LEUKOCYTOSIS

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

JAMES N. PARKER, M.D.
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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with leukocytosis 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 leukocytosis, 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 leukocytosis, 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 leukocytosis. 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 leukocytosis, 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 leukocytosis.

The Editors

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

CHAPTER 1. STUDIES ON LEUKOCYTOSIS

Overview

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

The Combined Health Information Database

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

- **Streptococcus Milleri: A Cause of Pyogenic Liver Abscess**

  Source: Journal of the National Medical Association. 93(7-8): 276-277. July-August 2001.

  Contact: Available from National Medical Association. 1012 Tenth Street, NW, Washington, DC 20001. (202) 347-1895, ext. 267. Website: www.NMAnet.org.

  Summary: Anemia, **leukocytosis** (high levels of white blood cells in the blood), elevated abnormal liver function enzymes, hypoalbuminemia (low levels of protein in the blood), fever, and right upper quadrand abdominal pain are common signs and symptoms of liver abscesses. Mortality is high: 100 percent without treatment, and 50 to 65 percent with medical treatment. The bacteria Streptococcus milleri has been found to be associated with liver abscesses significantly more frequently than any other streptococci. S. milleri is also a common cause of liver abscess in patients with Crohn's disease. This

article reports a case of S. milleri in a 47 year old patient with a history of hypertension, alcohol abuse, and tobacco smoking. The authors stress that increased awareness of S. milleri has come from better isolation of Streptococci species. The clinical importance of this awareness is that S. milleri is resistant to metronidazole. Therefore, patients with liver abscesses who receive metronidazole may not respond if S. milleri is the infecting organism. Effective antibiotics include ampicillin, erythromycin, clindamycin, and the cephalosporins. 1 figure. 1 table. 3 references.

- **Catheter-Associated Urinary Tract Infection Is Rarely Symptomatic: A Prospective Study of 1497 Catheterized Patients**

  Source: Archives of Internal Medicine. 160(5): 678-682. March 13, 2000.

  Contact: Available from American Medical Association. Subscriber Services Center, P.O. Box 10946, Chicago, IL 60610-0946. (800) 262-2350. Fax (312) 464-5831. E-mail: ama-subs@ama-assn.org.

  Summary: Catheter associated urinary tract infection (CAUTI) is the most common nosocomial infection (infections originating in the hospital), accounting for more than 1 million cases each year in hospitals and nursing homes in the United States. This article reports on a prospective study of 1,497 newly catheterized patients undertaken to define the clinical features of CAUTI. Every day that the catheter was in place, a quantitative urine culture and urine leukocyte count were obtained, and the patient was queried by a research worker regarding symptoms. To more precisely define the role of CAUTI in patients' symptoms, a subset of 1,034 patients (89 of whom developed CAUTI with more than 10 to the third colony forming units per milliliter), who did not have another potentially confounding site of infection besides the urinary tract, was analyzed. There were 235 new cases of nosocomial CAUTI during the study period. More than 90 percent of the infected patients were asymptomatic; only 123 infections (52 percent) were detected by patients' physicians using the hospital laboratory. In the subset analysis, there were no significant differences between patients with and without CAUTI in signs or symptoms commonly associated with urinary tract infection (fever, dysuria, urgency, or flank pain) or in **leukocytosis.** Only 1 of the 235 episodes of CAUTI that were prospectively studied was unequivocally associated with secondary bloodstream infection. The authors conclude that whereas CAUTI are a major reservoir of antibiotic resistant organisms in the hospital, they are rarely symptomatic and infrequently cause bloodstream infection. Symptoms referable to the urinary tract, fever, or peripheral **leukocytosis** have little predictive value for the diagnosis of CAUTI. 2 tables. 46 references.

- **Surgical Approach to Cecal Diverticulitis**

  Source: Journal of the American College of Surgeons. 188(6): 629-635. June 1999.

  Contact: Available from Journal of the American College of Surgeons. P.O. Box 2127, Marion, OH 43306-8227. (800) 214-8489 or (740) 382-3322. Fax (740) 382-5866.

  Summary: Cecal diverticulitis (diverticulitis, or pouches, in the first part of the large intestine) is a rare condition in the Western world, with a higher incidence in people of Asian descent. The treatment for cecal diverticulitis has ranged from expectant medical management, which is similar to uncomplicated left sided diverticulitis, to right hemicolectomy. This article reports on a retrospective chart review that was conducted of 49 patients treated for cecal diverticulitis at Olive View UCLA Medical Center from 1976 to 1998. The clinical presentation was similar to that of acute appendicitis, with abdominal pain, low grade fever, nausea or vomiting, abdominal tenderness, and

leukocytosis. Operations performed include right hemicolectomy in 39 patients (80 percent), diverticulectomy in 7 patients (14 percent), and appendectomy with drainage of intraabdominal abscess in 3 patients (6 percent). Of the 7 patients who had diverticulectomy, 1 required right hemicolectomy at 6 months followup for continued symptoms. Of the three patients who underwent appendectomy with drainage, all required subsequent hemicolectomy for continued inflammation. Of the 39 patients who received immediate hemicolectomies, there were complications in 7 (18 percent), with no mortality. The authors conclude by endorsing an aggressive operative approach to the management of cecal diverticulitis, with the resection of all clinically apparent disease at the time of the initial operation. In cases of a solitary diverticulum, they recommend the use of diverticulotomy when it is technically feasible. When confronted with multiple diverticuli and cecal phlegmon, or when neoplastic disease cannot be excluded, they advocate immediate right hemicolectomy. This procedure can be safely performed in the unprepared colon with few complications. Excisional treatment for cecal diverticulitis prevents the recurrence of symptoms, which may be more common in the Western populations. 2 figures. 1 table. 15 references.

- **Man with Acute Abdominal Pain and Diarrhea**

  Source: Consultant. 39(5): 1521-1522. May 1999.

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

  Summary: This article offers a brief case report, with a discussion of appropriate treatment. The case was a 57 year old man who began experiencing acute abdominal pain with mild diarrhea 2 weeks after his return from New Mexico. The pain originated in the hypogastrium and involved the lower quadrant and the perineum. The diarrhea was characterized as two loose stools on the first day and two watery stools on the second day. The patient did not note blood or pus in the stools. The patient's history was unremarkable except for mild exercise induced asthma. His physical condition was normal except for very mild end expiratory wheezing and some diffuse abdominal tenderness with guarding but no rebound in the left lower quadrant. No masses were felt on abdominal palpation, and there was no hepatosplenomegaly. Blood studies revealed a mild **leukocytosis;** stool was trace heme positive. The author asks readers to choose from a set of five management options for the first 12 hours of handling this patient. The author stresses that the differential diagnosis for a patient who presents with abdominal pain and mild diarrhea is broad. The acute nature of the pain and the lack of a toxic appearance in this case suggest either an infectious diarrheal disease or diverticulitis. A broad spectrum antibiotic (for instance, a fluoroquinolone such as trovafloxacin) with activity against the major gastrointestinal pathogens and the enteric flora found in diverticulitis is a good initial treatment for febrile patients with diarrhea of undetermined cause. The use of loperamide or narcotics as antimotility agents in patients with undiagnosed diarrhea and fever is a practice that should be discouraged. The authors stresses that physicians should consider surgery only if there is evidence of peritonitis or progression of disease with medical management. 4 references.

- **Fever: Thermal Regulation and Alteration in End Stage Renal Disease Patients**

  Source: American Nephrology Nurses Association Journal. 19(1): 13-18. February 1992.

  Summary: This article presents an overview of thermoregulatory mechanisms, the pathophysiology of fever, and alterations of the febrile response in end-stage renal disease (ESRD) patients. Topics include definitions of fever; mechanisms of thermal

regulation, including hypothalamic control of temperature; the pathophysiology of fever; fever management; uremia and body temperature; the possible mechanisms of hypothermia; and infection in ESRD patients. The author stresses that many ESRD patients do not exhibit the expected rise in white blood cell count or body temperature during clinical and laboratory-confirmed infections. Therefore, **leukocytosis** and fever cannot be relied on for the diagnosis of bacterial infection in ESRD patients. 3 figures. 4 tables. 16 references. (AA-M).

- **Guidelines for the Diagnosis and Management of Clostridium Difficile-Associated Diarrhea and Colitis**

  Source: American Journal of Gastroenterology. 92(5): 739-750. May 1997.

  Summary: This article presents guidelines for the diagnosis and management of Clostridium difficile-associated diarrhea and colitis in adults. Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. C. difficile causes a spectrum of diarrheal syndromes that vary widely in severity and merge with one another. The author considers the pathophysiology and epidemiology of C. difficile diarrhea, the clinical manifestations, diagnostic guidelines, primary treatment, management of relapses or recurrences of C. difficile diarrhea or colitis, and guidelines for prevention. The typical symptoms of C. difficile diarrhea are cramping abdominal pain, profuse diarrhea consisting of mucoid, greenish, smelling, water stools, low grade fever, and **leukocytosis.** These can start a few days after antibiotic therapy is begun or up to 8 weeks after its discontinuation. The differential diagnosis of C. difficile diarrhea includes benign or simple antibiotic-associated diarrhea, acute and chronic diarrhea caused by other enteric pathogens, adverse reactions to various medications other than antibiotics, ischemic colitis, idiopathic inflammatory bowel diseases, and intra-abdominal sepsis. One table presents guidelines for preventing C. difficile diarrhea; these include limiting the use of antimicrobial drugs, washing hands between contact with all patients, using stool isolation precautions for patients with C. difficile diarrhea, and educating the medical, nursing, and other appropriate staff members about the disease and its epidemiology. 4 tables. 63 references. (AA-M).

- **Life-Threatening Retroperitoneal Sepsis After Hemorrhoid Injection Sclerotherapy: Report of a Case**

  Source: Diseases of the Colon and Rectum. 42(3): 421-423. March 1999.

  Contact: Available from Williams and Wilkins. 352 West Camden Street, Baltimore, MD 21201-2436.

  Summary: This article reports a case of life threatening retroperitoneal sepsis after injection sclerotherapy for first degree hemorrhoids. A 50 year old man with symptomatic first degree hemorrhoids was seen in the outpatient department. An experienced surgical registrar injected three internal hemorrhoids with 3 to 5 mL of 5 percent oily phenol. Four days later, the patient was admitted as an emergency, complaining of tight central chest pain. For 6 hours he had experienced chills and pelvic pain radiating to his lower abdomen and the backs of his thighs. Anorectal instrumentation was not attempted, because the patient was reporting severe pelvic pain. Investigation revealed **leukocytosis,** raised creatinine kinase, and electrocardiographic changes suggestive of anteroseptal myocardial infarction. Streptokinase, cefotaxime, and metronidazole were administered. Later that day, his

pelvic pain worsened. He remained pyrexial (having a fever), developed tachycardia (rapid heartbeat), and went into urinary retention. Computed tomography revealed extensive retroperitoneal fluid but no localized abscess. Blood culture isolated gram negative bacilli, but exploratory laparotomy found no colonic lesion. The fecal stream was diverted with an end sigmoid colostomy and the rectal stump was oversewn. Hyperbaric oxygen, antibiotics, and intensive inotropic and ventilatory support were continued in the postoperative period. The patient eventually made a good recovery. The authors note that life threatening sepsis after injection sclerotherapy for hemorrhoids has been reported only once previously. One table summarizes the cases of life threatening complications after rubber band ligation of hemorrhoids. 1 table. 9 references.

- **Empirical Management of Urinary Tract Infections Complicating Transrectal Ultrasound Guided Prostate Biopsy**

  Source: Journal of Urology. 169(5): 1762-1765. May 2003.

  Summary: This article reports on a study of the empirical management of urinary tract infections (UTI) complicating transrectal ultrasound guided prostate biopsy. All 23 patients enrolled in the study underwent biopsy for acceptable indications and 95.7 percent had received antibiotic prophylaxis, including 69.5 percent with fluoroquinolones. Infection was typically accompanied by high fever, chills (78.3 percent of cases), and **leukocytosis** (56.5 percent). All positive blood cultures and 92.9 percent of positive urine cultures yielded Escherichia coli. Bacterial isolates showed high resistance to fluoroquinolones and trimethoprimsulfamethoxazole, and 100 percent susceptibility to second and third generation cephalosporin amikacin, carbapenem. 3 tables. 19 references.

- **Colitis: Key Components of the Evaluation**

  Source: Consultant. 38(2): 375-378, 381-383. February 1998.

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

  Summary: This article reviews the key components of the evaluation of colitis. Colitis is a nonspecific condition that has a variety of causes, including inflammatory bowel disease, infections, ischemia, radiation, and antibiotic therapy. The mainstays of evaluating patients who have colitis include the history and physical examination, sigmoidoscopy with mucosal biopsy, stool examination, and barium radiography. These tools are used to determine if colitis is present, how severe it is, the cause of the colitis, and the anatomic extent of the disease. In addition to the typical symptoms of colitis (diarrhea, abdominal pain, and tenesmus), the authors recommend that physicians look for signs of more severe disease, such as orthostasis, pallor, fever, fatigue, and tachycardia. Also, physicians should be alert for extraintestinal manifestations of chronic inflammatory bowel disease (IBD), such as mouth ulcers, erythema nodosum, and arthritis. Laboratory findings that may suggest severe colitis include a low hemoglobin level, **leukocytosis,** an elevated erythrocyte sedimentation rate, and hypoalbuminemia. After confirming the presence of colitis with proctosigmoidoscopy or flexible sigmoidoscopy, stool cultures and parasite testing should be ordered to identify the specific cause. Complications of colitis include toxic megacolon, perforation, hemorrhage, and obstruction in ischemic disease. 4 figures. 3 tables. 16 references. (AA-M).

Federally Funded Research on Leukocytosis

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

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

- **Project Title: CHARACTERIZATION & TREATMENT OF CATEGORY III PROSTATITIS**

  Principal Investigator & Institution: Nickel, J Curtis.; Queen's University at Kingston Kingston K7l 3N6, Canada Kingston, On

  Timing: Fiscal Year 2002; Project Start 27-MAR-1998; Project End 31-AUG-2004

  Summary: (Taken from the applicant's Abstract) Characterization and Treatment of Category III Prostatitis Background: Chronic abacterial prostatitis and prostatodynia (NIH Category III), remains a frustrating enigma for North American physicians and patients. Our definition of the syndrome is unclear, the etiology is obscure, the relevance of the only objective finding we have (**leukocytosis**) is unknown, symptoms are highly variable, the natural history of the disease has not been adequately studied and the clinical treatment trials are poorly designed, small and inconclusive. Objectives: To collaboratively develop validated NIH assessment instruments for the study of Category III prostatitis, analyze objective microscopic, microbiological, immunological and molecular biological parameters and develop a long term collaborative multicenter study in which a number of potential standardized treatment protocols could be tested. Research Design: Part 1: Retest, revalidate and revise as necessary the Principal Investigator's published prostatitis specific Symptom Frequency Questionnaire (SFQ) and Symptom Severity Index (SSI) in 100 prostatitis patients presently being studied and 100 age matched control patients. These modified indices would be subsequently used as the basis for a consensus and evidence based NIH prostatitis specific symptom assessment instrument to be tested prospectively in 200 prostatitis and 100 control patients. Part 2: Analyze objective microscopic, microbiological, immunological and molecular biological aspects of expressed prostatic secretions, semen and urine specimen after prostatic massage in these 300 patients. of potential standardized treatment protocols (conservative, antibiotic, alpha blockade and repetitive prostatic massage; alone or in combination) will be tested in patients enrolled in part l and part 2. Results from this 3 part study will be analyzed and correlated between groups and within groups, both concurrently and sequentially.

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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).

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

- **Project Title: EFFECT OF LEUKOREDUCTION ON INFECTION RISK IN TRAUMA**

  Principal Investigator & Institution: Nathens, Avery B.; Associate Professor; Surgery; University of Washington Grant & Contract Services Seattle, Wa 98105

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

  Summary: Severely injured patients often require transfusions of allogeneic blood products to restore intravascular blood volume. Many of these patients survive their initial resuscitation only to experience the late sequelae of nosocomial infection and multiple organ failure. Several lines of clinical and experimental evidence suggest that residual leukocytes present in allogeneic blood products have immunomodulatory effects. These effects might underlie the propensity of trauma patients to develop infection or organ failure. Strategies designed to limit the exposure of patients to allogeneic leukocytes may reduce the incidence of these post-injury sequelae. Pre-storage leukoreduction, a process leading to a 3 log order reduction in passenger leukocytes, represents one such strategy. We postulate that the leukoreduction of blood products will reduce the incidence of nosocomial infections and multiple organ failure in critically injured trauma patients requiring blood transfusion. This proposal seeks to accomplish the following: Specific aim 1: To evaluate whether there are differences in the rates of infection and in the severity of organ dysfunction in trauma patients receiving leukoreduced blood products compared to similar patients receiving standard allogeneic blood products. Specific aim 2a: To assess T-cell responsiveness and the dominant CD4 lymphocyte subset in trauma patients transfused with leukoreduced blood products compared to subjects receiving standard allogeneic blood products. Specific aim 2b: To assess the activational state of the monocyte and the neutrophil in trauma patients receiving leukoreduced blood products compared to those receiving standard allogeneic blood products. Given the large proportion of the United States' blood supply used for emergency transfusions and the risk of sequelae in this high risk population, the results of these studies may provide efficacy data to guide decisions regarding the processing of blood products and provide insight into the mechanisms of transfusion induced immunomodulation.

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

- **Project Title: ENDOTHELIN 1 IN SICKLE ACUTE CHEST SYNDROME**

  Principal Investigator & Institution: Kalra, Vijay K.; Professor; University of Southern California 2250 Alcazar Street, Csc-219 Los Angeles, Ca 90033

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

  Summary: Patients with sickle cell disease (SCD) experience recurrent episodes of vaso-occlusive crises(VOC). Following a VOC, patients often develop pulmonary symptoms resulting in a potentially life-threatening condition termed acute chest syndrome (ACS). ACS is the second most common cause of mortality in SCD. In the National Acute Chest Study, 38% of ACS cases in SCD were attributed to infection, fat embolism and infarction, while no identifiable cause was found in the remaining 62% of ACS cases. Recruitment of monocytes (Mo)/polymorphonuclear neutrophils(PMN) into the alveolar compartment is an important feature of acute lung injury. **Leukocytosis,** in the absence of infection, is commonly seen in SCD patients and is a predictor of severity and ACS. Studies in transgenic sickle mice (Tg HbS) reveal increased accumulation of leukocytes in the lung in response to an experimental lung insult. We find that endothelin-1(ET-1) is released from cultured human pulmonary endothelial cells

(HPEC) in response to deoxygenated sickle(SS) RBCs and initiates leukocyte transmigration.The goal of this project is to test the hypothesis that the interaction of SS RBC with HPEC initiates cellular signaling to cause Mo/PMN to transmigrate from the lumen of the blood vessel into the alveolar compartment, wherein activated Mo/PMN cause injury to the pulmonary alveolar epithelial cells (PAEC). SpecificAim 1, examines the effectof SS RBC with cultured HPEC on the transmigration of Mo/PMN and the role of endothelin-1 (ET-1) in this process. Specific Aim 2 delineates the effect of conditioned medium, elaborated from the interactionof SS RBC with HPEC, on the migration of Mo/PMN from the basolateral to apical direction across AEC monolayers. Specific Aim 3 explores the mechanism of transmigration of Mo/PMN in a co-culture model of HPEC and PAEC. Finally, Specific Aim 4 employs a Tg HbS mouse model to induce ACS and examines the effect of ET-1 receptor antagonists in preventing the accumulation and activation of Mo/PMN and resultant lung injury. Together, these coordinated investigations will improve our understanding of the molecular mechanisms by which Mo/PMN accumulatein the alveolar compartment in SCD leading to ACS and provide a rationale for therapeutic approaches to ameliorate ACS.

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

- **Project Title: FUNCTION OF MEF IN HEMATOPOIETIC CELLS**

  Principal Investigator & Institution: Nimer, Stephen D.; Professor and Head; Sloan-Kettering Institute for Cancer Res New York, Ny 100216007

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

  Summary: (provided by applicant): We cloned a novel member of the ETS family of transcription factors called MEF, from a human megakaryocytic leukemia cell line. MEF is a strong transcriptional activator that is expressed in immature and mature hematopoietic cells. We have demonstrated that MEF is phosphorylated by the cyclin A/CDK2 complex and have preliminarily shown that sequential phosphorylation leads to its degradation by the ubiquitin proteasome degradation pathway. After generating murine cDNA and genomic MEF clones, we created MEF "knock-out" mice which have defects in NK and NK T cell development and abnormalities in the hematopoietic stem cell compartment. MEF -7- NK cells cannot lyse tumor cells, probably because perforin, an MEF target gene, is not expressed. Based on the phenotype of these mice, and the cell cycle dependent regulation of MEF function, we propose to further characterize the biological effects of MEF on hematopoietic stem cells, NK and NK T cells by utilizing MEF-null mice for several bone marrow transplant models (and for target gene identification) and by overexpressing MEF in hematopoietic progenitor cells. We will define the mechanisms of MEF action by identifying and characterizing MEF target genes in hematopoietic cells and by further characterizing the cell cycle dependent regulation of MEF expression. The studies proposed will define the role of MEF in regulating gene expression involved in hematopoietic stem cell behavior and innate immunity. These studies will contribute greatly to advances in the fields of stem cell transplantation and immune regulation.

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

- **Project Title: GENE THERAPY OF SICKLE CELL DISEASE & BETA THALASSEMIA**

  Principal Investigator & Institution: Stamatoyannopoulos, George; Professor of Medicine and Genetics; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2002

Summary: Pre-clinical and clinical studies on gene therapy of sickle cell disease and beta thalassemia. The goal of this project is to perform the pre-clinical and clinical studies that are required for the eventual application of the therapeutic gene transfer in sickle cell disease and beta thalassemia. Specifically, 1) stem cell mobilization is required for the application of ex vivo stem cell gene therapy but the current approach based on administration of G-CF cannot be used in sickle cell disease because the resultant **leukocytosis** precipitates a sickle cell crisis with severe (or lethal) consequences. We will develop new approaches of mobilization that can be used safely in sickle cell disease. Two clinical studies will be done. The first is based on the assumption that recovery from the cytotoxic effects of hydroxyurea results in hematopoietic cell regeneration that is accompanied by increased rate of mobilization of stem/progenitor cells. The second approach is based on the evidence that mobilization using anti-VLA-4 antibody or Flt-3 ligand is characterized primarily by release of progenitor cells and small degree of **leukocytosis.** Preclinical studies using a combination of anti-VLA-4 with hydroxyurea, or anti-VLA-4 with Flt-3 ligand will be done in baboons to identify a treatment scheme that will result in optimal mobilization with minimal change in white blood cell numbers. The optimal treatment scheme will subsequently be applied to patients with sickle cell disease. 2) We will perform pre-clinical studies aimed to determine whether MLV-based "insulated" betagamma globin gene vectors can be used for clinical studies in sickle cell disease and beta thalassemia. Specifically, we will a) test whether such vectors can correct the defects in sickle cell and beta thalassemic mice; b) assess transduction rates, levels of expression of the transferred betagamma globin gene and vector toxicity in the baboon transplantation model; c) determine betagamma gene expression and transduction rates in primary human erythroid cells following transduction of BFU-E of patients with sickle cell disease or beta thalassemia; d) measure transduction rates of human stem cells in the SCID/NOD murine model. 3) Successful completion of these pre-clinical studies will allow us to proceed with a clinical study in patients with Hb S disease or beta thalassemia. a) Clinical grade vectors will be produce, b) the necessary regulatory requirements will be fulfilled, c) a clinical study of three patients with sickle cell disease and six with beta thalassemia will be initiated to test safety and function of globin gene vectors.

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- **Project Title: MOLECULAR PATHOBIOLOGY OF LANGERHANS CELL HISTIOCYTOSIS**

  Principal Investigator & Institution: Rollins, Barrett J.; Associate Professor; Dana-Farber Cancer Institute 44 Binney St Boston, Ma 02115

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

  Summary: Langerhans Cell Histiocytosis (LCH) is a disease in which tissue destruction is caused by accumulation of histiocytes related to Langerhans cells (LC), the antigen presenting dendritic cells of skin. Although these pathologic LC's (PLC's) are clonal and overexpress p53, the high rate of remission in response to local treatment has led to the consensus that LCH is not a malignancy. LCH lesions can be localized and easily treated, or disseminated and lead to multiorgan failure and death. LC's are motile cells and their trafficking in vivo is tightly regulated. Normal resting LC's express the chemokine receptor CCR6 which directs them to mucocutaneous inflammatory sites where its ligand is secreted. Once LC's ingest antigen and become activated, they down-regulate CCR6 and up-regulate CCR7. This attracts LC's to lymph nodes, the source of CCR7's ligands, where they present antigen to T cells. Our preliminary data demonstrate that despite having characteristics of activated LC's, PLC's show persistent

expression of CCR6 explaining, in part, their accumulation at inappropriate tissue sites. The experiments in this proposal are designed to elucidate the pathobiology and pathogenesis of LCH by testing the hypotheses that: (1) Dysregulated expression of chemokines and their receptors may be responsible for the persistence of PLC's in target organs; and (2) Clonal PLC's arise from LC's because of the expression of specific genes. To test these hypotheses, I propose the following specific aims: Specific Aim 1. Test primary LCH tissues for abnormalities in chemokine and chemokine receptor expression. This will be done using custom chip-based hybridization techniques and confirmed by immuno- histochemistry. Correlates will be made to a clinical database.

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- **Project Title: NEUTROPHIL HOMEOSTASIS AND LUNG SEQUESTRATION**

  Principal Investigator & Institution: Worthen, G Scott.; Associate Professor and Senior Faculty m; National Jewish Medical & Res Ctr and Research Center Denver, Co 80206

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

  Summary: (provided by applicant): The generation, release, and disposal of neutrophils in response to inflammation remains poorly understood. A number of neutrophil-dependent lung disorders, including the Adult Respiratory Distress Syndrome (ARDS) are characterized by release of immature neutrophils from marrow into the circulation. Using murine systems in vivo, a novel embryonic stem cell-derived in vitro system, and murine and human cells in vitro, we propose to test interrelated hypotheses that explore fundamental mechanisms of **leukocytosis** and lung sequestration. 1. During inflammation, systemic expression of G-CSF is induced by TNF and other cytoses. G-CSF not only increases the number of progenitors, but also retards apoptosis of developing neutrophils, amplifying the resultant generation of neutrophils. 2. G-CSF mobilizes immature neutrophils through modification of three systems - signaling of CXCR4 by SDF-1, the interaction between sialoadhesin and its ligand, and homotypic interactions between ALCAM on both stroma and hematopoietic cells. 3. Immature neutrophils mobilized by G-CSF are larger and demonstrate increased resistance to deformation, leading to their localization in the lung. We believe the results of these experiments will provide new information on fundamental aspects of normal homeostasis as well as insights into mechanisms of neutrophil-dependent inflammatory states.

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- **Project Title: PERSISTENCE OF CNS T. PALLIDUM IN HIV INFECTION**

  Principal Investigator & Institution: Marra, Christina M.; Associate Professor; Neurology; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2002; Project Start 30-SEP-1996; Project End 31-AUG-2004

  Summary: (provided by applicant): The overall goal of our original proposal was to test the hypothesis that concomitant HIV-1 infection impairs clearance of Treponema pallidum from the CSF. The progress that we have made in the first funding period supports our hypothesis. Specifically, individuals with more pronounced HIV-1-mediated immunosuppression are more likely to have neurosyphillis, and normalization of CSF WBC count and serum RPR after treatment for neurosyphilis is slower and less complete in HIV-1-infected individuals. Few studies have addressed the influence of concomitant HIV-1 on CNS infection by T. pallidum. In our study to date, we have enrolled and obtained CSF from 348 subjects with all stages of syphilis. Approximately three-quarters of our subjects are also HIV-1-infected. To date, 53