Colchicine

A 3-in-1 Medical Reference

Medical Dictionary

Bibliography &

Annotated Research Guide

to Internet References

ICON Group International, Inc.

COLCHICINE

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

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

ICON Health Publications
ICON Group International, Inc.
4370 La Jolla Village Drive, 4th Floor
San Diego, CA 92122 USA

Printed in the United States of America.

Last digit indicates print number: 10 9 8 7 6 4 5 3 2 1

Publisher, Health Care: Philip Parker, Ph.D.
Editor(s): James Parker, M.D., Philip Parker, Ph.D.

Publisher's note: The ideas, procedures, and suggestions contained in this book are not intended for the diagnosis or treatment of a health problem. As new medical or scientific information becomes available from academic and clinical research, recommended treatments and drug therapies may undergo changes. The authors, editors, and publisher have attempted to make the information in this book up to date and accurate in accord with accepted standards at the time of publication. The authors, editors, and publisher are not responsible for errors or omissions or for consequences from application of the book, and make no warranty, expressed or implied, in regard to the contents of this book. Any practice described in this book should be applied by the reader in accordance with professional standards of care used in regard to the unique circumstances that may apply in each situation. The reader is advised to always check product information (package inserts) for changes and new information regarding dosage and contraindications before prescribing any drug or pharmacological product. Caution is especially urged when using new or infrequently ordered drugs, herbal remedies, vitamins and supplements, alternative therapies, complementary therapies and medicines, and integrative medical treatments.

Cataloging-in-Publication Data

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

Colchicine: A Medical Dictionary, Bibliography, and Annotated Research Guide to Internet References / James N. Parker and Philip M. Parker, editors
p. cm.
Includes bibliographical references, glossary, and index.
ISBN: 0-497-00278-7
1. Colchicine-Popular works. I. Title.

Disclaimer

This publication is not intended to be used for the diagnosis or treatment of a health problem. It is sold with the understanding that the publisher, editors, and authors are not engaging in the rendering of medical, psychological, financial, legal, or other professional services.

References to any entity, product, service, or source of information that may be contained in this publication should not be considered an endorsement, either direct or implied, by the publisher, editors, or authors. ICON Group International, Inc., the editors, and the authors are not responsible for the content of any Web pages or publications referenced in this publication.

Copyright Notice

Acknowledgements

The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on colchicine. 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.

About ICON Health Publications

To discover more about ICON Health Publications, simply check with your preferred online booksellers, including Barnes&Noble.com and Amazon.com which currently carry all of our titles. Or, feel free to contact us directly for bulk purchases or institutional discounts:

ICON Group International, Inc.
4370 La Jolla Village Drive, Fourth Floor
San Diego, CA 92122 USA
Fax: 858-546-4341
Web site: **www.icongrouponline.com/health**

Table of Contents

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 colchicine 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 colchicine, 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 colchicine, 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 colchicine. 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 colchicine, 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 colchicine.

The Editors

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

CHAPTER 1. STUDIES ON COLCHICINE

Overview

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

The Combined Health Information Database

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

- **Diagnosis and Management of Gout**

  Source: American Family Physician. 59(7): 1799-1806. April 1, 1999.

  Contact: Available from American Academy of Family Physicians. 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2672. (800) 274-2237. Website: www.aafp.org.

  Summary: Gout is a disease resulting from the deposition of urate crystals caused by the overproduction or underexcretion of uric acid. The disease is often, but not always, associated with elevated serum uric acid levels. This article reviews the diagnosis and management of gout. Clinical manifestations include acute and chronic arthritis, tophi (nodular masses of monosodium urate crystals deposited in the soft tissues of the body), interstitial renal disease, and uric acid nephrolithiasis (kidney stones). The diagnosis is based on the identification of uric acid crystals in joints, tissues, or body fluids. Because

patients with gout typically have hypertension and impaired renal function, examination of the renal and cardiovascular systems is essential. Treatment goals include termination of the acute attack, prevention of recurrent attacks, and prevention of complications associated with the deposition of urate crystals in tissues. Pharmacologic management remains the mainstay of treatment. Acute attacks may be terminated with the use of nonsteroidal antiinflammatory agents (NSAIDs), **colchicine,** or intra articular injections of corticosteroids. Probenicid, sulfinpyrazone, and allopurinol can be used to prevent recurrent attacks. The authors note that obesity, alcohol intake, and certain foods and medications can contribute to hyperuricemia. These potentially exacerbating factors should be identified and modified. A patient information handout on gout, written by the authors of this article, is provided on a separate page in this same journal issue. 6 figures. 2 tables. 24 references.

- **Renal Amyloidosis in a Drug Abuser**

  Source: Journal of the American Society of Nephrology. 5(9): 1653-1658. March 1995.

  Contact: Available from Williams and Wilkins. 428 East Preston Street, Baltimore, MD 21202-3993. (800) 638-6423.

  Summary: In this article, the authors present the case of a patient who had a history of subcutaneous cocaine and heroin use and who developed nephrotic syndrome, with an elevated serum creatinine and a creatinine clearance of 61 mL/min. Renal biopsy demonstrated amyloidosis. Treatment with **colchicine** was initiated, and proteinuria decreased to near normal levels after 12 months. Concomitant with the decrease in proteinuria, creatinine clearance improved, although a repeat renal biopsy failed to show any significant improvement in amyloid burden. The authors suggest that **colchicine** may be a useful treatment in reversing the proteinuria of renal amyloidosis associated with drug abuse. Furthermore, clinical improvement may occur before any demonstrable regression in the amyloidosis. 1 figure. 3 tables. 25 references.

- **Alcoholic Liver Disease: Latest Guidelines for Detecting and Managing**

  Source: Consultant. 39(3): 799-800, 805-807. March 1999.

  Contact: Available from Cliggott Publishing Company. 55 Holly Hill Lane, Box 4010, Greenwich, CT 06831-0010.

  Summary: More than 11,000 Americans die each year of alcoholic cirrhosis of the liver. This article briefly summarizes the latest guidelines from the American College of Gastroenterology for detecting and managing alcoholic liver disease (ALD). The article notes that the problem of ALD is aggravated both by an imperfect knowledge of its pathogenesis and natural course and by the frequent failure to identify patients who are at risk or have subclinical disease. Susceptibility to the different forms of ALD also varies greatly among heavy drinkers, as does the severity of the disease. The article reviews the CAGE questionnaire, a screening tool used for alcohol abuse and dependency. Among the physical findings that may accompany ALD are those related to portal hypertension (ascites, splenomegaly, abdominal wall collaterals, and venous hum), hepatic injury (cutaneous telangiectasia, palmar erythema, finger clubbing, Dupuytrens contracture, and peripheral neuropathy), and, in men, feminization. Laboratory findings are reviewed, and the article notes that liver biopsy may be warranted to confirm the diagnosis of ALD, to exclude other causes of liver disease, or to assess the extent of liver damage, refine the prognosis, and guide therapeutic decisions. The amount of alcohol consumed is the most important risk factor for the development of ALD. The article reviews the management of patients with ALD,

including nutritional therapy, propylthiouracil, **colchicine,** and liver transplantation. 1 figure. 3 tables. 13 references.

- **Alcoholic Liver Disease: The ACG's Recommendations**

  Source: Journal of Critical Illness. 14(5): 264-268. May 1999.

  Contact: Available from Cliggott Publishing Company. 55 Holly Hill Lane, Greenwich, CT 06831-0010. (203) 661-0600.

  Summary: The problem of alcoholic liver disease (ALD) is aggravated both by the imperfect knowledge of its pathogenesis and natural course and by the frequent failure to identify patients who are at risk or have subclinical disease. Guidelines for the management of ALD were developed for the Practice Parameters Committee of the American College of Gastroenterology and published recently in the American Journal of Gastroenterology. This article provides a brief summary of these recommendations, which address detection and diagnosis, risk factors and prognosis, nutritional therapy, the use of propylthiouracil (PTU), the use of **colchicine,** liver transplantation, and treating alcoholic hepatitis. The author includes the CAGE questionnaire as a screening tool for alcohol abuse and dependency. Laboratory findings characteristic of ALD include elevated levels of aspartate aminotransferase and of alinine aminotransferase. Liver biopsy may be warranted to confirm the diagnosis of ALD; to exclude other causes of liver disease; or to assess the extent of liver damage, refine the prognosis, and guide therapeutic decisions. The amount of alcohol consumed is the most important risk factor for the development of ALD. A number of studies have shown that it is worthwhile to use aggressive nutritional therapy in ALD to prevent protein calorie malnutrition. Generally, patients with mild alcoholic hepatitis need only supportive and symptomatic care, while the most severely ill patients may fail to respond to any treatment. Aggressive therapy is most likely to benefit those between these two extremes. 1 figure. 3 tables. 14 references.

- **Alcoholic Liver Disease: Treatment Strategies for the Potentially Reversible Stages**

  Source: Postgraduate Medicine. 103(4): 261-264, 267-268, 273-275. January 1998.

  Contact: Available from McGraw-Hill, Inc. 1221 Avenue of the Americas, New York, NY 10020. (612) 832-7869.

  Summary: This article reviews treatment strategies for the potentially reversible stages of alcoholic liver disease. The authors note that although liver damage resulting from heavy drinking may be subclinical for a long period, steatosis may begin after even minor bouts of overconsumption. If alcohol consumption continues, alcoholic liver disease often is fatal. The authors discuss classification, clinical presentation, laboratory findings, nutritional considerations, treatment strategies, nutritional support, the pathogenesis of alcoholic liver disease, steroid therapy, other drug therapies, and liver transplantation. Most patients with clinically significant alcoholic liver disease have histologic findings typical of steatosis, alcoholic hepatitis, and cirrhosis. Abstinence from alcohol, in combination with proper nutrition and general supportive care, is required. Steatosis is reversible upon withdrawal of alcohol, but alcoholic hepatitis can persist even with abstinence and may progress to cirrhosis. Corticosteroid therapy may reduce short term mortality rates in patients with moderate or severe alcoholic hepatitis who have hepatic encephalopathy but no evidence of infection or gastrointestinal bleeding. Treatment with **colchicine** may decrease the risk of cirrhosis; however, once cirrhosis has developed, the liver damage is irreversible. Liver transplantation may be considered in patients with severe complications. 4 figures. 1 table. 31 references.

- **Primary Biliary Cirrhosis**

  Source: New England Journal of Medicine. 335(21): 1570-1580. November 21, 1996.

  Summary: This review article covers primary biliary cirrhosis, a chronic, progressive cholestatic liver disease of unknown cause that usually affects middle-aged women and eventually leads to liver failure and the need for liver transplantation. The author reports on the recent advances in the natural history, pathogenesis, and treatment of primary biliary cirrhosis in detail; in addition, the pathological features, diagnosis, and clinical manifestations are briefly covered. The author describes various drug regimens used to treat primary biliary cirrhosis, noting that there is no generally accepted treatment for the underlying disease process, but the results with ursodiol, **colchicine,** and methotrexate are encouraging. Glucocortoids do not appear to improve the course of the disease and may worsen osteoporosis. Azathioprine has limited efficacy and is no longer used. Penicillamine, an agent that induces cupriuria and has some antiinflammatory actions, is ineffective and presents troublesome side effects. The most common symptom that is relatively specific for primary biliary cirrhosis is pruritis (itching). Cholestyramine resin (4 g three times per day orally) will relieve pruritus in most patients. 1 figure. 153 references.

Federally Funded Research on Colchicine

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

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

- **Project Title: ANGIOGENESIS FOLLOWING STROKE**

  Principal Investigator & Institution: Lyden, Patrick D.; Professor; Veterans Medical Research Fdn/San Diego Foundation of San Diego San Diego, Ca 92161

  Timing: Fiscal Year 2003; Project Start 15-DEC-2002; Project End 30-NOV-2006

  Summary: (provided by applicant): Although peptide angiogenic signals may promote new vessel formation, may offer neuroprotection, and may facilitate neuronal migration during recovery, our pilot data suggests a different function after ischemia: the brain may utilize angiogenic signaling only to subserve removal of necrotic debris, i.e., "clean-up". Our central hypothesis is that after ischemia, angiogenic growth factors are secreted

[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).

to open blood brain barrier, stimulate macrophage infiltration, and to create vascular channels for removal of necrotic debris. Our aims are: we will measure capillary and neuronal density 30 days after focal brain ischemia to establish whether ischemia stimulates persisting microvessels, preserves neurons, or both. Then we will determine if microvessel or neuronal densities can be augmented with intra-arterial infusions of VEGF or bFGF or both. Do Macrophages Influence the Growth of New Microvessls? We will block macrophage entry into the brain by depleting them (whole body irradiation) or inhibiting them (colchicine/chloroquine), and expect to see a marked reduction of both macrophages and microvessels near the ischemic zone. We will increase macrophage entry into the ischemic zone with tissue necrosis factor, macrophage inflammatory protein-I, or monocyte chemoattractant protein-1 and expect to find more microvessels and macrophages. We will inhibit VEGF activity immediately after ischemia with anti-VEGFR antibody, a VEGFR-Fc fusion protein, and a tyrosine kinase inhibitor specific for VEGFR. Does Angiopoietin-2 Signal Microvessel Degradation? We will provide VEGF beginning 10 days after stroke and continuing to 17 days after stroke, to blunt the degradation signal; we predict that microvessels will persist. We will administer a TIE-2 receptor-Fc binding protein from Day 10 to 17 after stroke to bind and remove TIE-2 ligands (especially Ang-2), again predicting that microvessels will persist. Does angiogenic signaling ameliorate cognitive deficit after stroke? Using a bioassay suited to studying pharmacological synergism, we will study protective effects of VEGF, bFGF, or both using a bioassay and a spatial navigation test.

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

- **Project Title: ASTHMA CLINICAL RESEARCH NETWORK**

  Principal Investigator & Institution: Israel, Elliot; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 30-SEP-1993; Project End 31-AUG-2004

  Summary: This application is for the continuation of the Asthma Clinical Research Network or ACRN. The ACRN is an interactive network of 6 research centers conducting studies of novel therapeutic approaches to asthma. The need for such a network was suggested by epidemiological data showing increases in the mortality, morbidity, prevalence, and costs of asthma, by clinical and basic research studies showing that asthma is linked to inflammation in the airways, and by the accelerating rate of development of potentially highly effective, but also potentially costly novel treatments for asthma. Defining the place of these new therapies was seen as requiring collaborative, multi-center studies examining large numbers of subjects reflecting the diversity of the U.S. population. In its first 5 years, the ACRN established an interactive infrastructure to meet this need and has added a clinical research site at Harlem Hospital in New York, which serves a predominantly minority population. The ACRN completed and published trials of the effects of regular use of a beta-agonist in subjects with mild asthma (BAGS) and of the efficacy of the anti-inflammatory agent, **colchicine,** as an alternate to an inhaled corticosteriod in moderate asthma. It is now conducting two additional trials comparing the effects of a long-acting beta-agonist, an inhaled corticosteriod, and the combination of the two in altering clinical outcomes, physiologic outcomes, and airway inflammation in moderate or severe asthma. A fifth study, establishing doses of different inhaled corticosteriods with equivalent effects on cortisol secretion, is about to be started. Data from completed trials, and associated ancillary studies, has been presented at national meeting to the ATS, ACCP, and AAAAI. This application specifically outlines the goals of the ACRN over the next five years. The studies proposed include: 1) A comparison of the clinical efficacy of doses of

different inhaled corticosteriods with equal systemic effects (as estimated from the study described above), 2) A prospective study of the effects of regular use of an inhaled beta-agonist in subjects stratified by genotype for the beta-adrenergic receptor, 3) A study analyzing the efficacy of a leukotriene pathway antagonist in enabling reduction or elimination of inhaled corticosteriod therapy in subjects with mild or moderate persistent asthma; and 4) six other studies from which 3 will be chosen for execution during the next five years. Other studies will be considered if new information becomes available suggesting the need for additional trials.

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

- **Project Title: ASTHMA CLINICAL RESEARCH NETWORK**

  Principal Investigator & Institution: Dimango, Emily A.; Medicine; Columbia University Health Sciences Po Box 49 New York, Ny 10032

  Timing: Fiscal Year 2002; Project Start 08-DEC-1995; Project End 31-AUG-2004

  Summary: This application proposes to continue the participation of investigators at the New York City Center in an interactive network of six centers, the Asthma Clinical Research Network (ACRN) in conducting studies of novel therapies for asthma and in disseminating findings to the practicing community. The need for such a network was suggested by increases in the mortality, morbidity, prevalence, and costs of asthma, by research studies showing that asthma is linked to airway inflammation, and by the accelerating rate of development of potentially effective, but also potentially costly treatments. Defining the place of these new therapies was seen as requiring collaborative, multi-center studies examining subjects reflecting the diversity of the U.S. population. In its first 5 years, the ACRN established an interactive infrastructure and added a research site at Harlem Hospital, New York, which serves a predominantly minority population. The ACRN completed and published trials of the effects of regular use of a beta-agonist in mild asthma (BAGS) and of the efficacy of **colchicine** as an alternate to an inhaled corticosteroid (ICS) in moderate asthma. It is now conducting trials comparing a long-acting beta-agonist, an ICS, and the combination of the two in moderate to severe asthma. We are about to start a 5th study to establish doses of different ICS with equivalent effects on cortisol secretion. These studies have been presented at meetings of the ATS, ACCP, and AAAAI, as have 10-12 ancillary studies analyzing the performance of clinical research. The ACRN has also reported its findings from subgroup analysis of the BAGS study: that subjects with different genotypes for the beta-adrenergic receptor are differently affected by regular use of albuterol. This application proposes continued participation of the NYC Asthma Clinical Research group in the multicentered, collaborative trials of the ACRN. The studies proposed include a comparison of the clinical efficacy of doses of different inhaled corticosteriods with equal systemic effects, a prospective study of regular use of an inhaled beta-agonist in subjects stratified by genotype for the beta-adrenergic receptor, a study of the efficacy of a leukotriene pathway antagonist in enabling reduction or elimination of inhaled corticosteriod therapy in subjects with mild or moderate persistent asthma, and other studies illustrated briefly in this application, but modified or replaced by the ACRN Steering Committee in response to new information or the release of new forms of therapy.

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

- **Project Title: ASTHMA CLINICAL RESEARCH NETWORK (ACRN)**

  Principal Investigator & Institution: Martin, Richard J.; Department of Medicine; National Jewish Medical & Res Ctr and Research Center Denver, Co 80206

Timing: Fiscal Year 2002; Project Start 30-SEP-1993; Project End 31-AUG-2004

Summary: This application proposes to continue the participation of investigators at National Jewish Medical and Research Center in an interactive network of six centers, the Asthma Clinical Research Network (ACRN) in conducting studies of novel therapies for asthma and in disseminating findings to the practicing community. The need for such a network was suggested by increases in the mortality, morbidity, prevalence, and costs of asthma, by research studies showing that asthma is linked to airway inflammation, and by the accelerating rate of development of potentially effective, but also potentially costly treatments. Defining the place of these new therapies was seen as requiring collaborative, multi-center studies examining subjects reflecting the diversity of the U.S. population. In its first 5 years, the ACRN established an interactive infrastructure and added a research site at Harlem Hospital, New York, which serves a predominantly minority population. The ACRN completed and published trials of the effects of regular use of a Beta- agonist in mild asthma ("BAGS") and of the efficacy of **colchicine** as an alternate to an inhaled corticosteroid (ICS) in moderate asthma. It is now conducting trials comparing a long-acting Beta-agonist, an ICS, and the combination of the two in moderate to severe asthma. We are about to start a 5th study to establish doses of different ICS with equivalent effects on cortisol secretion. These studies have been presented at meetings of the ATS, ACCP, and AAAAI, as have 10-12 ancillary studies analyzing the performance of clinical research. The ACRN has also reported its findings from subgroup analysis of the "BAGS" study: that subjects with different genotypes for the Beta-adrenergic receptor are differently affected by regular use of albuterol. This application proposes continued participation of the National Jewish Asthma Clinical Research group in the multicentered, collaborative trials of the ACRN. The studies proposed include a comparison of the clinical efficacy of doses of different inhaled corticosteroids with equal systemic effects, a prospective study of regular use of an inhaled Beta-agonist in subjects stratified by genotype for the Beta-adrenergic receptor, a study of the efficacy of a leukotriene pathway antagonist in enabling reduction or elimination of inhaled corticosteroid therapy in subjects with mild or moderate persistent asthma, and other studies illustrated briefly in this application, but modified or replaced by the ACRN Steering Committee in response to new information or the release of new forms of therapy.

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

- **Project Title: ASTHMA CLINICAL RESEARCH NETWORK CENTER**

  Principal Investigator & Institution: Boushey, Homer A.; Professor of Medicine; Cardiovascular Research Inst; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

  Timing: Fiscal Year 2002; Project Start 30-SEP-1993; Project End 31-AUG-2004

  Summary: This application proposes to continue the participation of investigators at UCSF in an interactive network of six centers, the Asthma Clinical Research Network (ACRN) in conducting studies of novel therapies for asthma and in disseminating findings to the practicing community. The need for such a network was suggested by increases in the mortality, morbidity, prevalence, and costs of asthma, by research studies showing that asthma is linked to airway inflammation, and by the accelerating rate of development of potentially effective, but also potentially costly treatments. Defining the place of these new therapies was seen as requiring collaborative, multi-center studies examining subjects reflecting the diversity of the U.S. population. In its first 5 years, the ACRN established an interactive infrastructure and added a research site at Harlem Hospital, New York, which serves a predominantly minority population.

The ACRN completed and published trials of the effects of regular use of a Beta-agonist in mild asthma("BAGS") and of the efficacy of **colchicine** as an alternate to an inhaled corticosteroid (ICS) in moderate asthma. It is now conducting trials comparing a long-acting Beta-agonist, an ICS, and the combination of the two in moderate to severe asthma. We are about to start a 5th study to establish doses of different ICS with equivalent effects on cortisol secretion. These studies have been presented at meetings of the ATS, ACCP, and AAAAI, as have 10-12 ancillary studies analyzing the performance of clinical research. The ACRN has also reported its findings from subgroup analysis of the "BAGS" study: that subjects with different genotypes for the Beta-adrenergic receptor are differently affected by regular use of albuterol. This application proposes continued participation of the UCSF Asthma Clinical Research group in the multicentered, collaborative trials of the ACRN. The studies proposed include a comparison of the clinical efficacy of doses of different inhaled corticosteroids with equal systemic effects, a prospective study of regular use of an inhaled Beta-agonist in subjects stratified by genotypes for the Beta-adrenergic receptor, a study of the efficacy of a leukotriene pathway antagonist in enabling reduction or elimination of inhaled corticosteroid therapy in subjects with mild or moderate persistent asthma, and other studies illustrated briefly in this application, but modified or replaced by the ACRN Steering Committee in response to new information or the release of new forms of therapy.

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

- **Project Title: BIOPHYSICAL MECHANISMS IN LEUKOCYTES AND MELANOCYTES**

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

  Timing: Fiscal Year 2002; Project Start 01-JUN-1977; Project End 31-AUG-2004

  Summary: This abstract is not available.

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

- **Project Title: CHARACTERIZATION OF CANDIDA ALBICANS MICROTUBULES**

  Principal Investigator & Institution: Wilson, Leslie; Professor; Biological Sciences; University of California Santa Barbara 3227 Cheadle Hall Santa Barbara, Ca 93106

  Timing: Fiscal Year 2002; Project Start 15-MAY-2001; Project End 30-APR-2004

  Summary: Candida albicans, an opportunistic pathogen, can cause vaginal, oral and lung infections in immunocompromised individuals and systemic tissue damages in acquired immunodeficiency patients. The chemotherapy of C. albicans infections is limited because of the strong similarities between C. albicans cells and human cells. However, the mitotic spindles in mammalian and Candida cells are constructed differently. In addition, significant differences exist in the sequences of fungal and mammalian tubulins, which are the building block units of mitotic spindles. Little information is available at biochemical and functional levels about Candida tubulin, and virtually nothing is known regarding the polymerization and dynamics properties of Candida microtubules. The thinking is that understanding the differences between fungal cell tubulin and mammalian tubulin could lead to development of new and selective drugs for the treatment of fungal diseases. Therefore, it is proposed to develop a large-scale purification strategy for C. Albicans tubulin based upon previous success in this laboratory with tubulin from Saccharomyces cerevisiae. The tubulin will be

characterized biochemically, and the polymerization and dynamic properties of Candida microtubules determined. Finally, the mechanism of interaction of two known microtubule-targeted antifungal drugs (benomyl and griseofulvin) with the Candida tubulin will be determined and the mechanisms by which the drugs modulate the polymerization and dynamics properties of the tubulin will be elucidated.

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

- **Project Title: COLCHICINE IN THE TREATMENT OF PULMONARY FIBROSIS**

  Principal Investigator & Institution: Rom, William N.; New York University School of Medicine 550 1St Ave New York, Ny 10016

  Timing: Fiscal Year 2002

  Summary: This abstract is not available.

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

- **Project Title: COLCHICINE THERAPY IN CHILDHOOD CIRRHOSIS**

  Principal Investigator & Institution: Sokol, Ronald J.; Professor; University of Colorado Hlth Sciences Ctr P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2002; Project Start 01-MAR-2002; Project End 28-FEB-2003

  Summary: This abstract is not available.

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

- **Project Title: CYTOGENETICS OF MEIOSIS OF MAIZE**

  Principal Investigator & Institution: Cande, W Z.; Molecular and Cell Biology; University of California Berkeley Berkeley, Ca 947205940

  Timing: Fiscal Year 2002; Project Start 01-AUG-1994; Project End 30-JUN-2003

  Summary: Our goal is to understand the mechanism of chromosome segregation during meiosis, particularly how homologous chromosomes pair and synapse. The maize male meiocyte is the only system where there is a large collection of mutants that affect meiosis, and it is possible to do superb cytology. We have collected 3-D images on a deconvolution light microscope system using fluorescence in situ hybridization (FISH) probes and antibodies against RAD51 to describe the rearrangements of telomeres, chromosomes and the recombination machinery during the homology search. There is no premeiotic association of homologs; rather, homologous chromosomes approach each other at the end of leptotene as telomeres associate with the nuclear envelope (NE) and cluster (bouqet formation). We will use FISH probes which light up multiple spots on one specific chromosome arm, FISH centromere specific probes, and antibodies against the recombination machinery (RAD51, MSH2/6) to analyze in 3-D homolog alignment as pairing is initiated. Analysis of the pairing behavior of chromosomal derivatives deficient in synapsis such as rings, deficiency heterozygotes, ditelocentrics and reciprocal translocations will allow us to test the requirements for chromosome ends, telomeric sequences, and subtelomeric or internal homology, for successful pairing. We will analyze the pairing behavior of chromosomes in mutants known to be deficient in the early stages of the homology search (afd, dsy1) or in later stages (as1, dy1, dsy2, etc.). We are developing novel screens based on partial pollen abortion or altered recombination rates to find new meiotic mutants. We are using directed transposon tagging to clone new mutants or existing mutants which are defective in pairing. We assume that the homology search is dependent on the active movement of chromosomes, mediated by telomere-NE associations. We will analyze homolog