HISTOPLASMOSIS

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 histoplasmosis 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 histoplasmosis, 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 histoplasmosis, 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 histoplasmosis. 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 histoplasmosis, 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 histoplasmosis.

The Editors

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

CHAPTER 1. STUDIES ON HISTOPLASMOSIS

Overview

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

The Combined Health Information Database

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

- **Oral Mycoses in HIV Infection**

  Source: Oral Surgery, Oral Medicine, Oral Pathology. 73(2): 171-180. February 1992.

  Summary: This article discusses oral mycoses in HIV infection, an increasingly common problem. Oral candidiasis is by far the most prevalent; fewer than 10 cases of cryptococcosis, **histoplasmosis,** and geotrichosis have thus far been reported. The author notes that oral candidiasis is one of the earliest premonitory signs of HIV infection and may present as erythematous, pseudomembranous, hyperplastic, or papillary variants, or as angular cheilitis. The author reviews cumulative data from 23 surveys (incorporating 3387 adults), which suggest that in general, oral candidiasis may develop in one-third to half of HIV-seropositive patients. The author reviews these and related concepts pertaining to oral mycoses in HIV infection. 6 tables. 97 references. (AA-M).

- **Review of Oral Fungal Infections and Appropriate Therapy**

  Source: JADA. Journal of the American Dental Association. 126(1): 63-72. January 1995.

  Summary: This article reviews oral fungal infections and the therapeutic options for each. The authors emphasize that dental health care providers must recognize oral fungal pathogens that often are markers for early signs of immune deterioration. Topics covered include localized fungal infections, including the various types of oral candidiasis; deep-seated fungal infections, including aspergillosis, cryptococcosis, **histoplasmosis,** geotrichosis, blastomycosis, and mucormycosis; diagnostic considerations for these deep-seated fungal infections; antifungal medications; polyene antibiotic antifungals, including amphotericin B and nystatin; azole antifungals, including clotrimazole, miconazole, ketoconazole, fluconazole, and itraconazole; and the cost of therapy. Throughout the article, the authors discuss the impact of these fungal infections on individuals with immunosuppressive diseases. 4 tables. 56 references. (AA-M).

- **Infectious Granulomatous Diseases of the Head and Neck**

  Source: Current Opinion in Otolaryngology and Head and Neck Surgery. 2(3): 281-290. June 1994.

  Summary: This article reviews recent advances in the etiology, diagnosis, and treatment of infectious granulomatous diseases affecting the head and neck. These advances include trials of new antimicrobial and antifungal agents, innovative surgical and laser techniques, clarification of specific histologic and radiographic findings, and new approaches to organism isolation and identification. The authors review these developments in a discussion of the otolaryngologic approach to actinomycosis, rhinoscleroma, rhinosporidiosis, aspergillosis, mucormycosis, blastomycosis, **histoplasmosis,** tuberculous and atypical mycobacteria, cat-scratch disease, and syphilis. 95 references (11 annotated). (AA).

- **Fungal Infections of the Genitourinary System**

  Source: Journal of Urology. Volume 149: 1377-1388. June 1993.

  Summary: This review article covers fungal infections that have the potential to cause disease of the genitourinary system. Topics covered include taxonomy and pathogenicity; primary infections, including blastomycosis, coccidioidomycosis, and **histoplasmosis;** opportunistic fungi, including aspergillosis, cryptococcosis, and candidiasis; and rare and unusual infections, including geotrichosis, hansenula fabianii, paecilomyces, parococcidioidomycosis, phycomycosis, penicillium, pseudallescheria boydii, rhinosporidiosis, sporotrichosis, and trichosporon; and fungal infection and the renal transplant patient. The authors also discuss and summarize antifungal therapy. 6 figures. 181 references.

Federally Funded Research on Histoplasmosis

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

[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

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 histoplasmosis.

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

- **Project Title: ANTIFUNGAL THERAPY FOR HISTOPLASMOSIS**

  Principal Investigator & Institution: Goldman, Mitchell; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

  Timing: Fiscal Year 2002

  Summary: This abstract is not available.

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

- **Project Title: GENOMIC RESOURCES FOR HISTOPLASMA CAPSULATUM**

  Principal Investigator & Institution: Mardis, Elaine R.; Research Associate Professor; Genetics; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-AUG-2004

  Summary: (provided by applicant): The goal of this proposal is to produce comprehensive genomic resources for the fungal pathogen Histoplasma capsulatum. This resource will enhance and expedite the ability of H. capsulatum researchers to make key advances in the study of fungal pathogenesis. H. capsulatum, the etiologic agent of **histoplasmosis,** is a primary fungal pathogen that is endemic in the Ohio River Valley through the midwestern United States into Texas and is a leading pathogen affecting AIDS patients in the Midwest. This proposal represents a close collaboration between the Genome Sequencing Center at Washington University and biologists in the H. capsulatum community to create a fundamental resource for further exploration of H. capsulatum biology. Specifically, we will accomplish the following aims: 1. Construct a BAC clone-based physical map of the H. capsulatum genome, by fingerprinting each BAC and aligning overlapping BACs according to shared restriction fragment patterns. 2. Produce a highly accurate, complete genome sequence for Histoplasma capsulatum strain G217B with less than 1 error per 10000 nucleotides. The sequencing strategy used will entail a combination of paired-end plasmid and M13 sequencing reads from both whole genome shotgun and BAC-specific libraries. 3. Produce a reduced coverage (approximately 2-fold) genome sequence of the related Histoplasma capsulatum strain G186AR. The sequencing strategy used will entail paired-end reads from a whole genome shotgun library, with comparative assembly onto the existing G217B genome sequence. 4. Develop a microarray resource consisting of oligonucleotide sequences corresponding to each predicted gene in Histoplasma capsulatum strain G217B. Resulting arrays will be used to establish the relative expression level of each gene in both mycelial and yeast forms of the fungus. 5. Combine the resources developed in this project - BAC clone physical map, gene predictions and other sequence features, strain-

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(FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

specific DNA sequence variations, and microarray results - to fully annotate the resulting Histoplasma capsulatum genome sequence and encompass the information within an accessible database resource patterned after ACeDB.

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

- **Project Title: INTERACTION OF H. CAPSULATUM WITH DENDRITIC CELLS**

  Principal Investigator & Institution: Newman, Simon L.; Professor; Internal Medicine; University of Cincinnati 2624 Clifton Ave Cincinnati, Oh 45221

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

  Summary: (provided by applicant): Histoplasma capsulatum (Hc) is a dimorphic fungal pathogen of worldwide importance that causes a broad spectrum of disease activity. Although the course of infection is mild in most immunocompetent individuals, Hc may produce progressive disseminated infections in individuals immunocompromised by hematologic malignancies, cytotoxic therapy, or in individuals with the acquired immunodeficiency syndrome (AIDS). Infection with Hc is acquired by inhalation of microconidia into the pulmonary alveoli. The conidia convert into the pathogenic yeast phase, and yeasts are phagocytized by alveolar macrophages (AM). Dividing yeasts destroy the AM, and then they are ingested by other AM, and by inflammatory neutrophils and macrophages (M-phi). Repetition of this cycle leads to dissemination of Hc via blood and lymphatics. Maturation of specific cell-mediated immunity (CMI) against Hc activates M-phi to halt yeast proliferation with gradual resolution of the disease process. Although, dendritic cells (DC) are the most potent antigen-presenting cells (APC) of the immune system, and are critical for the induction of CMI, their role in host defense against fungi has been largely ignored. The overall goal of the proposed research is to understand the biology and biochemistry of the interaction of Hc with DC, and to characterize the role of DC in the induction of protective immunity to Hc. The major objectives of the proposal are: 1) To determine if murine lung DC ingest and restrict the conversion of Hc conidia into yeasts. Specifically we will determine if lung DC phagocytose Hc conidia, determine if recognition is via VLA-5, determine the intracellular fate of conidia, identify the cytokines produced by Hc-infected DC, and determine why Hc is recognized by different receptors on M-phi and DC. 2) To identify the functional correlates for antigen presentation between Hc-infected DC and T cells with respect to T cell proliferation, cytokine production, and the requirement for co-stimulatory molecules, and to determine if DC-Hc-T cell interaction produces cytokines that activate M-phi anti-histoplasma activity. 3) To determine if Hc antigen-pulsed DC confer protective immunity in a murine model of pulmonary **histoplasmosis,** and to define the immunologic parameters of protective immunity in immunocompetent and immunocompromised mice. The results of these studies should provide significant insight into the pathogenesis of **histoplasmosis** and aid in the design of novel vaccine strategies for the prevention of disease.

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

- **Project Title: IV ITRACONAZOLE VS AMPHOTERICIN B IN BLASTOMYCOSIS OR HISTOPLASMOSIS**

  Principal Investigator & Institution: Pappas, Peter G.; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

  Timing: Fiscal Year 2002

  Summary: The primary purpose of this study is to assess the safety of IV itraconazole compared to the standard of care (Amphotericin B). The study will also assess the

clinical, microbiological, and overall response to therapy at the end of IV induction therapy (7-14 days) and after PO consolidation therapy at 2, 12, and 24 weeks. Patients will be randomized to either an initial treatment with IV itraconazole twice a day for two days (loading dose) and then once a day for five additional days or amphotericin-B IV for seven days. Extended treatment would be allowed if the patient's clinical condition required it. IV treatment will be followed by consolidation therapy with itraconazole capsules once daily or twice a day for up to one year. During induction therapy (7-14 days) IV itraconazole is infused over a one-hour period of time. IV Amphotericin-B is infused over a 1-6 hour period of time depending on the patient's side effects to therapy. During consolidation therapy oral itraconazole is given either once a day or twice a day for up to one year.

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

- **Project Title: LUNG IMAGE DATABASE WITH PATHOLOGIC CORRELATES**

  Principal Investigator & Institution: Mclennan, Geoffrey; Associate Professor of Medicine; Internal Medicine; University of Iowa Iowa City, Ia 52242

  Timing: Fiscal Year 2002; Project Start 20-JUL-2001; Project End 30-JUN-2006

  Summary: (Provided by Applicant) This application is in response to a specific request to establish a generalized CT-derived database representing ground truth in lung cancer and is not hypothesis-driven. Our broad goal is to help in the building of this database, and through that effort assist with the methodical development of appropriate lung cancer screening tools and protocols. Our group, with recognized experience in cooperative national projects, and with a broad perspective, will provide for the consortium : a well characterized group of study subjects with lung cancer, and with common lung cancer mimics such as **histoplasmosis,** supported by excellent radiologists and pathologists. expertise in the development of CT imaging protocols. a functional electronic transfer system for CT data sets from multiple sites, analysis and archiving of such data sets, expertise in DICOM standards, and in the issuing of web-based reports. methods for temporal matching of CT data points, important in the longitudinal follow-up of patients, and in matching excised inflated lobe data and histopathological data to the original patient CT. expertise in computational morphology, (i.e. the mathematical description of complex structures, their visualization, and their derived CT images). We intend to apply this to a subset of resected lung tumors to help define pathological and CT ground truth. Image reconstruction algorithms. This is critically important for the identification and implementation of needed improvements in CT methods to maximize the chance of detection of subtle early lesions within the lung parenchyma and airways. data from two different CT manufacturers multi-slice helical CT scanners. with mathematically derived virtual lung models, including early lung cancer development, for use in design of scanning and reconstruction methods.

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

- **Project Title: MOLECULAR MECHANISMS OF HISTOPLASMA PATHOGENESIS**

  Principal Investigator & Institution: Goldman, William E.; Professor; Molecular Microbiology; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2002; Project Start 01-JUL-1988; Project End 29-FEB-2004

  Summary: Histoplasma capsulatum is a complex pathogen that can cause a wide variety of syndromes, depending on the pathway of infection. Understanding the spectrum of **histoplasmosis** demands a thorough approach to answering a central biological

question: How does H. capsulatum survive and proliferate within host cells? Biochemical, cell biological, and molecular genetic studies will be combined over the next 5 years with the following 3 specific aims: I. Understanding the molecular basis of the rough/smooth yeast phenotypic variation. This spontaneous variation correlates with the loss of cell wall 1-(1.3)-glucan, which will be studied in terms of its regulation and its relationship to virulence. The primary genetic strategy is to identify genes involved in this variation by complementation cloning in H. capsulatum, using a shuttle plasmid to transform a genomic library from the wild-type (rough) strain into an isogenic variant (smooth) strain. II. Defining the role and regulation of a calcium-binding protein (CBP) in calcium acquisition and virulence. CBP is a major secreted product of the yeast form H. capsulatum and correlates with the yeast's ability to grow in calcium-limited conditions. The native CBP I gene will be disrupted using a strategy that employs two genetic markers to enrich for allelic replacement events. In addition, a laZ-based reporter system will be exploited to identify trans-acting regulators that modulate CPB 1 expression. III. Generating physically marked mutants in virulence-associated phenotypes. This takes advantage of the technique of restriction enzyme-mediated integration (REMI) to generate a bank of insertion mutants of H. capsulatum. These will be screened/selected for defects in phenotypes that are already suspected to be associated with virulence.

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

- **Project Title: MOLECULAR PATHOGENESIS OF PULMONARY HISTOPLASMOSIS**

  Principal Investigator & Institution: Woods, Jon P.; Associate Professor; Medical Microbiol & Immunology; University of Wisconsin Madison 750 University Ave Madison, Wi 53706

  Timing: Fiscal Year 2002; Project Start 30-SEP-1995; Project End 31-AUG-2005

  Summary: Description (Adapted from applicant's abstract): The targets of this proposal are the functions and regulatory mechanisms of two Histoplasma capsulatum (Hc) genes that are up-regulated early in macrophage infection and may be important for pathogenic success in the hostile host environment. **Histoplasmosis** is the most common endemic mycoses in the world and is particularly dangerous for immunocompromised patients. Disease manifestations may be pulmonary or systemic, resulting from the respiratory route of infection and dissemination through the mononuclear phagocytic system. From host inhalation of mold elements through conversion to a budding yeast, entry in macrophages, and survival within a harsh intracellular compartment, this dimorphic fungus successfully faces a wide range of environmental stimuli and threats from host defense mechanisms. The ability for adaption to the host by a soil microorganisms is intriguing from an evolutionary standpoint and clinically significant. Examining genes that are specifically up regulated during infection can elucidate pathogenic mechanisms and the nature of the host micro-environmental niche in which the fungus persists. Such studies may also reveal new vaccine candidates or therapeutic drug targets. Differential display (dddRT-PCR) and in vivo expression technology (IVET) was used to identify a number of Hc early response genes including yps-3 and a gene encoding a small transcript in antisense orientation to a homology of an immunogenic protein found in the cell wall and culture supernatant. Its predicted homology with mammalian EGF-like proteins and a domain of the Blastomyces dermatitis WI-1 antigen is consistent with potential roles in attachment or intracellular signaling. DdRT-PCR was used identify yps-3 up regulation during infection and moreover revealed 3' untranslated region processing and alternate polyadenylation

associated with novel sequence motifs. The first aim is to determine the function, pathogenic role and in vivo regulatory mechanisms for yps-3. IVET was used to identify up regulation during infection of the other gene targeted in this proposal. Our second aim is to determine the function of this gene, including its role in potential antisense down regulation of the protein kinase homolog as part of the fungus's adaption to the host intracellular environment. Both yps-3 and IVET-identified gene are up regulated within four hours after intracellular infection. The third aim is to determine the environmental stimuli regulating expression, using specific conditions relevant to Hc pathogenesis as well as macrophage cell culture and mouse infection models. These studies are designed to characterize unique biological aspects of each gene as well as potentially shared features of fungal adaptive responsiveness in a pathogenically relevant setting.

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

- **Project Title: SUBMACULAR SURGERY TRIALS PATHOLOGY CENTER**

  Principal Investigator & Institution: Grossniklaus, Hans E.; Professor; Ophthalmology; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2002; Project Start 01-AUG-1999; Project End 30-APR-2004

  Summary: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the United States. When the neovascular form of AMD, choroidal neovascularization (CNV), occurs under the fovea (subfoveal CNV), it leads to central vision loss and functional blindness. Subfoveal CNV may also occur in the ocular **histoplasmosis** syndrome (OHS), leading to disability in young adults. Fluorescein angiography has shown that CNV may have classic and occult patterns, each of which correlates with a different clinical outcome. Histologic studies have shown type l and type 2 topographies of CNV with theoretically differing clinical outcomes after surgery. The Submacular Surgery Trials is a phase III randomized clinical trials in which surgeons remove CNV specimens from patients with AMD and OHS. In this proposal, CNV specimens obtained from the SST are studied using light and electron microscopy and immunohistochemical stains to determine the structural and biochemical counterparts to classic and occult fluorescein angiographic patterns. The hypothesis that surgically removed type 1 CNV correlates with different clinical outcome than surgically removed type2 CNV compared with unoperated patients will be tested, and if there is a difference in outcome, fundus features of type 1 versus type2 CNV will be determined. Additionally, eyes obtained post-mortem from patients enrolled in the SST will be studied for pathologic correlation with clinical findings and outcomes.

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

- **Project Title: SUBMACULAR SURGERY TRIALS--COORDINATING CENTER**

  Principal Investigator & Institution: Hawkins, Barbara S.; Professor; Ophthalmology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 01-MAY-1997; Project End 30-APR-2005

  Summary: This abstract is not available.

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

- **Project Title: SUBMACULAR SURGERY TRIALS--PHOTOGRAPH READING CENTER**

  Principal Investigator & Institution: Bressler, Susan B.; Professor; Ophthalmology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 01-MAY-1997; Project End 30-APR-2004

  Summary: (Applicant's Abstract) The purpose of the Submacular Surgery Trials (SST) is to evaluate submacular surgical removal of choroidal neovascular lesions secondary to age-related macular degeneration, ocular **histoplasmosis,** and unknown causes in four randomized clinical trials, each for a different lesion type and presumed etiology. Only one eye (study eye) of each patient is expected to be eligible for one of the SST clinical trials. Patients assigned at random to the control arm will be managed by either observation (no treatment) or laser photocoagulation, depending upon the type of lesion and the findings from earlier clinical trials of treatment of choroidal neovascularization. The primary outcome for each trial will be change in visual acuity from baseline to the two-year examination, with better or same visual acuity as at baseline deemed a successful outcome. The principal secondary outcome will be change in health-related quality of life from baseline to the two-year interview, as assessed using the Medical Outcomes Study SF-36 questionnaire. Other outcomes of particular interest include adverse events, such as repeated surgery or other treatment of the study eye and loss of measurable visual acuity in the study eye. The participating centers will be 50 to 55 clinical centers where patients will be evaluated for eligibility, treated, and followed clinically; the Study Chairman's Office which is responsible for overall leadership and direction of the SST; the SST Coordinating Center which is responsible for providing scientific leadership and logistic support to the SST investigative team; and the SST Photograph Reading Center which is responsible for assessing the ability of the ophthalmologists to identify and enroll eligible patients and to adhere to the treatment protocol. Approximately 1600 patients will be enrolled in the four clinical trials and randomly assigned to one of the two treatment arms of the trial for which eligible by personnel at the SST Coordinating Center. An independent Data and Safety Monitoring Committee will review the data at least twice each year to assess the risks and benefits of surgery. This application is for funding to support the activities of the SST Photograph Reading Center. CENTER TRACK RECORD: The Photographic Reading Center has had extensive experience in serving in this capacity for other similar clinical trials such as the Macular Photocoagulation Study (MPS) and the Roferon-A in Neovascular AMD Study as well as the SST Pilot Study. Much of our understanding of the problem of CNV derives from investigations centered at the Wilmer Photograph Reading Facility. They have contributed in a major way to the definitions of the variety of lesions that may present and their associated prognoses and treatments. Their past experience has no doubt enabled them to define procedures which insure quality in all aspects of the functioning of a reading center. They appreciate the important external and internal procedures critical to the integrity of a study of this kind. These include such issues as development of photographic protocols, training of photographers and ophthalmologists, assessment of photograph quality and interpretation relative to inclusion and exclusion criteria, documentation of treatment adherence to protocol, evaluation of adverse events, evaluation of follow-up photos and archival activities. Internal issues as administration, photographic management and reading, data analysis and reporting, quality assurance are all described fully and give reason to be assured that they will be addressed appropriately. While there are real advantages to having the Reading Center and Study Chairman s Office (as well as the Coordinating Center) at the same institution to foster communication and coordinate effort, there is the possible weakness of proximity leading to a less stringent evaluation of performance. This

concern is somewhat mitigated as past experience has shown that collaborative efforts among this group have been admirably productive. INVESTIGATOR(S): Susan Bressler, M.D. would serve as the Principal Investigator of the SST Photograph Reading Center. Her previous experience includes acting a Principal and Co-Investigator for Reading Centers in other NEI-sponsored studies, particularly in the area of macular degeneration. Andrew P. Schachat, M.D. will act as Co-Investigator of the Photograph Reading Center. He has been the P.I. of the Reading Center in three other NEI-sponsored trials and has played important roles as a clinical ophthalmologist in other trials. The individuals identified as Senior Leader, Deborah Phillips, and Photograph Reading Coordinator, Rochelle Cooper, have served for many years in these capacities in other clinical trials. FACILITIES/ADMINISTRATIVE ARRANGEMENTS: The SST Photograph Reading Center is housed in the Wilmer Reading Center of the Retinal Vascular Center, where other reading centers for multi-center clinical trials are housed. It is not clear that dedicated space is available. The Reading Center is administratively distinct from the Coordinating Center. The scientific conduct of the Center is directed by Dr. Susan Bressler and assessed by the Director, Judith Alexander. Regular meetings are held with the Reading Center staff, the Study Chairman s Office, and the Coordinating Center. Communication with the clinical centers will be open and will serve to enhance photography related adherence to protocol and quality and to identify any perceived need for protocol modification. BUDGET NOTE: NEI Staff should evaluate the requested budget in light of their experience with the budget needs of reading centers in other clinical trials. ADMINISTRATIVE NOTE: Awards, if made, are limited to 5 years.

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

- **Project Title: SUBMACULAR SURGERY TRIALS--STUDY CHAIRMAN'S OFFICE GRANT**

  Principal Investigator & Institution: Bressler, Neil M.; Professor of Opthalmology; Ophthalmology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 30-SEP-1996; Project End 30-APR-2002

  Summary: The purpose of the Submacular Surgery Trials (SST) is to evaluate surgical removal of subfoveal choroidal neovascular lesions secondary to age-related macular degeneration, which is the most prevalent cause of irreversible severe vision loss in Americans over 65, ocular **histoplasmosis,** and unknown causes in four randomized clinical trials, each for a different lesion type and presumed etiology. Only one eye (study eye) of each patient is expected to be eligible for one of the four SST clinical trials. Patients assigned at random to the control arrn will be managed by either observation (no treatment) or laser photocoagulation, depending upon the type of lesion and the findings from earlier clinical trials of treatment of choroidal neovascularization. The primary outcome for each trial will be change in visual acuity of the study eye from baseline to the two-year examination, with better or same visual acuity as at baseline deemed a successfitl outcome. The principal secondary outcome will be change in health-related quality of life from baseline to the two-year interview, as assessed using the Medical Outcomes Study SF-36 questionnaire. Other outcomes of particular interest include adverse events, such as repeated surgery or other treatment of the study eye and loss of measurable visual acuity in the study eye. A parallel economic analysis of surgical management will be undertaken. Patients will be evaluated for eligibility, treated, and followed for clinical outcomes at 50 to 55 collaborating clinical centers. Other SST centers will be the Study Chairman's Office, responsible for overall leadership and direction of the SST; the SST Coordinating Center, responsible for providing scientific leadership and logistic support to the SST investigative team; and the SST

Photograph Reading Center, responsible for assessing the ability of the ophthalmologists to identify and enroll eligible patients and to adhere to the treatment protocol. 1600 patients will be enrolled in the SST in a two-year period and randomly assigned to one of the two treatment arrns of the trial for which eligible by personnel at the SST Coordinating Center. An independent Data and Safety Monitoring Committee will review the data at least twice each year to assess the risks and benefits of surgery. This application is for funding to support the activities of the SST Study Chairman's Office.

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

- **Project Title: T CELL RECEPTOR USAGE IN PULMONARY HISTOPLASMOSIS**

  Principal Investigator & Institution: Deepe, George S.; Professor; Internal Medicine; University of Cincinnati 2624 Clifton Ave Cincinnati, Oh 45221

  Timing: Fiscal Year 2003; Project Start 15-JUL-1997; Project End 30-JUN-2007

  Summary: This abstract is not available.

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

- **43-kilodalton glycoprotein from Paracoccidioides brasiliensis: immunochemical reactions with sera from patients with paracoccidioidomycosis, histoplasmosis, or Jorge Lobo's disease.** by Puccia R, Travassos LR.; 1991 Aug; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=270171
- **Activities of Sordarins in Murine Histoplasmosis.** by Graybill JR, Najvar L, Fothergill A, Bocanegra R, de las Heras FG.; 1999 Jul; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=89349
- **Antibodies in Histoplasmosis.** by Markowitz H.; 1967 Jan; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=314965

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

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

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