity of the resulting antibodies will be measured by ELISA and Biosensor based techniques. Aim 2 will be approached by the generation of mice transgenic for anti- MPO-light chain only, heavy chain only, and both. This approach will allow to study at which level of their maturation anti-MPO B cells are regulated. These two aims will help fill an important gap in our current knowledge of these mechanisms involved in the generation and regulation of the anti- MPO autoimmune responses.

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

- **Project Title: AUGEMENTING PEPTIDE-SPECIFIC TOLERANCE IN IMMUNENEPHRIT***

  Principal Investigator & Institution: Singh, Ram R.; Associate Professor; Internal Medicine; University of Cincinnati 2624 Clifton Ave Cincinnati, Oh 45221

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

  Summary: (provided by applicant): Induction of immune tolerance to self-antigens can ameliorate systemic autoimmune diseases such as lupus, anti-glomerular basement membrane **glomerulonephritis** and Goodpasture's syndrome in experimental models. Current approaches of autoantigen-specific Th cell tolerance induction, however, are cumbersome and expensive, as they require multiple intravenous injections of large doses of antigenic peptides; such approaches usually confer a limited and short-lasting therapeutic benefit in systemic autoimmune diseases. To overcome these limitations, we will develop a minigene approach of in vivo peptide delivery. Because antigens delivered as plasmid DNA tend to be 'immunogenic', and successful therapy depends on tolerizing Th cells, this application will explore how gene delivery of antigens can be modified to induce tolerance in CD4+ Th cells in vivo. Our hypothesis is that minigenes that encode self-peptides can be administered in ways that induce tolerance in peptide-specific autoreactive Th cells. Specifically, we will test if the minigenes that encode self-peptides specifically tolerize peptide-specific, MHC class II-restricted CD4+ Th cells that could otherwise provide help for the production of autoantibodies, if they: a) are

administered orally or i.v. in high doses; b) encode multiple tandem repeats of a single epitope; or c) encode multiple tandem repeats of multiple epitopes. We will explore these possibilities using a mouse model of immune-mediated **glomerulonephritis** and peptides derived from the VH region of anti-DNA mAbs or nucleosome core histones. Tolerance induction in autoreactive T helper cells may ameliorate autoantibody-mediated diseases such as lupus, anti-glomerular basement membrane **glomerulonephritis** and Goodpasture's syndrome. The methods developed for the induction of T cell tolerance may have implications for the vaccination and treatment of various immune-mediated disorders.

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- **Project Title: AUTOMATED, QUANTITATIVE IMMUNOFLUORESCENT ASSAY**

  Principal Investigator & Institution: Newton, Kenneth R.; Hyperion, Inc. 14100 Sw 136Th St Miami, Fl 33186

  Timing: Fiscal Year 2003; Project Start 01-JUL-2000; Project End 30-JUN-2005

  Summary: (provided by applicant): Diagnosis of auto-immune and connective tissue diseases such as Systemic Lupus Erythematosus, Sjorgren syndrome and scleroderma often makes use of an Immunofluorescent assay (IFA) for antinuclear antibodies (ANA). More detailed diagnostic support may also utilize an IFA test for double-stranded DNA (dsDNA). IFA tests detecting Anti-Neutrophil Cytoplasmic Autoantibodies (ANCA) are diagnostic for systemic necrotizing vasculitis and **glomerulonephritis.** All these IFA tests require significant laboratory preparation time from highly trained technicians using current, manual techniques. The VisiQuant system developed as a prototype in Phase I, combined with Hyperion's Hyprep automated assay preparation system will automate both preparation and reading of the IFA tests, achieving significant cost savings and potential error reduction. During the Phase II project period, an updated VisiQuant Microscope will be introduced along with improved ANA assay and preparation procedure. The assay will be improved by applying results of a study of assay parameters and conditions. The Microscope will be upgraded by incorporating engineering enhancements to the optics and electronics, including features to optimize the joint operation of the Microscope with the HyPrep, and software improvements to the fluorescence intensity algorithm. New test kits for dsDNA based on Crithidia luciliae and for ANCA will be developed, tested and brought to market. Development work in automated image classification will lead to a complementary product that finds the best match to each sample image from a standard ANA image pattern library. Further development of the image classification software will be done based on input from the consultants. This will lead to an advanced Image Classification system to be brought to market at the end of the Phase II period. Image classification to support ANCA test will be started but is not expected to be ready for market until after completion of this project. These developments will result in Hyperion obtaining more than 18% share of the global market for autoimmune IFA based IVD tests by 2010. The development team includes personnel with many years of experience in dye chemistry, immunology in vitro device development, instrument development and image processing.

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

- **Project Title: CELLULAR REGULATION OF PROSTAGLANDIN SYNTHESIS**

  Principal Investigator & Institution: Sorokin, Andrey; Medicine; Medical College of Wisconsin Po Box26509 Milwaukee, Wi 532260509

Timing: Fiscal Year 2002; Project Start 01-JUL-1989; Project End 30-JUN-2004

Summary: (Adapted from Investigator's Abstract): This is a competitive renewal of a grant, which has for several years examined the mechanisms of regulation of prostaglandin endoperoxide synthase (PGHS). Glomerular mesangial cells (GMC) play a key role in the genesis of several glomerular diseases such as glomerulosclerosis and proliferative **glomerulonephritis,** which are characterized by GMC injury and proliferation. Proinflammatory agents can induce cellular synthesis of eicosanoids, namely oxygenated products of arachidonic acid, that can regulate GMC matrix synthesis and proliferation. This application examines the intracellular signaling mechanisms regulating the expression and actions of PGHS, which catalyses prostaglandin production from arachidonic acid. PGHS is of particular interest, being the principal target of NSAIDS. A combination of in vitro and in vivo studies will be used to test the hypothesis that PGHS-2 expression is regulated by mitogen activated protein kinases (MAPKs), and that over expression of PGHS-2 has anti-apoptotic effects mediated through differential gene expression. Three Specific Aims have been outlined. Specific Aim 1 will evaluate the hypothesis that activation of MAPKs represents the convergence point of divergent stimuli of PGHS-2 expression, and this is negatively regulated by dual-specificity phosphatases. Here, the effects on PGHS-2 expression after adenovirus mediated transfer of genes encoding wild type and mutant ERK, JNK and p38 MAPKs, and dual-specificity phosphatases will be studied in kidney cells. Specific Aim 2 will examine the hypothesis that PGHS-2 expression leads to anti-apoptotic effects in several cell types. Here the effect of adenovirus-mediated transfer of PGHS-2 gene into primary cells on apoptotic parameters will be studied. The mechanism of the anti-apoptotic effect will be studied by identifying genes controlled by PGHS-2 expression using cDNA micro-arrays. In Specific Aim 3, the in vivo relevance of PGHS-2 expression and relation to the MAPK cascade will be evaluated using two rat models of **glomerulonephritis** (GN). Here, PGHS-2 expression and prostaglandin production will be assessed in rat glomeruli and correlated with MAPK activation and the histopathology of GN at defined time points of the disease.

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- **Project Title: CELLULAR SIGNALING IN RENAL PATHOPHYSIOLOGY**

  Principal Investigator & Institution: Grande, Joseph Peter.; Professor; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2004; Project Start 01-JAN-1975; Project End 31-DEC-2008

  Summary: (provided by applicant): Progressive renal disease is characterized by the proliferation of glomerular and interstitial cells, the influx and activation of circulating inflammatory cells, and the excessive production and deposition of extracellular matrix macromolecules. Previous studies supported by this grant have demonstrated the importance of the cAMP-PKA pathway in regulation of mesangial cell (MC) proliferation and have identified a potential role of cyclic 3'-5' nucleotide phosphodiesterase (PDE) isozymes as therapeutic agents to treat acute renal injury. However, it is not known whether PDE inhibitors will prevent the development or slow the progression of chronic renal disease. The central hypothesis to be tested is that cAMP isozyme-speciflc PDE inhibitors, through negative crosstalk with critical mitogenic, inflammatory, and matrix signaling pathways, are capable of preventing the onset and development of progressive renal disease. Recent studies have provided evidence that these critical pathways are regulated through interactions between cAMP-PKA and TGF-beta1 signaling. Initial studies will define the mechanism by which cAMP induces TGF-beta expression and will delineate pathways through which cAMP and

TGF-beta1 interact to suppress MC mitogenesis (Specific Aim 1). In Specific Aim 2, the hypothesis that PDE4 inhibitors suppress MCP-1 expression through inhibition of TGF-beta-stimulated MAPK pathway(s) leading to down regulation of Nf-KB will be tested. In Specific Aim 3, the role of the cAMP-PKA pathway in collagen IV production and catabolism will be defined. The hypothesis that cAMP agonists are capable of "uncoupling" the cicatricial response to elevated TGF-beta1 levels through down regulation of the ERK and/or p38 pathways will be tested. The in vivo relevance of these studies to define the role of the cAMP-PKA pathway in MC proliferation, production of inflammatory mediators, and matrix production will be established in the chronic Thy 1 model (Specific Aim 4). Through careful semi-quantitative histopathologic analysis and identification of markers of acute and chronic renal injury, it will be possible to identify maladaptive signaling pathways that are associated with the transformation of acute injury into chronic, progressive renal disease and to define the role of PDE inhibitors in preventing or ameliorating this process. These studies will reveal insights into basic mechanisms underlying progressive renal disease and may provide the rational basis for the design of newer, more specific pharmacotherapeutic agents to treat chronic renal disease.

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- **Project Title: CHARACTERIZATION OF A NEW MOUSE MODEL FOR LUPUS**

  Principal Investigator & Institution: Lim, Bing; Associate Professor; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

  Timing: Fiscal Year 2003; Project Start 19-SEP-2003; Project End 31-DEC-2007

  Summary: (provided by applicant): The central goal of this proposal is to exploit the use of a new mutant murine strain to advance the understanding of autoimmune disorders. A new line of mice has been derived in which animals develop a severe generalized lymphadenopathy together with autoimmune **glomerulonephritis** and hyperimmunoglobulinemia. Significantly, the animals produce auto antibodies against double-stranded DNA and Sm antigen, both of which are specific markers for Systemic Lupus Erythematosus (SLE). Immune function studies showed a combination of severe lymphoid dysfunction and developmental defect not seen in other murine autoimmune disease models. The disease is passed with a Mendelian frequency consistent with a recessive mutation of an autosomal gene. Therefore, the disease arose from a spontaneous mutation of a gene which we have named lag (lymphoproliferative autoimmune glomerulonephropathy). Using chromosomal satellite markers to scan the murine genome, preliminary data indicate that a putative locus for the lag gene is the telomeric end of chromosome 2. This is not a region that has been linked before to autoimmune disease. The goal of this proposal is to exploit this remarkable new murine model to learn about autoimmune disease. In Specific Aim 1, we will map the location of the gene and identify the lag gene by combining positional cloning with a candidate gene approach. In Aim 2 we will characterize the disease process for the lag phenotype and identify the cells causing the disease. In Aim 3 we will examine in detail the effect of the lag mutation on T cell development. In Aim 4 we will investigate how the lag mutation affects T cell function. To support these studies, various TCRxlag transgenic animals will be generated to help the study of lymphocyte development, function and signaling. We anticipate that our proposal to study this murine model carefully will contribute a significant amount of new information for understanding the diverse genetic and molecular bases of autoimmune diseases. The identification of new genes and new pathways may uncover new targets for the development of drugs to suppress the immune system in a specific way, instead of globally. The discovery of new disease

genes may also be very useful in the management, care and diagnosis of the large number of patients with autoimmune diseases.

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- **Project Title: CHROMOSOME 6P AND DEVELOPMENTAL DEFECTS**

  Principal Investigator & Institution: Rosen, Fred S.; Professor of Pediatrics; Cbr Institute for Biomedical Research 800 Huntington Ave Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 01-JUL-1999; Project End 30-JUN-2004

  Summary: Systemic lupus erythematosus (SLE) is an autoimmune disorder which affects over 200,000 women in the USA and it is characterized by anti-nuclear antibodies and a high incidence of **glomerulonephritis.** A major risk factor for SLE is deficiency in early classical pathway complement components C1, C2 or C4. This association presents a paradox because it is not expected that an immune deficiency would result in an autoimmune disease. One explanation is that early complement is involved in maintenance of B cell tolerance and in its absence, self-reactive B cells accumulate in the periphery where they potentially may be activated. The goal of this proposal is to test this hypothesis and it is divided into 3 specific aims: (i) Test the hypothesis that early classical pathway complement components C1, C4 and C3 are directly involved in negative selection of self-reactive B lymphocytes. The approach used in this aim is to breed mice deficient in C1, C4, or C3 with two well established immunoglobulin transgenic models (anti-HEL and anti-dsDNA) and determine if complement is essential in B cell anergy. (ii) The second aim will test the hypothesis that deficiency in classical pathway complement results in increased severity of disease in a well defined mouse model of lupus, i.e. lpr strain. The advantage of this aim is that it will examine the importance of early complement in the autoimmune response to natural lupus antigens such as dsDNA and nuclear proteins. (iii) The third aim will test the hypothesis that impaired self-tolerance in C4null mice can be rescued by protein replacement or gene therapy and if so compare C4A and C4B isotypes. It will also examine the mechanism of C4 in B cell tolerance using a fusion protein of C4d linked to sHEL antigen to uncouple solubilization of immune complexes from targeting of antigen to the lymphoid compartment via C4d. This aim is important as it will establish the feasibility of protein or gene therapy in lupus and clarify our understanding of B cell tolerance.

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- **Project Title: CLUSTERIN AND RENAL INJURY**

  Principal Investigator & Institution: Rosenberg, Mark E.; Professor of Medicine; Medicine; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2002; Project Start 01-MAY-1996; Project End 31-JUL-2005

  Summary: Clusterin is a circulating glycoprotein which is also widely distributed throughout the body and further induced following injury and disease. Deficiency of clusterin impairs immune complex clearance and leads to a progressive glomerulopathy characterized by immune complex deposition in the mesangium. The objective of this grant is to use the model of clusterin deficiency to study the physiologic and pathophysiologic function of clusterin focusing on its role in the pathogenesis of immune complex mediated disease. In SPECIFIC AIM 1, the the role of clusterin in the clearance of immune complexes will be studied by comparing the in vivo clearance of injected immune complexes in clusterin deficient and wild-type mice. The ability of clusterin to facilitate the uptake and degradation of immune complexes by Kupffer and

endothelial cells, components of the liver reticuloendothelial system, will then be tested. Finally the amino acid sequences of clusterin responsible for its interaction with immune complexes will be identified using a panel of peptides derived from the clusterin sequence. In SPECIFIC AIM 2, we will test whether clusterin modulate the interaction of immune complexes with Fc receptors present on mesangial or mononuclear cells. We will first examine the Fc receptor expression in mesangial cells from clusterin deficient and wildtype mice. We will then examine the effect of clusterin on immune complex binding and activation of cultured mesangial cells isolated from clusterin deficient and wild type mice. The effect of clusterin on the immune complex mediated inflammatory response seen in the Arthus reaction will be studied to determine if clusterin deficiency modulates an in vivo Fc receptor dependent immune reaction. In SPECIFIC AIM 3, the ability of clusterin to modify immune complex mediated disease will be tested in two induced models of **glomerulonephritis** (GN), one to in situ formed immune complexes (nephrotoxic serum nephritis) and the other to circulating immune complexes (apoferritin GN). We will then study a genetic model (SLE) of immune complex mediated GN in clusterin deficient and wild type mice. In summary, capitalizing on the striking glomerular pathology of the clusterin knock-out mice, we expect to provide new and fundamental understanding Capitalizing on the striking glomerular pathology of the clusterin knockout mice, we expect to provide new and fundamental understanding of the glomerular accumulation and inflammatory processing of immune complexes. These finding should have wide importance not only to the mechanism of and susceptibility to "immune complex" renal disease, but also for basic pathways of systemic clearance of toxic and/or denatured proteins.

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- **Project Title: COLLAGEN IV CHAINS IN KIDNEY DEVELOPMENT AND FUNCTION**

  Principal Investigator & Institution: Miner, Jeffrey H.; Associate Professor; Medicine; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2002; Project Start 01-FEB-1998; Project End 31-JAN-2004

  Summary: At all stages of their development, cells of the nephrone are coated by a basement membrane, an extracellular matrix containing collagen IV alpha chain trimers laminin alpha-beta-gamma chain trimers, entactin/nidogen, and a heparan sulfate proteoglycan. Components of the basement membrane are involved in glomerular development in the embryo and contribute to glomerular function in the adult. Collagen IV alpha chain trimers form a network which is the most abundant component of all basement membranes. These are six genetically distinct alpha chains that have been identified. Two, the alpha1 and alpha2 chains, are found widely in basement membranes throughout the body. The other four, alpha3-alpha6, exhibit a restricted pattern of accumulation, including a subset of kidney basement membranes: alpha3-alpha5 are found in the glomerular basement membrane (GMB) and in a subset of tubules, while alpha6 is absent from the GBM but is present in Bowman's capsular basement membrane and in some tubules. In humans, the hereditary **glomerulonephritis** known as Alport syndrome is caused my mutation in any one of the collagen alpha3-alpha5 chains, underscoring their importance in GBM function. Several years ago we began an effort to study the structure, regulation, and function of the collagen alpha3- alpha5(IV) chains in mice. This initial effort has culminated in the generation of a knockout mouse with a targeted mutation in the collagen alpha3(IV) gene. These mice exhibit many features of human Alport syndrome, including delayed onset nephritis leading to end stage renal disease, an absence of collagen alpha3-

alpha5(IV) immunoreactivity in the kidney and in the lung, and in a split, thickened GBM with a characteristic "basket weave" appearance. We now propose to use these mice to gain new insights into the mechanism of collagen IV chain assembly and into the pathogenesis of Alport syndrome. We will make cell lines from the mutant mice and use them as a model system for determining which portions of collagen alpha3(IV) are necessary for proper assembly of the collagen alpha3-alpha5(IV) network. We will attempt to rescue the mutation in vivo by making transgenic mice that express cDNAs encoding collagen alpha3(IV). Finally, the effect of genetic background on progression to end stage renal disease, which we have identified in preliminary studies, will be characterized in detail. The results obtained under the auspices of this proposal will have important implication for the pathogenesis of Alport syndrome in man and for approaches current under development that will use gene therapy to treat the human disease.

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- **Project Title: COMPLEMENT AND B CELL TOLERANCE IN A MURINE MODEL OF SLE**

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

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

  Summary: (Adapted from Applicant's Abstract) Deficiencies in the classical pathway of the complement system are among the strongest genetic risk factors known for developing systemic lupus erythematosus (SLE). Studies from the Carroll lab have shown that murine complement deficiency breaks tolerance to self antigens in Goodnow's HEL/anti-HEL double transgenic model and also in non-autoimmune mice homozygous for fas^lpr. Loss of tolerance is demonstrated by altered B cell fate in the former and ANA positive immune complex **glomerulonephritis** in the latter. My preliminary observations suggest that in a non-autoimmune genetic background (mixed C57BL/6 and 129), even isolated deficiency of C4 (C4^-/-) or of its receptor CD21/CD35 (Cr2^-/-) are risk factors for developing autoantibodies to DNA. In this proposal I hypothesize that complement deficiency predisposes to human autoimmune disease because components of the classical pathway are required for induction or maintenance of a self-tolerant B cell repertoire. With particular attention to the anti- DNA response that is a hallmark of SLE and SLE nephritis, I will test this hypothesis in several ways. As potential models of human disease, C4^-/- and Cr2^-/- mice will be studied through their natural lifetime with serologic, cytologic and histologic methods to document their spontaneous evolution of anti-DNA autoreactivity and also to seek evidence of renal sequelae. Immunostimulation will be used to potentiate premature autoreactivity in these animals to better delineate defects in B cell regulation, and reconstitution experiments will be designed to confirm the genetic basis of observed autoreactive phenotypes. Lastly, I will generate a novel murine model of SLE by breeding the complement deficient animals to mice transgenic for anti-DNA antibodies. These complement deficient anti-DNA transgenic mice will constitute a unique opportunity to probe complement's role in the tolerogenic mechanisms of B cell receptor editing, clonal deletion and peripheral anergy. By combining immunologic, nephrologic and molecular analyses I propose to elucidate how classical complement deficiency predisposes to SLE.

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

- **Project Title: CORE--CLINICAL RESOURCES AND BIOSTATISTICS**

  Principal Investigator & Institution: Julian, Bruce A.; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

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

  Summary: The aim of this Program Project is to identify the genes and pathways responsible for development of familial IgA nephropathy (IgAN). The approaches in the 3 Projects will refine the genetic location of the recently identified disease locus on chromosome 6q22-23 (IGAM1), evaluate the biosynthesis of IgA1 and its glycosylation in B lymphocytes, and assess the pathogenic role of cir5cuylating immune complexes with undergalactosylated IgA1. These studies require many patients with well- defined clinical phenotypes and appropriate family members and controls. Patients with familial or sporadic IgAN, Henoch-Schonlein purpura (HSP), family members, and non-IgAN disease- and healthy control subjects in a 7-stage catchment area will be enrolled. To provide clinical resources and statistical support for the 3 Projects, Core A will collect blood and urine samples (and residual renal tissue if biopsy done within 30 days), compile clinical and laboratory data in aq centralized database, and correlate laboratory and clinical data. The Specific Aims of Core A are: 1. Enroll 1515 subjects for the 3 Projects: 20 pedigrees with 50 familial IgAN/HSP patients and about 150 of their family members, 150 Caucasian sporadic IgAN patients and 375 of their family members, 50 HSP patients and 125 of their family members, 50 African-American IgAN patients and 200 of their family members, 65 non-IgAN disease- controls, and 200 Caucasian and 100 African-American healthy controls. 2. Establish and manage the computerized database for the entire Program Project: (a) compile the demographic, clinical, laboratory, histopathologic, and genetic data; (b) coordinate and manage statistical analyses to ensure investigators have ready access to statistical consultation and support; (c) provide statistical expertise including sample-size estimation and power calculations, randomization procedures, and design of data collection forms; and (d) perform interim reviews and final analyses. 3. Coordinate collection and distribution of blood and urine samples from patients and controls, and establish immortalized cell lines from selected subjects. 4. Perform detailed histologic analyses of residual renal tissue of newly biopsied IgAN/HSP and non-IgAN **glomerulonephritis** patients from whom blood and urine samples will be obtained for contemporaneous in vitro studies. The findings from this Program Project will substantially increase the understanding of the pathogenesis of a common renal disease and may be the foundation for future development of a disease-specific therapy.

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

- **Project Title: CORE--PATHOLOGY**

  Principal Investigator & Institution: Truong, Luan D.; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

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

  Summary: The Morphology and Clinical Application Core (The Core) is a critical component of The Center. It serves three major functions: First, it maintains a comprehensive tissue bank, which includes human normal kidney tissue and kidney tissue with a large varieties of renal disease characterized by inflammation and makes them available to individual projects of The Center or to the human translational studies conducted by The Core. Second it helps analyze tissue samples generated from the individual projects of The Center. This function may include routine tissue preparation, electron microscopy, immunostaining, in situ hybridization, morphometry,

interpretation of the morphologic findings, and laser capture microscopy. Third, it tests the human relevance of the findings or the concepts generated from individual projects. For example, the idea that Smac 7 overexpression attenuates inflammation through suppression of NF-kappaB in a murine model of antiglomerular basement membrane **glomerulonephritis** will be tested for human relevance by immunostaining human tissue samples with various types of glomerulonephrirtis or tubulointerstitial nephritis for the expresion of Smad 7 and NF-kappaB actvation and correlating these findings with the severity of inflammation, Forth, it tests the hypotnesis that defective apoptosis of the inflammatory cells at site of tissue inflammation may lead to failure of resolution of inflammation and perpetuate the disease. For this purpose, the frequency of apoptotic inflammatory cells and their expression of pro-apoptotic and arnti-apoptotic molecules in the models from each project and in human tissue will be determined and correlated with the general disease activity.

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

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

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

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

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

function in immune tolerance in the liver. These studies will advance our knowledge of the regulation of T-cell function and tolerance, and may lead to a greater understanding of autoimmune diseases.

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

- **Project Title: CUX-1 AND CELL CYCLE REGULATION IN KIDNEY DEVELOPMENT**

  Principal Investigator & Institution: Vanden Heuvel, Gregory B.; Assistant Professor; Anatomy and Cell Biology; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

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

  Summary: (provided by applicant): The overall aim of this proposal is to determine the role of the homeobox gene Cux-1 in cell cycle regulation in the kidney. Cux-1 is the murine homologue of the Drosophila gene Cut, which is required for the proper development of the Malpighian tubules, the insect excretory and osmoregulatory organs. Mammalian Cut homologues function as transcriptional repressors of genes specifying terminal differentiation in multiple cell lineages. Cux-1 is part of the network controlling G1-S transition, where it represses the expression of the cyclin kinase inhibitor (CKI) p21 in S phase. Recent studies demonstrate that deregulation of Cux-1 in transgenic mice results in down regulation of p27kip1 expression during nephrogenesis, renal hyperplasia, and mesangial cell proliferation. Mesangial cell proliferation is linked to matrix accumulation and precedes the development of glomeruloscierosis. The proposed studies will test the hypotheses that Cux-1 regulates cell proliferation during normal renal development, and that dereguletion of Cux-1 contributes to immune mediated and non-immune mediated renal injury. The specific aims are: (I) Perform morphological and physiological evaluations of developing kidneys in transgenic mice constitutively expressing Cux-1; (ii) perform studies on primary mesangial cells isolated from wild type and transgenic kidneys to determine whether PDGF and bFGF induced down regulation of the CKI p27 is mediated by Cux-1; (iii) evaluate whether Cux-1 binds to the p27 promoter, and determine whether Cux-1 represses p27 gene expression; (iv) determine if Cux-1 represses p21 and/or p27 during renal inflammatory injury, and whether this results in a further diminution of renal function. These studies will provide novel insights into the mechanisms of cell proliferation in renal disease, and may provide future therapeutic strategies for renal disease.

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

- **Project Title: DECORIN--MECHANISMS OF ANTIFIBROTIC EFFECTS**

  Principal Investigator & Institution: Border, Wayne A.; Professor; Internal Medicine; University of Utah Salt Lake City, Ut 84102

  Timing: Fiscal Year 2002; Project Start 30-SEP-1994; Project End 31-AUG-2004

  Summary: The proteoglycan decorin is a key biological modulator of extracellular matrix assembly and cell growth in health and in important pathological conditions like fibrotic disease and cancer. We reported that human decorin, delivered by intravascular injection or by skeletal muscle- based gene transfer is therapeutic in inhibiting fibrosis in experimental **glomerulonephritis.** These exciting results make decorin, a natural human protein, a novel candidate to treat a number of important human fibrotic diseases including progressive kidney diseases such as diabetic nephropathy and **glomerulonephritis.** The goal of this application is to advance understanding of decorin biology by elucidating molecular mechanisms by which decorin regulates extracellular

matrix assembly in vitro and in vivo. Major factors that have previously limited decorin research including insufficient high quality recombinant decorin and the absence of a decorin knockout mouse have been overcome by the establishment of strong collaborations that will provide these important tools. We will test the hypothesis that decorin is a multifunctional regulatory molecule that exerts its antifibrotic effects by simultaneously acting on several targets including: binding to collagen, suppressing cell proliferation and negatively regulating the fibrogenic cytokine TGF-beta and that the decorin knock out mouse will show increased susceptibility to fibrotic disease that can be reversed by decorin. Specifically we will do the following: 1) Determine if the decorin knockout mouse is more susceptible to fibrotic disease associated with anti-glomerular basement membrane **glomerulonephritis** and unilateral ureteral obstruction and whether the susceptibility can be reversed by administration of recombinant decorin 2) Produce recombinant decorin and biglycan as proteoglycans, core proteins and mutant forms in which various protein binding sites have been disrupted and test the functional properties of these molecules in vitro 3) Use the various mutant forms of decorin to analyze the mechanisms that underlie decorin's antifibrotic effects in vivo, including collagen binding, suppression of cell proliferation and neutralization of TGF-beta. The significance of this application is that it will apply new knowledge and technology to an area of investigation that is directly relevant to improved understanding of the pathogenesis of fibrotic diseases. Furthermore, this work will likely provide insights into decorin's antifibrotic effects that may suggest additional novel therapeutic interventions in important human fibrotic diseases as well as cancer.

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

- **Project Title: DIETARY LIPIDS AND EXPERIMENTAL IGA NEPHROPATHY**

  Principal Investigator & Institution: Pestka, James J.; Professor; Food Science & Human Nutrition; Michigan State University 301 Administration Bldg East Lansing, Mi 48824

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

  Summary: The goal of this research will be to understand specific mechanisms by which dietary polyunsaturated fatty acids (n-3 PUFA) in marine and plant oils impair development and progression of immunoglobulin A nephropathy (IgAN). Although IgAN is the most common **glomerulonephritis** worldwide, effective treatments for it remain elusive. Fish oil consumption has recently shown promise in retarding disease progression and renal failure in IgAN patients. An experimental mouse model is now available in which immunopathological hallmarks of IgAN are induced by dietary exposure to the mycotoxin vomitoxin (VT). Interestingly, replacement of corn oil in a semi-purified diet with menhaden fish oil markedly impairs immunopathogenesis in this model. The sequential activation of mitogen-activated protein kinases (MAPKs), up-regulation of interleukin-6 (IL-6) gene expression and polyclonal activation of IgA-secreting cells appear to be critical early events in VT-induced IgAN. The guiding hypothesis for this project is that ingestion of n-3 PUFA in fish oil attenuates VT-induced IgAN by interfering with upstream regulation of IL-6 gene expression. Five specific aims are proposed. In AIM 1, a sub-chronic VT feeding model will be used to determine the capacity of feeding fish oil or the n-3 PUFAs, eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), to attenuate VT-induced IgAN markers. In AIM 2, an acute VT exposure model will be used to evaluate the in vivo and ex vivo effects of feeding fish oil on IL-6 and IgA expression. In AIM 3, the role of transcription in n-3 PUFA-attenuated IL-6 expression will be assessed in VT-treated macrophage cultures by measuring transcription factor binding and nuclear runoff of IL-6 mRNA. In AIM 4, the role of post-transcriptional mechanisms in n-3 PUFA-attenuated IL-6 expression will be

evaluated by measuring IL-6 mRNA stability in macrophage cultures. In AIM 5, the effects of n-3 PUFAs on activation of the MAPKs SAPK/JNK 1/2, ERK1/2 and p38 will be assessed in macrophages cultured with VT. Long-term impacts of increased mechanistic understanding of n-PUFA effects in this model may include improved nutritional and pharmacological strategies for inhibiting the progression of IgAN and potentially other autoimmune diseases.

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- **Project Title: FAMILIAL IGA NEPHROPATHY: GENETIC AND METABOLIC STUDIES**

  Principal Investigator & Institution: Mestecky, Jiri F.; Professor; Microbiology; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

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

  Summary: IgA nephropathy (IgAN) is the most common primary **glomerulonephritis** in the world. Because of its frequently unfavorable cou7rse and lack of specific therapy, IgAN represents a serious healthy care and economic problem. The overall objective of the proposed Program Project is to determine the genetic and molecular basis of this common disease through integrated studies of patients with IgAN or Henoch-Schonlein purpura (HSP), commonly considered the systemic form of the disease process causing IgAN. We will enroll 20 multiplex families with 50 member5s afflicted with IgAN or HSP and 150 other family members; 150 Caucasian patients with sporadic IgAN (no affected relatives) and 375 of their family members, 50 patients with HSP and 125 of their relatives, 50 African-American patients with IgAN and 200 family members, 50 patients with non-IgAN **glomerulonephritis,** and 200 Caucasians and 100 African-Americans as health controls. This proposal is based on novel findings generated in the laboratories of the participating investigators, with respect to genetic, biosynthetic, and metabolic studies of IgA molecules, immune complexes, and relevant receptors involved in IgA catabolism. The Program Project consists of three component research project and two core facilities: Project 1: Genetic Studies of IgA Nephropathy Project 2: Biosynthesis and Glycosylation of IgA1 Molecules in IgA Nephropathy Project 3: Immune Complexes and Mesangial Cells in IgA Nephropathy Core A: Clinical Resources and Biostatistics Core B: Administrative The results generated through extensive collaboration among the participating investigators are likely to provide information concerning the genetic and molecular defects characteristic of IgAN, identify mechanisms of the pathogenesis of this disease, and ultimately provide a basis to develop rational therapeutic approaches.

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

- **Project Title: FRACTALKINE: ROLES IN CELL ADHESION AND ATHEROSCLEROSIS**

  Principal Investigator & Institution: Charo, Israel F.; Professor of Medicine; J. David Gladstone Institutes Box 419100, 365 Vermont St San Francisco, Ca 94103

  Timing: Fiscal Year 2002; Project Start 10-FEB-2000; Project End 31-JAN-2004

  Summary: The overall goal of this proposal is to determine the role of fractalkine in vascular disease. Fractalkine is a novel chemokine expressed on activated endothelial cells and recent data indicates that it binds cells expressing the fractalkine receptor, CX3CR1, with high affinity. Thus, unlike other chemokines, fractalkine appears to function not only as a chemoattractant, but also as an adhesion molecule. The cell adhesion properties of fractalkine may be due to its unique architecture. Virtually all

other known chemokines are secreted proteins. In contrast, fractalkine is a transmembrane domain protein with a chemokine-like domain located at the top of a mucin stalk. We have recently found that fractalkine captures cells flowing under physiologically relevant shear stress extremely rapidly and with high efficiency. In Specific Aim 1, we will use a novel cell adhesion assay to quantitatively compare the binding of CX3CR1-expressing cells to fractalkine with integrin-mediated cell adhesion. In Specific Aim 2, we will identify domains within fractalkine that are critical for mediating high-affinity adhesion to CX3CR1-expressing cells. We will create novel chimeras in which other chemokines are substituted for the chemokine-like domain of fractalkine. Using the assays developed under Specific Aim 1, we will determine whether the unique cell-binding properties of fractalkine are due to the presentation of the chemokine-like domain at the top of a rigid stalk or to unique properties of the chemokine itself. In Specific Aim 3, we will create CX3CR1 knockout mice to directly assess the role of fractalkine in vascular disease. We will breed these mice into appropriate genetic backgrounds to test the hypothesis that fractalkine plays an important role in two human diseases that require the capture of leukocytes from rapidly flowing blood: atherosclerosis and **glomerulonephritis.** The experiments proposed in this grant will use novel, quantitative in vitro assays and the creation of a fractalkine receptor knockout mouse to provide significant new information on the role of fractalkine in vascular disease.

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

- **Project Title: GENETIC /ENVIRONMENTAL INFLUENCES ON SLE NEPHRITIS**

  Principal Investigator & Institution: Gilkeson, Gary S.; Professor; Medical University of South Carolina P O Box 250854 Charleston, Sc 29425

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

  Summary: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the production of autoantibodies and immune complex mediated **glomerulonephritis.** African- Americans have a three-fold increased incidence of SLE, more frequently develop nephritis, more frequently progress to renal failure and have increased mortality compared to whites. The worse prognosis in African-Americans may represent a generalized predisposition towards renal failure following any renal injury rather than being lupus specific. Environmental exposures such as smoking and exposure to occupational or environmental agents (i.e., lead, mercury, silica) may affect the development and progression of lupus nephritis. Our central hypothesis is that there are specific genetic factors that interact with environmental exposures leading to progressive renal disease in African-Americans with lupus. The Carolina Lupus Study includes 265 SLE patients who were diagnosed between January 1, 1995 and July 31, 1999. This cohort of patients provides an opportunity to examine renal disease and its progression in African- American SLE patients matched with appropriate population based controls. The Gullah population lives on the sea islands of South Carolina. They are unique in their genetic homogeneity with minimal Caucasian admixture (<5%). A large ongoing study of diabetes (Sea Island Project) in this population has established a working framework onto which we propose to piggyback studies of SLE. Using these unique cohorts of patients and controls, we propose the following specific aims to address our hypothesis: 1) Determine the development and progression of renal disease in CLU patients in relation to specific genetic factors. We will assess if genes linked with renal disease in hypertension and diabetes in African-Americans are associated with development and/or progression of renal disease in lupus. 2) Determine the risk of development and progression of lupus nephritis in CLU patients in relation to comorbid

conditions (hypertension, diabetes), measures of socioeconomic status and/or modifiable environmental factors that have been associated with other forms of renal disease. 3) Perform pilot studies in the unique genetically homogenous Sea Island African-American Gullah population to assess the presence of lupus multiplex families, the prevalence of the genetic polymorphisms being assayed in Aim 1 and determine the prevalence of ANA positivity compared to control African- American cohorts.

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- **Project Title: GENETIC ANALYSIS OF T CELLS IN LUPUS**

  Principal Investigator & Institution: Craft, Joseph E.; Professor; Internal Medicine; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

  Timing: Fiscal Year 2002; Project Start 01-JUL-1996; Project End 30-JUN-2006

  Summary: (provided by applicant): Systemic lupus erythematosus (SLE) is characterized by IgG autoantibodies to certain intracellular components, including chromatin and ribonucleoproteins. Several inbred mouse strains also develop spontaneous lupus, with the same spectrum of autoantibodies. Certain of these specificities are pathogenic, including those against chromatin that induce immune-complex **glomerulonephritis.** Autoantibodies in lupus arise as a consequence of autoantigen-specific alpha/beta CD4+ T cell help, including T cells specific for peptides of chromatin-associated proteins. Such autoreactive T cells bypass normal tolerance mechanisms in the periphery; however, the mechanism of activation of T cells responsive to self peptides in lupus is unknown, as are the tissue source(s) of such peptides and the events leading to autoreactive CD4+ T cell-B cell collaboration with resultant pathogenic autoantibody production. In this proposal, an in vivo approach will be used to dissect the mechanisms that lead to peripheral T cell tolerance abrogation and T cell help for autoantibody production in lupus. It is hypothesized that these events arise in two stages: first, that lupus T cells have intrinsic (genetic) defects that render them susceptible to activation after contact with the ubiquitous self peptide-class II MI-IC complexes that are sufficient for CD4+ T cell survival in normal animals; second, that such activation, initiating tolerance loss with polyclonal expansion of autoreactive T cells, leads to oligoclonal T-B cell collaboration in the setting of specific autoantigen presentation by autoreactive B cells. The hypothesis will be addressed in two aims. First, it will be determined if normally displayed (ubiquitous) MHC-self peptide complexes can activate autoreactive T cells from Fas-intact mice MRL/+Fas-lpr mice, in comparison to non-autoimmune control T cells. Second, it will be determined if T cells from MRL/+Fas-lpr mice can provide B cell help in the setting of autoantigen presentation by autoreactive B cells, an event that leads to antigen-specific expansion of cells from both lineages. These objectives fit well within the overall context of this IRPO proposal centered around developing a better understanding of T cell-B cell interactions during the development and maintenance of systemic autoimmunity.

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- **Project Title: GENETIC BASIS OF SYSTEMIC AUTOIMMUNITY**

  Principal Investigator & Institution: Theofilopoulos, Argyrios N.; Professor; Scripps Research Institute Tpc7 La Jolla, Ca 92037

  Timing: Fiscal Year 2002; Project Start 01-SEP-1988; Project End 31-AUG-2003

  Summary: (Adapted from the applicant's abstract) - Susceptibility to systemic lupus erythematosus (SLE) is inherited as a complex multigenic trait with the added complication of gene heterogeneity. To define the genetics of this disease, the principal

investigator and others have taken advantage of the uniform genetic composition of inbred mouse strains, of which several spontaneously develop clinical and immunopathologic characteristics similar to human SLE. In the previous funding period, the chromosomal locations of autoimmune susceptibility loci for the four main lupus strains (NZB, NZW, BXSB, and MRL-Fas-lpr) were identified. These studies demonstrated a multiplicative threshold inheritance of disease traits, and that loci contribute to specific immunopathologic stages, in many instances beyond autoantibody production. Among the loci identified, four (Lmb 1 to 4) from the MRL-Fas-lpr x C57BL/6-Fas-lpr cross were significantly linked to traits with the highest likelihoods. This proposal focuses on the MRL-Fas-lpr and C57BL/6-Fas-lpr strains to define the contributions and identities of genes associated with susceptibility loci. Loci for two important traits with weaker linkages, **glomerulonephritis** and arthritis, will be more definitively mapped by combining additional (MRL-Fas-lpr x C57BL/6-Fas-lpr) F2 intercross mice to the previous set which they have studied. To determine the contributions, modes of inheritance, and interactions of susceptibility genes, congenic and derivative mice for these and the four Lmb loci will be generated and analyzed for autoimmune traits. Fine mapping will be performed using crosses of congenic mice and cloning of genes corresponding to susceptibility loci will be carried out by screening candidate genes or, if necessary, by physical cloning. Findings generated from these studies, they expect, will significantly enhance efforts to define the etiopathogenesis of autoimmunity, and may lead to new approaches in the diagnosis and therapy of human SLE.

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- **Project Title: GENETIC CONTROL IN LUPUS PRONE MICE**

  Principal Investigator & Institution: Mcduffie, Marcia J.; Professor; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2002; Project Start 27-SEP-2002; Project End 30-JUN-2003

  Summary: (provided by applicant): Two phenotypes map to distinct loci on chromosome 4 in lupus-prone NZM2328 mice: high levels of circulating anti-dsDNA antibodies and renal disease. After outcross to the C57L strain, we demonstrated through linkage analysis that levels of circulating antibodies reactive with dsDNA were controlled by locus in the centromeric half of chromosome 4 (Adaz1). The mapping data was confirmed by the generation of a congenic mouse strain bearing protective C57L alleles across this interval. This mouse strain (NZM.Lc4) does not generate high levels of antidsDNA antibodies in serum. However, these mice develop chronic **glomerulonephritis** associated with immunoglobulin and complement deposits with the same kinetics and prevalence as the parental NZM2328 strain. In another cross, we tested the ability of alleles from another "autoimmune" mouse strain to complement the susceptibility loci of NZM2328 by replacing selected chromosomes of NZM2328 with those from the diabetes prone NOD mouse. Using this consomic strategy, we have shown that NOD chromosome 4 is permissive for high circulating levels of anti-dsDNA antibodies in NZM.Nc4 mice. This demonstrates that NOD alleles at Adaz1 can substitute for NZM alleles to produce this phenotype. However, NZM.Nc4 mice are completely resistant to the development of lupus-like renal disease. This finding shows the presence of a second locus controlling susceptibility to renal disease on chromosome 4 even in the presence of the genomic interval on chromosome 1, which has also shown to be a major susceptibility locus for renal disease in New Zealand mouse lupus models. We will use these congenic and consomic strains to locate the genes responsible for controlling these two traits as the major focus of this project period (Aims 1 and 2). We

will determine the mechanism by which Adaz1 controls autoantibody levels in NZM2328 mice (Aim 3). In addition, the possibility of resistance to end-organ damage, responsible for the lack of chronic **glomerulonephritis** in NZM.Nc4 will be explored (Aim 4) The identification of the second major locus for SLE **glomerulonephritis** may offer an additional checkpoint for therapeutic intervention in lupus nephritis.

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- **Project Title: GENETIC EPIDEMIOLOGY OF KIDNEY ANOMALIES**

  Principal Investigator & Institution: Vats, Abhay N.; Assistant Professor; Children's Hosp Pittsburgh/Upmc Hlth Sys of Upmc Health Systems Pittsburgh, Pa 152132583

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

  Summary: Congenital anomalies of the kidney and urinary tract (CRUTA) are a major cause of renal dysfunction in childhood and span a wide range of urinary system malformations including ureteropelvic junction (UPJ) obstruction; vesicoureteral reflux (VUR); hypoplastic or multicystic dysplastic kidneys; and bladder outlet obstruction. Many of these anomalies often coexist; ie renal hypoplasia/dysplasia with UPJ obstruction. Also, VUR can often be seen in the contralateral side of individuals with ureteral duplication, or renal dysplasia. There is now growing evidence that these different renal and urologic malformations may be caused by mutations in the same gene(s). Although the etiology of CRUTA is probably multifactorial, it is likely that many of the CRUTA cases have a genetic cause. In fact many of these malformations often show familial clustering with variable penetrance. Recent studies have identified mutations in several genes involved in the development of kidney (such as PAX2, GATA3, EYA, and WT-1) that have been associated with CRUTA in humans. Recently mice, especially males, with a disrupted angiotensin type 2 receptor gene, have been shown to have a range of CRUTA. Also, Caucasian males with CRUTA have been reported to have a mutation in intron 1 of this gene. All of these studies point to the genetic heterogeneity of CRUTA. In addition to CRUTA, another common kidney disease, i.e. nephrotic syndrome (NS) / focal segmental glomerulosclerosis (FSGS), is increasingly thought to have a genetic basis and several cases ofNS/FSGS with VUR have been reported. Also over the last five years several genes, including NPHS1 (nephrin), ACTN4, and NPHS2 (podocin), and chromosomal regions (i.e. 1lq22, 19q13) have been identified for their association with NS / FSGS. However none of these NS/FSGS genes are associated with CRUTA. Although cases of 13q deletion syndrome have been previously identified with renal malformations, its association with SRNS has not been previously reported and no information is available on the critical regions on 13q associated with renal development. We identified eight children with 13q deletion, who had a range of CRUTA, with one child having steroid resistant nephrotic syndrome (SRNS). We performed cytogenetic and molecular genetic studies to identify the region(s) on 13q associated with renal development and disease and recently identified two critical regions, with one region lying on 13q22 and the other on 13q32. We wish to pursue further gene localization studies on chromosome 13 in this application in order to identify the causative genes.

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- **Project Title: GENETIC MODIFIERS OF TGF BETA 1 ACTION IN VIVO**

  Principal Investigator & Institution: Akhurst, Rosemary J.; Research Scientist; Cancer Center; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

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

Summary: Inactivation of the transforming growth factor beta1 (TGFbeta1) gene causes defects in angiogenesis and haematopoiesis that lead to prenatal death. The penetrance of this phenotype depends on genetic background. A major genetic modifier, tgfmod1, contributes over 50% of the genetic in control of the penetrance of TGFbeta1-/-embryo lethality. The overall goal of this project is to identify tgfmod1. A combined genetic and positional cloning approach will be taken. The identification of tgfmod1 will make a significant contribution to our understanding of embryonic angiogenesis and hematopoiesis in vivo, as well as that of TGFbeta1 regulation of these processes. Moreover, it will test the general approach of cloning genetic modifiers of embryo-lethal phenotypes, many of which have been found during generation of homozygous gene knock out mice. TGFbeta1 is implicated in many human diseases, including hereditary haemorrhagic telangiectasia (HHT), cancer, pathological angiogenesis, atherosclerosis, inflammation, osteoporosis, fibrosis, wound healing and **glomerulonephritis.** However, the severity of these disease phenotypes, including the single gene disorder, HHT, is very variable, suggesting the existence of modifying gene traits. Identification of genes that can modify the incidence and severity of diseases caused by mis-regulation of TGFbeta is therefore of value to general medicine. tgfmod1 will be definitively mapped to approximately 0.5cM, using our panel of reciprocal congenic mice, together with a proven functional genetic test cross. A BAC contig will be generated that spans this critical map region, and comparative genomic sequencing, together with a large selection of DNA sequence analysis software tools, will be used to identify every gene within the BAC contig. Candidate genes will be selected on the basis of their fine map location and gene expression pattern. Functional polymorphisms within candidate genes will be searched for by various molecular polymorphism detection techniques, DNA sequencing and RNA and protein analysis. Identity of tgfmod1 will be confirmed by genotype/phenotype correlation in several mouse strains, and by functional analysis, including transgenesis.

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- **Project Title: GENETIC POLYMORPHISMS IN WEGENER'S GRANULOMATOSIS**

  Principal Investigator & Institution: Edberg, Jeffrey C.; Associate Professor; Medicine; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

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

  Summary: (investigator's abstract): Wegener's Granulomatosis is one of the anti-neutrophil cytoplasmic antibody (ANCA) positive systemic vasculitides which is characterized by inflammatory lesions with granuloma formation in the upper and lower airways, by pauci-immune **glomerulonephritis** and by anti-proteinase 3 autoantibodies (PR#-ANCA). Although WG is idiopathic, there has been substantial interest in environmental factors as either etiologic or accelerating risk factors. Because of epidemiological studies implicating nasal carriage and therapeutic studies implicating efficacy of anti-staphylococcal agents at least for upper airway disease, Staphylococcus aureus has attracted substantial attention as one such environmental factor. Although consensus about etiology remains elusive, the nature of the host response has emerged as an important determinant for disease phenotype and severity. There are may examples of human disease, provoked by environmental exposures, which have important genetic factors contributing to both susceptibility and severity. HIV presents one such example. Thus the identification of important genetic factors in a disease such as WG is not only feasible but also potentially very fruitful in providing insights into pathogenesis and potential therapeutic targets. Building on the clinical trial

of Etanercept in WG (Wegener's Granulomatosis Etanercept Trial, WGET), we propose to develop a renewable genetic repository which will provide resources to all WGET investigators and to explore the relationship between the WG diathesis and genetic polymorphisms in candidate molecules, selected for their role in pathophysiology. We also propose to discover new polymorphisms in such molecules and apply these to this cohort. Accordingly, our specific aims are: 1) To establish a renewable biological resource of all WG patients screened and enrolled in the WGET clinical trial, including two ethnically and geographically matched controls for each patient; 2) To determine if known variations in genes involved in the innate inflammatory response, in lymphocyte activation and in target antigen biology influence the susceptibility to or severity of WG; 3) Recognizing that the knowledge base about biologically significant genetic variants will increase, we will determine, through direct discovery and through continual evaluation of SNP databases, if newly identified variation in gene categories outline in Specific Aim 2 influence the susceptibility to or severity of WG.

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- **Project Title: GENETIC STUDIES OF IMMUNOGLOBULIN A NEPHROPATHY**

  Principal Investigator & Institution: Lifton, Richard P.; Chairman, Department of Genetics; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

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

  Summary: The goal of Project 1 is to use a genetic approach to identify the genes and pathways responsible for the development of Immunoglobulin A nephropathy (IgAN). IgAN is the most common form of primary **glomerulonephritis** and a significant cause of renal failure worldwide. The primary etiology of this disorder is unknown and there is no effective treatment currently available. By a genome-wider analysis of linkage, we have shown that in 60% of families with IgAN the disease is linked to an interval on chromosome 6q22-23, now called IGAN1. This genetic interval is supported with a peak lod score of 5.6 and confines the location of the disease gene to a 6.5 cM region. We now propose to replicate our findings in a new set of pedigrees, and narrow the IGAN1 interval to permit identification of the underlying gene. This will be accomplished by meiotic mapping in 20 newly recruited kindreds with IgAN and by disequilibrium mapping using a dense set of single nucleotide polymorphisms in 150 patients with sporadic IgAN who will be recruited from the southeastern United States. We will then proceed to positionally clone the underlying gene. Secondly, we plan to research for additional IgAN loci and study the significance of IGAN1 and these other loci in the pathogenesis of a related disorder, Henoch Schonlein purpura. Finally, using the information gathered by Core A and Projects 2 and 3 of this Program Project, we will perform genotype-phenotype correlation studies to determine the role of allelic and locus heterogeneity on the development of IgAN of IgAN and its complications.

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

- **Project Title: GENETIC SUSCEPTIBILITY TO END STAGE RENAL DISEASE**

  Principal Investigator & Institution: Iyengar, Sudha K.; Associate Professor; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

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

  Summary: End-stage renal disease(ESRD) is a late-onset multifactorial disease that primarily occurs in a small subset of patients with diabetes mellitus, hypertension or chronic **glomerulonephritis.** ESRD incidence is rising with an annual mortality of about 20% in incident cases. ESRD clusters in families and familial aggregation is a more

powerful predictor of whether an individual with diabetes mellitus, hypertension or chronic **glomerulonephritis** will develop ESRD. However, no particular genetic mechanism responsible for the renal function damage that ultimately leads to ESRD has yet been identified.

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- **Project Title: GLOMERULAR CAPILLARY WALL: DEVELOPMENT AND DISEASE**

  Principal Investigator & Institution: Abrahamson, Dale R.; Professor and Chairperson; Anatomy and Cell Biology; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

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

  Summary: The kidney glomerular capillary wall is comprised of three elements: (1) an inner endothelial cell layer; (2) the glomerular basement membrane (GBM); and (3) an outer epithelial cell layer (podocytes). That this unique structure constitutes the glomerular filtration barrier has been well established, but how this structure develops during kidney organogenesis, is maintained in maturation normally, and becomes damaged in disease, is not fully understood. The purpose of our application is to establish a focused and complementary group of research projects that will define the development and assembly of the GBM and the molecular pathogenesis underlying selected glomerular diseases. Specifically, Project 1 will examine abnormal glomerular phenotypes in certain laminin and collagen IV mutant mice and rescue these phenotypes through metanephric grafting and inducible, cell-selective transgene expression strategies. Project 2 will study type IV collagen network formation and interaction with glomerular cell integrins using mass spectrometry, x-ray crystallography, and surface plasmon resonance, in combination with classic molecular and cellular methodologies. Project 3 will map the molecular location of pathogenic Goodpasture and Alport alloantigens on type IV collagen, examine the development of anti-GBM disease in a mouse expressing humanized type IV collagen, and in an Alport mouse model. Project 4 will examine the molecular regulation of extracellular matrix assembly and cell-matrix interactions in vivo in hydra and Zebrafish embryos as simplified model organisms, using antisense knock down and real-time imaging techniques, among other approaches. The Program is designed to promote extensive communication and sharing of resources among the Projects, which are also supported by an Administrative Core (A) and a Molecular Recognition Core (B). We anticipate that this Program will reveal fundamentally new information regarding glomerular structure in health and disease.

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- **Project Title: IDENTIFICATION OF SEVERAL SCAFFOLDING PROTEINS IN GLOMERULAR PODOCYTES (PALS1, MA**

  Principal Investigator & Institution: Margolis, Benjamin; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

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

  Summary: Scaffolding proteins play an important role in cell biology by organizing proteins important for cell signaling, gene transcription, protein targeting and cell polarity. This grant proposal will examine the importance of scaffolding proteins in glomerular podocytes, a cell that is plays an important role in many kidney diseases including diabetes and **glomerulonephritis.** This proposal focuses on scaffolding proteins containing PDZ domains. PDZ domains bind to the extreme carboxy-terminus

of many cell surface proteins controlling the targeting of these cell surface proteins. One group of PDZ domain scaffolding proteins is called Membrane Associated Guanylate Kinase (Maguk) Proteins. Maguk proteins combine a PDZ and SH3 domain with a catalytically inactive guanylate kinase domain. All the domains identified to date in Maguk proteins are involved in protein-protein interactions and our work has focused on these interactions. Pals1 is a tight junction Maguk protein that exists in a complex with several proteins including Crumbs and Patj. Drosophila homologues of Pals1, Patj and Crumbs are crucial for proper epithelial polarity in Drosophila and their mammalian counterparts likely fulfill a similar role in mammalian epithelia. In podocytes Pals1 is localized to the slit diaphragm. Another tight junction protein we have identified in the podocyte is a Maguk protein known as Magi-1. Magi-1 interacts with two actin binding podocyte proteins, synaptopodin and alpha actinin-4. This proposal will further examine the role of Magi-1 and Pals1 in podocyte function using biochemical, immunologic and genetic approaches. We hypothesize that these proteins are crucial for the proper organization of the slit diaphragm and overall polarity of glomerular podocytes. The proposal will utilize the ability of the transgenic mouse core of the University of Michigan O'Brien Renal Center to specifically alter gene expression in the podocyte in order to examine the role of Pals1 and Magi-1 in glomerular function.

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- **Project Title: IGA GLYCANS AND IMMUNE COMPLEXES IN IGA NEPHROPATHY**

  Principal Investigator & Institution: Tomana, Milan; Medicine; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

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

  Summary: (Applicant's Description Verbatim): IgA nephropathy (IgAN), the most common **glomerulonephritis** in the world is characterized by elevated levels of IgA1 in its polymeric form in circulation, presence of circulating immune complexes (CIC) and deposition of IgA1, frequently with C3 component of complement and IgG and/or IgM in glomerular mesangium. Earlier studies have shown that IgA1 in IgAN patients displays aberrant structural features in the heavy chain hinge region glycans. Carbohydrate analysis and lectin-binding studies have shown that the hinge region glycans bound by O-glycosidic bonds to Ser or Thr residues are deficient in galactose (Gal), resulting in an increased exposure of N-acetylgalactosamine (GalNAc). Furthermore, our earlier studies have shown that Gal deficient IgA1 molecules are present mainly in high molecular mass CIC that also contain IgG molecules. Our preliminary studies indicate that the interaction of Gal-deficient IgA1 with IgG, and probably other major isotypes, is based on antigen (IgA1) and antibody (IgG) recognition. Experimental approaches proposed in this application are designed to test the following hypothesis: An altered glycosylation of IgA1 hinge region results, due to the Gal deficiency, in exposure of GalNAc-Ser/Thr associated antigenic determinant(s) which are recognized by ubiquitous, naturally occurring antibodies, predominantly of the IgG isotype, which are involved in the formation of CIC and mesangial depositions. The following specific aims are proposed to test this hypothesis: 1) Determine the localization of antigenic determinants in IgA1 with aberrantly glycosylated hinge region glycans, involved in the formation of CIC; 2) Examine whether the Gal-deficient molecules are of systemic or mucosal origin; 3) Characterize the specificities and molecular properties of IgG, IgA, and IgM antibodies that bind to epitopes in the aberrantly glycosylated IgA1 hinge region; 4) Investigate the biological consequences of the formation of CIC containing Gal-deficient IgA1 and IgG. With GalNAc-Ser/Thr

specificity; 5) Determine whether immune complexes composed of Gal-deficient IgA1-IgG with GalNAc-Ser/Thr binding activity are present in mesangial deposits of patients with IgAN; and 6) Correlate levels of Gal-deficient serum or secretory IgA1 and levels of IgG, IgA1, or IgM antibodies with GalNAc-Ser/Thr specificity with disease activity. Results of these studies may lead to the elucidation of molecular defects of IgA1 in IgAN and provide experimental basis for rational approach to the treatment.

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- **Project Title: IMMUNE MECHANISMS IN PRISTANE INDUCED LUPUS NEPHRITIS**

  Principal Investigator & Institution: Reeves, Westley H.; Professor; Medicine; University of Florida Gainesville, Fl 32611

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

  Summary: Intraperitoneal injection of pristane (2,6, 10, 14- tetramethylpentadecane) induces a lupus-like syndrome in nearly all "normal" strains of inbred mice. This syndrome is characterized by disease-specific autoantibody production (anti-Sm, RNP, Su, ribosomal P, double stranded DNA), hypergammaglobulinemia, and severe immune complex-mediated **glomerulonephritis** closely resembling lupus nephritis. In preliminary studies, it was shown that the disease develops in two phases, each with characteristic types of autoantibodies. cytokines, and renal involvement. Microbial stimulation was found to be an important co-factor in progression to the second. more severe, phase. This project will examine the hypothesis that immune complex deposition is necessary, but not sufficient, for the development of nephritis in pristane-induced lupus. Further, it is hypothesized that a systemic abnormality in macrophage or monocyte phenotype resulting from pristane and/or microbial stimulation leads to the production of proinflammatory cytokines and disease progression. The goal of this project is to define pathways leading to **glomerulonephritis** in pristane-treated mice and ultimately to relate them to human lupus nephritis. Three specific aims are proposed. The pathology of the renal lesions will be defined in Aim 1. Mesangial and mesangiocapillary lesions will be studied by immunohistochemical techniques to determine whether hypercellularity reflects proliferation of endogenous (mesangial or endothelial) cells vs. influx of exogenous macrophages, lymphocytes or neutrophils. In addition, mesangial matrix deposition will be evaluated, and the time course of the renal changes will be studied. The roles of pro-vs. anti- inflammatory cytokines will be evaluated in Aim 2. Cytokine production in the glomerulus will be compared with that by phagocytes in the peritoneal exudate, spleen and liver to see if systemic abnormalities are present. Expression of cytokine-inducible markers will be studied as a means to evaluate whether the effects of pro-or anti-inflammatory cytokines predominate. The contribution of microbial stimulation to the development of nephritis in pristane-induced lupus will be examined in Aim 3. It is hypothesized that enhanced intestinal permeability resulting from pristane injection increases the translocation of microbial products, such as lipopolysaccharide, into the bloodstream. This may cause systemic activation of monocytes and macrophages, which then are recruited to the glomerulus in response to immune complex deposition, causing progression instead of resolution of the renal lesion. In view of the widespread susceptibility among "normal" mice to pristane-induced lupus, it seems likely that pristane causes lupus- like disease by its effects on a common, distal, part of a lupus pathway, largely bypassing the genetic abnormalities that predispose to spontaneous forms of the disease. The mechanisms involved in this new inducible model of SLE may, therefore, be common to other forms of lupus, including human SLE. Future studies will address the question of whether

renal abnormalities similar to those induced by pristane are involved in the pathogenesis of human lupus nephritis.

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- **Project Title: IN VIVO ROLE OF CTLA-4 IN COSTIMULATION AND AUTOIMMUNITY**

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

  Timing: Fiscal Year 2002; Project Start 01-FEB-1997; Project End 31-JAN-2007

  Summary: (provided by applicant): The B7:CD28/CTLA-4 costimulatory pathway has a critical role in regulating T cell activation, differentiation and tolerance, and is a promising therapeutic target. PD-1 is structurally related to CTLA-4 and has an ITIM motif in its cytoplasmic tail. PD-1 deficient mice develop an autoimmune-like disease. Our recent studies show that the newly discovered B7 homologues, PD-L1 and PD-L2, are ligands for PD-1, and can inhibit T cell proliferation and cytokine production in vitro. The expression of PD-L1 and PD-L2 on nonlymphoid tissues, as well as professional APCs, supports a role for this pathway in regulating peripheral T cell tolerance. The delineation of this pathway has revealed a new means by which T cell responses are regulated, and raised questions about its role in regulating T cell activation and tolerance, and its relationship with the B7:CD28/CTLA-4 pathway. The goals of this project are to investigate the roles of PD-L1 and PD-L2 in regulating T cell activation and tolerance, and interactions between the B7:CD28/CTLA-4 and PD-l:PD-L1/PD-L2 pathways: We will 1) analyze the function of PD-Li and PD-L2 in regulating naive and activated antigen-specific T cells and helper T cell dependent humoral immune responses. We have generated anti-PD-Ll and anti-PD-L2 mAbs and are generating mice lacking PD-L1 and/or PD-L2. These tools provide a definitive means for determining when and how PD-L1 and PD-L2 exert their effects during an immune response, 2) investigate the roles of PD-L1 and PD-L2 in regulating peripheral T cell tolerance. We will use DO.11 TCR Tg T cells to visualize the impact of blockade or elimination of PD-L1 and/or PD-L2 on the responses of antigen-specific CD4+ T cells to immunogenic and tolerogenic stimuli. 3) Analyze the interactions between the PD-1:PD-L1/PD-L2 and B7:CD28/CTLA-4 pathways. We will examine whether these pathways regulate the expression of each other, and evaluate functional interactions. The availability of mice lacking B7-1 and/or B7-2, together with mice lacking CD28 and/or CTLA-4, provide us with unique opportunities to analyze these interactions. These approaches should provide fundamental information about the role of the PD-1:PDL1/PD-L2 pathway in regulating T cell activation and tolerance, and its interactions with the B7:CD28/CTLA-4 pathway. These studies may thereby assist in the design of optimal therapeutic strategies for manipulating the B7:CD28/CTLA-4 pathway and indicate the therapeutic potential of PD-1:PD-L1/PD-L2 pathway manipulation.

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- **Project Title: INHIBITION OF LUPUS NEPHRITIS IN IRF-1 DEFICIENT MICE**

  Principal Investigator & Institution: Reilly, Christopher M.; Discipline Leader for Physiology; Biomedical Sciences and Pathobiology; Virginia Polytechnic Inst and St Univ 460 Turner Street, Suite 306 Blacksburg, Va 24060

  Timing: Fiscal Year 2002; Project Start 23-SEP-2002; Project End 31-MAY-2004

  Summary: (provided by applicant): MRL/Ipr mice spontaneously develop immune complex **glomerulonephritis** similar to human lupus. Prior to overt disease

manifestations, MRL/lpr mice overproduce nitric oxide (NO) secondary to increased gene expression of inducible nitric oxide synthase (iNOS). Blockade of iNOS pharmacologically reduces disease expression in MRL/lpr mice. Both macrophages and mesangial cells respond to IFN-gamma with increased production of iNOS and this response can be potentiated further by the addition of TNF-a. IFN-gamma constitutes one of the most potent macrophage activating factors. Either IFN-7 or IFN-y receptor gene deletion modulates disease activity in lupus mice although other adverse effects in these genetic knockouts were noted. Mesangial cells are the principal immunoregulatory cells in the glomerulus possessing both macrophage and smooth muscle cell characteristics. In addition to expressing Fc receptors, mesangial cells contain receptors that bind cytokines and chemokines including receptors for IFN-gamma and TNF-oc. Binding of IFN-gamma to its receptor induces transcription of various genes including IFN-gamma regulatory factor 1 (IRF-1). Many of the inflammatory effects of IFN-gamma in macrophages and mesangial cells are mediated through IRF-1 including up-regulation of IL-12, vascular cell adhesion molecule 1, interferon-p, major histocompatability complex I, and iNOS. The molecular events triggered by IRF-1 activation leading to iNOS expression are not completely elucidated. We hypothesize that IRF-1 plays a key role in the initiation and propagation of the inflammatory response in the murine lupus kidney. Targeting IRF-1 may thus serve as a novel mechanism for blocking inflammation in the lupus kidney. The specific aims described below investigate the role of IFN-y signaling and define the role of IRF-1 in lupus nephritis in MRL/lpr mice. Specific Aim 1: Determine the relationship between IFN-gamma, IRF-1 and NFKB activation on inflammatory mediator production including iNOS, IL-12, COX2, and TNF-c in mesangial cells. We will also determine the effects of specific immune modulators on IFN-y signaling and IRF-1 expression in macrophages and mesangial cells from MRL/lpr IRF-1 (-/-, +/-, +/+), B6 IRF-1 (-/-) and control, wIld type mice stimulated with LPS/TNF-oc. Specific Aim 2: Study the in vivo effect of gene deletion of IRF-1 on MRL/lpr mice by backcrossing C57BL6 (IRF-1- /-) mice onto the MRL/lpr background.

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- **Project Title: INTEGRINS IN KIDNEY EPITHELIAL MORPHOLOGY**

  Principal Investigator & Institution: Kreidberg, Jordan A.; Associate Professor of Pediatrics; Children's Hospital (Boston) Boston, Ma 021155737

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

  Summary: (Adapted from the Applicant's Abstract): Kidney disease is universally characterized by the loss of epithelial integrity, leading to physiological dysfunction with the potential for renal failure. A major common pathway through which epithelial cell damage occurs is by disruption of vital interactions between epithelial cells and their basement membranes. This is observed in polycystic kidney, congenital nephritic syndromes, diabetic nephropathy, and the various forms of **glomerulonephritis** that lead to the nephritic syndrome. The interaction of epithelial cells with the basement membrane is mediated by integrin receptors for the extracellular matix (ECM). Integrins are expressed on the basal membranes of epithelial cells and are believed to be the major class of receptors adhering cells to the basement membrane. Our studies on mice deficient in alpha3beta1 integrin have indicated that this receptors has important functions during the development of the kidneys, lungs, skin, and brain. By deriving immortalized epithelial cell lines from wild type and alpha3beta1 integrin-deficient collecting ducts, we have established a system for studying how integrins maintain epithelial morphology. In wild type cells a normal cortical cytoskeleton is present. In

contrast alpha3beta1 integrin-deficient cells assemle actin stress fibers. Our present results also indicate that alpha3beta1 integrin is required for cadherin:catenin complexes to maintain their association with the cytoskeleton. Our proposed experiments will test the hypothesis that Rho family GTPases act as downstream effectors of alpha3beta1 integrin to mediate cadherin:catenin mediated organization of the cortical cytoskeleton in epithelial cells. We will also test the hypothesis that the pattern of cytoskeletal assembly is determined by the integrin repertoire. These hypotheses will be tested by (1) analyzing downstream effectors of Rho family GTPases in epithelial cell lines from wild type and alpha3beta1 integrin-deficient kidney collecting ducts; (2) Analyzing cadherin:catenin:cytoskeletal interactions in cell lines transfected different with different integrin alpha-subunits; (3) assessing cadherin clustering in wild type and alpha3beta1 integrin-deficient cells, and (4) determining the effects of beta-catenin mutants on cytoskeletal assembly in wild type and alpha3beta1 integrin-deficient cells.

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- **Project Title: KIDNEY DERIVED SOMATOSTATIN**

  Principal Investigator & Institution: Turman, Martin A.; Professor and Chief; Pediatrics; University of Oklahoma Hlth Sciences Ctr Health Sciences Center Oklahoma City, Ok 73126

  Timing: Fiscal Year 2002; Project Start 10-FEB-1998; Project End 31-JAN-2004

  Summary: The broad, long-term objective of this project is to determine if somatostatin (SS) analogues inhibit the excessive renal cell proliferation and fibrogemesis characteristic of many renal diseses. The current proposal addresses the hypothesis that SS and SS analogues 1) inhibit human proximal tubular epithelial cell (PTEC) and mesangial cell (MC) proliferation; and 2) decrease production of the extracellular matrix component, fibronectin (FN) and transforming growth factor-beta1 (TGF-beta1) after induction of these genes with the fibrogenic cytokines, angiotensin II (AII), growth hormone (GH), insulin-like growth factor-1 (IGF-1) or TFG-beta1. Preliminary studies from this laboratory support this hypothesis by demonstrating that 1) PTEC and MC express SS and several SS receptor (sst) subtypes, thus establishing a putative autocrine/paracrine pathway by which SS could modulate renal cell function; 2) SS inhibits PTEC proliferation in serum-free medium; and 3) exposure of tubular cells to SS inhibits FN and TGF-beta1 promoter activity. The specific aims and methods for this project are to: 1) Determine if SS inhibits PTEC and MC proliferation and FN and TGF-beta1 production by testing the effect of SS on proliferation, and on FN and TGF-beta1 expression with recombinant plasmid and adenovirus gene promoter constructs, Northern blot analysis and immunoassays after exposure of cells to AII, TGF-beta1, GH and IGF-1. 2) Determine which sst subtypes mediate inhibition of PTEC and MC proliferation and production of FN and TGF-beta1 by a) testing the ability of sst subtype- selective SS analogues to inhibit MC and PTEC proliferation and production of FN and TGF-beta1, and b) testing for sst subtype expression by Northern, immunoblot, and competitive binding analysis. Many chronic renal diseases, such as diabetic nephropathy, polycystic kidney disease and **glomerulonephritis** are characterized by fibrogenesis and/or excessive renal cell proliferation. If SS analogues prove to be efficacious in decreasing renal cell proliferation and expression of FN and TGF-beta1, the vast clinical experience with SS analogues that has accumulated for the treatment of other diseases can be exploited to design a novel, yet safe, adjunctive treatment to slow the progression of chronic renal disease.

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- **Project Title: LEUKOCYTE ADHESION**

  Principal Investigator & Institution: Smith, C Wayne.; Professor; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

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

  Summary: This application focuses on the inflammatory process in the kidney with respect to the roles of the recently recognized family of Junctional Adhesion Molecules (JAMs). Published literature and our preliminary studies reveal that the three family members (JAM1, JAM2 and JAM3) are expressed in normal renal tissue in different but overlapping patterns involving epithelial and endothelial cells. In addition, JAMs are expressed on cells of hematopoietic lineage in different but overlapping patterns. JAM1 is the most studied and anti-JAM1 antibodies have been found to inhibit leukocyte transendothelial migration in vitro and some inflammation in vivo. We have recently found that JAM2 can bind to JAM3 and this interaction is augments adhesion between JAM2 and the beta1 integrin, VLA-4. Our general hypothesis is that JAM family members play significant roles in the inflammatory processes in the kidney, and that each member provides a distinct contribution. Aim 1. Define the adhesive interactions among leukocytes and endothelial cells that involve members of the JAM family (JAM1, 2 and 3). Screening studies in vitro will be performed to determine the ability of blood leukocyte subtypes to adhere to each JAM family member. Follow-up studies for any newly recognized interactions will address mechanisms and functional significance. We will analyze LFA-1 (CD11a/CD18) binding to JAM1, and we will analyze JAM3 binding to JAM2 and the role of VLA-4 (alpha4, beta1). Studies will utilize human cells (leukocytes and endothelial cells) and appropriate probes. Studies will also use cells from knockout mice when these animals become available to confirm the potential mechanisms in that species. Aim 2. Define contributions of JAMs to kidney inflammation. Screening studies in vivo will be performed to determine the distribution of JAM family members in human and murine renal tissue with and without inflammatory disease. We will develop mice with null and conditional knockouts of JAM2 and JAM3, and perform descriptive studies of kidney tissue in comparison to JAM1 knockouts. Two models of inflammation will be evaluated in these knockout mice - anti-glomerular basement membrane nephritis, and chronic obstructive uropathy.

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- **Project Title: LINKAGE CONSORTIUM FOR END-STAGE RENAL DISEASE**

  Principal Investigator & Institution: Elston, Robert C.; Professor; Epidemiology and Biostatistics; Case Western Reserve University 10900 Euclid Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2002; Project Start 30-SEP-1999; Project End 31-AUG-2004

  Summary: The geriatric population in the United States is the most rapidly expanding age group with individuals over age of 65 comprising approximately 12% of the US population. End stage renal disease (ESRD) is a major health problem in this population with an incidence that has been steadily increasing over the last 10 years. More than 70% of ESRD in this population is associated with either diabetes mellitus and/or hypertension. The remaining 30% can be ascribed to other causes, including **glomerulonephritis.** Numerous studies have suggested that genetic predisposition to diabetic nephropathy, but genes for nephropathy have not yet been identified. We and others have hypothesized that ESRD is a complex disease with multiple genes and environment potentially contributing to its etiology. Because of the complexity of ESRD, identification of genes for this disease may prove difficult. Lessons learned from genetic research in other complex diseases such as diabetes, hypertension, asthma and obesity

indicate that a concerted effort to establish a standardized collection of clinically well-defined families will prove beneficial in the discovery of ESRD genes. We propose to form a Genotyping and Data Coordinating Center (GADCC) for ESRD that will enable six different participating centers (PICs) to collect data from ESRD clinical populations ascertained through well-defined inclusion and exclusion criteria. To achieve this goal we will: (1) Establish an ESRD consortium, comprised of members from six PICs, with oversight by members from the National Institute of Digestive and Kidney Disease, and the External Advisory Committee, (2) Construct a state-of-the-art database for management of data across all six institutions, (3) Provide molecular and statistical genetic expertise and resources to the members of the consortium to map genes for nephropathy. Our overall goal is to establish a network of investigators, with well-characterized clinical populations, who will facilitate mapping of genes for ESRD in a timely manner using novel molecular and statistical genetic technologies.

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- **Project Title: MESANGIAL CELL TYROSINE PHOSPHATASE IN RENAL DISEASE**

  Principal Investigator & Institution: Bowen-Pope, Daniel F.; Professor; Pathology; University of Washington Grant & Contract Services Seattle, Wa 98105

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

  Summary: We have cloned and partially characterized a novel receptor-like protein tyrosine phosphatase, rPTP-GMC1 (Kidphos) that is expressed by mesangial cells that are migrating and proliferating in a rat model of proliferative **glomerulonephritis.** We have shown that Kidphos has low tyrosine phosphatase activity but can catalyze the dephosphorylation of the 3 position of inositol as well as can PTEN, a PTPase-like protein that has been demonstrated to play an important role in inositol phosphate signaling in vivo. We hypothesize that the 3-phosphatase activity of Kidphos plays a role in regulating the migration and/or proliferation of pericytes and pericyte-like (including mesangial cells and liver stellate cells) during development and in disease processes, and that the activity of Kidphos is determined through regulation of expression level as well as through regulation of catalytic activity/specificity by binding of a ligand/counter-receptor to the extracellular domain. We will test this hypothesis in the following specific aims: Aim 1. Determine the structure, biosynthesis, processing, and subcellular localization of Kidphos protein. Aim 2. Characterize the inositol phosphatase activity of Kidphos and its ability to regulate signaling through phosphatidylinositols. We will test the hypothesis that Kidphos has PIP3 3 phosphatase activity in vivo, and that this activity can regulate signaling downstream of P13Kinase, including proliferation, chemotaxis, and survival. Aim 3. Test the hypothesis that Kidphos is expressed by activated pericyte-like cells during development and in disease processes. Aim 4. Use targeted gene disruption and quantitative chimera analysis to test the hypothesis that Kidphos plays an important role in regulating the migration and/or proliferation of mesangial and pericyte-like cells during development and in disease. Aim 5. Identify the putative ligand/counter-receptor for Kidphos. Based on its deduced structure, we hypothesize that the extracellular domain of Kidphos interacts with a ligand or counter-receptor, and that this interaction regulates the activity or substrate access of the cytoplasmic phosphatase domain. In this aim, we describe the strategy we will use to identify, clone, and use this putative ligand.

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- **Project Title: MOLECULAR ANALYSIS OF HUMAN ANTI-GBM ANTIBODIES**

  Principal Investigator & Institution: Madaio, Michael P.; Professor of Medicine; Medicine; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

  Timing: Fiscal Year 2002; Project Start 01-SEP-1997; Project End 30-JUN-2006

  Summary: (provided by applicant): **Glomerulonephritis** mediated by antibodies (Ab) to the glomerular basement membrane (GBM) is the prototype of human glomerular disease produced by pathogenic Ab to intrinsic glomerular components. Although there has been intense investigation into identification of the target basement membrane antigen (Ag) and inflammatory mediators of this disease, less attention has been devoted to the structural features, immunobiology and genes encoding pathogenic human anti-GBM autoAb. Recent technical advances, however, make the selection and large scale production of human autoAb feasible. These advances, coupled with the identification, cloning, expression and availability of the major target autoAg (alpha3 type IV collagen, (alpha3 (IV) for human anti-GBM Ab, provide the ideal circumstances, necessary methodologies and molecular reagents to define the genetic and structural features of human anti-GBM Ab. In the past project period, we have utilized these and other approaches to examine human antiGBM Ab, and the results have defined autoAb, from different patients, as having high affinity and with shared structural features. Furthermore, a new model of anti-GBM disease was developed in Xenomouse II, a novel murine strain that expresses human, but not murine, immunoglobulins. Following immunization with (alpha3(IV), the mice develop crescentic **glomerulonephritis** mediated by human autoAb that share structural features with autoAb produced by patients. Further-more a pathogenic monoclonal Ab have been identified and characterized. In parallel genetic and structural analysis of Fab derived from nephritic patients has been initiated. Our goal is to extend these studies to examine autoAb from both patients and Xenomouse II to pursue the following Specific Aims: i) To define the structural properties of pathogenic human anti-alpha3 (IV) collagen Ab.and use this information ii) To develop small molecules with high affinity and specificity for human anti-GBM Ab. Our working hypothesis is that molecular and structural analysis of pathogenic autoAb, together with existing information pertaining to the relevant pathogenic epitopes of alpha3(IV) will lead to a more precise understanding of this particular autoAb-autoAg interaction, and that this information, coupled with an established model of nephritis mediated by human anti-GBM Ab, will be useful in the design and evaluation of specific inhibitors of autoAb deposition or/and autoAb production. The results also have the potential to provide insight into the origins of pathogenic human autoAb. Furthermore, since the autoAb response in patients with anti-GBM disease is focused on a specific and will defined autoAg (alpha3(IV), this condition represent the ideal situation, where evaluation of therapy directed against a specific subset of soluble and surface receptors on immunoreactive cells, to alter disease activity, can be evaluated. If successful, the strategy has the potential for application in the development of therapeutic strategies in other Ab-mediated diseases.

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

- **Project Title: MOLECULAR ASPECTS OF ALPORT RENAL DISEASE PROGRESSION**

  Principal Investigator & Institution: Cosgrove, Dominic E.; Staff Scientist Iii & Associate Professo; Father Flanagan's Boys' Home Boys Town, Ne 68010

  Timing: Fiscal Year 2002; Project Start 15-APR-1999; Project End 31-MAR-2003

Summary: Alport syndrome results from mutations in either the type IV collagen COL4A3, COL4A4, or COL4A5 genes. Pathology includes a juvenile onset progressive **glomerulonephritis** with glomerular basement membrane (GBM) rarefication and expansions of the mesangial matrix, culminating in death due to renal failure. A gene-knockout mouse model for Alport syndrome was produced in this laboratory, the renal pathology of which is remarkably similar to that observed in humans. Deposition of specific extracellular matrix proteins in the GBM follows course with basement membrane rarefication. This must be due to changes in their synthesis and/or turnover. The aims of this proposal focus on clarifying the role of synthesis and degradation of basement membrane collagens and associated proteins in Aport GBM disease progression. The possible role of integrin receptors, transforming growth factor beta 1 (TGF-beta1), and metalloproteinases (and their inhibitors) will be explored. Quantitative analysis (employing material from isolated glomeruli) will be used to determine relative levels of specific mRNAs (by norther blot) and their corresponding proteins (by western blot). In situ hybridization studies will determine which glomerular cell types synthesize these proteins. Observations with potential mechanistic significance will be tested using human renal biopsy tissues from normal and Alport patients. Whether TGF-beta1 or proteinuria is linked to induction of genes encoding extracellular matrix molecules will be probed using a combination approach of TGF-beta type I and II receptor inhibitor (FK506) molecules will be probed using a combination approach of TGF-beta1. A double knockout of the COL4A3 and integrin alpha1 chain has been produced, and shows a marked reduction in the rate of Alport renal disease progression. The molecular mechanism of this surprising effect will be explored. Identification of the molecular mechanisms underlying the imbalance in GBM homeostasis in Alport syndrome may reveal potential targets for pharmacologic intervention.

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

- **Project Title: MOLECULAR MECHANISMS IN HEREDITARY NEPHRITIS**

  Principal Investigator & Institution: Hudson, Billy G.; Chairman; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

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

  Summary: Alport Syndrome is a hereditary disorder characterized by progressive nephropathy which is frequently associated with sensorineural deafness and ocular abnormalities. The nephropathy has been linked to a structural abnormality in the glomerular basement membrane (GBM) which is caused by mutations in the gene encoding the alpha3, alpha4 and alpha 5 chains of type IV collagen. The most common form is X-linked, in which over 200 mutations have been found in the COL4A5 gene encoding the alpha5 chain. These mutations interfere with the formation of the alpha3(IV)/alpha4(IV)/alpha5(IV) supramolecular network of type IV collagen. Most male patients have near normal kidney function at birth, which deteriorates over time leading to end-stage renal disease by mechanisms that are not understood. The central thrust of this proposal is to test the hypothesis that the progression to end-stage renal disease in X -linked hereditary nephritis evolves from a congenital malformation of the glomerular basement membrane (GBM) which involves COL4A5 mutations that arrest a developmental switch from the immature alpha1(IV)/alpha2(IV) network to the nature alpha3(IV)/alpha4(IV)/alpha5(IV) network, and the persistence of this immature network predisposes the GBM to proteolytic degradation. The cornerstone of the research plan is a use of the canine X-linked model of the human disease in which the COL4A5 gene mutation is a premature stop codon. The specific aims are: Aim 1:

Determine the nature and timing of the switch from immature to mature GBM in normal dog kidney in comparison to affected male dogs. Aim 2: Determine which glomerular cells synthesize the alpha3(IV), alpha4(IV) chains. Aim 3: Examine the relationship between the expression of the alpha3(IV), alpha4(IV) and alpha5(IV) chains. Aim 4: Determine the temporal relationship at both the message nd protein levels of the expression of the alpha1(IV)-alpha6(IV) chains in normal dogs compared to affected male dogs during progression of their disease. Aim 5: Determine the susceptibility of type IV collage of GBM to proteolytic degradation in normal and affected male dogs. The achievement of these aims requires application of the techniques of molecular biology, biochemistry, immunochemistry and cell biology. It is anticipated that the achievement of the aims will yield new insights into the mechanisms underlying the pathogenesis of Alport Syndrome. An understanding of these mechanisms is fundamental to the development of therapeutic measures to correct the disorder by gene therapy or to delay progression to end stage renal disease.

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- **Project Title: MOLECULAR PATHOGENESIS OF ANTI-GBM ANTIBODY NEPHRITIS**

  Principal Investigator & Institution: Borza, Dorin-Bogdan; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

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

  Summary: Antibody-mediated glomerular injury is a major cause of **glomerulonephritis** leading to loss of renal function. Type IV collagen of the GBM is the target of pathogenic antibodies in Goodpasture's (GP) disease, Alport post-transplant nephritis, and experimental anti-GBM disease. Antibodies bind to the NC1 domains of the alpha3alpha4alpha5(IV) network, which are present in the native GBM as a hexamer complex. The recent mapping of the cryptic GP epitopes within the alpha3(IV) NC1 domain and the structural characterization of the alpha3alpha4alpha5(IV) NC1 hexamer set the stage for addressing new questions about the molecular pathogenesis of anti-GBM disease. How GP autoAbs bind to their epitopes, sequestered in the NC1 hexamers in the native GBM, and how the cryptic epitopes could be exposed to initiate an auto-immune response will be established. The location of the epitopes of Alport alloAbs will be mapped. The specificity of anti-GBM antibodies in animal models of anti-GBM nephritis, and whether they resemble GP autoAbs or Alport alloAbs, will be determined. The central hypothesis is that the etiologic agents and the targets of pathogenic anti-GBM Abs are: (a) cryptic epitopes, sequestered within the native NC1 hexamers of GBM, in GP disease; but (b) exposed epitopes, accessible in the NC1 hexamers, in Alport post-transplant nephritis. The rationale is that immune tolerance toward native GBM components restricts the repertoire of anti-GBM Abs to cryptic epitopes in GP disease, but not in Alport syndrome, in which the GBM alpha3alpha4alpha5(IV) network is absent. Four specific hypotheses will be tested: (1) Pathogenic GP autoAbs, unlike Alport alloAbs, bind only to a sub-population of NC1 hexamers that are not cross-linked in the native GBM network and contain alpha3 NC1 monomers. (2) Alport allo-epitopes are accessible in the GBM network and map to the surface of the NC1 hexamer. (3) The GP epitopes of alpha3(IV)NC1 are nephritogenic and will induce pathogenic GP-like autoAbs in mice immunized with alpha3 NC1 monomers, chimeras containing the epitopes, and dissociated--but not native--GBM NC1 hexamers. (4) The specificity and pathogenicity of anti-GBM Abs are modulated by immune tolerance and by the association state (monomer vs. hexamer) of nephritogenic NC1 domains. It is anticipated that completion of these aims will provide a better

understanding of the molecular etiology and pathogenesis of human GP disease and Alport post-transplant nephritis, will establish animal models that more closely resemble human anti-GBM disease, and may identify new molecular targets for prevention or therapeutic intervention.

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

- **Project Title: P450 EICOSANOIDS AND RENAL FUNCTION IN HYPERTENSION**

  Principal Investigator & Institution: Roman, Richard J.; Professor; Physiology; Medical College of Wisconsin Po Box26509 Milwaukee, Wi 532260509

  Timing: Fiscal Year 2002; Project Start 01-JUL-1986; Project End 31-MAR-2005

  Summary: (Adapted from the Investigator's Abstract): Recent studies have indicated that cytochrome P450 (CYP) metabolites of arachidonic acid (AA), in particular 20-HETE, play a central role in the regulation of renal tubular and vascular function and the long-term control of arterial pressure. During the last funding period, this investigator identified a gene of the cytochrome P4504A family that is differentially expressed in the kidney of Dahl S and Lewis rats and that cosegregates with the development of hypertension in an F2 cross of Dahl S and Lewis rats. To further explore the role of this system in the control of renal function, they have developed (in collaboration with Dr. J. Rapp) congenic strains of rats in which overlapping segments of chromosome 5 of the Lewis rat, that include or exclude the P4504A region, have been introgressed into the Dahl S genetic background by greater than 8 generation of selective back-cross breedings. They now propose to determine whether the P4504A genes play a causal role on altering renal function and/or the development of hypertension and glomerulosclerosis in Dahl S rats by: 1) comparing blood pressure, renal function and the expression of P4504A enzymes in congenic strains of rats in which the P4504A alleles of normotensive Lewis rats have been introgressed into the Dahl S genetic background; 2) determining whether selective intrarenal blockade of the formation of 20-HETE can "rescue" the hypertensive and renal phenotypes in P4504A congenic Dahl S rats; 3) cloning and sequencing the 5'-flanking regions of the P4504A2 and 4A3 genes to determine whether there are sequence variants that can explain the differences in the expression of these genes in the outer medullas of the kidneys of Dahl S and Lewis rats. These studies will provide important new information regarding the role of P450 metabolites of AA in the regulation of renal function and will determine whether this pathway plays a primary or secondary role in the development of hypertension and/or glomerular disease in Dahl S rats.

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

- **Project Title: PATHOGENESIS OF MEMBRANOUS GLOMERULONEPHROPATHY**

  Principal Investigator & Institution: Makker, Sudesh P.; Professor of Pediatrics and Chief; Pediatrics; University of California Davis Sponsored Programs, 118 Everson Hall Davis, Ca 956165200

  Timing: Fiscal Year 2000; Project Start 10-SEP-1983; Project End 30-NOV-2004

  Summary: (Adapted from Investigator's Abstract): The investigators' long-term goal is to understand the mechanisms involved in the pathogenesis of membranous glomerulonephropathy (MGN). They will work with the accepted experimental model of MGN, active Heymann Nephritis (HN) of rat, and concentrate their studies on the putative autoantigen, gp330, a key participant in the mechanisms of pathogenesis. Their specific aims are: A) Identify the location and structure (amino acid sequence) of the B-cell epitopes of gp330 involved in the disease. To achieve this they will isolate gp330

proteolytic fragments reactive with autoantibodies, microsequence the fragments, localize them in gp330 sequence, clone into expression vectors the corresponding cDNA's prepared by PCR amplification, test expressed fusion proteins for autoantibodies-reactivity by immunoblotting and ELISA, and for immunogenicity by immunizing rats. They will narrow down the location of the continuous and discontinuous epitope(s) by analyzing smaller clones produced by PCR, synthesize overlapping peptides spanning the epitope regions and identify the precise amino acid sequence of autoantibodies-reactive linear epitope(s) and the sequences possibly involved in the discontinuous epitopes, and test the pathogenic potential of all of the identified epitopes. B) Test the identified sequences for tolerogenic and therapeutic potential in active HN by synthesizing the putative peptide(s) or protein fragments in larger quantities, administering these peptide/protein fragments into animals, and then assessing the disease parameters. Data from these studies will provide important new information on the structure of the B cell epitopes of gp330 involved in active HN. This knowledge will lead to 1) a greater understanding of the pathogenesis of this disease at the molecular level and, 2) possibly its treatment with specific immunomodulation.

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

- **Project Title: PATHOGENESIS OF MURINE SYSTEMIC LUPUS ERYTHEMATOSUS**

  Principal Investigator & Institution: Kono, Dwight H.; Associate Professor; Scripps Research Institute Tpc7 La Jolla, Ca 92037

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

  Summary: (Adapted from the Investigator's abstract): Genetic susceptibility is the major predisposing factor thus far identified for spontaneous systemic lupus erythematosus (SLE) in both humans and animal models of the disease. Previously, the investigator identified in an (NZB x NZW)F2 intercross 8 loci designated Lbw1-Lbw8 on chromosomes 17, 4, 5, 6, 7, 18, 1, and 11, respectively, that exhibited evidence of linkage to one or more of four major SLE disease traits. Five of these loci have been confirmed in other crosses. The investigator has generated congenic lines for Lbw2, a locus on chromosomes 4 required for hemolytic anemia, and Lbw5, a locus on chromosome 7. Lbw5 is an autoimmune accelerator that increases the production of IgG autoantibodies and promotes hemolytic anemia, **glomerulonephritis** and early mortality in NZB mice. In this application the investigator proposes to: 1) define the genetics of immunoglobulin and autoantibody responses and the relationship of autoantibody specificity to other traits. This will be done by linkage analysis using an expanded set of BWF2 mice; 2) generate congenic lines for Lbw1, 2, 4, 5 and 7 to examine the effects of susceptibility and resistance alleles at these loci on clinical and immunologic manifestations; and 3) undertake positional cloning of Lbw2 and Lbw5.

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

- **Project Title: PHARMACOKINETICS & GENOMICS IN GLOMERULAR DISEASES**

  Principal Investigator & Institution: Joy, Melanie S.; Medicine; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

  Timing: Fiscal Year 2004; Project Start 01-SEP-2004; Project End 31-AUG-2009

  Summary: (provided by applicant): Treatment approaches for autoimmune related kidney diseases such as ANCA vasculitis have been relatively non-altered over the last several years and are associated with toxicity and treatment failures. Our long term-goal is to evaluate the pharmacokinetic and pharmacogenomic factors associated with drug

metabolism and transport in order to understand and improve renal treatment responses in ANCA vasculitis. The central hypothesis is that the metabolism of cyclophosphamide and transport of glucocorticoids are different in individual patients with ANCA vasculitis and these differences account for variations in renal outcomes. The outcomes differences are due to genotypic and phenotypic variations in drug transport by P-glycoprotein and drug metabolism by CYP 450 metabolizing enzymes, that lead to inadequate dosing of glucocorticoids and cyclophosphamide. This proposal will phenotype and genotype ANCA vasculitis patients (for metabolism of cyclophosphamide and transport of P-glycoprotein) to investigate the role of activity and polymorphisms to renal outcome responses to treatment. Leukocyte expression of the genes encoding P-glycoprotein and CYP 450 enzymes for assessment of phenotype will also be analyzed by microarray technology to explore the potential for further evaluation of this noninvasive testing method for prediction of phenotype. Functional phenotyping with probe drugs will be performed to evaluate P-glycoprotein (fexofenadine), and relevant CYP 450 enzymes [CYP 2C9 (flurbiprofen), 2B6 (bupropion), and 3A4 (erythromycin)]. Together with renal and other clinical outcome measures, the planned genotyping and phenotyping assessments tests should provide some understanding of treatment outcome differences. The correlations between genotype and phenotype will also be evaluated. The research projects described are the planned 5-year K23 career development for Dr. Melanie S. Joy, Assistant Professor in the Division of Nephrology. Her mentor, Dr. Ronald Falk, is the Division Chief of Nephrology and an expert in the diagnosis and treatment of glomerular diseases. Her co-mentor, Dr. Kim Brouwer, is an expert in the area of drug transport and metabolism. Together with her mentors, the applicant has devised a combined didactic, clinical, and laboratory research plan, using resources from the Schools of Medicine and Pharmacy. The goal of this plan is to enhance the applicant's skills to become an independent nephrology clinical investigator with expertise in drug transport and metabolism. The selection of collaborators with expertise in the areas of this grant will enhance the career development of Dr. Joy

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- **Project Title: PHOSPHOLIPASE A2 AND SIGNAL TRANSDUCTION**

  Principal Investigator & Institution: Bonventre, Joseph V.; Professor; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2002; Project Start 01-APR-1987; Project End 31-MAR-2007

  Summary: Description (provided by applicant) Our proposed studies will focus on defining the roles played by group IVA cytosolic phospholipase A2 (cPLA2) and group IIa and V sPLA2 enzymes in mesangial cell signaling pathways important for growth regulation and inflammation. We will capitalize on the (cPLA2 /-, IIaPLA2-/-), (cPLA2-/-, IIaPLA2+/+) mice, as well as littermate control (cPLA2+/+, LA2-/-) and (cPLA2+/+, IIaPLA2+/+) mice which we have generated, the unique lines of mesangial cells derived from these mice, and reagents we have generated for PLIP and TRIP-Brl, two nuclear proteins which we have cloned. In Specific Aim 1 we will determine the role of cPLA2, the group IIa and V sPLAs, and the cPLA2-interacting protein, PLIP, in a mesangial cell PI-3kinase/Akt/GSK-3b/b-catenin signaling pathway which we propose regulates cyclin, cyclin-dependent kinase (cdk) and cyclin-dependent kinase inhibitors (cdkIs) and other proteins important for this cell's proliferative response to growth factors and inflammatory cytokines. The importance of nuclear translocation of components of the signaling pathway will be explored. The relative roles of cPLA2, groups IIa and V PLA2 and PLIP (and the alternatively spliced Tip60) on ERK activation, c-Myc expression, and

TRIP-Br levels will be evaluated. We will also attempt to identify the effector of cPLA2-induced modulation of the PI3-kinase/Akt/GSK-3beta and cdkI/cyclin signaling systems, evaluating specifically the potential roles of noncyclooxygenase products of arachidonic acid and NADPH oxidase. In Specific Aim 2 we will determine the role of cPLA2 in TNFa- and IL-1beta-induced apoptosis and generation and secretion of inflammatory mediators and determine how the absence of cPLA2 and or group IIa PLA2 alters the response of the glomerulus in experimental models of **glomerulonephritis,** Cytokine signaling is important for inflammatory responses as well as proliferative ones. Effects of PLIP/Tip60 on cytokine-induced apoptosis will be evaluated. We will use our unique cell lines to dissect the role of arachidonic acid generated by PLA2 or group IIa or V sPLA2 on oxidant stress in the cell and evaluate the roles played by arachidonate and oxidants in eicosanoid production and NF-kB action. The effects of cPLA2, PLIP and groups IIa and V PLA2 on mesangial cell secretion of monocyte chemoattractant protein (MCP-1) and role of phospholipase D2 activity will in secretion of MCP-1 and group IIa PLA2 be explored.

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

- **Project Title: PHOSPHORYLATION IN RENAL CELL INJURY**

  Principal Investigator & Institution: Choudhury, Goutam G.; Medicine; University of Texas Hlth Sci Ctr San Ant 7703 Floyd Curl Dr San Antonio, Tx 78229

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

  Summary: (Adapted from the Applicant's Abstract): Platelet-derived growth factor receptor b (PDGFR) is expressed in injured glomeruli and in activated cultured mesangial cells. Activation of PDGFR stimulates mesangial cell proliferation and migration, phenotypes manifest in many glomerular diseases including mesangioproliferative **glomerulonephritis** (GN). We recently demonstrated that PDGFR-stimulated phosphatidylinositol 3 kinase (PI 3K) activity is necessary for proliferation and migration of cultured mesangial cells. A serine threonine kinase, Akt, has been identified as a downstream target of PI 3K. Our hypothesis is that Akt regulates mesangial cell activation which includes proliferation and migration of these cells during glomerular injury. We propose to characterize pathways by which Akt functions in cultured mesangial cells and in vivo in a model of anti-Thy-1-induced GN in rats. Akt kinase activity will be determined during progression of GN. The role of Akt kinase in mesangial cell activation will be determined by examining the effect of dominant negative and constitutively active versions of this protein on mesangial cell proliferation and migration. Proteins that regulate Akt kinase activity or represent substrates for this enzyme will be identified using a yeast two-hybrid protein-protein interaction strategy. Open reading frames of interacting proteins will be determined by nucleotide sequencing. Characterization of these proteins will be carried out by raising antipeptide and GST-fusion protein antibodies. Regulation of the Akt activity by these Akt-associated proteins will be studied in vitro and in cultured mesangial cells. The role of these proteins in pathways involving Akt and regulating mesangial cell proliferation and migration will be determined. Our preliminary data indicate that cross-talk between PDGFR tyrosine kinase and bone morphogenetic protein receptor serine threonine kinases exists in mesangial cells. We have recently demonstrated that activation of receptor serine threonine kinase by bone morphogenetic protein 2 (BMP-2), a member of TGFb superfamily, inhibits PDGF-induced DNA synthesis in the absence of matrix expansion. This inhibition is due to inhibition of PDGF-induced Erk1/2 type of MAPK (mitogen-activated protein kinase). In our second specific aim, we will use BMP-2 in a therapeutic approach to treat mesangioproliferative GN in rats. An adenovirus vector

expressing BMP-2 will be constructed. Adenovirus-mediated gene transfer and engineered mesangial cell vectors will be used to express BMP-2 in vivo to inhibit mesangial cell proliferation in GN, without inducing extracellular matrix expansion. Activities of PI 3 kinase, MAPK and Akt will be determined in the glomerular lysates from vector-targeted animals. These studies will identify important signaling mechanisms involved in glomerular pathology and help to establish effective therapeutic modalities for treatment of proliferative forms of GN.

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- **Project Title: PILOT/FEASIBILITY PROGRAM**

  Principal Investigator & Institution: Fogo, Agnes B.; Professor; Vanderbilt University 3319 West End Ave. Nashville, Tn 372036917

  Timing: Fiscal Year 2002; Project Start 01-APR-1992; Project End 31-MAR-2007

  Summary: Visceral glomerular epithelial cells (podocytes) are a component of the glomerular filtration barrier. Due to a lack of ability for post-natal proliferation, the podocyte is a most vulnerable component of the glomerulus, and podocyte injury triggers irreversible change sin many glomerular diseases. The ultimate goal of this project is to elucidate the molecular mechanisms of podocyte damage through the study of the pathogenesis of HIV-1 associated nephropathy (IVAN). In HIVAN, glomeruli show a characteristic change, i.e., collapsing focal segmental glomerulosclerosis (FSGS), in which podocytes lose differentiation markers, proliferative and undergo apoptosis. Similar podocyte dysregulation is observed in idiopathic collapsing glomerulopathy and the FSGS variant with cellular lesion. In addition, down-regulation of differentiation markers occurs also in more common glomerular diseases, including minimal change disease and mesangial proliferative **glomerulonephritis.** Previous transgenic mouse studies showed than when HIV-1 DNA containing vif, vpr, rev and tat is expressed by the authentic LTR promoter, the kidney develops a renal disease faithfully mimicking human HIVAN. Renal cross transplantation between the transgenic and wild-type mice revealed that the transgene expressed in the kidney causes the renal disease. Based on this information, the following specific aims will be investigated during the first two years. Aim #1. Generation of transgenic mice in which podocyte-specific expression of HIV-1 gene that is essential for the pathogenesis of HIVAN by transgenic mice. These studies will be followed by identification of the specific molecule(s) in podocytes that are associated with the product of the pathogenic HIV-1 gene to ascertain the common mechanism(s) of podocyte dysregulation. Genetic studies of inherited polycystic kidney disease (PKD) in human and animal models have clearly shown that mutations at multiple loci result in various forms of PKD. While the cystogenesis itself is thought to be a primary cause of renal injury, several studies have stressed the important relationship between the onset of tubulointerstitial fibrosis, and the progression to end-stage renal disease. The PI has characterized a mouse model for PKD caused by three independent mutations, kat, kat21, kjat3J, that map to the same locus on Chromosome 8. By positional cloning, she has identified the gene mutated as the NIMA (Never In Mitosis A) related kinase, Nek1. The PI hypothesizes that in the kidney, NEK1 protein belongs to a signaling pathway that promotes the full maturation in renal tubular epithelial cells. The PI has also shown that the loss of Nek1 function leads to an increase in TGFbeta1 mRNA levels in renal interstitial as well as tubular cells. Therefore, these altered/immature renal epithelial cells may not only facilitate renal cystogenesis but also contribute directly to tubulointerstitial fibrosis. The PI is currently examining in her funded RO1 how the loss of Nek1 function leads to renal cystogenesis. In this pilot proposal she will pursue a new area of research: investigating the role of Nek1-null

tubular epithelial cells in interstitial fibrosis. The hypotheses to be tested are: 1. The loss of Nek1 expression in renal tubular cells increases the activation of TGFbeta1 in those cells 2. The loss of Nek1 expression in renal tubular cells increases epithelial-mesenchymal transdifferentiation.

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

- **Project Title: PILOT-CHARACTERIZATION OF CXCL 16 IN RENAL INFLAMMATION**

  Principal Investigator & Institution: Garcia, Gabriela E.; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

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

  Summary: CXCL16 is a novel, unique CXC chemokine with characteristics of CC chemokines and structurally related to CX3CL1 since both are membrane bound chemokines. CXCL16 is expressed in antigen presenting cells including CD19 + B cells and CD14 + monocyte/macrophages. We have found that this chemokines is also expressed in glomerular endothelial cells. This chemokine was markedly induced in the glomeruli of Wistar-Kyoto rats with anti-glomerular basement membrane (GBM) antibody (Ab) **glomerulonephritis** (GN) throughout the disease and CXCL16 induced migratory response of glomerular infiltrate isolated from this model of GN. This data suggest that CXCL16 may play a critical role in the leukocyte influx in immune-mediated inflammation in the kidney. We propose to study the mechanism of CXCL16 regulation and signaling in glomerular endothelial cells as well as the CXCL16/CXCR6 interactions mainly between glomerlular endothelial cells and monocyte/macrophages. We will study the potential role of CXCL16 in leukocyte capture and firm adhesion and whether this effects can be mediated under physiological flow conditions. We will further dissect this multidomain chemokine to determine the functional domain(s) in CXCL16-mediated adhesion. In in vivo studies we will analyze the functional role of CXCL16 during the progression of acute injury to renal fibrosis in a model of GN and tubulointerstitial nephritis by generating blocking antibodies. Further we will investigate whether blocking CXCL16 could intervene in the progressive phase of established GN and tubulointerstitial nephritis. These findings are expected to offer an approach to therapy that influences the regulation of chemokine/chemokine receptor to modulate renal diseases that may be CXCL16 associated, including tubulointerstitial nephritis, GN and endothelium-related inflammatory diseases such as vasculitis, allograft rejection, ischemia/reperfusion injury and atherosclerosis.

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

- **Project Title: PILOT--STANNIOCALCIN-1 INFLAMMATION**

  Principal Investigator & Institution: Sheikh-Hamad, David; Associate Professor; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

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

  Summary: Stanniocalcin-1 (STC1) is a calcium-regulating hcrmone in bony fish. It is produced and stored in the corpuscle of Stannius, an accessory organ to the kidney. Elevation of ionized calcium in the fish plasma induces synthesis and secretion of STC1 into the blood. Upon circulation in the gill, it inhibits calcium influx from the aquatic environment, while in the gut, it inhibits calcium uptake. T'he mammalian homologue of this hormone is produced in multiple organs and is thought to function in an autocrine and/or paracrine manner. The cumulative data suggest that it inhibits calcium flux in cardiomyocytes, glut epithelium and neuronal cells. In neuronal cells, it is

upregulated following ischemic injury and appears to have a cytoprotective effect in a manner that requires inhibition of calcium flux into the cells. Recent findings from our laboratory revealed striking upregulation of STC1 in the proximal tubules following ischemic or obstructive renal injury in humans. In addition, STC1 protein decorated the plasma membrane of inflammatory cells in the injured tissue. These findings suggested the involvement of STC1 in tissue inflammation, indeed, STC1 attenuated MCP1-mediated intracellular calcium increas and chemotaxis (using a trans-filter assay) in the macrophage-like Raw264.7 cells. The following specific aims are intended to elucidate the molecular mechanisms that underlie this process. Specific Aim I: will test the hypothesis that STC1 inhibits chemotaxis in other mononuclear cells (lymphocytes) in a manner that involves alterations in intracellular calcium currents. Specific Aim II: will examine the hypothesis that STC1 is an anti-inflammatory molecule. This will be tested using STC1 in an in vivo model of rat (WKY) anti-GBM (glomerular basement membrane) **glomerulonephritis.**

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

- **Project Title: PLATELET CELL ADHESION MOLECULES**

  Principal Investigator & Institution: Furie, Bruce; Chief, Coagulation Unit; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

  Timing: Fiscal Year 2002; Project Start 01-DEC-1994; Project End 30-NOV-2003

  Summary: P-selectin is a cell adhesion molecule that resides in the storage granules of platelets and endothelial cells. Upon cell stimulation, the protein is translocated to the plasma membrane where it functions as a leukocyte receptor for PSGL-1 on neutrophils and monocytes. The current application represents a continuation of studies of the biology of P-selectin and PSGL-1. Since PSGL-1 has been shown to bind to all selectins, the kinetic and equilibrium binding of soluble PSGL-1 to soluble P-selectin, E-selectin and L-selectin will be analyzed by fluorescence spectroscopy. During the past grant period, we have prepared a PSGL-1 deficient mouse by homologous recombination and have completed the initial characterization. Cells from this mouse will be used to establish the physiologic role of PSGL-1 in selectin function by comparing the interaction of PSGL-1 (-/-), (+/-) and (+/+) leukocytes with P-selectin, E- selectin and L-selectin under rolling conditions in a parallel plate ex vivo assay using neutrophils and T lymphocytes. The PSGL-1 deficient mouse and double knockout mice including PSGL-1 null/P-selectin null mice, PSGL-1 null/E-selectin null mice and PSGL-1 null/L-selectin null mice will be employed in model systems to determine the physiologic function of PSGL-1. Pathologic processes to be studied include models of non- immune mediated and T-cell mediated skin inflammation, leukocyte rolling following trauma and TNF, experimental **glomerulonephritis,** chemical peritonitis, bacterial pneumonitis, thrombosis, atherosclerosis, wound healing and platelet rolling. To understand the molecular basis of signal transduction and effector function induced by platelet activation or P-selectin binding to the P-selectin ligand on leukocytes, the induction of Ca2+ flux in platelets by PSGL-1 via P-selectin will be analyzed. Furthermore, binding of cytoplasmic tails of P-selectin and PSGL-1 to cytoplasmic signalling proteins in platelets and monocytes respectively will be examined using dimer constructs of cytoplasmic tails. If these studies indicate that PSGL-1 and ESL-1 are not physiologically critical counterreceptors for E-selectin or that there is evidence for another P- selectin ligand, we propose to expression clone a novel E-selectin ligand from a leukocyte library prepared from WEHI cells and a novel P-selectin ligand from a library prepared from neutrophils isolated from the PSGL-1 null mouse. The putative ligands will undergo characterization of their full length cDNAs and comparison of their predicted amino

acid sequences with that of the PSGL-1, ESL-1 and GlyCAM-1. These studies will contribute to our understanding of the physiologically relevant receptors and counterreceptors that define cell-cell interaction during inflammation.

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

- **Project Title: PRE&POST-DOCTORAL TRAINING IN NEPHROLOGY&HYPERTENSION**

  Principal Investigator & Institution: Gluck, Stephen L.; Professor; Medicine; University of Florida Gainesville, Fl 32611

  Timing: Fiscal Year 2002; Project Start 01-JUL-1985; Project End 30-JUN-2007

  Summary: provided by applicant): The goal of the proposed research training program is to prepare trainees for a successful academic research career by providing expert and comprehensive mentoring in laboratory or clinical research pertinent to kidney disease. The program proposed in this application has the faculty expertise, infrastructure, and research opportunities to provide outstanding training. The training program is organized into five thematic administrative units designed to provide greater interdisciplinary collaboration, adminstrative cohesiveness, and enhance research opportunities for trainees: the Core Nephrology Unit; the Diabetes, Human Genetics, and Gene Therapy Unit; the **Glomerulonephritis** and Renal Immunology Unit; the Stem Cell and Developmental Biology Unit; and the Clinical Research Training Unit. The program has thirty training mentors from different basic and clinical departments; the number of faculty has been increased substantially to provide a greater scope, depth and opportunities for interdisciplinary research in the basic sciences to accommodate the increasingly complex and technologic nature of research and the need to have greater participation of the basic sciences in the training of M.D. basic science investigators in nephrology. The research encompassed by the training program is highly pertinent to normal renal physiology and kidney disease. It includes the physiology, molecular biology and cell biology of tubular epithelial cells ion transport, the biochemistry of signaling pathways in kidney epithelia, the cell biology of the calcium receptor and other G-protein coupled receptors in renal epithelia, the early gene response to oxidative renal injury, the biochemical basis of renal tubular injury, and the cell biology and biochemistry of vascular endothelium. The training program also broadly encompasses the immunology, genetics, glomerular inflammation, and epithelial stem cell differentiation. Trainees will have full access to the entire graduate school curriculum, The clinical investigation program includes offering trainees the opportunity to apply for and enroll in the K30 APPCI program, which provides rigorous training in clinical epidemiology, biostatistics, outcomes research, study resign and a mentored clinical research program. Trainees are required to participate in a weekly formal research conference as well as weekly research-in-progress conferences in which both trainees and mentors responsible for supervision of research present their research.

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

- **Project Title: PREDICTION OF LUPUS OUTCOME BY GENE EXPRESSION PATTERNS**

  Principal Investigator & Institution: Winchester, Robert J.; Professor; Pediatrics; Columbia University Health Sciences Po Box 49 New York, Ny 10032

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-DEC-2006

  Summary: (provided by applicant): Support is sought for performing mechanistic studies to define the gene expression profiles of glomeruli isolated from biopsy sections

of lupus **glomerulonephritis** with the overall goals of determining whether the glomerular gene expression phenotype will predict outcome and efficacy in an ongoing parent trial. The parent trial compares administration of CellCept versus IV Cytoxan for initiating control of biopsy-proven lupus nephritis. We have demonstrated the feasibility of studying gene expression profiles by microarray analysis in glomeruli isolated from frozen biopsy sections by laser microdissection t6 characterize the molecular pathologic mechanisms leading to lupus nephritis. This work revealed considerable heterogeneity in gene expression patterns in samples classified as proliferative **glomerulonephritis,** suggesting the feasibility of lupus renal biopsy subclassification by gene expression criteria. The expressed genes formed 8 main clusters and the presence or absence of genes comprising these clusters in a given sample divided the biopsies into 3 distinct types. The hypothesis underlying the proposed studies is that differences in molecular pathologic mechanisms revealed by the various transcriptional phenotypes will predict the heterogeneous natural history and therapeutic outcome of lupus. The first aim of the proposed mechanistic studies is to cluster glomerular gene expression patterns in diagnostic renal biopsies performed in the current trial and use them to extend understanding of pathways involved in the molecular pathogenesis of lupus glomerulitis. Parallel quantitative PCR for selected genes found through the microarray assessment will be performed to validate the patterns found and determine if their differential expression can be used as a surrogate. The second aim will correlate the clusters and pathways with conventional pathologic features to identify the molecular basis of the pathologic findings. The third aim will determine whether particular outcomes of the trial could be predicted by the gene expression phenotype of the initial renal biopsy. In particular we will address, first, whether one gene expression type, characterized by apoptosis, TNF signaling and fibrosis, is highly correlated with poor outcome and thus predict the subset of non-responders to Cytoxan or CellCept. Second, whether CellCept will prove to be efficacious in a different gene expression subset, suggesting it could be used in these cases as a less toxic alternative to Cytoxan.

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

- **Project Title: PROTEOMIC AND MRNA PROFILING OF URINE AND URINE SEDIMENT**

  Principal Investigator & Institution: Rovin, Brad H.; Professor; Internal Medicine; Ohio State University 1960 Kenny Road Columbus, Oh 43210

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

  Summary: (provided by applicant): The objective of this project is to validate urine protein and gene expression profiling as tools to derive novel mechanistic and diagnostic information from the urine of patients with **glomerulonephritis.** Although previous investigations have examined urine to gain insight into the pathogenesis of renal disease, and to identify clinically relevant markers of disease activity, severity, or prognosis, such studies were limited to analysis of a relatively small number of pre-chosen candidate proteins. It is postulated that by examining the entire urinary proteome during **glomerulonephritis,** as well as the proteins and genes expressed by leukocytes present in nephritic urine, previously unrecognized patterns of protein expression will emerge. Investigation of these protein networks will lead to new insights into the pathogenesis of glomerular disease. Furthermore, by characterizing patterns of protein expression associated with distinct phases of disease activity, novel prognostic indicators will be identified. These themes will be developed in two Specific Aims. In Aim 1, two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) will be used to

map the urine proteins of a well-characterized cohort of patients with SLE nephritis before, during, and after relapse of renal disease. These studies will define how the urinary proteome changes from inactive disease through active SLE. Differentially expressed proteins from these different phases of disease activity will be further identified by mass spectrometry (MS). It is predicted that the protein networks engaged before relapse will reflect mechanisms of disease activation, while proteins expressed in active disease will represent mediators of renal injury, and proteins expressed during treatment will determine therapeutic success or failure. Aim 2 will extend proteomics to the leukocytes present in the urine of patients with active SLE nephritis. Additionally, cDNA microarray analysis will be used to characterize genes expressed by these white blood cells. Urinary gene and protein expression will be compared to that of simultaneously obtained peripheral blood mononuclear cells. It is anticipated that differentially expressed proteins and genes will reflect intra-renal inflammatory events. The results of this project are expected to demonstrate the relevance of urinary proteomic and cDNA microarray analyses by identifying previously unrecognized protein networks active in SLE nephritis that challenge existing paradigms of renal disease pathogenesis.

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- **Project Title: PROXIMAL DETERMINANTS OF NEPHRITOGENIC AUTOIMMUNITY**

  Principal Investigator & Institution: Foster, Mary H.; Associate Professor; Medicine; Duke University Durham, Nc 27710

  Timing: Fiscal Year 2003; Project Start 01-JAN-1998; Project End 30-JUN-2007

  Summary: (provided by applicant): Autoimmunity is the antecedent to most **glomerulonephritis,** the most common cause of end stage renal disease worldwide. Yet rudimentary understanding of etiology compels reliance on non-specific toxic immunosuppressive therapy. We developed Ig transgenic (Tg) mice bearing B cells reactive with nephritogenic antigens (Ag) as tools to dissect mechanisms controlling humoral autoimmunity that destroys kidney. We postulate that: a) B cells reactive with structurally diverse self-Ag relevant to renal injury are regulated by diverse mechanisms; b) There are differences in molecular pathways maintaining B cell tolerance to nephritogenic Ag in autoimmune vs nonautoimmune individuals, and between individuals bearing different constellations of susceptibility genes; and, c) There are fundamental differences in regulation of B cells that promote nephritis in systemic versus organ-restricted disease. This predicts that different regulatory mechanisms are breached in different autoimmune nephritides. We will use Ig Tg models to pursue the following Specific Aims: 1) Determine the role of deletion and anergy in regulating B cells reactive with basement membrane, the only confirmed target in human autoimmune nephritis. Inactivated Rag or endogenous Ig genes will link cell fate to Ag specificity using anti-laminin LamH/LamL and duat specific LamH/VSR "monoclonal" H+L Ig Tg mice in which collateral regulatory influences are eliminated. 2) Dissect the molecular basis of genetic modification of B cell tolerance. Microarray will be used to monitor and analyze transcriptional profiles in receptor-stimulated tolerant Tg cells from autoimmune MRL and nonsusceptible B6 mice to reveal central regulatory pathways. The LamH Tg, with a well defined tolerance phenotype, will also be established on nephritis-prone (NZBxNZW)F1 and BXSB strains to determine if a single Ag-receptor interaction is differentially tolerogenic in genetically disparate disease-susceptible hosts. 3) Determine and compare the fate of kidney-reactive 238H Ig and anti-alpha3(IV) NC1 collagen Tg B cells associated with nephritis

in systemic versus renal-limited autoimmunity, respectively. This will assess contributions of nucleic acid crossreactivity and Ag sequestration, factors known to impact immune deposition, to regulation of nephritogenic B cells. Collectively these studies will identify regulatory pathways to be targeted for tailored pharmacologic intervention in immunologic renal disease.

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

- **Project Title: REGULATION OF CD154 IN SYSTEMIC LUPUS ERYTHEMATOSUS**

  Principal Investigator & Institution: Cron, Randall Q.; Assistant Professor; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 191044399

  Timing: Fiscal Year 2003; Project Start 27-JAN-2003; Project End 30-NOV-2007

  Summary: (provided by applicant): Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by pathogenic autoantibodies that are dependent on T lymphocyte interactions with autoantibody producing B lymphocytes. This interaction is reliant on CD40-ligand (CD154), which is expressed on the surface of activated CD4 T cells and which engages its cognate cell surface receptor, CD40, on B cells. Because of its critical and pleiotropic role in the immune system, CD154 expression is normally tightly regulated. Several recent reports have described dysregulated (increased and prolonged levels) expression of CD154 in patients with SLE relative to normal controls. Similar findings have been made in lupus-prone mice, and treatment of these mice with a neutralizing anti-CD154 monoclonal antibody delays and reduces the incidence of **glomerulonephritis,** a hallmark of SLE. However, similar approaches in humans have not proven efficacious due to unanticipated side-effects involving coagulation. The expression of CD154, like that of other T cell cytokine genes, is controlled at the level of gene transcription and mRNA stability. Therefore, understanding the cis-acting (DNA and RNA regulatory) elements and trans-acting (transcription factor and RNA binding) proteins that control CD154 expression will be critical to understanding both the normal and perturbed regulation of the gene. The initial goal of this study is to establish if transcriptional and/or post-transcriptionally-mediated increases in CD154 mRNA contribute to the increased expression of CD154 in SLE. Potential regulatory cis-elements will be tested for transcriptional or mRNA stabilizing activity in SLE and normal human T cells using reporter genes. Next, transcription factors and/or RNA binding proteins that are involved in the overexpression of CD154 in SLE will be studied. Elucidating the molecular mechanisms that regulate CD154 expression in both normal controls and SLE patients will lead to a greater understanding of the pathogenesis of SLE and to potential new approaches for intervention. Moreover, because of the contributory role of CD154 to other autoimmune diseases, information relevant to the pathology and treatment of arthritis and other autoimmune disorders will also be obtained. Defining the major regulatory regions of the CD154 gene will have potential relevance to any process in which CD154 plays a role. For example, such knowledge may allow for the development of better gene therapy for deficiencies of CD154 and other activation-dependent genes, or more selective immunosuppression of graft rejection.

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

- **Project Title: REGULATION OF CD32A IN NEUTROPHILS**

  Principal Investigator & Institution: Selvaraj, Periasamy; Associate Professor; Pathology and Lab Medicine; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2003; Project Start 15-DEC-2002; Project End 30-NOV-2007

Summary: (provided by applicant): In many autoimmune diseases such as arthritis, and lupus the tissue injury is caused by the interaction of inflammatory cells such as neutrophils with the immune complexes (IC) deposited on tissues. Such a tissue injury also results in **glomerulonephritis** leading to kidney failure and death in these disease states. Recent studies with gone knock out mice have clearly demonstrated that Fc gamma receptors (FcgammaRs) play a major role in IC mediated autoimmune diseases. Therefore understanding the regulation of function FcgammaRs has important therapeutic implications. In humans, two types of low affinity FcgammaRs for IgG, CD32A and CD16B, are coexpressed on neutrophils. Both bind ligands with overlapping specificity, however, only CD32A is capable delivering signal for phagocytosis. Recent studies from our laboratory have demonstrated that CD32A is functionally inactive in resting neutrophils. However, once neutrophils are activated by fMLP, a bacterial chemoattractant peptide, CD32A is converted to a functionally active state and can bind ligand efficiently. On the contrary, activation of neutrophils with PMA, a neutrophil activating phorbol ester, completely abolished CD32A binding to antibody-coated erythrocytes. Interestingly, the neutrophils expressed on cultured cell lines are constitutively active. These results suggest that the avidity modulation is cell type and activation signal specific and the regulation of ligand binding may be one of the mechanisms by which human neutrophil regulates CD32A function. We hypothesize that the molecular changes that occur during neutrophil activation alter the functional state of CD32A. In this grant we propose to determine the molecular basis for this signal specific and cell type dependent regulation of CD32A functional state. Specifically, we will: 1. determine whether the neutrophil activators alter the CD32A-dependent EA binding by influencing the 2D and 3D affinity of CD32A; 3, determine whether phosphorylation of ITAM motif of CD32A is altered by cell activation and correlates with change in ligand binding using immunoblotting, 2D amino acid analysis, and CD32A cytoplasmic domain mutation studies; 3. analyze whether neutrophil activation alters the cytoskeleton interaction of CD32A, receptor clustering, and change in the lateral mobility of CD32A. Since neutrophil activation occurs in vivo during infectious and autoimmune diseases it can be hypothesized that dysregulation of CD32A functional state occurs in vivo leading to the expression of high avidity CD32A which enables the neutrophils bind IC efficiently resulting in tissue injury in these diseases. The data obtained from the proposed research will be useful in understanding and designing therapies to inhibit IC mediated tissue injury in autoimmune and infectious diseases.

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- **Project Title: REGULATORY AND EFFECTOR T CELLS IN SLE**

  Principal Investigator & Institution: Tung, Kenneth Sk.; Professor; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2002; Project Start 27-SEP-2002; Project End 30-JUN-2003

  Summary: (provided by applicant): Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with protean clinical presentation and variable outcome; and **glomerulonephritis** (GN) is a serious manifestation of SLE. SLE patients and lupus prone mice exhibit abnormalities in B cell and T cell tolerance and their responsive state. They produce autoantibody (autoAb) response to multiple self antigens (Ag) and have immune complex (IQ deposits in tissues. The CD4+CD25+ regulatory T cells normally prevent organ specific autoimmune disease occurrence. Herein we investigate the role of the regulatory T cells in SLE by studying the effect of thymectomized on day 3 (d3tx) in lupus prone mice. The d3tx lupus prone NZM2328 mice exhibited earlier autoAb

response, accumulated more glomerular IC, and developed accelerated acute GN. Remarkably, severe acute GN occurred in - 90% of male NZM2328 mice that are normally more resistant to lupus GN. These results have led to the following hypotheses. First, regulatory T cells can negatively influence development of SLE. Second, acute lupus GN is a T cellmediated autoimmune disease that targets the renal glomerulus. The CD4+CD25effector T cells participate in renal glomerular injury by targeting either renal Ag or Ag provided by the glomerular 1C. Thus, in SLE, autoreactive T cells: 1) drive an autoAb response, and 2) directly elicit acute GN. Third, acute GN is a checkpoint in lupus GN, from which the male mice regress and the female mice progress to chronic GN. Thus male NZM2328 mice may have less effective or more regulatory T cell function. The model will also permit the study on factors responsible for the progression and regression of lupus GN. We will investigate these hypotheses in Aim I of our proposal. A very different story emerged from the study on the lupus prone female SNF1 mice. Following d3tx, an accelerated autoAb response was also noted but this was associated with significant reduction in fatal GN. Analysis of their serum and glomerular autoAb isotypes revealed an autoimmune response with a strong Th2-bias. In Aim 2, we will test the hypothesis that d3tx of the SNF1 mice retains the nonpathogenic neonatal Th2 responsiveness. At the same time, they had a reduced Ag specific Th1 response that is required for pathogenic autoAb production and for lupus GN. Finally, we will seek an explanation for the different responses to d3tx between the two lupus prone mice. Accordingly, we will determine the outcome of CD4+CD25+ T cell depletion by methods other than d3tx in SNF1 mice.

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- **Project Title: REGULATORY T CELLS IN SYSTEMIC LUPUS ERYTHEMATOSUS**

  Principal Investigator & Institution: Bagavant, Harini; Pathology; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

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

  Summary: (provided by applicant): My graduate thesis was in the field of Reproductive Immunology specifically, the study of immune responses and ovarian function in primates immunized with egg protein antigens. My post-doctoral work was on the development of Contraceptive Vaccine in primates in Dr. Tung's laboratory, a part of the Center for Recombinant Gamete Contraceptive Vaccinogens at the University of Virginia (UVA). I had to take a break in my research for over one year due to family health problems. I returned to Dr. Tung's lab in July 2000 to complete and publish my post-doctoral work. At this time, Dr. Tung's lab was studying the loss of CD4+CD25+ regulatory T cell function induced by neonatal thymectomy between days 1-4 after birth (d3tx) as a cause of organ specific autoimmune disease. In addition, Drs. Fu, Tung and McDuffie had established a Specialized Center of Research for Systemic Lupus Erythematosus (SLE) at UVA. I got interested in the mechanisms of immunoregulation and initiated a project to study the role of regulatory T cells in SLE, which is a systemic autoimmune disease affecting multiple organs and characterized by the presence of circulating autoantibodies (Aab) to nuclear and cytoplasmic antigens. The project has given us exciting leads for future study and form the basis of the present proposal. We will use the d3tx model of CD4+CD25+ regulatory T cell depletion in murine SLE. Two mouse strains studied, SNF1 and NZM2328, spontaneously develop Aab and fatal **glomerulonephritis** (GN). D3tx in SNF1 mice accelerated Aab but protected from fatal GN. In contrast, d3tx exacerbated Aab and GN in NZM2328 mice compared to sham thymectomized (stx) mice. In addition, reconstitution of d3tx NZM2328 mice with CD25+T cells prevented exacerbation of SLE. These data suggest the hypothesis that

CD4+CD25+ regulatory T cells influence induction of SLE in NZM2328 mice. Spontaneous SLE in NZM2328 has a gender bias, predominantly affecting females. However, depletion of regulatory T cells by d3tx results in comparable GN in both sexes. This leads to the second hypothesis that regulatory T cell function dictates the gender bias of GN in NZM2328 mice. I had a productive post-doctoral fellowship in the area of Reproductive Immunology, however, additional training in cellular immunology and renal pathology would be essential for my development as an independent scientist in lupus research. This award will help to overcome the lag period in my career induced by my leave of absence and return to a new field of study, and will facilitate my aim of becoming an independent scientist.

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- **Project Title: RENAL SENESCENCE AND TRANSPLANTATION**

  Principal Investigator & Institution: Myers, Bryan D.; Professor; Medicine; Stanford University Stanford, Ca 94305

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

  Summary: (provided by applicant): Elderly cadaveric donors >60 years old are reluctantly used tbr kidney transplantation (Tx), because an aged renal allograft has been shown to be associated with a short half-life. We now propose to elucidate the relationship between renal senescence and acceleration of chronic allograft nephropathy (CAN) in recipients of aged cadaveric transplants. We have developed sensitive methods for evaluating injury to the human kidney, which we now propose to combine with novel techniques of urine cytology and glomerular gene expression. We will use this approach serially to quantify the extent and course of the CAN that complicates senescence in aged recipient-donor pairs (>60 yr; group 1, N=25). Youthful Tx recipient-donor pairs (60 yr; Group 3, N-19), who will serve as a comparison group for group 1. We wish to test four hypotheses in groups 1 and 2, and a fifth hypothesis in group 3. Hypothesis #1 is that a combination of renal senescence and CAN leads to progressive, incremental glomerulopenia in allografts from aged donors. We will use physiologic and morphometric techniques serially, along with mathematical modeling and MRangiography, to determine filtration capacity (Kf) and glomerular number longitudinally for 48 months in groups 1 and 2. Hypothesis #2 is that limited reversibility in the elderly of postischemic/reperfusion tubular injury (delayed graft function) results in formation of atubular, and hence non-functional glomeruli. Serial biopsies will be used to relate initial tubular injury to the incidence of atubular glomeruli at 48 months. Hypothesis #3 is that loss from aged Tx kidneys of podocytes, a cell type that does not replicate in vivo, leads to podocytopenia and glomerulosclerosis. We will determine podocyte number per glomerulus in serial biopsies. We will then quantify podocyturia in an effort to account for any incremental podocytopenia over 48 months. We will also explore altered expression of podocyte-related genes in glomeruli obtained by biopsy using RT-PCR. Hypothesis #4 is that analysis at harvesting and at Tx of aged, donor kidney function, structure and expression of senescence- and podocyte-related genes will permit prediction of 48- month graft function and survival, thereby permitting optimal selection prospectively of aged donors in the future. Hypothesis #5 is that the 2-fold complement of glomeruli grafted during a dual Tx, in group 3, will prevent a "remnant kidney" phenomenon, thereby preserving glomerular filtration capacity and number at >2x group 1 values.

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- **Project Title: ROLE OF ANTI-PROTEINASE-3 IN WEGENER'S VASCULOPATHY**

  Principal Investigator & Institution: James, Judith A.; Associate Professor; Oklahoma Medical Research Foundation Oklahoma City, Ok 731045005

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

  Summary: Wegener's granulomatosis (WG) is a multisystem disease of unknown etiology which is characterized by small to medium vessel vasculitis, pauci-immune **glomerulonephritis,** necrosis/granuloma formation of the respiratory tracts and autoantibodies to neutrophilic components. Although the underlying pathophysiology of this disorder remains an enigma, several lines of evidence strongly support c-ANCA, particularly anti-PR3, has a role in disease pathogenesis. Unfortunately, the specific mechanisms that initiate and perpetuate this anti-PR3 response remain to be elucidated. One approach to delineate a potential etiology for these autoantibodies, and/or to understand their role in the pathogenesis of vasculitis would be to fully characterize the antigenic determinants of the PR3 autoantigen. By defining the common autoantigenic targets of PR3 we could arrive at molecular mimicry triggers for this autoimmune response. An animal model of WG autoimmunity could show to what tissues particular epitopes are targeted. Over the past decade our lab has conducted extensive work on the immunochemistry of lupus autoantigens (1-7). These previous studies provide the technical background for this proposal. Epitope mapping experiments of the spliceosomal autoantigens have led to our peptide induced model of lupus autoimmunity (8,9). We will now apply these well-honed techniques, as well as a similar scientific strategy, to analyze the humoral fine specificity of the WG reponse to PR3. Early work in the lab of Ralph Williams suggests that sequential eptiopes are common targets of PR3. Exciting new results from our co-PI's lab uncover a potential mechanism of anti-PR3 vascular damage. He has observed that PR3 can bind to endothelial protein C receptor (EPCR), a regulatory protein in the protein C anticoagulant pathway and that this binding is inhibited by c-ANCA. He has also observed that EPCR can inhibit tight neutrophil to activated endothelium and the subsequent spreading/activation. These observations lead to the hypothesis that EPCR plays a role in regulating leukocyte adhesion and activation, in part through interactions with PR3, and that antibodies to PR3 disrupt this physiological regulation contributing to the vascular damage in WG. This RFA response seeks to integrate the strengths of two labs to build on these early observations and to identify the common humoral epitopes of PR3, to track the development of the humoral autoimmune response of WG patients to PR3 over time, to develop an animal model of vasculitis, to evaluate EPCRs influence on the c-ANCA-PR3 interaction, and to identify the common T cell targets in WG.

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

- **Project Title: ROLE OF CD45 IN HEMATOPOIESIS AND LYMPHOMAGENESIS**

  Principal Investigator & Institution: Hermiston, Michelle L.; Pediatrics; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

  Timing: Fiscal Year 2003; Project Start 11-JUL-2003; Project End 30-JUN-2006

  Summary: (provided by applicant): Lymphocyte homeostasis requires the coordinate regulation of signaling cascades governing proliferation, differentiation, and death. Dysregulation of these processes is a necessary prerequisite for the development of lymphoid malignancies. Our lab recently reported a novel murine model containing a mutation that disrupts the negative regulation of the receptor-like protein tyrosine phosphatase CD45 during dimerization. These mice develop a profound lymphoproliferative disorder with polyclonal activation of T and B cells, massive

splenomegaly, and premature death. A subset also develops stigmata of autoimmunity including anti-double stranded DNA antibody formation and immune complex-mediated **glomerulonephritis.** To define the cell type responsible for disease generation, the CD45 mutant mice were mated to mice deficient in T, B, or T and B cells. Genetic elimination of B cells, but not T cells results in ablation of the autoimmune and lymphoproliferative disorders. In contrast, absence of T cells resulted in a dramatic increase in the prevalence of lymphoma. These observations support the hypothesis that precise regulation of CD45 function by dimerization is essential for the maintenance of homeostasis within the hematopoietic system. Disruption of this function can have profound consequences leading to lymphoproliferation, autoimmunity, and malignancy. The goal of this proposal is to define the molecular and cellular basis for the breakdown of homeostasis and to identify the steps required for the development of lymphomas. The first aim tests B cell-intrinsic mechanisms that contribute to disease initiation. The second aim focuses on contributions from the microenvironment that may enhance B cell expansion and the mechanisms by which T cells inhibit lymphomagenesis. In the third aim, biochemical and gene expression analyses are used to address the molecular basis by which the CD45 mutation contributes to disease. Array CGH and ENU mutagenesis are used to begin to identify cooperating events that contribute to the progression from hyperproliferating to malignant state. These studies should provide important insights into the links between immune regulation, autoimmunity, and lymphoid malignancies as well as improve our understanding of the mechanisms governing immune surveillance.

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- **Project Title: ROLE OF SMAD SIGNALING IN RENAL INFLAMMATION**

  Principal Investigator & Institution: Lan, Hui Y.; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

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

  Summary: Glomerulonephritis is a major cause of end stage renal disease (ESRD). While the pathogenic rote of proinflammatory cytokines, chemokines, and adhesion molecules in giomerulonephritis has been extensively studied, the renal protective role of anti-inflammatory cytokines such as TGF-beta has received little attention. In this proposed research, we will explore the role of TGF-beta in the resolution of renal inflammation and explore three novel mechanisms. First, we will examine the hypothesis that TGF-beta may signal through its inhibitory signaling protein, Smad7, to counter-regulate the activation of NF.kappaB by inhibition of IkappaBalpha degradation (phosphorylation). This is important since NF.kappaB has been shown to play a key role in **glomerulonephritis.** Second, we will further investigate the mechanisms of TGF-beta/Smad7 in the renal inflammation by overexpression of Smad7 in vitro and in vivo. We expect that inhibition of NF.kappaB-driven immune and inflammatory responses including expression of MHC class II, cytokines (IL-1, TNFalpha), chemokine (MCP-1), adhesion molecules (ICAM-1), iNOS, macrophage/T cell infiltration, and cell proliferation is the mechanisms by which Smad7 plays a role in anti-renal inflammation. Finally, we will determine the functional role of Smad7 in the resolution of renal inflammation and develop a novel therapeutic strategy by gene transfer of inducible Smad7 in a rat model of crescentic **glomerulonephritis.** These studies will therefore explore the underlying mechanisms of TGF-beta/Smad7 in negative regulation of renal fibrosis and renal inflammation. Outcomes from these studies will allow the identification of a unique negative regulating rote for Smad7 in the pathogenesis of renal fibrosis and inflammation. Importantly, inhibition of both renal inflammation and

fibrosis by overexpression of Smad7 will provide new information for the development of novel therapeutic strategies to combat kidney diseases.

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- **Project Title: ROLE OF T CELLS IN MEDIATING GLOMERULONEPHRITIS**

  Principal Investigator & Institution: Lou, Yahuan; Diagnostic Sciences; University of Texas Hlth Sci Ctr Houston Box 20036 Houston, Tx 77225

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

  Summary: (provided by applicant): In this application, we propose to investigate how antigen specific CD4+ T cells mediate glomerular injury, the first key step leading to **glomerulonephritis** (GN).T cell mechanisms have emerged as potentially the most important mediators in GN. However, antigen specific T cells are largely unanalyzed in existing GN models. It is unknown whether and how antigen specific T cells mediate glomerular injury in GN. Guided by our experience in T cell mediated autoimmune disease we are investigating the roles of T cells specific to autoantigen Col4alpha3NC1, a critical component of glomerular basement membrane, in a rat GN model. We discovered: 1) a 13-mer T cell peptide of Col4alpha3NC1 induced fatal GN similar to human late stage cresentic GN; 2) Col4alpha3NC1 specific CD4+ T cells of TH-1 type transferred severe GN in the naive recipients; 3) transfer of the T cells induced influx of monocytes/T cells into renal cortex. Thus, antigen specific CD4+ T cells may directly mediate glomerular injury and cause GN. Our hypothetical mechanism of glomerular injury mediated by antigen specific CD4+ T cells is as follows: 1. CD4+ T cells specific to autoantigen Col4alpha3NC1 are activated through molecular mimicry by microbial antigens; 2. activated T cells recognize a subpopulation of MHC class II+ glomerular cells; 3. recognition triggers monocytes/T cells influx into glomeruli; glomerular inflammation is initiated and maintained. With our unique model based on Col4alpha3 specific CD4 T cells and the T cell epitope, we will test our hypotheses: 1) We will identify a mimicking T cell peptide from microbial antigens based on the characterization of the 13-mer T cell peptide; 2) We will investigate the antigen presenting capacity of the MHC class II+ glomerular cell subpopulation, which may serve as the target for CD4+ T cells; 3) We will investigate the roles of infiltrating monocytes and T cells in the initiation and maintenance of glomerular inflammation after T cell transfer.

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

- **Project Title: ROLE OF THE COMPLEMENT SYSTEM IN GLOMERULONEPHRITIS**

  Principal Investigator & Institution: Quigg, Richard J.; Professor; Medicine; University of Chicago 5801 S Ellis Ave Chicago, Il 60637

  Timing: Fiscal Year 2002; Project Start 15-AUG-1989; Project End 30-JUN-2006

  Summary: (provided by applicant): The objective of the work proposed in this application is to understand the role of the complement system in immune-mediated glomerulonephntis (GN). Rat models of GN will be studied, including the Heymann nephritis (HN) model of membranous nephropathy, the Thy-1 model of mesangial proliferative GN, and immune complex GN which models lupus, postinfectious and membranoproliferative GN. In HN, complement appears to be activated directly on the glomerular epithelial cell (GEC), leading to injury of this key component of the glomerular capillary wall and the development of proteinuria. Overall, evidence exists that systemic inhibition of complement activation will protect against disease in HN,

yet, has a number of untoward effects. The first specific aim will examine the utility of targeting the potent complement inhibitor, Crry, specifically to the GEC. Recombinant chimeric molecules will contain Crry coupled to monoclonal antibodies targeting GEC antigens or complement receptor 2 targeting iC3b/C3d in immune complexes. Studies will be performed to model these inhibitors in vitro followed by studies in the PHN model in vivo. The second specific aim exploits the current capacity to examine gene changes in a massively parallel fashion. The underlying hypotheses in this aim are that genes relevant to the pathogenesis of complement-dependent glomerular disease models are measurably altered relative to control animals, and that studies in cultured cells are surrogates to events occurring in vivo. Studies will be performed using Affymetrix U34A arrays examining 7000 known rat genes. Individual and clustered gene changes occurring in response to complement-mediated GEC and mesangial cell injury in vitro and in vivo will be identified, allowing determination of which gene changes are complement-dependent, antibody-dependent, and shared between cultured cells and diseased glomeruli. The third specific aim will examine complement receptors and regulators that affect the glomerulus, either because of their direct presence in glomeruli (decay accelerating factor and factor H-related protein) or because of their influence on glomeruli by processing immune complexes (factor H). Studies will examine the expression of these proteins and their mRNA in experimental glomerular diseases, as well as the effect of altering their function in health and disease states. These studies will define the biological role of these complement regulatory proteins. Successful performance of the studies proposed here will provide insight into the role of the complement system in glomerular diseases, as well as potential strategies for treating these disorders

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- **Project Title: ROLE OF VEGF IN GLOMERULAR ENDOTHELIAL HEALTH & DISEASES**

  Principal Investigator & Institution: Karumanchi, S Ananth.; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

  Timing: Fiscal Year 2004; Project Start 01-JUN-2004; Project End 31-MAY-2008

  Summary: (provided by applicant): Glomerular endothelial damage plays an important role in the pathogenesis of several proteinuric renal disorders such as preeclampsia (PE), thrombotic microangiopathic purpuras (TTP), renal transplant rejection and various endocapillary glomerulonephritides. However, the mechanisms of endothelial damage and proteinuria in these disorders are poorly understood. It has been shown that vascular endothelial growth factor (VEGF) is not only an essential molecule for glomerulogenesis and kidney development, but also important for glomerular capillary repair in experimental models of glomerular disorders such as glomerulonephritides and TTP. VEGF is also abundantly expressed in the adult glomerulus during nondiseased states, but its role in glomerular health and disease is unclear. Recently, we have demonstrated that excess placental production of sFIt-1 (a circulating VEGF antagonist) in patients with PE is responsible for proteinuria, hypertension and. qlomerular endotheliosis, the classic pathologic lesion of PE. Moreover, massive proteinuria with glomerular endotheliosis has been recently described in glomerular podocyte-specific VEGF knockout mice. Additionally, VEGF signaling inhibitors usage in clinical cancer trials have resulted in proteinuria and hypertension in humans. Therefore, we hypothesize that VEGF and its receptors play an important role in not only maintaining glomerular endothelial health but also in maintaining normal glomerular integrity and the barrier to proteinuria. Disruption of VEGF signaling by

antagonists may result in proteinuria in the short term and glomerulosclerosis in the long term. In this proposal, we will first characterize our sFIt-1 induced model of proteinuria and endotheliosis to understand the mechanisms of proteinuria in VEGF-deficient states. We will then elucidate the VEGF signaling pathways that mediate the barrier against proteinuria and maintain endothelial health using chimeric VEGF receptors in glomerular endothelial cell culture studies in vitro to be followed by definitive in vivo studies in rats using VEGF receptor agonists (such as placental growth factor that activates only Fit-1 and not FIk-l) and neutralizing antibodies against various VEGF receptors. We will then study the long-term renal and vascular consequences of VEGF blockade in rats specifically seeking the development of glomerulosclerosis and hypertension. Finally, we will study the effects of VEGF inhibitors and VEGF agonists in anti-Thyl.1 nephritis, a well-characterized experimental model of **glomerulonephritis,** in which capillary repair is thought to be important for the resolution of nephritis. Together, these studies will facilitate us to achieve our goal of understanding the role of VEGF and glomerular endothelial cell dysfunction in the pathogenesis of proteinuria and may lead to novel therapeutic options for glomerular endothelial diseases as well as clarify the renal toxicity profile of VEGF signaling inhibitors being developed for other diseases such as cancer.

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- **Project Title: SLIT AND SLIT SIGNALING**

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

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

  Summary: The objective of this proposal is to determine how chemokines and newly identified chemokine antagonists, Slits, are regulated, interact with each other, and contribute to inflammation in response to renal injuries. Past research in chernokines has been focused mostly on positive regulation. Thus, in all these situations chemokines are invariably studied as activators or attractants. Recently, we have found that one of the neural axon guidance cues, Slits, was expressed outside of the nervous system, Slit-2 was expressed in the kidney and lung. Leukocytes have been considered as early and important effectors in renal inflammation. Previous studies have shown upregulation of chemokines and downregulation of Slit2 during **glomerulonephritis** and Slit treatment significantly attenuated nephritic injury. It was reported that Slit/Robe may function through Robe's binding to GTPase activating proteins (GAPs, srGAPs) Recently, we have found that Racl and Cdc42, small GTP binding proteins known for their roles in actin polymerization and cell motility, were shown to be negatively regulated in macrophage-like cells by Slit2. We plan to study the expression and regulation of chemokines, Slits, and Robe in the model of renal ischemia/reperfusion and further determine the role of Slit/Robe in negative regulation of leukocyte accumulation in this model. Another goal of this project is to characterize Slit/Robe mediated signaling of small G proteins in leukocytes. Differences between activation of GTPases between neurons and leukocyte suggests that Slit/Robe in ieukocytes may use other signaling molecules in addition to srGAPs, therefore, we plan to further clone Robe-interacting proteins in mononuclear cells by Two-Hybrid System. The proposed studies will shed new light on how chemokines and Slit interact in leukocyte-dependent renal injury, and uncover the signaling pathway of Slit/Robo, and insights gained from our study will lead to the development of new therapeutic strategies of chemokine-dependent renal injuries in human.

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

- **Project Title: SPECIALIZED CENTER OF RESEARCH IN SYSTEMIC LUPUS ERYTHE***

  Principal Investigator & Institution: Fu, Shu Man M.; Professor & Chief; Internal Medicine; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2002; Project Start 01-JUL-1998; Project End 30-JUN-2007

  Summary: (provided by applicant): Systemic lupus Erythematosus is a prototypic autoimmune disease affecting multiple systems. This disease causes significant morbidity and mortality. The University of Virginia Specialized Center of Research in Systemic Lupus Erythematosus (UVa SCOR in SLE) was established in July 1998 with funding from the NIAMS. The Center has successfully fostered a multi-discipline approach to study the pathogenesis of this disease. The consortiums between the University of Virginia and the Mayo Clinic and the Johns Hopkins Hospital have strengthened the SCOR. Studies on a new strain of lupus- prone mice NZM2328 have led to the identification of new SLE susceptibility loci, the distinction between acute and chronic **glomerulonephritis,** and most importantly the dissociation of ANA, anti-dsDNA and anti-nucleosome antibody production from chronic **glomerulonephritis.** Significant information has been obtained regarding the mechanism of epitope spreading in the autoantibody diversification to SLE-related autoantigens. The identification of crossreactive T cells is a major advance in the understanding of this process. Two 3-day thymectomy models to study the role of CD25+ regulatory T cells have been developed. Models for Sjogren's syndrome/autoimmune sialoadenitis have been created. Studies of the DR and DQ transgenic mice provide evidence for the importance of the DR antigens in determining the specificities of the autoantibodies produced. Studies involving serial patient samples provide evidence for fluctuation of autoantibody titers without clear correlation with patients' clinical courses. A collaboration between the University of Virginia and the National Institute of Immunology in India has established a program to study the role of DR in the generation of anti-Sm antibody responses by exploring the ethnic and environmental differences between the India and the U.S. populations. Studies on the role of estrogen receptors in the pathogenesis of SLE show interesting preliminary data. These advances form the basis for the competitive renewal. The competitive renewal application will continue to develop the interdisciplinary approach to study the immunological, genetic and environment factors important in the pathogenesis of SLE. The SCOR renewal application has four projects and three cores. The projects are 1) HLA-D Molecules, T Cell Epitopes and Autoantibody Specificities in SLE; 2) Regulatory and Effector T Cells in SLE; 3) Genetic Control in Lupus-prone NZM2328; and 4) Estrogen Receptors in SLE and the UVa Lupus Cohort. The proposed studies are to provide experimental evidence to support the stated hypothesis that molecular mimics (environmental factors) may initiate an autoimmune response, and the diversification of the autoimmune response with inflammation leads to end-organ damage in appropriate hosts. The three cores are 1) Administrative Core, 2) Cell Sciences and Immunochemistry Core, and 3) Mouse Genetics Core. These cores will serve all the projects and will continue to facilitate interaction among investigators within the UVa SCOR in SLE. The SCOR continues to represent both inter- and intra-institutional collaboration. It is expected that this interactive approach will continue to provide new insights into the immunological and genetic factors important in SLE.

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

- **Project Title: TARGETED GENE DELIVERY AND ACTIVATION BY ULTRASOUND**

  Principal Investigator & Institution: Zhong, Pei; Associate Research Professor; Mech Engr & Materials Science; Duke University Durham, Nc 27710

  Timing: Fiscal Year 2003; Project Start 08-SEP-2003; Project End 31-JUL-2008

  Summary: (provided by applicant): The success of gene therapy relies critically on the development of new technologies that can be used to produce site-specific gene delivery without causing systemic toxicity and immunogenic response, as well as the ability to regulate transgene expression in vivo. Despite extensive efforts in the past, these primary obstacles in gene therapy still exist. This proposal aims to develop novel ultrasound systems that have the potential to overcome these obstacles by providing new techniques for 1) targeted gene delivery to internal organs and 2) spatial and temporal regulation of transgene expression in vivo. In preliminary studies, we have already demonstrated the feasibility of ultrasound-mediated gene transfer in vitro using cultured HeLa cells and lithotripter shock wave (LSW)-mediated site-specific gene delivery in vivo in porcine kidney. We have also shown that ultrasound can be used as a simple and convenient physical means to activate transgene expression under the control of heat shock protein (hsp) 70B promoter. The work outlined in this proposal will be a significant expansion of these preliminary studies and will encompass a multidisciplinary and comprehensive investigation combining innovative engineering approaches with modem techniques in cell and molecular biology, and animal experimentations. Our specific aims are: 1. Development of novel ultrasound systems for targeted gene delivery and activation. 2. Physical characterization of the acoustic fields and associated cavitation bubble dynamics produced by the novel ultrasound systems both in water and in tissue phantoms. 3. Optimization of ultrasound-mediated gene delivery in vitro. 4. Ultrasound-targeted gene delivery in porcine kidney, and 5. Ultrasound-regulated gene delivery and activation in skeletal muscle -a novel approach for erythropoietin (Epo) gene therapy in a rat model with chronic renal failure. Because ultrasound can penetrate deep into tissue and be focused on specific organs of the body, the prospect for ultrasound-targeted gene delivery and activation in vivo is very appealing. Such a versatile physical method for gene delivery and activation could be of great value for molecular therapies of a wide range of diseases, including cancer, cardiovascular disease, and various renal disorders (polycystic kidney, renal cancer, acute **glomerulonephritis,** and chronic interstitial disease).

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

- **Project Title: THE MANNOSE-BINDING LECTIN AND AUTOIMMUNITY**

  Principal Investigator & Institution: Ezekowitz, Alan B.; Professor and Chief of Pediatrics Servic; Cbr Institute for Biomedical Research 800 Huntington Ave Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 30-JUN-2007

  Summary: The predominant interest of our laboratory is to study the innate immune system in vertebrates and insects. Our focus is to define the structure and function of pattern recognition molecules that appear to selectively recognize the patterns of oligosaccharides that decorate microorganisms from self-glycoproteins. The mannose-binding lectin (MBL) is one such molecule which functions like an ante-antibody and is regarded as a prototypic mammalian pattern recognition molecule. MBL appears to play a role in first line host defense in the lag period that is required to generate a long lasting adaptive immune response. A hallmark of innate immunity is that it is now recognized

as a necessary antecedent for the development of an adaptive immune response. Little or no attention has been paid as to whether MBL is able to interact and prime the development of adaptive immunity, in particular systemic lupus erythematosis (SLE), we believe that MBL plays a role B cell homeostasis. The goal of this proposal is to explore this question by making use of unique MBL null mou7se models that we have generated in our laboratory in conjunction with other known lupus prone animal models.

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- **Project Title: THE ROLE OF CYCLOXGENISE 2 IN PROGRESSIVE NEPHRON DESTRU**

  Principal Investigator & Institution: Harris, Raymond C.; Professor; Vanderbilt University 3319 West End Ave. Nashville, Tn 372036917

  Timing: Fiscal Year 2002; Project Start 01-SEP-1987; Project End 31-JUL-2007

  Summary: (Taken directly from the application) Cyclooxygenase-2 (COX-2) expression increases in the kidney cortex in both inflammatory and "non-inflammatory" progressive renal injury. We and others have identified three sites in kidney cortex that exhibit increased COX-2 expression in progressive injury: infiltrating leukocytes in glomerulus, the macula densa and surrounding cTALH and tubulointerstitium and glomerular podocytes. The three Specific Aims of this proposal are designed to address mechanisms of regulation of COX-2 expression and the pathophysiologic consequences of increased expression in these cell types. We will utilize three mouse models of progressive renal injury: a model of progressive glomerulosclerosis and tubulointerstitial injury secondary to loss of functioning renal mass, a model of diabetic nephropathy and a model of crescenteric **glomerulonephritis** In Specific Aim #1, we will examine COX-2 expression in these models of progressive renal injury and will determine the effect of specific COX-I and COX-2 inhibitors on disease progression. Leukocyte infiltration of glomerulus and tubulointerstitium is a hallmark of both inflammatory and non-inflammatory progressive renal injury. In this aim, we will also define the potential role of leukocyte-generated prostanoids derived from COX-2 by subjecting mice to lethal irradiation and bone marrow transplant with cells derived from COX-2-/-mice in order block COX-2 expression in infiltrating cells. In Specific Aim #2, we will examine the effect of increased COX-2 in the macula densa and surrounding cTALH on renal hemodynamics in hyperfiltering states and determine pathophysiologic mechanisms underlying this increased expression. In Specific Aim #3, we propose to examine the role of COX-2 expression on glomerular podocyte function under basal conditions and in response to glomerular injury. For these studies, we will either selectively overexpress COX-2 in podocytes by developing transgenic mice in which increased COX-2 expression is directed by the nephrin promoter or selectively delete podocyte COX-2 by developing and crossing loxP targeted COX-2 mice with nephrin-Cre mice.

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- **Project Title: THE ROLE OF DENDRITIC CELLS IN RENAL IMMUNE RESPONSES**

  Principal Investigator & Institution: Griffin, Matthew D.; Assistant Professor of Medicine; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

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

  Summary: (provided by applicant): Infiltration of the renal parenchyma by inflammatory cells, including lymphocytes, is a common feature of kidney diseases even

in the apparent absence of exogenous immune stimuli. The mechanisms underlying T-lymphocyte activation in kidney disease are poorly understood, as are the mechanisms that prevent immune activation in the healthy kidney. This experimental protocol will examine the dynamic behavior, responses, and functions of Dendritic cells (DCs) -a migratory population of cells with specialized function in antigen uptake and presentation - within the kidney and its draining lymphoid tissue during health and explore their role in different forms of renal injury. All organs, including the kidney, have a resident population of DCs although the density, distribution and turnover vary. DC "maturation" is induced by the inflammatory products of disease or injury. Mature DCs migrate from an organ to its draining lymph node where they activate T-cells to initiate cellular immune responses. In the absence of maturing stimuli, DCs may also transfer antigens to lymphoid tissue in order to activate regulatory mechanisms that prevent autoimmunity. Modulation of DC-T-cell interactions is recognized as an important therapeutic target for the prevention/treatment of immune-mediated disease. The primary hypotheses of the proposal are that: (a) trafficking of protein antigens from the kidney to the draining Iymph nodes occurs during health and actively maintains immune tolerance to renal tissue, and (b) alterations in renal DC phenotype and turnover result from diverse forms of kidney injury and contribute significantly to inflammatory renal parenchvmal damage. The experimental strategy will focus strongly on the use of in vivo techniques that directly examine DC-mediated antigen trafficking and presentation in the kidney and renal lymph nodes of mice. The first Specific Aim, to determine the biology of renal DCs during health, will employ in vivo BrdU-labeling to determine DC turnover, congenic bone marrow transfer to examine the precursor origins of renal DCs, unilateral inoculation of fluorescent particles or proteins into the kidney to track renal DC-mediated antigen trafficking, generation of transgenic mice expressing a kidney-restricted neo-antigen, and adoptive transfer of antigen-specific TCR transgenic T-cells. The second Specific Aim, to determine the role of renal DCs in the pathophysiology of diverse form of renal injury, will apply these same in vivo experimental strategies to animals subjected to one of the following four types of renal injury: (a) ischemia, (b) urinary obstruction, (c) acute **glomerulonephritis,** (d) genetically-based collagen deficiency (a model of Alport's nephritis). In these experiments, the disease-associated alterations to renal DC turnover, surface phenotype, and antigen trafficking as well as antigen-specific T-cell activation within the draining lymph nodes, and infiltration of the renal parenchyma by activated T-cells will be characterized. For both Specific Aims, observational studies will be followed by mechanistic studies involving blockade of specific molecular pathways, depletion of regulatory cell populations, and cross-breeding to genetically modified strains. Analytic tools will include flow cytometry, immunohistochemistry, immunofluorescence microscopy, morphometric analysis, cytokine/chemokine ELISA.

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- **Project Title: THE ROLE OF THE CYP4F3 GENE IN INFLAMMATION**

  Principal Investigator & Institution: Christmas, Peter; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2002; Project Start 01-AUG-2001; Project End 30-JUN-2004

  Summary: (provided by applicant) Recently we cloned and characterized the gene for cytochrome P450 4F3 (CYP4F3). The gene contains 14 exons and 13 introns, and undergoes alternative splicing to generate two splice forms containing either exon 3 or exon 4. These isoforms catalyze omega-hydroxylation of different substrates. The isoform expressing exon 4 (CYP4F3A) utilizes the inflammatory mediator leukotriene B4

(LTB4) as its substrate and renders it inactive for pro-inflammatory functions such as neutrophil chemoattraction. LTB4 has been implicated as a pathological mediator in inflammatory disorders such as inflammatory bowel disease, **glomerulonephritis,** and asthma. The uniquely low Km of CYP4F3A for LTB4, and its unique localization among CYP4 enzymes to myeloid cells, suggest that its expression plays a central role in the control of LTB4-mediated inflammation. The isoform of CYP4F3 expressing exon 3 (CYP4F3B) utilizes arachidonic acid as a substrate and generates 20-HETE, an intracellular activator of protein kinase C and Ca2+/calmodulin-dependent kinase II. 20-HETE is a preeminent eicosanoid in the kidney where it performs a vasoactive and natriuretic function, but it is also active in many other tissues. Preliminary data suggests that the range of CYP4F3 expression is extended beyond myeloid cells by alternative promoter usage. The hypothesis of this proposal is that coordinated tissue-specific expression and splicing determine whether the CYP4F3 gene functions to inactivate a bioactive eicosanoid (LTB4) in inflammation, or generate a bioactive eicosanoid (20-HETE). The goals of the proposal are to determine how the expression of the different functional forms of CYP4F3 are regulated. In Specific Aim 1, the tissue-specific regulation of CYP4F3 gene expression will be investigated. Luciferase reporter constructs, DNase I footprinting, EMSA, and site-directed mutagenesis will be employed to identify promoter elements that regulate transcription in myeloid cells, and non-hematopoietic tissues such as liver. An initial characterization of DNA elements that regulate splicing will be performed using minigene constructs in splicing assays. In Specific Aim 2, the functional consequences of CYP4F3 expression will be studied. The possibility of additional roles for CYP4F3A in inflammatory signal transduction pathways will be investigated. We will determine if reactive oxygen species generated during CYP4F3A-dependent LTB4 metabolism can activate stress-activated protein kinases (SAPKs) via the dissociation of ASK1 and thioredoxin. The tissue localization of CYP4F3 gene products in the gastrointestinal tract and kidney will be analyzed by immunohistochemistry, in situ hybridization, and isoform-specific PCR.

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- **Project Title: VASCULAR ENDOTHELIAL CADHERIN FUNCTION IN INFLAMMATION**

  Principal Investigator & Institution: Shaw, Sunil K.; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

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

  Summary: Candidate: The applicant has researched mucosal lymphocyte homing and recirculation for the past 8 years. Accomplishments include contributions at both molecular and cell biological levels to interaction of intra- epithelial lymphocytes with epithelial cells. Environment: Brigham and Women's hospital, affiliated with Harvard University, is recognized as a leader in medical research, and will provide a supportive and stimulating environment. The mentor's lab at the Vascular Research Division has access to specialized equipment and tissues necessary for this research. Research: Gastritis, ulceration, celiac sprue, Crohn disease and ulcerative colitis, **glomerulonephritis,** interstitial nephritis and pyelonephritis are all characterized by the activation of inflammatory cells leading to tissue injury. Leukocyte transmigration and accompanying increased vascular permeability are critical steps during the inflammatory response. Thus, integrity of the organ vasculature is necessary for normal system function, and the endothelial barrier must be breached to lead to tissue injury in these diseases. Although much is known about leukocyte-endothelial adhesion and inflammation, less information is available concerning the role played by endothelial

cells in regulating permeability and leukocytes and macromolecules. Vascular endothelial cadherin is located at endothelial adherens and junctions and may regulate monolayer permeability to leukocytes and inflammatory factors. The objective of this proposal is to study the role of VE-cadherin in barrier function and cell growth in vascular endothelial cells by disruption via a dominant negative mechanism. A high efficiency if transfection will be achieved using an adenoviral expression system. This approach will allow specific disruption of one component of the adherens junction, and allow subsequent analysis of endothelial specific functions. These techniques will be used to probe the function of adherens junctions in endothelium from various vascular beds and their contribution to inflammation. The proposed studies are anticipated to allow a better understanding of the role of endothelial adherens junctions in normal and disease conditions, and may lead to novel therapeutic approaches and targets for intervention.

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- **Project Title: VAV GDP/GTP EXCHANGE FACTORS IN CHEMOTAXIS**

  Principal Investigator & Institution: Brugge, Joan S.; Professor; Cbr Institute for Biomedical Research 800 Huntington Ave Boston, Ma 02115

  Timing: Fiscal Year 2003; Project Start 16-DEC-2002; Project End 30-NOV-2007

  Summary: (provided by the Applicant): Leukocyte chemotaxis plays a critical in the body's defense against microorganisms and hyperactivity of these cells leads to a variety of pathologic states including inflammation, vasculitis, and **glomerulonephritis.** Chemotaxis is dependent on the dynamic activity of adhesive and actin cytoskeletal structures that regulate cell motility. Rho GTPases are central players in the regulation of cell adhesion and actin cytoskeletal polymerization and assembly into cytoskeletal structures. We have found that Vav family Rho GTPase exchange factors are required for chemotaxis mediated by the chemoattractant fMLP and for macrophage migration on an extracellular matrix. This conclusion was based on studies of mice deficient in two Vav family members, Vav1 and Vav3. This proposal will examine the mechanisms involved in activation of Vav by chemoattractants and integrins and establish the mechanisms whereby this multidomain scaffolding protein regulates actin cytoskeletal structures and controls cell migration. The latter will involve defining regions of Vav that are required for motility and identification of effectors that mediate the activity of these domains. In addition we will analyze neutrophil and macrophage motility in mice lacking all three Vav family members since they are all expressed in these two cell types. These studies promise to elucidate pathways that are important in the host defense again microorganisms and pathologic inflammatory states.

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

- **Project Title: WEIBEL PALADE BODY FORMATION AND ROLE IN HEMOSTASIS**

  Principal Investigator & Institution: Wagner, Denisa D.; Professor; Cbr Institute for Biomedical Research 800 Huntington Ave Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 01-JUL-1988; Project End 30-JUN-2003

  Summary: Following a vascular injury or during inflammation, endothelial cells rapidly release the contents of their storage granules, called Weibel- Palade bodies (WPBs). The major soluble component of these granules is von Willebrand factor (vWf). vWf is a large multimeric glycoprotein that has a dual role in hemostasis: it promotes platelet adhesion and it protects factor VIII (FVIII) against proteolysis. vWf is synthesized with a prosequence which directs multimer formation through an as yet unknown mechanism.

The formation of the WPBs and the function of vWf after secretion are the main topics of this proposal. We will be greatly assisted by the existence of vWf-deficient mice that we prepared during the last grant period. The proposal has four specific aims. I) Weibel-Palade body formation. We will examine whether the vWf prosequence has a disulfide isomerase enzymatic activity, which would explain its role in vWf multimerization. We will continue our studies on the molecular mechanisms involved in granulogenesis. II) Role of vWf in normal physiology. We will evaluate the effect of vWf-deficiency of FVIII half life and secretion. We will examine whether there is a feedback mechanism by which vWf or its prosequence modulates FVIII biosynthesis. We will study the role of vWf in platelet thrombus formation in vitro and in vivo using a new intravital microscopy model we have developed. The importance of vWf will be compared with that of other platelet adhesion molecules, i.e., fibrinogen and beta3 integrins. III) Role of vWf in various diseases. We will test the role of vWf in diseases in which platelets are thought to play an important part, e.g., septic shock, stroke and atherosclerosis. IV) Generation and characterization of new mutant mice. We will produce combinations of genetic defects by crossing the vWf-deficient mice with other mutant strains. We will evaluate the effect of gene dosage of vWf in homeostasis and disease by producing mice with twice the normal level of vWf. Our research will employ a variety of techniques including protein chemistry, cell culture, intravital microscopy, animal experimentation, and finally, genetic engineering of a targeted gene duplication in mice. Learning about the mechanisms involved in WPB formation and secretion is clinically relevant, as the main treatment of patients with low vWf relies on releasing the stored protein pool. An understanding of the exact roles that vWf plays in platelet adhesion and thrombus formation may lead to new anti-thrombotic therapies which could become applicable in diseases where platelet adhesion and/or aggregation is part of the disease process.

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

E-Journals: PubMed Central[3]

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

- **Abrogation of Macrophage-dependent Injury in Experimental Glomerulonephritis in the Rabbit USE OF AN ANTIMACROPHAGE SERUM.** by Holdsworth SR, Neale TJ, Wilson CB.; 1981 Sep;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=370850

[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.

- **Anti-interferon globulin inhibits the development of glomerulonephritis in mice infected at birth with lymphocytic choriomeningitis virus.** by Gresser J, Morel-Maroger L, Verroust P, Riviere Y, Guillon JC.; 1978 Jul; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=392787
- **Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice.** by Xiao H, Heeringa P, Hu P, Liu Z, Zhao M, Aratani Y, Maeda N, Falk RJ, Jennette JC.; 2002 Oct 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=151154
- **Anti-Nuclear Antibody Production and Immune-Complex Glomerulonephritis in BALB/c Mice Treated With Pristane.** by Satoh M, Kumar A, Kanwar YS, Reeves WH.; 1995 Nov 21; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=40545
- **Autoimmune glomerulonephritis with spontaneous formation of splenic germinal centers in mice lacking the estrogen receptor alpha gene.** by Shim GJ, Kis LL, Warner M, Gustafsson JA.; 2004 Feb 10; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=341834
- **Cryoglobulinemia induced by a murine IgG3 rheumatoid factor: skin vasculitis and glomerulonephritis arise from distinct pathogenic mechanisms.** by Reininger L, Berney T, Shibata T, Spertini F, Merino R, Izui S.; 1990 Dec; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=55310
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The National Library of Medicine: PubMed

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To generate your own bibliography of studies dealing with glomerulonephritis, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type "glomerulonephritis" (or synonyms) into the search box, and click "Go." The following is the type of output you can expect from PubMed for glomerulonephritis (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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  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11676362

- **Vascular endothelial growth factor enhances glomerular capillary repair and accelerates resolution of experimentally induced glomerulonephritis.**
  Author(s): Masuda Y, Shimizu A, Mori T, Ishiwata T, Kitamura H, Ohashi R, Ishizaki M, Asano G, Sugisaki Y, Yamanaka N.
  Source: American Journal of Pathology. 2001 August; 159(2): 599-608.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11485918

- **Vasculitis and rapidly progressive glomerulonephritis in the elderly.**
  Author(s): Higgins RM, Goldsmith DJ, Connolly J, Scoble JE, Hendry BM, Ackrill P, Venning MC.
  Source: Postgraduate Medical Journal. 1996 January; 72(843): 41-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8746284

- **Visual impairment caused by retinal abnormalities in mesangiocapillary (membranoproliferative) glomerulonephritis type II ("dense deposit disease").**
  Author(s): Colville D, Guymer R, Sinclair RA, Savige J.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation. 2003 August; 42(2): E2-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12900843

- **What sensitized cells just might be doing in glomerulonephritis.**
  Author(s): Bolton WK.
  Source: The Journal of Clinical Investigation. 2002 March; 109(6): 713-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11901177

- **When noncongophilic glomerular fibrils do not represent fibrillary glomerulonephritis: nonspecific mesangial fibrils in sclerosing glomeruli.**
  Author(s): Kronz JD, Neu AM, Nadasdy T.
  Source: Clinical Nephrology. 1998 October; 50(4): 218-23.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9799066

- **Wilson cirrhosis associated with membranoproliferative glomerulonephritis.**
  Author(s): Gunduz Z, Dusunsel R, Anarat A.
  Source: Nephron. 1996; 74(2): 497-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8893211

- **WT1 is a key regulator of podocyte function: reduced expression levels cause crescentic glomerulonephritis and mesangial sclerosis.**
  Author(s): Guo JK, Menke AL, Gubler MC, Clarke AR, Harrison D, Hammes A, Hastie ND, Schedl A.
  Source: Human Molecular Genetics. 2002 March 15; 11(6): 651-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11912180

- **Younger onset myeloperoxidase-specific antineutrophil cytoplasmic antibody- (MPO-ANCA) related glomerulonephritis accompanied with nephrotic syndrome.**
  Author(s): Kaneko Y, Kamijo Y, Kobayashi N, Higuchi M, Ehara T, Hora K, Shigematsu H, Kiyosawa K.
  Source: Clinical Nephrology. 2003 October; 60(4): 275-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14579943

CHAPTER 2. NUTRITION AND GLOMERULONEPHRITIS

Overview

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

Finding Nutrition Studies on Glomerulonephritis

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

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

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

- **Crescentic glomerulonephritis in children.**
  Author(s): Renal Unit, Hospital for Sick Children, London, UK.
  Source: Jardim, H M Leake, J Risdon, R A Barratt, T M Dillon, M J Pediatr-Nephrol. 1992 May; 6(3): 231-5 0931-041X
- **Studies on treatment of glomerulonephritis by TCM yi-qi huo-xue methods.**
  Source: Wei, M Huang, Q F Zeng, S P Lang, Z W J-Tradit-Chin-Med. 1988 March; 8(1): 55-60 0254-6272
- **Treatment of mesangiocapillary glomerulonephritis with alternate-day prednisone--a report of the International Study of Kidney Disease in Children.**
  Author(s): Albert Einstein College of Medicine, Bronx, New York.
  Source: Tarshish, P Bernstein, J Tobin, J N Edelmann, C M Pediatr-Nephrol. 1992 March; 6(2): 123-30 0931-041X

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**

CHAPTER 3. ALTERNATIVE MEDICINE AND GLOMERULONEPHRITIS

Overview

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

- **A comparison of the effect of ramipril, felodipine and placebo on glomerular filtration rate, albuminuria, blood pressure and vasoactive hormones in chronic glomerulonephritis. A randomized, prospective, double-blind, placebo-controlled study over two years.**
  Author(s): Pedersen EB, Bech JN, Nielsen CB, Kornerup HJ, Hansen HE, Spencer ES, Solling J, Jensen KT.
  Source: Scandinavian Journal of Clinical and Laboratory Investigation. 1997 December; 57(8): 673-81.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9458489

- **Accelerated decay of the cell bound C4b2a complex by serum of patients with membranoproliferative glomerulonephritis and acute poststreptococcal glomerulonephritis.**
  Author(s): Tanuma Y, Ohi H, Hatano M.

Source: Clinical Immunology and Immunopathology. 1992 March; 62(3): 270-6.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1541053

- **Acute poststreptococcal glomerulonephritis: public health implications of recent clusters in New South Wales and epidemiology of hospital admissions.**
Author(s): Muscatello DJ, O'Grady KA, Neville K, McAnulty J.
Source: Epidemiology and Infection. 2001 June; 126(3): 365-72.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11467793

- **Alteration of mercuric chloride-induced autoimmune glomerulonephritis in brown-Norway rats by herring oil, evening primrose oil and OKY-046 a selective TXA-synthetase inhibitor.**
Author(s): Papanikolaou N.
Source: Prostaglandins Leukot Med. 1987 May; 27(2-3): 129-49.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3475724

- **Bone-marrow-derived cells contribute to glomerular endothelial repair in experimental glomerulonephritis.**
Author(s): Rookmaaker MB, Smits AM, Tolboom H, Van 't Wout K, Martens AC, Goldschmeding R, Joles JA, Van Zonneveld AJ, Grone HJ, Rabelink TJ, Verhaar MC.
Source: American Journal of Pathology. 2003 August; 163(2): 553-62.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12875975

- **Bone-marrow-derived macrophages genetically modified to produce IL-10 reduce injury in experimental glomerulonephritis.**
Author(s): Wilson HM, Stewart KN, Brown PA, Anegon I, Chettibi S, Rees AJ, Kluth DC.
Source: Molecular Therapy : the Journal of the American Society of Gene Therapy. 2002 December; 6(6): 710-7.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12498767

- **Clinical evaluation and characterization of a unique C3 breakdown factor detected in a patient with acute glomerulonephritis.**
Author(s): Fujita T, Ohi H, Seki M, Miyaji H, Hatano M.
Source: Nephron. 1987; 47(1): 56-61.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3627335

- **Collagenase activity of rat kidney with glomerulonephritis during the heterologous phase.**
Author(s): Lubec G.
Source: Clinica Chimica Acta; International Journal of Clinical Chemistry. 1977 April 1; 76(1): 89-94.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=192495

- **Collagenase activity of rat kidney with immune complex glomerulonephritis.**
  Author(s): Lubec G, Ratzenhofer E.
  Source: Clinica Chimica Acta; International Journal of Clinical Chemistry. 1978 January 2; 82(1-2): 205-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=201399

- **Crescentic IgA glomerulonephritis following interleukin-2 therapy for hepatocellular carcinoma of the liver.**
  Author(s): Chan TM, Cheng IK, Wong KL, Chan KW, Lai CL.
  Source: American Journal of Nephrology. 1991; 11(6): 493-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1668057

- **Dietary marine lipid alleviates autoimmune glomerulonephritis in mice.**
  Author(s): Robinson DR.
  Source: Adv Prostaglandin Thromboxane Leukot Res. 1985; 15: 377-9. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2936125

- **Dietary proteins affect proteinuria in primary membranous glomerulonephritis with nephrotic syndrome and normal renal function.**
  Author(s): Cupisti A, Morelli E, Ciardella F, Schipani G, Guidi A, Barsotti G.
  Source: Contrib Nephrol. 1990; 83: 166-9. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2100708

- **Differential treatment for membranoproliferative glomerulonephritis with TCM prescriptions plus triptoryph tablets--a report of 30 cases.**
  Author(s): Ju J, Lian Y, Bo S.
  Source: J Tradit Chin Med. 2003 September; 23(3): 177-9. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14535177

- **Effect of ageing of serum on consumption of antibody by beta-1C-globulin determinants; evidence for circulating breakdown products in glomerulonephritis.**
  Author(s): West CD, Winter S, Forristal J, Davis NC.
  Source: Clinical and Experimental Immunology. 1968 January; 3(1): 57-62.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=4171046

- **Effect of combined immunosuppressive-cytostatic treatment on antibody-dependent cellular cytotoxicity of patients with chronic glomerulonephritis.**
  Author(s): Lang I, Fekete B, Kenez B, Nagy ZK, Gergely P.
  Source: Acta Med Acad Sci Hung. 1977; 34(4): 247-50.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=618056

- **Effect of thromboxane A2-synthetase inhibitor OKY-046 and evening primrose oil (Efamol) on mercuric chloride induced autoimmune glomerulonephritis in Brown-Norway rats.**
  Author(s): Papanikolaou N, Hatziantoniou C, Gkika EL.
  Source: Prog Clin Biol Res. 1987; 242: 43-9. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3671393

- **Effects of heat therapy on renal hemodynamics, compensatory hypertrophy and glomerulonephritis in rats.**
  Author(s): Tsai TJ, Chen CF.
  Source: Nephron. 1993; 63(2): 207-13.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8450914

- **Effects of TCM therapy on the progression of chronic renal failure caused by primary glomerulonephritis.**
  Author(s): Xiong NN, Zou YQ, Huang XW, Gong LJ, Yu CH, Zou YX.
  Source: J Tradit Chin Med. 1988 June; 8(2): 107-11. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3412003

- **Endemic occurrence of glomerulonephritis associated with streptococcal impetigo.**
  Author(s): Kobayashi S, Ikeda T, Okada H, Suzuki Y, Ishii M, Ohtake T, Oda T, Hishida A.
  Source: American Journal of Nephrology. 1995; 15(4): 356-60.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7573198

- **Evidence for in vivo breakdown of beta-10-globulin in hypocomplementemic glomerulonephritis.**
  Author(s): West CD, Winter S, Forristal J, McConville JM, Davis NC.
  Source: The Journal of Clinical Investigation. 1967 April; 46(4): 539-48.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=4164258

- **Experimental and clinical studies of "Shen Yan Ling" in treatment of chronic glomerulonephritis.**
  Author(s): Wang SQ, Du XR, Lu HW, Wang TL, Li H.
  Source: J Tradit Chin Med. 1989 June; 9(2): 132-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2779276

- **Experimental studies on immune-complex in situ type glomerulonephritis in rabbits treated with mai-luo-tong and natural indigo.**
  Author(s): Sun SL, Yi HP, Wang QL, Huang SZ, Liu XC.
  Source: J Tongji Med Univ. 1994; 14(3): 153-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7807600

- **Glomerulonephritis and immunosuppression associated with dietary essential fatty acid deficiency in gilthead sea bream, Sparus aurata L., juveniles.**
  Author(s): Montero D, Socorro J, Tort L, Caballero MJ, Robaina LE, Vergara JM, Izquierdo MS.
  Source: Journal of Fish Diseases. 2004 May; 27(5): 297-306.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15139908

- **Glomerulonephritis preceding late relapse of Hodgkin's disease.**
  Author(s): Lynn WA, Marcus RE.
  Source: Postgraduate Medical Journal. 1988 May; 64(751): 395-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3200784

- **Heart function in patients with chronic glomerulonephritis and mildly to moderately impaired renal function. An echocardiographic study.**
  Author(s): Schroeder AP, Kristensen BO, Nielsen CB, Pedersen EB.
  Source: Blood Pressure. 1997 September; 6(5): 286-93.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9359999

- **Hemostasis, platelet functions, serotonin and serum lipids during omega-3 fatty acid treatment in patients with glomerulonephritis.**
  Author(s): Malyszko JS, Malyszko J, Pawlak D, Buczko W, Mysliwiec M.
  Source: Nephron. 1998 September; 80(1): 94-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9730718

- **Henoch-Schonlein IgA glomerulonephritis complicating myeloma kidneys: case report.**
  Author(s): Arrizabalaga P, Saurina A, Sole M, Blade J.
  Source: Annals of Hematology. 2003 August; 82(8): 526-8. Epub 2003 July 03.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12844235

- **Henoch-Schonlein purpura associated with segmental and focal proliferative glomerulonephritis in a patient with Hodgkin's disease.**
  Author(s): Blanco P, Denisi R, Rispal P, Deminiere C, Pellegrin JL, Leng B, Aparicio M.
  Source: Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association. 1999 January; 14(1): 179-80.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10052501

- **Human glomerulonephritis and the C3 nephritic factor (C3NeF).**
  Author(s): Berthoux FC, Carpenter CB, Freyria AM, Traeger J, Merrill JP.
  Source: Clinical Nephrology. 1976 March; 5(3): 93-100.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=57022

- **Immune complex glomerulonephritis with unusual microfibrillar deposits associated with primary bone marrow lymphoma.**
  Author(s): Kohan DE, Perkins SL, Terreros DA.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation. 1993 January; 21(1): 47-51.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8418626

- **Immunopharmacological studies of the aqueous extract of Cinnamomum cassia (CCAq). II. Effect of CCAq on experimental glomerulonephritis.**
  Author(s): Nagai H, Shimazawa T, Takizawa T, Koda A, Yagi A, Nishioka I.
  Source: Japanese Journal of Pharmacology. 1982 October; 32(5): 823-31.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7176217

- **In vivo treatment with a monoclonal antibody to T helper cells in experimental autoimmune glomerulonephritis in the BN rat.**
  Author(s): Reynolds J, Pusey CD.
  Source: Clinical and Experimental Immunology. 1994 January; 95(1): 122-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8287595

- **L-Arginine supplementation increases mesangial cell injury and subsequent tissue fibrosis in experimental glomerulonephritis.**
  Author(s): Peters H, Border WA, Noble NA.
  Source: Kidney International. 1999 June; 55(6): 2264-73.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10354274

- **Lovastatin in glomerulonephritis patients with hyperlipidaemia and heavy proteinuria.**
  Author(s): Chan PC, Robinson JD, Yeung WC, Cheng IK, Yeung HW, Tsang MT.
  Source: Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association. 1992; 7(2): 93-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1314986

- **Membranoproliferative glomerulonephritis following gemcitabine and vinorelbine chemotherapy for peritoneal mesothelioma.**
  Author(s): Fracasso PM, Tan BR Jr, Grieff M, Stephenson J Jr, Liapis H, Umbeck NL, Von Hoff DD, Rowinsky EK.
  Source: Journal of the National Cancer Institute. 1999 October 20; 91(20): 1779-80.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10528031

- **Membranous glomerulonephritis in chronic lymphocytic leukemia.**
  Author(s): Ziakas PD, Giannouli S, Psimenou E, Nakopoulou L, Voulgarelis M.

Source: American Journal of Hematology. 2004 July; 76(3): 271-4.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15224365

- **Mucosal immunity in primary glomerulonephritis. III. Study of intestinal permeability.**
  Author(s): Rostoker G, Wirquin V, Terzidis H, Petit-Phar M, Chaumette MT, Delchier JC, Belghiti D, Lang P, Dubert JM, Meignan M, et al.
  Source: Nephron. 1993; 63(3): 286-90.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8446265

- **NO mediates antifibrotic actions of L-arginine supplementation following induction of anti-thy1 glomerulonephritis.**
  Author(s): Peters H, Daig U, Martini S, Ruckert M, Schaper F, Liefeldt L, Kramer S, Neumayer HH.
  Source: Kidney International. 2003 August; 64(2): 509-18.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12846746

- **Observations on therapeutic effects of huangdan decoction and Tripterygium Wilfordii compound tablet on membranous glomerulonephritis in rats.**
  Author(s): Zheng JF, Chen SY.
  Source: J Tongji Med Univ. 1995; 15(1): 31-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7783260

- **Pregnancy aggravates proteinuria in subclinical glomerulonephritis in the rat.**
  Author(s): Faas MM, Bakker WW, Poelman RT, Schuiling GA.
  Source: The Journal of Laboratory and Clinical Medicine. 1999 September; 134(3): 267-74.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10482312

- **Prevention of glomerulonephritis and prolonged survival in New Zealand Black/New Zealand White F1 hybrid mice fed an essential fatty acid-deficient diet.**
  Author(s): Hurd ER, Johnston JM, Okita JR, MacDonald PC, Ziff M, Gilliam JW.
  Source: The Journal of Clinical Investigation. 1981 February; 67(2): 476-85.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=6450777

- **Professor Wang Gang's experience in treating chronic glomerulonephritis.**
  Author(s): Zhou E.
  Source: J Tradit Chin Med. 2003 June; 23(2): 90-5. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12875061

- **Protective effect of polyunsaturated fatty acid supplementation in apoferritin induced murine glomerulonephritis.**
  Author(s): Kher V, Barcelli U, Weiss M, Gallon L, Pajel P, Laskarzewski P, Pollak VE.

Source: Prostaglandins Leukot Med. 1986 June; 22(3): 323-34.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3014561

- **Recent advances in the prophylaxis and treatment of chronic glomerulonephritis with combined TCM and WM.**
  Author(s): Chen MF.
  Source: J Tradit Chin Med. 1983 June; 3(2): 151-62. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=6555451

- **Recurrence of glomerulonephritis following renal transplantation. Scientific Advisory Board of the ERA-EDTA Registry. European Renal Association-European Dialysis and Transplant Association.**
  Author(s): Briggs JD, Jones E.
  Source: Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association. 1999 March; 14(3): 564-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10193799

- **Searching for acute poststreptococcal glomerulonephritis-associated Streptococcus pyogenes in Australian aboriginal communities.**
  Author(s): Goodfellow AM, Gardiner DL.
  Source: Advances in Experimental Medicine and Biology. 1997; 418: 103-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9331610

- **Serial alterations of glomerular matrix-degrading metalloproteinase activity in anti-thymocyte-induced glomerulonephritis in rats.**
  Author(s): Sato Y, Fujimoto S, Hamai K, Eto T.
  Source: Nephron. 1998; 78(2): 195-200.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9496737

- **Serum C'3 lytic system in patients with glomerulonephritis.**
  Author(s): Spitzer RE, Vallota EH, Forristal J, Sudora E, Stitzel A, Davis NC, West CD.
  Source: Science. 1969 April 25; 164(878): 436-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=4180576

- **Significance of C3 nephritic factor (C3NeF) in non-hypocomplementaemic serum with membranoproliferative glomerulonephritis (MPGN).**
  Author(s): Ohi H, Watanabe S, Fujita T, Yasugi T.
  Source: Clinical and Experimental Immunology. 1992 September; 89(3): 479-84.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1516262

- **Studies on treatment of glomerulonephritis by TCM yi-qi huo-xue methods.**
  Author(s): Wei M, Huang QF, Zeng SP, Lang ZW.

Source: J Tradit Chin Med. 1988 March; 8(1): 55-60. No Abstract Available.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3393020

- **Study on the therapeutic effects of traditional Chinese drugs in experimental glomerulonephritis.**
  Author(s): Wei M, Zhu L, Huang Q, Xu W, Li B.
  Source: J Tradit Chin Med. 1993 December; 13(4): 287-93. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8139280

- **Suppressive effects of Perilla frutescens on mesangioproliferative glomerulonephritis in rats.**
  Author(s): Makino T, Nakamura T, Ono T, Muso E, Honda G.
  Source: Biological & Pharmaceutical Bulletin. 2001 February; 24(2): 172-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11217087

- **Suppressive effects of rosmarinic acid on mesangioproliferative glomerulonephritis in rats.**
  Author(s): Makino T, Ono T, Liu N, Nakamura T, Muso E, Honda G.
  Source: Nephron. 2002 December; 92(4): 898-904.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12399637

- **Suppressive effects of sairei-to on monoclonal antibody 1-22-3-induced glomerulonephritis: analysis of effective components.**
  Author(s): Li P, Kawachi H, Morioka T, Orikasa M, Oite T, Shi ZS, Shimizu F.
  Source: Pathology International. 1997 July; 47(7): 430-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9234380

- **Tandem antifibrotic actions of L-arginine supplementation and low protein diet during the repair phase of experimental glomerulonephritis.**
  Author(s): Peters H, Border WA, Noble NA.
  Source: Kidney International. 2000 March; 57(3): 992-1001.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10720952

- **The effect of fish-oil dietary supplement on the progression of mesangial IgA glomerulonephritis.**
  Author(s): Cheng IK, Chan PC, Chan MK.
  Source: Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association. 1990; 5(4): 241-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2113220

- **Transfection of rat kidney with human 15-lipoxygenase suppresses inflammation and preserves function in experimental glomerulonephritis.**

Author(s): Munger KA, Montero A, Fukunaga M, Uda S, Yura T, Imai E, Kaneda Y, Valdivielso JM, Badr KF.
Source: Proceedings of the National Academy of Sciences of the United States of America. 1999 November 9; 96(23): 13375-80.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10557328

- **Treatment of ANCA-positive, pauci-immune extracapillary glomerulonephritis with etoposide.**
  Author(s): Jensen DM, Pedersen RS.
  Source: Nephron. 1995; 69(3): 341-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7753274

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 glomerulonephritis; 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:

- **Herbs and Supplements**

  Hibiscus
  Alternative names: Hibiscus, Roselle; Hibiscus sp.
  Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Motherwort
Alternative names: Leonurus cardiaca
Source: Healthnotes, Inc.; www.healthnotes.com

General References

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

CHAPTER 4. DISSERTATIONS ON GLOMERULONEPHRITIS

Overview

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

Dissertations on Glomerulonephritis

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 glomerulonephritis. 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:

- **Experimental streptococcal glomerulonephritis in rabbits and further studies on the nature of nephrotoxin** by Ng, Wei-wei; PhD from MCGILL UNIVERSITY (CANADA), 1972
  http://wwwlib.umi.com/dissertations/fullcit/NK11953
- **Streptococcal glomerulonephritis immunological studies** by Day, Noorbibi K; ADVDEG from MCGILL UNIVERSITY (CANADA), 1967
  http://wwwlib.umi.com/dissertations/fullcit/NK01302

Keeping Current

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

CHAPTER 5. PATENTS ON GLOMERULONEPHRITIS

Overview

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

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

Patents on Glomerulonephritis

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

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

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

- **Method and means for treating glomerulonephritis**

  Inventor(s): Fellstrom; Bengt (Knivsta, SE), Hallgren; Roger (Balinge, SE)

  Assignee(s): Pharmalink AB (Upplands Vasby, SE)

  Patent Number: 6,239,120

  Date filed: March 11, 1999

  Abstract: The invention provides the use of a glucocorticoid having a first pass metabolism in the liver of at least 90% as active substance, for the manufacturing of a medicament for oral or rectal administration in the treatment of **glomerulonephritis** by releasing the active substance in the intestine. The invention also provides a method for treatment of **glomerulonephritis** in a native kidney or a kidney transplant with the glucocorticoid as defined above. The invention also comprises a composition comprising the active substance and a pharmaceutically acceptable carrier, adjuvant or diluent designed for oral or rectal administration.

  Excerpt(s): The present invention relates to a method and means for treating **glomerulonephritis.** The functional units of the kidney, such as the glomeruli may suffer from inflammation. An inflammatory attack in the glomeruli is termed **glomerulonephritis** and can be classified into subgroups such as membraneous **glomerulonephritis,** focal segmental glomerulosclerosis, mesangial diffuse proliferative **glomerulonephritis,** endocapillary or extracapillary proliferative **glomerulonephritis.** Using histopathological techniques these subgroups vary with respect to microscopical or immunohistochemical picture. One cause of inflammation is due to the deposition of immunoglobulin A (IgA) in glomeruli. This condition is termed IgA nephropathy (1-3), and is the most common form of **glomerulonephritis** in a global perspective. Assessment of the degree of severity of **glomerulonephritis** is based on different investigation results. The most important findings are 1) the degree of urinary excretion of protein (proteinuria) and 2) the filtering function of the kidney, which can be assessed by serum creatinine (screatinine). Histological examination of material from kidney (renal biopsy) yields information about the type of renal damage as well as the severity of the injury. The outcome of a **glomerulonephritis** is variable and is dependent upon the histological and the immunohistochemical findings in a renal biopsy. Patients with IgA nephropathy having a constant proteinuria often develop renal failure and uraemia after 5 to 20 years of illness (4).

  Web site: http://www.delphion.com/details?pn=US06239120__

- **Method for treating inflammatory diseases by administering a thrombin inhibitor**

  Inventor(s): Shafer; Jules (Gwynedd Valley, PA), Visco; Denise M. (Fanwood, NJ)

  Assignee(s): Merck & Co., Inc. (Rahway, NJ)

  Patent Number: 6,362,190

  Date filed: May 10, 2001

  Abstract: The invention is a method for treating an inflammatory disease in a patient which comprises treating the patient with an oral composition comprising a thrombin

inhibitor. Such diseases include but are not limited to nephritis, systemic lupus erythematosus, rheumatoid arthritis, **glomerulonephritis** and sarcoidosis.

Excerpt(s): This invention relates to methods for treating inflammatory diseases by administration of a thrombin inhibitor. Anti-inflammatory drugs include non steroidal anti-inflammatory drugs (NSAIDs) which exert anti-inflammatory, analgesic and antipyretic activity. These include salicylates such as aspirin, sodium salicylate, choline salicylate, salicylsalicylic acid, diflunisal, and salsalate; indoleacetic acids such as indomethacin and sulindac; pyrazoles such as phenylbutazone, oxyphenbutazone; pyrrolealkanoic acids such as tolmetin; phenylacetic acids such as ibuprofen, feroprofen, flurbiprofen, and ketoprofen; fenamates such as mefanamic acid, and meclofenamate; oxicams such as piroxicam; and naphthaleneacetic acids such as naproxen. Nearly all act by inhibiting cyclo-oxygenase activity. Aspirin, for example, acetylates and irreversibly inactivates cyclo-oxygenase. Others, such as indomethacin, inhibit cyclo-oxygenase activity reversibly by binding in a stereospecific manner to one or another subunit of the enzyme. NSAIDs are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process but are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. Adrenal corticosteroids, which are alternatives to NSAIDs for treating inflammatory diseases, have even more drastic side effects, especially when long term therapy is involved. These steroids, including hydrocortisone, prednisolone, 6 alpha-methylprednisolone, triamcinolone, dexamethasone and betaroethasone, affect inflammation by a possible mechanism whereby they bind to intracellular glucocorticoid receptors to subsequently initiate a series of cellular events involving synthesis of new phospholipid inhibitory proteins, or lipocortins, that can affect the inflammatory and the teratogenic responses of certain cells exposed to glucocorticoids. The anti-inflammatory effect of glucocorticoids has been well documented.

Web site: http://www.delphion.com/details?pn=US06362190__

- **Method of inhibiting glomerulonephritis**

  Inventor(s): Tipping; Peter G. (Clayton, AU), Wun; Tze-Chein (St. Louis, MO)

  Assignee(s): G. D. Searle & Co. (Chicago, IL)

  Patent Number: 5,824,660

  Date filed: June 10, 1996

  Abstract: There is disclosed a method of inhibiting fibrin dependent **glomerulonephritis** which comprises administering to a warm-blooded mammal a heparin/TFPI complex which consists of a weight ratio of at least 1.25 parts of heparin to one part of TFPI.

  Excerpt(s): The present invention relates to a method of inhibiting **glomerulonephritis** and, more particularly, to inhibition of fibrin-dependent **glomerulonephritis** by administration of heparin/TFPI complexes. Tissue factor pathway inhibitor (TFPI) is the naturally occurring inhibitor of tissue factor (TF), the major in vivo activator of the coagulation cascade (1,2). TFPI is thought to inhibit TF/VIIa activity in a two-step reaction. First, TFPI binds and inhibits factor Xa, then the TFPI/Xa complex binds to TF/VIIa resulting in inhibition of TF/VIIa activity (3,4). In man, TFPI exists free in the circulation and also in association with lipoproteins and in platelets. The major pool of TFPI is on the surface of endothelial cells (1,5). In rabbits, TFPI is not lipoprotein bound

and plasma TFPI has a molecular weight between 43 and 45 kD (6,7). TFPI bound to endothelial cells may play a critical role in controlling factor Xa generation and coagulation at sites of local endothelial cell injury.

Web site: http://www.delphion.com/details?pn=US05824660__

- **Protein having proteinase inhibitor activity**

  Inventor(s): Davies; Christopher (Walnut Creek, CA), Delaria; Kathy (Walnut Creek, CA), Roczniak; Steve (Lafayette, CA)

  Assignee(s): Bayer Corporation (Berkeley, CA)

  Patent Number: 6,294,648

  Date filed: July 20, 1999

  Abstract: BTL.009 is a novel human serine proteinase inhibitor of the Kunitz family that exhibits greater potency towards neutral serine proteinases, particularly leukocyte elastase, and chymotrypsin than towards trypsin-like proteinases. BTL.009, or variants thereof, may be employed as therapeutics in diseases such as emphysema, idiopathic pulmonary fibrosis, adult respiratory distress syndrome, cystic fibrosis, rheumatoid arthritis, organ failure, and **glomerulonephritis** in which uncontrolled proteolysis due to neutral serine proteinase activity results in tissue damage.

  Excerpt(s): This invention relates to newly identified polynucleotides, polypeptides encoded by such polynucleotides, the use of such polynucleotides and polypeptides, as well as the production of such polynucleotides and polypeptides. More particularly, the polypeptide of the present invention has been identified as a member of the Kunitz serine proteinase inhibitor family and is hereinafter referred to as BTL.009. The inflammatory response after surgeries, trauma and infection involves neutrophil activation and infiltration into the injured tissue. The activated neutrophils release the neutral serine proteinases leukocyte elastase, cathepsin G and proteinase 3, which, if not properly controlled, cause abnormal connective tissue turnover and result in severe damage to healthy tissue (1-3, 81). The uncontrolled proteolysis can lead to a myriad of diseases including emphysema, idiopathic pulmonary fibrosis, adult respiratory distress syndrome, cystic fibrosis, rheumatoid arthritis, organ failure, and **glomerulonephritis.** Proteins capable of inhibiting the neutral serine proteinases released by neutrophils can have therapeutic efficacy in treating inflammatory diseases. In patients suffering from hyperdynamic septic shock, plasma levels of the serine proteinase inhibitors antithrombin III, alpha 2-macroglobulin and inter-alpha-trypsin inhibitor, as well as those of various clotting, complement and other plasma factors, are significantly decreased (5). In an experimental endotoxemia model, the reduction in the plasma levels of these factors was considerably diminished by the intravenous injection of a soybean-derived leukocyte elastase and cathepsin G inhibitor, indicating that these neutral proteinases are at least partially responsible for the proteolysis of the plasma factors. In addition, the survival rate in the rat lethal peritonitis model (cecal ligation and puncture-induced septic shock model) was improved by treatment with the second domain of human urinary trypsin inhibitor (2), which has been shown to inhibit leukocyte elastase and cathepsin G (6, 7).

  Web site: http://www.delphion.com/details?pn=US06294648__

- **Use of.alpha.1.beta.1 integrin receptor inhibitors and TGF-.beta.1 inhibitors in the treatment of kidney disease**

  Inventor(s): Cosgrove; Dominic (Omaha, NE)

  Assignee(s): Boys Town National Research Hospital (Omaha, NE)

  Patent Number: 6,492,325

  Date filed: April 15, 1999

  Abstract: The present invention provides methods for treating (i.e., delaying the onset of, slowing the progression of, and/or reversing) kidney disorders (e.g., renal **glomerulonephritis** and/or renal fibrosis). Certain of these methods involve administering an.alpha.1.beta.1 integrin receptor inhibitor optionally in combination with a TGF-.beta.1 inhibitor. The present invention also provides a mouse model for kidney disease wherein the mouse does not express a normal collagen type 4 composition in the GBM (i.e., it does not incorporate collagen.alpha.3(IV),.alpha.4(IV), and.alpha.5(IV) chains into its glomerular basement membrane) and does not express the.alpha.1.beta.1 integrin receptor.

  Excerpt(s): This invention relates to the field of kidney disease (i.e., kidney disorder) characterized by **glomerulonephritis** and/or fibrosis. In particular, this invention relates to the use of.alpha.1.beta.1 integrin receptor inhibitors in kidney disorders. Further, this invention relates to the use of.alpha.1.beta.1 integrin inhibitors in combination with TGF-.beta.1 inhibitors in kidney disorders. In the United States, approximately 12,000 people currently live with Alport syndrome. This inherited disorder results in progressive renal disease that is only treatable by dialysis and kidney transplant. Transplanted kidneys are usually rejected. Thus, alternative treatments are needed. However, there is currently no treatment that addresses the mechanism of the disease onset or progression. Thus, what is needed is a treatment method that attacks the mechanism of disease onset and/or progression, one that could substantially slow disease conditions, such as renal **glomerulonephritis** and renal fibrosis. A number of kidney diseases are associated with alterations in matrix homeostasis, where the delicate balance of synthesis and turnover of structural molecules is interrupted. As one example, Alport syndrome is a disease resulting in progressive renal failure and is associated with sensorineural hearing loss. Male carriers are most affected and ultrastructural studies reveal abnormalities in the glomerular basement membrane (GBM) of affected individuals. About one in 20,000 people have Alport syndrome, making the disease one of the more prevalent known genetic disorders. See, for example, Atkin et al., "Alport Syndrome" In R. W. Schrier & C. W. Gottschalk (Eds.), Diseases of the Kidney, 4th ed., Chap. 19, Little Brown, Boston, pp. 617-641, 1988. X-linked Alport syndrome is caused by any of a series of mutations in the collagen 4A5 gene (Barker et al., Science, 248:1224-1227, 1990). At least 60 different mutations in the gene have been identified. The autosomal form of Alport syndrome displays the same range of phenotypes as the X-linked form and results from mutations in either basement membrane collagen gene 4A3 (COL4A3) or 4A4 (COL4A4). See, for example, Lemmink et al., Hum. Mol. Gen., 3:1269-1273, 1994, and Mochizuki et al., Nature Genet., 8:77-81, 1994. Other diseases of the basement membrane include Goodpasture syndrome, which is due to an acute autoimmune response directed against an epitope on the NCl domain of collagen 4A3 (Hudson et al., Kidney Int., 43:135-139, 1993), and diffuse leiomyomatosis, a benign smooth muscle tumor that is associated with a deletion of both collagen 4A5 and 4A6 (Zhou et al., Science, 261:1167-1169, 1993).

  Web site: http://www.delphion.com/details?pn=US06492325__

- **Use of antibodies specific to human complement component C5 for the treatment of glomerulonephritis**

  Inventor(s): Matis; Louis (Southport, CT), Rollins; Scott (Monroe, CT), Wang; Yi (Orange, CT)

  Assignee(s): Alexion Pharmaceuticals, Inc. (New Haven, CT)

  Patent Number: 6,074,642

  Date filed: May 2, 1994

  Abstract: The use of anti-C5 antibodies, e.g., monoclonal antibodies, to treat **glomerulonephritis** (GN) is disclosed. The administration of such antibodies at low dosage levels has been found to significantly reduce glomerular inflammation/enlargement and other pathologic conditions associated with GN.

  Excerpt(s): The present invention relates to the treatment of **glomerulonephritis** (GN). In particular, the invention relates to the use of antibodies specific to human complement component C5 to accomplish such therapeutic treatment. The formation of immune complexes is the typical consequence of the interaction of antigens with specific antibodies. The inflammatory response that ensues when such complexes accumulate in a limited area is an important element of normal host defenses, leading to immune complex clearance and antigen destruction by phagocytic cells. In contrast, immune complex diseases are reflections of excess complex formation or retarded clearance, usually under conditions of exceptional antigen challenge or immunologic dysregulation. Under such circumstances, immune complexes are deposited or formed at specific tissue sites and resulting inflammatory responses lead to disease states due to localized or systemic tissue damage. The kidney, and more specifically the kidney structure known as the glomerulus, is a particularly important site of immune complex deposition resulting in the development of serious disease conditions. The glomerulus is a key structural and functional element of the kidney. Each glomerulus is found as part of a larger structure that serves as the main functional unit of the kidney and is called a nephron. About a million nephrons are found in each kidney. Each glomerulus is a network of up to fifty parallel capillaries encased in a structure known as Bowman's capsule. The area inside Bowman's capsule that is not taken up by the glomerular capillaries is known as Bowman's space. The glomerulus functions as a filter, separating water and certain solutes from the proteins and cells of the blood into Bowman's space for further processing in the convoluted tubules, loop of Henle, and collecting duct of the nephron.

  Web site: http://www.delphion.com/details?pn=US06074642__

Patent Applications on Glomerulonephritis

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

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

- **Methods of modulating immune coagulation**

  Inventor(s): Levy, Gary; (Thornhill, CA)

  Correspondence: Micheline Gravelle; Bereskin & Parr; 40 King Street West; Toronto; ON; M5h 3y2; CA

  Patent Application Number: 20030099654

  Date filed: July 12, 2001

  Abstract: Methods for mediating immune coagulation using novel antibodies and compounds are described. A protein Fgl2 having direct prothrombinase activity has been identified. Inhibitors of Fgl2 are useful in preventing and treating diseases which require a reduction in immune coagulation including bacterial and viral infections, allograft and xenograft rejection, **glomerulonephritis,** cancer, a number of gastrointestinal diseases and fetal loss.

  Excerpt(s): The present invention relates to methods for modulating immune coagulation using novel antibodies and compounds that modulate immune coagulation. Activation of the coagulation pathways is an important part of immune and inflammatory reactions and is associated with bacterial and viral infections (e.g. endotoxin shock, viral hepatitis), **glomerulonephritis** (GN), cancer, a number of gastrointestinal diseases, allograft and xeno graft rejection and spontaneous or stress-triggered fetal loss. Immune coagulation is mediated by a number of coagulants that, when triggered, activate specific ligands resulting in cleavage and activation of coagulation pathways that lead to fibrin deposition. The molecular events leading to expression of immune coagulants involve natural antibodies binding both to antigens on endothelial cells and Fc receptors on macrophages and endothelial cells. An additional mechanism is immune complex-mediated induction of macrophage procoagulants. These events lead to thrombin production which initiates platelet activation and ultimately fibrin deposition. In 50% of hepatitis patients moderate to severe consumptive coagulopathy or disseminated intravascular coagulopathy is found associated with fulminant hepatitis. Thrombi formation is observed around necrotic areas (Sinclair et al., 1990 and Lee, W. M., 1993). As a consequence of hepatitis, levels of factors II, V, VII, and X are decreased in the liver, reflecting both consumptive coagulopathy and a decrease in hepatic synthetic function. Also, the levels of thrombin-antithrombin complexes are high and platelet counts are low (Lee, W. M., 1993). These results indicate that the host immune system, including the coagulation pathway, is disrupted as a result of HBV infection. The limited host range of HBV and the difficulty to propagate the virus in tissue culture have hampered the understanding of HBV and hepatitis B.

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

- **Process to study changes in gene expression in granulocytic cells**

  Inventor(s): Goguen, Jon; (Holden, MA), Newburger, Peter; (Waban, MA), Prashar, Yatindra; (Monmouth Junction, NJ), Weissman, Sherman M.; (New Haven, CT), Yerramilli, Subrahmanyam V.; (Montgomery Village, MD)

  Correspondence: Morgan Lewis & Bockius Llp; 1111 Pennsylvania Avenue NW; Washington; DC; 20004; US

  Patent Application Number: 20030082512

  Date filed: December 6, 2001

Abstract: The present invention comprises methods of identifying an agent that modulates sterile inflammatory disease by preparing a gene expression profile of a granulocytic cell population isolated from a subject having a sterile inflammatory disease; treating it with an agent; and comparing that profile to a profile prepared from untreated granulocytic cells isolated from a subject known to have sterile inflammatory disease. The invention also includes methods to identify such agents by treating an isolated polymorphonuclear white blood cell population from a patient with a sterile inflammatory disease with an agent and comparing it to a gene expression profile of an untreated polymorponuclear white blood cell population isolated from a patient with a sterile inflammatory disease. Agents that modulate **glomerulonephritis** are of particular importance.

Excerpt(s): This application is related to application serial No. 08/510,032, Ser. No. 60/056,844 and application Ser. No. 08/688,514, all of which are herein incorporated by reference in their entirety. All published articles, patents and other publications cited throughout this application are herein incorporated by reference in their entirety. This invention relates to compositions and methods useful to identify agents that modulate the response of granulocytes to inflammatory and infectious conditions. Granulocytes (i.e., neutrophils, eosinophils and basophils) are involved in the immune response elicited by inflammation and infection.

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

- **Proliferative glomerular nephritis-associated gene**

Inventor(s): Kikuchi, Yasuhiro; (Tokyo, JP), Sakurada, Kazuhiro; (Tokyo, JP), Sekine, Susumu; (Tokyo, JP), Takeuchi, Kyoko; (Tokyo, JP)

Correspondence: Fitzpatrick Cella Harper & Scinto; 30 Rockefeller Plaza; New York; NY; 10112; US

Patent Application Number: 20040086857

Date filed: June 4, 2003

Abstract: A gene which is useful in searching for a therapeutic agent which restores tissue that suffered damage in a renal disease, a polypeptide encoded by the gene and an antibody which recognizes the polypeptide, are provided.A gene whose expression level changes depending on progression and recovery of the pathology in a proliferative **glomerulonephritis** model animal is obtained, and a polypeptide encoded by the gene and an antibody which recognizes the polypeptide are produced. These gene, polypeptide and antibody can be used in the search for an agent for restoring kidney tissue that suffered damage and an agent for diagnosing kidney disorder.

Excerpt(s): The present invention relates to complementary DNA (cDNA) for mRNA obtained by using a subtraction method and differential hybridization method based on mRNA whose expression level increases at a recovery period of proliferative **glomerulonephritis,** and a polypeptide encoded by the cDNA. The present invention further relates to an antibody against the polypeptide, a method of detecting the polypeptide and the DNA, and a diagnostic agent and therapeutic agent for renal disease which comprise the DNA, polypeptide, antibody or the like. The kidney has a high reserve function, and in many cases even when the remaining functions are half the normal functions, symptoms due to functional disorder are not observed. Damage of nephron composed of highly differentiated cell groups is irreversible, and degeneration of tissue structure beginning in glomerulosclerosis is accompanied by tubular disorder

and stromal fibrosis and ultimately results in a serious condition of renal failure which requires kidney dialysis. It is generally thought that this process is not related to the type of the primary disease, and is roughly common among the diseases. In clinical practice, administration of steroid agents, oral absorbents, antihypertensive agents, ACE inhibitors and the like, low protein diet treatment method and the like are employed for the main purpose of lightening the burden on remaining nephron and extending the period until the introduction of dialysis. However, there are many unknown points regarding the mechanism of onset and progress of renal failure, and a method for basic remedy has not been established. In proliferative **glomerulonephritis** occurring in children and some animal models, it is known that natural healing occurs without progressing towards continuous decreasing of renal functions after the glomerulus or renal tubule is damaged, however, the mechanism of this natural healing is also not clarified. Analysis at the molecular level of the pathologic progression of proliferative **glomerulonephritis** or of the mechanism of natural healing is considered to be important for the diagnosis of renal disease and the development of therapeutic agents. An effective means for this purpose is, for example, comprehensively obtaining and analyzing a group of genes whose expression level changes in accordance with the progress of a renal disease and the recovery therefrom. It is not practical to conduct such an analysis by using tissue of an actual renal disease patient in respect of the obtainment of tissue and the non-uniformity of symptoms among patients. It is considered that by using a suitable model animal of proliferative **glomerulonephritis,** obtainment of comprehensive group of genes and analysis at the molecular level can be relatively easily conducted. It is considered that, in principle, genes obtained in this manner include factors which are markers of progression or recovery of pathology, as well as factors which actively promote recovery.

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

- **Treatment of immune complex disease with anti-CD40L antibodies**

  Inventor(s): Kalled, Susan L.; (Jamaica Plain, MA), Thomas, David W.; (Wellesley, MA)

  Correspondence: Fish & Neave; 1251 Avenue OF The Americas; 50th Floor; New York; NY; 10020-1105; US

  Patent Application Number: 20030031668

  Date filed: September 27, 2002

  Abstract: This invention relates to methods for treatment of nephritis associated with immune complex disease using anti-CD40L compounds. According to one embodiment of this invention, anti-CD40L compounds are administered to a patient with immune complex disease who has received a kidney allograft, to inhibit the development of immune complex **glomerulonephritis** within the grafted kidney.

  Excerpt(s): The invention relates to administration of anti-CD40L compounds to patients for treatment of immune complex **glomerulonephritis,** and in particular, lupus nephritis. The present invention relates to methods and compositions for the treatment of immune complex **glomerulonephritis.** More particularly, this invention relates to the use of compounds that bind to the ligand for the CD40 surface molecule of B and various other cells, alone or in combination with other agents, for treating or reducing the advancement, severity, symptoms or effects of nephritis associated with antibody-mediated disease, such as lupus or drug-induced serum sickness. According to one embodiment, this invention employs the monoclonal antibody 5c8. Immune complex disease is mediated by the deposition of immune complexes in certain tissues, including

the renal glomerulus and blood vessel walls. The complexes are aggregates of antigen and antibodies. The antigens may be autoantigens, when the body produces antibodies against components of its own tissues, or exogenous antigens, such as infectious agents or drugs. In each case, deposits of immune complexes within blood vessels can cause skin eruptions, pericarditis, and vasculitis. Immune complex deposits within the glomerulus can interfere with the filtering capability of the kidney, leading in extreme cases to renal failure and death.

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

- **Use of alpha1beta1 integrin receptor inhibitors and TGF-beta1 inhibitors in the treatment of kidney disease**

  Inventor(s): Cosgrove, Dominic; (Omaha, NE)

  Correspondence: Mueting, Raasch & Gebhardt, P.A.; P.O. Box 581415; Minneapolis; MN; 55458; US

  Patent Application Number: 20020094956

  Date filed: March 12, 2002

  Abstract: The present invention provides methods for treating (i.e., delaying the onset of, slowing the progression of, and/or reversing) kidney disorders (e.g., renal **glomerulonephritis** and/or renal fibrosis). Certain of these methods involve administering an.alpha.1.beta.1 integrin receptor inhibitor optionally in combination with a TGF-.beta.1 inhibitor. The present invention also provides a mouse model for kidney disease wherein the mouse does not express a normal collagen type 4 composition in the GBM (i.e., it does not incorporate collagen.alpha.3(IV),.alpha.4(IV), and.alpha.5(IV) chains into its glomerular basement membrane) and does not express the.alpha.1.beta.1 integrin receptor.

  Excerpt(s): The present application is a Continuation-In-Part of U.S. patent application Ser. No. 09/150,485, filed on Sep. 9, 1998, which is a Continuation-In-Part of U.S. patent application Ser. No. 09/088,766, filed on Jun. 2, 1998, which claims the benefit of U.S. Provisional Application Serial No. 60/086,587, filed on May 22, 1998. This invention relates to the field of kidney disease (i.e., kidney disorder) characterized by **glomerulonephritis** and/or fibrosis. In particular, this invention relates to the use of a.alpha.1.beta.1 integrin receptor inhibitors in kidney disorders. Further, this invention relates to the use of.alpha.1.beta.1 integrin inhibitors in combination with TGF-.beta.1 inhibitors in kidney disorders. In the United States, approximately 12,000 people currently live with Alport syndrome. This inherited disorder results in progressive renal disease that is only treatable by dialysis and kidney transplant. Transplanted kidneys are usually rejected. Thus, alternative treatments are needed. However, there is currently no treatment that addresses the mechanism of the disease onset or progression. Thus, what is needed is a treatment method that attacks the mechanism of disease onset and/or progression, one that could substantially slow disease conditions, such as renal **glomerulonephritis** and renal fibrosis.

  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 glomerulonephritis, 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 "glomerulonephritis" (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 glomerulonephritis.

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

CHAPTER 6. BOOKS ON GLOMERULONEPHRITIS

Overview

This chapter provides bibliographic book references relating to glomerulonephritis. In addition to online booksellers such as **www.amazon.com** and **www.bn.com**, excellent sources for book titles on glomerulonephritis 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 "glomerulonephritis" (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 glomerulonephritis:

- **New Clinical Applications-Nephrology: Glomerulonephritis**

  Source: Hingham, MA: Kluwer Academic Publishers. 1990. 198 p.

  Contact: Available from Kluwer Academic Publishers. P.O. Box 358, Accord Station, Hingham, MA02018-0358. (617) 871-6600. PRICE: $54. ISBN: 0746201095.

  Summary: This book examines the clinical, pathological, and etiological factors involved in the common forms of **glomerulonephritis.** Improved pathological techniques and criteria have permitted a more accurate diagnosis and prognosis to be established for many patients. With increased understanding of the immunological mechanisms involved, it has become apparent that many patients presenting with a variety of symptoms and signs may have **glomerulonephritis** as their primary pathological process. Each of the 6 chapters of the book is written by a recognized expert in the field, and provides information of relevance and practical importance to nephrologists and

other practicing clinicians. These chapters focus on: minimal change nephropathy; membranous nephropathy; infection-associated **glomerulonephritis;** immunoglobulin IgA nephropathy; plasmapheresis in **glomerulonephritis;** and proliferation of glomerular cells. The emphasis is on interpreting research findings in terms of current practical utility, rather than on future theoretical aspects. Illustrations and tabular data are presented throughout the text, and literature citations are appended to each chapter.

- **Atlas of Diseases of the Kidney. Volume 2: Glomerulonephritis and Vasculitis/Tubulointerstitial Disease**

  Source: Philadelphia, PA: Current Medicine, Inc. 1999. [204 p.].

  Contact: Available from Blackwell Science, Inc. 350 Main Street, Malden, MA 02148. (800) 215-1000 or (781) 388-8250. Fax (781) 388-8270. E-mail: csbooks@blacksci.com. PRICE: $75.00 plus shipping and handling. ISBN: 0632043873.

  Summary: This volume is one in a series of five in the Atlas of Diseases of the Kidney, a set that offers educational images including colored photographs, schematics, tables, and algorithms. In this volume, the first section covers **glomerulonephritis** and vasculitis; the second section covers tubulointerstitial disease. Twelve chapters cover normal vascular and glomerular anatomy; the primary glomerulopathies; heredofamilial and congenital glomerular disorders; infection associated glomerulopathies; vascular disorders; renal interstitium and major features of chronic tubulointerstitial nephritis; urinary tract infection; reflux and obstructive nephropathy; cystic diseases of the kidney; toxic nephropathies; metabolic causes of tubulointerstitial disease; and renal tubular disorders. Each chapter features a detailed introduction and lengthy captions for each of the illustrations and diagrams offered. The first section relies heavily on images provided by analysis of renal biopsy; the section on vascular diseases of the kidney emphasizes microscopic images that illustrate essential or characteristic features of disease. A subject index for Volume 2 and a section of full color plates concludes the book.

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 "glomerulonephritis" at online booksellers' Web sites, you may discover non-medical books that use the generic term "glomerulonephritis" (or a synonym) in their titles. The following is indicative of the results you might find when searching for "glomerulonephritis" (sorted alphabetically by title; follow the hyperlink to view more details at Amazon.com):

- **Antiglobulins, Cryoglobulins and Glomerulonephritis** by C. Ponticelli; ISBN: 0898388104; http://www.amazon.com/exec/obidos/ASIN/0898388104/icongroupinterna
- **Issues in Glomerulonephritis and Renin System (Contributions to Nephrology, Vol 43)** by E. Ritz, S.G. Massry; ISBN: 3805539126; http://www.amazon.com/exec/obidos/ASIN/3805539126/icongroupinterna

- **Nonsteroidal Anti-inflammatory Drugs in the Treatment of Chronic Glomerulonephritis** by Y. Vanrenterghem; ISBN: 9061862817; http://www.amazon.com/exec/obidos/ASIN/9061862817/icongroupinterna
- **Pat Urinary Glomerulonephritis** by Corbin; ISBN: 0397572077; http://www.amazon.com/exec/obidos/ASIN/0397572077/icongroupinterna
- **Pathogenesis Complications and Treatment of Glomerulonephritis** by Giulio A. Cinotti, Shaul G. Massry; ISBN: 3805549083; http://www.amazon.com/exec/obidos/ASIN/3805549083/icongroupinterna
- **Postinfectious Glomerulonephritis** by Karin Sorger; ISBN: 0895742233; http://www.amazon.com/exec/obidos/ASIN/0895742233/icongroupinterna
- **Progress in glomerulonephritis (Perspectives in nephrology and hypertension)**; ISBN: 0471044245; http://www.amazon.com/exec/obidos/ASIN/0471044245/icongroupinterna
- **Rapidly Progressive Glomerulonephritis (Oxford Clinical Nephrology Series)** by Charles Pusey, et al; ISBN: 0192626361; http://www.amazon.com/exec/obidos/ASIN/0192626361/icongroupinterna
- **The Treatment of Glomerulonephritis (Developments in Nephrology)** by Charles D. Pusey; ISBN: 0792353323; http://www.amazon.com/exec/obidos/ASIN/0792353323/icongroupinterna
- **Treatment of Primary Glomerulonephritis** by Claudio Ponticelli, Richard J. Glassock; ISBN: 0192626663; http://www.amazon.com/exec/obidos/ASIN/0192626663/icongroupinterna
- **Ultrastructural immunoperoxidase study of experimental and human glomerulonephritis (Acta Universitatis Tamperensis)** by Immo Rantala; ISBN: 9514414268; http://www.amazon.com/exec/obidos/ASIN/9514414268/icongroupinterna

Chapters on Glomerulonephritis

In order to find chapters that specifically relate to glomerulonephritis, an excellent source of abstracts is the Combined Health Information Database. You will need to limit your search to book chapters and glomerulonephritis 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 "glomerulonephritis" (or synonyms) into the "For these words:" box. The following is a typical result when searching for book chapters on glomerulonephritis:

- **Glomerulonephritis in Children**

  Source: in Gearhart, J.P.; Rink, R.C.; Mouriquand, P.D. Pediatric Urology. Philadelphia, PA: W.B. Saunders Company. 2001. p. 288-300.

  Contact: Available from Elsevier, Health Sciences Division. The Curtis Center, 625 Walnut Street, Philadelphia, PA 19106. (800) 523-1649. E-mail: custserv.ehs@elsevier.com. Website: www.us.elsevierhealth.com. PRICE: $239.00 plus shipping and handling. ISBN: 072168680X.

Summary: Glomerulonephritis (GN) is a common cause of chronic kidney failure in children. This chapter on **glomerulonephritis** is from a comprehensive textbook on pediatric urology that emphasizes the pathophysiology of various disorders. The author notes that GN during childhood may also lead to end stage renal disease (ESRD) or other complications that do not become apparent until adulthood. GN also causes substantial morbidity, whereas therapy for glomerular diseases including corticosteroids and immunosuppressive agents contributes to side effects and morbidity. The natural history and long term prognosis of different forms of GN are quite variable. Prompt diagnosis and the initiation of specific therapy when indicated, and avoiding unnecessary therapy, are important in managing the child with GN so that maximal renal (kidney) function can be preserved and side effects of therapy can be minimized. The author reviews the clinical manifestations, laboratory and pathologic features, pathophysiology, and potential treatment strategies for the various glomerulonephritides that occur in children. 8 figures. 3 tables. 100 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.

- **Plasmapheresis in Glomerulonephritis**

  Source: in Catto, G.R.D. New Clinical Applications-Nephrology: Glomerulonephritis. Hingham, MA: Kluwer Academic Publishers. p. 139-162. 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: Therapeutic plasmapheresis is a technique in which whole blood is withdrawn from a patient and pumped into a device that separates cellular elements from plasma; the cells are then returned to the patient, together with substitution fluid and the plasma is discarded. This authoritative review focuses on: the effects of plasma exchange in **glomerulonephritis;** clinical applications of plasma exchange in **glomerulonephritis;** the similarity of anti-glomerular basement membrane disease and Goodpasture's syndrome; systemic vasculitis and rapidly progressive nephritis; systemic lupus erythematosus; mixed essential cryoglobulinemia; and primary **glomerulonephritis.** It is concluded that, despite the wide application of plasma

exchange in immunological diseases, including **glomerulonephritis,** over the past decade there is still little firm evidence for its effectiveness. However, this may not be the case for treatment of severe **glomerulonephritis,** which would otherwise lead to a requirement for renal replacement therapy. 88 references.

- **Recurrence of Glomerulonephritis After Renal Transplantation**

  Source: in Andreucci, V.E. International Yearbook of Nephrology 1990. Hingham, MA: Kluwer Academic Publishers. 1990. p. 37-51.

  Contact: Available from Kluwer Academic Publishers. P.O. Box 358, Accord Station, Hingham, MA02018-0358. (617) 871-6600.

  Summary: This chapter reviews the prevalence and nature of recurrent glomerulonephritic disease in the renal allograft recipient. Specific attention is given to: the various forms of recurrent **glomerulonephritis** (focal and segmental hyalinosis and sclerosis, or focal glomerulosclerosis; membranous **glomerulonephritis;** immunoglobulin IgA **glomerulonephritis;** Henoch Schonlein purpura nephritis; mesangiocapillary **glomerulonephritis,** Types I and II; anti-glomerular basement membrane nephritis; idiopathic rapidly progressive (crescentic) **glomerulonephritis;** systemic lupus erythematosus; and Wegener's granulomatosis and microscopic polyarteritis); and non- glomerulonephritic recurring glomerular lesions (diabetic nephropathy; amyloidosis; Fabry's disease; hemolytic-uremic syndrome). While histopathological features of **glomerulonephritis** in the renal allograft recipient are common, the number of cases with progressive renal failure appear to be much less common. 79 references.

- **Acute Glomerulonephritis and Glomerulonephritis in Bacterial Endocarditis**

  Source: in Suki, W.N.; Massry, S.G., eds. Therapy of Renal Diseases and Related Disorders, 2nd ed. Hingham, MA: Kluwer Academic Publishers. 1991. p. 305-315.

  Contact: Available from Kluwer Academic Publishers. P.O. Box 358, Accord Station, Hingham, MA 02018. (617) 871-6600. PRICE: $315. ISBN: 0792306767.

  Summary: This chapter, from a medical text on the therapy of renal disease and related disorders, discusses acute **glomerulonephritis** and **glomerulonephritis** in bacterial endocarditis. The authors discuss the pathophysiology, prevention, therapeutic approaches, and prognosis for **glomerulonephritis.** In addition, the clinical features, therapy, and prognosis of **glomerulonephritis** in bacterial endocarditis is discussed. 129 references.

- **Changing Views on the Treatment of Glomerulonephritis**

  Source: in Andreucci, V.E.; Fine, L.G., eds. International Yearbook of Nephrology 1991. Hingham, MA: Kluwer Academic Publishers. 1990. p. 73-95.

  Contact: Available from Kluwer Academic Publishers. P.O. Box 358, Accord Station, Hingham, MA02018-0358. (617) 871-6600. PRICE: $135.00. ISBN: 0792310020.

  Summary: This chapter, from an international yearbook in nephrology, discusses the changing views on the treatment of **glomerulonephritis.** The authors review ways in which knowledge of pathogenesis can be used to develop new treatments and to improve prognosis. This approach is compared with the development of treatments through empiricism alone. The authors illustrate the general principles using three

conditions: focal necrotizing **glomerulonephritis,** minimal change nephropathy, and idiopathic membranous nephropathy. 1 figure. 5 tables. 175 references.

Directories

In addition to the references and resources discussed earlier in this chapter, a number of directories relating to glomerulonephritis have been published that consolidate information across various sources. The Combined Health Information Database lists the following, which you may wish to consult in your local medical library:[10]

- **Research Program 1995-1996**

  Source: New York, NY: National Kidney Foundation. 1995. 68 p.

  Contact: Available from National Kidney Foundation. 30 East 33rd Street, New York, NY 10016. (800) 622-9010. PRICE: Single copy free.

  Summary: This Research Program book lists the recipients of the National Kidney Foundation's various fellowships and grants and summarizes their projects for 1995-1996. The foundation provides four channels for research funding: Research Fellowships, Young Investigator Grants, the Clinical Scientist Award, and Affiliate Research Awards. The book provides the name of the researcher, his or her affiliation, an abstract of the work being undertaken, and a summary of the researcher's vitae. Funded research includes work in the areas of polycystic kidney disease; glomerular filtration; animal studies; genetics; diabetic kidney disease; sodium metabolism; hypertension; the nephrotic syndrome; renal allograft rejection; HIV-associated nephropathy; **glomerulonephritis;** and cystinuria.

[10] You will need to limit your search to "Directory" and "glomerulonephritis" using the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find directories, use the drop boxes at the bottom of the search page where "You may refine your search by." For publication date, select "All Years." Select your preferred language and the format option "Directory." Type "glomerulonephritis" (or synonyms) into the "For these words:" box. You should check back periodically with this database as it is updated every three months.

CHAPTER 7. MULTIMEDIA ON GLOMERULONEPHRITIS

Overview

In this chapter, we show you how to keep current on multimedia sources of information on glomerulonephritis. 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 glomerulonephritis is the Combined Health Information Database. You will need to limit your search to "Videorecording" and "glomerulonephritis" 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 "glomerulonephritis" (or synonyms) into the "For these words:" box. The following is a typical result when searching for video recordings on glomerulonephritis:

- **Nephrology Update**

  Source: Cleveland, OH: Cleveland Clinic Foundation. 1992. (videocassettes, proceedings/minutes).

  Contact: Available from CME Video. 2000 Crawford Place, Suite 100, Mount Laurel, NJ 08054. (800) 284-8433. PRICE: $495; plus $18.25 shipping and handling; Group Practice Package $150 plus $5.25 shipping and handling. Program Number 076.

  Summary: This Video Education Program presents 23 hours of presentations and problem-solving workshops. Topics include the clinical applications of basic renal physiology; the biology of mesangial cell structure and function; the diagnosis and management of hypercalcemia; mechanisms of dialysis-induced hypotension; HIV nephropathy; renal artery stenosis; the pathogenesis of renal stones; **glomerulonephritis;** dietary treatment in chronic renal disease; drug-induced acute and chronic interstitial nephritis; issues in metabolic acidosis; prostatic disease;

hypertension; systemic lupus erythematosus nephritis; and the thrombotic angiopathies. Workshops cover topics including: management issues in dialysis patients, access, adequacy and nutrition; complex acid-base disorders; and intensive care unit (ICU) nephrology. All tapes are indexed with Quik-Scan for fast reference to presentations of special interest to the viewer. The program is accompanied by the original course syllabus, including supplemental reference information.

- **Choices: Options for Living with Kidney Failure**

  Source: McGaw Park, IL: Baxter Healthcare Corporation. 1997 (videocassette).

  Contact: Available from community service section of Blockbuster video stores. PRICE: Free rental. Also available to health professionals from Baxter Healthcare Corporation. (888) 736-2543. 1620 Waukegan Road, McGaw Park, IL 60085.

  Summary: This videotape program helps viewers newly diagnosed with kidney failure to understand their treatment options and to make more informed choices for their own health care. The narrator reminds viewers that many members make up the health care team, but stresses that patients are the most important member of that team. The program reviews the functions of the kidneys, including clean the blood, make red blood cells, help maintain healthy bones and other bodily functions, balance body fluids and chemical levels, and retain valuable substances. Graphics demonstrate each of these functions. The narrator reviews the symptoms of kidney failure, and then real patients tell their own experiences of their movement into chronic kidney failure. The program outlines the common causes of chronic kidney failure, including diabetes, **glomerulonephritis,** hypertension (high blood pressure), polycystic kidney disease, and infections. The remainder of the program outlines each of the treatment options: hemodialysis, peritoneal dialysis, automated peritoneal dialysis (APD), and kidney transplantation. For each type, the program offers live footage of real patients using that treatment, drawings and graphics that demonstrate how the treatment works, and interviews with patients talking about how that treatment affects their lives. The program summarizes the reasons why each treatment option may be appropriate or inappropriate for a specific patient. The program concludes with a list of general guidelines that can help to reduce treatment side effects and with a list of associations to contact for more information.

CHAPTER 8. PERIODICALS AND NEWS ON GLOMERULONEPHRITIS

Overview

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

News Services and Press Releases

One of the simplest ways of tracking press releases on glomerulonephritis 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 "glomerulonephritis" (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 glomerulonephritis. 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 "glomerulonephritis" (or synonyms). The following was recently listed in this archive for glomerulonephritis:

- **Effects of interferon therapy for glomerulonephritis appear contradictory**
  Source: Reuters Medical News
  Date: June 10, 1999

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 "glomerulonephritis" (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 "glomerulonephritis" (or synonyms). If you know the name of a company that is relevant to glomerulonephritis, 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 "glomerulonephritis" (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 "glomerulonephritis" (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 glomerulonephritis:

- **Dialysis: Need for Artificial Kidney Treatment is Increasing**

  Source: Mayo Clinic Health Letter. 15(2): 1-3. February 1997.

  Contact: Available from Mayo Clinic Health Letter. Subscription Services, P.O. Box 53889, Boulder, CO 80322-3889. (800) 333-9037.

  Summary: This newsletter article reminds readers of the kidney's role in 'removing the garbage' from the body. The author explains how dialysis takes over the kidney's role. The author first describes how many different diseases or events can damage the kidneys and cause them to fail. Common conditions include diabetes, high blood pressure, and an inflammation of the kidneys called **glomerulonephritis.** The author goes on to describe hemodialysis and peritoneal dialysis. Hemodialysis removes waste and fluid by filtering the blood through an artificial kidney, called a dialyzer. Peritoneal dialysis uses the network of blood vessels in the abdominal cavity (the peritoneal membrane) to clean waste and excess fluid out of the body. The author concludes with a brief discussion on factors to consider when choosing a method of dialysis. Combined with medications and an appropriate diet, dialysis gives those with kidney failure a chance to live and enjoy life long after these organs have stopped working. 2 figures.

- **Early Recognition of Systemic Lupus Erythematosus**

  Source: Lupus Journal. p. 1-4. 1995.

  Contact: Available from Maryland Lupus Foundation. 7400 York Road, Baltimore, MD 21204. (410) 337-9000.

  Summary: This special publication, prepared by the Maryland Lupus Foundation, presents the latest information on the recognition and diagnosis of systemic lupus erythematosus (SLE). Topics include the importance of early recognition of SLE; guidelines for laboratory testing and criteria for SLE classification; symptoms, including rashes, mucous membrane involvement, Raynaud's syndrome, serositis, heart and lung involvement, and the affect of SLE on the renal and neurologic systems; and the role of laboratory tests to confirm the clinical impression, particularly autoantibody tests. The author notes that **glomerulonephritis** and nephrotic syndrome are the most common renal disorders seen. The author also reiterates that in this disorder, more than any other, the presenting clinical pattern can be dramatically variable both for a specific individual and the population in general. 1 figure.

Academic Periodicals covering Glomerulonephritis

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to glomerulonephritis. In addition to these sources, you can search for articles covering glomerulonephritis 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 9. 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 glomerulonephritis. 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 Phamacopeia 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 glomerulonephritis. 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 glomerulonephritis:

Albumin Microspheres Sonicated

- **Systemic - U.S. Brands:** Optison
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203714.html

Azathioprine

- **Systemic - U.S. Brands:** Imuran
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202077.html

Corticosteroids

- **Dental - U.S. Brands:** Kenalog in Orabase; Orabase-HCA; Oracort; Oralone
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202010.html
- **Inhalation - U.S. Brands:** AeroBid; AeroBid-M; Azmacort; Beclovent; Pulmicort Respules; Pulmicort Turbuhaler; Qvar; Vanceril; Vanceril 84 mcg Double Strength
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202011.html
- **Nasal - U.S. Brands:** Beconase; Beconase AQ; Dexacort Turbinaire; Flonase; Nasacort; Nasacort AQ; Nasalide; Nasarel; Nasonex; Rhinocort; Vancenase; Vancenase AQ 84 mcg; Vancenase pockethaler
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202012.html
- **Ophthalmic - U.S. Brands:** AK-Dex; AK-Pred; AK-Tate; Baldex; Decadron; Dexair; Dexotic; Econopred; Econopred Plus; Eflone; Flarex; Fluor-Op; FML Forte; FML Liquifilm; FML S.O.P.; HMS Liquifilm; Inflamase Forte; Inflamase Mild; I-Pred; Lite Pred; Maxidex; Ocu-Dex; Ocu-Pred; Ocu-Pred Forte; Ocu-Pred-A; Pred Forte; Pred Mild; Predair; Predair A; Predair Forte; Storz-Dexa; Ultra Pred
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202013.html
- **Otic - U.S. Brands:** Decadron
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202014.html
- **Rectal - U.S. Brands:** Anucort-HC; Anu-Med HC; Anuprep HC; Anusol-HC; Anutone-HC; Anuzone-HC; Cort-Dome; Cortenema; Cortifoam; Hemorrhoidal HC; Hemril-HC Uniserts; Proctocort; Proctosol-HC; Rectasol-HC
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203366.html

Urea

- **Intra-amniotic - U.S. Brands:** Ureaphil
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202584.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/**.

PDR*health*

The PDR*health* 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. PDR*health* can be searched by brand name, generic name, or indication. It features multiple drug interactions reports. Search PDR*health* 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.

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 Institute[11]:

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

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

[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 Gateway[14]

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 "glomerulonephritis" (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	34469
Books / Periodicals / Audio Visual	216
Consumer Health	568
Meeting Abstracts	31
Other Collections	279
Total	35563

HSTAT[16]

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 "glomerulonephritis" (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

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[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 Biologists[19]

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/cliniweb/**.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see **http://www.mwsearch.com/**.

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[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 glomerulonephritis 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 glomerulonephritis. 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 glomerulonephritis. 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 "glomerulonephritis":

Kidney Diseases
http://www.nlm.nih.gov/medlineplus/kidneydiseases.html

Kidney Failure
http://www.nlm.nih.gov/medlineplus/kidneyfailure.html

Kidney Transplantation
http://www.nlm.nih.gov/medlineplus/kidneytransplantation.html

Streptococcal Infections
http://www.nlm.nih.gov/medlineplus/streptococcalinfections.html

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

The 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 glomerulonephritis. 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:

- **Glomerulonephritis**

  Source: New York, NY: National Kidney Foundation. 1998. 7 p.

  Contact: National Kidney Foundation. 30 East 33rd Street, New York, NY 10016. (800) 622-9010. Website: www.kidney.org. PRICE: Single copy free; bulk copies available.

  Summary: The types of kidney diseases called nephritis are described in this pamphlet. The two forms, acute **glomerulonephritis** (acute nephritis) and chronic **glomerulonephritis** (chronic nephritis) differ in that there is spontaneous recovery in the acute form whereas in the chronic form there is progressive damage to the kidney tissues. Symptoms, treatment, causes and prevention of **glomerulonephritis** are also discussed.

- **Glomerulonephritis (Post-Infectious, Acute or Chronic Glomerulonephritis)**

  Source: in Griffith, H.W. Instructions for Patients. 5th ed. Philadelphia, PA: W.B. Saunders Company. 1994. p. 190.

  Contact: Available from W.B. Saunders Company. Book Order Fulfillment, 6277 Sea Harbor Drive, Orlando, FL 32887-4430. (800) 545-2522. Fax (800) 874-6418. PRICE: $49.95. ISBN: 0721649300 (English); 0721669972 (Spanish).

  Summary: This fact sheet on **glomerulonephritis** is from a compilation of instructions for patients, published in book format. The fact sheet provides information on

postinfectious, acute, or chronic **glomerulonephritis,** and includes a description of the condition, frequent signs and symptoms, causes, risk factors, preventive measures, expected outcome, and possible complications; treatment, including general measures, medication, activity guidelines, and diet; and when to contact one's health care provider. The fact sheet can be photocopied and distributed to patients as a reinforcement of oral instructions and as a teaching tool. The book in which the fact sheet appears is available in English or Spanish.

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 glomerulonephritis. 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 glomerulonephritis. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with glomerulonephritis.

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 glomerulonephritis. 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 "glomerulonephritis" (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 "glomerulonephritis". 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 "glomerulonephritis" (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 "glomerulonephritis" (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

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[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/**

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[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.lsuhsc.edu/**
- **Maine:** Franklin Memorial Hospital Medical Library (Franklin Memorial Hospital, Farmington), **http://www.fchn.org/fmh/lib.htm**
- **Maine:** Gerrish-True Health Sciences Library (Central Maine Medical Center, Lewiston), **http://www.cmmc.org/library/library.html**
- **Maine:** Hadley Parrot Health Science Library (Eastern Maine Healthcare, Bangor), **http://www.emh.org/hll/hpl/guide.htm**
- **Maine:** Maine Medical Center Library (Maine Medical Center, Portland), **http://www.mmc.org/library/**
- **Maine:** Parkview Hospital (Brunswick), **http://www.parkviewhospital.org/**
- **Maine:** Southern Maine Medical Center Health Sciences Library (Southern Maine Medical Center, Biddeford), **http://www.smmc.org/services/service.php3?choice=10**
- **Maine:** Stephens Memorial Hospital's Health Information Library (Western Maine Health, Norway), **http://www.wmhcc.org/Library/**

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

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

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

ONLINE GLOSSARIES

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

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

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

- **Basic Guidelines for Glomerulonephritis**

  Glomerulonephritis
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000484.htm

- **Signs & Symptoms for Glomerulonephritis**

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

  Blood in the urine
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003138.htm

  Blood in the vomit
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003118.htm

  Blood pressure, high
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003082.htm

Bruising
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003235.htm

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

Confusion
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003205.htm

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

Decreased sensation
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003206.htm

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

Drowsiness
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003208.htm

Edema
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003103.htm

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

General ill feeling
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003089.htm

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

Hiccups
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003068.htm

High blood pressure
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003082.htm

Hyperpigmentation
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003242.htm

Itching
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003217.htm

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

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

Muscle twitching
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003296.htm

Nausea
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003117.htm

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

Nosebleed - symptom
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003106.htm

Pruritus
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003217.htm

Seizures
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003200.htm

Somnolence
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003208.htm

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

Urination, excessive volume
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003146.htm

Vomiting
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003117.htm

Weight loss
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003107.htm

- **Diagnostics and Tests for Glomerulonephritis**

Abdominal CT scan
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003789.htm

Abdominal MRI
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003796.htm

Abdominal ultrasound
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003777.htm

Albumin
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003480.htm

ALT
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003473.htm

Anti-glomerular basement membrane
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003524.htm

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

Blood pressure
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003398.htm

BUN
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003474.htm

Casts
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003586.htm

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

Complement
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003456.htm

Complement component 3
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003539.htm

Creatinine
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003475.htm

Creatinine - urine
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003610.htm

Creatinine clearance
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003611.htm

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

Dialysis
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003421.htm

IVP
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003782.htm

Kidney biopsy
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003907.htm

MRI
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003335.htm

Protein, urine
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003580.htm

RBC; urine
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003582.htm

Renal scan
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003790.htm

Total protein
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003483.htm

Ultrasound
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003336.htm

Uric acid, urine
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003616.htm

Urinalysis
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003579.htm

Urine concentration test
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003608.htm

Urine specific gravity
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003587.htm

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

- **Nutrition for Glomerulonephritis**

Protein
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002467.htm

- **Surgery and Procedures for Glomerulonephritis**

Kidney transplant
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003005.htm

- **Background Topics for Glomerulonephritis**

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

Bleeding
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000045.htm

Kidney disease
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000457.htm

Kidney disease - support group
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002172.htm

Kidney diseases
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000457.htm

Mercury
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002476.htm

Support groups
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002150.htm

Online Dictionary Directories

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

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

GLOMERULONEPHRITIS 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]

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

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]

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]

Acetylgalactosamine: The N-acetyl derivative of galactosamine. [NIH]

Acidosis: A pathologic condition resulting from accumulation of acid or depletion of the alkaline reserve (bicarbonate content) in the blood and body tissues, and characterized by an increase in hydrogen ion concentration. [EU]

Acoustic: Having to do with sound or hearing. [NIH]

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

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

Acute renal: A condition in which the kidneys suddenly stop working. In most cases, kidneys can recover from almost complete loss of function. [NIH]

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

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]

Adherens Junctions: Anchoring points where the cytoskeleton of neighboring cells are connected to each other. They are composed of specialized areas of the plasma membrane where bundles of microfilaments attach to the membrane through the transmembrane linkers, cadherins, which in turn attach through their extracellular domains to cadherins in the neighboring cell membranes. In sheets of cells, they form into adhesion belts (zonula adherens) that go all the way around a cell. [NIH]

Adhesions: Pathological processes consisting of the union of the opposing surfaces of a

wound. [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]

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]

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

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

Adrenergic beta-Antagonists: Drugs that bind to but do not activate beta-adrenergic receptors thereby blocking the actions of beta-adrenergic agonists. Adrenergic beta-antagonists are used for treatment of hypertension, cardiac arrythmias, angina pectoris, glaucoma, migraine headaches, and anxiety. [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]

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]

Ageing: A physiological or morphological change in the life of an organism or its parts, generally irreversible and typically associated with a decline in growth and reproductive vigor. [NIH]

Agonists: Drugs that trigger an action from a cell or another drug. [NIH]

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

Albumin: 1. Any protein that is soluble in water and moderately concentrated salt solutions and is coagulable by heat. 2. Serum albumin; the major plasma protein (approximately 60 per cent of the total), which is responsible for much of the plasma colloidal osmotic pressure and serves as a transport protein carrying large organic anions, such as fatty acids, bilirubin,

and many drugs, and also carrying certain hormones, such as cortisol and thyroxine, when their specific binding globulins are saturated. Albumin is synthesized in the liver. Low serum levels occur in protein malnutrition, active inflammation and serious hepatic and renal disease. [EU]

Albuminuria: More than normal amounts of a protein called albumin in the urine. Albuminuria may be a sign of kidney disease. [NIH]

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

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

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

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

Allo: A female hormone. [NIH]

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

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

Alopecia: Absence of hair from areas where it is normally present. [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]

Alternative Splicing: A process whereby multiple protein isoforms are generated from a single gene. Alternative splicing involves the splicing together of nonconsecutive exons during the processing of some, but not all, transcripts of the gene. Thus a particular exon may be connected to any one of several alternative exons to form messenger RNA. The alternative forms produce proteins in which one part is common while the other part is different. [NIH]

Amber: A yellowish fossil resin, the gum of several species of coniferous trees, found in the alluvial deposits of northeastern Germany. It is used in molecular biology in the analysis of organic matter fossilized in amber. [NIH]

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

Amino acid: Any organic compound containing an amino (-NH2 and a carboxyl (- COOH) group. The 20 a-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 acids residues in polypeptide chains. There are also several important amino acids, such as the neurotransmitter y-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]

Amplification: The production of additional copies of a chromosomal DNA sequence,

found as either intrachromosomal or extrachromosomal DNA. [NIH]

Amyloid: A general term for a variety of different proteins that accumulate as extracellular fibrils of 7-10 nm and have common structural features, including a beta-pleated sheet conformation and the ability to bind such dyes as Congo red and thioflavine (Kandel, Schwartz, and Jessel, Principles of Neural Science, 3rd ed). [NIH]

Amyloidosis: A group of diseases in which protein is deposited in specific organs (localized amyloidosis) or throughout the body (systemic amyloidosis). Amyloidosis may be either primary (with no known cause) or secondary (caused by another disease, including some types of cancer). Generally, primary amyloidosis affects the nerves, skin, tongue, joints, heart, and liver; secondary amyloidosis often affects the spleen, kidneys, liver, and adrenal glands. [NIH]

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

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

Analgesic: An agent that alleviates pain without causing loss of consciousness. [EU]

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]

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]

Anergy: Absence of immune response to particular substances. [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]

Angiitis: Inflammation of a vessel, chiefly of a blood or a lymph vessel; called also vasculitis. [EU]

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]

Angiotensin converting enzyme inhibitor: A drug used to decrease pressure inside blood vessels. [NIH]

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

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

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

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]

Antagonism: Interference with, or inhibition of, the growth of a living organism by another living organism, due either to creation of unfavorable conditions (e. g. exhaustion of food supplies) or to production of a specific antibiotic substance (e. g. penicillin). [NIH]

Antecedent: Existing or occurring before in time or order often with consequential effects. [EU]

Anthraquinones: An anthracene ring which contains two ketone moieties in any position. Can be substituted in any position except on the ketone groups. [NIH]

Antiallergic: Counteracting allergy or allergic conditions. [EU]

Antibacterial: A substance that destroys bacteria or suppresses their growth or reproduction. [EU]

Antibiotic: A drug used to treat infections caused by bacteria and other microorganisms. [NIH]

Antibodies: Immunoglobulin molecules having a specific amino acid sequence by virtue of which they interact only with the antigen that induced their synthesis in cells of the lymphoid series (especially plasma cells), or with an antigen closely related to it. [NIH]

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]

Antibody: A type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen. [NIH]

Anticoagulant: A drug that helps prevent blood clots from forming. Also called a blood thinner. [NIH]

Antidiuretic: Suppressing the rate of urine formation. [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]

Antihypertensive: An agent that reduces high blood pressure. [EU]

Antihypertensive Agents: Drugs used in the treatment of acute or chronic hypertension regardless of pharmacological mechanism. Among the antihypertensive agents are diuretics (especially diuretics, thiazide), adrenergic beta-antagonists, adrenergic alpha-antagonists, angiotensin-converting enzyme inhibitors, calcium channel blockers, ganglionic blockers, and vasodilator agents. [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]

Antineoplastic: Inhibiting or preventing the development of neoplasms, checking the maturation and proliferation of malignant cells. [EU]

Antioxidant: A substance that prevents damage caused by free radicals. Free radicals are highly reactive chemicals that often contain oxygen. They are produced when molecules are split to give products that have unpaired electrons. This process is called oxidation. [NIH]

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]

Antipyretic: An agent that relieves or reduces fever. Called also antifebrile, antithermic and febrifuge. [EU]

Antiseptic: A substance that inhibits the growth and development of microorganisms without necessarily killing them. [EU]

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]

Anus: The opening of the rectum to the outside of the body. [NIH]

Aorta: The main trunk of the systemic arteries. [NIH]

Aortic Aneurysm: Aneurysm of the aorta. [NIH]

Apheresis: Components being separated out, as leukapheresis, plasmapheresis, plateletpheresis. [NIH]

Apolipoproteins: The protein components of lipoproteins which remain after the lipids to which the proteins are bound have been removed. They play an important role in lipid transport and metabolism. [NIH]

Apoptosis: One of the two mechanisms by which cell death occurs (the other being the pathological process of necrosis). Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be intrinsically programmed. It is characterized by distinctive morphologic changes in the nucleus and cytoplasm, chromatin cleavage at regularly spaced sites, and the endonucleolytic cleavage of genomic DNA (DNA fragmentation) at internucleosomal sites. This mode of cell death serves as a balance to mitosis in regulating the size of animal tissues and in mediating pathologic processes associated with tumor growth. [NIH]

Aqueous: Having to do with water. [NIH]

Arachidonate 12-Lipoxygenase: An enzyme that catalyzes the oxidation of arachidonic acid to yield 12-hydroperoxyarachidonate (12-HPETE) which is itself rapidly converted by a peroxidase to 12-hydroxy-5,8,10,14-eicosatetraenoate (12-HETE). The 12-hydroperoxides are preferentially formed in platelets. EC 1.13.11.31. [NIH]

Arachidonate 15-Lipoxygenase: An enzyme that catalyzes the oxidation of arachidonic acid to yield 15-hydroperoxyarachidonate (15-HPETE) which is rapidly converted to 15-hydroxy-5,8,11,13-eicosatetraenoate (15-HETE). The 15-hydroperoxides are preferentially formed in neutrophils and lymphocytes. EC 1.13.11.33. [NIH]

Arachidonate Lipoxygenases: Enzymes catalyzing the oxidation of arachidonic acid to hydroperoxyarachidonates (HPETES). These products are then rapidly converted by a peroxidase to hydroxyeicosatetraenoic acids (HETES). The positional specificity of the enzyme reaction varies from tissue to tissue. The final lipoxygenase pathway leads to the leukotrienes. EC 1.13.11.- . [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]

Arenavirus: The only genus in the family Arenaviridae. It contains two groups LCM-Lassa complex viruses and Tacaribe complex viruses, which are distinguished by antigenic relationships and geographic distribution. [NIH]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Argipressin: Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH2, cyclic 1-6 disulfide. The usual mammalian antidiuretic hormone, it is a cyclic nonapeptide with arginine in position 8 of the chain. Argipressin is used to treat diabetes insipidus and as hemostatic because of its vasoconstrictor action. [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]

Asbestos: Fibrous incombustible mineral composed of magnesium and calcium silicates with or without other elements. It is relatively inert chemically and used in thermal insulation and fireproofing. Inhalation of dust causes asbestosis and later lung and gastrointestinal neoplasms. [NIH]

Aseptic: Free from infection or septic material; sterile. [EU]

Aspirin: A drug that reduces pain, fever, inflammation, and blood clotting. Aspirin belongs to the family of drugs called nonsteroidal anti-inflammatory agents. It is also being studied in cancer prevention. [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]

Asymptomatic: Having no signs or symptoms of disease. [NIH]

Atrophy: Decrease in the size of a cell, tissue, organ, or multiple organs, associated with a variety of pathological conditions such as abnormal cellular changes, ischemia, malnutrition, or hormonal changes. [NIH]

Attenuated: Strain with weakened or reduced virulence. [NIH]

Atypical: Irregular; not conformable to the type; in microbiology, applied specifically to strains of unusual type. [EU]

Autoantibodies: Antibodies that react with self-antigens (autoantigens) of the organism that produced them. [NIH]

Autoantigens: Endogenous tissue constituents that have the ability to interact with autoantibodies and cause an immune response. [NIH]

Autoimmune disease: A condition in which the body recognizes its own tissues as foreign and directs an immune response against them. [NIH]

Autoimmunity: Process whereby the immune system reacts against the body's own tissues. Autoimmunity may produce or be caused by autoimmune diseases. [NIH]

Autologous: Taken from an individual's own tissues, cells, or DNA. [NIH]

Avian: A plasmodial infection in birds. [NIH]

Avidity: The strength of the interaction of an antiserum with a multivalent antigen. [NIH]

Axons: Nerve fibers that are capable of rapidly conducting impulses away from the neuron cell body. [NIH]

Azotemia: An excess of urea or other nitrogenous compounds in the blood. [EU]

Back Pain: Acute or chronic pain located in the posterior regions of the trunk, including the thoracic, lumbar, sacral, or adjacent regions. [NIH]

Bacteria: Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccal, rodlike or bacillary, and spiral or spirochetal. [NIH]

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]

Basement Membrane: Ubiquitous supportive tissue adjacent to epithelium and around smooth and striated muscle cells. This tissue contains intrinsic macromolecular components such as collagen, laminin, and sulfated proteoglycans. As seen by light microscopy one of its subdivisions is the basal (basement) lamina. [NIH]

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]

Beta-pleated: Particular three-dimensional pattern of amyloidoses. [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 duct: A tube through which bile passes in and out of the liver. [NIH]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

Biochemical reactions: In living cells, chemical reactions that help sustain life and allow cells to grow. [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]

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]

Biopterin: A natural product that has been considered as a growth factor for some insects. [NIH]

Biosynthesis: The building up of a chemical compound in the physiologic processes of a living organism. [EU]

Biotechnology: Body of knowledge related to the use of organisms, cells or cell-derived constituents for the purpose of developing products which are technically, scientifically and clinically useful. Alteration of biologic function at the molecular level (i.e., genetic engineering) is a central focus; laboratory methods used include transfection and cloning technologies, sequence and structure analysis algorithms, computer databases, and gene and protein structure function analysis and prediction. [NIH]

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 Coagulation: The process of the interaction of blood coagulation factors that results in an insoluble fibrin clot. [NIH]

Blood Coagulation Factors: Endogenous substances, usually proteins, that are involved in the blood coagulation process. [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 vessel: A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

Blot: To transfer DNA, RNA, or proteins to an immobilizing matrix such as nitrocellulose. [NIH]

Blotting, Western: Identification of proteins or peptides that have been electrophoretically separated by blotting and transferred to strips of nitrocellulose paper. The blots are then detected by radiolabeled antibody probes. [NIH]

Body Fluids: Liquid components of living organisms. [NIH]

Bone Marrow: The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells. [NIH]

Bone Marrow Transplantation: The transference of bone marrow from one human or animal to another. [NIH]

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]

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]

Breeding: The science or art of changing the constitution of a population of plants or animals through sexual reproduction. [NIH]

Brucellosis: Infection caused by bacteria of the genus Brucella mainly involving the reticuloendothelial system. This condition is characterized by fever, weakness, malaise, and weight loss. [NIH]

Buccal: Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

Bupropion: A unicyclic, aminoketone antidepressant. The mechanism of its therapeutic actions is not well understood, but it does appear to block dopamine uptake. The hydrochloride is available as an aid to smoking cessation treatment. [NIH]

Bypass: A surgical procedure in which the doctor creates a new pathway for the flow of

body fluids. [NIH]

Cadherins: A group of functionally related glycoproteins responsible for the calcium-dependent cell-to-cell adhesion mechanism. They are divided into subclasses E-, P-, and N-cadherins, which are distinct in immunological specificity and tissue distribution. They promote cell adhesion via a homophilic mechanism. These compounds play a role in the construction of tissues and of the whole animal body. [NIH]

Calcifediol: The major circulating metabolite of vitamin D3 produced in the liver and the best indicator of the body's vitamin D stores. It is effective in the treatment of rickets and osteomalacia, both in azotemic and non-azotemic patients. Calcifediol also has mineralizing properties. [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]

Calcitriol: The physiologically active form of vitamin D. It is formed primarily in the kidney by enzymatic hydroxylation of 25-hydroxycholecalciferol (calcifediol). Its production is stimulated by low blood calcium levels and parathyroid hormone. Calcitriol increases intestinal absorption of calcium and phosphorus, and in concert with parathyroid hormone increases bone resorption. [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]

Calcium channel blocker: A drug used to relax the blood vessel and heart muscle, causing pressure inside blood vessels to drop. It also can regulate heart rhythm. [NIH]

Calcium Channel Blockers: A class of drugs that act by selective inhibition of calcium influx through cell membranes or on the release and binding of calcium in intracellular pools. Since they are inducers of vascular and other smooth muscle relaxation, they are used in the drug therapy of hypertension and cerebrovascular spasms, as myocardial protective agents, and in the relaxation of uterine spasms. [NIH]

Callus: A callosity or hard, thick skin; the bone-like reparative substance that is formed round the edges and fragments of broken bone. [NIH]

Calmodulin: A heat-stable, low-molecular-weight activator protein found mainly in the brain and heart. The binding of calcium ions to this protein allows this protein to bind to cyclic nucleotide phosphodiesterases and to adenyl cyclase with subsequent activation. Thereby this protein modulates cyclic AMP and cyclic GMP levels. [NIH]

Capillary: Any one of the minute vessels that connect the arterioles and venules, forming a network in nearly all parts of the body. Their walls act as semipermeable membranes for the interchange of various substances, including fluids, between the blood and tissue fluid; called also vas capillare. [EU]

Capsular: Cataract which is initiated by an opacification at the surface of the lens. [NIH]

Capsules: Hard or soft soluble containers used for the oral administration of medicine. [NIH]

Carbohydrate: An aldehyde or ketone derivative of a polyhydric alcohol, particularly of the

pentahydric and hexahydric alcohols. They are so named because the hydrogen and oxygen are usually in the proportion to form water, (CH2O)n. The most important carbohydrates are the starches, sugars, celluloses, and gums. They are classified into mono-, di-, tri-, poly- and heterosaccharides. [EU]

Carbon Dioxide: A colorless, odorless gas that can be formed by the body and is necessary for the respiration cycle of plants and animals. [NIH]

Carboxy: Cannabinoid. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Carcinogens: Substances that increase the risk of neoplasms in humans or animals. Both genotoxic chemicals, which affect DNA directly, and nongenotoxic chemicals, which induce neoplasms by other mechanism, are included. [NIH]

Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs. [NIH]

Cardiac: Having to do with the heart. [NIH]

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]

Cardiomegaly: Hypertrophy or enlargement of the heart. [NIH]

Cardiomyopathy: A general diagnostic term designating primary myocardial disease, often of obscure or unknown etiology. [EU]

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]

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]

Cassia: Leguminous plants Cassia senna L. (or C. acutifolia) and C. angustifolia that contain anthraquinones which are used as laxatives. [NIH]

Catabolism: Any destructive metabolic process by which organisms convert substances into excreted compounds. [EU]

Causal: Pertaining to a cause; directed against a cause. [EU]

Causality: The relating of causes to the effects they produce. Causes are termed necessary when they must always precede an effect and sufficient when they initiate or produce an effect. Any of several factors may be associated with the potential disease causation or outcome, including predisposing factors, enabling factors, precipitating factors, reinforcing factors, and risk factors. [NIH]

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 Cycle: The complex series of phenomena, occurring between the end of one cell division and the end of the next, by which cellular material is divided between daughter cells. [NIH]

Cell Death: The termination of the cell's ability to carry out vital functions such as metabolism, growth, reproduction, responsiveness, and adaptability. [NIH]

Cell Differentiation: Progressive restriction of the developmental potential and increasing specialization of function which takes place during the development of the embryo and leads to the formation of specialized cells, tissues, and organs. [NIH]

Cell Division: The fission of a cell. [NIH]

Cell 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 motility: The ability of a cell to move. [NIH]

Cell Polarity: Orientation of intracellular structures especially with respect to the apical and basolateral domains of the plasma membrane. Polarized cells must direct proteins from the Golgi apparatus to the appropriate domain since tight junctions prevent proteins from diffusing between the two domains. [NIH]

Cell proliferation: An increase in the number of cells as a result of cell growth and cell division. [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]

Central Nervous System: The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [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]

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]

Chemotaxis: The movement of cells or organisms toward or away from a substance in response to its concentration gradient. [NIH]

Chemotherapeutic agent: A drug used to treat cancer. [NIH]

Chemotherapy: Treatment with anticancer drugs. [NIH]

Chimera: An individual that contains cell populations derived from different zygotes. [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]

Cholesterol Esters: Fatty acid esters of cholesterol which constitute about two-thirds of the cholesterol in the plasma. The accumulation of cholesterol esters in the arterial intima is a characteristic feature of atherosclerosis. [NIH]

Choline: A basic constituent of lecithin that is found in many plants and animal organs. It is important as a precursor of acetylcholine, as a methyl donor in various metabolic processes, and in lipid metabolism. [NIH]

Chromatin: The material of chromosomes. It is a complex of DNA, histones, and nonhistone proteins (chromosomal proteins, non-histone) found within the nucleus of a cell. [NIH]

Chromosomal: Pertaining to chromosomes. [EU]

Chromosome: Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes. [NIH]

Chronic: A disease or condition that persists or progresses over a long period of time. [NIH]

Chronic Disease: Disease or ailment of long duration. [NIH]

Chronic lymphocytic leukemia: A slowly progressing disease in which too many white blood cells (called lymphocytes) are found in the body. [NIH]

Chronic renal: Slow and progressive loss of kidney function over several years, often resulting in end-stage renal disease. People with end-stage renal disease need dialysis or transplantation to replace the work of the kidneys. [NIH]

Chylomicrons: A class of lipoproteins that carry dietary cholesterol and triglycerides from the small intestines to the tissues. [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]

Cicatricial: Ectropion due to scar tissue on the margins or the surrounding surfaces of the eyelids. [NIH]

Cirrhosis: A type of chronic, progressive liver disease. [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]

Clinical Medicine: The study and practice of medicine by direct examination of the patient. [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]

Clonal Deletion: Removal, via cell death, of immature lymphocytes that interact with antigens during maturation. For T-lymphocytes this occurs in the thymus and ensures that mature T-lymphocytes are self tolerant. B-lymphocytes may also undergo clonal deletion. [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]

Coagulants: Exogenous substances used to promote blood coagulation. The endogenous blood coagulation factors are considered to be coagulants only when administered as drugs. [NIH]

Codon: A set of three nucleotides in a protein coding sequence that specifies individual amino acids or a termination signal (codon, terminator). Most codons are universal, but some organisms do not produce the transfer RNAs (RNA, transfer) complementary to all codons. These codons are referred to as unassigned codons (codons, nonsense). [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]

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]

Complement Activation: The sequential activation of serum components C1 through C9, initiated by an erythrocyte-antibody complex or by microbial polysaccharides and properdin, and producing an inflammatory response. [NIH]

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]

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]

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]

Cone: One of the special retinal receptor elements which are presumed to be primarily concerned with perception of light and color stimuli when the eye is adapted to light. [NIH]

Confusion: A mental state characterized by bewilderment, emotional disturbance, lack of clear thinking, and perceptual disorientation. [NIH]

Conjugated: Acting or operating as if joined; simultaneous. [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]

Constipation: Infrequent or difficult evacuation of feces. [NIH]

Constriction: The act of constricting. [NIH]

Consultation: A deliberation between two or more physicians concerning the diagnosis and the proper method of treatment in a case. [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]

Contralateral: Having to do with the opposite side of the body. [NIH]

Controlled study: An experiment or clinical trial that includes a comparison (control) group.

[NIH]

Convulsions: A general term referring to sudden and often violent motor activity of cerebral or brainstem origin. Convulsions may also occur in the absence of an electrical cerebral discharge (e.g., in response to hypotension). [NIH]

Corn Oil: Oil from corn or corn plant. [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 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]

Corpuscle: A small mass or body; a sensory nerve end bulb; a cell, especially that of the blood or the lymph. [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 (adrenocorticotropic 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]

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]

Cost Savings: Reductions in all or any portion of the costs of providing goods or services. Savings may be incurred by the provider or the consumer. [NIH]

Creatinine: A compound that is excreted from the body in urine. Creatinine levels are measured to monitor kidney function. [NIH]

Crossing-over: The exchange of corresponding segments between chromatids of homologous chromosomes during meiosia, forming a chiasma. [NIH]

Cryoglobulinemia: A condition characterized by the presence of abnormal or abnormal quantities of cryoglobulins in the blood. They are precipitated into the microvasculature on exposure to cold and cause restricted blood flow in exposed areas. [NIH]

Cues: Signals for an action; that specific portion of a perceptual field or pattern of stimuli to which a subject has learned to respond. [NIH]

Cultured cell line: Cells of a single type that have been grown in the laboratory for several generations (cell divisions). [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]

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]

Cysteine: A thiol-containing non-essential amino acid that is oxidized to form cystine. [NIH]

Cytochrome: Any electron transfer hemoprotein having a mode of action in which the transfer of a single electron is effected by a reversible valence change of the central iron atom of the heme prosthetic group between the +2 and +3 oxidation states; classified as cytochromes a in which the heme contains a formyl side chain, cytochromes b, which contain protoheme or a closely similar heme that is not covalently bound to the protein, cytochromes c in which protoheme or other heme is covalently bound to the protein, and cytochromes d in which the iron-tetrapyrrole has fewer conjugated double bonds than the hemes have. Well-known cytochromes have been numbered consecutively within groups and are designated by subscripts (beginning with no subscript), e.g. cytochromes c, c1, C2, . New cytochromes are named according to the wavelength in nanometres of the absorption maximum of the a-band of the iron (II) form in pyridine, e.g., c-555. [EU]

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]

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]

Cytoskeletal Proteins: Major constituent of the cytoskeleton found in the cytoplasm of eukaryotic cells. They form a flexible framework for the cell, provide attachment points for organelles and formed bodies, and make communication between parts of the cell possible. [NIH]

Cytoskeleton: The network of filaments, tubules, and interconnecting filamentous bridges which give shape, structure, and organization to the cytoplasm. [NIH]

Cytostatic: An agent that suppresses cell growth and multiplication. [EU]

Cytotoxic: Cell-killing. [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]

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]

Degenerative: Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

Deletion: A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [NIH]

Dendrites: Extensions of the nerve cell body. They are short and branched and receive stimuli from other neurons. [NIH]

Density: The logarithm to the base 10 of the opacity of an exposed and processed film. [NIH]

Desensitization: The prevention or reduction of immediate hypersensitivity reactions by administration of graded doses of allergen; called also hyposensitization and immunotherapy. [EU]

Desmin: An intermediate filament protein found predominantly in smooth, skeletal, and cardiac muscle cells. Localized at the Z line. MW 50,000 to 55,000 is species dependent. [NIH]

Desmopressin: A synthetic analog of the natural hormone 8-arginine vasopressin (argipressin). Its action is mediated by the vasopressin receptor V2. It has prolonged antidiuretic activity, but little pressor effects. It also modulates levels of circulating factor VIII and von Willebrand factor. [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]

Dextran Sulfate: Long-chain polymer of glucose containing 17-20% sulfur. It has been used as an anticoagulant and also has been shown to inhibit the binding of HIV-1 to CD4+ T-lymphocytes. It is commonly used as both an experimental and clinical laboratory reagent and has been investigated for use as an antiviral agent, in the treatment of hypolipidemia, and for the prevention of free radical damage, among other applications. [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]

Dialysate: A cleansing liquid used in the two major forms of dialysis--hemodialysis and peritoneal dialysis. [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]

Diaphragm: The musculofibrous partition that separates the thoracic cavity from the abdominal cavity. Contraction of the diaphragm increases the volume of the thoracic cavity aiding inspiration. [NIH]

Diastolic: Of or pertaining to the diastole. [EU]

Diathesis: A constitution or condition of the body which makes the tissues react in special ways to certain extrinsic stimuli and thus tends to make the person more than usually

susceptible to certain diseases. [EU]

Diffusion: The tendency of a gas or solute to pass from a point of higher pressure or concentration to a point of lower pressure or concentration and to distribute itself throughout the available space; a major mechanism of biological transport. [NIH]

Diflunisal: A salicylate derivative and anti-inflammatory analgesic with actions and side effects similar to those of aspirin. [NIH]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Dilated cardiomyopathy: Heart muscle disease that leads to enlargement of the heart's chambers, robbing the heart of its pumping ability. [NIH]

Dimerization: The process by which two molecules of the same chemical composition form a condensation product or polymer. [NIH]

Dipyridamole: A drug that prevents blood cell clumping and enhances the effectiveness of fluorouracil and other chemotherapeutic agents. [NIH]

Direct: 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

Disinfectant: An agent that disinfects; applied particularly to agents used on inanimate objects. [EU]

Dislocation: The displacement of any part, more especially of a bone. Called also luxation. [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]

Diuresis: Increased excretion of urine. [EU]

Diuretic: A drug that increases the production of urine. [NIH]

Diuretics, Thiazide: Diuretics characterized as analogs of 1,2,4-benzothiadiazine-1,1-dioxide. All have a common mechanism of action and differ primarily in the dose required to produce a given effect. They act directly on the kidney to increase the excretion of sodium chloride and water and also increase excretion of potassium ions. [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]

Double-blind: Pertaining to a clinical trial or other experiment in which neither the subject

nor the person administering treatment knows which treatment any particular subject is receiving. [EU]

Drive: A state of internal activity of an organism that is a necessary condition before a given stimulus will elicit a class of responses; e.g., a certain level of hunger (drive) must be present before food will elicit an eating response. [NIH]

Drug Interactions: The action of a drug that may affect the activity, metabolism, or toxicity of another drug. [NIH]

Drug Tolerance: Progressive diminution of the susceptibility of a human or animal to the effects of a drug, resulting from its continued administration. It should be differentiated from drug resistance wherein an organism, disease, or tissue fails to respond to the intended effectiveness of a chemical or drug. It should also be differentiated from maximum tolerated dose and no-observed-adverse-effect level. [NIH]

Drusen: Tiny yellow or white deposits in the retina or optic nerve head. [NIH]

Duct: A tube through which body fluids pass. [NIH]

Duodenum: The first part of the small intestine. [NIH]

Dyes: Chemical substances that are used to stain and color other materials. The coloring may or may not be permanent. Dyes can also be used as therapeutic agents and test reagents in medicine and scientific research. [NIH]

Dysmenorrhea: Painful menstruation. [NIH]

Dysplasia: Cells that look abnormal under a microscope but are not cancer. [NIH]

Dyspnea: Difficult or labored breathing. [NIH]

Eclampsia: Onset of convulsions or coma in a previously diagnosed pre-eclamptic patient. [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]

Efferent: Nerve fibers which conduct impulses from the central nervous system to muscles and glands. [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]

Eicosanoids: A class of oxygenated, endogenous, unsaturated fatty acids derived from arachidonic acid. They include prostaglandins, leukotrienes, thromboxanes, and hydroxyeicosatetraenoic acid compounds (HETE). They are hormone-like substances that act near the site of synthesis without altering functions throughout the body. [NIH]

Elastin: The protein that gives flexibility to tissues. [NIH]

Electrolyte: A substance that dissociates into ions when fused or in solution, and thus becomes capable of conducting electricity; an ionic solute. [EU]

Electrons: Stable elementary particles having the smallest known negative charge, present in all elements; also called negatrons. Positively charged electrons are called positrons. The numbers, energies and arrangement of electrons around atomic nuclei determine the chemical identities of elements. Beams of electrons are called cathode rays or beta rays, the

latter being a high-energy biproduct of nuclear decay. [NIH]

Electrophoresis: An electrochemical process in which macromolecules or colloidal particles with a net electric charge migrate in a solution under the influence of an electric current. [NIH]

Emboli: Bit of foreign matter which enters the blood stream at one point and is carried until it is lodged or impacted in an artery and obstructs it. It may be a blood clot, an air bubble, fat or other tissue, or clumps of bacteria. [NIH]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Emphysema: A pathological accumulation of air in tissues or organs. [NIH]

Enalapril: An angiotensin-converting enzyme inhibitor that is used to treat hypertension. [NIH]

Encephalitis: Inflammation of the brain due to infection, autoimmune processes, toxins, and other conditions. Viral infections (see encephalitis, viral) are a relatively frequent cause of this condition. [NIH]

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]

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]

Endocrine System: The system of glands that release their secretions (hormones) directly into the circulatory system. In addition to the endocrine glands, included are the chromaffin system and the neurosecretory systems. [NIH]

Endocytosis: Cellular uptake of extracellular materials within membrane-limited vacuoles or microvesicles. Endosomes play a central role in endocytosis. [NIH]

Endogenous: Produced inside an organism or cell. The opposite is external (exogenous) production. [NIH]

Endometrium: The layer of tissue that lines the uterus. [NIH]

Endothelial cell: The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart. [NIH]

Endothelium: A layer of epithelium that lines the heart, blood vessels (endothelium, vascular), lymph vessels (endothelium, lymphatic), and the serous cavities of the body. [NIH]

Endothelium, Lymphatic: Unbroken cellular lining (intima) of the lymph vessels (e.g., the high endothelial lymphatic venules). It is more permeable than vascular endothelium, lacking selective absorption and functioning mainly to remove plasma proteins that have filtered through the capillaries into the tissue spaces. [NIH]

Endothelium, Vascular: Single pavement layer of cells which line the luminal surface of the entire vascular system and regulate the transport of macromolecules and blood components from interstitium to lumen; this function has been most intensively studied in the blood

capillaries. [NIH]

Endothelium-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes it. [NIH]

Endotoxemia: A condition characterized by the presence of endotoxins in the blood. If endotoxemia is the result of gram-negative rod-shaped bacteria, shock may occur. [NIH]

Endotoxic: Of, relating to, or acting as an endotoxin (= a heat-stable toxin, associated with the outer membranes of certain gram-negative bacteria. Endotoxins are not secreted and are released only when the cells are disrupted). [EU]

Endotoxins: Toxins closely associated with the living cytoplasm or cell wall of certain microorganisms, which do not readily diffuse into the culture medium, but are released upon lysis of the cells. [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]

Enterohepatic: Of or involving the intestine and liver. [EU]

Enterohepatic Circulation: Recycling through liver by excretion in bile, reabsorption from intestines into portal circulation, passage back into liver, and re-excretion in bile. [NIH]

Enteropeptidase: A specialized proteolytic enzyme secreted by intestinal cells. It converts trypsinogen into its active form trypsin by removing the N-terminal peptide. EC 3.4.21.9. [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]

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]

Eosinophils: Granular leukocytes with a nucleus that usually has two lobes connected by a slender thread of chromatin, and cytoplasm containing coarse, round granules that are uniform in size and stainable by eosin. [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]

Epidemiological: Relating to, or involving epidemiology. [EU]

Epidermis: Nonvascular layer of the skin. It is made up, from within outward, of five layers: 1) basal layer (stratum basale epidermidis); 2) spinous layer (stratum spinosum epidermidis); 3) granular layer (stratum granulosum epidermidis); 4) clear layer (stratum lucidum epidermidis); and 5) horny layer (stratum corneum epidermidis). [NIH]

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]

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]

Erythropoietin: Glycoprotein hormone, secreted chiefly by the kidney in the adult and the liver in the fetus, that acts on erythroid stem cells of the bone marrow to stimulate proliferation and differentiation. [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]

Estrogen receptor: ER. Protein found on some cancer cells to which estrogen will attach. [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]

Evoke: The electric response recorded from the cerebral cortex after stimulation of a peripheral sense organ. [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]

Excrete: To get rid of waste from the body. [NIH]

Exhaustion: The feeling of weariness of mind and body. [NIH]

Exogenous: Developed or originating outside the organism, as exogenous disease. [EU]

Exon: The part of the DNA that encodes the information for the actual amino acid sequence of the protein. In many eucaryotic genes, the coding sequences consist of a series of exons alternating with intron sequences. [NIH]

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 Matrix Proteins: Macromolecular organic compounds that contain carbon, hydrogen, oxygen, nitrogen, and usually, sulfur. These macromolecules (proteins) form an intricate meshwork in which cells are embedded to construct tissues. Variations in the relative types of macromolecules and their organization determine the type of extracellular matrix, each adapted to the functional requirements of the tissue. The two main classes of macromolecules that form the extracellular matrix are: glycosaminoglycans, usually linked to proteins (proteoglycans), and fibrous proteins (e.g., collagen, elastin, fibronectins and laminin). [NIH]

Extracellular Space: Interstitial space between cells, occupied by fluid as well as amorphous and fibrous substances. [NIH]

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]

Family Health: The health status of the family as a unit including the impact of the health of one member of the family on the family as a unit and on individual family members; also, the impact of family organization or disorganization on the health status of its members. [NIH]

Family Planning: Programs or services designed to assist the family in controlling reproduction by either improving or diminishing fertility. [NIH]

Fat: Total lipids including phospholipids. [NIH]

Febrile: Pertaining to or characterized by fever. [EU]

Felodipine: A dihydropyridine calcium antagonist with positive inotropic effects. It lowers blood pressure by reducing peripheral vascular resistance through a highly selective action on smooth muscle in arteriolar resistance vessels. [NIH]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [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]

Fibrinolysis: The natural enzymatic dissolution of fibrin. [NIH]

Fibroblasts: Connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules. [NIH]

Fibronectin: An adhesive glycoprotein. One form circulates in plasma, acting as an opsonin; another is a cell-surface protein which mediates cellular adhesive interactions. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

Filtration: The passage of a liquid through a filter, accomplished by gravity, pressure, or vacuum (suction). [EU]

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 transverses 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]

Flurbiprofen: An anti-inflammatory analgesic and antipyretic of the phenylalkynoic acid series. It has been shown to reduce bone resorption in periodontal disease by inhibiting carbonic anhydrase. [NIH]

Fold: A plication or doubling of various parts of the body. [NIH]

Forearm: The part between the elbow and the wrist. [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]

Fundus: The larger part of a hollow organ that is farthest away from the organ's opening. The bladder, gallbladder, stomach, uterus, eye, and cavity of the middle ear all have a fundus. [NIH]

Furosemide: A sulfamyl saluretic and diuretic. It has a fast onset and short duration of action and is used in edema and chronic renal insufficiency. [NIH]

Gallbladder: The pear-shaped organ that sits below the liver. Bile is concentrated and stored in the gallbladder. [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]

Ganglia: Clusters of multipolar neurons surrounded by a capsule of loosely organized connective tissue located outside the central nervous system. [NIH]

Ganglionic Blockers: Agents having as their major action the interruption of neural transmission at nicotinic receptors on postganglionic autonomic neurons. Because their actions are so broad, including blocking of sympathetic and parasympathetic systems, their therapeutic use has been largely supplanted by more specific drugs. They may still be used in the control of blood pressure in patients with acute dissecting aortic aneurysm and for the induction of hypotension in surgery. [NIH]

Gas: Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

Gastric: Having to do with the stomach. [NIH]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal stromal tumor: GIST. A type of tumor that usually begins in cells in the wall of the gastrointestinal tract. It can be benign or malignant. [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]

Gemcitabine: An anticancer drug that belongs to the family of drugs called antimetabolites. [NIH]

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

Gene Deletion: A genetic rearrangement through loss of segments of DNA or RNA, bringing sequences which are normally separated into close proximity. This deletion may be detected using cytogenetic techniques and can also be inferred from the phenotype, indicating a deletion at one specific locus. [NIH]

Gene Dosage: The number of copies of a given gene present in a cell or nucleus. An increase in gene dosage can result in the formation of higher levels of gene product, provided that the gene is not subject to autogenous regulation. [NIH]

Gene Duplication: It encodes the major envelope protein and includes all the specifications for HBsAg. [NIH]

Gene Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Gene Expression Profiling: The determination of the pattern of genes expressed i.e., transcribed, under specific circumstances or in a specific cell. [NIH]

Gene Therapy: The introduction of new genes into cells for the purpose of treating disease by restoring or adding gene expression. Techniques include insertion of retroviral vectors, transfection, homologous recombination, and injection of new genes into the nuclei of single cell embryos. The entire gene therapy process may consist of multiple steps. The new genes may be introduced into proliferating cells in vivo (e.g., bone marrow) or in vitro (e.g., fibroblast cultures) and the modified cells transferred to the site where the gene expression is required. Gene therapy may be particularly useful for treating enzyme deficiency diseases, hemoglobinopathies, and leukemias and may also prove useful in restoring drug sensitivity, particularly for leukemia. [NIH]

Genetic Code: The specifications for how information, stored in nucleic acid sequence (base sequence), is translated into protein sequence (amino acid sequence). The start, stop, and order of amino acids of a protein is specified by consecutive triplets of nucleotides called codons (codon). [NIH]

Genetic Engineering: Directed modification of the gene complement of a living organism by such techniques as altering the DNA, substituting genetic material by means of a virus, transplanting whole nuclei, transplanting cell hybrids, etc. [NIH]

Genetics: The biological science that deals with the phenomena and mechanisms of

heredity. [NIH]

Genital: Pertaining to the genitalia. [EU]

Genotype: The genetic constitution of the individual; the characterization of the genes. [NIH]

Geriatric: Pertaining to the treatment of the aged. [EU]

Germinal Center: The activated center of a lymphoid follicle in secondary lymphoid tissue where B-lymphocytes are stimulated by antigens and helper T cells (T-lymphocytes, helper-inducer) are stimulated to generate memory cells. [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]

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]

Glomerular: Pertaining to or of the nature of a glomerulus, especially a renal glomerulus. [EU]

Glomerular Filtration Rate: The volume of water filtered out of plasma through glomerular capillary walls into Bowman's capsules per unit of time. It is considered to be equivalent to inulin clearance. [NIH]

Glomerular Mesangium: The thin membrane which helps to support the capillary loops in a renal glomerulus. It is connective tissue composed of mesangial cells - myofibroblasts phenotypically related to vascular smooth muscle cells (muscle, smooth, vascular), phagocytes, and the mesangial extracellular matrix. [NIH]

Glomeruli: Plural of glomerulus. [NIH]

Glomerulosclerosis: Scarring of the glomeruli. It may result from diabetes mellitus (diabetic glomerulosclerosis) or from deposits in parts of the glomerulus (focal segmental glomerulosclerosis). The most common signs of glomerulosclerosis are proteinuria and kidney failure. [NIH]

Glomerulus: A tiny set of looping blood vessels in the nephron where blood is filtered in the kidney. [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]

Glycerol: A trihydroxy sugar alcohol that is an intermediate in carbohydrate and lipid metabolism. It is used as a solvent, emollient, pharmaceutical agent, and sweetening agent. [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]

Glycosaminoglycans: Heteropolysaccharides which contain an N-acetylated hexosamine in a characteristic repeating disaccharide unit. The repeating structure of each disaccharide involves alternate 1,4- and 1,3-linkages consisting of either N-acetylglucosamine or N-acetylgalactosamine. [NIH]

Glycosidic: Formed by elimination of water between the anomeric hydroxyl of one sugar and a hydroxyl of another sugar molecule. [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]

Goiter: Enlargement of the thyroid gland. [NIH]

Gonadal: Pertaining to a gonad. [EU]

Gout: Hereditary metabolic disorder characterized by recurrent acute arthritis, hyperuricemia and deposition of sodium urate in and around the joints, sometimes with formation of uric acid calculi. [NIH]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Graft: Healthy skin, bone, or other tissue taken from one part of the body and used to replace diseased or injured tissue removed from another part of the body. [NIH]

Graft Rejection: An immune response with both cellular and humoral components, directed against an allogeneic transplant, whose tissue antigens are not compatible with those of the recipient. [NIH]

Grafting: The operation of transfer of tissue from one site to another. [NIH]

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]

Granulocyte: A type of white blood cell that fights bacterial infection. Neutrophils, eosinophils, and basophils are granulocytes. [NIH]

Granuloma: A relatively small nodular inflammatory lesion containing grouped mononuclear phagocytes, caused by infectious and noninfectious agents. [NIH]

Growth factors: Substances made by the body that function to regulate cell division and cell survival. Some growth factors are also produced in the laboratory and used in biological therapy. [NIH]

Guanylate Cyclase: An enzyme that catalyzes the conversion of GTP to 3',5'-cyclic GMP and pyrophosphate. It also acts on ITP and dGTP. (From Enzyme Nomenclature, 1992) EC 4.6.1.2. [NIH]

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]

Haemodialysis: The removal of certain elements from the blood by virtue of the difference in the rates of their diffusion through a semipermeable membrane, e.g., by means of a haemodialyzer. [EU]

Half-Life: The time it takes for a substance (drug, radioactive nuclide, or other) to lose half of its pharmacologic, physiologic, or radiologic activity. [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]

Health Status: The level of health of the individual, group, or population as subjectively assessed by the individual or by more objective measures. [NIH]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Heart failure: Loss of pumping ability by the heart, often accompanied by fatigue, breathlessness, and excess fluid accumulation in body tissues. [NIH]

Hematopoiesis: The development and formation of various types of blood cells. [NIH]

Hematopoietic tissue: Tissue in which new blood cells are formed. [NIH]

Hematuria: Presence of blood in the urine. [NIH]

Heme: The color-furnishing portion of hemoglobin. It is found free in tissues and as the prosthetic group in many hemeproteins. [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]

Hemodynamics: The movements of the blood and the forces involved in systemic or regional blood circulation. [NIH]

Hemoglobin: One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal conentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

Hemoglobinopathies: A group of inherited disorders characterized by structural alterations within the hemoglobin molecule. [NIH]

Hemolytic: A disease that affects the blood and blood vessels. It destroys red blood cells, cells that cause the blood to clot, and the lining of blood vessels. HUS is often caused by the Escherichia coli bacterium in contaminated food. People with HUS may develop acute renal failure. [NIH]

Hemolytic-Uremic Syndrome: Syndrome of hemolytic anemia, thrombocytopenia, and acute renal failure, with pathological finding of thrombotic microangiopathy in kidney and renal cortical necrosis. [NIH]

Hemorrhage: Bleeding or escape of blood from a vessel. [NIH]

Hemostasis: The process which spontaneously arrests the flow of blood from vessels carrying blood under pressure. It is accomplished by contraction of the vessels, adhesion

and aggregation of formed blood elements, and the process of blood or plasma coagulation. [NIH]

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]

Hepatic: Refers to the liver. [NIH]

Hepatitis: Inflammation of the liver and liver disease involving degenerative or necrotic alterations of hepatocytes. [NIH]

Hepatitis B: Hepatitis caused by hepatitis B virus. It may be transmitted by transfusion of contaminated blood or blood products. [NIH]

Hepatocellular: Pertaining to or affecting liver cells. [EU]

Hepatocellular carcinoma: A type of adenocarcinoma, the most common type of liver tumor. [NIH]

Hepatocytes: The main structural component of the liver. They are specialized epithelial cells that are organized into interconnected plates called lobules. [NIH]

Hepatorenal Syndrome: Renal failure in those with liver disease, usually liver cirrhosis or obstructive jaundice. Historically called Heyd disease, urohepatic syndrome, or bile nephrosis. [NIH]

Hereditary: Of, relating to, or denoting factors that can be transmitted genetically from one generation to another. [NIH]

Heredity: 1. The genetic transmission of a particular quality or trait from parent to offspring. 2. The genetic constitution of an individual. [EU]

Heterodimers: Zippered pair of nonidentical proteins. [NIH]

Heterogeneity: The property of one or more samples or populations which implies that they are not identical in respect of some or all of their parameters, e. g. heterogeneity of variance. [NIH]

Histology: The study of tissues and cells under a microscope. [NIH]

Histones: Small chromosomal proteins (approx 12-20 kD) possessing an open, unfolded structure and attached to the DNA in cell nuclei by ionic linkages. Classification into the various types (designated histone I, histone II, etc.) is based on the relative amounts of arginine and lysine in each. [NIH]

Homeobox: Distinctive sequence of DNA bases. [NIH]

Homeostasis: The processes whereby the internal environment of an organism tends to remain balanced and stable. [NIH]

Homodimer: Protein-binding "activation domains" always combine with identical proteins. [NIH]

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]

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]

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]

Hydra: A genus of freshwater cnidarians, of interest because of their complex organization and because their adult organization corresponds roughly to the gastrula of higher animals. [NIH]

Hydrocortisone: The main glucocorticoid secreted by the adrenal cortex. Its synthetic counterpart is used, either as an injection or topically, in the treatment of inflammation, allergy, collagen diseases, asthma, adrenocortical deficiency, shock, and some neoplastic conditions. [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]

Hydrophobic: Not readily absorbing water, or being adversely affected by water, as a hydrophobic colloid. [EU]

Hydroxylation: Hydroxylate, to introduce hydroxyl into (a compound or radical) usually by replacement of hydrogen. [EU]

Hydroxylysine: A hydroxylated derivative of the amino acid lysine that is present in certain collagens. [NIH]

Hydroxyproline: A hydroxylated form of the imino acid proline. A deficiency in ascorbic acid can result in impaired hydroxyproline formation. [NIH]

Hypercalcemia: Abnormally high level of calcium in the blood. [NIH]

Hyperlipidaemia: A general term for elevated concentrations of any or all of the lipids in the plasma, including hyperlipoproteinaemia, hypercholesterolaemia, etc. [EU]

Hyperplasia: An increase in the number of cells in a tissue or organ, not due to tumor formation. It differs from hypertrophy, which is an increase in bulk without an increase in the number of cells. [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]

Hypertrophy: General increase in bulk of a part or organ, not due to tumor formation, nor to an increase in the number of cells. [NIH]

Hypoplasia: Incomplete development or underdevelopment of an organ or tissue. [EU]

Hypotension: Abnormally low blood pressure. [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]

Ibuprofen: A nonsteroidal anti-inflammatory agent with analgesic properties used in the therapy of rheumatism and arthritis. [NIH]

Idiopathic: Describes a disease of unknown cause. [NIH]

Immune Complex Diseases: Group of diseases mediated by the deposition of large soluble complexes of antigen and antibody with resultant damage to tissue. Besides serum sickness and the arthus reaction, evidence supports a pathogenic role for immune complexes in many other systemic immunologic diseases including glomerulonephritis, systemic lupus erythematosus and polyarteritis nodosa. [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]

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]

Immunoblotting: Immunologic methods for isolating and quantitatively measuring immunoreactive substances. When used with immune reagents such as monoclonal antibodies, the process is known generically as western blot analysis (blotting, western). [NIH]

Immunochemistry: Field of chemistry that pertains to immunological phenomena and the study of chemical reactions related to antigen stimulation of tissues. It includes physicochemical interactions between antigens and antibodies. [NIH]

Immunodeficiency: The decreased ability of the body to fight infection and disease. [NIH]

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]

Immunologic Diseases: Disorders caused by abnormal or absent immunologic mechanisms, whether humoral, cell-mediated or both. [NIH]

Immunology: The study of the body's immune system. [NIH]

Immunosuppression: Deliberate prevention or diminution of the host's immune response. It may be nonspecific as in the administration of immunosuppressive agents (drugs or radiation) or by lymphocyte depletion or may be specific as in desensitization or the simultaneous administration of antigen and immunosuppressive drugs. [NIH]

Immunosuppressive: Describes the ability to lower immune system responses. [NIH]

Immunosuppressive Agents: Agents that suppress immune function by one of several mechanisms of action. Classical cytotoxic immunosuppressants act by inhibiting DNA synthesis. Others may act through activation of suppressor T-cell populations or by inhibiting the activation of helper cells. While immunosuppression has been brought about in the past primarily to prevent rejection of transplanted organs, new applications involving mediation of the effects of interleukins and other cytokines are emerging. [NIH]

Immunosuppressive therapy: Therapy used to decrease the body's immune response, such as drugs given to prevent transplant rejection. [NIH]

Immunotherapy: Manipulation of the host's immune system in treatment of disease. It includes both active and passive immunization as well as immunosuppressive therapy to prevent graft rejection. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

Impetigo: A common superficial bacterial infection caused by staphylococcus aureus or group A beta-hemolytic streptococci. Characteristics include pustular lesions that rupture and discharge a thin, amber-colored fluid that dries and forms a crust. This condition is commonly located on the face, especially about the mouth and nose. [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]

Indomethacin: A non-steroidal anti-inflammatory agent (NSAID) that inhibits the enzyme cyclooxygenase necessary for the formation of prostaglandins and other autacoids. It also inhibits the motility of polymorphonuclear leukocytes. [NIH]

Induction: The act or process of inducing or causing to occur, especially the production of a specific morphogenetic effect in the developing embryo through the influence of evocators or organizers, or the production of anaesthesia or unconsciousness by use of appropriate agents. [EU]

Infantile: Pertaining to an infant or to infancy. [EU]

Infarction: A pathological process consisting of a sudden insufficient blood supply to an area, which results in necrosis of that area. It is usually caused by a thrombus, an embolus,

or a vascular torsion. [NIH]

Infection: 1. Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response. The infection may remain localized, subclinical, and temporary if the body's defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute, or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system. 2. An infectious disease. [EU]

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]

Ingestion: Taking into the body by mouth [NIH]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

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]

Inotropic: Affecting the force or energy of muscular contractions. [EU]

Insight: The capacity to understand one's own motives, to be aware of one's own psychodynamics, to appreciate the meaning of symbolic behavior. [NIH]

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]

Insulin-like: Muscular growth factor. [NIH]

Integrins: A family of transmembrane glycoproteins consisting of noncovalent heterodimers. They interact with a wide variety of ligands including extracellular matrix glycoproteins, complement, and other cells, while their intracellular domains interact with the cytoskeleton. The integrins consist of at least three identified families: the cytoadhesin receptors, the leukocyte adhesion receptors, and the very-late-antigen receptors. Each family contains a common beta-subunit combined with one or more distinct alpha-subunits. These receptors participate in cell-matrix and cell-cell adhesion in many physiologically important

processes, including embryological development, hemostasis, thrombosis, wound healing, immune and nonimmune defense mechanisms, and oncogenic transformation. [NIH]

Intensive Care: Advanced and highly specialized care provided to medical or surgical patients whose conditions are life-threatening and require comprehensive care and constant monitoring. It is usually administered in specially equipped units of a health care facility. [NIH]

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-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-6: Factor that stimulates the growth and differentiation of human B-cells and is also a growth factor for hybridomas and plasmacytomas. It is produced by many different cells including T-cells, monocytes, and fibroblasts. [NIH]

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]

Intermediate Filaments: Cytoplasmic filaments intermediate in diameter (about 10 nanometers) between the microfilaments and the microtubules. They may be composed of any of a number of different proteins and form a ring around the cell nucleus. [NIH]

Intermittent: Occurring at separated intervals; having periods of cessation of activity. [EU]

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]

Intracellular: Inside a cell. [NIH]

Intravascular: Within a vessel or vessels. [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]

Inulin: A starch found in the tubers and roots of many plants. Since it is hydrolyzable to fructose, it is classified as a fructosan. It has been used in physiologic investigation for determination of the rate of glomerular function. [NIH]

Ion Transport: The movement of ions across energy-transducing cell membranes. Transport can be active or passive. Passive ion transport (facilitated diffusion) derives its energy from the concentration gradient of the ion itself and allows the transport of a single solute in one direction (uniport). Active ion transport is usually coupled to an energy-yielding chemical or photochemical reaction such as ATP hydrolysis. This form of primary active transport is called an ion pump. Secondary active transport utilizes the voltage and ion gradients produced by the primary transport to drive the cotransport of other ions or molecules. These may be transported in the same (symport) or opposite (antiport) direction. [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]

Ischemia: Deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel. [EU]

Isozymes: The multiple forms of a single enzyme. [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]

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]

Ketoprofen: An ibuprofen-type anti-inflammatory analgesic and antipyretic. It is used in the treatment of rheumatoid arthritis and osteoarthritis. [NIH]

Kidney Cortex: The outer zone of the kidney, beneath the capsule, consisting of kidney glomerulus; kidney tubules, distal; and kidney tubules, proximal. [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 Failure, Acute: A clinical syndrome characterized by a sudden decrease in glomerular filtration rate, often to values of less than 1 to 2 ml per minute. It is usually

associated with oliguria (urine volumes of less than 400 ml per day) and is always associated with biochemical consequences of the reduction in glomerular filtration rate such as a rise in blood urea nitrogen (BUN) and serum creatinine concentrations. [NIH]

Kidney Failure, Chronic: An irreversible and usually progressive reduction in renal function in which both kidneys have been damaged by a variety of diseases to the extent that they are unable to adequately remove the metabolic products from the blood and regulate the body's electrolyte composition and acid-base balance. Chronic kidney failure requires hemodialysis or surgery, usually kidney transplantation. [NIH]

Kidney Glomerulus: A cluster of convoluted capillaries beginning at each nephric tubule in the kidney and held together by connective tissue. [NIH]

Kidney Transplantation: The transference of a kidney from one human or animal to another. [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]

Lag: The time elapsing between application of a stimulus and the resulting reaction. [NIH]

Laminin: Large, noncollagenous glycoprotein with antigenic properties. It is localized in the basement membrane lamina lucida and functions to bind epithelial cells to the basement membrane. Evidence suggests that the protein plays a role in tumor invasion. [NIH]

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]

Latent: Phoria which occurs at one distance or another and which usually has no troublesome effect. [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]

Leiomyoma: A benign tumor derived from smooth muscle tissue, also known as a fibroid tumor. They rarely occur outside of the uterus and the gastrointestinal tract but can occur in the skin and subcutaneous tissues, probably arising from the smooth muscle of small blood vessels in these tissues. [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]

Lesion: An area of abnormal tissue change. [NIH]

Lethal: Deadly, fatal. [EU]

Leucocyte: All the white cells of the blood and their precursors (myeloid cell series, lymphoid cell series) but commonly used to indicate granulocytes exclusive of lymphocytes. [NIH]

Leukaemia: An acute or chronic disease of unknown cause in man and other warm-blooded animals that involves the blood-forming organs, is characterized by an abnormal increase in the number of leucocytes in the tissues of the body with or without a corresponding increase of those in the circulating blood, and is classified according of the type leucocyte most prominently involved. [EU]

Leukapheresis: The preparation of leukocyte concentrates with the return of red cells and leukocyte-poor plasma to the donor. [NIH]

Leukemia: Cancer of blood-forming tissue. [NIH]

Leukocyte Elastase: An enzyme that catalyzes the hydrolysis of proteins, including elastin. It cleaves preferentially bonds at the carboxyl side of Ala and Val, with greater specificity for Ala. EC 3.4.21.37. [NIH]

Leukocytes: White blood cells. These include granular leukocytes (basophils, eosinophils, and neutrophils) as well as non-granular leukocytes (lymphocytes and monocytes). [NIH]

Ligands: A RNA simulation method developed by the MIT. [NIH]

Ligation: Application of a ligature to tie a vessel or strangulate a part. [NIH]

Linkage: The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

Lipid: Fat. [NIH]

Lipid A: Lipid A is the biologically active component of lipopolysaccharides. It shows strong endotoxic activity and exhibits immunogenic properties. [NIH]

Lipodystrophy: A collection of rare conditions resulting from defective fat metabolism and characterized by atrophy of the subcutaneous fat. They include total, congenital or acquired, partial, abdominal infantile, and localized lipodystrophy. [NIH]

Lipopolysaccharide: Substance consisting of polysaccaride 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]

Lipoxygenase: An enzyme of the oxidoreductase class that catalyzes reactions between linoleate and other fatty acids and oxygen to form hydroperoxy-fatty acid derivatives. Related enzymes in this class include the arachidonate lipoxygenases, arachidonate 5-lipoxygenase, arachidonate 12-lipoxygenase, and arachidonate 15-lipoxygenase. EC 1.13.11.12. [NIH]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Liver Cirrhosis: Liver disease in which the normal microcirculation, the gross vascular anatomy, and the hepatic architecture have been variably destroyed and altered with fibrous septa surrounding regenerated or regenerating parenchymal nodules. [NIH]

Liver Transplantation: The transference of a part of or an entire liver from one human or animal to another. [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]

Lod: The lowest analyte content which, if actually present, will be detected with reasonable statistical certainty and can be identified according to the identification criteria of the method. If both accuracy and precision are constant over a concentration range. [NIH]

Lod Score: The total relative probability, expressed on a logarithmic scale, that a linkage relationship exists among selected loci. Lod is an acronym for "logarithmic odds." [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]

Low-density lipoprotein: Lipoprotein that contains most of the cholesterol in the blood. LDL carries cholesterol to the tissues of the body, including the arteries. A high level of LDL increases the risk of heart disease. LDL typically contains 60 to 70 percent of the total serum cholesterol and both are directly correlated with CHD risk. [NIH]

Lucida: An instrument, invented by Wollaton, consisting essentially of a prism or a mirror through which an object can be viewed so as to appear on a plane surface seen in direct view and on which the outline of the object may be traced. [NIH]

Lumbar: Pertaining to the loins, the part of the back between the thorax and the pelvis. [EU]

Lupus: A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

Lupus Nephritis: Glomerulonephritis associated with systemic lupus erythematosus. It is classified into four histologic types: mesangial, focal, diffuse, and membranous. [NIH]

Luxation: The displacement of the particular surface of a bone from its normal joint, without fracture. [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]

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 Depletion: Immunosuppression by reduction of circulating lymphocytes or by T-cell depletion of bone marrow. The former may be accomplished in vivo by thoracic duct drainage or administration of antilymphocyte serum. The latter is performed ex vivo on bone marrow before its transplantation. [NIH]

Lymphocytic: Referring to lymphocytes, a type of white blood cell. [NIH]

Lymphocytic Choriomeningitis Virus: The type species of arenavirus, part of the LCM-Lassa complex viruses, producing an inapparent infection in house and laboratory mice. In humans, infection with LCMV can be inapparent, or can present with an influenza-like illness, a benign aseptic meningitis, or a severe meningoencephalomyelitis. The virus can also infect monkeys, dogs, field mice, guinea pigs, and hamsters, the latter an epidemiologically important host. [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]

Lymphoproliferative: Disorders characterized by proliferation of lymphoid tissue, general

or unspecified. [NIH]

Lymphoproliferative Disorders: Disorders characterized by proliferation of lymphoid tissue, general or unspecified. [NIH]

Lysine: An essential amino acid. It is often added to animal feed. [NIH]

Lytic: 1. Pertaining to lysis or to a lysin. 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]

Macula: A stain, spot, or thickening. Often used alone to refer to the macula retinae. [EU]

Macula Lutea: An oval area in the retina, 3 to 5 mm in diameter, usually located temporal to the superior pole of the eye and slightly below the level of the optic disk. [NIH]

Macular Degeneration: Degenerative changes in the macula lutea of the retina. [NIH]

Malaise: A vague feeling of bodily discomfort. [EU]

Malformation: A morphologic defect resulting from an intrinsically abnormal developmental process. [EU]

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]

Malignant mesothelioma: A rare type of cancer in which malignant cells are found in the sac lining the chest or abdomen. Exposure to airborne asbestos particles increases one's risk of developing malignant mesothelioma. [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]

Matrix metalloproteinase: A member of a group of enzymes that can break down proteins, such as collagen, that are normally found in the spaces between cells in tissues (i.e., extracellular matrix proteins). Because these enzymes need zinc or calcium atoms to work properly, they are called metalloproteinases. Matrix metalloproteinases are involved in wound healing, angiogenesis, and tumor cell metastasis. [NIH]

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]

Melanin: The substance that gives the skin its color. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

Membranoproliferative: A disease that occurs primarily in children and young adults. Over time, inflammation leads to scarring in the glomeruli, causing proteinuria, hematuria, and sometimes chronic renal failure or end-stage renal disease. [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]

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]

Mental: Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

Mental Health: The state wherein the person is well adjusted. [NIH]

Mental Processes: Conceptual functions or thinking in all its forms. [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]

Mercuric Chloride: Mercury chloride (HgCl2). A highly toxic compound that volatizes slightly at ordinary temperature and appreciably at 100 degrees C. It is corrosive to mucous membranes and used as a topical antiseptic and disinfectant. [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]

Mesothelioma: A benign (noncancerous) or malignant (cancerous) tumor affecting the lining of the chest or abdomen. Exposure to asbestos particles in the air increases the risk of developing malignant mesothelioma. [NIH]

Metabolic acidosis: (met-ah-BOL-ik as-id-O-sis): A condition in which the blood is too acidic. It may be caused by severe illness or sepsis (bacteria in the bloodstream). [NIH]

Metabolite: Any substance produced by metabolism or by a metabolic process. [EU]

Metastasis: The spread of cancer from one part of the body to another. Tumors formed from cells that have spread are called "secondary tumors" and contain cells that are like those in the original (primary) tumor. The plural is metastases. [NIH]

Methylprednisolone: (6 alpha,11 beta)-11,17,21-Trihydroxy-6-methylpregna-1,4-diene-3,2-dione. A prednisolone derivative which has pharmacological actions similar to prednisolone. [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, Transgenic: Laboratory mice that have been produced from a genetically manipulated egg or embryo. The technique involves microinjection of DNA fragments from another species into the nucleus of the fertilized egg. [NIH]

Microbe: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microbiology: The study of microorganisms such as fungi, bacteria, algae, archaea, and viruses. [NIH]

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]

Microfilaments: The smallest of the cytoskeletal filaments. They are composed chiefly of actin. [NIH]

Microorganism: An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms. [NIH]

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [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]

Minocycline: A semisynthetic antibiotic effective against tetracycline-resistant staphylococcus infections. [NIH]

Mitochondrial Swelling: Increase in volume of mitochondria due to an influx of fluid; it occurs in hypotonic solutions due to osmotic pressure and in isotonic solutions as a result of altered permeability of the membranes of respiring mitochondria. [NIH]

Mitogen-Activated Protein Kinase Kinases: A serine-threonine protein kinase family whose members are components in protein kinase cascades activated by diverse stimuli. These MAPK kinases phosphorylate mitogen-activated protein kinases and are themselves phosphorylated by MAP kinase kinase kinases. JNK kinases (also known as SAPK kinases) are a subfamily. EC 2.7.10.- [NIH]

Mitogen-Activated Protein Kinases: A superfamily of protein-serine-threonine kinases that are activated by diverse stimuli via protein kinase cascades. They are the final components of the cascades, activated by phosphorylation by mitogen-activated protein kinase kinases which in turn are activated by mitogen-activated protein kinase kinase kinases (MAP kinase kinase kinases). Families of these mitogen-activated protein kinases (MAPKs) include extracellular signal-regulated kinases (ERKs), stress-activated protein kinases (SAPKs) (also known as c-jun terminal kinases (JNKs)), and p38-mitogen-activated protein kinases. EC 2,7,1.- [NIH]

Mitosis: A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

Mitotic: Cell resulting from mitosis. [NIH]

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]

Modulator: A specific inductor that brings out characteristics peculiar to a definite region. [EU]

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]

Morphological: Relating to the configuration or the structure of live organs. [NIH]

Morphology: The science of the form and structure of organisms (plants, animals, and other forms of life). [NIH]

Motility: The ability to move spontaneously. [EU]

Motion Sickness: Sickness caused by motion, as sea sickness, train sickness, car sickness, and air sickness. [NIH]

Mucosa: A mucous membrane, or tunica mucosa. [EU]

Mucus: The viscous secretion of mucous membranes. It contains mucin, white blood cells, water, inorganic salts, and exfoliated cells. [NIH]

Multicystic Dysplastic Kidney: A severe form of dysplasia where the kidney typically appears as a bunch of grapes without a reniform configuration or calyceal drainage system. It occurs in-utero and is the most common form of nongenetic renal cystic disease. [NIH]

Multivalent: Pertaining to a group of 5 or more homologous or partly homologous chromosomes during the zygotene stage of prophase to first metaphasis in meiosis. [NIH]

Multivariate Analysis: A set of techniques used when variation in several variables has to be studied simultaneously. In statistics, multivariate analysis is interpreted as any analytic method that allows simultaneous study of two or more dependent variables. [NIH]

Muscle Fibers: Large single cells, either cylindrical or prismatic in shape, that form the basic unit of muscle tissue. They consist of a soft contractile substance enclosed in a tubular sheath. [NIH]

Muscle, Smooth, Vascular: The nonstriated, involuntary muscle tissue of blood vessels. [NIH]

Mutagenesis: Process of generating genetic mutations. It may occur spontaneously or be induced by mutagens. [NIH]

Mutagens: Chemical agents that increase the rate of genetic mutation by interfering with the function of nucleic acids. A clastogen is a specific mutagen that causes breaks in chromosomes. [NIH]

Mycophenolate mofetil: A drug that is being studied for its effectiveness in preventing graft-versus-host disease and autoimmune disorders. [NIH]

Myelin: The fatty substance that covers and protects nerves. [NIH]

Myeloid Cells: Cells which include the monocytes and the granulocytes. [NIH]

Myeloma: Cancer that arises in plasma cells, a type of white blood cell. [NIH]

Myocardial Reperfusion: Generally, restoration of blood supply to heart tissue which is ischemic due to decrease in normal blood supply. The decrease may result from any source including atherosclerotic obstruction, narrowing of the artery, or surgical clamping. Reperfusion can be induced to treat ischemia. Methods include chemical dissolution of an occluding thrombus, administration of vasodilator drugs, angioplasty, catheterization, and artery bypass graft surgery. However, it is thought that reperfusion can itself further damage the ischemic tissue, causing myocardial reperfusion injury. [NIH]

Myocardial Reperfusion Injury: Functional, metabolic, or structural changes in ischemic heart muscle thought to result from reperfusion to the ischemic areas. Changes can be fatal to muscle cells and may include edema with explosive cell swelling and disintegration, sarcolemma disruption, fragmentation of mitochondria, contraction band necrosis, enzyme washout, and calcium overload. Other damage may include hemorrhage and ventricular arrhythmias. One possible mechanism of damage is thought to be oxygen free radicals. Treatment currently includes the introduction of scavengers of oxygen free radicals, and injury is thought to be prevented by warm blood cardioplegic infusion prior to reperfusion. [NIH]

Myocardium: The muscle tissue of the heart composed of striated, involuntary muscle known as cardiac muscle. [NIH]

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]

Myositis: Inflammation of a voluntary muscle. [EU]

Naphthaleneacetic Acids: Naphthalene derivatives containing the -CH2CCO2H radical at the 1-position, the 2-position, or both. Compounds are used as plant growth regulators to delay sprouting, exert weed control, thin fruit, etc. [NIH]

Naproxen: An anti-inflammatory agent with analgesic and antipyretic properties. Both the acid and its sodium salt are used in the treatment of rheumatoid arthritis and other rheumatic or musculoskeletal disorders, dysmenorrhea, and acute gout. [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]

Necrosis: A pathological process caused by the progressive degradative action of enzymes that is generally associated with severe cellular trauma. It is characterized by mitochondrial swelling, nuclear flocculation, uncontrolled cell lysis, and ultimately cell death. [NIH]

Neonatal: Pertaining to the first four weeks after birth. [EU]

Neoplasms: New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms. [NIH]

Neoplastic: Pertaining to or like a neoplasm (= any new and abnormal growth); pertaining

to neoplasia (= the formation of a neoplasm). [EU]

Neopterin: A pteridine derivative present in body fluids; elevated levels result from immune system activation, malignant disease, allograft rejection, and viral infections. (From Stedman, 26th ed) Neopterin also serves as a precursor in the biosynthesis of biopterin. [NIH]

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]

Nephrons: The functional units of the kidney, consisting of the glomerulus and the attached tubule. [NIH]

Nephropathy: Disease of the kidneys. [EU]

Nephrosis: Descriptive histopathologic term for renal disease without an inflammatory component. [NIH]

Nephrotic: Pertaining to, resembling, or caused by nephrosis. [EU]

Nephrotic Syndrome: Clinical association of heavy proteinuria, hypoalbuminemia, and generalized edema. [NIH]

Nephrotoxic: Toxic or destructive to kidney cells. [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 neutral 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]

Neuroendocrine: Having to do with the interactions between the nervous system and the endocrine system. Describes certain cells that release hormones into the blood in response to stimulation of the nervous system. [NIH]

Neurologic: Having to do with nerves or the nervous system. [NIH]

Neuromuscular: Pertaining to muscles and nerves. [EU]

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]

Neurotransmitter: Any of a group of substances that are released on excitation from the axon terminal of a presynaptic neuron of the central or peripheral nervous system and travel across the synaptic cleft to either excite or inhibit the target cell. Among the many substances that have the properties of a neurotransmitter are acetylcholine, norepinephrine, epinephrine, dopamine, glycine, y-aminobutyrate, glutamic acid, substance P, enkephalins, endorphins, and serotonin. [EU]

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]

Neutropenia: An abnormal decrease in the number of neutrophils, a type of white blood cell. [NIH]

Neutrophil: A type of white blood cell. [NIH]

Neutrophil Activation: The process in which the neutrophil is stimulated by diverse substances, resulting in degranulation and/or generation of reactive oxygen products, and culminating in the destruction of invading pathogens. The stimulatory substances, including opsonized particles, immune complexes, and chemotactic factors, bind to specific cell-surface receptors on the neutrophil. [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]

Normotensive: 1. Characterized by normal tone, tension, or pressure, as by normal blood pressure. 2. A person with normal blood pressure. [EU]

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 Proteins: Proteins found in the nucleus of a cell. Do not confuse with nucleoproteins which are proteins conjugated with nucleic acids, that are not necessarily present in the nucleus. [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]

Nucleoproteins: Proteins conjugated with nucleic acids. [NIH]

Nucleosomes: The repeating structural units of chromatin, each consisting of approximately 200 base pairs of DNA wound around a protein core. This core is composed of the histones H2A, H2B, H3, and H4. [NIH]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Ocular: 1. Of, pertaining to, or affecting the eye. 2. Eyepiece. [EU]

Odour: A volatile emanation that is perceived by the sense of smell. [EU]

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]

Oliguria: Clinical manifestation of the urinary system consisting of a decrease in the amount of urine secreted. [NIH]

Omega-3 fatty acid: A type of fat obtained in the diet and involved in immunity. [NIH]

Omentum: A fold of the peritoneum (the thin tissue that lines the abdomen) that surrounds the stomach and other organs in the abdomen. [NIH]

Oncogenic: Chemical, viral, radioactive or other agent that causes cancer; carcinogenic. [NIH]

Opacity: Degree of density (area most dense taken for reading). [NIH]

Opsin: A protein formed, together with retinene, by the chemical breakdown of meta-rhodopsin. [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]

Optic nerve head: The circular area (disc) where the optic nerve connects to the retina. [NIH]

Organ Culture: The growth in aseptic culture of plant organs such as roots or shoots, beginning with organ primordia or segments and maintaining the characteristics of the organ. [NIH]

Organelles: Specific particles of membrane-bound organized living substances present in eukaryotic cells, such as the mitochondria; the golgi apparatus; endoplasmic reticulum; lysomomes; plastids; and vacuoles. [NIH]

Organogenesis: Clonal propagation which involves culturing explants from roots, leaves, or stems to form undifferentiated callus tissue; after the cells form shoots, they are separated and rooted. Alternatively, if the callus is put in liquid culture, somatic embryos form. [NIH]

Osmosis: Tendency of fluids (e.g., water) to move from the less concentrated to the more concentrated side of a semipermeable membrane. [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]

Osmotic Fragility: Red blood cell sensitivity to change in osmotic pressure. When exposed to a hypotonic concentration of sodium in a solution, red cells take in more water, swell until the capacity of the cell membrane is exceeded, and burst. [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]

Overexpress: An excess of a particular protein on the surface of a cell. [NIH]

Oxidants: Oxidizing agents or electron-accepting molecules in chemical reactions in which electrons are transferred from one molecule to another (oxidation-reduction). In vivo, it

appears that phagocyte-generated oxidants function as tumor promoters or cocarcinogens rather than as complete carcinogens perhaps because of the high levels of endogenous antioxidant defenses. It is also thought that oxidative damage in joints may trigger the autoimmune response that characterizes the persistence of the rheumatoid disease process. [NIH]

Oxidation: The act of oxidizing or state of being oxidized. Chemically it consists in the increase of positive charges on an atom or the loss of negative charges. Most biological oxidations are accomplished by the removal of a pair of hydrogen atoms (dehydrogenation) from a molecule. Such oxidations must be accompanied by reduction of an acceptor molecule. Univalent o. indicates loss of one electron; divalent o., the loss of two electrons. [EU]

Oxidation-Reduction: A chemical reaction in which an electron is transferred from one molecule to another. The electron-donating molecule is the reducing agent or reductant; the electron-accepting molecule is the oxidizing agent or oxidant. Reducing and oxidizing agents function as conjugate reductant-oxidant pairs or redox pairs (Lehninger, Principles of Biochemistry, 1982, p471). [NIH]

Oxygenase: Enzyme which breaks down heme, the iron-containing oxygen-carrying constituent of the red blood cells. [NIH]

Palliative: 1. Affording relief, but not cure. 2. An alleviating medicine. [EU]

Pancreas: A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the Islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

Pancreatic: Having to do with the pancreas. [NIH]

Pancreatic Juice: The fluid containing digestive enzymes secreted by the pancreas in response to food in the duodenum. [NIH]

Parasite: An animal or a plant that lives on or in an organism of another species and gets at least some of its nutrition from that other organism. [NIH]

Parasitic: Having to do with or being a parasite. A parasite is an animal or a plant that lives on or in an organism of another species and gets at least some of its nutrients from it. [NIH]

Parathyroid: 1. Situated beside the thyroid gland. 2. One of the parathyroid glands. 3. A sterile preparation of the water-soluble principle(s) of the parathyroid glands, ad-ministered parenterally as an antihypocalcaemic, especially in the treatment of acute hypoparathyroidism with tetany. [EU]

Parathyroid hormone: A substance made by the parathyroid gland that helps the body store and use calcium. Also called parathormone, parathyrin, or PTH. [NIH]

Parenchyma: The essential elements of an organ; used in anatomical nomenclature as a general term to designate the functional elements of an organ, as distinguished from its framework, or stroma. [EU]

Parotid: The space that contains the parotid gland, the facial nerve, the external carotid artery, and the retromandibular vein. [NIH]

Partial remission: The shrinking, but not complete disappearance, of a tumor in response to therapy. Also called partial response. [NIH]

Particle: A tiny mass of material. [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]

Pathophysiology: Altered functions in an individual or an organ due to disease. [NIH]

Patient Education: The teaching or training of patients concerning their own health needs. [NIH]

Pelvic: Pertaining to the pelvis. [EU]

Pelvis: The lower part of the abdomen, located between the hip bones. [NIH]

Penicillin: An antibiotic drug used to treat infection. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Perciformes: The most diversified of all fish orders and the largest vertebrate order. It includes many of the commonly known fish such as porgies, croakers, mullets, dolphin fish, etc. [NIH]

Pericarditis: Inflammation of the pericardium. [EU]

Pericytes: Smooth muscle cell that wraps around normal blood vessels. [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]

Peripheral blood: Blood circulating throughout the body. [NIH]

Peripheral Nerves: The nerves outside of the brain and spinal cord, including the autonomic, cranial, and spinal nerves. Peripheral nerves contain non-neuronal cells and connective tissue as well as axons. The connective tissue layers include, from the outside to the inside, the epineurium, the perineurium, and the endoneurium. [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]

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]

Peritonitis: Inflammation of the peritoneum; a condition marked by exudations in the peritoneum of serum, fibrin, cells, and pus. It is attended by abdominal pain and tenderness, constipation, vomiting, and moderate fever. [EU]

Phagocyte: An immune system cell that can surround and kill microorganisms and remove dead cells. Phagocytes include macrophages. [NIH]

Phagocytosis: The engulfing of microorganisms, other cells, and foreign particles by phagocytic cells. [NIH]

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]

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]

Phenylalanine: An aromatic amino acid that is essential in the animal diet. It is a precursor of melanin, dopamine, noradrenalin, and thyroxine. [NIH]

Phorbol: Class of chemicals that promotes the development of tumors. [NIH]

Phosphatidic Acids: Fatty acid derivatives of glycerophosphates. They are composed of glycerol bound in ester linkage with 1 mole of phosphoric acid at the terminal 3-hydroxyl group and with 2 moles of fatty acids at the other two hydroxyl groups. [NIH]

Phosphatidylinositols: Derivatives of phosphatidic acids in which the phosphoric acid is bound in ester linkage to the hexahydroxy alcohol, myo-inositol. Complete hydrolysis yields 1 mole of glycerol, phosphoric acid, myo-inositol, and 2 moles of fatty acids. [NIH]

Phosphodiesterase: Effector enzyme that regulates the levels of a second messenger, the cyclic GMP. [NIH]

Phospholipids: Lipids containing one or more phosphate groups, particularly those derived from either glycerol (phosphoglycerides; glycerophospholipids) or sphingosine (sphingolipids). They are polar lipids that are of great importance for the structure and function of cell membranes and are the most abundant of membrane lipids, although not stored in large amounts in the system. [NIH]

Phosphorus: A non-metallic element that is found in the blood, muscles, nevers, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

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]

Photoreceptor: Receptor capable of being activated by light stimuli, as a rod or cone cell of the eye. [NIH]

Physicochemical: Pertaining to physics and chemistry. [EU]

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]

Pigments: Any normal or abnormal coloring matter in plants, animals, or micro-organisms. [NIH]

Piroxicam: 4-Hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide. A non-steroidal anti-inflammatory agent that is well established in the treatment of rheumatoid arthritis and osteoarthritis. Its usefulness has also been demonstrated in the treatment of musculoskeletal disorders, dysmenorrhea, and postoperative pain. Its long half-life enables it to be administered once daily. The drug has also been shown to be

effective if administered rectally. Gastrointestinal complaints are the most frequently reported side effects. [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]

Plant Growth Regulators: Any of the hormones produced naturally in plants and active in controlling growth and other functions. There are three primary classes: auxins, cytokinins, and gibberellins. [NIH]

Plant Oils: Oils derived from plants or plant products. [NIH]

Plants: Multicellular, eukaryotic life forms of the kingdom Plantae. They are characterized by a mainly photosynthetic mode of nutrition; essentially unlimited growth at localized regions of cell divisions (meristems); cellulose within cells providing rigidity; the absence of organs of locomotion; absense of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plasma: The clear, yellowish, fluid part of the blood that carries the blood cells. The proteins that form blood clots are in plasma. [NIH]

Plasma cells: A type of white blood cell that produces antibodies. [NIH]

Plasmapheresis: Procedure whereby plasma is separated and extracted from anticoagulated whole blood and the red cells retransfused to the donor. Plasmapheresis is also employed for therapeutic use. [NIH]

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]

Platelet-Derived Growth Factor: Mitogenic peptide growth hormone carried in the alpha-granules of platelets. It is released when platelets adhere to traumatized tissues. Connective

tissue cells near the traumatized region respond by initiating the process of replication. [NIH]

Plateletpheresis: The preparation of platelet concentrates with the return of red cells and platelet-poor plasma to the donor. [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]

Poisoning: A condition or physical state produced by the ingestion, injection or inhalation of, or exposure to a deleterious agent. [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]

Polycystic: An inherited disorder characterized by many grape-like clusters of fluid-filled cysts that make both kidneys larger over time. These cysts take over and destroy working kidney tissue. PKD may cause chronic renal failure and end-stage renal disease. [NIH]

Polymorphism: The occurrence together of two or more distinct forms in the same population. [NIH]

Polymyxin: Basic polypeptide antibiotic group obtained from Bacillus polymyxa. They affect the cell membrane by detergent action and may cause neuromuscular and kidney damage. At least eleven different members of the polymyxin group have been identified, each designated by a letter. [NIH]

Polypeptide: A peptide which on hydrolysis yields more than two amino acids; called tripeptides, tetrapeptides, etc. according to the number of amino acids contained. [EU]

Polyradiculoneuropathy: Diseases characterized by injury or dysfunction involving multiple peripheral nerves and nerve roots. The process may primarily affect myelin or nerve axons. Two of the more common demyelinating forms are acute inflammatory polyradiculopathy (Guillain-Barre syndrome) and polyradiculoneuropathy, chronic inflammatory demyelinating. Polyradiculoneuritis refers to inflammation of multiple peripheral nerves and spinal nerve roots. [NIH]

Polyradiculopathy: Disease or injury involving multiple spinal nerve roots. Polyradiculitis refers to inflammation of multiple spinal nerve roots. [NIH]

Polysaccharide: A type of carbohydrate. It contains sugar molecules that are linked together chemically. [NIH]

Polyunsaturated fat: An unsaturated fat found in greatest amounts in foods derived from plants, including safflower, sunflower, corn, and soybean oils. [NIH]

Posterior: Situated in back of, or in the back part of, or affecting the back or dorsal surface of the body. In lower animals, it refers to the caudal end of the body. [EU]

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]

Postoperative: After surgery. [NIH]

Potentiate: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [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 throughout 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]

Precipitating Factors: Factors associated with the definitive onset of a disease, illness, accident, behavioral response, or course of action. Usually one factor is more important or more obviously recognizable than others, if several are involved, and one may often be regarded as "necessary". Examples include exposure to specific disease; amount or level of an infectious organism, drug, or noxious agent, etc. [NIH]

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]

Preeclampsia: A toxaemia of late pregnancy characterized by hypertension, edema, and proteinuria, when convulsions and coma are associated, it is called eclampsia. [EU]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

Prevalence: The total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time. [NIH]

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]

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 antiovulatory agent when administered on days 5-25 of the menstrual cycle. [NIH]

Prognostic factor: A situation or condition, or a characteristic of a patient, that can be used to estimate the chance of recovery from a disease, or the chance of the disease recurring (coming back). [NIH]

Progression: Increase in the size of a tumor or spread of cancer in the body. [NIH]

Progressive: Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

Proline: A non-essential amino acid that is synthesized from glutamic acid. It is an essential component of collagen and is important for proper functioning of joints and tendons. [NIH]

Promoter: A chemical substance that increases the activity of a carcinogenic process. [NIH]

Prone: Having the front portion of the body downwards. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Prostaglandins: A group of compounds derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway. They are extremely potent mediators of a diverse group of physiological processes. [NIH]

Prostaglandins A: (13E,15S)-15-Hydroxy-9-oxoprosta-10,13-dien-1-oic acid (PGA(1)); (5Z,13E,15S)-15-hydroxy-9-oxoprosta-5,10,13-trien-1-oic acid (PGA(2)); (5Z,13E,15S,17Z)-15-hydroxy-9-oxoprosta-5,10,13,17-tetraen-1-oic acid (PGA(3)). A group of naturally occurring secondary prostaglandins derived from PGE. PGA(1) and PGA(2) as well as their 19-hydroxy derivatives are found in many organs and tissues. [NIH]

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 Isoforms: Different forms of a protein that may be produced from different genes, or from the same gene by alternative splicing. [NIH]

Protein Kinase C: An enzyme that phosphorylates proteins on serine or threonine residues in the presence of physiological concentrations of calcium and membrane phospholipids. The additional presence of diacylglycerols markedly increases its sensitivity to both calcium and phospholipids. The sensitivity of the enzyme can also be increased by phorbol esters and it is believed that protein kinase C is the receptor protein of tumor-promoting phorbol esters. EC 2.7.1.-. [NIH]

Protein Kinases: A family of enzymes that catalyze the conversion of ATP and a protein to ADP and a phosphoprotein. EC 2.7.1.37. [NIH]

Protein S: The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

Proteins: Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

Protein-Serine-Threonine Kinases: A group of enzymes that catalyzes the phosphorylation of serine or threonine residues in proteins, with ATP or other nucleotides as phosphate

donors. EC 2.7.10. [NIH]

Proteinuria: The presence of protein in the urine, indicating that the kidneys are not working properly. [NIH]

Proteoglycan: A molecule that contains both protein and glycosaminoglycans, which are a type of polysaccharide. Proteoglycans are found in cartilage and other connective tissues. [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]

Pruritus: An intense itching sensation that produces the urge to rub or scratch the skin to obtain relief. [NIH]

Psychology: The science dealing with the study of mental processes and behavior in man and animals. [NIH]

Public Health: Branch of medicine concerned with the prevention and control of disease and disability, and the promotion of physical and mental health of the population on the international, national, state, or municipal level. [NIH]

Public Policy: A course or method of action selected, usually by a government, from among alternatives to guide and determine present and future decisions. [NIH]

Publishing: "The business or profession of the commercial production and issuance of literature" (Webster's 3d). It includes the publisher, publication processes, editing and editors. Production may be by conventional printing methods or by electronic publishing. [NIH]

Pulmonary: Relating to the lungs. [NIH]

Pulmonary Artery: The short wide vessel arising from the conus arteriosus of the right ventricle and conveying unaerated blood to the lungs. [NIH]

Pulmonary Edema: An accumulation of an excessive amount of watery fluid in the lungs, may be caused by acute exposure to dangerous concentrations of irritant gasses. [NIH]

Pulmonary Embolism: Embolism in the pulmonary artery or one of its branches. [NIH]

Pulmonary Fibrosis: Chronic inflammation and progressive fibrosis of the pulmonary alveolar walls, with steadily progressive dyspnea, resulting finally in death from oxygen lack or right heart failure. [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]

Pustular: Pertaining to or of the nature of a pustule; consisting of pustules (= a visible collection of pus within or beneath the epidermis). [EU]

Pyelonephritis: Inflammation of the kidney and its pelvis, beginning in the interstitium and rapidly extending to involve the tubules, glomeruli, and blood vessels; due to bacterial infection. [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 Health Care: The levels of excellence which characterize the health service or health care provided based on accepted standards of quality. [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]

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]

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]

Ramipril: A long-acting angiotensin-converting enzyme inhibitor. It is a prodrug that is transformed in the liver to its active metabolite ramiprilat. [NIH]

Random Allocation: A process involving chance used in therapeutic trials or other research endeavor for allocating experimental subjects, human or animal, between treatment and control groups, or among treatment groups. It may also apply to experiments on inanimate objects. [NIH]

Randomization: Also called random allocation. Is allocation of individuals to groups, e.g., for experimental and control regimens, by chance. Within the limits of chance variation, random allocation should make the control and experimental groups similar at the start of an investigation and ensure that personal judgment and prejudices of the investigator do not influence allocation. [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]

Reactive Oxygen Species: Reactive intermediate oxygen species including both radicals and non-radicals. These substances are constantly formed in the human body and have been shown to kill bacteria and inactivate proteins, and have been implicated in a number of diseases. Scientific data exist that link the reactive oxygen species produced by inflammatory phagocytes to cancer development. [NIH]

Reading Frames: The sequence of codons by which translation may occur. A segment of mRNA 5'AUCCGA3' could be translated in three reading frames, 5'AUC. or 5'UCC. or 5'CCG., depending on the location of the start codon. [NIH]

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]

Receptors, Serotonin: Cell-surface proteins that bind serotonin and trigger intracellular changes which influence the behavior of cells. Several types of serotonin receptors have been recognized which differ in their pharmacology, molecular biology, and mode of action. [NIH]

Receptors, Transforming Growth Factor beta: Cell-surface proteins that bind transforming growth factor beta and trigger changes influencing the behavior of cells. Two types of transforming growth factor receptors have been recognized. They differ in affinity for different members of the transforming growth factor beta family and in cellular mechanisms of action. [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]

Recombinant Proteins: Proteins prepared by recombinant DNA technology. [NIH]

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]

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]

Relapse: The return of signs and symptoms of cancer after a period of improvement. [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 Artery: A branch of the abdominal aorta which supplies the kidneys, adrenal glands and ureters. [NIH]

Renal failure: Progressive renal insufficiency and uremia, due to irreversible and progressive renal glomerular tubular or interstitial disease. [NIH]

Renal Replacement Therapy: Procedures which temporarily or permanently remedy insufficient cleansing of body fluids by the kidneys. [NIH]

Renal tubular: A defect in the kidneys that hinders their normal excretion of acids. Failure to excrete acids can lead to weak bones, kidney stones, and poor growth in children. [NIH]

Renal vein thrombosis: Blood clots in the vessel that carries blood away from the kidney. This can occur in people with the nephrotic syndrome. [NIH]

Renin: An enzyme which is secreted by the kidney and is formed from prorenin in plasma and kidney. The enzyme cleaves the Leu-Leu bond in angiotensinogen to generate angiotensin I. EC 3.4.23.15. (Formerly EC 3.4.99.19). [NIH]

Renin-Angiotensin System: A system consisting of renin, angiotensin-converting enzyme, and angiotensin II. Renin, an enzyme produced in the kidney, acts on angiotensinogen, an alpha-2 globulin produced by the liver, forming angiotensin I. The converting enzyme contained in the lung acts on angiotensin I in the plasma converting it to angiotensin II, the most powerful directly pressor substance known. It causes contraction of the arteriolar smooth muscle and has other indirect actions mediated through the adrenal cortex. [NIH]

Reperfusion: Restoration of blood supply to tissue which is ischemic due to decrease in normal blood supply. The decrease may result from any source including atherosclerotic obstruction, narrowing of the artery, or surgical clamping. It is primarily a procedure for treating infarction or other ischemia, by enabling viable ischemic tissue to recover, thus limiting further necrosis. However, it is thought that reperfusion can itself further damage the ischemic tissue, causing reperfusion injury. [NIH]

Reperfusion Injury: Functional, metabolic, or structural changes, including necrosis, in ischemic tissues thought to result from reperfusion to ischemic areas of the tissue. The most common instance is myocardial reperfusion injury. [NIH]

Resorption: The loss of substance through physiologic or pathologic means, such as loss of dentin and cementum of a tooth, or of the alveolar process of the mandible or maxilla. [EU]

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 distress syndrome: A lung disease that occurs primarily in premature infants; the newborn must struggle for each breath and blueing of its skin reflects the baby's inability to get enough oxygen. [NIH]

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]

Retinae: A congenital notch or cleft of the retina, usually located inferiorly. [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]

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]

Retroperitoneal: Having to do with the area outside or behind the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). [NIH]

Retroperitoneal Fibrosis: A slowly progressive condition of unknown etiology, characterized by deposition of fibrous tissue in the retroperitoneal space compressing the ureters, great vessels, bile duct, and other structures. When associated with abdominal aortic aneurysm, it may be called chronic periaortitis or inflammatory perianeurysmal fibrosis. [NIH]

Retroperitoneal Space: An area occupying the most posterior aspect of the abdominal cavity. It is bounded laterally by the borders of the quadratus lumborum muscles and extends from the diaphragm to the brim of the true pelvis, where it continues as the pelvic extraperitoneal space. [NIH]

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]

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]

Ribavirin: 1-beta-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide. A nucleoside antimetabolite antiviral agent that blocks nucleic acid synthesis and is used against both RNA and DNA viruses. [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]

Rod: A reception for vision, located in the retina. [NIH]

Salicylate: Non-steroidal anti-inflammatory drugs. [NIH]

Saline: A solution of salt and water. [NIH]

Salivary: The duct that convey saliva to the mouth. [NIH]

Salivary glands: Glands in the mouth that produce saliva. [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]

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]

Scleroderma: A chronic disorder marked by hardening and thickening of the skin. Scleroderma can be localized or it can affect the entire body (systemic). [NIH]

Sclerosis: A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Sea Bream: A species of perciformes commonly used in saline aquaculture. [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]

Sediment: A precipitate, especially one that is formed spontaneously. [EU]

Sedimentation: The act of causing the deposit of sediment, especially by the use of a centrifugal machine. [EU]

Segmental: Describing or pertaining to a structure which is repeated in similar form in successive segments of an organism, or which is undergoing segmentation. [NIH]

Segmentation: The process by which muscles in the intestines move food and wastes through the body. [NIH]

Segregation: The separation in meiotic cell division of homologous chromosome pairs and their contained allelomorphic gene pairs. [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]

Senna: Preparations of Cassia senna L. and C. angustifolia of the Leguminosae. They contain sennosides, which are anthraquinone type cathartics and are used in many different preparations as laxatives. [NIH]

Sepsis: The presence of bacteria in the bloodstream. [NIH]

Septic: Produced by or due to decomposition by microorganisms; putrefactive. [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]

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]

Serologic: Analysis of a person's serum, especially specific immune or lytic serums. [NIH]

Serositis: Inflammation of a serous membrane. [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]

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]

Shunt: A surgically created diversion of fluid (e.g., blood or cerebrospinal fluid) from one area of the body to another area of the body. [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]

Signs and Symptoms: Clinical manifestations that can be either objective when observed by a physician, or subjective when perceived by the patient. [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]

Smoking Cessation: Discontinuation of the habit of smoking, the inhaling and exhaling of tobacco smoke. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Smooth Muscle Tumor: A tumor composed of smooth muscle tissue, as opposed to leiomyoma, a tumor derived from smooth muscle. [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]

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]

Sodium salicylate: A drug that belongs to the family of drugs called nonsteroidal anti-inflammatory drugs. Sodium salicylate may be tolerated by people who are sensitive to aspirin. [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 mutations: Alterations in DNA that occur after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases. [NIH]

Somatostatin: A polypeptide hormone produced in the hypothalamus, and other tissues and organs. It inhibits the release of human growth hormone, and also modulates important physiological functions of the kidney, pancreas, and gastrointestinal tract. Somatostatin receptors are widely expressed throughout the body. Somatostatin also acts as a neurotransmitter in the central and peripheral nervous systems. [NIH]

Soybean Oil: Oil from soybean or soybean plant. [NIH]

Specialist: In medicine, one who concentrates on 1 special branch of medical science. [NIH]

Species: A taxonomic category subordinate to a genus (or subgenus) and superior to a subspecies or variety, composed of individuals possessing common characters distinguishing them from other categories of individuals of the same taxonomic level. In taxonomic nomenclature, species are designated by the genus name followed by a Latin or Latinized adjective or noun. [EU]

Specificity: Degree of selectivity shown by an antibody with respect to the number and types of antigens with which the antibody combines, as well as with respect to the rates and the extents of these reactions. [NIH]

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]

Spinal Nerve Roots: The paired bundles of nerve fibers entering and leaving the spinal cord

at each segment. The dorsal and ventral nerve roots join to form the mixed segmental spinal nerves. The dorsal roots are generally afferent, formed by the central projections of the spinal (dorsal root) ganglia sensory cells, and the ventral roots efferent, comprising the axons of spinal motor and autonomic preganglionic neurons. There are, however, some exceptions to this afferent/efferent rule. [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]

Sprue: A non febrile tropical disease of uncertain origin. [NIH]

Stabilization: The creation of a stable state. [EU]

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]

Staphylococcus aureus: Potentially pathogenic bacteria found in nasal membranes, skin, hair follicles, and perineum of warm-blooded animals. They may cause a wide range of infections and intoxications. [NIH]

Stellate: Star shaped. [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]

Stenosis: Narrowing or stricture of a duct or canal. [EU]

Sterile: Unable to produce children. [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]

Stool: The waste matter discharged in a bowel movement; feces. [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]

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 Fibers: Bundles of actin filaments (microfilaments) and myosin-II that span across the cell attaching to the cell membrane at focal adhesions and to the network of intermediate filaments that surrounds the nucleus. [NIH]

Stricture: The abnormal narrowing of a body opening. Also called stenosis. [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]

Subacute: Somewhat acute; between acute and chronic. [EU]

Subclinical: Without clinical manifestations; said of the early stage(s) of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests, or of a very mild form of an infection or other disease or abnormality. [EU]

Subcutaneous: Beneath the skin. [NIH]

Subspecies: A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

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]

Suction: The removal of secretions, gas or fluid from hollow or tubular organs or cavities by means of a tube and a device that acts on negative pressure. [NIH]

Sulfur: An element that is a member of the chalcogen family. It has an atomic symbol S, atomic number 16, and atomic weight 32.066. It is found in the amino acids cysteine and methionine. [NIH]

Sulindac: A sulfinylindene derivative whose sulfinyl moiety is converted in vivo to an active anti-inflammatory analgesic that undergoes enterohepatic circulation to maintain constant blood levels without causing gastrointestinal side effects. [NIH]

Supplementation: Adding nutrients to the diet. [NIH]

Support group: A group of people with similar disease who meet to discuss how better to cope with their cancer and treatment. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in which the process of exclusion is not conscious. [NIH]

Suppurative: Consisting of, containing, associated with, or identified by the formation of pus. [NIH]

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]

Survival Rate: The proportion of survivors in a group, e.g., of patients, studied and followed over a period, or the proportion of persons in a specified group alive at the beginning of a time interval who survive to the end of the interval. It is often studied using life table methods. [NIH]

Systemic: Affecting the entire body. [NIH]

Systemic lupus erythematosus: SLE. A chronic inflammatory connective tissue disease marked by skin rashes, joint pain and swelling, inflammation of the kidneys, inflammation of the fibrous tissue surrounding the heart (i.e., the pericardium), as well as other problems. Not all affected individuals display all of these problems. May be referred to as lupus. [NIH]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

Telangiectasia: The permanent enlargement of blood vessels, causing redness in the skin or mucous membranes. [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]

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]

Thioredoxin: A hydrogen-carrying protein that participates in a variety of biochemical reactions including ribonucleotide reduction. Thioredoxin is oxidized from a dithiol to a disulfide during ribonucleotide reduction. The disulfide form is then reduced by NADPH in a reaction catalyzed by thioredoxin reductase. [NIH]

Thoracic: Having to do with the chest. [NIH]

Threonine: An essential amino acid occurring naturally in the L-form, which is the active form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

Threshold: For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [NIH]

Thrombin: An enzyme formed from prothrombin that converts fibrinogen to fibrin. (Dorland, 27th ed) EC 3.4.21.5. [NIH]

Thrombocytes: Blood cells that help prevent bleeding by causing blood clots to form. Also called platelets. [NIH]

Thrombocytopenia: A decrease in the number of blood platelets. [NIH]

Thrombocytosis: Increased numbers of platelets in the peripheral blood. [EU]

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]

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]

Thymus: An organ that is part of the lymphatic system, in which T lymphocytes grow and multiply. The thymus is in the chest behind the breastbone. [NIH]

Thyroid: A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

Thyroid Gland: A highly vascular endocrine gland consisting of two lobes, one on either side of the trachea, joined by a narrow isthmus; it produces the thyroid hormones which are concerned in regulating the metabolic rate of the body. [NIH]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

Tissue Culture: Maintaining or growing of tissue, organ primordia, or the whole or part of an organ in vitro so as to preserve its architecture and/or function (Dorland, 28th ed). Tissue culture includes both organ culture and cell culture. [NIH]

Tolerance: 1. The ability to endure unusually large doses of a drug or toxin. 2. Acquired drug tolerance; a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response. [EU]

Tolmetin: An anti-inflammatory antipyretic and analgesic similar in mode of action to indomethacin. It has been proposed as an antirheumatic agent. [NIH]

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]

Tone: 1. The normal degree of vigour and tension; in muscle, the resistance to passive elongation or stretch; tonus. 2. A particular quality of sound or of voice. 3. To make permanent, or to change, the colour of silver stain by chemical treatment, usually with a heavy metal. [EU]

Tonus: A state of slight tension usually present in muscles even when they are not undergoing active contraction. [NIH]

Topical: On the surface of the body. [NIH]

Toxaemia: 1. The condition resulting from the spread of bacterial products (toxins) by the bloodstream. 2. A condition resulting from metabolic disturbances, e.g. toxaemia of pregnancy. [EU]

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]

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]

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 Failure: A measure of the quality of health care by assessment of unsuccessful results of management and procedures used in combating disease, in individual cases or series. [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]

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]

Tuberculosis: Any of the infectious diseases of man and other animals caused by species of Mycobacterium. [NIH]

Tumor Necrosis Factor: Serum glycoprotein produced by activated macrophages and other mammalian mononuclear leukocytes which has necrotizing activity against tumor cell lines and increases ability to reject tumor transplants. It mimics the action of endotoxin but differs from it. It has a molecular weight of less than 70,000 kDa. [NIH]

Typhoid fever: The most important member of the enteric group of fevers which also includes the paratyphoids. [NIH]

Typhoid fever: The most important member of the enteric group of fevers which also includes the paratyphoids. [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]

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]

Uraemia: 1. An excess in the blood of urea, creatinine, and other nitrogenous end products of protein and amino acids metabolism; more correctly referred to as azotemia. 2. In current usage the entire constellation of signs and symptoms of chronic renal failure, including nausea, vomiting anorexia, a metallic taste in the mouth, a uraemic odour of the breath, pruritus, uraemic frost on the skin, neuromuscular disorders, pain and twitching in the muscles, hypertension, edema, mental confusion, and acid-base and electrolyte imbalances. [EU]

Urea: A compound (CO(NH2)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]

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]

Urinate: To release urine from the bladder to the outside. [NIH]

Urine: Fluid containing water and waste products. Urine is made by the kidneys, stored in the bladder, and leaves the body through the urethra. [NIH]

Urology: A surgical specialty concerned with the study, diagnosis, and treatment of diseases of the urinary tract in both sexes and the genital tract in the male. It includes the specialty of andrology which addresses both male genital diseases and male infertility. [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]

Vaccination: Administration of vaccines to stimulate the host's immune response. This includes any preparation intended for active immunological prophylaxis. [NIH]

Vaccines: Suspensions of killed or attenuated microorganisms (bacteria, viruses, fungi, protozoa, or rickettsiae), antigenic proteins derived from them, or synthetic constructs, administered for the prevention, amelioration, or treatment of infectious and other diseases. [NIH]

Vacuoles: Any spaces or cavities within a cell. They may function in digestion, storage, secretion, or excretion. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vascular endothelial growth factor: VEGF. A substance made by cells that stimulates new blood vessel formation. [NIH]

Vasculitis: Inflammation of a blood vessel. [NIH]

Vasoactive: Exerting an effect upon the calibre of blood vessels. [EU]

Vasodilator: An agent that widens blood vessels. [NIH]

Vector: Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

Vein: Vessel-carrying blood from various parts of the body to the heart. [NIH]

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]

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]

Vesicoureteral: An abnormal condition in which urine backs up into the ureters, and occasionally into the kidneys, raising the risk of infection. [NIH]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Vimentin: An intermediate filament protein found in most differentiating cells, in cells grown in tissue culture, and in certain fully differentiated cells. Its insolubility suggests that it serves a structural function in the cytoplasm. MW 52,000. [NIH]

Vinca Alkaloids: A class of alkaloids from the genus of apocyanaceous woody herbs including periwinkles. They are some of the most useful antineoplastic agents. [NIH]

Vinorelbine: An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. [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]

Virulence: The degree of pathogenicity within a group or species of microorganisms or viruses as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. [NIH]

Virus: Submicroscopic organism that causes infectious disease. In cancer therapy, some viruses may be made into vaccines that help the body build an immune response to, and kill, tumor cells. [NIH]

Viscera: Any of the large interior organs in any one of the three great cavities of the body, especially in the abdomen. [NIH]

Vitamin A: A substance used in cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Vitro: Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

Vivo: Outside of or removed from the body of a living organism. [NIH]

White blood cell: A type of cell in the immune system that helps the body fight infection and disease. White blood cells include lymphocytes, granulocytes, macrophages, and others. [NIH]

Wound Healing: Restoration of integrity to traumatized tissue. [NIH]

Xenograft: The cells of one species transplanted to another species. [NIH]

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

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]

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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