Morphine

A Medical Dictionary, Bibliography,
and Annotated Research Guide to
Internet References

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and Philip M. Parker, Ph.D., Editors

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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 morphine 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 morphine, 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 morphine, 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 morphine. 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 morphine, 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 morphine.

The Editors

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

CHAPTER 1. STUDIES ON MORPHINE

Overview

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

The Combined Health Information Database

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

- **Effect of Transcutaneous Electrical Nerve Stimulation for Pain Relief on Patients Undergoing Hemorrhoidectomy: Prospective, Randomized, Controlled Trial**

  Source: Diseases of the Colon and Rectum. 42(2): 180-185. February 1999.

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

  Summary: Pain control after hemorrhoids have been surgically removed (hemorrhoidectomy) remains a challenging problem. This article reports on a study that investigated the effect of transcutaneous electrical nerve stimulation (TENS) on pain relief in patients undergoing hemorrhoidectomy. Sixty patients with symptomatic hemorrhoids were randomly allocated into two groups, the acupoint group and the nonpoint control group. TENS was applied to those patients who received

hemorrhoidectomy, and patient controlled analgesia was achieved by injection of **morphine** through ambulatory infusion pumps. The measures included pain score, analgesic doses administered by the patients, and postoperative complications. Pain scores from 0 (no pain) to 10 (agonizing pain) were evaluated 8, 12, 16, and 24 hours after hemorrhoidectomy. The means for the control group and the acupoint group, respectively, were 5.9 and 4.1 at 8 hours, 5.7 and 3.5 at 12 hours, 4.1 and 2.3 at 16 hours, and 3.2 and 1.9 at 24 hours. There was a significant difference between treatment groups in **morphine** use, with 11.6 mg in the control groups and a mean of 6.2 in the acupoint group. The acupoint group tended to have less postoperative acute urinary retention and less need for analgesics than the control group. The authors conclude that TENS is effective for pain relief in patients receiving hemorrhoidectomy. Its efficacy and safety could assist outpatient pain management after hemorrhoidectomy. 3 figures. 2 tables. 23 references.

- **Oral Management of the Patient with End-Stage Liver Disease and the Liver Transplant Patient**

  Source: Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 86(1): 55-64. July 1998.

  Contact: Available from Mosby, Inc. 11830 Westline Industrial Drive, St. Louis, MO 63146-3318. (800) 453-4351 or (314) 453-4351.

  Summary: This article addresses the oral management of the patient with end stage liver disease and the liver transplant patient. The authors emphasize that the patient with end stage liver disease, who is in need of a liver transplant, should have a pretransplant dental evaluation. Such a patient faces lifelong immunosuppression with an increased risk of infection. The article discusses both the need for control of oral diseases before liver transplantation and guidelines for oral care in the immediately postoperative and long term transplant patient. Specific indications for antibiotic prophylaxis and antibiotic regimens are presented; in addition, the adverse reactions and side effects of immunosuppressant drugs are discussed. The authors review pertinent drug interactions related to the dental management of patients with end stage liver disease, and present specific management recommendations. Specific drugs covered include cyclosporine, FK 506, prednisone, monoclonal antibody (OKT3), azathioprine, antilymphocyte globulin (ATG), **morphine,** codeine, nonsteroidal antiinflammatory drugs (NSAIDs), sedatives and anxiolytic drugs, local anesthetics, barbiturates, and propofol. 5 tables. 95 references. (AA-M).

- **Radiation-and Chemotherapy-induced Mucositis in Oncology: Results of Multicenter Phase III Studies**

  Source: Journal of Oral Laser Applications. 2(2): 115-120. Summer 2002.

  Contact: Available from Quintessence Publishing Co., Inc. 551 Kimberly Drive, Carol Stream, Ill. 60188. (630) 682-3223. Website: www.quintessenz.de. Email: info@quintessenz.de.

  Summary: This article reports on a randomized, multicenter trial that was conducted to evaluate low-level He:Ne laser therapy (LLLT) for the prevention of acute radiation-induced oropharyngeal mucosal lesions. The study was open to patients with cancer of the oropharynx, hypopharynx, and oral cavity who were being treated by external radiotherapy. Patients were randomly assigned to either laser treatment (L positive) or sham treatment (L negative). Laser applications delayed time of onset, attenuated the peak severity, and shortened the duration of oral mucositis. The difference between L

positive and L negative patients was statistically significant from week 4 to week 7. Results on decrease in pain intensity were also quite convincing. Laser applications reduced the incidence and duration of **morphine** administration. Ability to swallow was also improved. The authors conclude that low level He:Ne laser seems to be a safe and efficient method for the prevention of radiation-induced stomatitis and chemo-induced mucositis, with a tremendous potential interest for combined modality treatment. 10 figures. 22 references.

- **Hip Fracture: Caring for a Fragile Population**

  Source: AJN. American Journal of Nursing. 99(2): 36-41. February 1999.

  Summary: This journal article provides nurses with information on caring for elderly persons who have a hip fracture. This type of injury and its postoperative complications can dramatically diminish the quality of life for many older patients. The article describes the most common sites and types of hip fractures, medical and surgical treatments, postoperative complications, and the prevention of postoperative complications. The main causes of hip fracture are fragile bone tissue as a result of osteoporosis and falls. Most hip fractures occur in the femoral neck or intertrochanteric region. Femoral neck fractures are classified as displaced, impacted, and comminuted. Intertrochanteric fractures are often comminuted. Signs and symptoms of hip fractures include excruciating pain in the high or thigh; adduction, external rotation, or shortening of the leg; and reluctance to move or put weight on the affected extremity. The most frequent surgical intervention for cervical neck fracture is a total hip arthroplasty. Another option is percutaneous pinning, which involves the use of pins or nails to stabilize the fracture. Intertrochanteric fractures are usually repaired by internal fixation. The most common method of postoperative pain management is intramuscular narcotic injection or parenteral **morphine** sulfate delivered as patient controlled analgesia. Common postoperative complications include urinary tract infection and urinary retention, changes in mental status, deep vein thrombosis and pulmonary embolism, hip dislocation, and ineffective coping. The goal of rehabilitation therapy is to restore function so that patients can care for themselves independently. A continuing education test accompanies the article. 10 references.

Federally Funded Research on Morphine

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

[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).

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

- **Project Title: A 3-FACTOR MODEL OF DRUG EFFECTS ON OPERANT RESPONDING**

  Principal Investigator & Institution: Gonzalez, Fernando A.; Morris Brown College 643 Martin Luther King Dr Nw Atlanta, Ga 30314

  Timing: Fiscal Year 2001; Project Start 01-JUN-1999; Project End 31-DEC-2005

  Summary: (Applicant?s Abstract): Hermstein?s mathematical formulation of the matching law (1970) has been applied to data from operant conditioning procedures to disentangle the changes in responding attributable to drug-induced alterations in motivation from the changes attributable to drug-induced motor function impairment. The goal has been to develop an assay procedure and a classification system for the mode of behavioral action of drugs that have predictive value about the range of behavioral effects of drugs and their abuse potential. The behavioral procedure most often used in the studies is a Multiple Variable-Interval schedule (MultVI) consisting of five components that vary from 5 to 300 s. The generated response rate data are fitted by the single alternative equation of the matching law to obtain the value of the two parameters of the equation: k and rb. A common interpretation of k has been that it reflects, exclusively, the organism?s motor capacity to respond. The parameter rb is presumed to denote motivational factors. Results of studies conducted in our lab cast doubt on the above interpretation of the parameters. The same studies, however, confirm that k and rb are not affected by drugs in the same way, and that they may reveal different underlying actions of the drug. An alternative mathematical model, not burdened by theoretical implications of the matching law, is herein proposed. The model contains an additional parameter that reflects a third factor that underlies responding under operant procedures: stimulus control. Experiments will be conducted to test the validity of the proposed model by manipulating variables that affect (1) facility to respond, (2) reinforcer efficacy and (3) stimulus control. The effects of acute injections of d-amphetamine, gammahydroxybutyrate, **morphine,** diazepam and pimozide on the parameters of the model will be studied with rats trained to respond under a six-component MultVI schedule. The effects of chronic administration of the drugs and the development of tolerance or sensitization as denoted by the three parameters will also be investigated. The project will provide minority undergraduates with research experience by involving them in all phases of the study as Research Assistants.

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

- **Project Title: ACCUMBENS-PALLIDAL GABA AND MORPHINE REINFORCEMENT**

  Principal Investigator & Institution: Hemby, Scott E.; Assistant Professor; Pharmacology; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-JUL-2006

  Summary: (provided by applicant): Opiate abuse continues to be a major public health concern in the United States, especially in light of the dramatic increase in the number of first time users. The development of more effective pharmacotherapies requires a more detailed understanding of the neurochemical, molecular and behavioral variables that

mediate opiate reinforcement. To date, a vast majority of animal studies assess the biological underpinnings of opiate reinforcement in the absence physical dependence, even though physical dependence is a characteristic of human opiate abuse. GABAergic medium spiny neurons projecting from the NAc to the ventral pallidum (VP) are likely neuronal loci for the reinforcing effects of opiates and are necessary for the expression of opiate self-administration. The long-term objective of this proposal is to further the understanding of the involvement of the accumbens-pallidal pathway in **morphine** self-administration in physically dependent rats. The first series of studies will assess the correlation of VP GABA with the effects of **morphine** administration in dependent rats. More specifically, these experiments will determine extracellular GABA concentrations ([GABA]e) in the ventromedial VP and dorsolateral VP, projection terminal regions of the shell and core accumbal-pallidal MSNs, respectively. These effects will be compared with subjects receiving yoked **morphine** and saline to assess the contribution of VP GABA in the reinforcing and direct pharmacological effects of **morphine** respectively. The second series of experiments will determine the role of VP GABA-A and -B receptors in mediating **morphine** self-administration. The effects of systemic and intra-VP administration of selective antagonists will be compared with food-maintained responding. A second series of experiments. In a third series of experiments, regional and single cell gene expression techniques will be employed to assess morphine-induced regulation of cAMP pathway transcripts in accumbens-pallidal MSN projections from the NAc shell to the ventromedial VP and NAc core to the dorsolateral VP. Changes in the expression levels of multiple genes will be assessed in terms of **morphine** reinforcement and direct pharmacological effects of the drug.

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

- **Project Title: ADENYLYL CYCLASE G BG STIMULATION AND OPIOID TOLERANCE**

  Principal Investigator & Institution: Gintzler, Alan R.; Professor; Biochemistry; Suny Downstate Medical Center 450 Clarkson Ave New York, Ny 11203

  Timing: Fiscal Year 2001; Project Start 01-AUG-1999; Project End 31-MAY-2004

  Summary: Adenylyl cyclase (AC) 'superactivation' has long held a central position in models of opioid tolerance. The enclosed application will explore a new, complementary hypothesis that opioid tolerance also results from changes in the consequences of opioid receptor activation of Gi. Specifically, it is postulated that chronic opioid treatment induces a shift from opioid receptor- Galphai inhibition to Gbetagamma (Gi-derived) stimulation of AC activity. This would result from the induction of Gbetagamma-stimulated ACs and increases in AC isoform-specific phosphorylation after chronic **morphine.** In chronic morphine-treated tissue and cell lines, stimulatory responsiveness of some AC isoforms, assessed in the absence of exogenous opioid, is significantly reduced. The switch from inhibitory to stimulatory opioid receptor signaling would compensate for this attenuated activity. Consequently, despite the continued presence of inhibitory concentrations of opioid, 'normal' activity of these isoforms would be maintained, i.e., opioid tolerance would ensue. Although the myenteric plexus has been of enormous value in formulating the above hypothesis, its proof will require the use of simpler, cell culture systems such as CHO and HEK 293 cell lines, stably transfected with the mu opioid receptor. The specific aims are: (1) Determine the effect of chronic opioid treatment on levels of mRNA encoding Gbetagamma-stimulated AC isoforms and AC protein. (2) Determine the effect of chronic opioid treatment on inhibitory vs stimulatory opioid receptor-AC signaling. (3) Determine if the chronic morphine-induced shift from inhibitory to stimulatory opioid receptor signaling is mediated via

augmented Gbetagamma stimulation of AC. (4) Determine the specific AC isoform(s) (I, II, IV VII) and sites therein that manifest augmented phosphorylation following chronic **morphine.** Altered content of G proteins and opioid receptor coupling thereto has been a predominant focus of attempts to elucidate neurochemical underpinnings of tolerance. The formulation that chronic **morphine** induces changes in the relative abundance and phosphorylation state of specific AC isoforms which in turn alters the consequences of opioid receptor activation of Gi is novel. It represents a new approach to probing narcotic tolerance which could result in more effective pharmacotherapies for managing pain.

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

- **Project Title: AIDS AND OPIATES: A MONKEY MODEL**

  Principal Investigator & Institution: Donahoe, Robert M.; Associate Professor; Psychiatry and Behavioral Scis; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2002; Project Start 10-FEB-1997; Project End 31-JAN-2006

  Summary: (provided by applicant): IV-drug abuse is a prominent risk factor in AIDS. Credible support can be found that opiates have no effect on AIDS progression, or are exacerbatory, or inhibitory. In a pilot monkey study, we found that AIDS progression was slowed by **morphine** dependency. We have subsequently initiated a large. (20 rhesus/group, **morphine** vs saline) study to confirm this observation. This competitive renewal application is directed at continuing this effort. Monkeys have been on opiates and virus for 1-1/2 yr. AIDS progression rate with our model cannot be judged until 3-4 yr post-virus infection. So, it is too soon to know whether opiate dependency is altering AIDS progression in this study. To date, only 2 control monkeys have died from AIDS. Mean viral titers do not differ between groups, which suggests that their progression rates will be similar; yet, monkeys on opiates show viral-immune interactions interpretable as being protective. Thus, we plan to continue this study until an endpoint in rates of progression is reached where differences between test and control animals, if they exist, will be obvious (predicted in yr-2 of the proposed grant). Viral titers and mutation rates, and potentially contributing factors like the ability of the host to repair DNA damage are all being followed in conjunction with a variety of relevant immune measures. These analyses are expected to yield important interdependent correlates of AIDS progression that will help qualify the progression outcome. An overlying second hypothesis is also being explored, i.e., that a well-maintained opiate-dependency will retard progression of neuro-AIDS. Neuropathology has been reported as elevated in heroin addicts, making this a particularly relevant current issue. We will continue examining CSF from our monkeys for this purpose to see if opiates alter viral and immune status in this compartment, and whether blood brain barrier integrity is affected. Preliminary data suggest that opiates do alter inflammation in the CSF. Also, biopsied lymph-node tissues are being examined for noradrenergic nerve integrity simultaneous with viral and immune measures. A variety of postmortem tests are planned, too, to assess somatic and neural pathology in terms of morphology, viral detection, cytokine profiles, and inflammation to look for quantitative and qualitative differences in animals exposed to **morphine** versus saline. This effort is being extended by a subcontract to Dr. Linda Chang to use MR Spectroscopy to test neural tissues for cell loss. Finally, many of the aforementioned types of tests, along with neuroendocrine tests, are to be used before monkeys are sacrificed in yr-4, to see whether opiate-withdrawal exacerbates virus production. These studies will test a counterhypothesis to our 'protective' hypothesis. That is, does the stress of opiate withdrawal exacerbate

AIDS by inducing AIDS virus production? In the end, we expect these studies to improve knowledge about whether and how opiates modify the progression of AIDS.

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

- **Project Title: BEHAVIORAL PHARMACOLOGY OF NARCOTIC ANTAGONISTS**

  Principal Investigator & Institution: Holtzman, Stephen G.; Professor; Pharmacology; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2001; Project Start 01-JUN-1975; Project End 31-AUG-2003

  Summary: (Applicant's Abstract) Chronic exposure to morphine-like drugs results in physical dependence and marked sensitivity to effects of opioid antagonists. Recent data indicate that pretreatment of rats with a single dose of **morphine** also increases dramatically sensitivity to opioid antagonists, as measured behaviorally. The proposed research will test the hypothesis that this phenomenon reflects acute physical dependence mediated primarily by the mu-opioid receptor, as well as derivative hypotheses and theoretical models. The pharmacological, neurochemical, and neuroanatomical bases of the phenomenon and its generality across species and drug class will be examined systematically. Several well-validated methodologies will be used in order to obtain converging evidence, for example, a) Drug discrimination: an animal model of subjective drug effects, with resolution to distinguish among effects mediated by different opioid receptors and to detect interoceptive stimuli associated with antagonist-precipitated opioid withdrawal. b) Autotitration intracranial self-stimulation: enables concurrent quantitation of effects of opioid drugs and drug withdrawal on operant responding and threshold for rewarding brain stimulation. c) In vivo microdialysis: a means of correlating behavioral measures with changes in extracellular levels of catecholamines in specific brain regions. d) Tail-flick test: a measure of pain threshold. Compared to chronic opioid dependence, acute dependence has received little research attention despite the fact that it is a robust phenomenon that occurs in humans as well as in laboratory animals. Acute agonist-induced sensitization to opioid antagonists appears to be an exquisite example of neuronal plasticity, reflecting the first hours of the drug-receptor interactions that lead to chronic physical dependence upon opioids.

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

- **Project Title: BIFUNCTIONAL OPIOID/CCK LIGANDS FOR PAIN**

  Principal Investigator & Institution: Porreca, Frank F.; Professor of Pharmacology and Anesthesio; Pharmacology; University of Arizona P O Box 3308 Tucson, Az 857223308

  Timing: Fiscal Year 2001; Project Start 15-MAY-1999; Project End 31-MAR-2003

  Summary: This proposal is based on the hypothesis that a molecule which has CCK receptor antagonist actions and opioid agonist actions will offer therapeutic advantage for the management of the pathological pain states associated with nerve injury (i.e., neuropathic pain), as well as acute pain, with minimal (or no) development of tolerance and physical dependence. CCK is an endogenous "antiopioid" which blocks **morphine** antinociception. CCK antagonists enhance **morphine** antinociception and block **morphine** antinociceptive tolerance. Levels, and/or availability, of spinal CCK are believed to be differentially altered by neuropathic or inflammatory pain suggesting the importance of CCK in pathological states to limit the actions of opioids for pain relief. Thus, inflammation has been suggested to decrease spinal CCK levels/availability and enhance **morphine** antinociception, while nerve-injury increases spinal CCK levels/availability and decrease **morphine** antinociception. We propose to exploit these

known opioid-CCK interactions in nerve-injury associated nociception (i.e., "pain"), as well as in acute pain, by testing the hypothesis that bifunctional molecules with a profile of CCK antagonist and opioid agonist can be discovered and be of therapeutic benefit for acute and nerve-injury related pain without significant development of antinociceptive tolerance and, possibly, without or with reduced physical dependence. This hypothesis will be tested by synthetic efforts aimed at modifying the structure of our lead compound, SNF 9007, which displays low nM affinity for CCKB and delta opioid receptors and agonist activity at both sites. Our synthetic efforts will attempt to discover a molecule which has high affinity and antagonist properties at CCKA or CCKB receptors (i.e., "balanced" CCK receptor antagonist) and high affinity and agonist properties at opioid mu or delta receptors. Novel molecules will be evaluated for affinity at CCK and opioid receptors, as well as agonist/antagonist activity at these receptors. Appropriate candidates will then be evaluated in both acute and nerve-injury associated nociception. Single and repeated administration of the molecules will be performed to evaluate the possible development of antinociceptive tolerance, and possible physical dependence will be determined by precipitation with naloxone. It is expected that this work will lead to novel and potentially useful medications for treatment of (a) neuropathic and acute pain (b) chronic pain without tolerance and (c) pain in those tolerant to opioids. This novel mechanism of action should yield therapeutic utility as well as provide an increased understanding of opioid-CCK interactions in normal and pathological pain states.

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

- **Project Title: CAREER DEVELOPMENT PROGRAM IN FUNCTIONAL NEUROIMAGING**

  Principal Investigator & Institution: Byas-Smith, Michael G.; Anesthesiology; Emory University 1784 North Decatur Road Atlanta, Ga 30322

  Timing: Fiscal Year 2001; Project Start 30-SEP-1995; Project End 31-AUG-2002

  Summary: Morphine continues to be the mainstay therapy for managing intense pain. Unfortunately, some patients who initially have good pain relief lose pain control despite advancing the dose and potency of medications. Evolving tolerance, neuropathic pain and/or ascending nociceptive stimulus intensity from disease are possible explanations. Rendering a cure is the goal, but often no remedy is available. To the extent that tolerance diminished pain control, curtailment of tolerance will improve patient care. The ultimate goal of the research is to expand our understanding and improve management of uncontrollable pain syndromes. The major goals of this Scientist Development Award are: I) to develop in the nominee special skills and knowledge in the use of Positron Emission Tomography (PET) and the neuropharmacology of opioids; and 2) develop clinically relevant techniques in PET to assess neurophysiologic responses to pain and therapy. The skills acquired in the training program will be applied to protocols which test the hypotheses that pain and opiates alter neuroactivation responses measurable with PET and that dextromethorphan, an NMDA receptor antagonist, attenuates tolerance to opiates. Seventy patients naive to chronic **morphine** use will be recruited. Each patient will be assigned to one of two treatment groups receiving **morphine** with either dextromethorphan or placebo therapy. Patients will be admitted to the hospital (GCRC) for 24 hours to begin therapy and optimally titrate and establish their daily **morphine** dosing regimen. Upon discharge, scheduled slow release **morphine** and P.R.N. administered immediate release **morphine** will be prescribe along with the test drug/placebo. Diaries, telecommunications and clinic follow-up will be used to monitor

daily pain ihtensity, side-effects and **morphine** use. Thirty of the seventy patients will undergo a pain activation study before and after the clinical trial to establish their neuroactivation pattern (H2-15-O bolus technique) with and without intraspinal fentanyl injection. These results will be compared to neuroactivation pain studies performed in eighteen normals before and after intraspinal fentanyl. These research activities are the perfect complement to the nominees educational plan and career objectives. The research is relevant and meaningful to patient care and provides a venue for the nominee to practice the concepts and principles gained from the tutorials and coursework. These integrated activities will allow for the development of an independent clinical scientist using PET to explore the problems of pain and the limitations of currently available analgesic medications.

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

- **Project Title: CHARACTERIZATION OF TOXICITY WITH SPINAL OPIATES**

  Principal Investigator & Institution: Yaksh, Tony L.; Professor; Anesthesiology; University of California San Diego 9500 Gilman Dr, Dept. 0934 La Jolla, Ca 92093

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-JUL-2006

  Summary: (provided by applicant): Continuous intrathecal infusion of concentrated **morphine** is widely used in pain therapy. Surprisingly, until recently there has been no study of the safety of such infusions. We investigated the effects of 28-day intrathecal **morphine** infusion in a canine model. Unexpectedly, at high **morphine** concentrations (as used in humans), we noted an aseptic mass of inflammatory cells (granuloma) arising from the dura-arachnoid, not the parenchyma, proximal to the catheter tip. Granulomas were not seen with vehicle or a variety of non-opioid agents. The alpha2 adrenergic agonist clonidine suppressed the granuloma. These observations lead to four hypotheses. 1. Granuloma induction by **morphine** is proportional to local concentration in cerebrospinal fluid and not simply total dose. 2: Effect is mediated by an opioid agonist action and is not limited to **morphine.** 3. The granuloma results from a local degranulation of dural mast cells leading to movement of inflammatory cells from the dural vessels. Accordingly, granuloma-inducing potency will be proportional to the ability to degranulate dural mast cells in ex vivo dural preparations. 4. Granuloma-inducing effects and dural mast cell activation are suppressed by local alpha2 receptor agonists and by a mast cell stabilizer. We will address these hypotheses using the canine model to examine the effects of continuous intrathecal infusion of equipotent doses of mu opioid agonists (morphine, morphine-6-glucuronide, L-methadone, hydromorphone, fentanyl or DAMGO) or equimolar concentrations of inactive opioid molecules (naloxone, morphine-3-glucronidc, D-methadone). In vivo treatment with a mast cell stabilizer, nedocromil sodium, will be examined for its effect on granuloma formation. In parallel studies, kinetics studies will permit comparisons based on measured CSF concentrations. Interaction between **morphine** and alpha2 agonists (clonidine, dexmedetomidine) will be studied by co-delivery. Granuloma formation and local mast cell degranulation and cytokines will be assessed histochemically and by CSF analysis. In summary, our initial work, provides the first definitive preclinieal data defining the effect, the attenuation by clonidine, and a novel mechanistic hypothesis for drug-induced degranulation of dural mast cells which suggests a novel method for the ex vivo screening of new agents. These studies are significant: 1) increasing incidence of reports of morphine-granulomas emphasize it is not rare; 2) our investigation of other opioids provide the first time assessment of the spinal safety of agents which are now in wide clinical use; and 3) this issue impacts on all agents targeted for intrathecal delivery. Accordingly, data obtained here regarding the role of local CSF concentration, the safety

of non-morphine agents and the potential ameliorating effects of adjuvant agents all provide novel information to refine the utility of this important therapeutic regime.

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

- **Project Title: CHRONIC MORPHINE: REGULATION OF ION CONDUCTANCES**

  Principal Investigator & Institution: Williams, John T.; Senior Scientist; None; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2002; Project Start 01-APR-1993; Project End 31-JUL-2007

  Summary: Chronic use of **morphine** results in tolerance to and dependence on the drug. One mechanism underlying cellular tolerance is an uncoupling of the opioid receptor from effects such that greater receptor occupancy is required to obtain a given response. This uncoupling mechanism has been studied using effectors that include; potassium and calcium conductances and the inhibition of adenylyl cyclase. A similar phenomenon is observed with acute opioid desensitization. Acute desensitization is thought to involve at least two linked processes, receptor uncoupling through an arresting dependent mechanism and removal of receptors from the plasma membrane through an internalization mechanism. Unlike more protracted forms of tolerance, acute desensitization is reversible within minutes and therefore easier to study in vitro. One goal of this proposal is to define the events that mediate the initiation and recovery from acute opioid desensitization. This goal has two parts, one is to characterize acute desensitization and determine the role of receptor internalization in that process. Given that receptor trafficking is an important form of receptor regulation, the second goal is to characterize how chronic **morphine** treatment alters desensitization and internalization of the opioid receptor. With a better understanding of the events that mediate desensitization and internalization the processes leading to long term tolerance may be more easily identified. The second goal is to identify post-synaptic cellular adaptations to chronic opioid treatment. These adaptations oppose the initial effect of opioid such that normal function is attained even in the continued presence of **morphine.** Thus adaptive mechanisms underlie an important form of tolerance. Two cell types will be examined the neurons in the locus coeruleus and interneurons of the VTA. There is an extensive knowledge of opioid actions in these areas, however, the identification and characterization of a post-synaptic adaptive mechanism studied in isolation has yet to be presented. Knowledge of alterations in regulation of ion channels during withdrawal form **morphine** may help in the development of more efficient protocols for the prevention of relapse to drug use.

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- **Project Title: COCAINE ADDICTION--ALTERATIONS IN REWARD CIRCUITRY**

  Principal Investigator & Institution: Breiter, Hans C.; Assistant Professor; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

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

  Summary: (provided by applicant) This proposal, entitled "Cocaine addiction: Mapping alterations in reward circuitry," is a request for a NIDA R01 submitted in response to the RFA "Cognitive Approaches to Addictive Processes (RFA DA-01-001). To study reward circuitry in humans, the investigators have developed multiple drug infusion protocols and cognitive neuroscience studies for use with functional magnetic resonance imaging (fMRI). This R01 research proposal asks two fundamental questions: (1) Does a common circuitry process reward expectancy and reward outcome information across distinct categories of reward, and (2) How does this circuitry function differently in drug naive

vs. cocaine dependent subjects for distinct categories of reward? To address these questions, this proposal outlines a strategy to evaluate the function of reward circuitry with regard to expectancy and reward outcome across three distinct categories of rewarding stimuli, namely pharmacological (morphine), monetary, and social reward. It further seeks to compare the function of this circuitry across matched cohorts of drug dependent subjects and healthy volunteers. The experiments proposed have already been successfully performed in separate cohorts of healthy controls, and piloted in cocaine dependent subjects. These studies demonstrate unique patterns of activation for the nucleus accumbens, amygdala, sublenticular extended amygdala of the basal forebrain, ventral tegmentum, and orbital gyrus with regard to reward expectancy and reward outcome. Specific Aim 1 is designed to evaluate the consistency of the fMRI response with regard to reward expectancy and reward outcome within the same individuals receiving three distinct categories of reward. These rewards include a pharmacological reward in the form of low-dose **morphine** infusions, non-drug reward in the form of money, and social reward in the form of beautiful vs. average faces. Specific Aims 2-4 apply each of these experiments to matched cohorts of cocaine dependent subjects and healthy controls to evaluate reward circuitry differences in the processing of expectancy information and outcome information between groups. Across these experiments, it is predicted that reward circuitry function will be diminished for non-drug reward in drug-dependent subjects relative to healthy volunteers, and that this alteration will be most pronounced for expectancy systems processing probability information about rewarding stimuli.

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- **Project Title: COCAINE INDUCED OPIOID, DOPAMINE AND BEHAVIORAL CHANGES**

  Principal Investigator & Institution: Unterwald, Ellen M.; Associate Professor; Pharmacology; Temple University 406 Usb, 083-45 Philadelphia, Pa 19122

  Timing: Fiscal Year 2001; Project Start 01-JUL-1996; Project End 31-MAR-2003

  Summary: APPLICANT'S ABSTRACT: The goal of the proposed research is to identify neurochemical alterations that occur during in vivo exposure to cocaine and to elucidate their functional significance. The identification of neurobiological imbalances that occur due to prolonged exposure to cocaine is critical for understanding the long-term consequences of cocaine abuse and for developing effective pharmacological treatment strategies. In previous studies, cocaine was administered to rats in three daily injections given at one-hour intervals for 14 days to mimic the binge-pattern of administration that often occurs in human cocaine abusers. Results demonstrate that mu and kappa opioid receptors and Dl dopamine receptors are upregulated in several brain regions of rats treated chronically with cocaine. In addition, the ability of delta opioid receptor agonists to inhibit adenylyl cyclase activity is attenuated, suggesting a functional uncoupling of delta opioid receptors and G-proteins. These finding are the basis of the proposed research, with the following specific aims. Studies will be performed to determine the impact of dosing regimen on the neurochemical alterations produced by cocaine. The effect of cocaine administered by several paradigms that produce either behavioral sensitization or tolerance on opioid receptors, dopamine receptors, and dopamine transporter sites will be determined. To investigate the functional consequences of cocaine-induced receptor alterations, the ability of opioid and dopamine receptor agonists to regulate adenylyl cyclase activity will be determined in brain regions of control and cocaine treated rats. Adenylyl cyclase activity will be assessed by measuring the accumulation of cAMP in the nucleus accumbens, caudate putamen, and olfactory

tubercle. Cocaine-induced changes in opioid receptor binding and opioid receptor-regulated adenylyl cyclase activity may be due to changes in the coupling of opioid receptors and G-proteins. The state of opioid receptor coupling will be investigated by determining the sensitivity of opioid agonist binding to guanine nucleotides and by comparing the affinities of opioid agonists and antagonists in brain sections from control and cocaine-treated animals. Receptor/G protein coupling will be assessed in several specific brain regions by performing these assays on tissue sections and generating autoradiograms. Finally, the regulation of opioid receptors dopamine receptors, and adenylyl cyclase activity during cocaine administration will be determined in murine models. Studies in mice will establish that the neurochemical perturbations caused by cocaine administration are relevant across species, and, hence, may be more generalizable to human cocaine abuse. In addition, the mechanism of cocaine's actions on opioid and dopamine systems will be investigated by studying this regulation in transgenic mice, in mice with targeted gene deletions (gene knock-outs), and in mice with a particular genetic trait such as a genetic preference for cocaine, **morphine,** and ethanol. For example, the role of Dl receptors in cocaine-induced opioid receptor regulation will be investigated by determining the effects of cocaine on opioid receptor expression in mice that are devoid of Dl receptors. Collectively, these studies will identify the neurochemical perturbations that occur during chronic cocaine exposure and identify the cellular and molecular mechanisms of this regulation. The potential outcome of these studies may be the information necessary for the development of more selective pharmacotherapeutic agents for the chronic management of cocaine addiction.

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- **Project Title: CUE-TRIGGERED REWARD SEEKING**

  Principal Investigator & Institution: Berridge, Kent C.; Psychology; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

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

  Summary: (provided by applicant): This project investigates biopsychological mechanisms of how reward cues trigger intense seeking behavior for their reward. For example, drug cues can cause human addicts to relapse into compulsive drug seeking behavior, even after long abstinence from drug use. We call this phenomenon, cue-triggered 'wanting' of reward, due to excessive attribution of incentive salience to the reward conditioned stimulus. We have developed a behavioral model to study the neurobehavioral mechanism of cue-triggered incentive motivation in rats, the pure conditioned incentive paradigm. Using a natural reward, sucrose, allows exposure of incentive salience 'wanting' mechanisms without contamination by drug withdrawal. We demonstrated that microinjection of amphetamine into nucleus accumbens specifically enhanced cue-triggered 'wanting' for sucrose reward by over 400%. Our behavioral model ruled out alternative explanations for mesolimbic mediation of cue effects (conditioned reinforcement, associative habits, etc.). We have also found that sensitization-related changes caused by prior amphetamine administration leads to a persistent increase in cue-triggered 'wanting' for reward as predicted by the incentive-sensitization hypothesis. In the proposed studies, we will investigate the role of specific dopamine receptors in cue-triggered 'wanting' (using microinjection of specific dopamine agonists and antagonists). We will also clarify the neuroanatomical roles of accumbens shell versus core (in a microinjection mapping experiment and using excitotoxic lesions). Importantly, we will assess whether mesolimbic activation that increase cue-triggered 'wanting' for sucrose also increases 'liking' for sucrose (using the taste reactivity measure of sucrose 'liking'). Finally, we will test the duration of the

sensitization-related increase in cue-triggered 'wanting' caused by prior cocaine, amphetamine or **morphine** administration, and will investigate the interaction of sensitization with mesolimbic activation by drug microinjection. These studies will clarify basic mechanisms of natural cue-triggered 'wanting', and will be useful in understanding mechanisms of cue-triggered relapse in human drug addiction.

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- **Project Title: DEVELOPMENT OF NEW ASYMMETRIC CATALYTIC PROCESSES**

  Principal Investigator & Institution: Wulff, William D.; Professor; Chemistry; Michigan State University 301 Administration Bldg East Lansing, Mi 48824

  Timing: Fiscal Year 2002; Project Start 05-JUN-2002; Project End 31-MAY-2006

  Summary: This proposal has as its goal the development of asymmetric catalytic versions of several synthetically important reactions. Efficient catalysts for asymmetric Diels-Alder reactions and aziridination of imines with diazo compounds have been developed with the vaulted biaryl ligands VAPOL and VANOL Future efforts will be directed to determining the scope, mechanism and synthetic applicstions of these existing processes. The information that has already been gained in the study of the Diels-Alder reaction has been used to design new ligands that are tailored for octahedral Lewis acids. Derivatives of the VAPOL ligand will also be explored as a platform for organo-palladium chemistry. If successful, these ligands will be screened for allylic substitutions, cycloisomerizations of enynes, [3 + 2] cycloadditions of TMM complexes and oxy(aza) palladation / carbonylation reactions. The scope of the asymmetric aziridination will be explored with respect to the imine and diazo substrates in both inter- and intramolecular modes. A method is proposed for the first general method for the alkylation of aziridine -2-carboxylates. Methods will explored for the development of a general method for the synthesis of both alpha-amino acids and beta-amino acids from the asymmetric catalytic aziridination reaction. Some of the targets for the aziridination reaction include **morphine,** the diamine portion of ritonavir, sphingolipids and the antitumor agent FR-900482.

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- **Project Title: DRUG ABUSE, SUBSTANCE P AND HIV**

  Principal Investigator & Institution: Ho, Wenzhe; Professor; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 19104

  Timing: Fiscal Year 2001; Project Start 01-FEB-2000; Project End 31-DEC-2003

  Summary: Description (adapted from applicant's abstract): The biologic effects of substance abuse, in particular the effects on the immune system, may significantly contribute to the neuropathogenesis of HIV infection. Opioids and substance P (SP) modulate immune function and may affect HIV infection of immune cells. The overall goal of this investigation is to understand the mechanisms of interaction of opioids and SP in the immunopathogenesis of HIV infection in human immune cell s. Our hypothesis is that opioids affect HIV infection of immune cells by affecting neuropeptides, such as SP. We have demonstrated that SP modulates mononuclear phagocyte function and affects HIV infection n in vitro. In addition, we have recently demonstrated that monocytes and lymphocytes express SP and its receptor (Ho et al., J. Immunol. 1997, Lai et al., J. Neuroimmunol, 1998). Furthermore, our preliminary in vitro experiments demonstrate that **morphine** enhances SP gene expression and stimulates SP production in human monocytes/macrophages. In this investigation, we will address four specific aims: First, we will determine whether opioids affect expression of SP and

its receptor in human immune cells (microglia, monocytes/macrophages, and lymphocytes). Second, we will determine whether opioids and/or SP affect expression of HIV receptors (CD4, CCR3, CCR-5, and CXCR4) and production of beta chemokines (Rantes, MIP-1 a, b) in these immune cells. Third, we will determine whether interaction of **morphine** (or other opioid receptor agonists) and SP modulates HIV replication, and whether specific antagonists for different opioid receptors or SP receptors play a role in blocking HIV infection of monocytes/macrophage (including microglia) and lymphocytes. And finally, we will determine SP levels in peripheral blood samples from HIV positive and HIV negative individuals who are currently receiving methadone maintenance treatment, as well as HIV+ and HIV- controls. The results of these studies should advance our understanding of opioids and SP as cofactors in the immunopathogenesis of HIV infection of drug abusers. These studies may also provide clues toward development of therapeutic strategies for HIV infection and AIDS.

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- **Project Title: DRUG DISCRIMINATION AND TOLERANCE TO COMMONLY ABUSED DRUGS**

  Principal Investigator & Institution: Stahl, Jeanne M.; Morris Brown College 643 Martin Luther King Dr Nw Atlanta, Ga 30314

  Timing: Fiscal Year 2001; Project Start 01-JUN-1999; Project End 31-DEC-2005

  Summary: (Applicant?s Abstract): There are 10 aims for this project involving two different lines of research. We propose to do the following: (1) to investigate the effects of three levels of weight reduction (0 percent, 10 percent, and 20 percent) on rate of acquisition and asymptotic performance on a two-lever drug discrimination task with gamma-hydroxybutyrate (GHB) vs. saline; (2) To test the discriminative stimulus properties of GHB, gamma-butyrolactone (GBL), flunitrazepam (Rohypnol), and ethanol; (3) To investigate discriminative stimulus properties of GHB and GBL when given as mixtures with ethanol; (4) To partially replicate and extend preliminary results on the effect of reinforcer type on the development of tolerance to reinforcer magnitude; (5) To determine the extent to which reinforcement context affects the development and degree of tolerance to amphetamine and **morphine;** (6) To determine the extent to which reinforcer magnitude affects the development and degree of tolerance to amphetamine and **morphine;** (7) To elucidate the role of behavioral variables in modulating the behavioral effects of drugs and to highlight their potential for the treatment of drug abuse; (8) To write a comprehensive review of the literature on the status of the concept of state dependent learning (SDL) vs. drug discrimination, to seek feedback from the few existing SDL researchers, and publish in a review journal; (9) To design experiments to partially replicate and extend our research with the Maier 3-table reasoning problem to determine whether rats that demonstrate a performance deficit when experiences are given under **morphine** and saline demonstrate similar deficits when tested with combinations of methadone and saline or buprenorphine and & saline; and (10) To expose high school, undergraduate, and graduate minority students to a variety of research methods used in behavioral pharmacology in order to prepare them for admission to and retention in excellent graduate research programs and, potentially, drug abuse research careers. Students will be involved in every aspect of this research including research ethics, animal care and handling, animal behavioral testing, data analysis, library research, literature review, and preparation of papers for presentation and publication.

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- **Project Title: EFFECT OF MORPHINE ON IMMUNE RESISTANCE TO T GONDII**

  Principal Investigator & Institution: Johnson, Lawrence L.; Trudeau Institute, Inc. Saranac Lake, Ny 12983

  Timing: Fiscal Year 2001; Project Start 30-SEP-2000; Project End 31-AUG-2003

  Summary: (Applicant's Abstract) The broad goal of the proposed studies is to determine the effect of **morphine** on the generation and expression of immunity to the protozoan parasite, Toxoplasma gondii, a major opportunistic pathogen of the CNS in AIDS patients. The work will focus on the impact of **morphine** in three physiologically pertinent experimental models of Toxoplasma infection: (i) chronic primary CNS infection, (11) a vaccination model, and (iii) exposure to **morphine** in utero. We will examine the effect of **morphine** on parameters of immune resistance in mice chronically infected with an ordinarily avirulent strain of T. gondil. Lymphocytes in peripheral blood, spleen, and the brain of morphine-treated and untreated mice with or without established chronic infections will be analyzed with regard to numbers, expression of markers of activation, and capacity to produce relevant cytokines and chemokines. We will also determine the effect of **morphine** on the generation and expression of immunity in mice given a Toxoplasma vaccine. Morphine-treated or untreated mice will be vaccinated with an avirulent strain of T. gondii, and the quality of their subsequent acquired immunity evaluated. In other experiments, mice will first be vaccinated then treated later with **morphine** to evaluate the effect of **morphine** on the expression of immunity that has already been generated. Finally, we will determine the effect of **morphine** on the development of immunity in mice exposed to **morphine** in utero. Pregnant mice will be treated with **morphine** and the immunological development and functional capabilities of their offspring evaluated postnatally and as adults in the context of anti-Toxoplasma immunity. Together, these studies will provide a comprehensive immunological foundation upon which to build detailed further analyses of the effects of an opioid drug on immunity to opportunistic infection.

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- **Project Title: EFFECTS OF DRUGS IN AN ANIMAL MODEL OF RELAPSE**

  Principal Investigator & Institution: Odum, Amy; Assistant Professor; Psychology; University of New Hampshire Service Building Durham, Nh 038243585

  Timing: Fiscal Year 2001; Project Start 01-SEP-2001; Project End 31-AUG-2003

  Summary: (provided by the applicant) Relapse is a persistent problem in treatment of drug dependence. Although individuals who abuse drugs may achieve periods of abstinence, they frequently reinitiate drug use. Often, relapse is precipitated by brief exposure to the drug that results in loss of control and return to regular drug use. The drug self-administration reinstatement procedure is an important animal model of relapse. Animals first learn to self-administer a drug, and then the opportunity for drug deliveries is removed. Re-exposure to the drug produces reliable reinstatement of extinguished drug seeking. Although this procedure has provided important advances in the understanding of relapse, the process by which drugs reinstate extinguished behavior is not clear. The incentive motivational account, an influential model of relapse, maintains that presentations of a rewarding stimulus such as a drug increase the organism's motivation to acquire that stimulus. Other possible mechanisms of reinstatement, however, are difficult to assess because the drug may have several simultaneous effects that cannot be disentangled in the drug self-administration procedure. In addition to functioning as reinforcers, drugs may also function as signals (discriminative stimuli) for drug availability. Drugs could also produce direct

(unlearned and unspecific) rate-increasing effects on behavior unrelated to the reinforcing effects. Examining the role of drugs in reinstating behavior maintained by food separates the reinforcing, discriminative, and direct effects of drugs because the function of the drug as a reinforcer is removed. The proposed experiments will evaluate whether drug-induced reinstatement is specific to behavior maintained by drugs by examining 1) the discriminative effects and 2) the direct effects of drugs in reinstating extinguished behavior previously maintained by food. Experiment 1 will examine the reinstating effects of the psychomotor stimulant cocaine and Experiment 2 will examine the reinstating effects of the opiate **morphine.** In summary, successful maintenance of abstinence is critical to the health and well being of former drug users. The proposed experiments will help to elucidate the various mechanisms involved in reinstatement to provide the basis for the development of better behavioral and pharmacological treatments to prevent relapse to drug abuse.

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- **Project Title: EFFECTS OF MORPHINE ON PULMONARY INFLUENZA INFECTION**

  Principal Investigator & Institution: Coussons-Read, Mary E.; Psychology; University of Colorado at Denver Campus Box 129 Denver, Co 802173364

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

  Summary: (Adapted from the Applicant's Abstract): Respiratory illness is a leading cause of death among HIV-positive intravenous opioid users. It is critical to understand the effects of opioid use on respiratory immunity and how such effects may impact HIV disease. The proposed AREA project uses an animal model to address this issue by characterizing the effects of **morphine** on pulmonary immunity and influenza virus infection in rats. The project will be conducted at the University of Colorado at Denver (UCD), which is an urban university that serves many nontraditional students, trains significant numbers of graduates who pursue careers in the biomedical sciences, and is not a major recipient of NIH support. This AREA project utilizes a Rat-Adapted Influenza Virus (RAIV) model, and preliminary data show that **morphine** treatment impairs both resting pulmonary immunity and the innate pulmonary immune response to RAIV. Specific Aim 1 extends these findings by examining dose-effect relationships in the impact of sub-chronic and chronic **morphine** treatment on resting pulmonary immunity. Lymphocyte proliferation to mitogen and superantigen, natural killer cell activity, and phenotypic distribution of lymphocytes will be used to assess resting pulmonary immune status. Specific Aim 2 will assess the dose-dependency and mechanism of morphine's effects on the innate pulmonary immune response to RAIV infection. Viral replication, pulmonary inflammation, and characterization of pulmonary cell types after infection will be used to measure the response to RAIV. Specific Aim 3 will test the hypothesis that **morphine** treatment will cause dose-dependent reductions in RAIV-specific acquired immunity, and that activation of opioid receptors is responsible for these effects. Measurements of anti-RAIV antibodies, RAIV-specific lymphocyte proliferation, and RAIV-specific CTL activity in the lungs and peripheral blood will be used to assess acquired immunity. Future studies will utilize RAIV and bacterial infection to increase understanding of how interactions between infection, drug use, and the immune system may adversely affect HIV infection in humans. Importantly, this project will establish a new and meritorious research program that will provide increased research opportunities for UCD students.

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- **Project Title: ENKEPHALINS: NEUROPHARMACOLOGY AND ABUSE POTENTIAL**

  Principal Investigator & Institution: Dewey, William L.; Professor; Pharmacology and Toxicology; Virginia Commonwealth University Richmond, Va 232980568

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

  Summary: (provided by applicant): Acutely administered **morphine** produces antinociception via mu opioid receptor (MOR)-mediated intracellular changes that include a decrease in calcium concentration, and a decrease in the activity of adenylyl cyclase and protein kinases. Chronic administration of **morphine** results in tolerance to its antinociceptive effects and a reversal in the direction of these intracellular events. Our recent studies have implicated protein kinases, especially cAMP-dependent protein kinase (PKA) and protein kinase C (PKC), as well as other steps in the phosphatidylinositol cascade in **morphine** tolerance. We have reported that inhibition of either PKA or PKC, blockade of phospholipase C or blockade of 1P3 receptors all cause a reversal of **morphine** tolerance. In other studies we have elucidated the involvement of ATP-gated potassium channels in the actions of acute and chronic **morphine.** Again we found diametrically opposite effects in the acute versus chronic treatment regimens. The overall goal of the proposed studies is to utilize pharmacological, biochemical and anatomical approaches to determine the critical cellular events underlying the tolerance that develops to morphine-induced antinociception. We have proposed a comprehensive model that includes the steps in the MOR-mediated signal transduction cascade that we hypothesize are involved in tolerance to morphine-induced antinociception. The proposed experiments will test our hypotheses that constant phosphorylation of proteins is required for the maintenance of **morphine** tolerance and that inhibition of protein-kinase-mediated phosphorylation or upstream steps in their signaling cascades reverses **morphine** tolerance. We propose to elucidate the mechanisms that lead to the reversal of analgesic tolerance by examining mu opioid receptor levels and phosphorylation state, G-protein activation, adenylyl cyclase activity, and the phosphorylation state of L- and N-type calcium channels.

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- **Project Title: ETHANOL & NEUROTRANSMISSION IN NUCLEUS ACCUMBENS**

  Principal Investigator & Institution: Crews, Fulton T.; Director, Bowles Center for Alcohol Stu; Center for Alcohol Studies; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

  Timing: Fiscal Year 2001; Project Start 30-SEP-1999; Project End 31-AUG-2002

  Summary: This FIRCA proposal will investigate changes in acetylcholine (ACh) and dopamine (DA) release from the nucleus accumbens shell (NA) following chronic ethanol treatment. Chronic ethanol is known to cause damage to cholinergic neurons (Arendt, 1993) and to sensitize DA neurons to glutamate excitotoxicity (Crews et a1. 1998). Recent studies have indicated that endogenous opiates are involved in alcohol addiction, leading to the approval of naltrexone, an opiate antagonist, for treatment of alcohol dependence. Studies of **morphine** and ethanol dependence have indicated changes in the interaction of DA and ACh during dependence and physical withdrawal and sustained changes during prolonged abstinence. Fiserova et.al.,1998 found that acute **morphine** decreases ACh release whereas a **morphine** challenge weeks after chronic **morphine** during prolonged abstinence results in an increase in ACh response to **morphine.** Endogenous opiates in the NA regulate DA release which regulates release from ACh interneurons in the NA. The reversal of the opiate response is

consistent with studies of the effects of chronic ethanol on ACh release in hippocampus. These studies will be extended to NA with additional investigations of the interaction of DA and opiates on DA and ACh release. The Specific aims are: 1. It is hypothesized that physical withdrawal from chronic ethanol treatment will alter ACh release in the NA. A chronic binge ethanol treatment protocol well known to cause substantial physical dependence will be used. Levels of microdialysate ACh will be determined in diet controls or ethanol-treated groups just after the last dose and throughout the physical withdrawal syndrome (0-96hrs) as well as during prolonged abstinence, e.g., 15 and 35 days after the last dose of ethanol. It is expected that the hyperexcitability of withdrawal will damage ACh neurons, reducing basal ACh release levels during prolonged abstinence and altering neuronal architecture and/or receptor density. 2. Aim 2 will test the hypothesis that DA microdialysate levels decrease during withdrawal from chronic ethanol and remain decreased throughout prolonged abstinence due to changes in DA neuronal architecture and/or receptor density. 3. Aim 3 will test the hypothesis that chronic ethanol treatment followed by prolonged abstinence results in changes in the interaction of DA and ACh. In these studies challenges with various receptor specific drugs will be used to investigate mechanisms of changes in neurotransmission. Post mortem studies will determine if changes in the density or distribution of receptors occur that could underlie changes in neurotransmission.

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- **Project Title: G PROTEIN COUPLED RECEPTOR TRAFFICKING AND OPIATE DRUGS**

  Principal Investigator & Institution: Whistler, Jennifer L.; Ernest Gallo Clinic and Research Center 5858 Horton St, Ste 200 Emeryville, Ca 94608

  Timing: Fiscal Year 2003; Project Start 20-JUL-2003; Project End 31-MAY-2008

  Summary: (provided by applicant): A fundamental question in addiction biology is why opiate alkaloid drugs such as **morphine** and heroin have a high liability for inducing tolerance and addiction while endorphins and enkephalins, the native peptide ligands for opioid receptors do not. Following activation by agonists, opioid receptors are regulated by multiple mechanisms. Of these regulatory mechanisms, rapid endocytosis of opioid receptors is of particular interest because it is differentially regulated by peptide agonists and alkaloid drugs. Specifically, endogenous opioid peptides and certain opiate drugs such as etorphine and methadone stimulate the rapid internalization of mu opioid receptors. **Morphine** however, strongly activates receptor signaling but fails to stimulate the rapid internalization of mu opioid receptors. Furthermore, following endocytosis, individual receptors can be sorted differentially between recycling endosomes and lysosomes. This sorting mechanism can contribute to receptor regulation in two ways that have opposing effects on cell signaling. First, endocytosis can serve as a mechanism for receptor resensitization by delivering internalized receptors to endosomes from where they are recycled to the plasma membrane in a fully active state. Second, rapid internalization can serve as a first step toward receptor downregulation by delivering the receptors to endosomes from which they are sent to lysosomes for degradation. Most membrane proteins are rapidly recycled, presumably by default, because membrane itself is recycled continuously. Therefore it is likely that membrane receptors that are rapidly degraded following their endocytosis do so through a specific targeting mechanism. The post-endocytic sorting of individual receptors between recycling and degradative fates is biochemically specific and appears to be highly regulated, identifying this sorting step as a fundamental mechanism that controls the degradative down-regulation of a large number of

receptors relevant to neuropsychiatric research. Hence for each receptor/ligand pair, one must evaluate both the endocytic and post-endocytic properties. The specific aims outlined below are designed to elucidate the molecular basis for endocytosis and sorting of the opioid receptors and assess in a cell culture model what effects altered trafficking has on the development of tolerance and withdrawal.

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- **Project Title: GENE ARRAY ANALYSIS OF OPIOID SYSTEM MUTANT MICE**

  Principal Investigator & Institution: Pintar, John E.; Professor; Neuroscience and Cell Biology; Univ of Med/Dent Nj-R W Johnson Med Sch Robert Wood Johnson Medical Sch Piscataway, Nj 08854

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

  Summary: (provided by applicant): Microarray profiling provides the capability to analyze complex changes in gene expression that accompany specific genetic and physiologic alterations. Our combined laboratories have produced multiple mutations in the murine opioid system and have developed technology to characterize gene expression in these models using microarrays. We propose two aims in which opioid system KO mice will be used in gene array studies. We will first extend preliminary data that have identified genes that are up- and down-regulated in several opioid receptor mutants. We will identify and characterize genes affected by opioid system disruption in the brain and spinal cord of individual and combinatorial KO mice. Once changes in expression have been confirmed, bioinformatic approaches will be used to determine whether specific functional classes of genes are altered and in situ hybridization will be used identify their cellular sites of expression. Together, these approaches will identify specific genes whose expression is altered by opioid system mutation, reveal the extent of compensatory change that accompanies these mutations, either alone or in combination, and provide initial indications of the functional significance of any changes. Second, we will explore changes in gene expression that accompany **morphine** administration during the development of analgesic tolerance and dependence to this drug using the above models. We propose to screen acute and chronically morphine-treated wild-type, MOR-1, KOR-1, DOR-1, ORL-l and ENK knock-out mice using microarrays to identify morphine-regulated genes and to determine whether changes in some or all of these morphine-regulated genes are absent in any of the above mutant strains, which all demonstrate deficits in the development of **morphine** tolerance, dependence, or both. We will extend preliminary data indicating that multiple gene expression changes can be identified following chronic **morphine** exposure and that at least some of these changes do not arise in MOR-1 mutant mice; we expect that more restricted sets of genes may be altered in other strains, such as DOR-1, ENK, or ORL-l KOs, in which development of analgesic tolerance following chronic **morphine** treatment is either delayed or abolished. Taken together, these studies should provide detailed, novel information about the relationship between opioid system gene expression and that of other neurotransmitter systems, as well as illuminate the molecular basis for tolerance, dependence and sensitization, which are critical questions in drug abuse research.

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

- **Project Title: GENE THERAPY FOR PAIN**

  Principal Investigator & Institution: Fink, David J.; Professor; Neurology; University of Pittsburgh at Pittsburgh 350 Thackeray Hall Pittsburgh, Pa 15260

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

Summary: (provided by applicant): Pain is a subjective experience with affective and cognitive components, an "unpleasant sensory and emotional experience associated with actual or potential tissue damage that serves an essential role in alerting an individual to potentially harmful stimuli in the environment". But chronic pain, often disabling and refractory to treatment, represents a difficult medical problem with enormous societal impact. Herpes simplex virus (HSV) naturally targets with high efficiency to neurons of the dorsal root ganglion (DRG) from peripheral inoculation. We have demonstrated that HSV based vectors can be used to transduce neurons of the DRG to achieve an antinociceptive effect in models of inflammatory pain, neuropathic pain, and pain resulting from tumor in bone. The effect is local, synergistic with **morphine,** and persists despite tolerance to **morphine.** The preclinical data for this novel approach to the treatment of pain is compelling. In response to the RFA, we propose a series of studies to investigate the hypothesis that HSV-mediated gene transfer to the DRG may be used to treat chronic pain. These studies are designed to overcome the barriers that stand between preclinical proof-of-principle experiments and the development of a treatment for the human disease, and to create novel vectors to enhance gene therapy for specific types of pain. Five specific aims are outlined. Specific Aim 1. To define the duration and dose-response characteristics of the vector-mediated analgesic effect. Specific Aim 2. To construct a vector with a regulatable "switch" to control vector-mediated enkephalin expression in vivo. Specific Aim 3. To test the effect of prior immunity on vector transduction, the potential of the recombinant vector to reactivate latent virus, and to study the level and kinetics of the anti-nociceptive response following repeated vector re-inoculation. Specific Aim 4. To systematically evaluate biodistribution and biosafety of the recombinant enkephalin expressing vector in rodents. Specific Aim 5. To create and test novel HSV-based vectors in models of neuropathic, inflammatory, and cancer pain.

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- **Project Title: GENES AND PROTEINS LEADING TO ADDICTION**

  Principal Investigator & Institution: Friedman, Theodore C.; Assistant Professor; Internal Medicine; Charles R. Drew University of Med & Sci 1621 E 120Th St Los Angeles, Ca 90059

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

  Summary: (provided by applicant): Drug addiction is a complex state that results from compulsive drug intake, in which both neurotransmitter and hormonal systems are affected. The state is comprised of tolerance, sensitization, dependence and reward that lead to drug seeking and compulsive use. Many brain substances are altered with chronic drug use and are likely to be involved in the state of drug addiction. Therefore, the main goal of this proposal is to identify and characterize genes and gene products in specific brain regions in mice that are altered as the organism is exposed to acute and chronic opiates. We hypothesize that opiate use leads to altered neurohormonal levels mediated by changes in the processing enzymes that control the ratio of active hormone to prohormone. Two prohormone convertases, PC1 and PC2, are believed to be primarily responsible for the activation of many pro-neurohormones, e.g., PC1 generates ACTH and PC2 generates the endogenous opiate, b-endorphin, from the precursor, pro-opiomelanocortin (POMC). The regulation of PC1/PC2 is linked to the cAMP/cAMP response element binding protein (CREB)/cAMP response element (CRE) system. Agents such as opiates that alter CREB levels can be expected to change the activity of these prohormone processing enzymes and affect the biosynthesis of addiction-

mediating hormones with major biochemical and behavioral consequences to the organism. By affecting CREmediated gene transcription, opiates also likely modulate other genes and gene products that have not been investigated due to the lack of technology and information available. In this grant application, we propose to conduct a series of interconnecting experiments to test the hypothesis that acute and chronic **morphine** exposure regulates CRE-mediated gene expression in discrete brain regions. The specific aims are designed to test this hypothesis by: 1) determining the brain regions expressing CRE-responsive genes following **morphine** exposure; 2) monitoring the levels of the prohormone processing enzymes, PC1 and PC2, as well as bioactive peptide hormones in these regions; and 3) determining novel or uncharacterized genes/proteins regulated by various paradigms of **morphine** exposure in CRE-responsive mouse brain regions. The focus of this proposal will be to use two new technologies, ProteinChip Array (SELDI-TOF Mass Spectrophotometry) and Gene Chip Array, to characterize and identify genes and proteins involved in opiate use.

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- **Project Title: GENETIC ANALYSIS OF DRUG ADDICTION**

  Principal Investigator & Institution: Walters, Carrie L.; Animal Biology; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

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

  Summary: (provided by applicant): The transcription factor cAMP response element binding protein (CREB) has been implicated as a common mediator in the mechanisms of action of drugs of abuse. Our lab has produced a genetically engineered mouse that is lacking the alpha and deltaisoforms of this transcription factor and have shown that while the CREBalphadelta mutant mouse does not find **morphine** rewarding, this mouse finds cocaine more rewarding than wild type control mice. The objective of this proposal is to examine why there is a different response to **morphine** and cocaine and to determine if there are differential responses in these mice to other drugs of abuse. Because **morphine** and cocaine have different sites of action, we propose that there is a differential function and distribution of CREB in the mesolimbic dopamine reward pathway and that administration of drugs of abuse that have similar mechanisms of action will result in similar behavioral results. This hypothesis will be tested by the following aims: 1) Determine if there is a differential distribution and function of CREB in the mesolimbic dopamine reward pathway using Western blots, electrophoretic mobility shift assays and RT-PCR for downstream targets in a region-specific manner. 2) Determine if there is altered regulation of upstream components of the cAMP signal transduction pathways in these mutant mice. 3) Determine the role of CREB in the positive reinforcing properties of drugs of abuse with nicotine and alcohol.

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- **Project Title: GENETICS OF OPIOID INDUCED HYPERALGESIA**

  Principal Investigator & Institution: Clark, David J.; Anesthesia; Stanford University Stanford, Ca 94305

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-JUL-2005

  Summary: (provided by applicant): Opioids constitute the single most useful and commonly used class of analgesics for pain of moderate or severe intensity. The use of opioids for chronic pain has grown very rapidly in recent years, yet we have a poor understanding of some of the limitations of this form of therapy. Recently it has been reported both from work in humans and animal models that the chronic administration

of opioids can lead to a state of hyperalgesia termed opioid-induced hyperalgesia (OIH). This phenomenon may limit the utility of opioids used for the treatment of chronic pain. Our understanding of OIH to this point has relied primarily on the use of pharmacological tools and has grown to include data supporting roles for monoxide signaling systems like heme oxygenase and nitric oxide synthase, the NMDA receptor, dynorphin and alterations in various nociceptive and regulatory pathways. We lack, however, data concerning the genetics of susceptibility to OIH. Where employed by other investigators genetic studies involving mice have provided unique incites into the mechanisms of nociception and analgesia. We propose to employ a genomic mapping strategy in which behavioral observations concerning the susceptibility of several strains of mice to the development of OIH after the repeated administration of **morphine** are coupled with a recently developed computational algorithm and a single nucleotide polymorphism (SNP) database to identify segments of the genome likely to be involved in susceptibility to OIH. In addition, we will be able to collect data concerning the basal sensitivity of these strains to **morphine,** as well as the extent of tolerance developed and the degree of physical dependence induced by repeated administration of this opioid. Thus a second dimension of the studies will be to make mechanistic comparisons between the phenomena of OIH, **morphine** induced analgesia, tolerance and physical dependence. These data will be collected over the two years of support requested (stage 1) and will form the foundation for stage 2 studies in which specific experiments will be designed to further refine our map and to examine the roles of genes chosen from the high probability mapping regions in the development of OIH. Thus our overall goal is to bring a unique and complimentary approach to the ongoing studies of OIH by using genomics to objectively identify genes involved in this phenomenon.

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- **Project Title: GLUCURONYL TRANSFERASE ACTIVITY IN THE FETAL PRIMATE**

  Principal Investigator & Institution: Garland, Marianne; Assistant Professor; Pediatrics; Columbia University Health Sciences New York, Ny 10032

  Timing: Fiscal Year 2001; Project Start 29-SEP-2000; Project End 31-AUG-2005

  Summary: A broad pharmocipia of drugs are used in pregnancy. Despite this, our knowledge of the disposition of drug to the fetus and how the fetus metabolizes various drugs is limited. Glucuronyltransferase, a common phase II conjugation system, is down regulated in the fetus and undergoes induction near birth. Despite the limited activity of this enzyme in utero, we have shown that fetal glucuronidation of drugs can have significant effects on fetal concentration of both drugs and their metabolites in the fetus. Drug concentrations are diminished and metabolite concentrations can exceed those in the mother. Furthermore. premature induction of these enzymes could lead to more pronounced effects. To predict the likely effect a drug will have on the fetus, pharmacokinetic models are required to estimate fetal drug and metabolite concentrations. Using glucuronyltransferase as a model, the goal of this proposal, is to establish the role of fetal metabolism in overall maternal-fetal pharmacokinetics. Our overall hypothesis is that fetal metabolism accounts for a significant amount of the observed nonplacental clearance of drug from the fetus. In addition, measures of glucuronyltransferase expression during fetal life will predict the observable changes in fetal drug and metabolite concentrations. We propose to test these hypotheses by a series of experiments in the fetal baboon. A novel pharmacokinetic approach to the quantification of the rate of formation of glucuronide metabolites in the fetal baboon will be combined with biochemical assays of glucuronyltransferase activity and quantitative measures of expressed protein (protein immunoanalysis and steady-state

mRNA) in fetal tissues. We will quantify the rate of glucuronide formation of buprenorphine, imipramine, acetominophen, and **morphine** in the fetal baboon across late gestation and correlate this with biochemical measures of enzyme-activity. We will quantify the change in metabolism following exposure to phenobarbital and dexamethasone, known inducers of glucuronyltransferase, and then quantify the effect this has on steady-state fetal-to-maternal ratios following maternal drug administration. In conjunction with recent advances in pharmacologic therapy for pregnant women, there is a pressing need for developing pharmacokinetic models which reliably define drug levels in the fetus. The long-term goal of this research is to reverse a trend which left the fetus as a therapeutic orphan.

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- **Project Title: HISTAMINERGIC MECHANISMS OF ANTINOCICEPTION**

  Principal Investigator & Institution: Hough, Lindsay.; Professor & Associate. Director; Pharmacology & Neuroscience; Albany Medical College of Union Univ Union University Albany, Ny 12208

  Timing: Fiscal Year 2001; Project Start 01-JUL-1984; Project End 31-MAY-2004

  Summary: (adapted from applicant's abstract): A new class of non-opioid pain-relieving drugs has recently been discovered that is chemically related to histamine. The prototype (named improgan) shows the following characteristics after direct injection into the rodent brain: a) highly effective, morphine-like antinociception on thermal and mechanical tests, b) no impairment of motor coordination or locomotor activity, c) a non-opioid mechanism that is independent of known receptors for histamine and 60 other targets, d) lack of tolerance with daily dosing, and e) unique structure-activity relationships among chemical congeners, suggesting the possible existence of a novel histamine receptor. However, little is known about the sites and mechanisms of action of improgan. To approach these issues, the following studies will be performed in rats. 1) Microinjection mapping studies will identify the CNS areas mediating improgan analgesia. Sites known to comprise the endogenous pain-relieving system will be studied (the periaqueductal grey, the rostral ventral medulla [including the nucleus raphe magnus] and the spinal cord). 2) The effects of these microinjections will be assessed on two measures of motor function (rotorod test and locomotor activity) to assess the specificity of improgan analgesia. 3) Microinjection studies with transmitter agonists and antagonists will identify the supraspinal and spinal transmitter mechanisms that mediate improgan analgesia. 4) Two kinds of experiments will search for the improgan receptor: a) the improgan-induced modulation of 35S-GTPgammaS binding in brain membranes will be studied, and b) homogenate and autoradiography techniques will study the binding of a radiolabeled derivative of improgan. These studies may also help to develop an in vitro assay for improgan-like activity. 5) To determine if improgan-like analgesics are effective in preclinical models of human inflammatory pain, the activity of improgan will be studied in the formalin nociceptive test in rats. The proposed experiments will characterize the fundamental neuronal mechanisms of non-opioid analgesia, and may lead to the discovery of a new histamine receptor, and/or to the development of new pharmacotherapies for acute and chronic pain.

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- **Project Title: HORMONE REGULATION OF PAIN PERCEPTION**

  Principal Investigator & Institution: Quinones, Vanya; Hunter College 695 Park Ave New York, Ny 10021

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

Summary: Gender differences have been observed in pain and opioid sensitivity. In general, females have lower nociceptive thresholds and achieve less analgesia from morphine-like (mu) opioids. During different reproductive stages female rats experience different pain thresholds, suggesting that the hormonal environment may modulate their nociceptive responses. The proposed studies will examine pain and opioid sensitivity in ovariectomized (OVX) rats with and without steroid replacement Behavior and gene expression will be concurrently examined. We will measure not only the response to an acute thermal stimulus (tail flick) but also models of subacute (formalin and intrathecal, IT NMDA) and chronic (nerve constriction) nociception and a test for mechanical sensitivity. Because the glutamatergic receptor system is an important modulator of pain sensitivity in animals and humans and in the development of **morphine** tolerance, we will examine this system together with the opioid system. Steroids can have powerful effects on gene expression and therefore we will measure their effects on glutamate and opioid receptors and neuropeptide mRNA and protein levels. The project will be conducted as an integrated mentoring and collaborative relationship between investigators at Hunter College of the City University of New York and Weill Medical College of Cornell University of New York and Weill Medical College of Cornell University. The Quinones' group will focus on understanding the role of steroids in the modulation of pain (nociception-tail flick and formalin tests) and opioid (mu and kappa) sensitivity (acute, development of tolerance and efficacy of NMDA receptor antagonists). The Inturrisi group will train Quinones' group in, not only the techniques necessary to produce the pain and opioid tolerance models, but also in the design and analysis (e.g., dose-response) of the proposed studies. The mentoring experience will extend to Hunter College students, who will have the opportunity to obtain further training in this area of neuroscience resulting in the expansion of neuroscience research at Hunter. The research expertise acquired through the mentoring-collaborative interactions will ensure that Dr. Quinones is more competitive in obtaining future independent funding. Research into the mechanisms underlying gender differences in pain and opioid sensitivity is of considerable interest since it can reveal systems, e.g., hormonal which modulate pain and opioid responsiveness, and therefore can provide a new understanding of how females cope with the aversive stimuli that may accompany copulation, parturition, and nursing. The proposed studies may also provide new insights into pain management approaches for females including those utilizing estrogen or progesterone based contraceptives or estrogen replacement treatment after menopause.

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- **Project Title: HYPOTHALAMIC PITUITARY ADRENAL AXIS**

  Principal Investigator & Institution: Zhou, Yan; Rockefeller University New York, Ny 100216399

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

  Summary: (provided by applicant): We hypothesize that (1) disruptions of the hypothalamic-pituitary-adrenal (HPA) axis, whether inherent or drug-induced, are central to the development of addictive diseases and in relapse to drug abuse by abstinent former opiate and cocaine addicts, (2) changes of gene expression in the HPA axis and specific brain regions underlie this disruption, and (3) the changes of HPA gene expression and hormonal responses are modulated by both dopaminergic and opioidergic systems. During the last five years, we extended our studies in humans to address changes of HPA gene expression by drugs of abuse using several animal

models. The goal of the present proposal for each specific aim is to extend our recent work to study changes in HPA gene expression (quantitative measures of specific mRNA levels) following chronic drug exposure, withdrawal and challenge. We will determine alterations of levels of the following mRNAs: (a) CRF, CRF type I and type II receptors, (b) endogenous opioid system (preprodynorphin, preproenkephalin, proopiornelanocortin and mu, delta, kappa receptors), (c) orphanin FQ and its receptor, and (d) two glucocorticoid receptors, within the HPA axis and specific brain regions (including the hypothalamus, pituitary, amygdala, frontal cortex, hippocampus, and pons/medulla). Most studies will be conducted in Fischer rats, one in Lewis rats, with inherent differences in preference for drugs of abuse, and one in Sprague-Dawley rats. Some studies will be conducted in transgenic mice with engineered disruption of specific HPA related opioid and dopamine genes. The specific aims are to: (1) extend recent studies of acute and chronic intermittent **morphine** to examine chronic effects of heroin and of early and prolonged withdrawal from chronic heroin with respect to HPA gene expression, hormonal responses, and behavior, (2) extend recent studies of acute, sub-acute or chronic "binge" cocaine to examine the effects of ascending dose chronic "binge" cocaine and to examine early and prolonged withdrawal from chronic "binge" cocaine with respect to HPA gene expression and hormonal responses, (3) extend recent studies of the involvement of dopaminergic and opioidergic systems in changes of HPA gene expression and hormonal responses induced by cocaine or **morphine,** and (4) study the functional integrity of the HPA axis to specific neuroendocrine stimuli following chronic "binge" cocaine and its withdrawal.

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- **Project Title: IMPORTANCE OF SLEEP & GENOTYPE IN DRUG ABUSE STUDIES**

  Principal Investigator & Institution: Dugovic, Christine; None; Northwestern University Office of Sponsored Programs Chicago, Il 60611

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

  Summary: (provided by applicant): It has been well established that both genetic background and the environment can have pronounced effects on how mice respond to drugs of abuse, including both psychostimulants and the opiates. In particular, different strains of mice respond differentially to drug treatment, and acut7e sleep deprivation alters the response to a number of drugs of abuse. However, essentially nothing is known about how the genetic background affects the response to drugs of abuse in animals with disrupted sleep. Examining the effects of sleep disruption on the response to drugs of abuse in mice with different genetic backgrounds is particularly important since one of the hallmarks of substance abuse in humans is disrupted sleep. Poor sleep, whether due to genetic or environmental causes, may in itself predispose one to abuse and drug addiction. One of the overall objectives of the proposed studies is to determine if the effects of acute sleep deprivation on the response to drugs of abuse in mice is dependent on genetic background. Since very little is known about the effects of chronic sleep loss on the response to drugs of abuse, a second overall objective will address this question and determine if the genetic background influences the effects of chronic partial sleep deprivation on the response to drugs of abuse. Six different strains of mice will be used to test hypotheses. that genetic differences in either sensitivity or sensitization of the locomotor response to either cocaine or **morphine** are affected by either acute or chronic partial sleep deprivation. The completion of the proposed studies is expected to not only lead to a better understanding of how genetic differences predispose mice to be more or less responsive to cocaine and/or **morphine** under both baseline and sleep deprivation conditions, but also will provide new insights for

optimizing the genetic animal models to be used for ultimately elucidating the genetic, neurochemical and biochemical mechanisms underlying the actions of drugs of abuse. The use of these genetic animal models is expected to lead to new genetic and pharmacological strategies for the treatment of drug abuse and addiction.

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- **Project Title: INTERACTIONS OF CAUSAL VARIABLES IN SMOKING INITIATION**

  Principal Investigator & Institution: Adams, Jann H.; Morehouse College 830 Westview Dr Sw Atlanta, Ga 30314

  Timing: Fiscal Year 2001; Project Start 01-JUN-1999; Project End 31-DEC-2005

  Summary: (Applicant?s Abstract): The number of young adults who smoke is steadily increasing. In 1993 25 percent of young adults between the ages of 18-24 years were smokers. Previous research had identified a number of factors which may be associated with smoking initiation, including perceived stress (Cohen & Lichtenstein, 1990), social support (Cohen & Wills, 1985), self-esteem (Shedler & Block, 1990), psychological adjustment (Romans & colleagues, 1993; Glassman, 1993; Shiffman, 1985; Stone, Dembroski, Costa & MacDougall, 1990; Cinciripini, Nezami, & Mace, 1989; Emmons, Weidner & Collins, 1989). The goal of this project is to outline a model that researchers could use to predict smoking initiation in young adults. This study will examine the association among stress reactivity, coping styles, psychological adjustment and smoking in young adults in order to better understand factors associated with greatest risk for beginning to smoke. Four hundred African American and Caucasian young adults between 18-20 years will be exposed to two psychological stressors while recordings of heart rate and blood pressure are taken. Participants will complete numerous measures of coping and psychological adjustment. Statistical analyses will include discriminant analyses and multivariate repeated measures of analysis of variance to assess hypotheses predicting poorer coping poorer psychological adjustment, and greater cardiovascular reactivity to stress among smokers. Clarifying the relationships among factors associated with smoking initiation in young people will assist in identifying individuals at risk for smoking.

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- **Project Title: MALE IDUS IN VIET NAM: ETHNO-EPIDEMIOLOGY OF HIV RISK**

  Principal Investigator & Institution: Clatts, Michael C.; Director; National Development & Res Institutes Research Institutes, Inc. New York, Ny 10010

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

  Summary: (provided by applicant): South East Asia has witnessed a rapid increase in unintended medical consequences associated with high-risk drug injection practices, including increases in the prevalence and incidence of viral pathogens prevalent in IDU populations such as HIV-1, HBV, and HCV. These trends raise grave concerns about the future spread of HIV infection in South East Asia and may portend the emergence of a self-sustaining epidemic in the region. Of particular concern, is the rapid increase in new infections among young, male heroin IDUs in Viet Nam. Structured as a unique type of collaboration between HIV researchers at NDRI and public health researchers and community-based physicians at Hanoi Medical University, this study has the dual goal of developing an epidemiological profile of injection-mediated risk among young male heroin users, while simultaneously advancing the technical capacity of researchers in Viet Nam to respond to the emerging HIV epidemic among IDUs. Specific aims of the

proposed demonstration project include: [1] To develop an epidemiological typology of the physical settings, situational events, social groups, and economic exchanges, in which young men use opiate-based drugs, including opium, morphine-base, and heroin, as well as the knowledge, attitudes, and beliefs regarding HIV risk in the injection of these substances; [2] To describe variability in behavioral practices employed in the preparation and injection of heroin-based drug solutions, including local drug marketing patterns, drug-acquisition strategies, and drug-sharing practices that may facilitate transmission of blood-borne pathogens; [3] To describe individual, social, and economic correlates of injectors' apprenticeship into heroin injection, including the pedagogical processes in which IDUs learn to prepare and inject heroin, their rationale for initiating and maintaining injection as a mode of drug (heroin) administration, and the early social course of heroin dependence; [4] To describe the accumulation of unintended medical consequences associated with the onset of heroin injection, particularly HIV and other viral pathogens prevalent among IDU populations; and [5] To extend concepts and methods adapted from anthropological ethnography in conducting epidemiological research among "out-of-treatment" populations in the U.S., with the goal of enhancing the technical capacity of researchers in Viet Nam in identifying and monitoring emerging trends associated with drug abuse and HIV.

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- **Project Title: MODULATION OF CELL-MEDIATED IMMUNE FUNCTION BY OPIATES**

  Principal Investigator & Institution: Peterson, Phillip K.; Professor and Director; Minneapolis Medical Research Fdn, Inc. 600 Hfa Bldg Minneapolis, Mn 55404

  Timing: Fiscal Year 2001; Project Start 01-MAY-1987; Project End 31-MAR-2003

  Summary: Because they impair cell-mediated immunity, opiates have been implicated as a cofactor in the progression of HIV-1 infection in the injection drug use (IDU) population. However, little data are available regarding the impact of opiates on cellular defenses at critical sites of infection in AIDS, e.g., the central nervous system (CNS). In this application, experiments are proposed for testing the hypothesis that opiates modulate the function of microglia and astrocytes (the brain's immune cells) and thus promote the pathogenesis of HIV-1 and Toxoplasma gondii, two of the most important causes of CNS disease in AIDS patients. Because of studies showing that endogenous opioid peptides and cocaine share many of the immunomodulatory activities of **morphine,** these agents will also be investigated. Two approaches will be taken, one involving in vitro murine brain cell culture models and the other involving murine models of toxoplasmic encephalitis. The aims of the in vitro studies have evolved from preliminary studies demonstrating that **morphine** alters the production by microglia and astrocytes of two key classes of immune mediators: cytokines and free radicals. Purified neonatal murine microglial cells, purified astrocytes, or cocultures of these glial cells with neuronal cells will be used to characterize: 1) the effects of **morphine,** endogenous opioid peptides, and cocaine on cytokine release from microglia and astrocytes and on the generation of free radicals by microglia, 2) the influence of **morphine,** endogenous opioid peptides, and cocaine on microglia- and astrocyte-mediated neuronal cell injury, 3) the impact of **morphine** and cocaine on glial cell-induced upregulation of HIV- 1 expression in chronically infected promonocytic cells and the effect of these drugs on HIV-1-induced neurotoxicity, and 4) the effect of **morphine** on microglial cell defense against T. gondii and the influence of **morphine** on T. gondii-mediated neurotoxicity. The specific aim of the in vivo studies will be to characterize the effect of chronic **morphine** administration on CNS toxoplasmosis. For

the in vitro studies, the immunomodulatory activities of endogenous opioids that are found within the brain will be studied by using opioid receptor agonists and antagonists that are highly selective for delta and kappa sites. The focus of the in vitro and in vivo studies, and the related methodologies, will be those cytokines (tumor necrosis factor-alpha, transforming growth factor-beta, interleukin[IL]-1, IL-6) and free radicals (superoxide, nitric oxide) implicated in the neuroimmunopathogenesis of HIV-1 or T. gondii. This research is a logical extension of our earlier work ont he effects of opiates and cocaine on peripheral immune cells to studies of immune cells of the brain, a principal target organ not only for drugs of abuse but also for HIV-1. The studies encompassed in the specific aims will contribute to our long-term objectives of understanding how opiates act as a cofactor in AIDS and of devising ways to interfere with the development of full-blown AIDS in the IDU population.

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- **Project Title: MOLECULAR BASES OF ADDICTIVE MEMORIES**

  Principal Investigator & Institution: Alberini, Cristina; Physiology and Biophysics; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-JUL-2005

  Summary: (provided by applicant): Drugs of abuse, such as **morphine,** cause long-lasting changes that underlie behaviors associated with drug addiction. It has been proposed that these changes are similar to those underlying memory formation. In agreement, many compounds that impair memory formation and inhibit memory-associated molecular pathway also attenuate drug tolerance and dependence. Newly formed memories are initially labile and require protein synthesis in order to be consolidated into a long-term memory. Furthermore, when a consolidated memory is recalled, it again becomes labile and requires protein synthesis in order to be maintained. The requirement for protein synthesis of addictive memories is virtually unknown. Here we propose to address several fundamental questions that will target the protein synthesis-dependent processes of addictive memory and other addictive behaviors. The results of these experiments will lay a foundation for further studies, which will examine molecules, pathways and pharmacological intervention in addiction. These investigations may produce significant breakthroughs that could help in the development of new therapies for drug addiction. The Aims of this project are: 1) To determine the temporal and anatomical specificity of protein synthesis requirement in addictive contextual associations. 2) To determine the behavioral specificity of the requirement for protein synthesis in addiction. 3) To determine whether the requirement for protein synthesis is a general mechanism underlying addictive memories.

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

- **Project Title: MOR EXPRESSING NEURONS IN PAIN AND MORPHINE ANALGESIA**

  Principal Investigator & Institution: Wiley, Ronald G.; Neurology; Vanderbilt University 3319 West End Ave. Nashville, Tn 372036917

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

  Summary: (provided by applicant): The use of neuropeptide-targeted cytotoxins to make selective neural lesions has achieved one noteworthy success in pain research to date, substance P-saporin. The general applicability of this first success in unknown, the present proposal seeks to extend this approach to target neurons that express the mu opiate receptor (MOR) using a targeted toxin composed of the mu opiate peptide,

dermorphin, to target the ribosome inactivating protein, saporin, selectively into neurons expressing MOR. There are numerous locations with putative central nervous system pain circuits where neurons express MOR. The site chosen in the present proposal is the substantia gelatinosa of the spinal cord dorsal horn. The goals of the present proposal are to determine if dermorphin-saporin has the desired targeting capability, to destroy MOR-expressing neurons, and to determine the effect of intrathecal dermorphin-saporin on pain perception using two thermal algesia assays, one reflex and one operant. Toxin will be administered into the lumbar subarachnoid space, and anatomic studies will determine the extent and specificity of the lesion. Thermal algesia testing will determine if the lesion differentially affects responses to high and low intensity noxious heat and if the lesion affects the analgesic potency of intrathecal **morphine.** Results of these experiments will establish if dermorphin-saporin is effective and selective in vivo, and if selective destruction of lamina II MOR-expressing neurons alters pain perception or the analgesic effects of intrathecal **morphine.** Many valuable future experiments and clinical applications may be possible if dermorphin-saporin proves effective.

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- **Project Title: MORPHINE ACTIONS ON THE IMMUNE SYSTEM**

  Principal Investigator & Institution: Chang, Sulie L.; Professor and Chair; Biology; Seton Hall University 400 S Orange Ave South Orange, Nj 07079

  Timing: Fiscal Year 2001; Project Start 01-MAR-1992; Project End 31-JAN-2002

  Summary: (Application Abstract) This is a renewal proposal of DA07058-06. The primary goal of this research is to examine the actions of **morphine** on the brain-immune axis. The neuro-endocrine-immune axis is influenced by a network of soluble polypeptide cytokines, such as interleukin-l (IL-1). Both **morphine** and IL-1 have been shown to modulate the immune response through direct actions on immune cells and indirect actions on a regulatory cascade mediated via the hypothalamic-pituitary-adrenal (HPA) axis. During the current funding period, we have used FOS proto-oncogene protein as a neuronal marker to show that both **morphine** and IL-1 activate the hypothalamic paraventricular nucleus (PVN). The PVN is a brain area critical for the functioning of the HPA axis and endocrine system. Chronic exposure to **morphine** desensitizes the FOS response in the PVN to subsequent treatment with either **morphine** or IL-1, and also attenuates the expression of IL-1 in the brain. In vivo infusion of an antisense to c-fos attenuates IL- 1-induced FOS activation in the PVN. Taken together, these data indicate that **morphine** use attenuates both the action and expression of IL- 1 in the brain. It has been suggested that the HPA is involved in morphine's effect on immune responses. Leukocyte-endothelial adhesion (LEA) is the initial step of the immune response cascade. Our continuation studies will address whether blockage of IL-1-induced FOS activation in the PVN has biological significance related to the HPA axis and LEA in the course of **morphine** tolerance with the following specific aims: (1) to characterize the AP-1 binding activity in the rat brain following treatment with either **morphine** or lL-1 using gel-shift mobility assay and Western blot analysis; (2) to characterize the effects of blockage of FOS activation on IL-1's modulation of the HPA axis by examining the mRNA levels of corticotropin releasing factor (CRF), pro-opiomelanocortin (POMC) by reverse-transcriptase polymerase chain reaction (RTPCR), CRF peptide, adrenocorticotropic hormone (ACTH), and corticosterone by radioimmunoassay (RIA); (3) to characterize the modulatory role of the HPA products, such as glucocorticoid, on LEA both in animal and in vitro cell models using intravital microscopy; cell culture and light microscopy; and (4) to characterize the expression of

IL- 1 in the central nervous system and periphery following chronic exposure to **morphine** using immunocytochemical staining, RT-PCR and Enzyme-linked immunosorbant assay (ELISA) techniques. These studies will elucidate the effects of **morphine** on the modulatory loop between the brain and the immune system. Specifically, these will establish the mechanisms by which **morphine** exposure affects IL-1-mediated pathways at the molecular, cellular and system levels.

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- **Project Title: MORPHINE LIKE BRAIN PEPTIDES--CELLULAR NEUROBIOLOGY**

  Principal Investigator & Institution: Siggins, George R.; Professor; Scripps Research Institute Tpc7 La Jolla, Ca 92037

  Timing: Fiscal Year 2001; Project Start 01-DEC-1983; Project End 31-MAR-2004

  Summary: (Adapted From The Applicant's Abstract): The purpose of the application is to continue and extend cellular neurophysiological studies on opioid peptides and opiates in two brain regions, the hippocampus and the nucleus accumbens, that contain proenkephalin- and prodynorphin-derived peptides. These regions were chosen because of their suggested roles in opiate reinforcement, as cellular models for opiate reward or dependence. The overall objective is to determine the physiological role of central opioid peptide-containing neurons in normal (Naive) subjects and those chronically-treated with opiates, using intracellular (current and voltage-clamp) and whole-cell clamp recording in rat brain slices in vitro. Our hippocampal studies during the last funding period have confirmed a dynorphin-induced augmentation of the M-current, a voltage-dependent K conductance, and have found that nociceptin (orphanin FQ), the agonist for orphan' receptor (ORL1), also augments IM via an opiate receptor mechanism and elicits another non-opiate receptor-mediated action likely to involve a K conductance. In addition, our studies in slices of nucleus accumbens core confirmed the opiate reduction of synaptic transmission in the nucleus accumbens and found pronounced interaction of opiates with glutamate receptor agonists, and especially with those acting on non-NMDA and NMDA receptor-mediated neurotransmission, in neurons from rats treated chronically with **morphine.** Therefore, our specific aims for the proposed funding period are to: 1) determine the second messenger(s) mediating the dynorphin and nociceptin effects on Im in CA1 hippocampal neurons. 2) Examine the effects of opioid on pharmacologically-isolated EPSCs and responses to NMDA, AMPA and kainate in CA1 of hippocampus. 3) Perform a battery of pharmacological tests to determine the site of action of chronic **morphine** treatment and possible changes in the postsynaptic NMDA receptor subunit composition in rat nucleus accumbens neurons. We also will use immunohistochemical methods, with selective antibodies to the NMAR2 subunits, and single-cell reverse transcriptase PCR, to determine if chronic **morphine** treatment causes a cellular and subcellular re- distribution of NMDA receptor subunits. These models will allow later test of several hypotheses, including those concerning neuroadaptative mechanisms following chronic opiate treatment. These studies should help more clearly specify the role of opioid and nociceptin peptides and their receptor in normal, opiate- seeking and opiate addictive-tolerant behavior, and help to provide a cellular basis for therapeusis of opiate craving'.

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- **Project Title: MORPHINE TOLERANCE IN BARRESTIN-2 KO MICE: BEYOND PAIN**

  Principal Investigator & Institution: Bohn, Laura M.; Cell Biology; Duke University Durham, Nc 27706

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

Summary: Morphine has been used for centuries to alleviate pain and still remains the analgesic standard to which newly developed drugs are compared. However, prolonged use of **morphine,** as well as other opiates, can lead to the development of tolerance, dependence, and ultimately, addiction. Recently, we showed that a G protein-coupled receptor regulatory element, betaarrestin-I, is required for mu opioid receptor (muOR) desensitization in vivo. Mice lacking the Betaarrestin-2 molecule, but not Betaarrestin-I, experience enhanced and prolonged **morphine** analgesia. Moreover, muOR desensitization proved to be essential in the development of **morphine** antinociceptive tolerance yet the presence of a functional desensitization mechanism was not required to develop **morphine** dependence. The dissociation of **morphine** tolerance and dependence in these mice raises the question whether other manifestations of muOR activation could be differently effected by a loss of Betaarestin-2. Using the Betaarrestin-2-knockout (betaarr2-KO) mice, we have the opportunity to evaluate whether other physiological parameters are subject to tolerance or sensitization after chronic **morphine** in an animal which lacks tolerance to **morphine** antinociceptive effects. We anticipate that not all of the physiological functions effected by chronic **morphine** will experience a change in regulation in the absence of Betaarrestin-2 just as the Betaarr2-KO mice experienced the same degree of **morphine** dependence as their wild-type littermates. This proposal aims to examine the following questions: AIM I: To test whether **morphine** tolerance occurs in the suppression of respiration or gastrointestinal transit in mice that lack **morphine** antinociceptive tolerance. AIM II: To test the effect of chronic **morphine** on the dopamine system in mice that lack **morphine** on the dopamine system in mice that lack **morphine** antinociceptive tolerance. AIM III: To examine the rewarding properties of **morphine** in mice that lack **morphine** antinoci ceptive tolerance. My hope is that this research plan will shed light on the role of muOR regulation in mediating the diverse physiological effects that occur with chronic **morphine** use or abuse. This research proposal has also been designed to direct my scientific development, allowing for the acquisition of diverse experimental approaches to better address the problem of drug abuse in an animal model. By combining the knowledge of systems relating to whole animal physiology, complex animal behaviors, as well as highly intricate neurochemical assessments, I hope to broaden my scientific approach in the pursuit of several independent avenues for my continuing research in the field of drug abuse. I envision that the observation made in the Betaarrestin-2 knockout mice, may lead to greater understanding of the mechanisms behind the potential for developing **morphine** tolerance, dependence, and addiction following chronic use or abuse.

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- **Project Title: MORPHINE-6 GLUCURONIDE--DEVELOPMENT OF BREATHING CONTROL**

  Principal Investigator & Institution: Olsen, George D.; Professor; Physiology and Pharmacology; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2001; Project Start 15-DEC-1993; Project End 31-DEC-2002

  Summary: The overall goal of this research is to examine the development of mu opioid receptors in the brainstem of the neonatal guinea pig in order to better understand the respiratory effects of chronic in utero **morphine** exposure and the role of morphine's active metabolite, morphine-6-beta-D-glucuronide (M6G), in respiratory depression. There are three main aspects to this proposal on the study of the mu opioid receptor that, when combined, make it unique. They are: 1) location, with the emphasis on the

respiratory nuclei of the brainstem; 2) development, with the emphasis on the neonatal animal during the first week after birth; and 3) treatment, with the emphasis on chronic intermittent versus a constant rate of in utero **morphine** exposure. The anatomical studies include the localization and quantitation of mu opioid receptors and receptor mRNA using immunohistochemistry, autoradiography, in situ hybridization and reverse transcriptase polymerase chain reaction (RT-PCR); the pharmacological studies include characterization of binding profiles of brainstem membranes and stably transfected CHO cells; and the functional studies include the determination of opioid-induced GTPgammaS binding in tissue and cells. These studies will provide new information about the role of mu receptors in development, morphine-induced respiratory depression, and importantly, the relationship of M6G binding (to mu and to a potential atypical site) in morphine-induced respiratory effects. The hypotheses are: 1) that there are developmental changes in D- Ala2-MePhe4-Gly-ol5-enkephalin (DAMGO) binding and opioid-induced GTPgammaS binding in brainstem respiratory nuclei during the first week of life; 2) that developmental changes in the mu opioid receptor are affected by in utero **morphine** exposure; and 3) that there are quantitative and qualitative differences between [3H]-DAMGO and [3H]-M6G binding and opioid-induced GTPgammaS binding in the brainstem during postnatal development and following in utero **morphine** exposure. Changes in opioid receptors associated with respiratory nuclei have consequences for the effects of **morphine** and M6G on breathing. This study is of significance for the fetus and neonate who are exposed in utero to heroin or other opioids because of maternal drug abuse, maintenance therapy of pregnant former opioid abusers or pain therapy.

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- **Project Title: MU OPIOID RECEPTOR GENE IN HEROIN ADDICTS**

  Principal Investigator & Institution: Yu, Lei; Professor; Cell Biol, Neurobiol/Anatomy; University of Cincinnati 2624 Clifton Ave Cincinnati, Oh 45221

  Timing: Fiscal Year 2001; Project Start 30-SEP-1994; Project End 31-JUL-2004

  Summary: Addiction to heroin is a major social problem, affecting over a million people in the United States. In the body and brain, heroin is hydrolyzed to **morphine,** which acts at the mu opioid receptor and results in a euphoric effect, thus conferring the reinforcing properties of the drug and contributing to addiction. Drug addiction is a complex process, thought to result from the interaction of social, environmental, and biological factors including a genetic component. In our original proposal, we hypothesized that genetic polymorphisms might exist in the mu opioid receptor and alter receptor function, contributing to variation in individual susceptibility to heroin abuse. During the current funding period we have observed five different single nucleiotide polymorphisms (SNPs); two of these SNPs were relatively common (10.5 percent and 6.6 percent allelic frequency), and both showed differential distributions among ethnic groups. One appeared to exert a protective effect against opioid addiction in one of the ethnic groups; it also altered beta-endorphin binding affinity and agonist potency. The other common variant occurred with a significantly higher frequency in former heroin addicts, suggesting a genetic predisposition for opioid dependence. In this competing renewal application, we propose to extend our study of the clinical and functional significance of genetic variation in the human mu opioid receptor. We will examine a larger number of study subjects, and determine the allele distribution in former heroin addicts and controls among different ethnic groups. We will also examine their impact on receptor modulation of neuronal Ca2+ channels and inhibition of adenylyl cyclase activity. Furthermore, we will determine the effects of the mu receptor

polymorphisms on the cellular responses to chronic **morphine** treatment, since the primary problems that develop during heroin addiction come from prolonged exposure to the opioid drug. Results from the proposed study in this renewal application will provide valuable information in two areas: First of all, by studying the effects of sequence variants on the cellular function of the mu receptor, we will understand how genetic polymorphisms impact on receptor activity and neuronal excitability. Furthermore, by determining distribution of these genetic variations between opioid-dependent individuals and normal controls, we will start to appreciate the role of genetic polymorphism is predisposition for or protection against opioid dependence.

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- **Project Title: NEOPAIN MULTICENTER TRIAL: DATA COORDINATING CENTER**

  Principal Investigator & Institution: Barton, Bruce A.; Senior Statistician and Vice President; Maryland Medical Research Institute, Inc 600 Wyndhurst Ave Baltimore, Md 21210

  Timing: Fiscal Year 2001; Project Start 01-JUN-1999; Project End 31-MAY-2004

  Summary: Frequent invasive procedures occur during neonatal intensive care causing pain and stress in preterm neonates during a critical period of increased brain plasticity. Repetitive painful experiences or prolonged exposure to analgesic drugs in preterm neonates may significantly alter their clinical and neurobehavioral outcomes. Analgesic practices recorded prospectively in 109 Neonatal Intensive Care Units (NICUs) showed that opioids and benzodiazepines were most commonly used, with large variations in clinical practice. No analgesia/sedation was given to 73.5 percent of neonates during NICU care or invasive procedures. A pilot randomized trial of **morphine,** midazolam, or placebo therapy in 69 preterm neonates showed reduced behavioral responses to pain and evidence of decreased incidence of death or neurologic injury in the **morphine** group. Trends for increased weight gain, earlier discharge, and other clinical outcomes support the need for and the feasibility of a definitive randomized trial. The NEOPAIN Multicenter Trial will randomize 940 ventilated neonates (24-32 weeks gestation) from 11 NICUs to receive continuous infusions of **morphine** or placebo. This design will provide 80 percent power for the detection of a 30 percent reduction in the composite outcome of neonatal death, Grade III or IV intraventricular hemorrhage, or periventricular leukomalacia. Data collection will include (maternal/infant) demographic, clinical and behavioral data. Other clinical outcomes include weight gain, severity of neonatal illness, and durations of NICU and hospital stay. Behavioral outcomes include neurobehavioral and psychometric testing at the time of hospital discharge. Trial coordination, data management and statistical analyses for the NOPAIN Trial are described in this application. The use of opioids (morphine and fentanyl) in preterm neonates is increasing without scientific evaluation and with scarce data on their clinical or adverse effects. The need for and clinical impact of prolonged analgesia in the NICU must be defined now before widespread use occurs. To provide data about the safety of opioid use, the effects of early pain/stress on the long-term neurobehavioral outcomes of prematurity in neonates without analgesia must be compared to the effects of analgesia use in neonates. This trial can provide those data. Thus, the results of this trial have the potential to significantly alter clinical practice in the NICU and reduce a major cause of severe morbidity and mortality in neonates.

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- **Project Title: NEURAL SUBSTRATE OF OPIATE ANALGESIA**

  Principal Investigator & Institution: Fields, Howard L.; Professor of Neurology; Medicine; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 94122

  Timing: Fiscal Year 2001; Project Start 01-FEB-1978; Project End 31-MAR-2004

  Summary: (applicant's abstract): Opioids are the most powerful analgesic agents presently available. However, there are significant limitations to their effectiveness. The general goal of the proposed research is to elucidate the circuitry underlying opioid analgesia and to determine the factors that limit the analgesic efficacy of opioids. This proposal is focused on opioid activated circuitry at the level of the brainstem and spinal cord. The rostral ventromedial medulla (RVM) is involved in brainstem control of nociceptive transmission. Opioid receptors and endogenous opioid peptides are found in this region, and microinjection of opioid agonists into RVM suppresses behavioral responses to noxious stimulation. Three classes of putative nociceptive modulating neurons have been identified in the RVM: Off cells, which suppress nociceptive transmission, are activated by **morphine.** On cells, which facilitate nociceptive processing, are inhibited by **morphine.** The other RVM neurons, neutral cells, are unaffected by **morphine.** We will use intracranial microinjection techniques, behavioral tests of nociceptive responsiveness, in vivo and in vitro single unit recording and application of putative neurotransmitter receptor agonists and antagonists to investigate RVM circuitry. We plan to determine how each class of RVM neuron modulates spinal cord dorsal horn nociceptive transmission. Another important goal of these studies is to determine the contribution of the mu, kappa, delta and orphanin opioid receptors to RVM-mediated modulation of nociception. Hopefully, by increasing knowledge of what limits the efficacy of opioid analgesia, new pharmacological strategies can be devised to produce more potent and selective analgesics.

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- **Project Title: NEURO-AIDS IN OPIATE DEPENDENT RHESUS MACAQUES**

  Principal Investigator & Institution: Cheney, Paul D.; Director; Physiology; University of Kansas Medical Center Msn 1039 Kansas City, Ks 66160

  Timing: Fiscal Year 2001; Project Start 30-SEP-1999; Project End 31-JAN-2005

  Summary: HIV-1 not only attacks the immune system leading to systemic AIDS but also enters the brain where it indirectly injures neurons and produces a constellation of symptoms known collectively as neuro- AIDS. Substantial evidence suggests that opiates may exacerbate the severity of HIV-1 disease and accelerate its progression to AIDS. In contrast, other studies have suggested that opiate exposure may have a protective effect and actually reduce the severity of disease and slow its progression to AIDS. Despite the importance of better understanding the linkages between drug abuse and the development of AIDS as well as AIDS-related neurological disease, there have been few studies of these relationships in animal models. To date, only two published studies have taken advantage of the simian immunodeficiency virus (SIV) infected macaque model, even though this model best reproduces the immunological, virological and neurological features of human HIV-disease. Over the past several years, we have focused our efforts on developing macaque models of neuro- AIDS. We recently completed studies on a cohort of nine rhesus macaques infected with neurovirulent strains of SIVmac. All monkeys in this cohort showed behavioral and neurophysiological impairments when tested on a battery that included reaction time, working memory and motor skill tasks as well as sensory and motor evoked potentials.

Neuropathological and stereological studies in the same monkeys demonstrated microglial nodules and multinucleate giant cells, the hallmarks of HIV brain infection, as well as significant neuronal cell loss. Recently, several pathogenic strains of chimeric simian-human immunodeficiency virus have been developed that contain the tat, rev, vpu, and env of HIV-1 in a genetic background of SIVmac239. One of these viruses, SHIVKU-2MC4, causes rapid CD4+ T cell depletion and neuro-AIDS following inoculation into rhesus macaques. This virus represents a significant advance as an animal model because the Env of HIV-1 has been implicated in HIV-1-induced neuropathogenesis and because the Env proteins of SIV and HIV-1 are only distantly related. In this application, we propose four specific aims that focus on the behavioral, neurological, immunological and virological consequences of opiate-dependence in SHIV-infected rhesus macaques. A fifth specific aim will investigate the cellular and molecular mechanisms by which **morphine** influences viral replication and co-receptor expression in lymphocyte and macrophage populations.

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- **Project Title: NEUROBIOLOGICAL FACTORS IN VULNERABILITY TO OPIOID ABUSE**

  Principal Investigator & Institution: Elmer, Gregory I.; Assistant Professor; Psychiatry; University of Maryland Balt Prof School Baltimore, Md 21201

  Timing: Fiscal Year 2001; Project Start 30-SEP-1997; Project End 31-AUG-2002

  Summary: This objective of this proposal is to characterize the behavioral and neural substrates that determine individual differences in the efficacy of **morphine** as a reinforcer and vulnerability to opioid-reinforced behavior. The specific hypothesis to be tested is that a significant relationship exists between individual differences in mesolimbic mu-opiate receptor concentration and the efficacy of **morphine** as a primary reinforcer. The projects outlined in this proposal will utilize genetically engineered animal models with behavior genetic and neuroanatomical techniques to investigate the relationship between regional mu-opiate receptor concentration and morphine-reinforced behavior. Inherited differences in regional mu-opiate receptor concentration (genetically engineered and naturally occurring) will be used as the independent variable to determine if differences in the distribution of mu-opiate receptors within the mesolimbic system significantly affect the efficacy of **morphine** as a reinforcer. Intravenous **morphine** self-administration behavior will be investigated in two sets of genetically engineered mice that overexpress the mu-opiate receptor, two commonly used recombinant inbred strains with high and low opiate receptor concentration and the two parental inbred strains used for transgenic animal production. Central mu-opiate receptor distribution in all genotypes will be characterized via autoradiographic techniques. Multivariate analysis of the relationship between mu-opiate receptor concentration in specific neuroanatomical regions and self- administration behavior will determine if a particular region or combination of regions accounts for the genetic variance seen in self- administration behavior. Overall, these projects will directly test the effect of genetically engineered alterations in CNS opiate-receptor concentration on the reinforcing effects of intravenous **morphine** injections and test the hypothesis that mu-opiate receptor concentration in one or more regions of the mesolimbic system are predictive of genotype-dependent differences in **morphine** self-administration behavior. if the results of the multivariate analysis identify a region or combination of regions that account for a significant portion of the variance seen in self-administration behavior, these results will provide a significant step towards identifying specific neural regions involved in the neurobiological substrates underlying vulnerability to opioid addiction.

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- **Project Title: NEUROCHEMICAL MECHANISM OF NARCOTIC ACTION**

  Principal Investigator & Institution: Loh, Horace H.; Frederick Stark Professor and Head; Pharmacology; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2001; Project Start 01-AUG-1989; Project End 31-JUL-2004

  Summary: (Applicant's Abstract) This is the fourth renewal (but third from my present post at the University of Minnesota), of my Career Research Scientist Award (K05 DA70554-27) which releases me from all the classroom teaching and most of the administrative duties at the University. The overall goal is to continue my long-standing research program in the molecular mechanisms of opioid actions and in the molecular basis of opioid tolerance. The current proposal is to test the hypothesis that the alteration in mu-opioid receptor synthesis and regulation is related to the mechanism of **morphine** action and **morphine** tolerance. To achieve this goal, we plan to carry out two independent but related studies: 1) to determine the regulation of mu-opioid receptor gene expression which controls the synthesis of receptors in specific cells. We hypothesize that the difference in spatial and temporal expression of mu-opioid receptor gene are caused by (or resultant of) characteristic interactions between cis- and transregulatory elements that exist in different cells (tissues) at different times. Therefore, we plan to define these elements using in vitro and in vivo models, 2) to determine the molecular mechanism of mu-opioid receptor regulation by a chemical modification (i.e., phosphorylation) and determine its possible relationship to **morphine** tolerance. In these studies we aim to elucidate the exact role of receptor phosphorylation/ dephosphorylation on cellular adaptation of chronic opioid treatment (i.e., tolerance). We also plan to pinpoint the exact phosphorylation sites of cloned opioid receptors which are involved in receptor desensitization as well as to determine the protein kinases (or other protein factors) that are involved in this process.

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

- **Project Title: NEUROLOGIC OUTCOMES AND PREEMPTIVE ANALGESIA IN NEONATES**

  Principal Investigator & Institution: Anand, Kanwaljeet S.; Professor; Arkansas Children's Hospital Res Inst Research Institute Little Rock, Ar 72202

  Timing: Fiscal Year 2001; Project Start 01-JUN-1999; Project End 31-MAY-2004

  Summary: This abstract is not available.

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

- **Project Title: NEURONAL MECHANISMS OF OPIOID ACTION**

  Principal Investigator & Institution: Zhu, Hong; Otolaryngology and Communicative Sciences; University of Mississippi Medical Center 2500 N State St Jackson, Ms 39216

  Timing: Fiscal Year 2003; Project Start 25-APR-2003; Project End 31-MAR-2005

  Summary: (provided by applicant): The noradrenergic locus coeruleus (LC) is enriched with opioid receptors and has been a useful model to study the neuronal mechanisms of opioid action. Recently, we found a novel effect of **morphine,** a classic opioid drug, on the firing pattern of LC neurons. Our electrophysiological studies show that a single dose of **morphine** induces long-lasting synchronous oscillatory discharges in the LC in addition to its well-known inhibitory effect (Zhu and Zhou, 2001). This morphine-

induced synchronous activity in the LC may have important implications in the development of opioid addiction. As a result of the synchronized LC firing, **morphine** may facilitate the release of neurotransmitter norepinephrine (NE) in widespread brain areas that receive noradrenergic LC input. NE, an important neuromodulator, has been shown to induce and facilitate synaptic plasticity in several brain regions. We propose that the morphine-induced synchronous activity in the LC is an important neuronal signal that induces synaptic plasticity in critical target areas, which are known to contribute to opioid addiction. This application will more thoroughly study the morphine-induced synchronous activity in the LC and its influence on the LC target areas. A unique strength of this application is that we employ a multiple-electrode recording technique that allows us to record several neurons simultaneously so that the temporal relationship among the activities of LC neurons can be studied. Three specific aims are proposed. Specific Aim 1 will further characterize the morphine-induced synchronous oscillatory discharges in the LC in an in vivo rat model. Effects of acute and repeated administration of **morphine** on synchronous activity in the LC will be examined. Specific Aim 2 will identify the specific mechanisms underlying the morphine-induced synchronous activity in the LC. We will examine the role of electrotonic coupling among LC neurons and the role of excitatory synaptic input in the morphine-induced LC synchrony. Specific aim 3 will study the role of LC input in the morphine-induced synaptic plasticity in the dentate gyrus of the hippocampus, an LC target area thought to be involved in opioid addiction. These experiments will improve our understanding of neuronal mechanisms of opioid action, which is crucial for understanding and perhaps treating of opioid addiction.

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- **Project Title: NEUROPROTECTION BY PACAP IN STROKE**

  Principal Investigator & Institution: Arimura, Akira A.; Professor; Medicine; Tulane University of Louisiana New Orleans, La New Orleans, La 70112

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

  Summary: Pituitary adenylate cyclase activating polypeptide (PACAP) was originally isolated from the hypothalamus based on its ability to stimulate adenylate cyclase in rat pituitary cell cultures. PACAP exists in two amidated forms with 38 (PACAP38) and 27 (PACAP27) amino acids, and PACAP38 is the major form in tissues. PACAP is a pleiotropic peptide that acts as a hypophysiotropic hormone, neurotransmitter and neuromodulator. More important, it functions as a neurotrophic factor that regulates neuronal development in the embryonic brain, and prevents neuronal damage in the adult brain. PACAP, at subpicomolar concentrations, is able to completely suppress the cell death induced by gp120 in neuron/glia co-cultures. Although PACAP exerts a direct neurotrophic effect on neuron cultures, nano- or subnanomolar concentrations of the peptide are required for this effect. Our study showed that intravenously administered PACAP38 prevented loss of pyramidal cells in the CA1 field of the hippocampus following global ischemia and reduced the infarct volume due to focal ischemia following the middle cerebral artery occlusion in the rat, even when the treatment was delayed. Although PACAP can enter the brain from the blood across the blood-brain barrier with an efficiency greater than other peptides and even **morphine,** the level which can be reached in the brain after systemic administration does not seem to reach nanomolar concentrations, but only subpicomolar concentrations. Based on these findings, we have hypothesized that te neuroprotective effect of subpicomolar concentrations of PACAP requires activation of astrocytes, and possibly microglia, which express the specific PACAP receptor (PAC1-R). It has been assumed that an

interaction between subpicomolar PACAP and a PAC1-R variant triggers an intracellular signaling cascade that leads to an increased expression of a neurotrophic factos(s). We propose to investigate these hypotheses using various in vitro models, and determine the signaling pathway as well as the key effector molecules involved in the neuroprotective action of PACAP. A better understanding of the mechanism of the neuroprotective action of PACAP38 will help to maximize the therapeutic efficacy of systemic administration of PACAP38 for neuronal damage resulting from stroke and other CNS disorders.

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

- **Project Title: NOREPINEPHRINE, EXTENDED AMYGDALA AND OPIATE WITHDRAWAL**

  Principal Investigator & Institution: Aston-Jones, Gary S.; Professor; Psychiatry; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

  Timing: Fiscal Year 2001; Project Start 01-AUG-1992; Project End 31-MAR-2003

  Summary: Applicant's Abstract Recent evidence from a variety of sources indicates that components of the 'extended amygdala' are importantly involved in opiate withdrawal (OW). This application seeks to extend our previous work on the noradrenergic locus coeruleus (LC) and OW by characterizing the role in OW of norepinephrine (NE) inputs to a key component of the extended amygdala, the bed nucleus of the stria terminalis (BNST). The BNST is the focus of this application because (I) it receives a very dense NE innervation, (ii) it is a key element of the extended amygdala that has been overlooked in studies of OW, and (iii) our recent data reveal that neurons in the BNST, and its NE afferents, are strongly responsive to OW. A set of coordinate anatomical and electrophysiological experiments are proposed that will characterize basic neurobiological attributes of NE in the BNST. Anatomical experiments will characterize the NE innervation of the medial and lateral subdivisions of the BNST, specifying innervation patterns and fiber morphologies. Using tract-tracing combined with immunohistochemistry, the sources of NE input to the different BNST subdivisions will also be identified. Electrophysiological studies will then confirm and characterize the inputs identified anatomically. The influence of the different NE afferents on BNST impulse activity will be determined, and the adrenoceptors involved in mediating responses will be identified. These studies will be some of the first to systematically investigate basic attributes of this dense noradrenergic projection to the extended amygdala. The role of this NE target area in OW will also be examined from the cellular to the behavioral level. We will determine the electrophysiological response of BNST neurons to OW; preliminary evidence for this application indicates that these cells will be strongly activated. The role of NE inputs from the different source cell groups in this OW response will be determined, and the adrenoceptor involved will be identified. Finally, in behavioral experiments the contribution of the NE-BNST synapse to somatic and aversive responses to OW will be determined. In particular, we will explore the role of the NE input to the BNST in conditioned withdrawal responses, a critical element in continued drug abuse and relapse. Together, the above experiments represent a comprehensive analysis of cellular substrates, and physiological and behavioral consequences, of the dense NE input to the BNST. These studies will provide much needed basic and withdrawal-related information on an important but neglected NE target in the extended amygdala.

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- **Project Title: NOVEL ANTI-PAIN MEDICATIONS FOR CANCER**

  Principal Investigator & Institution: Shefter, Eli; Irisys Research and Development, Llc 6190 Cornerstone E, Ste 106 San Diego, Ca 92121

  Timing: Fiscal Year 2001; Project Start 28-SEP-2001; Project End 31-AUG-2003

  Summary: (provided by applicant): The chemical synthesis and biological evaluation of novel, highly potent agents for the treatment of both severe acute and chronic pain associated with cancer and other diseases that has minimal side effects such as addiction liability, imniunosuppression and respiratory depression is very urgent. For "proof of principle," in Phase I, congeners of agents 100-fold more active than **morphine** will be synthesized and tested in vitro and in vivo for analgesic activity and safety. In later studies, additional lead optimization of the most promising drug candidate will be explored by parallel synthesis combinatorial chemistry. In Phase II, the optimized compounds will be tested in animals for analgesic activity and thorough safety evaluation. Because there is a great need for stable, long lasting, potent, orally active pain medication to treat pain associated with cancer and other diseases, the successful completion of the work proposed will lead to important new innovation in the pain medication field. The long-term goal of our work is to develop effective anti-pain agents in animals that can be taken forward into the clinic for testing as a human medication. We expect that development of the novel pain relief drug candidates proposed will provide new agents useful in the amelioration of human suffering. This will improve the quality of life for tens of thousands of Americans. PROPOSED COMMERCIAL APPLICATION: The need for potent, orally active pain medication to alleviate the severe pain experienced by patients with cancer and other diseases is immense. Procurement of a long lasting oral anti-pain medication that has significantly fewer side effects than narcotics currently in use will provide a therapeutic that is currently not available. The potential commercial application of the work is that the research could lead to a 'blockbuster' drug product.

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- **Project Title: OPERANT RESPONDING IN OPIOID-DEFICIENT MICE**

  Principal Investigator & Institution: Low, Malcolm J.; Professor/Scientist; None; Oregon Health & Science University Portland, or 972393098

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

  Summary: (provided by applicant): A widely held view of the mechanism underlying the reinforcing properties of opiates, thereby contributing to drug craving, is that drugs such as **morphine** and heroin usurp existing neural circuits that mediate the incentive value of natural reinforcers. If this is true, then one would expect that positive stimuli may be identical at the motivational level while differing at the perceptual or discriminative level. Pharmacology has suggested this to be the case, in that endogenous opioids modulate neural circuits involved in motivation to differing classes of stimuli, namely food and drugs of abuse. There remain many questions concerning the function of specific endogenous opioid peptides in the modulation of reward to positive stimuli. Our laboratory and others have generated mutant mice lacking specific opioid peptides or receptors to characterize the physiological function of these molecules. The proposed experiments are designed to test our hypothesis that the endogenous opioid peptides fulfill specific functions in modulating the incentive value of different classes of positive stimuli. The animal models we will use are fully congenic strains of C57BL/6J and DBA/2J mice harboring single mutations that result in the total absence of either Beta-endorphin, all forms of enkephalin, or a combination of both opioid peptide families.

The primary behavioral task to assess reward is operant responding for food, saccharin, or **morphine.** Since the incentive value of positive stimuli vary with motivational states, we will study operant responding in the mice under both deprived and non-deprived conditions. Additional behavioral tasks that will be assessed in all groups of mice to further test the specificity of differences in operant responding include response extinction, measurements of taste preference, and locomotor activity.

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- **Project Title: OPIATE BIVALENT LIGANDS: STRUCTURE/FUNCTION STUDIES**

  Principal Investigator & Institution: Law, Ping-Yee; Professor; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

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

  Summary: (provided by applicant): The putative homodimerization or the heterodimerization of the opioid receptors have been suggested with the co-immunoprecipitation, fluorescence energy transfer (FRET), and bioluminescence energy transfer (BRET) experiments. The possibility that opioid receptor could heterodimerize provides a mechanistic explanation for the observed delta-opioid receptor modulation of mu-opioid receptor tolerance in the presence of delta-opioid antagonists and in the delta-opioid receptor null mice. Hence, we hypothesize that the oligomerization of the mu and delta-opioid receptor results in the modulation of the mu-opioid receptor chronic responses, i.e., the reported delta-opioid antagonist inhibition of **morphine** tolerance is not a result of neural circuitry, but rather is a result of receptor-receptor interaction. In order to demonstrate this hypothesis, we will control the delta-opioid receptor expression using the ecdysone-inducible mammalian expression system in EcR293 cells stably expressing the mu-opioid receptor. The activities of the mu-opioid receptors in these cells will be examined at different levels of the delta-opioid receptor being induced. The ability of mu-opioid agonists to regulate the adenylyl cyclase or the ERK1/2 activities will be determined when the induced delta-opioid receptors are being activated or inactivated. The ability of mu-opioid agonists to elicit cellular adpatational responses such as desensitization, or receptor internalization at different levels of induced delta-opioid receptor will be examined. In addition to the conventional mu- and delta-opioid receptor selective ligands, the bivalent ligands developed in Component #1 of this program project grant will be used also. The bridging of two receptor binding sites within the oligomers, by the bivalent ligands with pharmacophores selective of respective receptors will allow us to examine the role of the receptor oligomers on these cellular processes. The effects of the bivalent ligands on the mu-opioid receptor activities, acute and chronic, will be examined in different levels of delta-opioid receptor being induced. These effects will be compared to those obtained with the monovalent ligands having the identical spacers. Our hypothesis will predict the existence of a bivalent ligand having mu-opioid agonist and delta-opioid antagonist pharmacophores that will not induce chronic responses in the mu-opioid receptor activation in the presence of induced delta-opioid receptor. The use of these bivalent ligands and the inducible receptor system will demonstrate further any pharmacological significance of probable opioid receptor oligomerization.

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- **Project Title: OPIATE MODULATION OF CORNEA PAIN PATHWAYS**

  Principal Investigator & Institution: Bereiter, David A.; Research Professor; Rhode Island Hospital (Providence, Ri) Providence, Ri 02903

Timing: Fiscal Year 2001; Project Start 01-APR-1988; Project End 31-JUL-2004

Summary: (Adapted from the Investigator's Abstract): The trigeminal nerve mediates pain sensation from craniofacial tissues including specialized structures such as the teeth, dura, and cornea. Pain that occurs during toothache, headache, and dry eye syndrome is a prevalent health problem, arises from varied etiology and often is difficult to manage. In addition to sensation, other aspects of pain (autonomic/endocrine reflexes, endogenous pain controls) can be altered by persistent trigeminal pain conditions. This proposal uses neurophysiological methods to test the central hypothesis that distinct groups of brainstem neurons mediate different aspects of corneal pain and that these neurons can be identified by their encoding properties, response to analgesic drugs, and efferent projection status. Specific Aim 1 defines the properties of trigeminal brainstem neurons that encode different corneal stimulus modalities (chemical, mechanical, cold). Corneal units that project to the sensory thalamus or superior salivatory nucleus/facial nucleus region are presumed to serve a role in sensory-discriminative or reflex autonomic/somatomotor functions, respectively. Specific Aims 2 and 3 assess the role of the longitudinal fiber system that connects rostral and caudal portions of trigeminal subnucleus caudalis in different aspects of cornea pain processing. Specific Aim 4 tests the hypothesis that receptors for glutamate mediate corneal input to trigeminal subnucleus caudalis and are necessary for the modulation of evoked activity seen after **morphine.** Specific Aim 5 tests the hypothesis that mu opioid agonists such as **morphine** act at sites outside the trigeminal brainstem complex to enhance corneal units at rostral portions of subnucleus caudalis and inhibit corneal units at the most caudal portions of subnucleus caudalis. These results will provide new information on the properties of trigeminal neurons that mediate the sensory-discriminative and ocular-specific reflex aspects of corneal pain and will lead to a better understanding of the brainstem organization that underlies craniofacial pain processing.

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- **Project Title: OPIATE RECEPTOR PHARMACOLOGY**

  Principal Investigator & Institution: Pasternak, Gavril W.; Professor of Neuroscience in Pyschiatry; Sloan-Kettering Institute for Cancer Res New York, Ny 10021

  Timing: Fiscal Year 2001; Project Start 01-AUG-1994; Project End 31-JUL-2004

  Summary: Opiates are important for the treatment of pain, but their abuse presents a major health proglem. Understanding opioid actions is crucial to their rational use clinically and the development of potential treatments for abuse. Opiates and the opioid peptides act through a family of receptors, of which a number have been cloned. Studies on the actions of these receptors carried out in tissue culture have provided important information regarding their biochemistry. However, these advances now need to be taken into behavioral systems. Recent work using antisense approaches has confirmed the importance of the cloned opioid receptors in opioid pharmacology. Antisense techniques can be used to selectively target individual exons, permitting the examination of splice variants. Using this antisense mapping approach against the MOR-1 clone, which encodes a mu receptor, we found different selectivity profiles for **morphine** and its extremely potent metabolite morphine-6beta-glucuronide (M6G), implying that they act through distinct receptors. This has now been confirmed in MOR-1 knockout mice. These animals are insensitive to **morphine,** but retain their sensitivity to M6G. The importance of this M6G receptor is enhanced by the additional observations that heroin and several highly potent clinical analgesics also act through the M6G receptor. Despite the inactivity of **morphine** in the knockout mice, heroin

retains its full analgesic activity. Thus, the M6G receptor might be considered a new heroin receptor. This concept provides important insights into future studies of the mu opioid system. Another member of the opioid receptor family has also proven very interesting. The orphan opioid receptor has led to the identification of a new series of peptides termed orphanin FQ or nociceptin. These agents have a complex pharmacology which will be explored in further detail. Finally, prior work has established that the sigma receptor activates a potent anti-opioid system within the central nervous system. This system is responsible for variations in analgesic sensitivity among some species. We recently cloned the murine sigma receptor and plan to utilize it to gain a better understanding at the molecular level of this system through antisense and other approaches.

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- **Project Title: OPIATES AND CNS DEVELOPMENT**

  Principal Investigator & Institution: Vathy, Ilona; Associate Profesor; Psychiatry and Behavioral Scis; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2001; Project Start 01-FEB-1990; Project End 31-JAN-2005

  Summary: (adapted from applicant's abstract): There is an ever-increasing need to understand the neurobiological consequences of maternal substance abuse. Drugs such as opiates can cross the placenta and induce long-term alterations in the developing CNS. Our work demonstrates that exposure to **morphine** during mid to late gestation induces long-term, sex-specific behavioral and neurochemical alterations in young adult male and female rats. It is noteworthy that these long-lasting, sex-specific changes in NE neurotransmission occur in brain regions known to participate in stress responses. If activation of the stress system in animals exposed prenatally to **morphine** is maladaptive and/or uncontrolled, the resulting dysphoria could increase drug abuse liability in adult offspring. Therefore, we now propose to test the hypothesis that prenatal **morphine** exposure alters the development of brain systems mediating endocrine and neural responses to stress and promotes drug abuse liability in both young adult male and female rats. Specific Aim 1 will test the hypothesis that prenatal **morphine** exposure increases acute stress-induced activation of the female HPA axis, possibly by reducing the sensitivity to negative feedback of adrenal steroids. RIA will be used to measure plasma ACTH and corticosterone (COR) levels before and several times after an acute stressor. Sensitivity of the brain to glucocorticoid negative feedback will also be evaluated. Binding assays will assess whether alteration in ACTH and COR release correlate with changes in glucocorticoid receptor (GR) binding in the hippocampus and hypothalamus. In situ hybridization experiments will assess the effects of prenatal **morphine** on GR mRNA in both the hippocampus and hypothalamus. Specific Aim 2 will test the hypothesis that prenatal **morphine** exposure enhances the reward-potentiating properties of drugs in young adult animals, using electrical brain-stimulation reward in conjunction with acute systemic administration of cocaine or **morphine.** Additional experiments will investigate whether prenatal **morphine** exposure enhances cocaine self-administration, and whether stress-induced relapse to cocaine self-administration is potentiated in prenatally morphine-exposed animals. Specific Aim 3 will test the hypothesis that prenatal **morphine** exposure alters NE release in brain structures involved in stress responses. In vivo brain microdialysis will assess basal and stress-induced NE release in the PVN and hippocampus. Specific Aim 4 will test the hypothesis that prenatal exposure to **morphine** alters neuronal plasticity in the hippocampus of exposed animals. The hippocampus plays a role in negative feedback inhibition of the HPA axis, and hippocampal GRs regulate the

magnitude of long-term potentiation (LTP) in the dentate gyrus (DG). Electrophysiological experiments will investigate the effects of prenatal **morphine** exposure on basal LTP and on mineralocorticoid receptor (MR) and GR modulation of LTP in the DG and CA1 regions of the hippocampus. We will also evaluate spatial learning and memory in an eight-arm radial maze, a hippocampal-dependent task. This research will provide valuable information regarding the mechanisms by which prenatal **morphine** exposure alters the sensitivity of the HPA axis, neural plasticity of the hippocampus and the propensity for drug abuse.

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- **Project Title: OPIATES--NEURONAL AND GLIAL VULNERABILITY TO HIV**

  Principal Investigator & Institution: Hauser, Kurt F.; Professor; Anatomy and Neurobiology; University of Kentucky 109 Kinkead Hall Lexington, Ky 40506

  Timing: Fiscal Year 2001; Project Start 30-SEP-2000; Project End 31-JUL-2005

  Summary: (Applicant's Abstract) Opiate drugs alter the pathogenesis of AIDS. The progression to AIDS dementia in HIV-1-positive individuals may be more rapid in opiate drug abusers than non-abusers. Brain regions with a high number/density of opioid receptors, such as the striaturn and hippocampus, display increased viral loads and are preferentially susceptible to HIV infection. Although HIV itself propagates in microglia and astroglia, HIV-1 protein "virotoxins," including gp120 and Tat, are subsequently released and cause the degeneration of neighboring neurons and glia. Despite evidence of an enhanced vulnerability of neurons and glia to HIV following opiate exposure, the reasons for the susceptibility are not understood since opioids can be neuroprotective or promote apoptosis. Our laboratory and others discovered that phenotypically distinct subsets of glia express mu opioid receptors, and chronic exposure to opiate drugs of abuse destabilize ion homeostasis and cytokine production in neurons and/or glia. Our preliminary data indicate that opiates exacerbate the toxicity to HIV virotoxin-exposed striatal neurons and destabilize Ca 2+ in astroglia. We predict the preferential susceptibility of HIV-1 afflicted individuals to opiates may result from the selective vulnerability of p opioid receptor-expressing neuronsandglia. Our hypothesis is that opiates will directly modify the toxic effects of HIV-1 proteins in opioid receptor-expressing neurons and astroglia. To test the hypothesis, we will explore the role of mu receptors using pharmacologic and genetic (mu receptor knockout mice) strategies. Aim 1 will assess the effects of opiate drugs on the pathogenesis of HIV-1 virotoxin-exposed (gp l20 or Tat) mu receptor-expressing striatal neurons, astroglia, and microglia. Aim 2 will identify morphine-induced alterations in viability, dendritic pathology, reactive astrogliosis, and microglial infiltration/activation in the striata of mice stereotaxically injected with gp120/Tat viral proteins in vivo. Aim 3 will determine whether mu opiates alter gpl20/Tat-induced destabilization of intracellular Ca 2+ and cytokine production. Our goal is to determine the mechanisms by which opioids contribute to the pathobiology of HIV infection in the central nervous system, and to identify interactive events that could be targeted for therapeutic intervention.

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- **Project Title: OPIOID AND NONOPIOID MECHANISM(S) OF NEUROPATHIC PAIN**

  Principal Investigator & Institution: Kolesnikov, Yuri A.; Sloan-Kettering Institute for Cancer Res New York, Ny 10021

Timing: Fiscal Year 2001; Project Start 05-FEB-1999; Project End 31-JAN-2002

Summary: Neuropathic pain syndromes commonly arise following traumatic injury to nerves and are often-times a problem associated with peripheral neuropathies such as those associated with HIV infection and diabetes, as well as post herpetic neuralgia. In cancer patients, neuropathic pain often follows compression or infiltration of nerves by tumors. The neuropathic pain syndromes are among the difficult to manage. Compelling evidence indicates that activation of NMDA/Nitric Oxide pathway contribute to the hyperalgesia and allodynia that occur following peripheral nerve injury or inflammation. However, recent work has uncovered a complexity not originally appreciated. A number of nNOS splice variants have been identified, including two lacking exon 2 and others lacking exons 9 and 10. Thus, at least four distinct molecular species of nNOS mRNA are expressed in neuronal tissue. The primary goal of this application is to study the molecular mechanism(s) of neuropathic pain, particularly as it relates to pain following peripheral nerve injury. Antisense approaches will utilized to correlate the cloned nNOS with its pharmacology. Initial studies from our laboratory demonstrate dramatic pharmacological differences between major form and the splice variant lacking exons 9 and 10 in **morphine** tolerance. Preliminary results indicate that these two splice variants also modulate neuropathic pain differently. Thus, they represent another target for my studies. Finally, data suggest that NMDA receptors mediated intracellular PKC translocation and NO production may be associated with development of both neurogenic/inflammatory hyperalgesia and **morphine** tolerance, providing yet another paradigm to examine. Throughout all these studies, the cellular and molecular processes associated with the expression **morphine** tolerance and neuropathic pain overlap. Addressing the basic mechanisms of these systems may provide insights into the development of new drugs and therapies.

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- **Project Title: OPIOID EFFECTS ON HYPOTHALAMIC NEURONAL EXCITABILITY**

  Principal Investigator & Institution: Kelly, Martin J.; Physiology and Pharmacology; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2001; Project Start 01-APR-1988; Project End 31-JUL-2003

  Summary: (Applicant's Abstract) The overall goal of the present proposal is to understand the cellular mechanism(s) by which the gonadal steroid 17 beta-estradiol (E2) modulates opioidergic (beta-endorphin) tone and subsequently the neurosecretion of hypothalamic peptides and amines and activation of reward pathways in the female. We use the guinea pig as a model because the ovulatory cycle mimics the human. Physiological levels of E2 rapidly uncouple mu-opioid and GABAB receptors from K+ channels (IKir) in beta-endorphin (betaEND) neurons via a protein kinase pathway. In addition, chronic opiate uncouples and down-regulates mu-opioid receptors. In Experiments 1, we will test the hypothesis that chronic **morphine** activates a protein kinase A (PKA) pathway to specifically uncouple mu-opioid receptors in arcuate neurons. We will measure: (a) changes in mu-opioid agonist potency in females treated with **morphine** using membrane permeable protein kinase inhibitors; (b) the time course of **morphine** actions; and (c) the effects of **morphine** on the coupling of the orphanin FQ receptor to IKir. In Experiments 2, we will test the hypothesis that E2 activates a protein kinase C (PKC) pathway to uncouple mu-opioid and GABAB receptors from IKir at the site of the G protein coupling. We will measure: (a) the changes in the potency of mu-opioid and GABAB agonists in ovariectomized females treated acutely with E2 using protein kinase activators and inhibitors; (b) changes in

agonist-stimulated 3H-GTPgammaS binding in ARC membranes and autoradiography of 3H-GTPgammaS in ARC slices following E2 treatment; and (c) elucidate the pathway by which longer-term (24 h) E2 uncouples mu-opioid and GABAB receptors. In Experiments 3, we will determine to which effector systems mu-opioid, K-opioid and orphanin FQ receptors are coupled in supraoptic (SON) vasopressin and oxytocin neurons and the effects of chronic **morphine.** We will: (a) further characterize the inhibition Ih by mu-opioid agonists, the inhibition of a Ca2+ T-current by K-opioid agonists and the specific K+ conductance(s) activated by OFQ; (b) ascertain the effects of chronic **morphine** on the p-opioid, K-opioid and OFQ responses in SON neurons; (c) measure the changes in mu-opioid, K-opioid and orphanin FQ receptors mRNA expression and receptor binding in the SON with chronic **morphine** treatment; and (d) characterize the opioid-mediated presynaptic inhibition of excitatory input to SON neurons in morphine-tolerant animals. These results should not only elucidate the mechanisms by which E2 and opioids regulate hypothalamic neurons but also their interaction in altering opioid tone in the female CNS, which will help us understand the gender differences in reward and homeostasis.

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- **Project Title: OPIOID GABA INTERACTIONS AND ANTINOCICEPTION**

  Principal Investigator & Institution: Kalyuzhny, Alexander E.; Neuroscience; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2001; Project Start 10-MAY-1999; Project End 31-MAR-2003

  Summary: The long-term goal of this proposal is to study the anatomical and pharmacological relationship of opioidergic system to GABAergic systems within the brainstem anti-nociceptive circuit of rats. Anti-nociceptive effects of opioids administered into ventral lateral periaqueductal grey matter, rostral ventral medulla and spinal cord dorsal horn appear to be mediate din part by neurons containing GABA. Our previous studies have demonstrated that neurons immunoreactive for GABA also express mu- opioid receptors in many brain regions, which suggests that opioids may directly affect GABA release. In addition, we have also reported that GAD-ir varicosities appose neurons expressing mu-opioid receptors, thus suggesting that opioid-sensitive neurons may be controlled by GABA. In preliminary studies, we have observed that GABA/A receptors in globus pallidus, hippocampus and DRG are co-localized with mu-opioid receptors. Thus, it appears that opioidergic and GABAergic systems in CNS are linked together. However, the anatomical and pharmacological relations between these two systems are poorly understood. Our studies will test the following hypotheses. 1). Co-expression of GABA-receptors and opioid receptors in neurons projecting from PAG to NRM, projecting from NRM to dorsal horn of the spinal cord, and neurons in the dorsal horn. This will be addressed by multi-color immunofluorescence using antibodies against one of the opioid receptors (mu-, addressed by multi-color immunofluorescence using antibodies against one of the opioid receptors (mu-, delta-, or kappa) combined with antibodies for GABA/A and GABA/B receptors. Immunocytochemistry will be combined with retrograde tract tracing technique. 2. Co-localization of GABA-receptors and endogenous opioid peptides and their relationship to neurons projecting from PAG to NRM, projecting from NRM to dorsal horn of the spinal cord, and neurons in the dorsal horn of the spinal cord. This will be addressed by employing multi-color immunofluorescence combining antibodies against GABA/A or GABA/B receptors with antibodies against Met-enkephalin, beta-endorphin, dynorphin/1-8 and endomorphin 2. 3. Pharmacological interactions between opioidergic and GABAergic systems. This will be done by

employing radio-ligand binding assay in isolated membrane preparations of the ventral lateral PAG, the RVM (including NRM), and the dorsal portion of the spinal cord. Tissues will be dissected from the animals treated with either **morphine** (acute and chronic) or GABA. Results of this study will contribute to our understanding of the mechanisms of opioid anti-nociception, and will suggest strategies for developing alterative, non-opioid, approaches for pain-treatment.

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- **Project Title: OPIOIDS WITH DELTA ANTAGONIST AND MU AGONIST ACTIVITY**

  Principal Investigator & Institution: Coop, Andrew; Assistant Professor; Pharmaceutical Sciences; University of Maryland Balt Prof School Baltimore, Md 21201

  Timing: Fiscal Year 2001; Project Start 01-FEB-2001; Project End 31-JAN-2006

  Summary: Chronic clinical pain remains poorly treated. The use of mu opioid analgesics such as **morphine** can treat the pain, but the severe undesired effects of **morphine** and other mu agonists limit their use. Indeed, the rapid development of tolerance causes ever-increasing doses to be administered, increasing the severity of the undesired effects. Recent work has shown the coadministration of a delta opioid antagonist, together with **morphine** causes a slower build-up of tolerance than administration of **morphine** alone. Further, the use of a peptide with a dual profile of mu agonism/delta antagonism has been reported to give rise to little tolerance. Thus, the aim of the current research is to develop potent non-peptide mu agonists, which also possess a profile of delta antagonism. The orvinols (e.g. etorphine) are a class of potent mu opioid agonists that also interact with kappa and delta receptors, generally displaying delta agonism. Our hypothesis is that the delta efficacy of the orvinols can be reduced by the introduction of an aromatic group in a position that corresponds to the position of the indole in the indolomorphinans (e.g. naltrindole, oxymorphindole) or the benzylidene in the opioid benzylidenes (e.g. benzylidenenaltrexone (BNTX)), two important classes of low efficacy delta opioid ligands. By reducing delta efficacy, decreasing kappa affinity, and retaining high mu efficacy, analogs of the orvinols with the desired profile will result. The approach to be used consists of the development of a pharmacophore model of delta antagonism using a novel molecular modeling approach, and the selection of target molecules with a suitably positioned aromatic ring. The novel model will be tested through the synthesis of simple morphinans containing aromatics that satisfy the pharmacophore. Information garnered from the simple morphinans will be applied to the design and synthesis of the target 5,14-bridged morphinan based orvinols selected by the model. Novel chemical methodology will be developed and applied to the synthesis of the 6,14-bridged targets, analogs very closely related to the orvinols. The ultimate goal of this proposal is to develop potent mu opioid analgesics, to which tolerance develops slowly, or not at all, in order to reduce the undesired effects seen in the chronic treatment of clinical pain.

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- **Project Title: P GLYCOPROTEIN INDUCTION--KINETIC/DYNAMIC IMPLICATIONS**

  Principal Investigator & Institution: Pollack, Gary M.; Professor and Chair; Drug Delivery & Disposition; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

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

Summary: (Applicant's abstract): Transport by P-glycoprotein (P-gp) is an important determinant of disposition for numerous pharmacological agents. A significant body of evidence has shown that decreases in P-gp activity can increase drug absorption from the GI tract, decrease drug/metabolite excretion in the liver and/or kidney, and enhance distribution of parent drug/active metabolites to target organs (e.g., the CNS) or pharmacologically relevant intracellular sites (e.g., leukocytes). Although the potential for induction of P-gp is well documented in the cancer chemotherapy literature, the implications of P-gp induction on the systemic disposition and pharmacological activity of P-gp substrates has yet to be addressed. Recent work in this laboratory has demonstrated that **morphine** is a substrate for P-gp-mediated transport, that alterations in P-gp activity influence **morphine** disposition and action and that **morphine** administration in vivo increases the P-gp content in rat brain. These observations are particularly important from a clinical perspective because of the key role of **morphine** in management of pain associated with cancer and other diseases requiring chronic analgesia. Therapeutic agents (e.g., anticancer drugs) that increase P-gp activity may decrease the efficacy of **morphine** in these patients. Conversely, induction of P-gp by **morphine** may limit the activity of other P-gp substrates. The long term objective of this research program is to explore the hypothesis that inducers of P-gp cause clinically relevant alterations in the disposition and action of P-gp substrates. The proposed project will utilize a multi-experimental approach to address the hypotheses that: 1) extent of P-gp induction in specific organs is a function of inducer potency and inducer concentration, 2) perturbations in the kinetics of a P-gp substrate can be predicted based on the degree of P-gp induction in organs/tissues, and 3) P-gp induction in humans can result in clinically significant alterations in the systemic disposition and action of P-gp substrates. In addressing these hypotheses, P-gp induction will be assessed in vitro in cultured hepatocytes (rat and human) and in vivo in selected organs, the impact of P-gp induction on drug disposition will be evaluated in isolated organ systems, and the implications of P-gp induction on systemic pharmacokinetics and pharmacodynamics will be examined in rats and humans. The potential importance of this research becomes apparent when one considers the number of therapeutic agents that are substrates of P-gp, the location of P-gp in organs of kinetic/dynamic importance, and the likelihood that numerous therapeutic, dietary, and environmental agents may modulate the activity of P-gp.

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- **Project Title: PHYSIOLOGICALLY ACTIVE NATURAL PRODUCTS**

  Principal Investigator & Institution: Taber, Douglass F.; Professor; Chemistry and Biochemistry; University of Delaware Newark, De 19716

  Timing: Fiscal Year 2001; Project Start 01-APR-2000; Project End 31-MAR-2004

  Summary: Both the recent resurgence of infectious disease and the abiding interest in new tools for neuropharmacology have driven the continuing effort to isolate and establish the structures of new active agents from natural sources. While some of these might well be useful leads for pharmaceutical development, often the structurally more complex agents will not be pursued, because of perceived difficulties with their synthesis. An investigation of a new method for the construction of carbocyclic rings, intramolecular alkylidene C-H insertion, is proposed. This already shows the promise of becoming a powerful tool for target-directed synthesis. Specific targets include the cognition-enhancing alkaloid huperzine A, **morphine,** the parent compound of the **morphine** alkaloids, and N-deacetyllappaconitine, representative of the Delphinium diterpenoid alkaloids.

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- **Project Title: PHYSIOLOGY OF RAPHE MAGNUS CELLS DURING WAKE AND SLEEP**

  Principal Investigator & Institution: Mason, Peggy; Associate Professor; Neurobiology/Pharmacology/Phys; University of Chicago 5801 S Ellis Ave Chicago, Il 60637

  Timing: Fiscal Year 2001; Project Start 15-AUG-1999; Project End 31-JUL-2004

  Summary: (adapted from applicant's abstract) Neurons in the medullary raphe magnus (RM) are important in nociceptive modulation. The responses of RM cells to noxious heat and to analgesic doses of opioids have led to the hypothesis that OFF cells inhibit and ON cells facilitate nociceptive transmission in the anesthetized animal. However, little is known of how RM contributes to nociceptive modulation in behaving animals. The proposed experiments focus on the physiology of non-serotonergic RM cells in unanesthetized, freely behaving rats. The experiments proposed in Aim 1 compare the neuronal responses to noxious heat and to systemic **morphine** in anesthetized and unanesthetized conditions. The remaining aims will further our understanding of how RM cells are activated in behaving rats. Recent experiments suggest that non-serotonergic RM cells have state-dependent discharge in a pattern that is correlated to their response to noxious heat. However, since only a small number of neurons were studied and since the protocol was not completed for many cells, our preliminary findings need to be confirmed and extended. Therefore, RM cells, characterized by their response to noxious heat, will be recorded in freely behaving, unrestrained rats as they cycle through waking, slow wave sleep and paradoxical sleep states. Unit discharge pattern and rate during sleep and wake states will be compared. Neuronal and behavioral responses, including motor and cardiovascular components, to thermal stimulation of either warm or noxious intensity, will be compared for stimuli applied during different behavioral states. Similarly, the responses of RM cells to innocuous mechanical and auditory stimulation will be tested and compared for stimuli applied during waking, slow wave sleep or paradoxical sleep states. Since sensory modulation commonly accompanies active movements, RM cell and motor responses to noxious thermal stimulation will be systematically studied during drinking, eating and grooming. The final aim will test whether RM cells contribute to the decrease in sleep time observed during chronic pain conditions. First, RM cell discharge will be continuously recorded during the development of arthritis and will be compared to the development of arthritic hyperalgesia and to the sleep/wake pattern exhibited by the animal. Second, microinjection of the GABAA receptor antagonist, bicuculline, which is known to activate RM OFF cells will be used to test whether OFF cell activation can increase sleep time in arthritic animals. To determine whether OFF cells act primarily on sleep/wake regulation or nociceptive transmission, the effects of bicuculline on sleep/wake pattern and spontaneous pain behaviors will be compared.

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- **Project Title: PROTEIN KINASE IN OPIOID RECEPTOR REGULATION & TOLERANCE**

  Principal Investigator & Institution: Yoburn, Byron C.; Professor of Pharmacology; Pharmaceutical Sciences; St. John's University Jamaica, Ny 11439

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

Summary: The overall objective of this project is to examine the pathways that mediate mu-opioid receptor regulation and opioid tolerance in the intact animal. It has been established that opioid agonists differ in their ability to regulate CNS mu-opioid receptors in vivo. Chronic treatment with high intrinsic efficacy opioid agonists (e.g., etorphine) downregulates mu opioid receptors, while at the same time producing tolerance and regulation of mu-opioid receptor mRNA levels. Chronic treatment with lower intrinsic efficacy opioid agonists (e.g., morphine) can induce tolerance without altering mu-receptor density or mu-receptor mRNA. At present, the basis for the different effects of treatment with high and low intrinsic efficacy opioid agonists in vivo are not known. However, compelling data raise the possibility that opioid tolerance and mu-opioid receptor regulation require the activation of different intracellular signaling systems. This project will test the hypothesis that opioid agonist-induced downregulation of mu-opioid receptors and regulation of mu-opioid receptor mRNA levels in vivo involves three signaling proteins: G-protein receptor kinase 2,beta arrestin 2 and dynamin. It is further hypothesized that morphine-induced tolerance is independent of this signaling pathway in vivo. Finally, it is hypothesized that the magnitude of opioid tolerance is increased by mu-opioid receptor downregulation. The experiments proposed in this application will use behavioral, biochemical and molecular pharmacological methods to determine the role of these proteins in mediating opioid agonist-induced tolerance, downregulation of mu-opioid receptors and regulation of mu- receptor mRNA in vivo. The results of these studies will significantly enhance our knowledge of the pathways that regulate chronic opioid effects in the intact, behaving animal. As such, these results may provide important insights for developing strategies to treat opioid drug abuse and pain.

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- **Project Title: PSYCHOMOTOR STIMULANTS AND AGGRESSION**

  Principal Investigator & Institution: Miczek, Klaus A.; Professor; Political Science; Tufts University Medford Boston Ave Medford, Ma 02155

  Timing: Fiscal Year 2001; Project Start 01-SEP-1979; Project End 31-JUL-2003

  Summary: (Applicant's Abstract) The proposed research is driven by the major public health and criminal justice concern with the link between the abuse of psychomotor stimulants and opiates to violence and being the victim of violence. The proposed studies seek to determine the sources of individual sensitivities to salient social events that promote or retard the self-administration of opioids and psychomotor stimulants. A second objective focuses on the reciprocal: How do self-administered psychostimulants and opioids intensify or exaggerate aggressive and defensive behavior and disrupt social behavior. A vertical research strategy is implemented that integrates behavioral, physiological, and neurochemical levels of analysis in the intact behaving animal under unambiguously defined social conditions. Three sets of aims and experiments are proposed: (1) How do behavioral, physiological, and neurochemical characteristics of aggression promote psychostimulant and opioid self-administration? The focus is on individuals (a) who display "impulsive" aggression (i.e., low provocation threshold, short latency, injurious, non-ritualized, no inhibition from signals of submission) and who prefer an immediate small reinforcer vs. a large delayed reinforcer, (b) who readily entrain cardiovascular and core temperature activity to repeated aggressive confrontations, and (c) who show a unique pattern of increased dopamine (DA) and decreased serotonin (5-HT) release in mesocorticolimbic systems while engaged in aggressive behavior. Are these individuals more likely to engage in opioid- and stimulant-sensitized motor activity, self-administer opioids, cocaine and d-amphetamine

in a binge-like pattern, withdraw more intensely, and relapse more readily? (2) How do social stress experiences that result from being the victim of aggression, impact on stimulant and opioid self-administration? Are individuals who (a) cope with being attacked by being passively submissive vs. actively defensive, (b) who show a large release of cortical DA release and inhibited striatal 5-HT activity, and (c) who readily entrain autonomic activity to recurrent confrontations, more likely to show sensitized motor activity, self-administer opioids, cocaine and d-amphetamine? (3) How do self-administered psychostimulants and opioids impact on aggressive behavior and responses to social stress? This aim is pursued in aggressive resident and defensive intruder animals, and the direct effects of specific doses of self-administered cocaine, d-amphetamine and **morphine** on aggressive and defensive behavior are assessed during social confrontations. Experiments are designed that determine how continuous access to psychostimulants and **morphine** disrupt social intercourse, how withdrawal from prolonged stimulant and opioid self-administration exaggerates defensive or aggressive behavior, and how autonomic and mesocorticolimbic DA and 5-HT mechanisms contribute to these effects.

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- **Project Title: REACTIVITY AND SELECTIVITY OF REACTIONS IN POLAR MEDIA**

  Principal Investigator & Institution: Grieco, Paul A.; Professor; Chemistry and Biochemistry; Montana State University (Bozeman) Bozeman, Mt 59717

  Timing: Fiscal Year 2001; Project Start 01-JUL-1980; Project End 31-MAR-2003

  Summary: The major focus of this grant renewal application is to further examine the reactivity and selectivity of a number of organic reactions in highly polar media such as 3.0-5.0 M lithium perchlorate-diethyl ether with applications to molecules of biological interest. During the course of this investigation we will continue to search for substitutes for lithium perchlorate in ether. In addition we remain focused on anions that are more weakly coordinating than perchlorate. This proposal is divided into three parts. The first section concentrates on studying the reaction of nucleophiles with oxabicyclo[2.2.1]heptanes and oxabicyclo [3.2.1]octanes i highly polar media. All the proposed studies will be of a fundamental nature in order to define the scope, limitations, and mechanism of this potentially very useful new reaction. Applications to the total synthesis of epothilone B, ulapualide A, aplyronine A, **morphine,** and the C(19)-C(27) aliphatic building block of rifamycin S are proposed. The second part of this grant application focuses on extending the ionic intramolecular Diels-Alder reaction in polar media for the construction of carbocyclic ring systems. Substrates will be examined wherein conformationally restricted tethered dienes are attached to the alpha, beta, and delta carbon atoms of the dienophiles. Application to syntheses of quadrone, magellaninone and pentalenene are proposed. In the third part of this grant application we will examine unique solvent systems (e.g. Li2B12H12-acetone, MgB12H12-acetone) in hopes of finding new opportunities for altering transition states while accelerating organic reactions. In addition we plan to examine lithium borates and lithium phosphates wherein the anions are chiral in hopes of catalyzing substitution reactions of allylic and benzylic acetates via single diastereomeric ion pairs which undergo facial discrimination in the attack by a nucleophile.

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- **Project Title: REPRODUCTIVE CONSEQUENCES OF PUBERTAL MORPHINE ABUSE**

  Principal Investigator & Institution: Byrnes, Elizabeth M.; Environmental/Population Hlth; Tufts University Boston Boston, Ma 02111

  Timing: Fiscal Year 2001; Project Start 27-SEP-2001; Project End 31-AUG-2003

  Summary: (provided by applicant): The present proposal will study the impact of opiate abuse during puberty on future reproductive health. In both the rat and human, puberty is a period during which the reproductive cycles and daily hormonal rhythms begin to emerge. Because endogenous opioids mediate some of these changes, artificially elevated levels of opioids during this period can interfere with reproductive development. While some of the acute effects of opiates like **morphine,** heroin, and methadone in pubertal females have been delineated, the long-term effects of opiate abuse during the tumultuous pubertal period are unknown. Recent preliminary studies indicate that administering **morphine** to female rats around the time of puberty results in reproductive alterations that can be observed weeks after drug withdrawal. Specifically, while these females give birth to healthy pups, the rate of growth of their offspring is reduced. Moreover, there appears to be a decrease in the suckling-induced release of prolactin. Given the positive correlation between prolactin secretion and milk yield, a reduction in prolactin secretion could underlie reduced pup growth. Using a chronic increasing dose regimen of **morphine** (twice daily injections from age 30 to 50 days old), the present set of studies will examine the possible neuroendocrine alterations that may subserve both the decrease [in] suckling-induced prolactin secretion and decreased pup growth. These include examination of the level of prolactin content and message in the anterior pituitary, the sensitivity of the mu-opioid and D2 dopamine receptor subtypes to modulate prolactin secretion, and the expression of prolactin receptors in the mammary gland. In addition, the longevity of alterations in suckling-induced prolactin secretion and reduced pup growth will be examined. The long-term objective of this proposal is to use these studies as an animal model of drug addiction in adolescent females. Given the recent rise in the number of adolescent girls abusing heroin, these studies will provide information on some of the potential reproductive consequences that may arise in the future for girls addicted to opiates during this sensitive developmental period.

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- **Project Title: SEX AND MENSTRUAL CYCLE EFFECTS ON PAIN AND ANALGESIA**

  Principal Investigator & Institution: Fillingim, Roger B.; Associate Professor; Operative Dentistry; University of Florida Gainesville, Fl 32611

  Timing: Fiscal Year 2001; Project Start 01-SEP-2000; Project End 31-MAR-2004

  Summary: The influence of sex and gender on pain perception and pain modulatory systems is a research topic of substantial basic science and clinical import. Studies in nonhuman animals and humans indicate greater sensitivity to experimental pain among females. Sex differences in opioid analgesia have also been reported, but are not well characterized in humans. The mechanisms underlying these sex-related differences in pain modulator have not been determined; although, considerable evidence from animals suggests that baseline pain sensitivity and opioid-mediated analgesia vary across the estrous cycle. However, among humans, findings relating pain sensitivity to menstrual cycle phase are inconsistent, and the effects of menstrual cycle phase an opioid analgesia have not been investigated. The studies proposed in this application

are designed to further elucidate the nature and mechanisms of sex- related differences in pain modulation by investigating baseline pain sensitivity and opioid analgesia as a function of sex, menstrual cycle phase and oral contraceptive use. Two clinically relevant laboratory pain induction procedures will be used in these studies: 1) temporal summation of thermal pain, and 2) ischemic arm pain. In the proposed study, responses to temporal summation and isochemic procedures will be obtained in females and males before and after administration of **morphine,** pentazocine and placebo (saline). In addition, two groups of females will be studies: females not taking oral contraceptives (OC) and females taking OC. Both groups of females will participate in each drug condition once during the follicular and once during the luteal phase of the menstrual cycle, and males will participate at similar time intervals. It is hypothesized that: 1) females, regardless of OC status, will exhibit greater baseline pain sensitivity than males, 2) females not taking OC will be more pain sensitive during the luteal compared to the follicular phase of the menstrual cycle, while females taking OC will show no change in pain responses across cycle phase; 3) males will exhibit greater **morphine** analgesia than females, while females will exhibit greater analgesia to pentazocine than males, and 4) females not taking OC will exhibit less opioid analgesia during the luteal versus the follicular phase of the menstrual cycle, while no menstrual cycle effects on analgesia will emerge for females taking OC.

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- **Project Title: SEX DIFFERENCES IN OPIOID-INDUCED IMMUNOMODULATION**

  Principal Investigator & Institution: Elliott, Jay C.; Psychology; University of North Carolina Chapel Hill Office of Sponsored Research Chapel Hill, Nc 27599

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

  Summary: (provided by applicant): There is little extant data concerning how sex may modulate the magnitude of opioid-induced immunomodulation. The present proposal addresses this important issue by extending the recently-identified finding that **morphine** and other mu-opioids produce significantly greater enhancement in female than male rats, of contact hypersensitivity (CHS), a cutaneous form of delayed-type hypersensitivity. Specific Aim I tests the hypothesis that **morphine** administered prior to the challenge phase of CHS induces sexually dimorphic effects on key mediators of CHS, including cytokine expression and T-lymphocyte infiltration. To that end, animals will be sacrificed at selected times following antigen challenge and the extent of CD4(and CD8(T-lymphocyte infiltration will be quantified by immunohistochemistry. To assess which molecular mediators are differentially expressed in males and females, cytokine levels will be quantified by Real-Time RT-PCR. Specific Aim II tests the hypothesis that kappa and delta opioids also produce differential effects on CHS in males and females through their activity at CNS opioid receptors. This aim will employ intracranial cannulation, drug microinjection techniques, and receptor antagonism to address this important issue. Specific Aim III will assess the role of a putative key hormonal determinant of observed sex differences by determining the effect of estradiol replacement in ovariectomized female rats on morphine's modulation of the CHS response. Together, these investigations will provide novel data concerning mechanisms of sexually dimorphic modulation of the clinically-relevant CHS response by a range of opioid drugs.

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- **Project Title: SEX DIFFERENCES IN VISCERAL PAIN: INFLUENCE OF GONADAL STEROIDS**

  Principal Investigator & Institution: Murhpy, Anne Z.; Univ of Maryland, Baltimore Baltimore, Md

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

  Summary: Irritable bowel syndrome (IBS), a common gastrointestinal disorder characterized by abdominal pain and a change in bowel habits, will affect up to 20% of the general population. Epidemiological studies have established that females are 2-5x more likely to suffer from IBS in comparison to males. A defining characteristic of IBS is severe gastrointestinal pain. Surprisingly, while an extensive body of research has been conducted examining the neural mechanisms underlying visceral pain, these studies have been conducted exclusively in males. Thus, it is not known how visceroceptive information is processed within the CNS of females. Similarly, the impact of gonadal steroids on visceral pain is also not known. Behavioral studies in Aim 1 will characterize the sex differences and influence of gonadal steroids on visceral pain. Our preliminary data indicate that there are profound sex differences in the visceral motor reflex, an indicator of visceral pain following noxious colorectal distention. Our data further show that the sexually dimorphic response to noxious visceral stimulation is estrogen dependent. Anatomical studies proposed in Aim 2 will test the hypothesis that sex differences in the organization and activation of the spinoparabrachial circuit provide the anatomical substrate for the dimorphic response to noxious visceral stimulation. Studies using acute somatic stimuli have reported that **morphine** produces a significantly greater degree of analgesia in males versus females, and our preliminary studies indicate that **morphine** alleviation of visceral pain is also sexually dimorphic. Studies proposed in Aim 3 will test the hypothesis that **morphine** produces a significantly greater degree of analgesia in males in comparison to females in a model of visceral pain. Immunocytochemical and molecular studies proposed in Aim 4 will test the hypothesis that opioid receptor expression within the lumbosacral spinal cord is sexually dimorphic. The influence of gonadal steroids on opioid receptor expression will also be examined. Together, these studies will begin to elucidate the neural mechanisms underlying sex differences in visceral pain.

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- **Project Title: SPINAL PLASTICITY IN DIABETIC NEUROPATHIC PAIN**

  Principal Investigator & Institution: Pan, Hui-Lin; Associate Professor; Anesthesia; Pennsylvania State Univ Hershey Med Ctr 500 University Dr Hershey, Pa 17033

  Timing: Fiscal Year 2001; Project Start 30-SEP-2000; Project End 31-AUG-2003

  Summary: Neuropathic pain is one of the most common and troublesome complications afflicting diabetic patients. Since diabetic neuropathic pain often is not adequately relieved by classical analgesics, it represents an important unmet medical need. The etiology of painful diabetic neuropathy remains poorly understood and likely involves both peripheral and central mechanisms. Generation of ectopic discharges from C-fiber afferent nerves and sensitization of spinal dorsal horn neurons may play a critical role in the development of neuropathic pain in diabetes. This exploratory (R21) proposal is designed as a first step to investigate mechanisms of neuropathic pain in a rodent model of diabetes. The major objective of this proposal is to study the mechanisms of increased spinal excitatory tone relevant to neuropathic pain in diabetes. Increased spinal glutamate synthesis and decreased inhibition of spinal glutamate release by the descending noradrenergic system may represent a functional basis for the development

of diabetic neuropathic pain and diminished analgesic effect of opioids and alpha2 adrenergic receptor agonists. Two hypotheses will be tested in this proposal: 1) Depletion of capsaicin-sensitive afferent nerves eliminates afferent ectopic discharges and attenuates increased spinal glutaminase activity, hyperexcitability of spinal dorsal horn neurons, and neuropathic pain in diabetes; and 2) The inhibitory action of **morphine** or alpha2 adrenergic receptor agonists on spinal glutamate release is diminished in diabetic neuropathy. Electrophysiological records of single-unit activity of afferents and spinal neurons, quantitative measurements of neurotransmitters and proteins, and behavioral assessment of pain will be used to test these novel hypotheses. The proposed studies will improve our understanding of the mechanisms of neuroplasticity associated with diabetic neuropathic pain. This new information also could provide a rationale for development of new therapies for patients with diabetic neuropathic pain.

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- **Project Title: STRAIN DIFFERENCES IN RESPONSE TO OPIOIDS**

  Principal Investigator & Institution: Wenger, Galen R.; Professor; Pharmacology and Toxicology; University of Arkansas Med Scis Ltl Rock 4301 W Markham St Little Rock, Ar 72205

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

  Summary: (provided by applicant): Recent advances in genomics have brought to the forefront the fact that the mouse has been drastically underutilized in the behavioral aspects of drug abuse research. The use of operant schedules of reinforcement has played a significant role in our understanding of drugs of abuse and the addictive process in both humans and laboratory species. However, until recently there have been only a small number of laboratories that have attempted to utilize the mouse in experiments involving operant schedules of reinforcement. Many years of research on the genetics of the mouse has supplied the scientific community with a tremendous number of inbred strains. Many of these strains have well defined genetic differences that result in significant differences in drug effects. For example, it has been shown that marked differences exist between C57Bl/6 and DBA/2 mice in response to many effects of **morphine** including analgesia, locomotor activity, hypothermia, Straub-tail, and voluntary oral **morphine** consumption. Similarly, although tolerance to the analgesic and locomotor response to **morphine** has been observed to be about equal in C57Bl/6 and DBA/2 mice, tolerance to the analgesic effects of **morphine** has been reported not to occur following chronic administration in 129 mice. Whether strain differences exist in the stimulus or reinforcing properties as measured by drug discrimination or IV self-administration procedures in response to opioid drugs in these strains is not known. Knowledge of such differences may provide significant insight into the role of genetic differences in opioid addiction and the mechanisms of drug action. The present study will use three inbred strains of mice (C57Bl/6J, DBA/2J and 129P3/J). The study will examine the ability of receptor subtype specific opioid agonists to function as discriminative stimuli, the degree to which the drug stimulus generalizes to agonists specific for other receptor subtypes, and the ability of antagonists to block the stimulus properties. Hopefully, by utilizing these well-defined strains, it will be possible to use the known differences in genetics to provide new insight into the abuse of opioids.

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- **Project Title: STRESSOR CONTROLLABILITY, DRUGS OF ABUSE, AND SEROTONIN**

  Principal Investigator & Institution: Maier, Steven F.; Professor; Psychology; University of Colorado at Boulder Boulder, Co 80309

  Timing: Fiscal Year 2001; Project Start 01-FEB-2001; Project End 31-JAN-2006

  Summary: (Adapted from the Investigator's Abstract) There are large individual differences in reactivity to drugs of abuse, but the causes of these differences are not well understood. The recent experience of "stress" is a factor known to potentiate drug reward processes in both humans and animals, but the aspects of stress that are critical and the neural mechanisms involved are not fully known. The proposed research explores the role of the degree of behavioral control that the individual has over the stressor as a feature modulating wither the stressor will alter drug reactivity, and focuses on stressor-induced sensitization of serotonergic (5-HT) neurons in the dorsal raphe nucleus (DRN) as a mediator. The hypothesis to be tested is that 1) uncontrollable (but not controllable) stressors sensitize DRN 5-HT neurons for a period of time, leading to exaggerated release of 5-HT in projection regions when the neurons are activated; 2) 5-HT released in the nucleus accumbens (NAc) and/or medial prefrontal cortex (mPFC) by neurons projecting from the DRN increases the extracellular level of DA in the these regions that is produced by drugs of abuse; 3) 5-HT released in the paraventricular nucleus increases the blood levels of corticosterone (CORT); 4) Drugs that activate DRN 5-HT neurons (e.g., morphine) in addition to acting on brain reward structures, will therefore produce greater levels of extracellular DA in the NAc/mPFC and CORT in blood for subjects that have recently received uncontrollable stressors; 4) uncontrollable (but not controllable) stressors will therefore potentiate behavioral responses to drugs that depend on NAc/mPFC DA and/or CORT, and this potentiation will occur for drugs that activate DRN 5-HT neurons. Conditioned place preference and locomotor activation are the behaviors to be examined, and **morphine,** amphetamine, heroin, nicotine, cocaine, and ethanol are the drugs that will be tested.

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- **Project Title: STRESSOR CONTROLLABILITY, DRUGS, & PREFRONTAL CORTEX**

  Principal Investigator & Institution: Bland, Sondra T.; Psychology; University of Colorado at Boulder Boulder, Co 80309

  Timing: Fiscal Year 2003; Project Start 01-FEB-2004; Project End 31-AUG-2005

  Summary: (provided by applicant): It has previously been shown that inescapable (IS), but not escapable (ES) shock potentiates the rewarding properties of **morphine** as measured by conditioned place preference (CPP) and psychomotor activation (PA), and that this potentiation may be mediated by dorsal raphe nucleus (DRN) serotonin (5-HT) neurons. The medial prefrontal cortex (mPFC) has been implicated in both reward and stress, and is a projection region of the DRN. The mPFC also contains dopaminergic afferents from the ventral tegmental area (VTA), which has long been the focus of studies exploring the rewarding properties of drugs. There is evidence to suggest that 5-HT and dopamine (DA) interact in the prefrontal cortex, and that this interaction is mediated via the 5-HT3 receptor. The involvement of PFC monoamines in the IS potentation of **morphine** reward has not been examined. The specific aims of this proposal are 1) to characterize the effects of stressor controllability on 5-HT sensitization and on **morphine** induced increases in dopamine (DA) in the medial prefrontal cortex (mPFC) and to determine whether these effects generalize to cocaine, 2) to determine the effects of DRN 5-HT neurons on **morphine** induced increases in 5-HT and DA in the

PFC, **morphine** conditioned place preference (CPP), and **morphine** induced psychomotor activation (PA), 3) to determine the role of the PFC 5-HT3 receptor in IS potentiation of induced increases in 5-HT and DA in the PFC, **morphine** CPP and PA, 4) to determine the necessity of direct action of **morphine** in the DRN on IS potentiation of **morphine** induced 5-HT and DA in the PFC, CPP, and PA.

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- **Project Title: SUCROSE AND/OR FAT INGESTION EFFECT ON OPIOIDS**

  Principal Investigator & Institution: Levine, Allen S.; Professor; Medicine; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2001; Project Start 01-AUG-1986; Project End 31-DEC-2003

  Summary: (Adapted From The Applicant's Abstract) Opioids represent one set of regulators thought to be involved in eating induced by the rewarding properties of food. Opioid antagonists are particularly effective at decreasing intake of preferred foods including high sucrose and/or high fat foods. For example, we found that extremely low doses of the opioid antagonist naloxone (0.01 mg/kg) decreased intake of a preferred food, whereas much higher dose (3-10 mg/kg) were needed to decrease eating stimulated by energy needs. We also found that dynorphin gene expression was higher in the arcuate nucleus of animals fed a highly palatable diet (high sucrose/fat diet) compared with those fed a less preferred high starch diet. Such data have led us to hypothesize that ingestion of palatable foods (sweet and/or fat) results in an increase in the release of endogenous opioids at brain sites involved in feeding behavior and/or "reward." We propose four sets of studies to test this hypothesis: Do palatable foods or solutions (containing sucrose, saccharin and/or fat) result in an increase in gene expression of opioid peptides in brain sites known to be involved in feeding behavior or reward? These sites include the nucleus of the solitary tract (NTS), paraventricular nucleus of the hypothalamus (PVN), central nucleus of the amygdala (CNA), ventral tegmental area (VTA) and shell of the nucleus accumbens (s-ACC). Does acute or chronic ingestion of sucrose alter the ability of rats to discriminate morphine? We hypothesize that ingestion of sucrose releases opioids or alters receptor binding/density leading to a change in potency, i.e., a leftward shift in the agonist dose response curve of a rat trained to discriminate **morphine.** Does chronic ingestion of sucrose result in cellular changes resembling opioid dependence? If sucrose results in the release of opioids one might speculate that rats would display mild opioid withdrawal upon cessation of sucrose availability or following injection of naloxone. We will use cFos immunohistochemistry to observe the pattern associated with chronic sucrose ingestion followed by naloxone injection. Comparison will be made to opioid dependent animals (relatively mild dependence). Must a rat ingest a "critical" amount of a palatable food before opioids are released? We believe that the reason that naloxone does not affect latency to feeding and only seems to effect maintenance of feeding is that opioids are only released after feeding begins. These experiments address how much food must be eaten (volume, time spent eating etc.) before naloxone administration decreases feeding.

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

- **Project Title: SYNTHESIS OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS**

  Principal Investigator & Institution: Stork, Gilbert; Chemistry; Columbia Univ New York Morningside 1210 Amsterdam Ave, Mc 2205 New York, Ny 10027

  Timing: Fiscal Year 2001; Project Start 01-SEP-1985; Project End 31-MAR-2003

Summary: (Principal Investigator's Abstract) The objective of the work for which NIH support is requested specifically lists problems having the goals of completing our synthetic routes to the **morphine** alkaloids, to taxol, and to quinine. As is generally known, our purpose is not really the synthesis per se, but rather the conviction, validated over the years, that total synthesis offers a great opportunity to discover relationships relating to the development of useful methodology to achieve specific connections or specific stereochemistry.

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

- **Project Title: SYSTEMICALLY-ACTIVE OPIOID PEPTIDE ANALOGS**

  Principal Investigator & Institution: Szeto, Hazel H.; Professor; Pharmacology; Weill Medical College of Cornell Univ New York, Ny 10021

  Timing: Fiscal Year 2003; Project Start 30-SEP-1994; Project End 31-AUG-2008

  Summary: (provided by applicant): This program project brings together six investigators from four institutions to work on three major problems in clinical medicine, namely the treatment of pain, tolerance and dependence, and myocardial ischemia. During the past 4 years, we have made significant progress towards the development of an opioid analgesic ([Dmt1]DALDA) that is superior compared to **morphine** in terms of potency, duration of action, and side effect profile. [Dmt1]DALDA has extremely high potency after intrathecal and systemic administration, is very long-acting, has no significant adverse effects, and can even protect cardiac function against ischemia-reperfusion injury. Furthermore, morphine-tolerant animals showed no cross-tolerance to [Dmt1]DALDA. The systemic potency of this highly polar 3+ net charge peptide was unexpected, and the ability of [Dmt1]DALDA to penetrate the BBB was a surprise. Our results show that [Dmt1]DALDA has enormous potential as a therapeutic agent. Its success was unexpected and led us to question our prevailing knowledge and understanding in opioid pharmacology and peptide pharmacokinetics. A number of novel hypotheses 1 were prompted by the findings with [Dmt1]DALDA and will be tested in this competitive renewal application. The overall specific aims of this Program Project are to determine: (i) the structural requirements for small peptides to penetrate cell membranes; (ii) the role of transporters and membrane permeability in peptide pharmacokinetics; (iii) the mechanisms behind the extraordinary antinociceptive potency of [Dmt1]DALDA, (iv) the reason why there is no cross-tolerance to [Dmt1]DALDA in morphine-tolerant animals; (v) the reason why tolerance to [Dmt1]DALDA is limited to the spinal cord; (vi) the ability of [Dmt1]DALDA to protect the heart during prolonged ischemia and reperfusion. The specific aims will be accomplished with the development of novel [Dmt1]DALDA analogs that will permit structure-activity relationships in animal and cellular studies, and radiolabelled and fluorescent analogs for cellular and biochemical studies. The information to be gained from the proposed studies may significantly influence the approach to peptide drug design and the treatment of pain, addiction, heart attacks and strokes.

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

- **Project Title: THALAMOSTRIATAL MECHANISMS OF MORPHINE ACTION**

  Principal Investigator & Institution: Harlan, Richard E.; Professor; Anatomy; Tulane University of Louisiana New Orleans, La New Orleans, La 70112

  Timing: Fiscal Year 2001; Project Start 01-FEB-2000; Project End 31-JAN-2004

  Summary: Drugs of abuse, such as heroin and **morphine,** have exacted an incalculable toll on society. Our understanding of the effects of opiates is still limited, in part due to

an incomplete knowledge of the neural circuitries affected by **morphine.** Several lines of evidence implicate the medial thalamus, especially the midline-intralaminar nuclei, in the subjective effects of opiates sought by drug abusers. Rich in mu opiate receptors, the midline-intralaminar thalamic nuclei regulate affective responses to visceral stimuli, relaying this information to specific regions of the striatum, a brain region well known to play an important role in drug abuse. Thus, thalamo-striatal neurons are a key to understanding effects of opiates on the brain. The long-term goal of this application is to test the hypothesis that **morphine** binds to mu opiate receptors found on GABAergic terminals of the medial thalamus, thus disinhibiting glutamatergic thalamo-striatal neurons. The resulting activation of striatal glutamate receptors stimulates expression of immediate-early genes, which then participate in the synaptic remodeling and neural plasticity of drug abuse. This hypothesis predicts that microinfusion of a mu receptor antagonist into the medial thalamus will block the striatal c-Fos expression to systemic **morphine** (Specific Aim number 1, part A); medial thalamic microinfusion of **morphine** will induce c-Fos expression in the striatum (Specific Aim number 1, part B); augmentation of thalamic GABA activity will block the striatal c- Fos response to systemic **morphine** (Specific Aim number 1, part C), and intrathalamic **morphine** will induce c-Fos in the same set of striatal neurons activated by systemic **morphine** (Specific Aim number 1, part D). If **morphine** activates thalamo-striatal neurons, then c-Fos should be expressed by thalamic neurons retrogradely labeled from the striatum (Specific Aim number 2). Mu opiate receptors should be co-localized with GABA in synapses of the medial thalamus (Specific Aim number 3). Following systemic **morphine** treatment, Fos-positive neurons should be post- synaptic to input from the thalamus, determined by combining anterograde tracing with localization of morphine-induced c-Fos in individually-injected neurons of the striatum (Specific Aim number 4). Since thalamo-striatal neurons are glutamatergic, **morphine** should induce c-Fos expression in striatal neurons that contain specific glutamate receptor subunits (Specific Aim number 5). This will be approached by double immunocytochemistry for c- Fos and glutamate receptor subunits, and by RNA profiling from individual striatal neurons categorized by morphine-induced c- Fos. These studies should greatly extend our understanding of the role of thalamo-striatal circuits in the actions of **morphine** on the brain.

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

- **Project Title: TRIGEMINAL PAIN PATHWAYS**

  Principal Investigator & Institution: Aicher, Sue A.; Associate Scientist; None; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2001; Project Start 01-FEB-1999; Project End 31-JAN-2003

  Summary: Trigeminal afferents containing glutamate and/or substance P (SP) convey noxious input from orofacial regions to the dorsal horn of trigeminal nucleus caudalis (Vc). The postsynaptic effects of glutamate released from these terminals are partially mediated through the NMDA receptor and can be inhibited by ligands of the mu opiate receptor (muOR). Three specific aims of this proposal will examine the cellular substrates for potential function of the NMDA and muORs in the rat trigeminal dorsal horn using electron microscopic immunocytochemistry. Aim 1a will test the hypothesis that NMDA receptors are located within neurons postsynaptic to SP terminals, supporting the notion that agonists of the NMDA receptor facilitate the postsynaptic effects of SP on second-order neurons. Aim 1b will determine if muORs are contained within SP terminals, which would imply that the antinociceptive effects of muOR ligands can be attributed to direct modulation of SP release rather than to actions on

interneurons. Aim 2 will examine the localization of NMDA receptors and muORs relative to trigeminothalamic and trigeminoparabrachial neurons that are known to be critical for the perception of head pain. These studies will use retrograde tracing from selected regions combined with immunocytochemical receptor localization. These experiments will test the hypotheses that: (a) NMDA receptors located on the plasma membranes of trigeminothalamic neurons are a substrate for glutamatergic excitation of these neurons; and (b) muORs on these cells are a potential substrate for antinociception. Preferential localization of receptors on cells projecting to thalamus may suggest models for targeted modulation of nociceptive transmission. Aim 3 will compare the subcellular localization of these receptors (NMDA and muOR) in normal and **morphine** tolerant rats. The muOR is critical for both the analgesia and tolerance produced by **morphine** and antagonists of the NMDA receptor can block **morphine** tolerance. These studies will determine if there is a change in receptor density and/or subcellular redistribution (e.g. shift of receptor from membrane to intracellular sites) that may be a mechanism for **morphine** tolerance. The experiments outlined in this proposal will demonstrate the subcellular localization of NMDA receptors and muORs in trigeminal nociceptive pathways which may be used as targets for new therapeutic strategies to control trigeminal pain, including tooth pain and headache.

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

- **Project Title: ULTRASTUCTURE, RECEPTORS, AND GENE EXPRESSION**

  Principal Investigator & Institution: Pickel, Virginia M.; Professor; Rockefeller University New York, Ny 100216399

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

  Summary: (provided by applicant): This project will explore the hypothesis that chronic administration of cocaine, heroin or **morphine,** results in changes in the opioidergic, dopaminergic, and glutarnatergic systems in mesocorticolimbic and nigrostriatal regions of the brain that persist for long periods following drug withdrawal. These regions will be systematically examined for persistent changes in receptor binding and gene expression during chronic administration and following withdrawal from heroin or **morphine** or cocaine. We also selected the amygdala for a detailed ultrastructural analysis, since neurons in this region are involved in opiate and cocaine withdrawal, and also potently influence the stress responsive axis. In the amygdala, neither the relevant mu- and kappa-opioid receptors nor the dopamine D1 and D2 receptors have been examined by high-resolution methods capable of distinguishing the critical pre- (axonal) or post- (dendritic) synaptic plasmalemmal sites for receptor activation. Also, there is presently no information on potentially important long-term changes in the plasmalernmal expression of opiate related glutarnatergic (NMDA or AMPA) or peptide (substance P, NK1) systems in amygdaloid subnuclei following chronic **morphine** administration. We will specifically test the hypotheses that 1) opioid and dopamine receptors are targeted to functional sites on plasma membranes of region-specific amygdaloid neurons distinguished by their transmitters, projections, and substance P or subtype-selective glutamate receptor expression in rat, 2) chronic **morphine** administration produces long-lasting changes in the plasmalernmal availability of subtype-specific glutamate, dopamine, and peptide receptors within the amygdala of the rat, 3) chronic heroin or **morphine** administration or withdrawal produces regionally selective changes in expression of opioid and opioid system-related genes, and 4) chronic "binge" cocaine administration and withdrawal produce regionally selective changes in binding to receptors and transporters, or the expression of opioid and opioid system-related genes. We will use sensitive and complementary methods

(light and electron microscopic immunocytochemistry, quantitative autoradiography, RNase protection, real-time optical RT-PCR, and microarray analyses) to directly address these fundamental unanswered questions regarding the normal distribution and drug-induced changes in receptor targeting, binding, and expression in animal models of human addiction.

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

- **Project Title: VERY LOW NALTREXONE TREATMENT OF OPIATE WITHDRAWAL**

  Principal Investigator & Institution: Van Bockstaele, Elisabeth J.; Associate Professor; Pathology, Anat/Cell Biology; Thomas Jefferson University Office of Research Administration Philadelphia, Pa 191075587

  Timing: Fiscal Year 2003; Project Start 15-MAR-2003; Project End 31-JAN-2006

  Summary: (provided by applicant): It is the intention of this R21 application to gather data regarding the feasibility of a novel opiate detoxification method, with the use of very low-dose naltrexone pretreatment to reduce withdrawal symptoms in **morphine** dependent rats. Pharmacological withdrawal management is often the first step in the treatment of opiate dependent patients. Although a wide range of detoxification techniques have been employed, there is a continuing search for more effective approaches. Recently, the use of opiate antagonists (i.e. naltrexone, naloxone) in detoxification protocols has been introduced to sharply decrease withdrawal duration, but at the cost of greatly increased symptom intensity requiring heavy sedation and even anesthesia. Resulting serious medical complications has discouraged and limited the use of this approach. On the other hand, experimental evidence on analgesic and dependence-reducing properties of very low doses of opiate antagonists points to an alternative strategy for the use of these antagonist drugs during detoxification. Although the behavioral manifestations of opiate withdrawal have been thoroughly described in animal models, the cellular bases underlying these changes have only recently been characterized. Several brain nuclei exhibit immediate early gene expression (e.g. c-fos), which is used as a marker of neuronal activation, in the course of withdrawal. Furthermore, alterations in intracellular messengers, including cyclic adenosine monophosphate (cAMP)-dependent protein kinases (PKA), and cAMP-response element-binding protein (CREB) have been shown following opiate withdrawal in the central nervous system. Specific purpose of this study is to test the hypothesis that pretreatment of opiate dependent rats with very-low doses of opiate antagonists ameliorates behavioral and biochemical expressions of withdrawal. Experiments in Aim I are proposed to examine whether naltrexone pretreatment reduces the aversive and somatic signs of withdrawal. To this end, behavioral expression of withdrawal will be rated according to a well-described score of behaviors. Aim II will examine the distribution of c-fos protein in brain regions known to be activated following withdrawal to test whether very low-dose naltrexone pretreatment diminishes the expression of c-fos in these brain areas. Finally, Aim Ill will use western blot analysis to examine levels of intracellular messengers known to be increased during withdrawal to determine whether these are altered following pretreatment with low-doses of naltrexone. The information collected will provide the necessary foundation for designing detoxification trials in humans.

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

- **Abolition of morphine-immunosuppression in mice lacking the [mu]-opioid receptor gene.** by Gaveriaux-Ruff C, Matthes HW, Peluso J, Kieffer BL.; 1998 May 26; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=27678
- **Acetylcholine enhancement in the nucleus accumbens prevents addictive behaviors of cocaine and morphine.** by Hikida T, Kitabatake Y, Pastan I, Nakanishi S.; 2003 May 13; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=156344
- **Altered gating of opiate receptor-modulated K + channels on amygdala neurons of morphine-dependent rats.** by Chen X, Marrero HG, Murphy R, Lin YJ, Freedman JE.; 2000 Dec 19; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=18980
- **Biological synthesis of the analgesic hydromorphone, an intermediate in the metabolism of morphine, by Pseudomonas putida M10.** by Hailes AM, Bruce NC.; 1993 Jul; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=182252
- **Blockade of Tolerance to Morphine but not to [kappa] Opioids by a Nitric Oxide Synthase Inhibitor.** by Kolesnikov YA, Pick CG, Ciszewska G, Pasternak GW.; 1993 Jun 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=46675
- **Cellular mechanisms of neuropathic pain, morphine tolerance, and their interactions.** by Mayer DJ, Mao J, Holt J, Price DD.; 1999 Jul 6; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=33610
- **Chronic morphine induces the concomitant phosphorylation and altered association of multiple signaling proteins: A novel mechanism for modulating cell signaling.** by Chakrabarti S, Oppermann M, Gintzler AR.; 2001 Mar 27; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=31204

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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.

- **Chronic Morphine Induces Visible Changes in the Morphology of Mesolimbic Dopamine Neurons.** by Sklair-Tavron L, Shi W, Lane SB, Harris HW, Bunney BS, Nestler EJ.; 1996 Oct 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=38308
- **Cost effectiveness analysis of intravenous ketorolac and morphine for treating pain after limb injury: double blind randomised controlled trial.** by Rainer TH, Jacobs P, Ng YC, Cheung NK, Tam M, Lam PK, Wong R, Cocks RA.; 2000 Nov 18; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=27526
- **Deletion of the M5 muscarinic acetylcholine receptor attenuates morphine reinforcement and withdrawal but not morphine analgesia.** by Basile AS, Fedorova I, Zapata A, Liu X, Shippenberg T, Duttaroy A, Yamada M, Wess J.; 2002 Aug 20; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=123277
- **Dopamine-dependent responses to morphine depend on glucocorticoid receptors.** by Marinelli M, Aouizerate B, Barrot M, Le Moal M, Piazza PV.; 1998 Jun 23; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=22744
- **Experimental study of the morphine de-addiction properties of Delphinium denudatum Wall.** by Rahman S, Ali Khan R, Kumar A.; 2002; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=116424
- **Functionally differentiating two neuronal nitric oxide synthase isoforms through antisense mapping: Evidence for opposing NO actions on morphine analgesia and tolerance.** by Kolesnikov YA, Pan YX, Babey AM, Jain S, Wilson R, Pasternak GW.; 1997 Jul 22; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=21584
- **Immunoregulatory effects of morphine on human lymphocytes.** by Nair MP, Schwartz SA, Polasani R, Hou J, Sweet A, Chadha KC.; 1997 Mar; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=170490
- **Intravenous Cocaine, Morphine, and Amphetamine Preferentially Increase Extracellular Dopamine in the "Shell" as Compared with the "Core" of the Rat Nucleus Accumbens.** by Pontieri FE, Tanda G, Chiara GD.; 1995 Dec 19; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=40345
- **Long-Term Sensitization to the Activation of Cerebral [delta]-Opioid Receptors by the Deltorphin Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH2 in Rats Exposed to Morphine.** by Melchiorri P, Maritati M, Negri L, Erspamer V.; 1992 May 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=48938
- **Mimics of the Binding Sites of Opioid Receptors Obtained by Molecular Imprinting of Enkephalin and Morphine.** by Anderson LI, Muller R, Vlatakis G, Mosbach K.; 1995 May 23; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=41792
- **Morphine disrupts long-range synchrony of gamma oscillations in hippocampal slices.** by Whittington MA, Traub RD, Faulkner HJ, Jefferys JG, Chettiar K.; 1998 May 12; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=20461

- **Morphine Induces c-fos and junB in Striatum and Nucleus Accumbens via D1 and N-Methyl-D-Aspartate Receptors.** by Liu J, Nickolenko J, Sharp FR.; 1994 Aug 30; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=44641
- **Morphine-activated opioid receptors elude desensitization by [beta]-arrestin.** by Whistler JL, von Zastrow M.; 1998 Aug 18; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=21436
- **Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical fractures.** by Kendall JM, Reeves BC, Latter VS.; 2001 Feb 3; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=26577
- **Of mortars and morphine: one physician's D-Day.** by Baker CE.; 2002 Dec 10; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=137359
- **Opiate receptor knockout mice define [mu] receptor roles in endogenous nociceptive responses and morphine-induced analgesia.** by Sora I, Takahashi N, Funada M, Ujike H, Revay RS, Donovan DM, Miner LL, Uhl GR.; 1997 Feb 18; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=19828
- **Oxidation of Morphine to 2,2[prime prime or minute]-Bimorphine by Cylindrocarpon didymum.** by Stabler PJ, Bruce NC.; 1998 Oct; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=106614
- **PD134308, A Selective Antagonist of Cholecystokinin Type B Receptor, Enhances the Analgesic Effect of Morphine and Synergistically Interacts with Intrathecal Galanin to Depress Spinal Nociceptive Reflexes.** by Wiesenfeld-Hallin Z, Xu X, Hughes J, Horwell DC, Hokfelt T.; 1990 Sep 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=54692
- **Potentiation of Vancomycin-Induced Histamine Release by Muscle Relaxants and Morphine in Rats.** by Shuto H, Sueyasu M, Otsuki S, Hara T, Tsuruta Y, Kataoka Y, Oishi R.; 1999 Dec; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=89581
- **Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain.** by Allan L, Hays H, Jensen NH, de Waroux BL, Bolt M, Donald R, Kalso E.; 2001 May 12; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=31593
- **Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea.** by Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C.; 2003 Sep 6; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=192892
- **Stimulation of the growth and respiration of a methylotrophic bacterium by morphine.** by Romeo J, Scheraga M, Umbreit WW.; 1977 Nov; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=242713
- **Substance P Markedly Potentiates the Antinociceptive Effects of Morphine Sulfate Administered at the Spinal Level.** by Kream RM, Kato T, Shimonaka H, Marchand JE, Wurm WH.; 1993 Apr 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=46341

- **The NK1 receptor mediates both the hyperalgesia and the resistance to morphine in mice lacking noradrenaline.** by Jasmin L, Tien D, Weinshenker D, Palmiter RD, Green PG, Janni G, Ohara PT.; 2002 Jan 22;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=117425
- **Transformation of 2,2[prime prime or minute]-Bimorphine to the Novel Compounds 10-[alpha]-S-Monohydroxy-2,2[prime prime or minute]-Bimorphine and 10,10[prime prime or minute]-[alpha],[alpha][prime prime or minute]-S,S[prime prime or minute]-Dihydroxy-2,2[prime prime or minute]-Bimorphine by Cylindrocarpon didymum.** by Stabler PJ, Holt PJ, Bruce NC.; 2001 Aug;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=93077
- **Transformations of morphine alkaloids by Pseudomonas putida M10.** by Long MT, Hailes AM, Kirby GW, Bruce NC.; 1995 Oct;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=167664
- **Ultra-Low Concentrations of Naloxone Selectively Antagonize Excitatory Effects of Morphine on Sensory Neurons, Thereby Increasing its Antinociceptive Potency and Attenuating Tolerance/Dependence During Chronic Cotreatment.** by Crain SM, Shen K.; 1995 Nov 7;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=40647

The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[6] The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

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

- **A background infusion of morphine does not enhance postoperative analgesia after cardiac surgery.**
  Author(s): Dal D, Kanbak M, Caglar M, Aypar U.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2003 May; 50(5): 476-9. English, French.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12734156&dopt=Abstract

[6] PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.

- **A combination of intrathecal morphine and remifentanil anesthesia for fast-track cardiac anesthesia and surgery.**
  Author(s): Bowler I, Djaiani G, Abel R, Pugh S, Dunne J, Hall J.
  Source: Journal of Cardiothoracic and Vascular Anesthesia. 2002 December; 16(6): 709-14.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12486651&dopt=Abstract

- **A comparison of 0.1% and 0.2% ropivacaine and bupivacaine combined with morphine for postoperative patient-controlled epidural analgesia after major abdominal surgery.**
  Author(s): Senard M, Joris JL, Ledoux D, Toussaint PJ, Lahaye-Goffart B, Lamy ML.
  Source: Anesthesia and Analgesia. 2002 August; 95(2): 444-9, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12145069&dopt=Abstract

- **A comparison of dexamethasone, ondansetron, and dexamethasone plus ondansetron as prophylactic antiemetic and antipruritic therapy in patients receiving intrathecal morphine for major orthopedic surgery.**
  Author(s): Szarvas S, Chellapuri RS, Harmon DC, Owens J, Murphy D, Shorten GD.
  Source: Anesthesia and Analgesia. 2003 July; 97(1): 259-63, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12818978&dopt=Abstract

- **A double-blinded, randomized comparison of intrathecal and epidural morphine for elective cesarean delivery.**
  Author(s): Sarvela J, Halonen P, Soikkeli A, Korttila K.
  Source: Anesthesia and Analgesia. 2002 August; 95(2): 436-40, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12145067&dopt=Abstract

- **A hymn to morphine.**
  Author(s): Gerritse A.
  Source: Can Oncol Nurs J. 2001 Summer; 11(3): 159. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11987247&dopt=Abstract

- **A new method to obtain and present complete information on the compatibility: study of its validity for eight binary mixtures of morphine with drugs frequently used in palliative care.**
  Author(s): Vermeire A, Remon JP, Schrijvers D, Demeulenaere P.
  Source: Palliative Medicine. 2002 September; 16(5): 417-24.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12380660&dopt=Abstract

- **A novel metabolic pathway of morphine: formation of morphine glucosides in cancer patients.**
  Author(s): Chen XY, Zhao LM, Zhong DF.
  Source: British Journal of Clinical Pharmacology. 2003 June; 55(6): 570-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12814451&dopt=Abstract

- **A pharmacogenetic study of uridine diphosphate-glucuronosyltransferase 2B7 in patients receiving morphine.**
  Author(s): Sawyer MB, Innocenti F, Das S, Cheng C, Ramirez J, Pantle-Fisher FH, Wright C, Badner J, Pei D, Boyett JM, Cook E Jr, Ratain MJ.
  Source: Clinical Pharmacology and Therapeutics. 2003 June; 73(6): 566-74.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12811366&dopt=Abstract

- **A phase 1 study of the cholecystokinin (CCK) B antagonist L-365,260 in human subjects taking morphine for intractable non-cancer pain.**
  Author(s): McCleane GJ.
  Source: Neuroscience Letters. 2002 November 8; 332(3): 210-2.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12399016&dopt=Abstract

- **A randomised controlled study on the use of anti-inflammatory drugs in patients with cancer pain on morphine therapy: effects on dose-escalation and a pharmacoeconomic analysis.**
  Author(s): Mercadante S, Fulfaro F, Casuccio A.
  Source: European Journal of Cancer (Oxford, England : 1990). 2002 July; 38(10): 1358-63.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12091067&dopt=Abstract

- **A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy.**
  Author(s): Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB.
  Source: Anesthesiology. 2002 September; 97(3): 560-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12218520&dopt=Abstract

- **A rapid GC-MS method for the determination of dihydrocodeine, codeine, norcodeine, morphine, normorphine and 6-MAM in urine.**
  Author(s): Meadway C, George S, Braithwaite R.
  Source: Forensic Science International. 2002 June 25; 127(1-2): 136-41.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12098538&dopt=Abstract

- **A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain.**
  Author(s): Weinbroum AA.
  Source: Anesthesia and Analgesia. 2003 March; 96(3): 789-95, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12598264&dopt=Abstract

- **Adding droperidol to morphine patient-controlled analgesia: effect on nausea and vomiting.**
  Author(s): Sanansilp V, Soontarinka S, Kantigal P, Visalyaputra S, Deesawat J, Phadermwongsa P, Parakkamodom S, Vudhikamraksa S.
  Source: J Med Assoc Thai. 2002 September; 85 Suppl 3: S923-33.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12452231&dopt=Abstract

- **Adjunctive analgesia with intravenous propacetamol does not reduce morphine-related adverse effects.**
  Author(s): Aubrun F, Kalfon F, Mottet P, Bellanger A, Langeron O, Coriat P, Riou B.
  Source: British Journal of Anaesthesia. 2003 March; 90(3): 314-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12594143&dopt=Abstract

- **Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants.**
  Author(s): Bouwmeester NJ, van den Anker JN, Hop WC, Anand KJ, Tibboel D.
  Source: British Journal of Anaesthesia. 2003 May; 90(5): 642-52.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12697593&dopt=Abstract

- **Allodynia after acute intrathecal morphine administration in a patient with neuropathic pain after spinal cord injury.**
  Author(s): Parisod E, Siddall PJ, Viney M, McClelland JM, Cousins MJ.
  Source: Anesthesia and Analgesia. 2003 July; 97(1): 183-6, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12818963&dopt=Abstract

- **Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study.**
  Author(s): Mercadante S, Arcuri E, Tirelli W, Villari P, Casuccio A.
  Source: Tumori. 2002 May-June; 88(3): 239-42.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12195763&dopt=Abstract

- **An ad libitum schedule for conversion of morphine to methadone in advanced cancer patients: an open uncontrolled prospective study in a Chinese population.**
  Author(s): Tse DM, Sham MM, Ng DK, Ma HM.
  Source: Palliative Medicine. 2003 March; 17(2): 206-11.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12701853&dopt=Abstract

- **An assessment of the efficacy and tolerability of a 'double dose' of normal-release morphine sulphate at bedtime.**
  Author(s): Todd J, Rees E, Gwilliam B, Davies A.
  Source: Palliative Medicine. 2002 November; 16(6): 507-12.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12465698&dopt=Abstract

- **An audit of 405 temporomandibular joint arthrocentesis with intra-articular morphine infusion.**
  Author(s): Kunjur J, Anand R, Brennan PA, Ilankovan V.
  Source: The British Journal of Oral & Maxillofacial Surgery. 2003 February; 41(1): 29-31.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12576037&dopt=Abstract

- **An optimal dose study of intrathecal morphine in gynecological patients.**
  Author(s): Rodanant O, Sirichotewithayakorn P, Sriprajittichai P, Charuluxananan S.
  Source: J Med Assoc Thai. 2003 June; 86 Suppl 2: S331-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12930007&dopt=Abstract

- **Analgesic effects of dextromethorphan and morphine in patients with chronic pain.**
  Author(s): Heiskanen T, Hartel B, Dahl ML, Seppala T, Kalso E.
  Source: Pain. 2002 April; 96(3): 261-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11972998&dopt=Abstract

- **Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial.**
  Author(s): Wu CL, Tella P, Staats PS, Vaslav R, Kazim DA, Wesselmann U, Raja SN.
  Source: Anesthesiology. 2002 April; 96(4): 841-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11964590&dopt=Abstract

- **Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers.**
  Author(s): Skarke C, Darimont J, Schmidt H, Geisslinger G, Lotsch J.
  Source: Clinical Pharmacology and Therapeutics. 2003 January; 73(1): 107-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12545149&dopt=Abstract

- **Analgesic efficacy of inhaled morphine in patients after bunionectomy surgery.**
  Author(s): Thipphawong JB, Babul N, Morishige RJ, Findlay HK, Reber KR, Millward GJ, Otulana BA.
  Source: Anesthesiology. 2003 September; 99(3): 693-700; Discussion 6A.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12960555&dopt=Abstract

- **Analgesic efficacy of morphine applied topically to painful ulcers.**
  Author(s): Zeppetella G, Paul J, Ribeiro MD.
  Source: Journal of Pain and Symptom Management. 2003 June; 25(6): 555-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12782436&dopt=Abstract

- **Antinociceptive effect of low-dose intrathecal neostigmine combined with intrathecal morphine following gynecologic surgery.**
  Author(s): Almeida RA, Lauretti GR, Mattos AL.
  Source: Anesthesiology. 2003 February; 98(2): 495-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12552210&dopt=Abstract

- **Avinza (morphine sulfate extended-release capsules).**
  Author(s): King CR, Khabazian A.
  Source: Clinical Journal of Oncology Nursing. 2003 July-August; 7(4): 458-60, 478.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12929281&dopt=Abstract

- **Can ketamine potentiate the analgesic effect of epidural morphine, preincisional or postincisional administration?**
  Author(s): Santawat U, Pongraweewan O, Lertakayamanee J, Rushatamukayanunt P, Phalakornkule N, Svasdi-Xuto O.
  Source: J Med Assoc Thai. 2002 September; 85 Suppl 3: S1024-30.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12452245&dopt=Abstract

- **Can single dose preoperative intrathecal morphine sulfate provide cost-effective postoperative analgesia and patient satisfaction during radical prostatectomy in the current era of cost containment?**
  Author(s): Eandi JA, de Vere White RW, Tunuguntla HS, Bohringer CH, Evans CP.
  Source: Prostate Cancer and Prostatic Diseases. 2002; 5(3): 226-30.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12496986&dopt=Abstract

- **Cardiovascular surgery patients' respiratory responses to morphine before extubation.**
  Author(s): Renaud KL.
  Source: Pain Management Nursing : Official Journal of the American Society of Pain Management Nurses. 2002 June; 3(2): 53-60.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12050836&dopt=Abstract

- **Cephalad movement of morphine and fentanyl in humans after intrathecal injection.**
  Author(s): Eisenach JC, Hood DD, Curry R, Shafer SL.
  Source: Anesthesiology. 2003 July; 99(1): 166-73.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12826857&dopt=Abstract

- **Changing M3G/M6G ratios and pharmacodynamics in a cancer patient during long-term morphine treatment.**
  Author(s): Andersen G, Christrup LL, Sjogren P, Hansen SH, Jensen NH.
  Source: Journal of Pain and Symptom Management. 2002 February; 23(2): 161-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11844638&dopt=Abstract

- **Characteristics and adequacy of intravenous morphine infusions in children in a paediatric oncology setting.**
  Author(s): Flogegard H, Ljungman G.
  Source: Medical and Pediatric Oncology. 2003 April; 40(4): 233-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12555251&dopt=Abstract

- **Chronic morphine treatment inhibits opioid receptor desensitization and internalization.**
  Author(s): Eisinger DA, Ammer H, Schulz R.
  Source: The Journal of Neuroscience : the Official Journal of the Society for Neuroscience. 2002 December 1; 22(23): 10192-200.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12451120&dopt=Abstract

- **Codeine and clinical impairment in samples in which morphine is not detected.**
  Author(s): Bachs L, Skurtveit S, Morland J.
  Source: European Journal of Clinical Pharmacology. 2003 April; 58(12): 785-9. Epub 2003 March 01.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12698303&dopt=Abstract

- **Combinations of morphine with ketamine for patient-controlled analgesia: a new optimization method.**
  Author(s): Sveticic G, Gentilini A, Eichenberger U, Luginbuhl M, Curatolo M.
  Source: Anesthesiology. 2003 May; 98(5): 1195-205.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12717142&dopt=Abstract

- **Combined intra-articular glucocorticoid, bupivacaine and morphine reduces pain and convalescence after diagnostic knee arthroscopy.**
  Author(s): Rasmussen S, Lorentzen JS, Larsen AS, Thomsen ST, Kehlet H.
  Source: Acta Orthopaedica Scandinavica. 2002 April; 73(2): 175-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12079015&dopt=Abstract

- **Combined intrathecal baclofen and morphine infusion for the treatment of spasticity related pain and central deafferentiation pain.**
  Author(s): Gatscher S, Becker R, Uhle E, Bertalanffy H.
  Source: Acta Neurochir Suppl. 2002; 79: 75-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11974992&dopt=Abstract

- **Comparative study of analgesic efficacy and morphine-sparing effect of intramuscular dexketoprofen trometamol with ketoprofen or placebo after major orthopaedic surgery.**
  Author(s): Hanna MH, Elliott KM, Stuart-Taylor ME, Roberts DR, Buggy D, Arthurs GJ.
  Source: British Journal of Clinical Pharmacology. 2003 February; 55(2): 126-33.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12580983&dopt=Abstract

- **Comparison between patient-controlled analgesia and subcutaneous morphine in elderly patients after total hip replacement.**
  Author(s): Keita H, Geachan N, Dahmani S, Couderc E, Armand C, Quazza M, Mantz J, Desmonts JM.
  Source: British Journal of Anaesthesia. 2003 January; 90(1): 53-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12488379&dopt=Abstract

- **Comparison between repeat bolus intrathecal morphine and an epidurally delivered bupivacaine and fentanyl combination in the management of post-thoracotomy pain with or without cyclooxygenase inhibition.**
  Author(s): McCrory C, Diviney D, Moriarty J, Luke D, Fitzgerald D.
  Source: Journal of Cardiothoracic and Vascular Anesthesia. 2002 October; 16(5): 607-11.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12407615&dopt=Abstract

- **Comparison of analgesic effects of intra-articular tenoxicam and morphine in anterior cruciate ligament reconstruction.**
  Author(s): Guler G, Karaoglu S, Velibasoglu H, Ramazanogullari N, Boyaci A.
  Source: Knee Surgery, Sports Traumatology, Arthroscopy : Official Journal of the Esska. 2002 July; 10(4): 229-32. Epub 2002 March 27.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12172717&dopt=Abstract

- **Comparison of different doses of epidural morphine for pain relief following cesarean section.**
  Author(s): Chumpathong S, Santawat U, Saunya P, Chimpalee R, Toomtong P.
  Source: J Med Assoc Thai. 2002 September; 85 Suppl 3: S956-62.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12452235&dopt=Abstract

- **Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for caesarean section under spinal anaesthesia.**
  Author(s): Cowan CM, Kendall JB, Barclay PM, Wilkes RG.
  Source: British Journal of Anaesthesia. 2002 September; 89(3): 452-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12402725&dopt=Abstract

- **Comparison of intrathecal isobaric bupivacaine-morphine and ropivacaine-morphine for Caesarean delivery.**
  Author(s): Ogun CO, Kirgiz EN, Duman A, Okesli S, Akyurek C.
  Source: British Journal of Anaesthesia. 2003 May; 90(5): 659-64.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12697595&dopt=Abstract

- **Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia.**
  Author(s): Jeffs SA, Hall JE, Morris S.
  Source: British Journal of Anaesthesia. 2002 September; 89(3): 424-7. Erratum In: Br J Anaesth. 2003 January; 90(1): 114.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12402720&dopt=Abstract

- **Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia.**
  Author(s): Carey C, Jagger S.
  Source: British Journal of Anaesthesia. 2003 February; 90(2): 253; Author Reply 253.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12538390&dopt=Abstract

- **Comparison of ropivacaine-fentanyl patient-controlled epidural analgesia with morphine intravenous patient-controlled analgesia for perioperative analgesia and recovery after open colon surgery.**
  Author(s): Steinberg RB, Liu SS, Wu CL, Mackey DC, Grass JA, Ahlen K, Jeppsson L.
  Source: Journal of Clinical Anesthesia. 2002 December; 14(8): 571-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12565114&dopt=Abstract

- **Comparison of the morphine-sparing effects of diclofenac sodium and ketorolac tromethamine after major orthopedic surgery.**
  Author(s): Alexander R, El-Moalem HE, Gan TJ.
  Source: Journal of Clinical Anesthesia. 2002 May; 14(3): 187-92.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12031750&dopt=Abstract

- **Compatibility of ropivacaine with morphine, sufentanil, fentanyl, or clonidine.**
  Author(s): Oster Svedberg K, McKenzie J, Larrivee-Elkins C.
  Source: Journal of Clinical Pharmacy and Therapeutics. 2002 February; 27(1): 39-45.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11846860&dopt=Abstract

- **Concerns of Japanese hospice inpatients about morphine therapy as a factor in pain management: a pilot study.**
  Author(s): Morita T, Tsunoda J, Inoue S, Chihara S.
  Source: Journal of Palliative Care. 2000 Winter; 16(4): 54-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11965937&dopt=Abstract

- **Continuous epidural, not intravenous, droperidol inhibits pruritus, nausea, and vomiting during epidural morphine analgesia.**
  Author(s): Nakata K, Mammoto T, Kita T, Taniguchi H, Kanbara N, Akamatsu T, Sakai T, Kishi Y.
  Source: Journal of Clinical Anesthesia. 2002 March; 14(2): 121-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11943525&dopt=Abstract

- **Continuous intraventricular clonidine infusion in controlled morphine withdrawal--case report.**
  Author(s): Lorenz M, Hussein S, Verner L.
  Source: Pain. 2002 August; 98(3): 335-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12127036&dopt=Abstract

- **Contribution of morphine-6-glucuronide to antinociception following intravenous administration of morphine to healthy volunteers.**
  Author(s): Murthy BR, Pollack GM, Brouwer KL.
  Source: Journal of Clinical Pharmacology. 2002 May; 42(5): 569-76.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12017351&dopt=Abstract

- **Conversion from intrathecal morphine to oral methadone.**
  Author(s): Gebhardt R, Kinney MA.
  Source: Regional Anesthesia and Pain Medicine. 2002 May-June; 27(3): 319-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12016609&dopt=Abstract

- **Costa Rica marks improvement in morphine consumption.**
  Author(s): Salas-Herrera IG, Monestel R.
  Source: Journal of Pain and Symptom Management. 2002 September; 24(3): 286-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12458107&dopt=Abstract

- **Could nitric oxide be an important mediator in opioid tolerance and morphine side effects?**
  Author(s): Devulder JE.
  Source: Journal of Clinical Anesthesia. 2002 March; 14(2): 81-2.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11943516&dopt=Abstract

- **Detection of opiate use in a methadone maintenance treatment population with the CEDIA 6-acetylmorphine and CEDIA DAU opiate assays.**
  Author(s): Spanbauer AC, Casseday S, Davoudzadeh D, Preston KL, Huestis MA.
  Source: Journal of Analytical Toxicology. 2001 October; 25(7): 515-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11599593&dopt=Abstract

- **Dexamethasone for prophylaxis of nausea and vomiting after epidural morphine for post-Caesarean section analgesia: comparison of droperidol and saline.**
  Author(s): Tzeng JI, Wang JJ, Ho ST, Tang CS, Liu YC, Lee SC.
  Source: British Journal of Anaesthesia. 2000 December; 85(6): 865-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11732521&dopt=Abstract

- **Dextromethorphan and intrathecal morphine for analgesia after Caesarean section under spinal anaesthesia.**
  Author(s): Choi DM, Kliffer AP, Douglas MJ.
  Source: British Journal of Anaesthesia. 2003 May; 90(5): 653-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12697594&dopt=Abstract

- **Dextromethorphan for the reduction of immediate and late postoperative pain and morphine consumption in orthopedic oncology patients: a randomized, placebo-controlled, double-blind study.**
  Author(s): Weinbroum AA, Gorodetzky A, Nirkin A, Kollender Y, Bickels J, Marouani N, Rudick V, Meller I.
  Source: Cancer. 2002 September 1; 95(5): 1164-70.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12209704&dopt=Abstract

- **Diazepam as an adjuvant analgesic to morphine for pain due to skeletal muscle spasm.**
  Author(s): Srivastava M, Walsh D.
  Source: Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer. 2003 January; 11(1): 66-9. Epub 2002 August 07.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12527958&dopt=Abstract

- **Diclofenac and/or propacetamol for postoperative pain management after cesarean delivery in patients receiving patient controlled analgesia morphine.**
  Author(s): Siddik SM, Aouad MT, Jalbout MI, Rizk LB, Kamar GH, Baraka AS.
  Source: Regional Anesthesia and Pain Medicine. 2001 July-August; 26(4): 310-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11464348&dopt=Abstract

- **Direct assessment and diminished production of morphine stimulated NO by diabetic endothelium from saphenous vein.**
  Author(s): Bilfinger TV, Vosswinkel JA, Cadet P, Rialas CM, Magazine HI, Stefano GB.
  Source: Acta Pharmacologica Sinica. 2002 February; 23(2): 97-102.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11866867&dopt=Abstract

- **Direct vs. indirect modulation of complex in vitro human retroviral infections by morphine.**
  Author(s): Nyland SB, Specter S, Ugen KE.
  Source: Advances in Experimental Medicine and Biology. 2001; 493: 49-58.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11727780&dopt=Abstract

- **Do patients prefer transdermal fentanyl or sustained-release oral morphine for treatment of chronic non-cancer pain?**
  Author(s): Heidemann AJ, Seaton TL.
  Source: The Journal of Family Practice. 2001 October; 50(10): 897.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11674896&dopt=Abstract

- **Does the A118G polymorphism at the mu-opioid receptor gene protect against morphine-6-glucuronide toxicity?**
  Author(s): Lotsch J, Zimmermann M, Darimont J, Marx C, Dudziak R, Skarke C, Geisslinger G.
  Source: Anesthesiology. 2002 October; 97(4): 814-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12357145&dopt=Abstract

- **Does the type of arthroscopic surgery modify the analgesic effect of intraarticular morphine and bupivacaine? A preliminary study.**
  Author(s): Marchal JM, Delgado-Martinez AD, Poncela M, Valenzuela J, de Dios Luna J.
  Source: The Clinical Journal of Pain. 2003 July-August; 19(4): 240-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12840618&dopt=Abstract

- **Double-blind evaluation of transdermal nitroglycerine as adjuvant to oral morphine for cancer pain management.**
  Author(s): Lauretti GR, Perez MV, Reis MP, Pereira NL.
  Source: Journal of Clinical Anesthesia. 2002 March; 14(2): 83-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11943517&dopt=Abstract

- **Double-blind randomized placebo-controlled trial of the effect of ketamine on postoperative morphine consumption in children following appendicectomy.**
  Author(s): Dix P, Martindale S, Stoddart PA.
  Source: Paediatric Anaesthesia. 2003 June; 13(5): 422-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12791116&dopt=Abstract

- **Dramatic response to nebulized morphine in an asthmatic patient with severe chronic cough.**
  Author(s): Rutherford RM, Azher T, Gilmartin JJ.
  Source: Ir Med J. 2002 April; 95(4): 113-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12090441&dopt=Abstract

- **Driving and intrathecal morphine administration.**
  Author(s): Van den Bosch G, De Doncker M, Vercruysse P, Maeyaert J, Vissers K, Neels H.
  Source: European Journal of Pain (London, England). 2001; 5(4): 443-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11743710&dopt=Abstract

- **Effect of combining naloxone and morphine for intravenous patient-controlled analgesia.**
  Author(s): Sartain JB, Barry JJ, Richardson CA, Branagan HC.
  Source: Anesthesiology. 2003 July; 99(1): 148-51.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12826854&dopt=Abstract

- **Effect of epidural bupivacaine vs combined epidural bupivacaine and morphine on gastrointestinal function and pain after major gynaecological surgery.**
  Author(s): Jorgensen H, Fomsgaard JS, Dirks J, Wetterslev J, Andreasson B, Dahl JB.
  Source: British Journal of Anaesthesia. 2001 November; 87(5): 727-32.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11878523&dopt=Abstract

- **Effect of intravenous alizapride on spinal morphine-induced pruritus.**
  Author(s): Horta ML, Vianna PT.
  Source: British Journal of Anaesthesia. 2003 August; 91(2): 287-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12878632&dopt=Abstract

- **Effect of morphine on sympathetic nerve activity in humans.**
  Author(s): Carter JR, Sauder CL, Ray CA.
  Source: Journal of Applied Physiology (Bethesda, Md. : 1985). 2002 November; 93(5): 1764-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12381764&dopt=Abstract

- **Effect of the addition of ketamine to morphine in patient-controlled analgesia.**
  Author(s): Murdoch CJ, Crooks BA, Miller CD.
  Source: Anaesthesia. 2002 May; 57(5): 484-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12004808&dopt=Abstract

- **Effect of timing of morphine administration during remifentanil-based anaesthesia on early recovery from anaesthesia and postoperative pain.**
  Author(s): Munoz HR, Guerrero ME, Brandes V, Cortinez LI.
  Source: British Journal of Anaesthesia. 2002 June; 88(6): 814-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12173199&dopt=Abstract

- **Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma.**
  Author(s): Cerchietti LC, Navigante AH, Bonomi MR, Zaderajko MA, Menendez PR, Pogany CE, Roth BM.
  Source: Cancer. 2002 November 15; 95(10): 2230-6. Erratum In: Cancer. 2003 February 15; 97(4): 1137.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12412178&dopt=Abstract

- **Effective pain relief from intra-articular saline with or without morphine 2 mg in patients with moderate-to-severe pain after knee arthroscopy: a randomized, double-blind controlled clinical study.**
  Author(s): Rosseland LA, Stubhaug A, Grevbo F, Reikeras O, Breivik H.
  Source: Acta Anaesthesiologica Scandinavica. 2003 July; 47(6): 732-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12803592&dopt=Abstract

- **Effects of infusion rate of intravenously administered morphine on physiological, psychomotor, and self-reported measures in humans.**
  Author(s): Marsch LA, Bickel WK, Badger GJ, Rathmell JP, Swedberg MD, Jonzon B, Norsten-Hoog C.
  Source: The Journal of Pharmacology and Experimental Therapeutics. 2001 December; 299(3): 1056-65.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11714895&dopt=Abstract

- **Effects of IV morphine in central pain: a randomized placebo-controlled study.**
  Author(s): Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D.
  Source: Neurology. 2002 February 26; 58(4): 554-63.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11865132&dopt=Abstract

- **Effects of morphine analgesia on diagnostic accuracy in Emergency Department patients with abdominal pain: a prospective, randomized trial.**
  Author(s): Thomas SH, Silen W, Cheema F, Reisner A, Aman S, Goldstein JN, Kumar AM, Stair TO.
  Source: Journal of the American College of Surgeons. 2003 January; 196(1): 18-31.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12517545&dopt=Abstract

- **Effects of morphine and time of day on pain and beta-endorphin.**
  Author(s): Rasmussen NA, Farr LA.
  Source: Biological Research for Nursing. 2003 October; 5(2): 105-16.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14531215&dopt=Abstract

- **Effects of morphine on tumour growth.**
  Author(s): Rasmussen M, Zhu W, Tonnesen J, Cadet P, Tonnesen E, Stefano GB.
  Source: Neuroendocrinol Lett. 2002 June; 23(3): 193-8. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12080278&dopt=Abstract

- **Effects of subcutaneous methylnaltrexone on morphine-induced peripherally mediated side effects: a double-blind randomized placebo-controlled trial.**
  Author(s): Yuan CS, Wei G, Foss JF, O'Connor M, Karrison T, Osinski J.
  Source: The Journal of Pharmacology and Experimental Therapeutics. 2002 January; 300(1): 118-23.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11752106&dopt=Abstract

- **Effects of systemic and epidural morphine on antidiuretic hormone levels in children.**
  Author(s): Bozkurt P, Kaya G, Yeker Y, Altintas F, Bakan M, Hacibekiroglu M, Kavunoglu G.
  Source: Paediatric Anaesthesia. 2003 July; 13(6): 508-14.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12846707&dopt=Abstract

- **Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial.**
  Author(s): Caldwell JR, Rapoport RJ, Davis JC, Offenberg HL, Marker HW, Roth SH, Yuan W, Eliot L, Babul N, Lynch PM.
  Source: Journal of Pain and Symptom Management. 2002 April; 23(4): 278-91.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11997197&dopt=Abstract

- **Efficacy of continuous versus intermittent morphine administration after major surgery in 0-3-year-old infants; a double-blind randomized controlled trial.**
  Author(s): van Dijk M, Bouwmeester NJ, Duivenvoorden HJ, Koot HM, Tibboel D, Passchier J, de Boer JB.
  Source: Pain. 2002 August; 98(3): 305-13.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12127032&dopt=Abstract

- **Efficacy of intrathecal morphine for analgesia following elective cesarean section: comparison with previous delivery.**
  Author(s): Terajima K, Onodera H, Kobayashi M, Yamanaka H, Ohno T, Konuma S, Ogawa R.
  Source: Journal of Nippon Medical School = Nihon Ika Daigaku Zasshi. 2003 August; 70(4): 327-33.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12928713&dopt=Abstract

- **Efficacy of the morphine-Adcon-L compound in the management of postoperative pain after lumbar microdiscectomy.**
  Author(s): Mastronardi L, Pappagallo M, Puzzilli F, Tatta C.
  Source: Neurosurgery. 2002 March; 50(3): 518-24; Discussion 524-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11841719&dopt=Abstract

- **Efficacy of topical microfibrillar collagen mixed with steroid hormone and morphine for postoperative pain control during lumbar laminectomy: a preliminary report.**
  Author(s): Chen TY.
  Source: Chang Gung Med J. 2002 February; 25(2): 81-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11952276&dopt=Abstract

- **Emetic effects of morphine and piritramide.**
  Author(s): Breitfeld C, Peters J, Vockel T, Lorenz C, Eikermann M.
  Source: British Journal of Anaesthesia. 2003 August; 91(2): 218-23.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12878621&dopt=Abstract

- **Enhanced endothelin-1 degradation by intravenous morphine in patients with congestive heart failure: role of neutral endopeptidase 24.11.**
  Author(s): Wang TL, Hung CR.
  Source: Heart (British Cardiac Society). 2003 February; 89(2): 211-2.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12527684&dopt=Abstract

- **Epidural administration of low-dose morphine combined with clonidine for postoperative analgesia after lumbar disc surgery.**
  Author(s): Bonhomme V, Doll A, Dewandre PY, Brichant JF, Ghassempour K, Hans P.
  Source: Journal of Neurosurgical Anesthesiology. 2002 January; 14(1): 1-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11773815&dopt=Abstract

- **Epidural analgesia compared with intravenous morphine patient-controlled analgesia: postoperative outcome measures after mastectomy with immediate TRAM flap breast reconstruction.**
  Author(s): Correll DJ, Viscusi ER, Grunwald Z, Moore JH Jr.
  Source: Regional Anesthesia and Pain Medicine. 2001 September-October; 26(5): 444-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11561265&dopt=Abstract

- **Epidural morphine alone is inadequate for postthoracotomy pain relief.**
  Author(s): Chua SK.
  Source: Anesthesia and Analgesia. 2002 December; 95(6): 1825; Author Reply 1825.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12456478&dopt=Abstract

- **Epidural morphine and neostigmine for postoperative analgesia after orthopedic surgery.**
  Author(s): Omais M, Lauretti GR, Paccola CA.
  Source: Anesthesia and Analgesia. 2002 December; 95(6): 1698-701, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12456442&dopt=Abstract

- **Epidural morphine delays the onset of tourniquet pain during epidural lidocaine anesthesia.**
  Author(s): Cherng CH, Wong CS, Chang FL, Ho ST, Lee CH.
  Source: Anesthesia and Analgesia. 2002 June; 94(6): 1614-6, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12032038&dopt=Abstract

- **Epidural morphine injection after combined spinal and epidural anaesthesia.**
  Author(s): Takenaka-Hamaya C, Hamaya Y, Dohi S.
  Source: European Journal of Anaesthesiology. 2002 September; 19(9): 672-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12243291&dopt=Abstract

- **Epidural versus intrathecal morphine for postoperative analgesia after Caesarean section.**
  Author(s): Duale C, Frey C, Bolandard F, Barriere A, Schoeffler P.
  Source: British Journal of Anaesthesia. 2003 November; 91(5): 690-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14570792&dopt=Abstract

- **Ethnicity influences morphine pharmacokinetics and pharmacodynamics.**
  Author(s): Cepeda MS, Farrar JT, Roa JH, Boston R, Meng QC, Ruiz F, Carr DB, Strom BL.
  Source: Clinical Pharmacology and Therapeutics. 2001 October; 70(4): 351-61.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11673751&dopt=Abstract

- **Fatal versus non-fatal heroin "overdose": blood morphine concentrations with fatal outcome in comparison to those of intoxicated drivers.**
  Author(s): Meissner C, Recker S, Reiter A, Friedrich HJ, Oehmichen M.
  Source: Forensic Science International. 2002 November 5; 130(1): 49-54.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12427450&dopt=Abstract

- **G protein-independent G1 cell cycle block and apoptosis with morphine in adenocarcinoma cells: involvement of p53 phosphorylation.**
  Author(s): Tegeder I, Grosch S, Schmidtko A, Haussler A, Schmidt H, Niederberger E, Scholich K, Geisslinger G.
  Source: Cancer Research. 2003 April 15; 63(8): 1846-52.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12702572&dopt=Abstract

- **Gas chromatography/negative-ion chemical ionisation mass spectrometry for the quantitative analysis of morphine in human plasma using pentafluorobenzyl carbonate derivatives.**
  Author(s): Leis HJ, Windischhofer W, Fauler G.
  Source: Rapid Communications in Mass Spectrometry : Rcm. 2002; 16(7): 646-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11921241&dopt=Abstract

- **GC/MS determination of pyrolysis products from diacetylmorphine and adulterants of street heroin samples.**
  Author(s): Brenneisen R, Hasler F.
  Source: J Forensic Sci. 2002 July; 47(4): 885-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12137001&dopt=Abstract

- **German doctor is investigated for killing 76 patients with morphine.**
  Author(s): Tuffs A.
  Source: Bmj (Clinical Research Ed.). 2003 October 11; 327(7419): 830.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14551077&dopt=Abstract

- **Hair morphine concentrations of fatal heroin overdose cases and living heroin users.**
  Author(s): Darke S, Hall W, Kaye S, Ross J, Duflou J.
  Source: Addiction (Abingdon, England). 2002 August; 97(8): 977-84.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12144600&dopt=Abstract

- **Heroin use by motorists in Sweden confirmed by analysis of 6-acetylmorphine in urine.**
  Author(s): Jones AW.
  Source: Journal of Analytical Toxicology. 2001 July-August; 25(5): 353-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11499891&dopt=Abstract

- **High prevalence of 6-acetylmorphine in morphine-positive oral fluid specimens.**
  Author(s): Presley L, Lehrer M, Seiter W, Hahn D, Rowland B, Smith M, Kardos KW, Fritch D, Salamone S, Niedbala RS, Cone EJ.
  Source: Forensic Science International. 2003 April 23; 133(1-2): 22-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12742685&dopt=Abstract

- **HIV gp120 and morphine alter mu opiate receptor expression in human vascular endothelium.**
  Author(s): Cadet P, Weeks BS, Bilfinger TV, Mantione KJ, Casares F, Stefano GB.
  Source: International Journal of Molecular Medicine. 2001 August; 8(2): 165-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11445868&dopt=Abstract

- **Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine.**
  Author(s): Bouwmeester NJ, Anand KJ, van Dijk M, Hop WC, Boomsma F, Tibboel D.
  Source: British Journal of Anaesthesia. 2001 September; 87(3): 390-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11517122&dopt=Abstract

- **Hypothermia and excessive sweating following intrathecal morphine in a parturient undergoing cesarean delivery.**
  Author(s): Sayyid SS, Jabbour DG, Baraka AS.
  Source: Regional Anesthesia and Pain Medicine. 2003 March-April; 28(2): 140-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12677625&dopt=Abstract

- **Identification of scFv antibody fragments that specifically recognise the heroin metabolite 6-monoacetylmorphine but not morphine.**
  Author(s): Moghaddam A, Borgen T, Stacy J, Kausmally L, Simonsen B, Marvik OJ, Brekke OH, Braunagel M.
  Source: Journal of Immunological Methods. 2003 September; 280(1-2): 139-55.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12972195&dopt=Abstract

- **Iliohypogastric-ilioinguinal peripheral nerve block for post-Cesarean delivery analgesia decreases morphine use but not opioid-related side effects.**
  Author(s): Bell EA, Jones BP, Olufolabi AJ, Dexter F, Phillips-Bute B, Greengrass RA, Penning DH, Reynolds JD; Duke Women's Anesthesia Research Group.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2002 August-September; 49(7): 694-700. English, French.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12193488&dopt=Abstract

- **Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial.**
  Author(s): Klepstad P, Kaasa S, Jystad A, Hval B, Borchgrevink PC.
  Source: Pain. 2003 January; 101(1-2): 193-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12507714&dopt=Abstract

- **In search of a role for the morphine metabolite morphine-3-glucuronide.**
  Author(s): Vaughan CW, Connor M.
  Source: Anesthesia and Analgesia. 2003 August; 97(2): 311-2.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12873910&dopt=Abstract

- **Increased plasma morphine metabolites in terminally ill cancer patients with delirium: an intra-individual comparison.**
  Author(s): Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S.
  Source: Journal of Pain and Symptom Management. 2002 February; 23(2): 107-13.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11844630&dopt=Abstract

- **Induction of early apoptosis marker by morphine in human lung and breast carcinoma cell lines.**
  Author(s): Hatsukari I, Hitosugi N, Matsumoto I, Nagasaka H, Sakagami H.
  Source: Anticancer Res. 2003 May-June; 23(3B): 2413-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12894522&dopt=Abstract

- **Influence of morphine sulfate on cocaine-induced coronary vasoconstriction.**
  Author(s): Saland KE, Hillis LD, Lange RA, Cigarroa JE.
  Source: The American Journal of Cardiology. 2002 October 1; 90(7): 810-1.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12356410&dopt=Abstract

- **Influences on serum concentrations of morphine, M6G and M3G during routine clinical drug monitoring: a prospective survey in 300 adult cancer patients.**
  Author(s): Klepstad P, Dale O, Kaasa S, Zahlsen K, Aamo T, Fayers P, Borchgrevink PC.
  Source: Acta Anaesthesiologica Scandinavica. 2003 July; 47(6): 725-31.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12803591&dopt=Abstract

- **Inhibition by peripheral electric stimulation of the reinstatement of morphine-induced place preference in rats and drug-craving in heroin addicts.**
  Author(s): Wang B, Zhang B, Ge X, Luo F, Han J.
  Source: Beijing Da Xue Xue Bao. 2003 June 18; 35(3): 241-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12914237&dopt=Abstract

- **Inhibition of morphine-potentiated HIV-1 replication in peripheral blood mononuclear cells with the nuclease-resistant 2-5A agonist analog, 2-5A(N6B).**
  Author(s): Homan JW, Steele AD, Martinand-Mari C, Rogers TJ, Henderson EE, Charubala R, Pfleiderer W, Reichenbach NL, Suhadolnik RJ.
  Source: Journal of Acquired Immune Deficiency Syndromes (1999). 2002 May 1; 30(1): 9-20.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12048358&dopt=Abstract

- **Interaction of a combination of morphine and ketamine on the nociceptive flexion reflex in human volunteers.**
  Author(s): Bossard AE, Guirimand F, Fletcher D, Gaude-Joindreau V, Chauvin M, Bouhassira D.
  Source: Pain. 2002 July; 98(1-2): 47-57.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12098616&dopt=Abstract

- **Interaction of morphine, fentanyl, sufentanil, alfentanil, and loperamide with the efflux drug transporter P-glycoprotein.**
  Author(s): Wandel C, Kim R, Wood M, Wood A.
  Source: Anesthesiology. 2002 April; 96(4): 913-20.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11964599&dopt=Abstract

- **Intra-articular morphine and postoperative analgesia after knee arthroscopy.**
  Author(s): Drosos GI, Vlachonikolis IG, Papoutsidakis AN, Gavalas NS, Anthopoulos G.
  Source: The Knee. 2002 December; 9(4): 335-40.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12424044&dopt=Abstract

- **Intra-articular morphine, ropivacaine, and morphine/ropivacaine for pain control after arthroscopy: preliminary observation.**
  Author(s): Doss NW, Splain SH, Crimi T, Michael R, Abadir AR, Gintautas J.
  Source: Proc West Pharmacol Soc. 2001; 44: 195-6. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11793981&dopt=Abstract

- **Intranasal delivery of morphine.**
  Author(s): Illum L, Watts P, Fisher AN, Hinchcliffe M, Norbury H, Jabbal-Gill I, Nankervis R, Davis SS.
  Source: The Journal of Pharmacology and Experimental Therapeutics. 2002 April; 301(1): 391-400.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11907197&dopt=Abstract

- **Intraspinal use of morphine.**
  Author(s): Gaudette KE, Weaver SJ.
  Source: The Annals of Pharmacotherapy. 2003 July-August; 37(7-8): 1132-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12841829&dopt=Abstract

- **Intra-synovial, compared to intra-articular morphine provides better pain relief following knee arthroscopy menisectomy.**
  Author(s): Kligman M, Bruskin A, Sckliamser J, Vered R, Roffman M.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2002 April; 49(4): 380-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11927477&dopt=Abstract

- **Intrathecal clonidine added to a bupivacaine-morphine spinal anesthetic improves postoperative analgesia for total knee arthroplasty.**
  Author(s): Sites BD, Beach M, Biggs R, Rohan C, Wiley C, Rassias A, Gregory J, Fanciullo G.
  Source: Anesthesia and Analgesia. 2003 April; 96(4): 1083-8, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12651665&dopt=Abstract

- **Intrathecal diamorphine or intrathecal fentanyl to supplement spinal anaesthesia for Caesarean section?**
  Author(s): Cooper DW.
  Source: British Journal of Anaesthesia. 2003 January; 90(1): 107; Author Reply 107.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12488396&dopt=Abstract

- **Intrathecal morphine after cardiac surgery.**
  Author(s): Boulanger A, Perreault S, Choiniere M, Prieto I, Lavoie C, Laflamme C.
  Source: The Annals of Pharmacotherapy. 2002 September; 36(9): 1337-43.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12196048&dopt=Abstract

- **Intrathecal morphine and clonidine for coronary artery bypass grafting.**
  Author(s): Lena P, Balarac N, Arnulf JJ, Teboul J, Bonnet F.
  Source: British Journal of Anaesthesia. 2003 March; 90(3): 300-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12594140&dopt=Abstract

- **Intrathecal morphine for off-pump coronary artery bypass patients.**
  Author(s): Jara FM, Klush J, Kilaru V.
  Source: Heart Surg Forum. 2001; 4(1): 57-60.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11510450&dopt=Abstract

- **Intrathecal morphine for postoperative analgesia: a randomized, controlled, dose-ranging study after hip and knee arthroplasty.**
  Author(s): Rathmell JP, Pino CA, Taylor R, Patrin T, Viani BA.
  Source: Anesthesia and Analgesia. 2003 November; 97(5): 1452-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14570664&dopt=Abstract

- **Intrathecal morphine overdose during combined spinal-epidural block for Caesarean delivery.**
  Author(s): Cannesson M, Nargues N, Bryssine B, Debon R, Boselli E, Chassard D.
  Source: British Journal of Anaesthesia. 2002 December; 89(6): 925-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12453940&dopt=Abstract

- **Intrathecal morphine provides better postoperative analgesia than psoas compartment block after primary hip arthroplasty.**
  Author(s): Souron V, Delaunay L, Schifrine P.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2003 June-July; 50(6): 574-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12826549&dopt=Abstract

- **Intrathecal sufentanil-morphine shortens the duration of intubation and improves analgesia in fast-track cardiac surgery.**
  Author(s): Bettex DA, Schmidlin D, Chassot PG, Schmid ER.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2002 August-September; 49(7): 711-7. English, French.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12193491&dopt=Abstract

- **Intravenous morphine for rapid control of severe cancer pain.**
  Author(s): Harris JT, Suresh Kumar K, Rajagopal MR.
  Source: Palliative Medicine. 2003 April; 17(3): 248-56.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12725478&dopt=Abstract

- **Intravesical diamorphine for bladder spasm.**
  Author(s): McCoubrie R, Jeffrey D.
  Source: Journal of Pain and Symptom Management. 2003 January; 25(1): 1-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12565179&dopt=Abstract

- **Intravesical morphine analgesia is not effective after bladder surgery in children: results of a randomied double-blind study.**
  Author(s): El-Ghoneimi A, Deffarges C, Hankard R, Jean-Eudes F, Aigrain Y, Jacqz-Aigrain E.
  Source: The Journal of Urology. 2002 August; 168(2): 694-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12131352&dopt=Abstract

- **Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration?**
  Author(s): Paqueron X, Lumbroso A, Mergoni P, Aubrun F, Langeron O, Coriat P, Riou B.
  Source: British Journal of Anaesthesia. 2002 November; 89(5): 697-701.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12393765&dopt=Abstract

- **Kappa-opioid receptors on lymphocytes of a human lymphocytic cell line: morphine-induced up-regulation as evidenced by competitive RT-PCR and indirect immunofluorescence.**
  Author(s): Suzuki S, Chuang LF, Doi RH, Bidlack JM, Chuang RY.
  Source: International Immunopharmacology. 2001 September; 1(9-10): 1733-42.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11562065&dopt=Abstract

- **KEPI, a PKC-dependent protein phosphatase 1 inhibitor regulated by morphine.**
  Author(s): Liu QR, Zhang PW, Zhen Q, Walther D, Wang XB, Uhl GR.
  Source: The Journal of Biological Chemistry. 2002 April 12; 277(15): 13312-20. Epub 2002 January 25.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11812771&dopt=Abstract

- **Ketamine combined with morphine for the management of pain in an opioid addict.**
  Author(s): Haller G, Waeber JL, Infante NK, Clergue F.
  Source: Anesthesiology. 2002 May; 96(5): 1265-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11981171&dopt=Abstract

- **Larger morphine doses may benefit some terminal patients.**
  Author(s): Schlismann C.
  Source: Rn. 2003 June; 66(6): 10.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12838898&dopt=Abstract

- **Late antinociception and lower untoward effects of concomitant intrathecal morphine and intravenous buprenorphine in humans.**
  Author(s): Beltrutti D, Niv D, Ben-Abraham R, Di Santo S, Weinbroum AA.
  Source: Journal of Clinical Anesthesia. 2002 September; 14(6): 441-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12393113&dopt=Abstract

- **LC determination of morphine and morphine glucuronides in human plasma by coulometric and UV detection.**
  Author(s): Ary K, Rona K.
  Source: Journal of Pharmaceutical and Biomedical Analysis. 2001 September; 26(2): 179-87.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11470195&dopt=Abstract

- **Less morphine, or more?**
  Author(s): Perkins EM.
  Source: Rn. 2002 November; 65(11): 51-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12465527&dopt=Abstract

- **Lidocaine with fentanyl, compared to morphine, marginally improves postoperative epidural analgesia in children.**
  Author(s): Reinoso-Barbero F, Saavedra B, Hervilla S, de Vicente J, Tabares B, Gomez-Criado MS.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2002 January; 49(1): 67-71.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11782331&dopt=Abstract

- **Limited phase I study of morphine-3-glucuronide.**
  Author(s): Penson RT, Joel SP, Clark S, Gloyne A, Slevin ML.
  Source: Journal of Pharmaceutical Sciences. 2001 November; 90(11): 1810-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11745739&dopt=Abstract

- **Local administration of morphine for analgesia after iliac bone graft harvest.**
  Author(s): Reuben SS, Vieira P, Faruqi S, Verghis A, Kilaru PA, Maciolek H.
  Source: Anesthesiology. 2001 August; 95(2): 390-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11506111&dopt=Abstract

- **Local administration of morphine for analgesia after iliac bone graft harvest.**
  Author(s): Sawyer RJ.
  Source: Anesthesiology. 2002 April; 96(4): 1033; Author Reply 1033-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11964620&dopt=Abstract

- **Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain.**
  Author(s): Tassain V, Attal N, Fletcher D, Brasseur L, Degieux P, Chauvin M, Bouhassira D.
  Source: Pain. 2003 July; 104(1-2): 389-400.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12855350&dopt=Abstract

- **Long-term cancer pain management in morphine pre-treated and opioid naive patients with transdermal fentanyl.**
  Author(s): Mystakidou K, Tsilika E, Parpa E, Kouloulias V, Kouvaris I, Georgaki S, Vlahos L.
  Source: International Journal of Cancer. Journal International Du Cancer. 2003 November 10; 107(3): 486-92.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14506751&dopt=Abstract

- **Long-term rectal administration of high-dose sustained-release morphine tablets.**
  Author(s): Walsh D, Tropiano PS.
  Source: Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer. 2002 November; 10(8): 653-5. Epub 2002 April 25.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12436225&dopt=Abstract

- **Loss of intrathecal morphine analgesia in terminal cancer patients is associated with high levels of excitatory amino acids in the CSF.**
  Author(s): Wong CS, Chang YC, Yeh CC, Huang GS, Cherng CH.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2002 June-July; 49(6): 561-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12067866&dopt=Abstract

- **Low-concentration morphine infusion does not compromise packed red blood cell transfusion.**
  Author(s): Wozniak E, Finley GA, Dooley KC, Barnard DR.
  Source: Journal of Pain and Symptom Management. 2001 August; 22(2): 668-71.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11495713&dopt=Abstract

- **Low-dose dexamethasone reduces nausea and vomiting after epidural morphine: a comparison of metoclopramide with saline.**
  Author(s): Tzeng JI, Hsing CH, Chu CC, Chen YH, Wang JJ.
  Source: Journal of Clinical Anesthesia. 2002 February; 14(1): 19-23.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11880017&dopt=Abstract

- **Low-dose ketorolac improves analgesia and reduces morphine requirements following posterior spinal fusion in adolescents.**
  Author(s): Munro HM, Walton SR, Malviya S, Merkel S, Voepel-Lewis T, Loder RT, Farley FA.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2002 May; 49(5): 461-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11983659&dopt=Abstract

- **Low-dose spinal morphine for postoperative analgesia following knee arthroplasty.**
  Author(s): Laffey JG, Flynn N.
  Source: British Journal of Anaesthesia. 2001 January; 86(1): 152-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11575402&dopt=Abstract

- **Meperidine or morphine for treatment of pancreatic pain?**
  Author(s): Paulson C.
  Source: Rn. 2002 May; 65(5): 10; Author Reply 10.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12046176&dopt=Abstract

- **Methadone, morphine and PTSD.**
  Author(s): Macleod AD, Duffy SG.
  Source: The Australian and New Zealand Journal of Psychiatry. 2002 December; 36(6): 816-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12406127&dopt=Abstract

- **Minimum dose of intrathecal diamorphine required to prevent intraoperative supplementation of spinal anaesthesia for Caesarean section.**
  Author(s): Saravanan S, Robinson AP, Qayoum Dar A, Columb MO, Lyons GR.
  Source: British Journal of Anaesthesia. 2003 September; 91(3): 368-72.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12925476&dopt=Abstract

- **Minute sphere acupressure does not reduce postoperative pain or morphine consumption.**
  Author(s): Sakurai M, Suleman MI, Morioka N, Akca O, Sessler DI.
  Source: Anesthesia and Analgesia. 2003 February; 96(2): 493-7, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12538202&dopt=Abstract

- **Modulation of infection and type 1 cytokine expression parameters by morphine during in vitro coinfection with human T-cell leukemia virus type I and HIV-1.**
  Author(s): Nyland SB, Cao C, Bai Y, Loughran TP, Ugen KE.
  Source: Journal of Acquired Immune Deficiency Syndromes (1999). 2003 April 1; 32(4): 406-16.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12640199&dopt=Abstract

- **Morphine and chronic cancer pain.**
  Author(s): Smit BJ.
  Source: South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde. 2001 October; 91(10): 786-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11732445&dopt=Abstract

- **Morphine and endomorphins differentially regulate micro-opioid receptor mRNA in SHSY-5Y human neuroblastoma cells.**
  Author(s): Yu X, Mao X, Blake AD, Li WX, Chang SL.
  Source: The Journal of Pharmacology and Experimental Therapeutics. 2003 August; 306(2): 447-54. Epub 2003 May 16.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12754318&dopt=Abstract

- **Morphine and hydromorphone for postoperative analgesia: focus on safety.**
  Author(s): Golembiewski JA.
  Source: Journal of Perianesthesia Nursing : Official Journal of the American Society of Perianesthesia Nurses / American Society of Perianesthesia Nurses. 2003 April; 18(2): 120-2.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12710006&dopt=Abstract

- **Morphine down regulates human vascular tissue estrogen receptor expression determined by real-time RT-PCR.**
  Author(s): Cadet P, Mantione K, Bilfinger TV, Stefano GB.
  Source: Neuroendocrinol Lett. 2002 April; 23(2): 95-100.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12011792&dopt=Abstract

- **Morphine enhances hepatitis C virus (HCV) replicon expression.**
  Author(s): Li Y, Zhang T, Douglas SD, Lai JP, Xiao WD, Pleasure DE, Ho WZ.
  Source: American Journal of Pathology. 2003 September; 163(3): 1167-75.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12937158&dopt=Abstract

- **Morphine enhances HIV infection of human blood mononuclear phagocytes through modulation of beta-chemokines and CCR5 receptor.**
  Author(s): Guo CJ, Li Y, Tian S, Wang X, Douglas SD, Ho WZ.
  Source: Journal of Investigative Medicine : the Official Publication of the American Federation for Clinical Research. 2002 November; 50(6): 435-42.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12425430&dopt=Abstract

- **Morphine for the relief of breathlessness in patients with chronic heart failure--a pilot study.**
  Author(s): Johnson MJ, McDonagh TA, Harkness A, McKay SE, Dargie HJ.
  Source: European Journal of Heart Failure : Journal of the Working Group on Heart Failure of the European Society of Cardiology. 2002 December; 4(6): 753-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12453546&dopt=Abstract

- **Morphine glucuronide-to-morphine plasma ratios are unaffected by the UGT2B7 H268Y and UGT1A1*28 polymorphisms in cancer patients on chronic morphine therapy.**
  Author(s): Holthe M, Klepstad P, Zahlsen K, Borchgrevink PC, Hagen L, Dale O, Kaasa S, Krokan HE, Skorpen F.
  Source: European Journal of Clinical Pharmacology. 2002 August; 58(5): 353-6. Epub 2002 July 13.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12185559&dopt=Abstract

- **Morphine in cancer pain management: a practical guide.**
  Author(s): Donnelly S, Davis MP, Walsh D, Naughton M; World Health Organization.
  Source: Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer. 2002 January; 10(1): 13-35. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11777184&dopt=Abstract

- **Morphine in tardive and idiopathic dystonia (short communication).**
  Author(s): Berg D, Becker G, Naumann M, Reiners K.
  Source: Journal of Neural Transmission (Vienna, Austria : 1996). 2001; 108(8-9): 1035-41.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11716139&dopt=Abstract

- **Morphine induces apoptosis of human microglia and neurons.**
  Author(s): Hu S, Sheng WS, Lokensgard JR, Peterson PK.
  Source: Neuropharmacology. 2002 May; 42(6): 829-36.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12015209&dopt=Abstract

- **Morphine inhibits indolactam V-induced U937 cell adhesion and gelatinase secretion.**
  Author(s): Weeks BS, Goldman S, Touma S, Payne M, Cadet P, Stefano GB.
  Source: Journal of Cellular Physiology. 2001 November; 189(2): 179-88.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11598903&dopt=Abstract

- **Morphine regulates gene expression of alpha- and beta-chemokines and their receptors on astroglial cells via the opioid mu receptor.**
  Author(s): Mahajan SD, Schwartz SA, Shanahan TC, Chawda RP, Nair MP.
  Source: Journal of Immunology (Baltimore, Md. : 1950). 2002 October 1; 169(7): 3589-99.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12244149&dopt=Abstract

- **Morphine responsiveness in a group of well-defined multiple sclerosis patients: a study with i.v. morphine.**
  Author(s): Kalman S, Osterberg A, Sorensen J, Boivie J, Bertler A.
  Source: European Journal of Pain (London, England). 2002; 6(1): 69-80.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11888230&dopt=Abstract

- **Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain - results of a double-blind placebo-controlled trial (MONTAS).**
  Author(s): Maier C, Hildebrandt J, Klinger R, Henrich-Eberl C, Lindena G; MONTAS Study Group.
  Source: Pain. 2002 June; 97(3): 223-33.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12044619&dopt=Abstract

- **Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth.**
  Author(s): Gupta K, Kshirsagar S, Chang L, Schwartz R, Law PY, Yee D, Hebbel RP.
  Source: Cancer Research. 2002 August 1; 62(15): 4491-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12154060&dopt=Abstract

- **Morphine suppresses lymphocyte apoptosis by blocking p53-mediated death signaling.**
  Author(s): Suzuki S, Chuang LF, Doi RH, Chuang RY.
  Source: Biochemical and Biophysical Research Communications. 2003 September 5; 308(4): 802-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12927789&dopt=Abstract

- **Morphine upregulates kappa-opioid receptors of human lymphocytes.**
  Author(s): Suzuki S, Chuang TK, Chuang LF, Doi RH, Chuang RY.
  Source: Advances in Experimental Medicine and Biology. 2001; 493: 81-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11727785&dopt=Abstract

- **Morphine withdrawal, treatments 1900-30.**
  Author(s): Malcolm MT.
  Source: History of Psychiatry. 1999 March; 10(37): 13-26.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11623818&dopt=Abstract

- **Morphine, pethidine and buprenorphine disposition in the cat.**
  Author(s): Taylor PM, Robertson SA, Dixon MJ, Ruprah M, Sear JW, Lascelles BD, Waters C, Bloomfield M.
  Source: Journal of Veterinary Pharmacology and Therapeutics. 2001 December; 24(6): 391-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11903869&dopt=Abstract

- **Morphine. Now.**
  Author(s): Vincent P.
  Source: The American Journal of Nursing. 2002 February; 102(2): 25.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11953515&dopt=Abstract

- **Morphine-6beta-glucuronide and morphine-3-glucuronide, opioid receptor agonists with different potencies.**
  Author(s): Ulens C, Baker L, Ratka A, Waumans D, Tytgat J.
  Source: Biochemical Pharmacology. 2001 November 1; 62(9): 1273-82.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11705461&dopt=Abstract

- **Morphine-6-glucuronide: an analgesic of the future?**
  Author(s): Lotsch J, Geisslinger G.
  Source: Clinical Pharmacokinetics. 2001; 40(7): 485-99. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11510626&dopt=Abstract

- **Morphine-induced macrophage apoptosis modulates migration of macrophages: use of in vitro model of urinary tract infection.**
  Author(s): Malik AA, Radhakrishnan N, Reddy K, Smith AD, Singhal PC.
  Source: Journal of Endourology / Endourological Society. 2002 October; 16(8): 605-10.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12470470&dopt=Abstract

- **Morphine-potentiated agonist-induced platelet aggregation through alpha2-adrenoceptors in human platelets.**
  Author(s): Sheu JR, Yeh GC, Fang CL, Lin CH, Hsiao G.
  Source: Journal of Cardiovascular Pharmacology. 2002 November; 40(5): 743-50.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12409983&dopt=Abstract

- **Nalbuphine reverses urinary effects of epidural morphine: a case report.**
  Author(s): Malinovsky JM, Lepage JY, Karam G, Pinaud M.
  Source: Journal of Clinical Anesthesia. 2002 November; 14(7): 535-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12477591&dopt=Abstract

- **Nalbuphine versus ondansetron for prevention of intrathecal morphine-induced pruritus after cesarean delivery.**
  Author(s): Charuluxananan S, Kyokong O, Somboonviboon W, Narasethakamol A, Promlok P.
  Source: Anesthesia and Analgesia. 2003 June; 96(6): 1789-93, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12761013&dopt=Abstract

- **Nalbuphine versus propofol for treatment of intrathecal morphine-induced pruritus after cesarean delivery.**
  Author(s): Charuluxananan S, Kyokong O, Somboonviboon W, Lertmaharit S, Ngamprasertwong P, Nimcharoendee K.
  Source: Anesthesia and Analgesia. 2001 July; 93(1): 162-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11429358&dopt=Abstract

- **Nebulised morphine for severe interstitial lung disease.**
  Author(s): Polosa R, Simidchiev A, Walters EH.
  Source: Cochrane Database Syst Rev. 2002; (3): Cd002872. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12137662&dopt=Abstract

- **Nebulized morphine as a treatment for dyspnea in a child with cystic fibrosis.**
  Author(s): Cohen SP, Dawson TC.
  Source: Pediatrics. 2002 September; 110(3): E38.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12205288&dopt=Abstract

- **Nebulized morphine for the relief of dyspnea.**
  Author(s): Mabe SR, Connelly JF.
  Source: American Journal of Health-System Pharmacy : Ajhp : Official Journal of the American Society of Health-System Pharmacists. 1995 January 15; 52(2): 146-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12879541&dopt=Abstract

- **Neuraxial morphine may trigger transient motor dysfunction after a noninjurious interval of spinal cord ischemia: a clinical and experimental study.**
  Author(s): Kakinohana M, Marsala M, Carter C, Davison JK, Yaksh TL.
  Source: Anesthesiology. 2003 April; 98(4): 862-70.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12657847&dopt=Abstract

- **Neuroadaptive responses in brainstem noradrenergic nuclei following chronic morphine exposure.**
  Author(s): Van Bockstaele EJ, Menko AS, Drolet G.
  Source: Molecular Neurobiology. 2001 April-June; 23(2-3): 155-71. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11817217&dopt=Abstract

- **No pain, no gain: clinical excellence and scientific rigour--lessons learned from IA morphine.**
  Author(s): Kalso E, Smith L, McQuay HJ, Andrew Moore R.
  Source: Pain. 2002 August; 98(3): 269-75. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12127028&dopt=Abstract

- **Nurse-initiated intravenous morphine in the emergency department: efficacy, rate of adverse events and impact on time to analgesia.**
  Author(s): Fry M, Holdgate A.
  Source: Emergency Medicine (Fremantle, W.A.). 2002 September; 14(3): 249-54.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12487041&dopt=Abstract

- **Occupational contact dermatitis from diacetylmorphine (heroin).**
  Author(s): Coenraads PJ, Hogen Esch AJ, Prevoo RL.
  Source: Contact Dermatitis. 2001 August; 45(2): 114.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11553127&dopt=Abstract

- **Opioid plasma concentration during switching from morphine to methadone: preliminary data.**
  Author(s): Mercadante S, Bianchi M, Villari P, Ferrera P, Casuccio A, Fulfaro F, Gebbia V.
  Source: Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer. 2003 May; 11(5): 326-31. Epub 2003 April 03.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12690541&dopt=Abstract

- **Opioid switching from morphine to transdermal fentanyl for toxicity reduction in palliative care.**
  Author(s): McNamara P.
  Source: Palliative Medicine. 2002 September; 16(5): 425-34.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12380661&dopt=Abstract

- **Optimizing the hydrolysis of codeine and morphine glucuronides in urine.**
  Author(s): Hackett LP, Dusci LJ, Ilett KF, Chiswell GM.
  Source: Therapeutic Drug Monitoring. 2002 October; 24(5): 652-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12352938&dopt=Abstract

- **Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients.**
  Author(s): Kannan TR, Saxena A, Bhatnagar S, Barry A.
  Source: Journal of Pain and Symptom Management. 2002 January; 23(1): 60-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11779670&dopt=Abstract

- **Orphanin FQ/nociceptin blocks chronic morphine-induced tyrosine hydroxylase upregulation.**
  Author(s): Thakker DR, Standifer KM.
  Source: Brain Research. Molecular Brain Research. 2002 September 30; 105(1-2): 38-46.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12399106&dopt=Abstract

- **Orthotopic liver transplant patients require less postoperative morphine than do patients undergoing hepatic resection.**
  Author(s): Moretti EW, Robertson KM, Tuttle-Newhall JE, Clavien PA, Gan TJ.
  Source: Journal of Clinical Anesthesia. 2002 September; 14(6): 416-20.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12393108&dopt=Abstract

- **Parecoxib sodium, a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty.**
  Author(s): Malan TP Jr, Marsh G, Hakki SI, Grossman E, Traylor L, Hubbard RC.
  Source: Anesthesiology. 2003 April; 98(4): 950-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12657858&dopt=Abstract

- **Pharmacodynamic effect of morphine-6-glucuronide versus morphine on hypoxic and hypercapnic breathing in healthy volunteers.**
  Author(s): Romberg R, Olofsen E, Sarton E, Teppema L, Dahan A.
  Source: Anesthesiology. 2003 October; 99(4): 788-98.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14508308&dopt=Abstract

- **Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, part I.**
  Author(s): Armstrong SC, Cozza KL.
  Source: Psychosomatics. 2003 March-April; 44(2): 167-71. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12618536&dopt=Abstract

- **Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, Part II.**
  Author(s): Armstrong SC, Cozza KL.
  Source: Psychosomatics. 2003 November-December; 44(6): 515-20.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14597688&dopt=Abstract

- **Pharmacokinetic modelling of morphine, morphine-3-glucuronide and morphine-6-glucuronide in plasma and cerebrospinal fluid of neurosurgical patients after short-term infusion of morphine.**
  Author(s): Meineke I, Freudenthaler S, Hofmann U, Schaeffeler E, Mikus G, Schwab M, Prange HW, Gleiter CH, Brockmoller J.
  Source: British Journal of Clinical Pharmacology. 2002 December; 54(6): 592-603.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12492606&dopt=Abstract

- **Pharmacokinetics of morphine are not altered in subjects with Gilbert's syndrome.**
  Author(s): Skarke C, Schmidt H, Geisslinger G, Darimont J, Lotsch J.
  Source: British Journal of Clinical Pharmacology. 2003 August; 56(2): 228-31.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12895198&dopt=Abstract

- **Pilot study of nasal morphine-chitosan for the relief of breakthrough pain in patients with cancer.**
  Author(s): Pavis H, Wilcock A, Edgecombe J, Carr D, Manderson C, Church A, Fisher A.
  Source: Journal of Pain and Symptom Management. 2002 December; 24(6): 598-602.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12551810&dopt=Abstract

- **Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain.**
  Author(s): Flock P.
  Source: Journal of Pain and Symptom Management. 2003 June; 25(6): 547-54.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12782435&dopt=Abstract

- **Plasma concentrations of morphine, morphine-6-glucuronide and morphine-3-glucuronide and their relationship with analgesia and side effects in patients with cancer-related pain.**
  Author(s): Quigley C, Joel S, Patel N, Baksh A, Slevin M.
  Source: Palliative Medicine. 2003 March; 17(2): 185-90.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12701850&dopt=Abstract

- **Possible exacerbation of adrenal suppression from intrathecal morphine in a patient receiving pulsed dexamethasone for multiple myeloma.**
  Author(s): Rajagopal A, Kala S, Bruera E.
  Source: Journal of Pain and Symptom Management. 2003 September; 26(3): 786-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12967726&dopt=Abstract

- **Postoperative analgesic effects of intravenous lornoxicam and morphine with pre-emtive ropivacaine skin infiltration and preperitoneal instillation after transabdominal hysterectomy.**
  Author(s): Visalyaputra S, Sanansilp V, Pechpaisit N, Choavarartana R, Sritisarn S, Ungpinitpong W, Permpolprasert L, Apidechakul P.
  Source: J Med Assoc Thai. 2002 September; 85 Suppl 3: S1010-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12452243&dopt=Abstract

- **Postoperative morphine consumption in the elderly patient.**
  Author(s): Aubrun F, Bunge D, Langeron O, Saillant G, Coriat P, Riou B.
  Source: Anesthesiology. 2003 July; 99(1): 160-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12826856&dopt=Abstract

- **Postoperative morphine use and hyperalgesia are reduced by preoperative but not intraoperative epidural analgesia: implications for preemptive analgesia and the prevention of central sensitization.**
  Author(s): Katz J, Cohen L, Schmid R, Chan VW, Wowk A.
  Source: Anesthesiology. 2003 June; 98(6): 1449-60.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12766657&dopt=Abstract

- **Postoperative pain relief after hepatic resection in cirrhotic patients: the efficacy of a single small dose of ketamine plus morphine epidurally.**
  Author(s): Taura P, Fuster J, Blasi A, Martinez-Ocon J, Anglada T, Beltran J, Balust J, Tercero J, Garcia-Valdecasas JC.
  Source: Anesthesia and Analgesia. 2003 February; 96(2): 475-80, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12538199&dopt=Abstract

- **Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study.**
  Author(s): Cerchietti LC, Navigante AH, Korte MW, Cohen AM, Quiroga PN, Villaamil EC, Bonomi MR, Roth BM.
  Source: Pain. 2003 September; 105(1-2): 265-73.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14499444&dopt=Abstract

- **Pre-emptive analgesic efficacy of tramadol compared with morphine after major abdominal surgery.**
  Author(s): Unlugenc H, Ozalevli M, Gunes Y, Guler T, Isik G.
  Source: British Journal of Anaesthesia. 2003 August; 91(2): 209-13.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12878619&dopt=Abstract

- **Preemptive diclofenac reduces morphine use after remifentanil-based anaesthesia for tonsillectomy.**
  Author(s): Oztekin S, Hepaguslar H, Kar AA, Ozzeybek D, Artikaslan O, Elar Z.
  Source: Paediatric Anaesthesia. 2002 October; 12(8): 694-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12472706&dopt=Abstract

- **Prehospital administration of morphine for isolated extremity injuries: a change in protocol reduces time to medication.**
  Author(s): Fullerton-Gleason L, Crandall C, Sklar DP.
  Source: Prehosp Emerg Care. 2002 October-December; 6(4): 411-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12385608&dopt=Abstract

- **Premixed solutions of diamorphine in ropivacaine for epidural anaesthesia: a study on their long-term stability.**
  Author(s): Sanchez del Aguila MJ, Jones MF, Vohra A.
  Source: British Journal of Anaesthesia. 2003 February; 90(2): 179-82.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12538374&dopt=Abstract

- **Preoperative oral administration of fast-release morphine sulfate reduces postoperative piritramide consumption.**
  Author(s): Reiter A, Zulus E, Hartmann T, Hoerauf K.
  Source: Wiener Klinische Wochenschrift. 2003 July 15; 115(12): 417-20.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12918185&dopt=Abstract

- **Prevention of postoperative nausea and vomiting after spinal morphine for Caesarean section: comparison of cyclizine, dexamethasone and placebo.**
  Author(s): Nortcliffe SA, Shah J, Buggy DJ.
  Source: British Journal of Anaesthesia. 2003 May; 90(5): 665-70.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12697596&dopt=Abstract

- **Prospective comparative study of the effectiveness of epidural morphine and ropivacaine for management of pain after spinal operations.**
  Author(s): Al-Khalaf B, Loew F, Fichtl M, Donauer E.
  Source: Acta Neurochirurgica. 2003 January; 145(1): 11-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12545257&dopt=Abstract

- **Quantitative gas chromatographic/mass spectrometric analysis of morphine glucuronides in human plasma by negative ion chemical ionization mass spectrometry.**
  Author(s): Leis HJ, Fauler G, Raspotnig G, Windischhofer W.
  Source: Journal of Mass Spectrometry : Jms. 2002 April; 37(4): 395-400.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11948846&dopt=Abstract

- **Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea.**
  Author(s): Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C.
  Source: Bmj (Clinical Research Ed.). 2003 September 6; 327(7414): 523-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12958109&dopt=Abstract

- **Randomized clinical trial of local bupivacaine perfusion versus parenteral morphine infusion for pain relief after laparotomy (Br J Surg 2001; 88: 357-9). Letter 1.**
  Author(s): Birchley D.
  Source: The British Journal of Surgery. 2001 September; 88(9): 1267; Author Reply 1267.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11531889&dopt=Abstract

- **Randomized clinical trial of local bupivacaine perfusion versus parenteral morphine infusion for pain relief after laparotomy (Br J Surg 2001; 88: 357-9). Letter 2.**
  Author(s): Sparkes D, Baylis R.
  Source: The British Journal of Surgery. 2001 September; 88(9): 1267.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11531886&dopt=Abstract

- **Randomized, double-blind, placebo-controlled study of the effect of rectal paracetamol on morphine consumption after abdominal hysterectomy.**
  Author(s): Kvalsvik O, Borchgrevink PC, Hagen L, Dale O.
  Source: Acta Anaesthesiologica Scandinavica. 2003 April; 47(4): 451-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12694145&dopt=Abstract

- **Rapid increase of morphine and benzodiazepine usage in the last three days of life in children with cancer is related to neuropathic pain.**
  Author(s): Dougherty M, DeBaun MR.
  Source: The Journal of Pediatrics. 2003 April; 142(4): 373-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12712053&dopt=Abstract

- **Rapid titration with intravenous morphine for severe cancer pain and immediate oral conversion.**
  Author(s): Mercadante S, Villari P, Ferrera P, Casuccio A, Fulfaro F.
  Source: Cancer. 2002 July 1; 95(1): 203-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12115334&dopt=Abstract

- **Re: increased plasma morphine metabolites and delirium.**
  Author(s): Davis MP.
  Source: Journal of Pain and Symptom Management. 2002 September; 24(3): 273; Author Reply 273-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12458096&dopt=Abstract

- **Recovery following tonsillectomy a comparison between tramadol and morphine for analgesia.**
  Author(s): Chew ST, Ip-Yam PC, Kong CF.
  Source: Singapore Med J. 2003 June; 44(6): 296-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14560861&dopt=Abstract

- **Rectally administered diclofenac (Voltaren) reduces vomiting compared with opioid (morphine) after strabismus surgery in children.**
  Author(s): Wennstrom B, Reinsfelt B.
  Source: Acta Anaesthesiologica Scandinavica. 2002 April; 46(4): 430-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11952445&dopt=Abstract

- **Reduction in postoperative pain after spinal fusion with instrumentation using intrathecal morphine.**
  Author(s): Urban MK, Jules-Elysee K, Urquhart B, Cammisa FP, Boachie-Adjei O.
  Source: Spine. 2002 March 1; 27(5): 535-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11880840&dopt=Abstract

- **Regulation of opioid receptor trafficking and morphine tolerance by receptor oligomerization.**
  Author(s): He L, Fong J, von Zastrow M, Whistler JL.
  Source: Cell. 2002 January 25; 108(2): 271-82.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11832216&dopt=Abstract

- **Relationship between acute morphine and the course of PTSD in children with burns.**
  Author(s): Saxe G, Stoddard F, Courtney D, Cunningham K, Chawla N, Sheridan R, King D, King L.
  Source: Journal of the American Academy of Child and Adolescent Psychiatry. 2001 August; 40(8): 915-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11501691&dopt=Abstract

- **Relationships among morphine metabolism, pain and side effects during long-term treatment: an update.**
  Author(s): Andersen G, Christrup L, Sjogren P.
  Source: Journal of Pain and Symptom Management. 2003 January; 25(1): 74-91. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12565191&dopt=Abstract

- **Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration.**
  Author(s): Aubrun F, Langeron O, Quesnel C, Coriat P, Riou B.
  Source: Anesthesiology. 2003 June; 98(6): 1415-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12766651&dopt=Abstract

- **Remifentanil vs morphine for patients in intensive care unit who need short-term mechanical ventilation.**
  Author(s): Chinachoti T, Kessler P, Kirkham A, Werawatganon T.
  Source: J Med Assoc Thai. 2002 September; 85 Suppl 3: S848-57.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12452221&dopt=Abstract

- **Repeated peripheral nerve blocks by the co-administration of ketamine, morphine, and bupivacaine attenuate trigeminal neuralgia.**
  Author(s): Chang FL, Huang GS, Cherng CH, Ho ST, Wong CS.
  Source: Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2003 February; 50(2): 201-2.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12560318&dopt=Abstract

- **Respiratory and miotic effects of morphine in healthy volunteers when P-glycoprotein is blocked by quinidine.**
  Author(s): Skarke C, Jarrar M, Erb K, Schmidt H, Geisslinger G, Lotsch J.
  Source: Clinical Pharmacology and Therapeutics. 2003 October; 74(4): 303-11.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14534517&dopt=Abstract

- **Rofecoxib reduces perioperative morphine consumption for abdominal hysterectomy and laparoscopic gastric banding.**
  Author(s): Meyer R.
  Source: Anaesthesia and Intensive Care. 2002 June; 30(3): 389-90.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12075660&dopt=Abstract

- **Role of oxidative stress and heme oxygenase activity in morphine-induced glomerular epithelial cell growth.**
  Author(s): Patel J, Manjappa N, Bhat R, Mehrotra P, Bhaskaran M, Singhal PC.
  Source: American Journal of Physiology. Renal Physiology. 2003 November; 285(5): F861-9. Epub 2003 June 17.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12812915&dopt=Abstract

- **Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial.**
  Author(s): Simons SH, van Dijk M, van Lingen RA, Roofthooft D, Duivenvoorden HJ, Jongeneel N, Bunkers C, Smink E, Anand KJ, van den Anker JN, Tibboel D.
  Source: Jama : the Journal of the American Medical Association. 2003 November 12; 290(18): 2419-27.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14612478&dopt=Abstract

- **Safety and potential benefits of low dose diamorphine during exercise in patients with chronic heart failure.**
  Author(s): Williams SG, Wright DJ, Marshall P, Reese A, Tzeng BH, Coats AJ, Tan LB.
  Source: Heart (British Cardiac Society). 2003 September; 89(9): 1085-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12923038&dopt=Abstract

- **Sedative effects of morphine and clonidine.**
  Author(s): Wattie ML, Jaggar SI.
  Source: British Journal of Anaesthesia. 2003 September; 91(3): 449; Author Reply 449-50.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12925496&dopt=Abstract

- **Sequence variations in the UDP-glucuronosyltransferase 2B7 (UGT2B7) gene: identification of 10 novel single nucleotide polymorphisms (SNPs) and analysis of their relevance to morphine glucuronidation in cancer patients.**
  Author(s): Holthe M, Rakvag TN, Klepstad P, Idle JR, Kaasa S, Krokan HE, Skorpen F.
  Source: The Pharmacogenomics Journal. 2003; 3(1): 17-26. Erratum In: Pharmacogenomics J. 2003; 3(4): 248.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12629580&dopt=Abstract

- **Sevoflurane anesthesia and intrathecal sufentanil-morphine for thymectomy in myasthenia gravis.**
  Author(s): Madi-Jebara S, Yazigi A, Hayek G, Haddad F, Antakly MC.
  Source: Journal of Clinical Anesthesia. 2002 November; 14(7): 558-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12477596&dopt=Abstract

- **Small dose bupivacaine-fentanyl spinal analgesia combined with morphine for labor.**
  Author(s): Hess PE, Vasudevan A, Snowman C, Pratt SD.
  Source: Anesthesia and Analgesia. 2003 July; 97(1): 247-52, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12818975&dopt=Abstract

- **Spinal morphine for post-operative analgesia after lumbar laminectomy with fusion.**
  Author(s): Techanivate A, Kiatgungwanglia P, Yingsakmongkol W.
  Source: J Med Assoc Thai. 2003 March; 86(3): 262-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12757067&dopt=Abstract

- **Stability and compatibility of morphine-clonidine admixtures in an implantable infusion system.**
  Author(s): Hildebrand KR, Elsberry DD, Hassenbusch SJ.
  Source: Journal of Pain and Symptom Management. 2003 May; 25(5): 464-71.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12727045&dopt=Abstract

- **Starting intravenous morphine in the postanesthesia care unit yielded better postoperative analgesia.**
  Author(s): Sanansilp V, Mahuntasanapong W, Phoncharoensomboon P.
  Source: J Med Assoc Thai. 2002 September; 85 Suppl 3: S934-41.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12452232&dopt=Abstract

- **Steady-state pharmacokinetic comparison of a new, extended-release, once-daily morphine formulation, Avinza, and a twice-daily controlled-release morphine formulation in patients with chronic moderate-to-severe pain.**
  Author(s): Portenoy RK, Sciberras A, Eliot L, Loewen G, Butler J, Devane J.
  Source: Journal of Pain and Symptom Management. 2002 April; 23(4): 292-300.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11997198&dopt=Abstract

- **Subacromial and intra-articular morphine versus bupivacaine after shoulder arthroscopy.**
  Author(s): Scoggin JF 3rd, Mayfield G, Awaya DJ, Pi M, Prentiss J, Takahashi J.
  Source: Arthroscopy : the Journal of Arthroscopic & Related Surgery : Official Publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2002 May-June; 18(5): 464-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11987055&dopt=Abstract

- **Successful use of oral methadone after failure of intravenous morphine and ketamine.**
  Author(s): Sartain JB, Mitchell SJ.
  Source: Anaesthesia and Intensive Care. 2002 August; 30(4): 487-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12180591&dopt=Abstract

- **Survey of doctors prescribing diamorphine (heroin) to opiate-dependent drug users in the United Kingdom.**
  Author(s): Metrebian N, Carnwath T, Stimson GV, Storz T.
  Source: Addiction (Abingdon, England). 2002 September; 97(9): 1155-61.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12199831&dopt=Abstract

- **The addition of a tramadol infusion to morphine patient-controlled analgesia after abdominal surgery: a double-blinded, placebo-controlled randomized trial.**
  Author(s): Webb AR, Leong S, Myles PS, Burn SJ.
  Source: Anesthesia and Analgesia. 2002 December; 95(6): 1713-8, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12456445&dopt=Abstract

- **The addition of antiemetics to the morphine solution in patient controlled analgesia syringes used by children after an appendicectomy does not reduce the incidence of postoperative nausea and vomiting.**
  Author(s): Munro FJ, Fisher S, Dickson U, Morton N.
  Source: Paediatric Anaesthesia. 2002 September; 12(7): 600-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12358655&dopt=Abstract

- **The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions.**
  Author(s): Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R.
  Source: Pain. 2003 September; 105(1-2): 79-88.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14499423&dopt=Abstract

- **The analgesic effect of oral morphine or pentazocine for extracorporeal shock wave lithotripsy.**
  Author(s): Han YY, Lu HC, Tsai HJ, Hseu SS, Chan KH, Tsai SK.
  Source: Acta Anaesthesiol Sin. 2003 March; 41(1): 27-32.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12747344&dopt=Abstract

- **The antiemetic efficacy of droperidol added to morphine patient-controlled analgesia: a randomized, controlled, multicenter dose-finding study.**
  Author(s): Culebras X, Corpataux JB, Gaggero G, Tramer MR.
  Source: Anesthesia and Analgesia. 2003 September; 97(3): 816-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12933408&dopt=Abstract

- **The combination of low dose of naloxone and morphine in patient-controlled (PCA) does not decrease opioid requirements in the postoperative period.**
  Author(s): Mehlisch DR.
  Source: Pain. 2003 January; 101(1-2): 209-11; Author Reply 211-2.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12507716&dopt=Abstract

- **The detection of morphine and codeine in human teeth: an aid in the identification and study of human skeletal remains.**
  Author(s): Cattaneo C, Gigli F, Lodi F, Grandi M.
  Source: J Forensic Odontostomatol. 2003 June; 21(1): 1-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12793124&dopt=Abstract

- **The duration time of urine morphine detection in heroin addicts by radioimmunoassay.**
  Author(s): Narongchai P, Sribanditmonkol P, Thampithug S, Narongchai S, Chitivuthikarn C.
  Source: J Med Assoc Thai. 2002 January; 85(1): 82-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12075726&dopt=Abstract

- **The effect of codeine in anti-cough syrup on morphine screen.**
  Author(s): Hsu CL, Hung DZ, Yang DY.
  Source: Zhonghua Yi Xue Za Zhi (Taipei). 2002 June; 65(6): 279-84.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12201569&dopt=Abstract

- **The effect of IVPCA morphine on post-hysterectomy bowel function.**
  Author(s): Chan KC, Cheng YJ, Huang GT, Wen YJ, Lin CJ, Chen LK, Sun WZ.
  Source: Acta Anaesthesiol Sin. 2002 June; 40(2): 61-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12194392&dopt=Abstract

- **The effects of morphine on human articular cartilage of the knee: an in vitro study.**
  Author(s): Jaureguito JW, Wilcox JF, Thisted RA, Phillips C, Cunningham B, Reider B.
  Source: Arthroscopy : the Journal of Arthroscopic & Related Surgery : Official Publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2002 July-August; 18(6): 631-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12098125&dopt=Abstract

- **The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery.**
  Author(s): Guillou N, Tanguy M, Seguin P, Branger B, Campion JP, Malledant Y.
  Source: Anesthesia and Analgesia. 2003 September; 97(3): 843-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12933413&dopt=Abstract

- **The efficacy and side effects of continuous infusion intravenous morphine (CIVM) for pain and symptoms due to advanced cancer.**
  Author(s): Glare P, Walsh D, Groh E, Nelson KA.
  Source: Am J Hosp Palliat Care. 2002 September-October; 19(5): 343-50.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12269781&dopt=Abstract

- **The prophylactic effect of tropisetron on epidural morphine-related nausea and vomiting: a comparison of dexamethasone with saline.**
  Author(s): Wang JJ, Tzeng JI, Ho ST, Chen JY, Chu CC, So EC.
  Source: Anesthesia and Analgesia. 2002 March; 94(3): 749-53; Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11867410&dopt=Abstract

- **Thoughts on intensive care: from morphine to Merlyn and Tolstoy to television.**
  Author(s): Franklin C.
  Source: Intensive Care Medicine. 2003 May; 29(5): 853. Epub 2003 March 25.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12655394&dopt=Abstract

- **Time series modeling of heroin and morphine drug action.**
  Author(s): Tschacher W, Haemmig R, Jacobshagen N.
  Source: Psychopharmacology. 2003 January; 165(2): 188-93. Epub 2002 October 29.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12404073&dopt=Abstract

- **Tissue-specific regulation of canine intestinal and hepatic phenol and morphine UDP-glucuronosyltransferases by beta-naphthoflavone in comparison with humans.**
  Author(s): Bock KW, Bock-Hennig BS, Munzel PA, Brandenburg JO, Kohle CT, Soars MG, Riley RJ, Burchell B, Richter O, Eichelbaum MF, Swedmark S, Orzechowski A.
  Source: Biochemical Pharmacology. 2002 May 1; 63(9): 1683-90.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12007571&dopt=Abstract

- **Tramadol infusion for postthoracotomy pain relief: a placebo-controlled comparison with epidural morphine.**
  Author(s): Bloch MB, Dyer RA, Heijke SA, James MF.
  Source: Anesthesia and Analgesia. 2002 March; 94(3): 523-8; Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11867369&dopt=Abstract

- **Transcutaneous electrical acupoint stimulation potentiates analgesic effect of morphine.**
  Author(s): Yuan CS, Attele AS, Dey L, Lynch JP, Guan X.
  Source: Journal of Clinical Pharmacology. 2002 August; 42(8): 899-903.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12162472&dopt=Abstract

- **Treatment of spasticity in a spinal cord-injured patient with intrathecal morphine due to intrathecal baclofen tolerance--a case report and review of literature.**
  Author(s): Soni BM, Mani RM, Oo T, Vaidyanathan S.
  Source: Spinal Cord : the Official Journal of the International Medical Society of Paraplegia. 2003 October; 41(10): 586-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14504619&dopt=Abstract

- **Unwanted effects of morphine-6-glucoronide and morphine.**
  Author(s): Cann C, Curran J, Milner T, Ho B.
  Source: Anaesthesia. 2002 December; 57(12): 1200-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12479189&dopt=Abstract

- **Urinary concentrations of morphine after the administration of herbal teas containing Papaveris fructus in relation to doping analysis.**
  Author(s): Van Thuyne W, Van Eenoo P, Delbeke FT.
  Source: Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences. 2003 March 5; 785(2): 245-51.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12554137&dopt=Abstract

- **Urinary concentrations of morphine and codeine after consumption of poppy seeds.**
  Author(s): Thevis M, Opfermann G, Schanzer W.
  Source: Journal of Analytical Toxicology. 2003 January-February; 27(1): 53-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12587685&dopt=Abstract

- **Urinary effects of morphine in preterm infants.**
  Author(s): Bengtsson BO, Wootton-Gorges SL, Poulain FR, Sherman MP.
  Source: Acta Paediatrica (Oslo, Norway : 1992). 2003; 92(2): 251-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12710656&dopt=Abstract

- **Urinary excretion profiles for total morphine, free morphine, and 6-acetylmorphine following smoked and intravenous heroin.**
  Author(s): Smith ML, Shimomura ET, Summers J, Paul BD, Jenkins AJ, Darwin WD, Cone EJ.
  Source: Journal of Analytical Toxicology. 2001 October; 25(7): 504-14.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11599592&dopt=Abstract

- **Use of continuous ambulatory infusions of concentrated subcutaneous (s.q.) hydromorphone versus intravenous (i.v.) morphine: cost implications for palliative care.**
  Author(s): Fudin J, Smith HS, Toledo-Binette CS, Kenney E, Yu AB, Boutin R.
  Source: Am J Hosp Palliat Care. 2000 September-October; 17(5): 347-53.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11886060&dopt=Abstract

- **Use of intrathecal morphine for postoperative pain relief after elective laparoscopic colorectal surgery.**
  Author(s): Kong SK, Onsiong SM, Chiu WK, Li MK.
  Source: Anaesthesia. 2002 December; 57(12): 1168-73.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12437707&dopt=Abstract

- **Use of morphine and 6-monoacetylmorphine in blood for the evaluation of possible risk factors for sudden death in 192 heroin users.**
  Author(s): Fugelstad A, Ahlner J, Brandt L, Ceder G, Eksborg S, Rajs J, Beck O.
  Source: Addiction (Abingdon, England). 2003 April; 98(4): 463-70.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12653816&dopt=Abstract

- **Use of morphine and adjuvant drugs according to the condition.**
  Author(s): Matoba M.
  Source: European Journal of Pain (London, England). 2001; 5 Suppl A: 59-62. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11798219&dopt=Abstract

- **Use of morphine for pain after intracranial surgery.**
  Author(s): Herbert C.
  Source: Prof Nurse. 2001 January; 16(4): 1029-33. Review.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12029729&dopt=Abstract

- **Ventilatory effects of morphine infusions in cyanotic versus acyanotic infants after thoracotomy.**
  Author(s): Lynn AM, Nespeca MK, Bratton SL, Shen DD.
  Source: Paediatric Anaesthesia. 2003 January; 13(1): 12-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12535033&dopt=Abstract

- **What is the optimal morphine dose to be administered intrathecally in postoperative analgesia of cardiac surgery?**
  Author(s): Tamayo E, Alvarez J, de Temino R, Martinez A, Florez S.
  Source: Journal of Cardiothoracic and Vascular Anesthesia. 2002 February; 16(1): 132-4; Author Reply 134-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11854894&dopt=Abstract

- **Withdrawal symptoms in a patient receiving intrathecal morphine via an infusion pump.**
  Author(s): Hu K, Connelly NR, Vieira P.
  Source: Journal of Clinical Anesthesia. 2002 December; 14(8): 595-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12565119&dopt=Abstract

CHAPTER 2. NUTRITION AND MORPHINE

Overview

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

Finding Nutrition Studies on Morphine

The National Institutes of Health's Office of Dietary Supplements (ODS) offers a searchable bibliographic database called the IBIDS (International Bibliographic Information on Dietary Supplements; National Institutes of Health, Building 31, Room 1B29, 31 Center Drive, MSC 2086, Bethesda, Maryland 20892-2086, Tel: 301-435-2920, Fax: 301-480-1845, E-mail: ods@nih.gov). The IBIDS contains over 460,000 scientific citations and summaries about dietary supplements and nutrition as well as references to published international, scientific literature on dietary supplements such as vitamins, minerals, and botanicals.[7] The IBIDS includes references and citations to both human and animal research studies.

As a service of the ODS, access to the IBIDS database is available free of charge at the following Web address: **http://ods.od.nih.gov/databases/ibids.html**. After entering the search area, you have three choices: (1) IBIDS Consumer Database, (2) Full IBIDS Database, or (3) Peer Reviewed Citations Only.

Now that you have selected a database, click on the "Advanced" tab. An advanced search allows you to retrieve up to 100 fully explained references in a comprehensive format. Type "morphine" (or synonyms) into the search box, and click "Go." To narrow the search, you can also select the "Title" field.

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

The following is a typical result when searching for recently indexed consumer information on morphine:

- **Montana's 'angels of mercy'. Morphine for the dying.**
  Source: Duignan Cabrera, A Newsweek. 1991 June 10; 117(23): 24 0028-9604
- **The case for morphine.**
  Source: Gorman, C Time. 1997 April 28; 149(17): 64-5 0040-781X

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

- **A new method to obtain and present complete information on the compatibility: study of its validity for eight binary mixtures of morphine with drugs frequently used in palliative care.**
  Author(s): Laboratory of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Ghent University, Belgium.
  Source: Vermeire, A Remon, J P Schrijvers, D Demeulenaere, P Palliat-Med. 2002 September; 16(5): 417-24 0269-2163
- **Altered nucleus accumbens circuitry mediates pain-induced antinociception in morphine-tolerant rats.**
  Author(s): Graduate Program in Oral Biology, University of California, San Francisco, California 94143-0440, USA.
  Source: Schmidt, Brian L Tambeli, Claudia H Barletta, Justine Luo, Lei Green, Paul Levine, Jon D Gear, Robert W J-Neurosci. 2002 August 1; 22(15): 6773-80 1529-2401
- **Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study.**
  Author(s): Anesthesia and Intensive Care Unit, Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Home Palliative Care Program, Societa Assistenza Malato Oncologico Terminale, Palermo, Italy. mercadsa@tin.it
  Source: Mercadante, S Arcuri, E Tirelli, W Villari, P Casuccio, A Tumori. 2002 May-June; 88(3): 239-42 0300-8916
- **Amphetamine and morphine produce a conditioned taste and place preference in the house musk shrew (Suncus murinus).**
  Author(s): Department of Psychology, Wilfrid Laurier University, Waterloo, Ontario, Canada N2L 3C5. lparker@wlu.ca
  Source: Parker, Linda A Corrick, Marion L Limebeer, Cheryl L Kwiatkowska, Magdalena J-Exp-Psychol-Anim-Behav-Process. 2002 January; 28(1): 75-82 0097-7403
- **An analysis of the effects of contextual cues on the development of morphine tolerance in rats.**
  Author(s): Department of Psychology, Kwansei Gakuin University, Nishinomiya, 662-8501 Japan.
  Source: Nakama Kitamura, M Kawai, N Hayashi, T Imada, H Nihon-Shinkei-Seishin-Yakurigaku-Zasshi. 2002 June; 22(3): 79-84 1340-2544
- **Baclofen prevents morphine withdrawal irrespective of seasonal variation.**
  Author(s): Catedra de Farmacologia, Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Argentina.
  Source: Kemmling, A K Rubio, M C Balerio, G N Behav-Pharmacol. 2002 February; 13(1): 87-92 0955-8810
- **Cardiovascular surgery patients' respiratory responses to morphine before extubation.**
  Author(s): Edward Hospital, Naperville, IL, USA. JTZHAWKS10@hotmail.com

Source: Renaud, Kimberley L Pain-Manag-Nurs. 2002 June; 3(2): 53-60 1524-9042

- **Chronic morphine induces downregulation of spinal glutamate transporters: implications in morphine tolerance and abnormal pain sensitivity.**
  Author(s): Massachusetts General Hospital Pain Center and Neural Plasticity Research Group, Department of Anesthesia and Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA. jmao@partners.org
  Source: Mao, J Sung, B Ji, R R Lim, G J-Neurosci. 2002 September 15; 22(18): 8312-23 1529-2401

- **Chronic morphine treatment inhibits opioid receptor desensitization and internalization.**
  Author(s): Institute of Pharmacology, Toxicology and Pharmacy, University of Munich, D-80539 Munich, Germany. eisinger@pharmtox.vetmed.uni-muenchen.de
  Source: Eisinger, D A Ammer, H Schulz, R J-Neurosci. 2002 December 1; 22(23): 10192-200 1529-2401

- **Combined intrathecal baclofen and morphine infusion for the treatment of spasticity related pain and central deafferentiation pain.**
  Author(s): Department of Neurosurgery, Philipps-University Hospital, Marburg, Germany.
  Source: Gatscher, S Becker, R Uhle, E Bertalanffy, H Acta-Neurochir-Suppl. 2002; 79: 75-6 0065-1419

- **Comparison of analgesic effects of intra-articular tenoxicam and morphine in anterior cruciate ligament reconstruction.**
  Author(s): Department of Anesthesiology, Medical School, Erciyes University, 38039 Kayseri, Turkey.
  Source: Guler, G Karaoglu, S Velibasoglu, H Ramazanogullari, N Boyaci, A Knee-Surg-Sports-Traumatol-Arthrosc. 2002 July; 10(4): 229-32 0942-2056

- **Comparison of morphine and kainic acid microinjections into identical PAG sites on the activity of RVM neurons.**
  Author(s): Instituto Venezolano de Investigaciones Cientificas, Caracas 1020-A, Venezuela. victort@cbb.ivic.ve
  Source: Tortorici, V Morgan, M M J-Neurophysiol. 2002 October; 88(4): 1707-15 0022-3077

- **Critical role of mast cells in morphine-mediated impairment of zymosan-induced peritonitis in mice.**
  Author(s): Department of Experimental Pathology, Institute of Medical Biology, University of Tromso, Norway.
  Source: Kolaczkowska, E Seljelid, R Plytycz, B Inflamm-Res. 2001 August; 50(8): 415-21 1023-3830

- **Cyclooxygenase-2 inhibition potentiates morphine antinociception at the spinal level in a postoperative pain model.**
  Author(s): Department of Anesthesiology, Rush Medical College at Rush-Presbyterian-St. Luke's Medical Center, Chicago IL 60612, USA. jkroin@rush.edu
  Source: Kroin, J S Buvanendran, A McCarthy, R J Hemmati, H Tuman, K J Reg-Anesth-Pain-Med. 2002 Sep-October; 27(5): 451-5 1098-7339

- **Detection of morphine in blood and urine samples from horses administered poppy seeds and morphine sulfate orally.**
  Author(s): K.L. Maddy Equine Analytical Chemistry Laboratory University of California, Davis, USA.

Source: Kollias Baker, Cynthia Sams, Richard J-Anal-Toxicol. 2002 March; 26(2): 81-6 0146-4760

- **Differential mechanisms of morphine antinociceptive tolerance revealed in (beta)arrestin-2 knock-out mice.**
  Author(s): Howard Hughes Medical Institute Laboratories, Department of Cell Biology, Duke University Medical Center, Durham, North Carolina 27710, USA.
  Source: Bohn, L M Lefkowitz, R J Caron, M G J-Neurosci. 2002 December 1; 22(23): 10494-500 1529-2401

- **Differential morphine tolerance development in the modulation of macrophage cytokine production in mice.**
  Author(s): Department of Pharmacology, University of Milan, via Vanvitelli 32, 20129 Milan, Italy.
  Source: Limiroli, Elena Gaspani, Leda Panerai, Alberto E Sacerdote, Paola J-Leukoc-Biol. 2002 July; 72(1): 43-8 0741-5400

- **Disruption of temporally organized behavior by morphine.**
  Author(s): Department of Psychology, West Virginia University, Morgantown 26506-6040, USA. tgk3@cdc.gov
  Source: Knealing, T W Schaal, D W J-Exp-Anal-Behavolume 2002 March; 77(2): 157-69 0022-5002

- **Dopamine D2L receptor knockout mice display deficits in positive and negative reinforcing properties of morphine and in avoidance learning.**
  Author(s): Department of Pharmacology, University of Pennsylvania School of Medicine, M102 John Morgan Building, Philadelphia, PA 19014, USA.
  Source: Smith, J W Fetsko, L A Xu, R Wang, Y Neuroscience. 2002; 113(4): 755-65 0306-4522

- **Drug trace discrimination with nicotine and morphine in rats.**
  Author(s): Section of Behavioural Pharmacology, Institute of Psychiatry, King's College London, UK. i.stolerman@iop.kcl.ac.uk
  Source: Stolerman, I P Childs, E Hahn, B Morley, A Behav-Pharmacol. 2002 February; 13(1): 49-58 0955-8810

- **Effect of intracerebroventricular injection of GABA receptor agents on morphine-induced antinociception in the formalin test.**
  Author(s): Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Iran.
  Source: Mahmoudi, M Zarrindast, M R J-Psychopharmacol. 2002 March; 16(1): 85-91 0269-8811

- **Effect of morphine on thioglycollate-induced peritonitis in chickens.**
  Author(s): Department of Vertebrate Physiology, Faculty of Biology, Warsaw University, Poland. pmajew@biol.uw.edu.pl
  Source: Majewski, P Markowska, M Laskowska, H Waloch, M Skwarlo Sonta, K Neuroendocrinol-Lett. 2002 April; 23(2): 161-7 0172-780X

- **Effects of naloxone and post-tetanic stimulation on isolated guinea-pig ileum followed by long exposure to morphine and bestatin.**
  Author(s): Institute of Experimental Animals, Department of Toxicology, Niigata College of Pharmacy, 5-13-2 Kamishin'ei-cho, Niigata-City, Niigata 950-2076, Japan.
  Source: Ozaki, M J-Toxicol-Sci. 2002 August; 27(3): 173-82 0388-1350

- **Excitotoxic lesions of the pedunculopontine differentially mediate morphine- and d-amphetamine-evoked striatal dopamine efflux and behaviors.**
  Author(s): Department of Psychology, Macquarie University, Sydney, NSW 2109, Australia.
  Source: Miller, A D Forster, G L Metcalf, K M Blaha, C D Neuroscience. 2002; 111(2): 351-62 0306-4522

- **Functional magnetic resonance neuroimaging of drug dependence: naloxone-precipitated morphine withdrawal.**
  Author(s): Neuroimaging Research Group, Department of Neurology, Institute of Psychiatry, Kings College London, 4 Windsor Walk, London, SE5 8BB, United Kingdom. a.lowe@iop.kcl.ac.uk
  Source: Lowe, A S Williams, S C Symms, M R Stolerman, I P Shoaib, M Neuroimage. 2002 October; 17(2): 902-10 1053-8119

- **GABAergic and glutamatergic afferents in the dorsal raphe nucleus mediate morphine-induced increases in serotonin efflux in the rat central nervous system.**
  Author(s): Department of Cell Biology and Neuroscience, Rutgers University, Piscataway, New Jersey, USA. rtao@hms.harvard.edu
  Source: Tao, R Auerbach, S B J-Pharmacol-Exp-Ther. 2002 November; 303(2): 704-10 0022-3565

- **Hair morphine concentrations of fatal heroin overdose cases and living heroin users.**
  Author(s): National Drug and Alcohol Research Centre, University of New South Wales, Austrlia. s.darke@unsw.edu
  Source: Darke, S Hall, W Kaye, S Ross, J Duflou, J Addiction. 2002 August; 97(8): 977-84 0965-2140

- **Increase of morphine withdrawal in mice lacking A2a receptors and no changes in CB1/A2a double knockout mice.**
  Author(s): Laboratori de Neurofarmacologia, Facultat de Ciencies de la Salut i de la Vida, Universitat Pompeu Fabra, C/Doctor Aiguader 80, 08003 Barcelona, Spain.
  Source: Berrendero, F Castane, A Ledent, C Parmentier, M Maldonado, R Valverde, O Eur-J-Neurosci. 2003 January; 17(2): 315-24 0953-816X

- **Induction of metallothioneins by ethanol and morphine.**
  Author(s): Department of Biochemistry and Molecular Biology, Medical University of Lublin.
  Source: Florianczyk, B Stryjecka Zimmer, M Ann-Univ-Mariae-Curie-Sklodowska-[Med]. 2001; 56: 183-7 0066-2240

- **Inhibition of spinal protein kinase Calpha expression by an antisense oligonucleotide attenuates morphine infusion-induced tolerance.**
  Author(s): Anesthesia Research Laboratory, Department of Anesthesiology, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92103-0818, USA. xyhua@ucsd.edu
  Source: Hua, X Y Moore, A Malkmus, S Murray, S F Dean, N Yaksh, T L Butler, M Neuroscience. 2002; 113(1): 99-107 0306-4522

- **Intra-synovial, compared to intra-articular morphine provides better pain relief following knee arthroscopy menisectomy.**
  Author(s): Department of Orthopaedic Surgery, Carmel Medical Center and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa Israel. kaligan@netvision.net.il
  Source: Kligman, Mordechai Bruskin, Alex Sckliamser, Jorge Vered, Rony Roffman, Moshe Can-J-Anaesth. 2002 April; 49(4): 380-3 0832-610X

- **Less morphine, or more?**
  Author(s): Genesee Region Home Care, Rochester, N.Y., USA.
  Source: Perkins, E M RN. 2002 November; 65(11): 51-4 0033-7021
- **Long-acting morphine for pain control in paediatric oncology.**
  Author(s): Vestische Kinderklinik, Datteln, University Witten/Herdecke, Germany. Boris.Zernikow@t-online.de
  Source: Zernikow, B Lindena, G Med-Pediatr-Oncol. 2001 April; 36(4): 451-8 0098-1532
- **Loss of intrathecal morphine analgesia in terminal cancer patients is associated with high levels of excitatory amino acids in the CSF.**
  Author(s): Department of Anesthesiology, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan.
  Source: Wong, Chih Shung Chang, Yi Chen Yeh, Chun Chang Huang, Go Shine Cherng, Chen Hwan Can-J-Anaesth. 2002 Jun-July; 49(6): 561-5 0832-610X
- **Low-dose ketorolac improves analgesia and reduces morphine requirements following posterior spinal fusion in adolescents.**
  Author(s): Department of Anesthesiology, University of Michigan Health System, Ann Arbor, Michigan, USA. hmunro@nemours.org
  Source: Munro, H M Walton, S R Malviya, S Merkel, S Voepel Lewis, T Loder, R T Farley, F A Can-J-Anaesth. 2002 May; 49(5): 461-6 0832-610X
- **Memantine does not block antiaggressive effects of morphine in mice.**
  Author(s): Area de Psicobiologia, Facultad de Psicologia, Universitat de Valencia, Valencia, Spain.
  Source: Rodriguez Arias, M Maldonado, C Aguilar, M A Minarro, J Behav-Pharmacol. 2002 May; 13(3): 249-52 0955-8810
- **Morphine down regulates human vascular tissue estrogen receptor expression determined by real-time RT-PCR.**
  Author(s): Neuroscience Research Institute, State University of New York at Old Westbury, NY 11568, USA.
  Source: Cadet, P Mantione, K Bilfinger, T V Stefano, G B Neuroendocrinol-Lett. 2002 April; 23(2): 95-100 0172-780X
- **Morphine enhances HIV infection of human blood mononuclear phagocytes through modulation of beta-chemokines and CCR5 receptor.**
  Author(s): Division of Immunologic and Infectious Diseases, Joseph Stokes Jr. Research Institute of The Children's Hospital of Philadelphia, PA 19104, USA.
  Source: Guo, C J Li, Y Tian, S Wang, X Douglas, S D Ho, W Z J-Investig-Med. 2002 November; 50(6): 435-42 1081-5589
- **Morphine promotes autonomic learning.**
  Author(s): Research Service, William Jennings Bryan Dorn Veterans Affairs Medical Center, Columbia, South Carolina 29209-1639, USA.
  Source: Hernandez Brooks, L L Singha, A K Watson, K L Exp-Clin-Psychopharmacol. 2002 May; 10(2): 113-28 1064-1297
- **Nebulised morphine for severe interstitial lung disease.**
  Author(s): Istituto Malattie Apparato Respiratorio, University of Catania, Via Passo Gravina 187, Catania, Italy. R.Polosa@soton.ac.uk
  Source: Polossa, R Simidchiev, A Walters, E H Cochrane-Database-Syst-Revolume 2002; (3): CD002872 1469-493X

- **Neuronal apoptosis associated with morphine tolerance: evidence for an opioid-induced neurotoxic mechanism.**
  Author(s): Massachusetts General Hospital Pain Center, Department of Anesthesia and Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA. jmao@partners.org
  Source: Mao, J Sung, B Ji, R R Lim, G J-Neurosci. 2002 September 1; 22(17): 7650-61 1529-2401

- **Pretreatment with cholera or pertussis toxin differentially modulates morphine- and beta-endorphin-induced antinociception in the mouse formalin test.**
  Author(s): Department of Pharmacology, Institute of Natural Medicine, Hallym University, Kangwon-do, South Korea.
  Source: Chung, K M Suh, H W Neuropeptides. 2001 Oct-December; 35(5-6): 197-203 0143-4179

- **Protective role of Bacopa monniera on morphine-induced brain mitochondrial enzyme activity in rats.**
  Author(s): Department of Biochemistry and Molecular Biology, University of Madras, Guindy Campus, 600 025, Chennai, India.
  Source: Sumathy, T Govindasamy, S Balakrishna, K Veluchamy, G Fitoterapia. 2002 August; 73(5): 381-5 0367-326X

- **Reinforcing effect of subcutaneous morphine in a modified Ettenberg runway.**
  Author(s): Division of Neurochemistry, Department of Psychiatry, University of Innsbruck, Austria. gerald.zernig@uibk.ac.at
  Source: Zernig, G Harbig, P Weiskirchner, I Auffinger, M Wakonigg, G Saria, A J-Mol-Neurosci. 2002 Feb-April; 18(1-2): 135-42 0895-8696

- **Stimulation of peripheral nociceptor endings by low dose morphine and its signaling mechanism.**
  Author(s): Department of Anesthesiology, Nagasaki University School of Medicine, Nagasaki, Japan
  Source: Ono, T Inoue, M Harunor Rashid, M Sumikawa, K Ueda, H Neurochem-Int. 2002 December; 41(6): 399-407 0197-0186

- **Sustained morphine exposure induces a spinal dynorphin-dependent enhancement of excitatory transmitter release from primary afferent fibers.**
  Author(s): Department of Pharmacology, University of Arizona, Tucson, Arizona 85724, USA.
  Source: Gardell, Luis R Wang, Ruizhong Burgess, Shannon E Ossipov, Michael H Vanderah, Todd W Malan, T Philip Jr Lai, Josephine Porreca, Frank J-Neurosci. 2002 August 1; 22(15): 6747-55 1529-2401

- **The effect of IVPCA morphine on post-hysterectomy bowel function.**
  Author(s): Department of Anesthesiology, National Taiwan University, College of Medicine and Hospital, Taipei, Taiwan, R.O.C.
  Source: Chan, K C Cheng, Y J Huang, G T Wen, Y J Lin, C J Chen, L K Sun, W Z Acta-Anaesthesiol-Sin. 2002 June; 40(2): 61-4 0529-5769

- **The effects of adenosine receptor agonists and antagonists on morphine state-dependent memory of passive avoidance.**
  Author(s): Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, P.O. Box 13145-784, Tehran, Iran.
  Source: Khavandgar, S Homayoun, H Torkaman Boutorabi, A Zarrindast, M R Neurobiol-Learn-Mem. 2002 September; 78(2): 390-405 1074-7427

- **The effects of morphine on chained and clocked fixed-interval schedule performance in pigeons.**
  Author(s): Department of Psychology, West Virginia University, Morgantown, West Virginia 26505, USA. Llieving@mix.wvu.edu
  Source: Lieving, L M Odum, A L Schaal, D W Behav-Pharmacol. 2002 May; 13(3): 221-8 0955-8810
- **The effects of simultaneous administration of alpha(2) -adrenergic agents with L-NAME or L-arginine on the development and expression of morphine dependence in mice.**
  Author(s): Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, PO Box 13145-784, Tehran, Iran. Zarinmr@ams.ac.ir
  Source: Zarrindast, M R Homayoun, H Khavandgar, S Fayaz Dastgerdi, M Fayaz Dastgerdi, M Behav-Pharmacol. 2002 March; 13(2): 117-25 0955-8810
- **The efficacy and side effects of continuous infusion intravenous morphine (CIVM) for pain and symptoms due to advanced cancer.**
  Author(s): Harry R. Horvitz Center for Palliative Medicine, Cleveland Clinic Taussig Cancer Center, Ohio, USA.
  Source: Glare, P Walsh, D Groh, E Nelson, K A Am-J-Hosp-Palliat-Care. 2002 Sep-October; 19(5): 343-50 1049-9091
- **The neurosteroid allopregnanolone increases dopamine release and dopaminergic response to morphine in the rat nucleus accumbens.**
  Author(s): Psychobiologie des Comportements Adaptatifs, INSERM U259, Universite Victor Segalen Bordeaux 2, Domaine de Carreire, Rue Camille Saint-Saens, 33077 Bordeaux Cedex, France.
  Source: Rouge Pont, F Mayo, W Marinelli, M Gingras, M Le Moal, M Piazza, P V Eur-J-Neurosci. 2002 July; 16(1): 169-73 0953-816X
- **The role of spinal neuroimmune activation in morphine tolerance/hyperalgesia in neuropathic and sham-operated rats.**
  Author(s): Department of Anesthesiology, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire 03756, USA.
  Source: Raghavendra, V Rutkowski, M D DeLeo, J A J-Neurosci. 2002 November 15; 22(22): 9980-9 1529-2401
- **Use of morphine for pain after intracranial surgery.**
  Author(s): Neurosurgery Unit, University Hospital of Wales, Cardiff.
  Source: Herbert, C Prof-Nurse. 2001 January; 16(4): 1029-33 0266-8130

Federal Resources on Nutrition

In addition to the IBIDS, the United States Department of Health and Human Services (HHS) and the United States Department of Agriculture (USDA) provide many sources of information on general nutrition and health. Recommended resources include:

- healthfinder®, HHS's gateway to health information, including diet and nutrition: **http://www.healthfinder.gov/scripts/SearchContext.asp?topic=238&page=0**
- The United States Department of Agriculture's Web site dedicated to nutrition information: **www.nutrition.gov**
- The Food and Drug Administration's Web site for federal food safety information: **www.foodsafety.gov**

- The National Action Plan on Overweight and Obesity sponsored by the United States Surgeon General: **http://www.surgeongeneral.gov/topics/obesity/**
- The Center for Food Safety and Applied Nutrition has an Internet site sponsored by the Food and Drug Administration and the Department of Health and Human Services: **http://vm.cfsan.fda.gov/**
- Center for Nutrition Policy and Promotion sponsored by the United States Department of Agriculture: **http://www.usda.gov/cnpp/**
- Food and Nutrition Information Center, National Agricultural Library sponsored by the United States Department of Agriculture: **http://www.nal.usda.gov/fnic/**
- Food and Nutrition Service sponsored by the United States Department of Agriculture: **http://www.fns.usda.gov/fns/**

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering food and nutrition. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=174&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/med_nutrition.html**
- Google: **http://directory.google.com/Top/Health/Nutrition/**
- Healthnotes: **http://www.healthnotes.com/**
- Open Directory Project: **http://dmoz.org/Health/Nutrition/**
- Yahoo.com: **http://dir.yahoo.com/Health/Nutrition/**
- WebMD®Health: **http://my.webmd.com/nutrition**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**

The following is a specific Web list relating to morphine; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **Food and Diet**

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

CHAPTER 3. ALTERNATIVE MEDICINE AND MORPHINE

Overview

In this chapter, we will begin by introducing you to official information sources on complementary and alternative medicine (CAM) relating to morphine. At the conclusion of this chapter, we will provide additional sources.

National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (**http://nccam.nih.gov/**) has created a link to the National Library of Medicine's databases to facilitate research for articles that specifically relate to morphine and complementary medicine. To search the database, go to the following Web site: **http://www.nlm.nih.gov/nccam/camonpubmed.html**. Select "CAM on PubMed." Enter "morphine" (or synonyms) into the search box. Click "Go." The following references provide information on particular aspects of complementary and alternative medicine that are related to morphine:

- **A quasi-experimental, dual-center study of morphine efficacy in patients with burns.**
  Author(s): Foertsch CE, O'Hara MW, Kealey GP, Foster LD, Schumacher EA.
  Source: The Journal of Burn Care & Rehabilitation. 1995 March-April; 16(2 Pt 1): 118-26.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7775504&dopt=Abstract

- **Abatement of morphine-induced slowing in gastrointestinal transit by Dai-kenchu-to, a traditional Japanese herbal medicine.**
  Author(s): Nakamura T, Sakai A, Isogami I, Noda K, Ueno K, Yano S.
  Source: Japanese Journal of Pharmacology. 2002 February; 88(2): 217-21.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11928724&dopt=Abstract

- **Alcoholic extract of 'Bacopa monniera' reduces the in vitro effects of morphine withdrawal in guinea-pig ileum.**
  Author(s): Sumathi T, Nayeem M, Balakrishna K, Veluchamy G, Devaraj SN.

Source: Journal of Ethnopharmacology. 2002 October; 82(2-3): 75-81.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12241980&dopt=Abstract

- **Alertness, cognition and morphine in patients with advanced cancer.**
Author(s): Clemons M, Regnard C, Appleton T.
Source: Cancer Treatment Reviews. 1996 November; 22(6): 451-68.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9134005&dopt=Abstract

- **Alkaloids from Brugmansia arborea (L.) Lagerhein reduce morphine withdrawal in vitro.**
Author(s): Capasso A, de Feo V.
Source: Phytotherapy Research : Ptr. 2003 August; 17(7): 826-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12916089&dopt=Abstract

- **Antagonism of morphine-induced antinociception by tetrandrine is dependent on serotonergic mechanisms.**
Author(s): Zhang YH, Fang LH.
Source: Life Sciences. 2001 August 10; 69(12): 1429-39.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11531166&dopt=Abstract

- **Antagonism of the acute pharmacological actions of morphine by panax ginseng extract.**
Author(s): Ramarao P, Bhargava HN.
Source: General Pharmacology. 1990; 21(6): 877-80.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2279687&dopt=Abstract

- **Antinarcotic effects of the standardized ginseng extract G115 on morphine.**
Author(s): Kim HS, Jang CG, Lee MK.
Source: Planta Medica. 1990 April; 56(2): 158-63.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2353061&dopt=Abstract

- **Antinarcotic effects of the velvet antler water extract on morphine in mice.**
Author(s): Kim HS, Lim HK, Park WK.
Source: Journal of Ethnopharmacology. 1999 July; 66(1): 41-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10432206&dopt=Abstract

- **Anti-stress effect of ginseng on the inhibition of the development of morphine tolerance in stressed mice.**
Author(s): Takahashi M, Tokuyama S, Kaneto H.
Source: Japanese Journal of Pharmacology. 1992 July; 59(3): 399-404.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1434134&dopt=Abstract

- **Biotransformation of nociceptin/orphanin FQ by enzyme activity from morphine-naive and morphine-treated cell cultures.**
  Author(s): Vlaskovska M, Kasakov L, Suder P, Silberring J, Terenius L.
  Source: Brain Research. 1999 February 13; 818(2): 212-20.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10082806&dopt=Abstract

- **Changes in urination/defecation, auditory startle response, and startle-induced ultrasonic vocalizations in rats undergoing morphine withdrawal: similarities and differences between acute and chronic dependence.**
  Author(s): Kalinichev M, Holtzman SG.
  Source: The Journal of Pharmacology and Experimental Therapeutics. 2003 February; 304(2): 603-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12538812&dopt=Abstract

- **Cholecystokinin antisense RNA increases the analgesic effect induced by electroacupuncture or low dose morphine: conversion of low responder rats into high responders.**
  Author(s): Tang NM, Dong HW, Wang XM, Tsui ZC, Han JS.
  Source: Pain. 1997 May; 71(1): 71-80.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9200176&dopt=Abstract

- **Chronic morphine exposure increases the phosphorylation of MAP kinases and the transcription factor CREB in dorsal root ganglion neurons: an in vitro and in vivo study.**
  Author(s): Ma W, Zheng WH, Powell K, Jhamandas K, Quirion R.
  Source: The European Journal of Neuroscience. 2001 October; 14(7): 1091-104.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11683901&dopt=Abstract

- **Combined traditional Chinese medicine and Western medicine. Relieving effects of Chinese herbs, ear-acupuncture and epidural morphine on postoperative pain in liver cancer.**
  Author(s): Li QS, Cao SH, Xie GM, Gan YH, Ma HJ, Lu JZ, Zhang ZH.
  Source: Chinese Medical Journal. 1994 April; 107(4): 289-94.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8088198&dopt=Abstract

- **Delayed recognition of podophyllum toxicity in a patient receiving epidural morphine.**
  Author(s): Conard PF, Hanna N, Rosenblum M, Gross JB.
  Source: Anesthesia and Analgesia. 1990 August; 71(2): 191-3.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2375521&dopt=Abstract

- **Determination of morphine and related alkaloids in crude morphine, poppy straw and opium preparations by micellar electrokinetic capillary chromatography.**
  Author(s): Trenerry VC, Wells RJ, Robertson J.

Source: J Chromatogr A. 1995 December 1; 718(1): 217-25.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8556164&dopt=Abstract

- **Effect of intrathecal morphine and electro-acupuncture on cellular immune function of rats and increment of mu-opioid receptor mRNA expression in PAG following intrathecal morphine.**
  Author(s): Sun T, Du LN, Wu GC, Cao XD.
  Source: Acupuncture & Electro-Therapeutics Research. 2000; 25(1): 1-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10830970&dopt=Abstract

- **Effect of morphine and electro-acupuncture (EA) on apoptosis of thymocytes.**
  Author(s): Zhang Y, Wu GC, He QZ, Cao XD.
  Source: Acupuncture & Electro-Therapeutics Research. 2000; 25(1): 17-26.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10830972&dopt=Abstract

- **Effect of P-6 acupressure on prevention of nausea and vomiting after epidural morphine for post-cesarean section pain relief.**
  Author(s): Ho CM, Hseu SS, Tsai SK, Lee TY.
  Source: Acta Anaesthesiologica Scandinavica. 1996 March; 40(3): 372-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8721471&dopt=Abstract

- **Effect of panax ginseng extract on the pharmacological actions of morphine in the rat.**
  Author(s): Bhargava HN, Ramarao P.
  Source: Prog Clin Biol Res. 1990; 328: 489-92. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2304964&dopt=Abstract

- **Effect of roots aqueous extract of Delphinium denudatum on morphine-induced tolerance in mice.**
  Author(s): Zafar S, Ahmad MA, Siddiqui TA.
  Source: Fitoterapia. 2002 December; 73(7-8): 553-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12490211&dopt=Abstract

- **Effect of Rosmarinus officinalis L. aerial parts extract on morphine withdrawal syndrome in mice.**
  Author(s): Hosseinzadeh H, Nourbakhsh M.
  Source: Phytotherapy Research : Ptr. 2003 September; 17(8): 938-41.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=13680829&dopt=Abstract

- **Effect of Salvia leriifolia leaf extract on morphine dependence in mice.**
  Author(s): Hosseinzadeh H, Lary P.

Source: Phytotherapy Research : Ptr. 2000 August; 14(5): 384-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10925411&dopt=Abstract

- **Effect of tetrandrine on morphine dependence in isolated guinea pig ileum.**
  Author(s): Liu ZH, Li JL, Li N, Tian CL, Zhang KG.
  Source: Zhongguo Yao Li Xue Bao. 1999 November; 20(11): 1000-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11270964&dopt=Abstract

- **Effect of undernutrition on morphine analgesia, haloperidol catalepsy and pentobarbitone sodium hypnosis in developing new born rats.**
  Author(s): Singh KP, Sanyal AK.
  Source: Indian Journal of Medical Sciences. 2003 April; 57(4): 164-70.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14510349&dopt=Abstract

- **Effects of Ferula gummosa Boiss. fractions on morphine dependence in mice.**
  Author(s): Ramezani M, Hosseinzadeh H, Mojtahedi K.
  Source: Journal of Ethnopharmacology. 2001 September; 77(1): 71-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11483380&dopt=Abstract

- **Effects of ginseng total saponin on morphine-induced hyperactivity and conditioned place preference in mice.**
  Author(s): Kim HS, Jang CG, Oh KW, Oh S, Rheu HM, Rhee GS, Seong YH, Park WK.
  Source: Journal of Ethnopharmacology. 1998 February; 60(1): 33-42.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9533430&dopt=Abstract

- **Effects of ginsenosides injected intrathecally or intracerebroventricularly on antinociception induced by morphine administrated intracerebroventricularly in the mouse.**
  Author(s): Suh HW, Song DK, Kim YH.
  Source: General Pharmacology. 1997 November; 29(5): 873-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9347341&dopt=Abstract

- **Effects of morphine and time of day on pain and beta-endorphin.**
  Author(s): Rasmussen NA, Farr LA.
  Source: Biological Research for Nursing. 2003 October; 5(2): 105-16.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14531215&dopt=Abstract

- **Effects of morphine-3-glucuronide and morphine on the K+-evoked release of [3H]-glutamic acid and [14C]-gamma-aminobutyric acid from rat brain synaptosomes.**
  Author(s): Bartlett SE, Smith MT.

Source: Life Sciences. 1996; 58(5): 447-54.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8594310&dopt=Abstract

- **Effects of Shilajit on the development of tolerance to morphine in mice.**
Author(s): Tiwari P, Ramarao P, Ghosal S.
Source: Phytotherapy Research : Ptr. 2001 March; 15(2): 177-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11268125&dopt=Abstract

- **Effects of the ginsenosides Rg1 and Rb1 on morphine-induced hyperactivity and reinforcement in mice.**
Author(s): Kim HS, Hong YT, Jang CG.
Source: The Journal of Pharmacy and Pharmacology. 1998 May; 50(5): 555-60.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9643450&dopt=Abstract

- **Electro-acupuncture (EA) induced attenuation of immunosuppression appearing after epidural or intrathecal injection of morphine in patients and rats.**
Author(s): Zhang Y, Du L, Wu G, Cao X.
Source: Acupuncture & Electro-Therapeutics Research. 1996 July-December; 21(3-4): 177-86.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9051165&dopt=Abstract

- **Electroacupuncture reduces morphine-induced emesis in ferrets: a pilot study.**
Author(s): Lao L, Wong RH, Berman B, Wynn RL.
Source: Journal of Alternative and Complementary Medicine (New York, N.Y.). 1995 Fall; 1(3): 257-61.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9395622&dopt=Abstract

- **Electroacupuncture reversed the inhibition of intestinal peristalsis induced by intrathecal injection of morphine in rabbits.**
Author(s): Dai JL, Ren ZJ, Fu ZM, Zhu YH, Xu SF.
Source: Chinese Medical Journal. 1993 March; 106(3): 220-4.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8325148&dopt=Abstract

- **Electroacupuncture, morphine and clonidine: a comparative study of analgesic effects.**
Author(s): Shankar N, Varshney A, Bhattacharya A, Sharma KN.
Source: Indian J Physiol Pharmacol. 1996 July; 40(3): 225-30.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8950137&dopt=Abstract

- **Endogenous orphanin FQ: evidence for a role in the modulation of electroacupuncture analgesia and the development of tolerance to analgesia produced by morphine and electroacupuncture.**
Author(s): Tian JH, Zhang W, Fang Y, Xu W, Grandy DK, Han JS.

Source: British Journal of Pharmacology. 1998 May; 124(1): 21-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9630338&dopt=Abstract

- **Evaluation of 3'-azido-3'-deoxythymidine, morphine, and codeine as probe substrates for UDP-glucuronosyltransferase 2B7 (UGT2B7) in human liver microsomes: specificity and influence of the UGT2B7*2 polymorphism.**
  Author(s): Court MH, Krishnaswamy S, Hao Q, Duan SX, Patten CJ, Von Moltke LL, Greenblatt DJ.
  Source: Drug Metabolism and Disposition: the Biological Fate of Chemicals. 2003 September; 31(9): 1125-33.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12920168&dopt=Abstract

- **Evidence for morphine downregulating immunocytes during cardiopulmonary bypass in a porcine model.**
  Author(s): Bilfinger TV, Kushnerik V, Bundz S, Liu Y, Stefano GB.
  Source: International Journal of Cardiology. 1996 April 26; 53 Suppl: S39-46.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8793592&dopt=Abstract

- **Excretion of morphine in urine following the ingestion of poppy seeds.**
  Author(s): Ferguson EW.
  Source: Military Medicine. 1990 March; 155(3): A8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2107461&dopt=Abstract

- **Experimental study of the morphine de-addiction properties of Delphinium denudatum Wall.**
  Author(s): Rahman S, Ali Khan R, Kumar A.
  Source: Bmc Complementary and Alternative Medicine [electronic Resource]. 2002 May 29; 2(1): 6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12036433&dopt=Abstract

- **Flavonoids reduce morphine withdrawal in-vitro.**
  Author(s): Capasso A, Piacente S, Pizza C, Sorrentino L.
  Source: The Journal of Pharmacy and Pharmacology. 1998 May; 50(5): 561-4.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9643451&dopt=Abstract

- **Flavonol glycosides from Aristeguietia discolor reduce morphine withdrawal in vitro.**
  Author(s): Capasso A, Saturnino P, Simone FD, Aquino R.
  Source: Phytotherapy Research : Ptr. 2000 November; 14(7): 538-40.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11054845&dopt=Abstract

- **Hepatic cytochrome P450 induction in goats. Effects of model inducers on the metabolism of alkoxyresorufins, testosterone and ethylmorphine, and on apoprotein and mRNA levels.**

Author(s): van't Klooster GA, Horbach GJ, Natsuhori M, Blaauboer BJ, Noordhoek J, van Miert AS.
Source: Biochemical Pharmacology. 1993 January 7; 45(1): 113-22.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8424805&dopt=Abstract

- **Hydroxyl radical-mediated conversion of morphine to morphinone.**
Author(s): Kumagai Y, Ikeda Y, Toki S.
Source: Xenobiotica; the Fate of Foreign Compounds in Biological Systems. 1992 May; 22(5): 507-13.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1384246&dopt=Abstract

- **Influence of a dietary alpha-linolenic acid deficiency on learning in the Morris water maze and on the effects of morphine.**
Author(s): Frances H, Coudereau JP, Sandouk P, Clement M, Monier C, Bourre JM.
Source: European Journal of Pharmacology. 1996 March 18; 298(3): 217-25.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8846819&dopt=Abstract

- **Influence of antineoplastic drugs on morphine analgesia and on morphine tolerance.**
Author(s): Genedani S, Bernardi M, Bertolini A.
Source: European Journal of Pharmacology. 1999 February 12; 367(1): 13-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10082259&dopt=Abstract

- **Influence of gossypin on the development of acute tolerance to morphine induced antinociception.**
Author(s): Ramaswamy S, Viswanathan S.
Source: Indian J Exp Biol. 1997 April; 35(4): 413-4.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9315244&dopt=Abstract

- **Inhibition by ginseng total saponin of the development of morphine reverse tolerance and dopamine receptor supersensitivity in mice.**
Author(s): Kin HS, Kang JG, Oh KW.
Source: General Pharmacology. 1995 September; 26(5): 1071-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7557253&dopt=Abstract

- **Inhibition by peripheral electric stimulation of the reinstatement of morphine-induced place preference in rats and drug-craving in heroin addicts.**
Author(s): Wang B, Zhang B, Ge X, Luo F, Han J.
Source: Beijing Da Xue Xue Bao. 2003 June 18; 35(3): 241-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12914237&dopt=Abstract

- **Inhibition of morphine tolerance and dependence by Withania somnifera in mice.**
Author(s): Kulkarni SK, Ninan I.

Source: Journal of Ethnopharmacology. 1997 August; 57(3): 213-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9292416&dopt=Abstract

- **Inhibitory effects of velvet antler water extract on morphine-induced conditioned place preference and DA receptor supersensitivity in mice.**
  Author(s): Kim HS, Lim HK.
  Source: Journal of Ethnopharmacology. 1999 July; 66(1): 25-31.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10432204&dopt=Abstract

- **Intrathecal Zn2+ attenuates morphine antinociception and the development of acute tolerance.**
  Author(s): Larson AA, Kovacs KJ, Spartz AK.
  Source: European Journal of Pharmacology. 2000 November 3; 407(3): 267-72.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11068022&dopt=Abstract

- **Isoquinoline alkaloids from Argemone mexicana reduce morphine withdrawal in guinea pig isolated ileum.**
  Author(s): Capasso A, Piacente S, Pizza C, De Tommasi N, Jativa C, Sorrentino L.
  Source: Planta Medica. 1997 August; 63(4): 326-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9270378&dopt=Abstract

- **Lesions of the pedunculopontine tegmental nucleus abolish catalepsy and locomotor depression induced by morphine.**
  Author(s): Olmstead MC, Franklin KB.
  Source: Brain Research. 1994 October 31; 662(1-2): 134-40.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7859066&dopt=Abstract

- **Locomotor activity after recovery from hypnosis: midazolam-morphine versus midazolam.**
  Author(s): Kissin I, Brown PT, Bradley EL Jr.
  Source: Anesthesia and Analgesia. 1992 December; 75(6): 929-31.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1443712&dopt=Abstract

- **Low frequency TENS is less effective than high frequency TENS at reducing inflammation-induced hyperalgesia in morphine-tolerant rats.**
  Author(s): Sluka KA, Judge MA, McColley MM, Reveiz PM, Taylor BM.
  Source: European Journal of Pain (London, England). 2000; 4(2): 185-93.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10957699&dopt=Abstract

- **Low-level hyperbaric exposure antagonizes locomotor effects of ethanol and n-propanol but not morphine in C57BL mice.**
  Author(s): Alkana RL, Davies DL, Morland J, Parker ES, Bejanian M.

Source: Alcoholism, Clinical and Experimental Research. 1995 June; 19(3): 693-700.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7573795&dopt=Abstract

- **Managing morphine-induced constipation: a controlled comparison of an Ayurvedic formulation and senna.**
Author(s): Ramesh PR, Kumar KS, Rajagopal MR, Balachandran P, Warrier PK.
Source: Journal of Pain and Symptom Management. 1998 October; 16(4): 240-4.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9803051&dopt=Abstract

- **Minute sphere acupressure does not reduce postoperative pain or morphine consumption.**
Author(s): Sakurai M, Suleman MI, Morioka N, Akca O, Sessler DI.
Source: Anesthesia and Analgesia. 2003 February; 96(2): 493-7, Table of Contents.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12538202&dopt=Abstract

- **Molecular cloning and functional expression of codeinone reductase: the penultimate enzyme in morphine biosynthesis in the opium poppy Papaver somniferum.**
Author(s): Unterlinner B, Lenz R, Kutchan TM.
Source: The Plant Journal : for Cell and Molecular Biology. 1999 June; 18(5): 465-75.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10417697&dopt=Abstract

- **Morphine analgesia mediated by activation of the acupuncture-analgesia-producing system.**
Author(s): Sato T, Takeshige C, Shimizu S.
Source: Acupuncture & Electro-Therapeutics Research. 1991; 16(1-2): 13-26.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1674831&dopt=Abstract

- **Morphine and somatostatin analogue reduce c-fos expression in trigeminal subnucleus caudalis produced by corneal stimulation in the rat.**
Author(s): Bereiter DA.
Source: Neuroscience. 1997 April; 77(3): 863-74.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9070758&dopt=Abstract

- **Morphine metabolism in the opium poppy and its possible physiological function. Biochemical characterization of the morphine metabolite, bismorphine.**
Author(s): Morimoto S, Suemori K, Moriwaki J, Taura F, Tanaka H, Aso M, Tanaka M, Suemune H, Shimohigashi Y, Shoyama Y.
Source: The Journal of Biological Chemistry. 2001 October 12; 276(41): 38179-84. Epub 2001 August 09.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11498543&dopt=Abstract

- **Morphine, 5-HT2 and 5-HT3 receptor antagonists reduce c-fos expression in the trigeminal nuclear complex following noxious chemical stimulation of the rat nasal**

mucosa.
Author(s): Ebersberger A, Anton F, Tolle TR, Zieglgansberger W.
Source: Brain Research. 1995 April 10; 676(2): 336-42.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7614003&dopt=Abstract

- **Morphine-3-glucuronide's neuro-excitatory effects are mediated via indirect activation of N-methyl-D-aspartic acid receptors: mechanistic studies in embryonic cultured hippocampal neurones.**
  Author(s): Hemstapat K, Monteith GR, Smith D, Smith MT.
  Source: Anesthesia and Analgesia. 2003 August; 97(2): 494-505, Table of Contents.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12873944&dopt=Abstract

- **Morphine-induced metabolic changes in human brain. Studies with positron emission tomography and [fluorine 18]fluorodeoxyglucose.**
  Author(s): London ED, Broussolle EP, Links JM, Wong DF, Cascella NG, Dannals RF, Sano M, Herning R, Snyder FR, Rippetoe LR, et al.
  Source: Archives of General Psychiatry. 1990 January; 47(1): 73-81.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2403775&dopt=Abstract

- **Mouse paw oedema induced by Habu snake (Trimeresurus flavoviridis) venom: inhibition by morphine, naloxone and methylnaloxone alone or in combinations.**
  Author(s): Detrait J, Jacob J.
  Source: Jpn J Exp Med. 1990 August; 60(4): 187-96.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1963452&dopt=Abstract

- **New protopine alkaloids from Aristolochia constricta reduce morphine withdrawal in vitro.**
  Author(s): Capasso A, De Tommasi N, Rastrelli L, De Simone F.
  Source: Phytotherapy Research : Ptr. 2000 December; 14(8): 653-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11114008&dopt=Abstract

- **Panax ginseng blocks morphine-induced thymic apoptosis by lowering plasma corticosterone level.**
  Author(s): Kim YR, Lee SY, Shin BA, Kim KM.
  Source: General Pharmacology. 1999 June; 32(6): 647-52.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10401989&dopt=Abstract

- **Pavlovian conditioning of morphine hyperthermia: assessment of interstimulus interval and CS-US overlap.**
  Author(s): Broadbent J, Cunningham CL.
  Source: Psychopharmacology. 1996 July; 126(2): 156-64.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8856835&dopt=Abstract

- **Peripheral electric stimulation inhibits morphine-induced place preference in rats.**
  Author(s): Wang B, Luo F, Xia YQ, Han JS.
  Source: Neuroreport. 2000 April 7; 11(5): 1017-20.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10790875&dopt=Abstract

- **Poppy seeds: differences in morphine and codeine content and variation in inter- and intra-individual excretion.**
  Author(s): Pelders MG, Ros JJ.
  Source: J Forensic Sci. 1996 March; 41(2): 209-12.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8871378&dopt=Abstract

- **Possible development of dependence on gossypin: role of gossypin on morphine dependence.**
  Author(s): Viswanathan S, Ramaswamy S, Thirugnasambantham P, Ramachandran S, Kameswaran L.
  Source: Indian J Exp Biol. 1990 December; 28(12): 1193-4. No Abstract Available.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2099336&dopt=Abstract

- **Preliminary study of fresh juice of Benincasa hispida on morphine addiction in mice.**
  Author(s): Grover JK, Rathi SS, Vats V.
  Source: Fitoterapia. 2000 December; 71(6): 707-9.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11077182&dopt=Abstract

- **Protective role of Bacopa monniera on morphine induced hepatotoxicity in rats.**
  Author(s): Sumathy T, Subramanian S, Govindasamy S, Balakrishna K, Veluchamy G.
  Source: Phytotherapy Research : Ptr. 2001 November; 15(7): 643-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11746853&dopt=Abstract

- **Protective role of Bacopa monniera on morphine-induced brain mitochondrial enzyme activity in rats.**
  Author(s): Sumathy T, Govindasamy S, Balakrishna K, Veluchamy G.
  Source: Fitoterapia. 2002 August; 73(5): 381-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12165332&dopt=Abstract

- **Protective role of Delphinium denudatum (Jadwar) against morphine induced tolerance and dependence in mice.**
  Author(s): Zafar S, Ahmad MA, Siddiqui TA.
  Source: Journal of Ethnopharmacology. 2001 November; 78(1): 95-8.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11585695&dopt=Abstract

- **Pseudoginsenoside-F11 attenuates morphine-induced signalling in Chinese hamster ovary-mu cells.**
  Author(s): Li Z, Xu NJ, Wu CF, Xiong Y, Fan HP, Zhang WB, Sun Y, Pei G.

Source: Neuroreport. 2001 May 25; 12(7): 1453-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11388428&dopt=Abstract

- **Sedative and hypnotic midazolam-morphine interactions in rats.**
Author(s): Kissin I, Brown PT, Bradley EL Jr.
Source: Anesthesia and Analgesia. 1990 August; 71(2): 137-43.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2375515&dopt=Abstract

- **Skin conductance responses to auditory stimuli and anticipatory responses before venepuncture in patients premedicated with diazepam or morphine.**
Author(s): Geddes SM, Gray WM, Millar K, Asbury AJ.
Source: British Journal of Anaesthesia. 1993 October; 71(4): 512-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8260299&dopt=Abstract

- **Suppression of morphine abstinence syndrome by body electroacupuncture of different frequencies in rats.**
Author(s): Han JS, Zhang RL.
Source: Drug and Alcohol Dependence. 1993 January; 31(2): 169-75.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8382148&dopt=Abstract

- **Suppression of morphine withdrawal by electroacupuncture in rats: dynorphin and kappa-opioid receptor implicated.**
Author(s): Wu LZ, Cui CL, Tian JB, Ji D, Han JS.
Source: Brain Research. 1999 December 18; 851(1-2): 290-6.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10642860&dopt=Abstract

- **Suppressive effects of central opioids on delayed type hypersensitivity to trinitrochlorobenzene: comparative study with morphine and electroacupuncture.**
Author(s): Kasahara T, Sakurai Y, Amemiya M, Oguchi K, Hisamitsu T.
Source: In Vivo. 1995 May-June; 9(3): 177-81.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8562877&dopt=Abstract

- **Synergistic effects of tumour necrosis factor and morphine on gut barrier function.**
Author(s): Leslie KA, Behme R, Clift A, Martin S, Grant D, Duff JH.
Source: Canadian Journal of Surgery. Journal Canadien De Chirurgie. 1994 April; 37(2): 143-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8156468&dopt=Abstract

- **Systemic morphine in combination with TENS produces an increased antihyperalgesia in rats with acute inflammation.**
Author(s): Sluka KA.

Source: The Journal of Pain : Official Journal of the American Pain Society. 2000 Autumn; 1(3): 204-11.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14622619&dopt=Abstract

- **Temporally graded, context-specific retrograde amnesia and its alleviation by context preexposure: effects of postconditioning exposures to morphine in the rat.**
  Author(s): McNally GP, Westbrook RF.
  Source: Journal of Experimental Psychology. Animal Behavior Processes. 2003 April; 29(2): 130-42.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12735277&dopt=Abstract

- **The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions.**
  Author(s): Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R.
  Source: Pain. 2003 September; 105(1-2): 79-88.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14499423&dopt=Abstract

- **The development and validation of the HLPC method for morphine content determination in poppy straw.**
  Author(s): Anyzewska M, Wojtasik E, Arent I.
  Source: Acta Pol Pharm. 2001 March-April; 58(2): 121-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11501789&dopt=Abstract

- **The effect of Panax ginseng on the development of tolerance to the pharmacological actions of morphine in the rat.**
  Author(s): Bhargava HN, Ramarao P.
  Source: General Pharmacology. 1991; 22(3): 521-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1869026&dopt=Abstract

- **The effects of fruit essential oil of the Pimpinella anisum on acquisition and expression of morphine induced conditioned place preference in mice.**
  Author(s): Sahraei H, Ghoshooni H, Hossein Salimi S, Mohseni Astani A, Shafaghi B, Falahi M, Kamalnegad M.
  Source: Journal of Ethnopharmacology. 2002 April; 80(1): 43-7.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11891086&dopt=Abstract

- **The influence of P-glycoprotein on morphine transport in Caco-2 cells. Comparison with paclitaxel.**
  Author(s): Crowe A.
  Source: European Journal of Pharmacology. 2002 April 5; 440(1): 7-16.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11959083&dopt=Abstract

- **The influence of preanalytical factors on concentrations of morphine and metabolites in patients receiving morphine.**
  Author(s): Westerling D, Bengtsson HI, Thysell C, Hoglund P.
  Source: Pharmacology & Toxicology. 1996 February; 78(2): 82-5.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8822039&dopt=Abstract

- **The role of manual acupuncture and morphine administration on the modulation of capsaicin-induced edema in rat paw. A blind controlled study.**
  Author(s): Ceccherelli F, Gagliardi G, Matterazzo G, Visentin R, Giron G.
  Source: Acupuncture & Electro-Therapeutics Research. 1996 January-March; 21(1): 7-14.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8791904&dopt=Abstract

- **Therapeutic suggestion has not effect on postoperative morphine requirements.**
  Author(s): van der Laan WH, van Leeuwen BL, Sebel PS, Winograd E, Baumann P, Bonke B.
  Source: Anesthesia and Analgesia. 1996 January; 82(1): 148-52.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8712392&dopt=Abstract

- **Tissue-specific regulation of canine intestinal and hepatic phenol and morphine UDP-glucuronosyltransferases by beta-naphthoflavone in comparison with humans.**
  Author(s): Bock KW, Bock-Hennig BS, Munzel PA, Brandenburg JO, Kohle CT, Soars MG, Riley RJ, Burchell B, Richter O, Eichelbaum MF, Swedmark S, Orzechowski A.
  Source: Biochemical Pharmacology. 2002 May 1; 63(9): 1683-90.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12007571&dopt=Abstract

- **TLC-UV densitometric and GC-MSD methods for simultaneous quantification of morphine and codeine in poppy capsules.**
  Author(s): Popa DS, Oprean R, Curea E, Preda N.
  Source: Journal of Pharmaceutical and Biomedical Analysis. 1998 December; 18(4-5): 645-50.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9919965&dopt=Abstract

- **Tolerance to the analgesic, but not discriminative stimulus effects of morphine after brief social defeat in rats.**
  Author(s): Miczek KA.
  Source: Psychopharmacology. 1991; 104(2): 181-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1876662&dopt=Abstract

- **Topical morphine in Ayurveda.**
  Author(s): Ramesh PR, Santhosh AR, Kumar KS.
  Source: Palliative Medicine. 1998 January; 12(1): 64.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9616464&dopt=Abstract

- **Trans-cranial electrical stimulation attenuates abrupt morphine withdrawal in rats assayed by remote computerized quantification of multiple motor behavior indices.**
  Author(s): Dougherty PM, Dong WQ, Faillace LA, Dafny N.
  Source: European Journal of Pharmacology. 1990 January 10; 175(2): 187-95.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2311653&dopt=Abstract

- **Transcutaneous electrical acupoint stimulation potentiates analgesic effect of morphine.**
  Author(s): Yuan CS, Attele AS, Dey L, Lynch JP, Guan X.
  Source: Journal of Clinical Pharmacology. 2002 August; 42(8): 899-903.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12162472&dopt=Abstract

- **Transcutaneous electrical stimulation with Limoge current potentiates morphine analgesia and attenuates opiate abstinence syndrome.**
  Author(s): Auriacombe M, Tignol J, Le Moal M, Stinus L.
  Source: Biological Psychiatry. 1990 October 15; 28(8): 650-6.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2173629&dopt=Abstract

- **Urinary concentrations of morphine after the administration of herbal teas containing Papaveris fructus in relation to doping analysis.**
  Author(s): Van Thuyne W, Van Eenoo P, Delbeke FT.
  Source: Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences. 2003 March 5; 785(2): 245-51.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12554137&dopt=Abstract

- **Verapamil and morphine.**
  Author(s): Hollman A.
  Source: British Heart Journal. 1991 September; 66(3): 198.
  http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1931346&dopt=Abstract

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering CAM and related topics. The following is a representative sample:

- Alternative Medicine Foundation, Inc.: **http://www.herbmed.org/**
- AOL: **http://search.aol.com/cat.adp?id=169&layer=&from=subcats**
- Chinese Medicine: **http://www.newcenturynutrition.com/**
- drkoop.com®: **http://www.drkoop.com/InteractiveMedicine/IndexC.html**
- Family Village: **http://www.familyvillage.wisc.edu/med_altn.htm**
- Google: **http://directory.google.com/Top/Health/Alternative/**
- Healthnotes: **http://www.healthnotes.com/**

- MedWebPlus: **http://medwebplus.com/subject/Alternative_and_Complementary_Medicine**
- Open Directory Project: **http://dmoz.org/Health/Alternative/**
- HealthGate: **http://www.tnp.com/**
- WebMD®Health: **http://my.webmd.com/drugs_and_herbs**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**
- Yahoo.com: **http://dir.yahoo.com/Health/Alternative_Medicine/**

The following is a specific Web list relating to morphine; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **General Overview**

  Abdominal Wall Inflammation
  Source: Integrative Medicine Communications; www.drkoop.com

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

  Food Poisoning
  Source: Integrative Medicine Communications; www.drkoop.com

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

  Pulmonary Edema
  Source: Integrative Medicine Communications; www.drkoop.com

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

  Water Retention
  Source: Integrative Medicine Communications; www.drkoop.com

- **Herbs and Supplements**

  Asian Ginseng
  Alternative names: Panax ginseng
  Source: Integrative Medicine Communications; www.drkoop.com

  Eleuthero
  Alternative names: Siberian Ginseng, Eleuthero; Acanthopanax/Eleutherococcus senticosus Rupr. & Maxim.
  Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Ephedra
Alternative names: Ephedra sinensis, Ma huang
Source: Integrative Medicine Communications; www.drkoop.com

Ephedra Sinensis
Source: Integrative Medicine Communications; www.drkoop.com

Hydrastis
Alternative names: Goldenseal; Hydrastis canadensis L.
Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Ma Huang
Source: Integrative Medicine Communications; www.drkoop.com

Ocimum
Alternative names: Basil, Albahaca; Ocimum basilicum
Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Panax
Alternative names: Ginseng; Panax ginseng
Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Panax Ginseng
Alternative names: Asian Ginseng
Source: Integrative Medicine Communications; www.drkoop.com

Piper Nigrum
Alternative names: Black Pepper
Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Sanguinaria
Alternative names: Bloodroot; Sanguinaria canadensis L.
Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

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

Uncaria Asian
Alternative names: Asian species; Uncaria sp.
Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Withania Ashwagandha
Alternative names: Ashwagandha; Withania somnifera L.
Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

Zingiber
Alternative names: Ginger; Zingiber officinale Roscoe
Source: Alternative Medicine Foundation, Inc.; www.amfoundation.org

General References

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

CHAPTER 4. DISSERTATIONS ON MORPHINE

Overview

In this chapter, we will give you a bibliography on recent dissertations relating to morphine. We will also provide you with information on how to use the Internet to stay current on dissertations. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical dissertations that use the generic term "morphine" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on morphine, we have not necessarily excluded non-medical dissertations in this bibliography.

Dissertations on Morphine

ProQuest Digital Dissertations, the largest archive of academic dissertations available, is located at the following Web address: **http://wwwlib.umi.com/dissertations**. From this archive, we have compiled the following list covering dissertations devoted to morphine. You will see that the information provided includes the dissertation's title, its author, and the institution with which the author is associated. The following covers recent dissertations found when using this search procedure:

- **Actions of Morphine on Cholinergic Transmission: Importance in Opiate Narcotic Dependence** by Frederickson, Robert C. A; PhD from The University of Manitoba (Canada), 1971
  http://wwwlib.umi.com/dissertations/fullcit/NK11470
- **An Investigation of the Development and Expression of Sensitization to the Locomotor Activating Effects of Amphetamine and Morphine** by Vezina, Paul; PhD from Concordia University (Canada), 1988
  http://wwwlib.umi.com/dissertations/fullcit/NL41638
- **Analgesia Induced by Morphine or Stress an Analysis of Mechanisms** by Kelly, Sandra; PhD from McGill University (Canada), 1985
  http://wwwlib.umi.com/dissertations/fullcit/NL24064

- **Analysis and Pharmacokinetics of Morphine Studies in Children during Balanced Anaesthesia and the Postoperative Period** by Vandenberghe, Hilde M; PhD from University of Toronto (Canada), 1983
  http://wwwlib.umi.com/dissertations/fullcit/NK59869
- **Behavioral Factors in Tolerance to Morphine in the Intact Organism** by Mucha, Ronald Francis; PhD from University of Toronto (Canada), 1980
  http://wwwlib.umi.com/dissertations/fullcit/NK43686
- **Cell Division and Macromolecular Synthesis in Tetrahymena Pyriformis : the Action Tetrahydrocannabinol, Morphine, Levorphanol and Levallorphan** by McClean, Daniel K; PhD from University of Toronto (Canada), 1972
  http://wwwlib.umi.com/dissertations/fullcit/NK15409
- **C-fos Levels in Lewis and Fischer Rat Strains Following a Dose of Morphine or Cocaine Shown to Differentially Induce Conditioned Taste Aversions** by Grabus, Sheri D.; PhD from The American University, 2002, 58 pages
  http://wwwlib.umi.com/dissertations/fullcit/3035442
- **Conditioned Inhibition in a Homeostatic Response System Evidence from Pharmacological Conditioning with Naloxone and Morphine** by Greeley, Janet D; PhD from University of Toronto (Canada), 1986
  http://wwwlib.umi.com/dissertations/fullcit/NL36122
- **Dissociation of the Anatomical, Pharmacological and Phenomenological Characteristics of Circling Elicited by Morphine and Muscimol Applied to the Ventral Mesencephalon** by Holmes, Lawrence John; PhD from Concordia University (Canada), 1986
  http://wwwlib.umi.com/dissertations/fullcit/NL30705
- **Effects of D-amphetamine and Morphine on Behavior Maintained by Fixed-interval Schedules** by Johnson, Jennifer L.; PhD from West Virginia University, 2002, 85 pages
  http://wwwlib.umi.com/dissertations/fullcit/3055922
- **Effects of Morphine on Intracranial Self-stimulation the Involvement of Associative Factors and the Role of Ventral Tegmental Dopamine Neurons** by Hand, Timothy Henry; PhD from McGill University (Canada), 1985
  http://wwwlib.umi.com/dissertations/fullcit/NL24030
- **Effects of Morphine, D-amphetamine, and Food Deprivation on Temporally Organized Behavior** by Knealing, Todd William; PhD from West Virginia University, 2002, 109 pages
  http://wwwlib.umi.com/dissertations/fullcit/3055926
- **Failure to Replicate an Environmental Effect of Morphine Hydrochloride Consumption a Possible Psychopharmacogenetic Link** by Petrie, Bruce Fraser; PhD from Simon Fraser University (Canada), 1986
  http://wwwlib.umi.com/dissertations/fullcit/NL30848
- **Gabab Receptors in the Ventral Tegmental Area Regulate Morphine-induced Motor Sensitization and Accumbal Fos Expression in C57bl/6 Mice** by Leite-Morris, Kimberly Anne; PhD from University of Rhode Island, 2002, 114 pages
  http://wwwlib.umi.com/dissertations/fullcit/3053112
- **Microiontophoretic Studies of Neurotransmitters and Morphine on Cat Spinal Cord Sensory Interneurones** by Dostrovsky, Jonathan Olifant; PhD from University of Toronto (Canada), 1974
  http://wwwlib.umi.com/dissertations/fullcit/NK31201

- **Modulation of Spinal Morphine Analgesia and Tolerance by Ultra-low Doses of Competitive and Functional Opioid Receptor Antagonists** by Abul-Husn, Noura Serene; MSC from Queen's University at Kingston (Canada), 2002, 99 pages
http://wwwlib.umi.com/dissertations/fullcit/MQ69341
- **Morphine Dependence in Rats** by Faveri, Mario Rinaldo; AdvDeg from The University of Western Ontario (Canada), 1968
http://wwwlib.umi.com/dissertations/fullcit/NK02973
- **Morphine Levels in Brain Tissue of Heroin Addicts** by Pare; Eileen Mercedes; PhD from University of Windsor (Canada), 1983
http://wwwlib.umi.com/dissertations/fullcit/NK62017
- **Morphine-induced Alterations of Tumor Cell Activity, and Tumor Cell-endothelial Cell Interactions: the Role of Nitric Oxide** by Chang, Jungshan; PhD from City University of New York, 2002, 145 pages
http://wwwlib.umi.com/dissertations/fullcit/3063814
- **Ontogeny of Glutamate Receptors Mediated Morphine Tolerance and Withdrawal in Rats** by Zhu, Hongbo; PhD from City University of New York, 2002, 249 pages
http://wwwlib.umi.com/dissertations/fullcit/3047281
- **Opioid Drug Discrimination: Characterization of the Morphine Stimulus** by Stevenson, Glenn William; PhD from The American University, 2002, 79 pages
http://wwwlib.umi.com/dissertations/fullcit/3048288
- **Pharmacology of Morphine Esters** by Owen, James Alexander; PhD from Queen's University at Kingston (Canada), 1982
http://wwwlib.umi.com/dissertations/fullcit/NK59020
- **Prenatal Morphine Exposure Alters Hippocampal Opioids and Seizures** by Schindler, Cheryl J.; PhD from Yeshiva University, 2002, 262 pages
http://wwwlib.umi.com/dissertations/fullcit/3051567
- **Regulation Ofmu Opiate Receptors by Endomorphin-1 and Morphine in Sh-sy5y Human Neuroblastoma Cells** by Horner, Kristen Ashley; PhD from Tulane University, 2002, 94 pages
http://wwwlib.umi.com/dissertations/fullcit/3069247
- **Studies on Morphine Analgesia in an Animal Model of Tonic Pain** by Abbott, Frances V; PhD from McGill University (Canada), 1981
http://wwwlib.umi.com/dissertations/fullcit/NK51834
- **Synthesis of (-)-morphine** by Neubert, Timothy Donald; PhD from University of Delaware, 2002, 85 pages
http://wwwlib.umi.com/dissertations/fullcit/3062040
- **The Activation and Expression of Endogenous Pain Control Mechanisms in Rats Exposed to Nociceptive Stimulation under the Influence of Morphine or Naloxone Implications for Models of Environment-specific Tolerance to the Analgesic Effect of Morphine** by Rochford, Joseph; PhD from Concordia University (Canada), 1985
http://wwwlib.umi.com/dissertations/fullcit/NL30701
- **The Influence of Placental Opioid-enhancing Factor on Morphine-inhibition of Gastrointestinal Transit** by Corpening, James W., II; PhD from State University of New York at Buffalo, 2002, 75 pages
http://wwwlib.umi.com/dissertations/fullcit/3052500

- **The Interaction of Morphine and Mk-801: Studies at the Behavioral and Molecular Level** by Hoshaw, Brian Andrew; PhD from Temple University, 2002, 109 pages
  http://wwwlib.umi.com/dissertations/fullcit/3079119
- **The Involvement of Cholinergic Mechanisms in Morphine Dependency** by Koven, Sheldon Jack; PhD from The University of Manitoba (Canada), 1979
  http://wwwlib.umi.com/dissertations/fullcit/NK43080
- **The Release of Acetylcholine : Studies on the Effects of Purines, Morphine, Methylxanthines and Atropine in the Myenter Plexus of the Guinea Pig Ileum and in the Central Nervous System** by Sawynok, Jana; PhD from Queen's University at Kingston (Canada), 1978
  http://wwwlib.umi.com/dissertations/fullcit/NK34652
- **The Role of Morphine-3-glucuronide, Morphine-6-glucuronide, and Gender Differences in Morphine Analgesia in Rats and Humans** by Baker, Lanning; PhD from Idaho State University, 2002, 113 pages
  http://wwwlib.umi.com/dissertations/fullcit/3059051
- **The Role of Sensory Neurotransmitters and Their Messengers in the Development of Spinal Morphine Tolerance** by Powell, Kelly Jennifer; PhD from Queen's University at Kingston (Canada), 2002, 184 pages
  http://wwwlib.umi.com/dissertations/fullcit/NQ69393
- **The Role of Type-2 Serotonin Receptors in Morphine-produced Analgesia** by Paul, Dennis John; PhD from The University of British Columbia (Canada), 1988
  http://wwwlib.umi.com/dissertations/fullcit/NL44591
- **The Synthesis of Morphine Isomers : the Preparation of Tetracyclic Isomorphinan Lactams** by Chang, Jaw-Kang; PhD from The University of New Brunswick (Canada), 1969
  http://wwwlib.umi.com/dissertations/fullcit/NK16181
- **The Total Synthesis of a Novel Morphine Analogue** by Wernic, Dominik; PhD from The University of New Brunswick (Canada), 1981
  http://wwwlib.umi.com/dissertations/fullcit/NL22862
- **Tolerance and Physical Dependence in Morphine Addiction** by Sykes, Susan E; PhD from University of Waterloo (Canada), 1977
  http://wwwlib.umi.com/dissertations/fullcit/NK36232

Keeping Current

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

CHAPTER 5. CLINICAL TRIALS AND MORPHINE

Overview

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

Recent Trials on Morphine

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

- **Morphine Plus Marijuana in Treating Pain Caused by Bone Metastases in Patients With Breast or Prostate Cancer**

  Condition(s): recurrent prostate cancer; stage IV prostate cancer; recurrent breast cancer; stage IV breast cancer; Pain

  Study Status: This study is currently recruiting patients.

  Sponsor(s): University of California, San Francisco; National Cancer Institute (NCI)

  Purpose - Excerpt: RATIONALE: Morphine helps to relieve the pain associated with bone metastases. Marijuana may be effective in controlling pain and nausea and vomiting. Combining morphine with marijuana may provide more pain relief and may help to reduce or prevent nausea and vomiting in patients treated with opioids. PURPOSE: Clinical trial to study the effectiveness of combining morphine with marijuana in treating pain caused by bone metastases in patients who have breast or prostate cancer.

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00052871

[8] These are listed at **www.ClinicalTrials.gov**.

- **Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification 1**

  Condition(s): Heroin Dependence; Morphine Dependence; Substance Withdrawal Syndrome

  Study Status: This study is no longer recruiting patients.

  Sponsor(s): National Institute on Drug Abuse (NIDA)

  Purpose - Excerpt: Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00032955

- **Buprenorphine/Naloxone versus Clonidine For Out-patient Opiate Detoxification 1**

  Condition(s): Heroin Dependence; Morphine Dependence; Substance Withdrawal Syndrome

  Study Status: This study is no longer recruiting patients.

  Sponsor(s): National Institute on Drug Abuse (NIDA)

  Purpose - Excerpt: Buprenorphine/Naloxone versus Clonidine For Out-patient Opiate Detoxification

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00032968

- **Morphine Gel for Bedsores**

  Condition(s): Decubitus Ulcer

  Study Status: This study is no longer recruiting patients.

  Sponsor(s): National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

  Purpose - Excerpt: This study tests the effectiveness of a morphine-containing gel for reducing pain caused by pressure ulcers, also known as bedsores or pressure sores. We will apply the gel containing morphine, or the gel alone, directly onto painful pressure ulcers and compare the results.

  Phase(s): Phase I; Phase II

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00007254

- **Study of Morphine in Postoperative Infants to Allow Normal Ventilation**

  Condition(s): Infant, Newborn, Diseases; Pain

  Study Status: This study is no longer recruiting patients.

Sponsor(s): FDA Office of Orphan Products Development; Children's Hospital and Medical Center - Seattle

Purpose - Excerpt: Objectives: I. Compare nonmechanically ventilated infants who receive morphine postoperatively as intermittent intravenous bolus doses or as a continuous intravenous infusion targeted to reach a steady-state concentration. II. Assess ventilation (blood gases, continuous oximetry, and CO2 response curves) and analgesia (infant pain score) between the two treatment groups of infants. III. Compare ventilation parameters (blood gases, CO2 response curves, and time to wean from assisted mechanical ventilation) in cyanotic and acyanotic infants after thoracotomies.

Study Type: Interventional

Contact(s): see Web site below

Web Site: http://clinicaltrials.gov/ct/show/NCT00004696

- **Phase III Randomized Controlled Study of Morphine and Nortriptyline in the Management of Postherpetic Neuralgia**

  Condition(s): Pain; Herpes Zoster

  Study Status: This study is completed.

  Sponsor(s): National Center for Research Resources (NCRR); National Institute of Neurological Disorders and Stroke (NINDS); Johns Hopkins University

  Purpose - Excerpt: Objectives: I. Determine whether opioid (morphine) treatment results in better management of pain than treatment with tricyclic antidepressant (nortriptyline). II. Assess the effects the two treatments have on affective and cognitive functions. III. Determine whether the presence of psychiatric comorbidity, particularly depression, can predict the outcome of the two treatments.

  Phase(s): Phase III

  Study Type: Interventional

  Contact(s): see Web site below

  Web Site: http://clinicaltrials.gov/ct/show/NCT00004390

Keeping Current on Clinical Trials

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

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

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

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

CHAPTER 6. PATENTS ON MORPHINE

Overview

Patents can be physical innovations (e.g. chemicals, pharmaceuticals, medical equipment) or processes (e.g. treatments or diagnostic procedures). The United States Patent and Trademark Office defines a patent as a grant of a property right to the inventor, issued by the Patent and Trademark Office.[9] Patents, therefore, are intellectual property. For the United States, the term of a new patent is 20 years from the date when the patent application was filed. If the inventor wishes to receive economic benefits, it is likely that the invention will become commercially available within 20 years of the initial filing. It is important to understand, therefore, that an inventor's patent does not indicate that a product or service is or will be commercially available. The patent implies only that the inventor has "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States. While this relates to U.S. patents, similar rules govern foreign patents.

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

Patents on Morphine

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

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

example of the type of information that you can expect to obtain from a patent search on morphine:

- **Compositions and methods comprising morphine gluconate**

  Inventor(s): Romeo; Vincent D. (Massapequa Park, NY), Sileno; Anthony P. (Brookhaven, NY), Behl; Charanjit R. (Hauppauge, NY)

  Assignee(s): Nastech Pharmaceutical Company, Inc. (Hauppauge, NY)

  Patent Number: 6,225,343

  Date filed: June 16, 1999

  Abstract: The present invention relates to a pharmaceutical composition which includes **morphine** gluconate or chemical equivalent thereof. In one embodiment, the present invention includes a method of making **morphine** gluconate or chemical equivalent thereof by mixing **morphine** sulfate with sodium gluconate. The present invention also includes a method for eliciting an analgesic or anesthetic response in a mammal which includes administering a therapeutically effective amount of a pharmaceutical composition including **morphine** gluconate or chemical equivalent thereof.

  Excerpt(s): The present invention relates to compositions and methods comprising **morphine** gluconate for eliciting an analgesic or anesthetic response in a mammal. Morphine is a centrally acting narcotic analgesic that acts as an agonist primarily at mu, kappa and perhaps delta receptors in the central nervous system. By acting on these receptors, **morphine** causes analgesia and anesthesia as a result of a receptor-mediated central action on pain perception, together with a receptor-medicated modulatory effect on the central transmission of noxious sensation. Some side effects caused by **morphine** include drowsiness, respiratory depression and euphoria. Various **morphine** compositions are known in the pharmaceutical arts. For example, **morphine** sulfate is one of the most commonly prescribed **morphine** compositions. Other **morphine** compositions such as **morphine** tartrate and **morphine** lactate are disclosed in U.S. Pat. No. 5,880,132 issued to Hill and U.S. Pat. No. 5,378,474 to Morella et al. for the treatment and prevention of pain or nociception. Some polar compositions of **morphine** including morphine-3-glucuronide and morphine-6-glucuronide are disclosed in U.S. Pat. No. 5,629,011 to Illum. While these references discuss different pharmaceutical compositions of **morphine,** none disclose **morphine** gluconate or a chemically modified equivalents thereof.

  Web site: http://www.delphion.com/details?pn=US06225343__

- **Crystalline form of morphine-6-glucuronide**

  Inventor(s): Franzmair; Rudolph (Linz, AT), Koch; Andreas (Linz, AT), Rovensky; Franz (Linz, AT), Schneider; Herwig (Linz, AT)

  Assignee(s): CeNeS Ltd. (Cambridge, GB)

  Patent Number: 6,172,206

  Date filed: November 4, 1999

  Abstract: A new crystalline form of morphine-6-glucuronide, referred to as Form A, characterized by its infrared spectrum pattern and/or by its x-ray powder diffraction image, the use thereof and a process for the preparation thereof.

Excerpt(s): The invention relates to a new crystalline form of morphine-6-glucuronide (M6G), known as Form A, its use and a process for preparing it. Morphine-6-glucuronide, a metabolite of **morphine,** has a powerful analgesic effect. The preparation of morphine-6-glucuronide by Konigs-Knorr Synthesis has already been described by H. Yoshimura et al. (Chem. Pharm. Bull. 1968, 16, 2114-2119 and Tetrahedron Letters 1968, 4, 483-486), P. A. Carrupt et al. (J. Med. Chem. 1991, 34, 1272-1275) and C. Lacy et al. (Tetrahedron Letters 1995, 36, 22, 3939-3950).

Web site: http://www.delphion.com/details?pn=US06172206__

- **Dextromethorphan and oxidase inhibitor for weaning patients from narcotics and anti-depressants**

  Inventor(s): Smith; Richard A. (7569 Cabrillo Ave., La Jolla, CA 92037)

  Assignee(s): none reported

  Patent Number: 6,207,674

  Date filed: December 22, 1999

  Abstract: Patients can be helped to break free of addictive or habit-forming narcotics and anti-depressants, by treatment using two drugs. One drug is dextromethorphan (DM), which has been used for decades as an anti-tussive (cough-suppressing) drug in cough syrups. The other drug is an oxidase inhibitor which suppresses activity of a liver enzyme called cytochrome P450-2D6 (also called debrisoquin hydroxylase, sparteine monooxygenase, cytochrome P450-DB, and CYP2D6). In most patients, this oxidase enzyme rapidly degrades DM and converts it into a metabolite called dextrorphan. An oxidase inhibitor (such as quinidine) which suppresses cytochrome P450-2D6 activity increases the half-life and concentration of DM in the circulating blood. When this combined treatment was administered orally to patients who had become dependent on **morphine** and anti-depressant drugs because of chronic intractable pain, it initially helped the patients reduce their dosages of **morphine** and other drugs, including anti-depressants. When additional testing was done, the combined treatment allowed patients to entirely terminate all use of **morphine** and anti-depressants, with minimal withdrawal or other adverse effects. Importantly, these same patients received no substantial benefit from taking dm by itself, without an oxidase inhibitor. Accordingly, the combination of dextromethorphan plus an anti-oxidase drug can allow at least some patients to break entirely free of narcotics and/or anti-depressants, even after years of use for chronic pain and other medical problems, even when they are not substantially helped by dextromethorphan alone.

  Excerpt(s): This invention is in the field of pharmacology, and relates to drug treatments for reducing the dependence of patients on habit-forming and potentially addictive drugs, including narcotics and anti-depressants. The term "narcotic" as used herein has the same meaning used in standard medical reference works, such as the "more recent" definitions used in Stedman's Medical Dictionary, 26th edition (Williams & Wilkins Publ., Baltimore, 1995) and in the "Analgesics" chapter in the "Drug Evaluations" subscription service published by the American Medical Association (Chicago). Briefly, "narcotics" as used in any definition (either classical or recent) includes: (1) opiate drugs, defined as any preparation or derivative of opium, a natural mixture derived from poppy plants that includes a number of medically important and/or habit-forming or addictive drugs, including **morphine,** codeine, noscapine, papaverine, thebaine, and heroin; and, (2) opioid drugs, which includes opiates as well as various synthetic narcotic drugs having similar or related chemical structures and effects. Such synthetic

narcotics include meperidine (sold under trademarks such as DEMEROL.TM.), hydrocodone (sold under trademarks such as VICODIN.TM.), hydromorphone (sold under trademarks such as DILAUDID.TM.), propoxyphene (sold under trademarks such as DARVON.TM.), oxycodone (sold under trademarks such as PERCODAN.TM. when mixed with aspirin, or PERCOCET.TM. when mixed with acetaminophen), levorphanol, fentanyl, and methadone. Under a more recent definition that has come to be accepted within the medical profession, the term "narcotics" has been broadened somewhat, to include other synthetic drugs which have "effects that are similar to opium and its derivatives". In order for a drug to be to classified as a "narcotic", its effects must include: (1) the ability to induce "significant alteration of mood and behavior"; (2) the ability to induce a condition of "stuporous analgesia"; and (3) a substantial risk of dependence, tolerance, and/or addiction.

Web site: http://www.delphion.com/details?pn=US06207674__

- **Effervescent granules and methods for their preparation**

  Inventor(s): McGinity; James W. (Austin, TX), Robinson; Joseph R (Madison, WI)

  Assignee(s): Ethypharm, Inc. (FR)

  Patent Number: 6,488,961

  Date filed: December 21, 1999

  Abstract: Disclosed here are effervescent granules having a controllable rate of effervescence. In some embodiments, the such granules comprise an acidic agent, an alkaline agent, a pharmacologically active agent, hot-melt extrudable binder capable of forming a eutectic mixture with the acidic agent and, optionally, a plasticizer. The effervescent granules are made by a hot-melt extrusion process. The present invention also provides a thermal heat process for preparing a pharmacologically active agent containing effervescent granule. In certain aspects, the granules contain pharmacologically active agents such as narcotics, antidiarrheal agents, antiviral agents, anxiolytic agents, a cholesterol lowering agent, an alpha adrenergic blocking agent, a phenanthrene derivative. By way of example, some of the narcotics that may be included in the granules and in the process of preparing the granules include, by way of example: phenanthrene derivatives (e.g., **morphine** sulfate), and **morphine** derivatives (e.g., hydromorphone hydrochloride).

  Excerpt(s): This invention relates to an effervescent composition and a method of preparing same. More specifically, it relates to an effervescent granule having a controllable rate of effervescence, the granule being made by a hot-melt extrusion process. Effervescent granules have found a variety of uses over the years. These include dental compositions containing enzymes, contact lens cleaners, washing powder compositions, beverage sweetening tablets, chewable dentifrices, denture cleaners, surgical instrument sterilizers, effervescent candies, as well as many pharmaceutical formulations such as for analgesics, antibiotics, ergotamines, digoxin, methadone and L-dopa. Film-coated effervescent granules are known in the art. Polymers such as cellulose acetate phthalate or hydroxypropyl methylcellulose have been used. Such coatings have been introduced in order to increase tablet stability as well as to control dissolution rate and to target particular regions of the gastrointestinal tract.

  Web site: http://www.delphion.com/details?pn=US06488961__

- **Inhibition of.beta.arrestin mediated effects prolongs and potentiates opioid receptor-mediated analgesia**

  Inventor(s): Bohn; Laura M. (Durham, NC), Caron; Marc G. (Hillsborough, NC), Lefkowitz; Robert J. (Durham, NC), Lin; Fang-Tsyr (Durham, NC)

  Assignee(s): Duke University (Durham, NC)

  Patent Number: 6,528,271

  Date filed: December 22, 1999

  Abstract: The present invention provides a.beta.arrestin knockout mouse useful for screeening compounds for efficacy in controlling pain, methods of controlling pain in subjects by inhibiting binding of.beta.arrestin to phosphorylated.mu. opioid receptors, and methods of screening a compound for activity in potentiating.mu. opioid receptor agonist activity (e.g., **morphine** activity) by determining whether or not said compound inhibits.beta.arrestin binding to a phosphorylated.mu. opioid receptor.

  Excerpt(s): The present invention concerns transgenic mice useful for screening compounds for their ability to control pain, methods of controlling pain in subjects in need thereof, methods of screening a compound for activity in controlling pain, and/or screening compounds for opioid receptor agonist activity. G protein coupled receptors (GPCRs) have important roles in mediating fundamental physiological processes such as vision, olfaction, cardiovascular function, and pain perception. Cellular communication through GPCRs requires the coordination of processes governing receptor activation, desensitization, and resensitization. However, the relative contribution of desensitization mechanisms to the overall homeostatic process still remains largely unexplored in vivo. GPCR kinases (GRKs) act to phosphorylate activated receptors and promote their interaction with.beta.arrestins. This, in turn, prevents further coupling with G proteins and disrupts normal activation of the second messenger signaling cascade. By this mechanism, GRKs and.beta.arrestins can act to dampen GPCR signaling, thereby leading to desensitization of the receptor (S. Ferguson, et al., Annu Rev Biochem 67, 653 (1998)). At least six GRKs (GRK1-6) and four arrestins (visual and cone arrestin,.beta.arrestin-1 and -2) have been discovered; however, the functional significance of such redundancy is unclear. Overexpression or inactivation of certain GRKs leads to modulation of receptor responsiveness (W. Koch, et al., Science 268, 1350 (1995); H. Rockman et al., Proc Natl Acad Sci USA 93, 9954 (1996); D. Choi et al. J Biol Chem 272, 17223 (1997); G. Iaccarino et al., Am J Physiol 275, H1298 (1998); K. Peppel, et al., J Biol Chem 272, 25425 (1997); H. Rockman, et al., J Biol Chem 273, 18180 (1998). J. Walker et al., Am J Physiol 276, R 1214 (1999)). In addition, mice that are deficient in.beta.arrestin-1 display increased cardiac contractility in response to.beta.-adrenergic receptor agonists (D. Conner et al., Circ Res 81, 1021 (1997)).

  Web site: http://www.delphion.com/details?pn=US06528271__

- **Method of reducing internal combustion engine emissions, and system for same**

  Inventor(s): Barkdoll; Michael P. (Knoxville, TN), Edgar; Bradley L. (Berkeley, CA), Holst; Mark R. (Concord, CA), Martin; Richard J. (San Jose, CA), Stilger; John D. (San Jose, CA), Young; John D. (Falkirk, GB)

  Assignee(s): Thermatrix, Inc. (San Jose, CA)

  Patent Number: 6,003,305

  Date filed: September 2, 1997

Abstract: A process is provided for preparing oxymorphone from **morphine** by:(1) reacting **morphine** with (1a) an acyl halide or anhydride to form 3-acylmorphine, or (1b) reacting **morphine** with benzyl-halide to form 3-benzylmorphine;(2) Oxidizing the 6-hydroxy group of the 3-acyl or 3-benzylmorphine so as to form the corresponding 3-acyl or 3-benzylmorphinone; and thereafter either by (3a) or (3b):(3a) introducing a.beta.-oriented hydroxy group at the 14-position of the 3-acyl- or 3-benzyl-morphinone with aqueous hydrogen peroxide and an acid at a temperature of about 15.degree. to about 70.degree. C. to form the 3-acyl or 3-benzyl-14-hydroxymorphinone;(3b) acylating the 3-acyl or 3-benzyl-morphinone with an acylating agent so as to form the dienol acylate followed by oxidizing the dienol acetate to the corresponding 3-acyl or 3-benzyl-14 -hydroxymorphinone;(4) hydrogenating the 3-acyl-14-hydroxymorphinone with a catalyst so as to form the 3-acyloxymorphone;(5) hydrolyzing the 3-acyl-oxymorphone with aqueous acidic or basic solution to form oxymorphone;(6) hydrogenating the 3-benzyl-14-hydroxymorphinone with a catalyst so as to form oxymorphone.

Excerpt(s): This invention relates to reducing pollutant concentration in a process gas stream. More particularly, this invention oxidizes soot and products of incomplete combustion in internal combustion engine exhaust emissions by use of a flameless thermal oxidizer. Such emissions produce well-known harmful effects to environmental quality and human health. For example, engine soot emissions contribute to reduced atmospheric visibility and particulate fall out, and have been found to contain carcinogenic polycyclic aromatic hydrocarbons, such as naphthalene, acenaphthylene, anthracene, and chrysene. B. S. Haynes and H. G. Wagner, Soot Formation, Progress in Energy and Combustion Science, Vol. 7, at p. 229 (1990). Further, because of its particle size, the particulate matter from diesel exhaust represents a respiratory health hazard. The particle size distribution of particulate matter from diesel engine exhaust is typically 80% minus 10 microns, and 77% minus one micron, based on aerodynamic particle diameter.

Web site: http://www.delphion.com/details?pn=US06003305__

- **Methods and devices for removing species**

  Inventor(s): Strahilevitz; Meir (P.O. Box 25008, Seattle, WA 98125-1908)

  Assignee(s): none reported

  Patent Number: 6,602,502

  Date filed: May 13, 1991

  Abstract: Immunoassays of psychoactive drugs including psychotomimetic drugs, narcotic drugs, and tetrahydrocannabinols and treatment methods based on the antigenic properties of protein conjugates of these drugs. These methods are based upon treating the psychoactive substances as haptens and utilizing their protein conjugates to produce antibodies to the psychoactive materials themselves. The immunoassay methods include both agglutination and agglutination-inhibition reactions. The treatment methods include treatment of both exogenous, administered drugs (such as cannabinols, LSD, heroin and morphine) endogenous substances (such as N,N-Dimethyltryptamine and 5-Methoxy-N,N-Dimethyltryptamine.

  Excerpt(s): This invention relates to improved immunoassays of psychotomimetic drugs, narcotic drugs, tetrahydrocannabinols and other psychoactive drugs. At the present time, there are certain methods used for the determination of psychotomimetic and narcotic drugs in biological materials. The techniques that are used in the present

time for the determination of drugs in biological materials, are described in detail in the Handbook of Analytical Toxicology (Irving Sunshine, Editor; The Chemical Rubber Company, Publisher; Cleveland, Ohio, 1969). They include in different combination for the different drugs: paper, thin layer and gas-liquid chromatographic methods, crystal tests, fluorescence, infrared, ultraviolet, thermal microscopy and animal pharmacology studies.

Web site: http://www.delphion.com/details?pn=US06602502__

- **Morphine and diamorphine salts of anionic non-narcotic analgesics of the substituted carboxylic acid type**

  Inventor(s): Asmussen; Bodo (Bendorf-Sayn, DE), Muller; Walter (Neuwied, DE), Riess; Walter (Ansbach, DE)

  Assignee(s): LTS Lohmann Therapie-Systeme GmbH (DE)

  Patent Number: 6,156,764

  Date filed: October 28, 1999

  Abstract: The present invention relates to **morphine** and diamorphine salts of anionic non-narcotic analgesics belonging to the type of substituted carboxylic acids, preferably the **morphine** and diamorphine salts of diclofenac (Formula 1); to processes for their production, the use of these salts in the treatment of diseases, as well as to pharmaceutical preparations comprising these salts.

  Excerpt(s): The present invention relates to **morphine** and diamorphine salts of anionic non-narcotic analgesics belonging to the type of substituted carboxylic acids, preferably the **morphine** and diamorphine salts of diclofenac (Formula 1). The present invention further relates to processes for their production, the use of these salts in the treatment of diseases, as well as to pharmaceutical preparations comprising these salts. Pain is one of the most frequent signs of a disease or a damage. Though pain is to be understood as a warning and protective function of the organism, patients concerned generally call for pain-killing or at least pain-relieving substances. For this reason, one of the most important concerns in medicine is to provide such substances. The function of these substances, so-called analgesics, is to reduce or suppress the sensation of pain when given in therapeutic doses without having a general narcotic effect in these doses. Based on their potency, therapeutic mechanism and side effects one distinguishes between two groups of analgesics: very potent analgesics acting on the central nervous system and low to moderately potent ones primarily having a peripheral action. Active substances acting on the central nervous system frequently involve a habit-forming potential which might develop into addiction. **Morphine** (Formula 3a) is one example of an active substance acting on the central nervous system and having such a risk. In the form of its inorganic salts, for example its hydrochloride or sulfate, **morphine** is commercially available for parenteral or peroral application to control acute posttraumatic or postoperative pain, as well as chronic pain, for example, in the state of advanced cancer. A derivative of **morphine,** diacetylmorphine (Formula 3b), also known as diamorphine or heroin, is dealt and consumed among drug addicts without any pharmacological, pharmaceutical, or pharmacokinetic control. Its qualified use in the treatment of drug addiction is a scientific and sociological problem that has not yet been solved.

  Web site: http://www.delphion.com/details?pn=US06156764__

- **Morphine-6-sulfate analogues and their use for the treatment of pain**

  Inventor(s): Butterfield; D. Allen (Lexington, KY), Crooks; Peter A. (Lexington, KY), Houdi; Abdulghani A. (Lexington, KY), Kottayil; Santosh G. (Schaumburg, IL)

  Assignee(s): The University of Kentucky Research Foundation (Lexington, KY)

  Patent Number: 6,403,602

  Date filed: December 31, 1997

  Abstract: 3-O-Acetylmorphine-6-sulfate analogues are potent, centrally-acting **morphine** derivatives. The compounds are useful for the treatment of pain.

  Excerpt(s): The present invention relates to 3-O-Acetylmorphine-6-sulfate compounds and their ester derivatives which are potent, centrally-acting **morphine** derivatives. The compounds are useful for the treatment of pain. The opiate analgesic **morphine,** when administered to humans, is converted by the liver into three major metabolites, viz. morphine-3-O-glucuronide (M3G), morphine-6-O-glucuronide (M6G) and morphine-3-O-sulfate (M3S) [9,19]. M6G is found in the systemic circulation in concentrations exceeding those of **morphine** itself, after both parenteral [12,19] and oral administration [12,18]. M6G is a very potent.mu.-receptor agonist [3] with a high affinity for both mu.sub.1 and mu.sub.2 receptors [1,14] and appears to cross the blood-brain barrier in spite of its high polarity compared to **morphine** [20]. Some **morphine** compounds are known in the art. For example, U.S. Pat. No. 5,219,861 to Kanematsu et al. relates to a novel morphine-6-thiol derivatives. Kanematsu discloses acetylthio-derivatives on the six position of **morphine** and esters on position three.

  Web site: http://www.delphion.com/details?pn=US06403602__

- **Mu-opiate receptor peptides**

  Inventor(s): Hackler; Laszlo (Metairie, LA), Kastin; Abba J. (Metairie, LA), Zadina; James E. (Metairie, LA)

  Assignee(s): Administrators of the Tulane Educational Fund (New Orleans, LA)

  Patent Number: 6,303,578

  Date filed: February 18, 1999

  Abstract: This invention relates to certain peptides and linear and cyclic analogs thereof that bind to the mu (morphine) opiate receptor with higher affinity, selectivity and potency than currently available peptides. This invention also relates to pharmaceutical preparations containing an effective amount of the peptides or salts thereof, and methods for providing analgesia, relief from gastrointestinal disorders such as diarrhea, and therapy for drug dependence containing a pharmaceutically effective amount of the peptides.

  Excerpt(s): This invention relates to peptides that bind with high affinity and selectivity to the mu (morphine) opiate receptor; pharmaceutical preparations containing an effective amount of the peptides or salts thereof; and methods for providing analgesia, relief from gastrointestinal disorders such as diarrhea, and therapy for drug dependence containing an effective amount of the peptides. Many peptides have been found that exhibit opiate-like activity by binding to opiate receptors. Three different types of opiate receptors have been found: delta (.delta.), kappa (.kappa.) and mu (.mu.). The major putative function for opiates is their role in alleviating pain. Other areas where opiates are well-suited for use in treatment are conditions relating to gastrointestinal disorders,

schizophrenia, obesity, blood pressure, convulsions, and seizures. Although the.delta. and.kappa. receptors may also mediate analgesia, activation of.mu. receptors is the primary and most effective means of inducing analgesia, and is the primary mechanism by which **morphine** acts. To date, opiates, opioid peptides, and analogs thereof, have demonstrated a limited degree of specificity and selectivity for the receptor or receptors to which they may bind. The less selective and specific an opiate may be, the greater the chance that increased side effects from the administration of the material will be observed. When an opiate activates more than one receptor, the biological response profile for each receptor is affected, thereby potentiating a spectrum of side effects which may or may not be adverse. Such adverse side effects include heaviness of the limbs, flush or pale complexion, clogged nasal and sinus passages, dizziness, and depression. Compounds that activate.kappa. receptors frequently induce dysphoria.

Web site: http://www.delphion.com/details?pn=US06303578__

- **Non-hydrolyzable analogs of heroin metabolites suitable for use in immunoassay**

  Inventor(s): Rouhani; Riaz (Concord, CA), Sigler; Gerald F. (Carmel, IN)

  Assignee(s): Microgenics Corporation (Fremont, CA)

  Patent Number: 6,262,265

  Date filed: June 18, 1999

  Abstract: Novel chemical analogs are disclosed for the essential heroin metabolite 6-O-acetyl **morphine** (6MAM). The analogs optionally can be made to contain protein reactive groups, and can be used to form protein conjugates, fluorescently labeled compounds, and solid-phase adsorbants. The proteins conjugates can be used in turn to raise antibodies reactive with 6MAM and having a low cross-reactivity with the closely related opiates, **morphine** and codeine. The antibodies can be used in combination with labeled analogs in exquisitely sensitive immunoassays suitable for testing for heroin abuse.

  Excerpt(s): This invention relates generally to the field of determining drug metabolites in biological samples. More specifically, it provides a system of analogs, conjugates and specific antibodies that can be used in assay systems for specific detection or quantitation of heroin abuse. Testing for heroin abuse is complicated by the fact that heroin undergoes rapid metabolism to 6-O-acetyl-morphine (also known as 6-monoacetylmorphine, 6MAM). After an intramuscular administration of heroin, 6MAM appears in urine almost immediately. Levels of 6MAM remain positive in urine for about 8 hours, as detected by standard techniques such as GC/MS (Cone et al., Anal. Toxicol. 15:1, 1991). Heroin is then broken down into **morphine,** which is a metabolite of other opiates such as codeine. A number of tests have been developed for measuring opiates in biological samples. Generally, immunoassays have been unsuccessful at discriminating between 6MAM and related compounds. Other opiate metabolites, such as morphine-3-glucuronide and morphine-6-glucuronide, may be present at levels approximately four to five orders of magnitude greater than 6MAM. Investigators have had to resort to more cumbersome and expensive techniques to determine the identity of an opiate in an unknown sample.

  Web site: http://www.delphion.com/details?pn=US06262265__

- **Oral morphine multiparticulate formulation**

  Inventor(s): Cunningham; Sean (Althone, IE), Moodley; Jagathesan (Althone, IE), Stark; Paul (Althone, IE)

  Assignee(s): Elan Corporation, plc (Dublin, IE)

  Patent Number: 6,066,339

  Date filed: November 25, 1997

  Abstract: An oral **morphine** multiparticulate formulation for once-daily administration to a patient, comprising sustained release particles each having a core containing water soluble **morphine** and an osmotic agent, the core being coated with a rate-controlling polymer coat comprised of ammonio methacrylate copolymers in an amount sufficient to achieve therapeutically effective plasma levels of **morphine** over at least 24 hours in the patient.

  Excerpt(s): This invention relates to an oral **morphine** formulation which is suitable for once-daily administration and which minimises the risk of side effects caused by **morphine** attributable to fluctuations in plasma **morphine** levels. Morphine is typically used in therapy in the form of **morphine** sulfate or a hydrate thereof. Morphine sulfate is an opioid compound with specific affinity for the receptors.mu.,.delta. and.kappa. The principal actions of therapeutic value are analgesia and sedation. The precise mechanism of the analgesic action is unknown. Specific opioid receptors have been located in the brain and the spinal cord and are likely to play a role in the expression of analgesic effects.

  Web site: http://www.delphion.com/details?pn=US06066339__

- **Papaver somniferum strain with high concentration of thebaine and oripavine**

  Inventor(s): Byrne; Christopher James (Westbury, AU), Fist; Anthony John (Norwood, AU), Gerlach; Wayne Lyle (Killara, AU)

  Assignee(s): Tasmanian Alkaloids Pty. Ltd. (AU)

  Patent Number: 6,067,749

  Date filed: July 11, 1996

  Abstract: There is disclosed an improved poppy straw of a stably reproducing Papaver somniferum for the extraction of thebaine and/or oripavine, the threshed straw having thebaine and oripavine constituting about 50% by weight or greater of the alkaloid combination consisting of **morphine,** codeine, thebaine and oripavine.

  Excerpt(s): The present invention relates to the improved production of thebaine and oripavine. More particularly, the present invention relates to the use of a mutagenized Papaver somniferum poppy plant to produce thebaine and oripavine in higher yield. In accordance with one conventional process, thebaine is oxidized to 14-hydroxycodeinone by use of m-chloroperbenzoic acid in an acetic acid/trifluoroacetic acid mixture or by a mixture of hydrogen peroxide and formic acid. 14-hydroxycodeinone is catalytically reduced to oxycodone. Oxycodone is a product sold for use as and analgesic and its production consumes large amounts of thebaine. Oxycodone can be, in turn, O-demethylated with boron tribromide to yield oxymorphone. After blocking of the hydroxyl groups with a suitable blocking agent, such as, acetyl groups, the oxymorphone derivative is reacted with cyanogen bromide in a von Braun demethylation to yield an N-cyanodihydronormorphinone derivative that is thereafter

hydrolyzed to 14-hydroxydihydronormorphinone (noroxymorphone). Noroxymorphone can be readily converted to nal-compounds by N-alkylation with appropriate alkyl halide, or acylation with appropriate acyl halide or anhydride, followed by reduction. A more generally applicable process, converts the oxycodone of the above process to noroxycodone by the von Braun N-demethylation followed by conversion to a 3-O-methyl-nal-compound using N-alkylation with an appropriate alkyl halide, or by alkylation with an appropriate alkyl halide, or acylation with appropriate acyl halide or anhydride, followed by reduction. The 3-O-methyl-nal-compound is reacted to a nal-compound by O-demethylation.

Web site: http://www.delphion.com/details?pn=US06067749__

- **Pharmaceutical composition for treating fecal incontinence**

  Inventor(s): Kamm; Michael A. (London, GB), Phillips; Robin K. S. (Northwood, GB)

  Assignee(s): S.L.A. Pharma AG (Liestal, CH)

  Patent Number: 6,635,678

  Date filed: August 24, 1999

  Abstract: Fecal incontinence and anal itch can be treated by administration, more particularly by local application to the anus, of an a adrenergic blocker, nitric oxide synthase inhibitor, prostaglandin F.sub.2.alpha., dopamine, **morphine**,.beta.-blockers, and 5-Hydroxytryptamine. The patients who benefit most from the invention are those who have a normal or low maximum anal resting pressure and a structurally intact internal anal sphincter muscle, and patients who have had major bowel resection and reanastomisis.

  Excerpt(s): This invention relates to the treatment of relief of fecal incontinence and anal itch (pruritis ani), particularly for patients who have had a major bowel resection and reanastomosis. Anal or fecal incontinence is the inability to voluntarily control the passage of feces or gas through the anus. It may occur either as fecal soiling or as rare episodes of incontinence for gas or watery stools. It is a very distressing condition that can result in self-inflicted social isolation and despair. Conventional treatments for fecal incontinence include drug therapy to improve stool consistency, such as **morphine,** loperamide and codeine phosphate to reduce gut motility, and laxatives to soften stools and relieve constipation. Biofeedback training is another treatment which involves muscle strengthening exercises to improve anal canal resting pressure, and squeeze pressure, and to teach symmetry of anal canal function. The most common form of treatment however, is surgical repair, such as the creation of a neo-sphincter which involves grafting on muscle from other parts of the anus, or a colostomy. (Gastroenterology in Practice, Summer 1995, p18-21; Dig Dis 1990; 8:179-188; and The New England Journal of Medicine, April 1992, p1002-1004). In mild cases of anal leakage, the patient will often try and plug the anus with a ball of cotton wall.

  Web site: http://www.delphion.com/details?pn=US06635678__

- **Powder-layered oral dosage forms**

  Inventor(s): Oshlack; Benjamin (New York, NY), Pedi; Frank (Yorktown Heights, NY)

  Assignee(s): Purdue Pharma L.P. (Norwalk, CT)

  Patent Number: 6,077,533

  Date filed: January 12, 1998

  Abstract: An oral dosage form of **morphine** is formulated by powder-layering an homogeneous mixture of **morphine** sulfate and hydrous lactose impalpable onto inert beads to obtain a multiparticulate product. A plurality of the powder-layered beads may be administered either in immediate release form or in an extended release form by coating with a hydrophobic material. In addition, multi-particulate oral dosage forms containing therapeutically effective agents containing a plurality of pharmaceutically acceptable inert beads powder-layered with homogeneous mixture of a therapeutically effective agent and hydrous lactose impalpable are also disclosed. A method of preparing the dosage forms as well as a method preparing spheroids containing the homogeneous mixture of therapeutically effective agent and hydrous lactose impalpable are also disclosed.

  Excerpt(s): One method of obtaining pharmaceutical products involves the use of an inert spherical bead which is coated with a drug in powder form. This technique, referred to in the art as "powder layering", generally involves the surface of the beads being coated with a binder solution, with the drug being applied onto the beads in powder form. This technique is usually suitable for the preparation of a wide range of drugs in immediate release form. Powder layering techniques are well-known in the art, and are generally considered to work best with drugs which are freely soluble in water. Such drugs may be powder-layered directly onto the surface of tacky inert beads alone, or with additional excipients. In certain instances, it is preferable to use a spheronizing agent to add in the processing (layering) of the drug onto the beads. This is the case when the drug to be powder-layered is not freely water soluble. U.S. Pat. No. 2,738,303 describes a sympathomimetic preparation which consists of small pellets coated with various thicknesses of a material slowly digestible or dispersible in the gastrointestinal tract. These pellets are prepared by placing small sugar pellets (non-pareil seeds) from 12-40 mesh in a rotating coating pan, wetting the sugar pellets using syrup U.S.P. or gelatin, and then coating them with a powder of the sympathomimetic. Thereafter, the powder-coated pellets are said to be extended by coating with a wax-fat coating such as a mixture of glyceryl monostearate and beeswax. In each of the examples, the non-pareil seeds were powder-layered to a low load (e.g., less than 50% of the total weight of the powder-layered pellet).

  Web site: http://www.delphion.com/details?pn=US06077533__

- **Preparation of codeine from morphine**

  Inventor(s): Hill; Lloyd P. (St. Louis, MO)

  Assignee(s): Mallinckrodt Inc. (St. Louis, MO)

  Patent Number: 6,579,985

  Date filed: October 21, 2002

  Abstract: An improved process for the preparation of codeine from **morphine** comprises the steps of a) reacting **morphine** with a methylating agent in the presence of a

hydrocarbon solvent at a temperature of 100 to 215.degree. C. under reflux conditions such that approximately 50% or more of the hydrocarbon solvent is returned to the reaction mixture to substantially avoid the formation of codeine methyl ether; and b) recovering codeine from the reaction mixture. The process may include step a) above followed by b) cooling the reaction mixture to approximately 85.degree. C. and adding water to terminate the reaction; c) raising the pH of the reaction mixture to approximately 11; d) separating the hydrocarbon solvent phase containing codeine and dimethylaniline; and e) adding a dilute mineral or organic acid and approximately 6 to 7 times the volume of water for each volume of hydrocarbon solvent to separate dimethylaniline and codeine.

Excerpt(s): This invention relates to the preparation of codeine from **morphine** and, more particularly, to an improved process for the preparation of codeine which provides for more complete control over the formation of the methylated by-product codeine methyl ether and for a more thorough separation of dimethylaniline and codeine. Codeine is widely used as an analgesic and is the methyl ether of **morphine.** While it occurs naturally in opium to a small extent, it has been prepared synthetically by methylation of the phenolic hydroxyl group in **morphine.** Thus, it is known to prepare codeine by the reaction of **morphine** with a methylating agent such as dimethyl sulfate or trimethylphenyl ammonium ethoxide or trimethylphenyl ammonium hydroxide in the presence of a base such as aqueous sodium hydroxide, or alcoholic sodium ethoxide. See W. R. Heumann, Bulletin on Narcotics, Vol. 10, No. 3, pp. 15-17 (1958); U.S. Pat. No. 4,764,615 and U.S. Pat. No. 6,204,337. Modified conditions of the process described by Heumann have been used commercially for some years. Currently employed processes suffer from significant yield loss, great recycle volume, high operator exposure, and extensive cycle times. The yield loss occurs partly from the current need to remove unreacted **morphine** and color bodies through precipitation, salt crystalilizations, and carbon treatment. Most of the precipitation and crystallization steps require manual digging of a centrifuge or filter. This creates much operator exposure and greater reliance on personal protection equipment. Allergic symptoms from the narcotics can result through extended exposure. Repetitive motion injuries can also occur from the manual digging.

Web site: http://www.delphion.com/details?pn=US06579985__

- **Preparation of naltrexone from codeine and 3-benzylmorphine**

  Inventor(s): Christodoulou; Aris P (New York, NY), Huang; Bao-Shan (Edison, NJ), Ji; Ben-Yi (Edison, NJ), Lu; Yansong (Edison, NJ)

  Assignee(s): Penick Corporation (Newark, NJ)

  Patent Number: 6,013,796

  Date filed: July 16, 1998

  Abstract: For the synthesis of 3-methylnaltrexone from codeine in this invention, codeine is converted to 6-acetylcodeine, which is N-demethylated to 6-acetylcodeine hydrochloride, followed by alkylating the nitrogen to form 17-cyclopropylmethylnorcodeine. The latter is oxidized to 17-cyclopropylmethylnorcodeinone. For the synthesis of naltrexone from **morphine** in this invention, **morphine** is converted to 3-benzylnormorphine as described above in the synthesis of noroxymorphone. 3-Benzylnormorphine is reacted with cyclopropylmethyl halide to produce 3-benzyl-17cyclopropylmethylnormorphine, a novel compound,

which is oxidized to 3-benzyl-17-cyclopropylmethyl-normorphinone, a novel compound, by Swern oxidation.

Excerpt(s): This invention relates in general to process for the conversion of normorphinone and its derivatives, which can be synthesized from **morphine,** to the corresponding 14-hydroxynormorphinone and its derivatives including oxycodone, oxymorphone, noroxymorphone, and naltrexone. Noroxymorphone is a key intermediate for the production of important narcotic analgesics and antagonists. In another aspect, the invention is directed to certain novel intermediates. 14-Hydroxy-substituted **morphine** derivatives are important narcotic analgesics and/or antagonists. These drugs include oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, and nalmefene. They are readily synthesized from thebaine, which is a minor component of gum opium. As the supply of thebaine is limited and the demand is increasing, therefore, the price of thebaine is high. As a result, many alternative approaches have been made for the preparation of 14-hydroxymorphine derivatives. The reported efforts for preparing these narcotics bearing a 14-hydroxy group from readily abundant starting materials **morphine** or codeine (a minor component of gum opium, which may also be synthesized by methylation of morphine) are summarized as the following: (1) the conversion of codeine to thebaine through dihydrocodeinone (5.4% yield, H. Rapoport, et al., J. Am. Chem Soc., vol. 89, 1967, p. 1942 and H. Rapoport, et al., J. Org. Chem., vol. 15, 1950, p. 1103), codeinone (20% yield, I. Seki, Chem. Pharm. Bull., vol. 18, 1970, p. 671 and H. Rapoport, et al., J. Am. Chem. Soc., vol. 77, 1955, p. 490) or 6-methyl ether of codeine (using manganese dioxide, 67% yield, R. B. Barber, et al., J. Med. Chem., vol. 18, 1975, p. 1074); (2) the oxidation of codeinone pyrrolidinyl di-enamine to 14-hydroxycodeinone (30-40% yield, I. Seki, Chem. Pharm. Bull., vol. 18, 1970, p. 671); (3) the direct allylic oxidation of codeine to the corresponding 14-hydroxy derivatives with, manganese dioxide (I. Brown, et al., J. Chem. Soc., 1960, p. 4139), and selenium dioxide plus t-butyl hydrogen peroxide (M. A. Schwartz, et al., J. Med. Chem., vol. 24, 1981, p. 1525); and (4) the six-step transformation of codeine to noroxycodone (52% yield) and noroxymorphone (43% yield) using photochemically generated singlet oxygen (M. A. Schwartz, et al., J. Med. Chem. vol. 24, 1981, p. 1525); and (5) the preparation of noroxymorphone from **morphine** through an intermediate with carbamate protection on the nitrogen atom (17-position) or a carbonate protecton at the 3 position and the carbamate protection at the 17 position of normorphinone dienol acetate with MCPBA in the substantial absence of water (37% yield, Wallace, U.S. Pat. No. 5,112,975). These processes suffer from either low yields, long steps, not amenable to scale-up, or involve the use of environmentally unfriendly heavy metals.

Web site: http://www.delphion.com/details?pn=US06013796__

- **Process for extracting and purifying morphine from opium**

  Inventor(s): Corcoran; Robert C. (Laramie, WY), Ma; Junning (North Wales, PA)

  Assignee(s): The Board of Regents of the University and Community College System of (Reno, NV)

  Patent Number: 6,054,584

  Date filed: November 19, 1996

  Abstract: A process for extracting **morphine** from opium is described. In the process, opium is extracted with a basic alcoholic solution. The basic alcoholic solution is filtered and the alcohol removed from the filtrate to leave a residue. The residue is then extracted with a basic aqueous solution having a pH of at least 11. The basic aqueous

solution may be filtered to remove any solid matter remaining after the aqueous extraction step, and then be stirred with a sufficient amount of a salt to avoid emulsion formation. The basic aqueous solution or filtrate is then extracted with benzene or toluene. Next, adjusting the pH of the basic aqueous filtrate to pH 8.5 to 9.5 allows the **morphine** to precipitate and be recovered.

Excerpt(s): This invention relates to an improved process for the extraction and purification of **morphine** from opium. The object of this invention is to provide a more economical method of preparing **morphine** that utilizes less environmentally toxic solvents. Morphine is useful as an analgesic drug. It is also used as the starting material for the preparation of codeine, which is another analgesic and antitussive drug. **Morphine** occurs naturally in opium to the extent of 9 to 17% by weight, depending upon the opium source. There are many alternative methods of extracting and purifying **morphine** from opium. However, these methods suffer from several disadvantages, such as prolonged extraction times, low efficiencies and the involvement of hazardous chemicals such as chloroform and sulfur dioxide. What is needed is a cost-effective process which does not require large amounts of potentially toxic or hazardous solvents. When viewed from this perspective, none of the current methods are entirely satisfactory.

Web site: http://www.delphion.com/details?pn=US06054584__

- **Salts of opioid analgesics, particularly morphine, and methods of using same**

  Inventor(s): Illum; Lisbeth (Nottingham, GB), Lafferty; Ian (Leicestershire, GB), Smith; Alan (Nottingham, GB), Watts; Peter (Nottingham, GB)

  Assignee(s): West Pharmaceutical Services Drug Delivery & Clinical Research Centre (Nottingham, GB)

  Patent Number: 6,387,917

  Date filed: October 19, 2000

  Abstract: The methane sulphonate salt of **morphine** and compositions thereof have medicinal uses, particularly in the treatment of pain. Compositions comprising a methane sulphonate salt of an opioid analgesic also have medicinal uses, adapted for nasal delivery.

  Excerpt(s): The present invention relates generally to new salts of opioid analgesics and more particularly to a new salt of **morphine,** which can be used in the treatment of pain following parenteral or non-parenteral administration. Morphine is an opioid analgesic that is widely used to relieve severe pain, although it is also used to a lesser extent for its cough suppressant and anti-diarrheal properties. It was first isolated from an opium extract in the early 1800's but is still used as the gold standard with which new drugs with opioid activity are compared. The drug is basic in nature, the pKa of the tertiary amine is 7.93 (Therapeutic Drugs, 2d Ed, Dollery (ed.), Churchill Livingstone, Edinburgh (1999)). Salts of **morphine,** such as the hydrochloride and, more usually, the sulphate, are available commercially. The drug can be administered by injection (intravenous, intramuscular, epidural, intra-articular, intrathecal) or by oral and rectal routes. More recently, the delivery of **morphine** via the nasal route in the form of a nasal spray or gel has been described (International Patent Application publication WO-82/03768). This route affords rapid onset of action and convenience to patients and/or the care-giver. Intranasal **morphine** has been found to be especially useful in the treatment of breakthrough pain and in the treatment of post-surgical pain.

Web site: http://www.delphion.com/details?pn=US06387917__

- **Sequential benzylic oxidations of the naloxone ring system**

  Inventor(s): Cain; Gary A. (Wilmington, DE), Drummond, Jr.; Spencer (Wilmington, DE)

  Assignee(s): Endo Pharmaceuticals, Inc. (Chadds Ford, PA)

  Patent Number: 6,166,211

  Date filed: March 7, 2000

  Abstract: The present invention pertains to a process for the preparation of the 10-keto analogs of morphinan compounds. In the case of compounds having a 3-hydroxyl group, the 3-methyl ether protected analog is synthesized by selective phenolic methylation in the presence of the basic amino group. When nalbuphine, **morphine,** or codeine is used as the starting material, the additional 6-hydroxyl group is protected using acetylation. The protected analog is selectively oxidized by treatment with cerium ammonium nitrate to provide the 10-(S)-hydroxy adduct. The 10-(S)-hydroxy adduct is further oxidized to the 10-keto analog. Any protecting groups that were added prior to oxidation are cleaved subsequent to oxidation to form the desired 10-ketomorphinan.

  Excerpt(s): This invention relates to a process for forming 10-keto derivatives of morphinan compounds. Methods have been reported in the literature for the synthesis of a small number of structurally related 10-ketomorphinans. Methods using CrO.sub.3 as an oxidant (S. Archer et al., J. Med. Chem. 28: 974-976, 1985, and H. Rapoport et al., J. Am. Chem., 77:4330-4335, 1955) suffer from extremely low yields. Methods which use SeO.sub.2 as oxidant (R. T. Uyeda et al., Tetrahedron Lett., 30:5725-5728, 1989) necessitate rendering the ring nitrogen into a non-basic amide form, thereby adding extra synthetic steps. Commonly used methods for effecting 10-oxidations use a phenolic 3-methyl ether protected analog. The classical conditions for morphinan 3-methyl ether synthesis require the highly toxic, rather volatile dimethyl sulfate in aqueous NaOH (S. Archer et al., J. Med. Chem. 28: 974-976, 1985, and H. Rapoport et al., J. Am. Chem., 77:4330-4335, 1955). Cerium ammonium nitrate (CAN) has been reported to effect benzylic oxidations on electron rich aromatic compounds in alcoholic (or HOAc) solutions to provide benzyl ether (or acetate) mono adducts (K. Isobe et al., Chem. Pharm. Bull 42: 197-1994). It is therefore an object of the present invention to apply these principals to find a useful oxidation scheme to provide the benzylic 10-hydroxyl adduct. Although CAN has been reported under certain conditions to oxidize simple toluenes to aldehydes and ketones (S. B. Lang et al., J. Chem. Soc. (C)2915, 1968 and references therein), no 10-keto adduct was observed by.sup.1 H NMR in the crude oxidation product. The 10-(S)-alcohol was readily oxidized into the 10-ketone analog with the Dess-Martin periodinane (Dess, D. B. and Martin, J. C., J. Org. Chem. 48, 4155-4158, 1983; Dess, D. B. and Martin, J. C., J. Am. Chem Soc. 113, 7277-7287, 1991; Ireland, R. E. and Liu, L., J. Org. Chem. 58, 2899, 1993; Schrieber, S. L. and Meyer, S. D., J. Org. Chem. 59, 7549-7552, 1994). These pharmaceutical compounds are related to morphinans which have effects such as analgesia, sedation, mood alteration. The 10-keto morphinan compounds are the degradation products of morphinans and may therefore be related to the age and condition of the original morphinan compounds.

  Web site: http://www.delphion.com/details?pn=US06166211__

- **Solid-phase synthesis of codeine from morphine**

  Inventor(s): Corcoran; Robert C. (Laramie, WY), Ma; Junning (North Wales, PA)

  Assignee(s): The Board of Regents of the University and Community College System of (Reno, NV)

  Patent Number: 5,981,750

  Date filed: November 19, 1996

  Abstract: The specification describes a methylation resin comprising methyl(dialkyl)anilinium salts or methyl(diaryl)anilinium salts covalently bonded to the resin. The methylation resin is used in the solid-phase synthesis of codeine from **morphine.** Accordingly, the specification describes a process for methylating **morphine** to form codeine by loading **morphine** onto a methylation resin comprising methyl(dialkyl)anilinium salts or methyl(diaryl)anilinium salts covalently bonded to the resin; contacting the loaded resin with sufficient hydrocarbon or ether solvent to cover the loaded resin; and heating the loaded resin in the hydrocarbon or ether solvent under sufficient conditions to form codeine. The methylating resin may be used to methylate phenolic moieties on other compounds and to esterify compounds containing carboxylic acid moieties.

  Excerpt(s): This invention relates to a polymeric alkylating reagent and its use in alkylation reactions. In a particular embodiment, this invention relates to a methylation resin and its use in a novel method for synthesizing codeine from **morphine.** Codeine is widely used as both an analgesic and antitussive drug. Codeine occurs naturally in opium to the extent of 0.3% to 4% depending on the source. Codeine is the methyl ether derivative of **morphine,** another naturally occurring opiate alkaloid. **Morphine** is present in opium in the range of 9% to 17% by weight. Although **morphine** is more abundant and a more potent analgesic drug than codeine, the market demand for codeine far exceeds that for **morphine.** Codeine is generally prepared by methylating **morphine.** A trimethylanilinium salt is generally used as the methylating reagent with the counter anion being ethoxide, chloride or hydroxide. The reaction is generally run in toluene or xylene, and when the counter anion is chloride the reaction must be run in the presence of an organic base, such as sodium ethoxide, to remove the proton from the phenoxy group of **morphine. Morphine** is usually first dissolved in absolute ethanol and then added to the solution of the methylating reagent in a hydrocarbon solvent. Ethanol is distilled out during the reaction.

  Web site: http://www.delphion.com/details?pn=US05981750__

- **Sublingual oral dosage form**

  Inventor(s): Ugarkovic; Sonja Jovan (Skopje, MK)

  Assignee(s): Alkaloid Ad (Skopje, MK)

  Patent Number: 6,572,891

  Date filed: September 8, 2000

  Abstract: A pharmaceutical sublingual solid dosage form comprising a **morphine** salt together with excipients including a saccharide, a binder and a disintegrant. A method of manufacturing the dosage form is also described, together with packaging suitable for long term storage of the dosage form.

Excerpt(s): This invention relates to a pharmaceutical oral dosage, particularly to a formulation for administration of a salt of **morphine** or a **morphine** derivative. In particular the present invention is concerned with a formulation containing **morphine** sulphate. Morphine is used for control of moderate to severe pain and **morphine** salts have historically been administered by different routes. Solutions or delay release oral formulations have been used for treatment of chronic pain, for example in cancer patients. However adverse effects include gastrointestinal disturbances, constipation and difficulty in establishing the correct dosage. Metabolism of **morphine** by the liver makes higher doses necessary. Controlled release formulations are difficult to administer to patients suffering from swallowing disorders. Poor absorption from controlled release buccal tablets has also been reported. Formulations containing **morphine** are well documented in the prior art.

Web site: http://www.delphion.com/details?pn=US06572891__

- **Surgical method and composition therefor**

  Inventor(s): Hurlbert; R. John (Alberta, CA), Needham; Charles W. (Norwalk, CT), Sonntag; Volker K. H. (Phoenix, AZ), Theodore; Nicholas (Phoenix, AZ)

  Assignee(s): C. R. Bard, Inc. (Murray Hill, NJ)

  Patent Number: 6,261,582

  Date filed: May 29, 1998

  Abstract: Administration of a morphine-based analgesic paste directly to the epidural space during lumbar decompressive surgery significantly improves post-operative pain control, reduces prescribed analgesic consumption, and improves overall health perception for a period of up to 6 weeks following surgery. In a series of 60 patients no treatment related complications attributable to the paste were observed. This post-operative pain control strategy may provide a new gold-standard of care patients undergoing lumbar disectomy or laminectomy.

  Excerpt(s): This invention relates to a surgical method and analgesic compositions for use in surgery. A composition of the present invention is applied during surgery to reduce pain. Following surgery, all patients experience some degree of discomfort associated with tissue dissection and removal of tissue during the surgery, at the operative site. Precise mechanisms involved in the production of pain are not fully understood. Pain management is largely composed of systemic administration of narcotics, either orally or parenterally, in the acute and convalescing postoperative state. Systemic administration can be accompanied by side effects, including nausea, vomiting, headache, dizziness, mental disturbance, sedation, constipation, respiratory depression and hypotension. Patient discomfort from pain and side effects of medication can impede patient mobilization, result in longer hospital stays and delay a person's return to normal activities such as employment. In lumbar surgery, for example, pain arises from the skin incision, dissection and retraction of paraspinal musculature, removal of bony and ligamentous structures, and from direct trauma to the neural elements. Although the relative contribution of each of these is unknown, and might well vary, it is known that local measures such as local anaesthetic infiltration or epidural block, directed towards all of the mentioned structures can reduce postoperative pain.

  Web site: http://www.delphion.com/details?pn=US06261582__

- **Sustained release compositions and a method of preparing pharmaceutical compositions**

  Inventor(s): Heafield; Joanne (Fenstanton, GB), Knott; Trevor John (Bishop's Stortford, GB), Leslie; Stewart Thomas (Cambridge, GB), Malkowska; Sandra Therese Antoinette (Ely, GB), Miller; Ronald Brown (Basel, CH), Prater; Derek Allan (Milton, GB), Smith; Kevin John (Histon, GB)

  Assignee(s): Euro-Celtique, S.A. (Petrusse, LU)

  Patent Number: 6,143,328

  Date filed: March 8, 1999

  Abstract: Sustained release pharmaceutical formulations containing **morphine,** or a pharmaceutically acceptable salt thereof, as active ingredient, suitable for administration on a once daily basis, are disclosed. In a first aspect, an orally administrable sustained release unit dosage form gives a peak plasma level at 1.0 to 6 hours after administration. In a second aspect, the formulation provides a W.sub.50 for the M-6-G metabolite for **morphine** of between 4 and 12 hours. A third aspect concerns the pharmaceutical unit dosage form obtained by compressing multiparticulates comprising a pharmaceutically active substance in a matrix of hydrophobic fusible material having a melting point of from 35 to 150.degree. C.

  Excerpt(s): This invention is concerned with improvements in and relating to sustained release compositions and, more particularly, is concerned with sustained release orally administrable dosage unit forms containing **morphine,** or a pharmaceutically acceptable salt thereof, as active ingredient. The present invention also relates generally to a method of manufacturing an orally administrable dosage form, preferably sustained release granules/multiparticulates and compressed multiparticulates, such multiparticulates having diameters ranging from 0.1 to 3.0 mm; the method of the invention provides multiparticulates in an unexpectedly high yield. Morphine is an opioid analgesic well established for use in the treatment of pain, especially moderate to severe pain. Morphine-containing compositions in sustained release form are currently commercially available as so-called "twice-a-day" formulations, that is formulations having a duration of activity of 12 hours or more and accordingly requiring to be administered twice a day.

  Web site: http://www.delphion.com/details?pn=US06143328__

- **Topical application of opioid analgesic drugs such as morphine**

  Inventor(s): Elkhoury; George F. (1561 Ramillo Ave., Long Beach, CA 90815)

  Assignee(s): none reported

  Patent Number: 6,143,278

  Date filed: February 23, 1998

  Abstract: The invention is directed to methods and pharmaceutical compositions for the topical administration of opioid analgesic drugs such as **morphine.** In particular, the invention relates to topical administration of an opioid analgesic agent, e.g., **morphine** sulfate, in admixture with a skin- or mucosal-specific penetration enhancer, to produce a localized analgesic effect in inflamed or non-inflamed skin or mucosal tissue, and without a transdermal or transmucosal migration of opioid agent, e.g., into the systemic circulation.

Excerpt(s): Morphine is the prototype of the class of opioid analgesic drugs which exert their effects by activating opioid receptors within the brain. When **morphine** is referred to individually in this application, this reference is meant to encompass other opioid drugs and is not meant to be **morphine** exclusively. Historically, narcotics have been used since the 18th century in the forms of oral or injectable **morphine** or opium in order to accomplish pain relief. **Morphine** is considered to be unsurpassed as an analgesic for severe pain. Unfortunately, **morphine** and other opioid drugs have a number of severe side effects which hamper their wide spread use and acceptance by both physicians and patients. These side effects include: addiction, nausea, inhibition of breathing, somnolence and dysphoria, all of which are mediated by morphine's action within the brain. It is still the current belief that narcotics ingested or injected will cross to the blood stream and from there go to the brain where there are **morphine** receptors. At that time, the narcotics are believed to attach to these **morphine** receptors and create a dullness of the pain but with all of the side effects described above. Of course, the worst potential effect is the addiction that can occur if the **morphine** is used beyond a few days or weeks on a continuous basis. Because of the fear of addiction, the use of **morphine** as an analgesic has been restricted. In addition, major research efforts have been directed toward the development of morphine-like drugs that act within the brain but are devoid of the side effects. The market for these other drugs has never fully materialized because these drugs were not perceived as having the same analgesic properties of **morphine** and because typically these drugs were not produced to be both available in oral and injectable formats.

Web site: http://www.delphion.com/details?pn=US06143278__

- **Transdermal delivery of buprenorphine preparations**

  Inventor(s): Hu; Oliver Yoa-Pu (Taipei, TW)

  Assignee(s): National Science Council (Taipei, TW)

  Patent Number: 6,004,969

  Date filed: October 9, 1997

  Abstract: Buprenorphine is a potent analgesic agent, it has been shown to be as effective as **morphine.** The main clinical application of buprenorphine is to relief postoperative pains or for patients in the terminal phase of cancer. The chance of becoming addiction and abuse is low, therefore it is pretty safe for clinical use. The half life of buprenorphine is short, since its hepatic extraction (extraction ratio is 0.7 to 0.9) and metabolism are high. For these reasons, oral administration of buprenorphine becomes impractical due to the need of giving drug frequiently. The present invention is related to enhancers used in transdermal preparations of narcotic analgesic agents. This invention employs pure components of Chinese herbs in a fixed ratio as transdermal penetration enhancers. Compositions of these transdermal preparations usually include 0.1 to 50% of narcotic analgesic agent, 0.1 to 70% of pure components from Chinese herb as transdermal penetration enhancers, and other necessary excipients for transdermal delivery. Studies for the present invention in nude mice revealed that a transdermal preparation containing 10% of terpineol can delivery 15 mg of buprenorphine through 10 cm.sup.2 skin area in 48 hours, which satisfied the need of practical use.

  Excerpt(s): The chemical name of Buprenorphine is 21-cyclo-propylmethyl-7-.alpha.-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14 -endoethano-6,7, 8,14-tetrahydroripavine. It is a semi-synthesized hydrophobic derivative of thebaine. It is an analgesic agent which serves as a mu-receptor agonist and a kappa receptor antagonist. Similarly to **morphine,**

buprenorphine exerts analgesic function in central nervous system(CNS). At present, the common routes for administration of marketed buprenorphine preparations include sublingual, intravenous (IV) , intramuscular (IM), and spinal injection. Oral administration of buprenorphine is impractical due to poor gastrointestinal absorption, a high hepatic extraction ratio about 0.7 to 0.9, and a high first pass effect. Transdermal delivery is a controlled drug delivery system. It controls the release of drug continuously to the surface of skin, then the drug penetrates skin and enters capillary blood circulation system. Blood circulation later brings the drug to the target organ and exerts its action. The advantage of transdermal drug delivery is its convenience and ease of removing away from skin, thus the chance of dose dumping is minimized. In general, the surface area of an adult is 2 square meter, and capillary blood flowing throughtout body surface area accounts for one third of the whole blood circulation, this offers an unique advantage for transdermal drug delivery system. In addition, transdermal drug delivery system not only avoids some side effects of traditional preparations, but also controls the release of drug. For these reasons, transdermal drug delivery system is practical in clinical use. Some physical and chemical properties of a drug, such as concentration, partition coefficient, molecular weight, and polarity may affect the efficiency of transdermal drug delivery. Other physical and chemical factors of the transdermal system, such as the polarity of the base, the solubility of drug in the base, the compositions in the preparation, and the viscosity of each component may also affect the efficiency of drug delivery. In addition, the physiological or pathological condition of the skin, lipoid membrane of the skin surface, hydration condition and the temperature of the skin, different sites of the skin, trauma, injury, and possibility of metabolism may also affect the transdermal drug delivery. At the present time, the most common problem for a transdermal drug delivery system is the lack of safe enhancers. It is proposed that the use of pure components from popular Chinese herbs as enhancers would offer a strong potential future for transdermal drug delivery system.

Web site: http://www.delphion.com/details?pn=US06004969__

- **Treatment of addiction and addiction-related behavior**

  Inventor(s): Ashby, Jr.; Charles R. (Miller Place, NY), Brodie; Jonathan D. (Cos Cob, CT), Dewey; Stephen L. (Manorville, NY)

  Assignee(s): Brookhaven Science Associates (Upton, NY)

  Patent Number: 6,541,520

  Date filed: December 11, 1998

  Abstract: The present invention provides a highly efficient method for treating substance addiction and for changing addiction-related behavior of a mammal suffering from substance addiction. The method includes administering to a mammal an effective amount of gamma vinylGABA or a pharmaceutically acceptable salt thereof. The present invention also provides a method of treatment of cocaine, **morphine,** heroin, nicotine, amphetamine, methamphetamine, or ethanol addiction by treating a mammal with an effective amount of gamma vinylGABA or a pharmaceutically acceptable salt thereof. In one embodiment, the method of the present invention includes administering to the mammal an effective amount of a composition which increases central nervous system GABA levels wherein the effective amount is sufficient to diminish, inhibit or eliminate behavior associated with craving or use of drugs of abuse. The composition includes GVG, gabapentin, valproic acid, progabide, gamma-hydroxybutyric acid,

fengabine, cetylGABA, topiramate or tiagabine or a pharmaceutically acceptable salt thereof, or an enantiomer or a racemic mixture thereof.

Excerpt(s): This invention relates to the use of an irreversible inhibitor of GABA-transaminase for the treatment of substance addiction and modification of behavior associated with substance addiction. Substance addiction, such as drug abuse, and the resulting addiction-related behavior are enormous social and economic problems that continue to grow with devastating consequences. Substance addiction can occur by use of legal and illegal substances. Nicotine, cocaine, amphetamine, methamphetamine, ethanol, heroin, **morphine** and other addictive substances are readily available and routinely used by large segments of the United States population. Many drugs of abuse are naturally occurring. For example, cocaine is a naturally occurring nonamphetamine stimulant derived from the leaves of the coca plant, Erythroylon coca. Coca leaves contain only about one-half of one percent pure cocaine alkaloid. When chewed, only relatively modest amounts of cocaine are liberated, and gastrointestinal absorption is slow. Certainly, this explains why the practice of chewing coca leaves has never been a public health problem in Latin America. The situation changes sharply with the abuse of the alkaloid itself.

Web site: http://www.delphion.com/details?pn=US06541520__

- **Use of conantokins**

Inventor(s): Layer; Richard T. (Salt Lake City, UT), McCabe; R. Tyler (Salt Lake City, UT), McIntosh; J. Michael (Salt Lake City, UT), Olivera; Baldomero M. (Salt Lake City, UT), Zhou; Li-Ming (Salt Lake City, UT)

Assignee(s): Cognetix, Inc. (Salt Lake City, UT), University of Utah Research Foundation (Salt Lake City, UT)

Patent Number: 6,172,041

Date filed: February 10, 1999

Abstract: The present invention is directed to the use of conantokin peptides, conantokin peptide derivatives and conantokin peptide chimeras, referred to collectively as conantokins, having 10-30 amino acids, including preferably two or more.gamma.-carboxyglutamic acid residues, for the treatment of neurologic and psychiatric disorders, such as anticonvulsant agents, neuroprotective agents or analgesic agents. Neurologic disorders and psychiatric disorders include epilepsy, convulsions, neurotoxic injury (associated with conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal cord trauma, myocardial infarct, physical trauma, drowning, suffocation, perinatal asphyxia, or hypoglycemic events), neurodegeneration (associated with Alzheimer's disease, senile dementia, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Parkinson's disease, Huntington's disease, Down's Syndrome, Korsakoff's disease, schizophrenia, AIDS dementia, multi-infarct dementia, Binswanger dementia and neuronal damage associated with uncontrolled seizures), chemical toxicity (such as addiction, **morphine** tolerance, opiate tolerance, opioid tolerance and barbiturate tolerance), pain (acute, chronic, migraine), anxiety, major depression, manic-depressive illness, obsessive-compulsive disorder, schizophrenia and mood disorders (such as bipolar disorder, unipolar depression, dysthymia and seasonal effective disorder) and dystonia (movement disorder), sleep disorder, muscle relaxation and urinary incontinence. In addition, the conantokins are useful for treating HIV infection, ophthalmic indications and memory, learning or cognitive deficits.

Excerpt(s): The invention relates to the use of relatively short peptides, about 10-30 residues in length, which are naturally available in minute amounts in the venom of the cone snails or analogous to the naturaly available peptides, and which include preferably one to two or more.gamma.-carboxyglutamic acid residues for the treatment of neurologic and psychiatric disorders, such as anticonvulsant agents, as neuroprotective agents or for the management of pain. The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference, and for convenience are referenced in the following text by author and date and are listed alphabetically by author in the appended bibliography. The predatory cone snails (Conus) have developed a unique biological strategy. Their venom contains relatively small peptides that are targeted to various neuromuscular receptors and may be equivalent in their pharmacological diversity to the alkaloids of plants or secondary metabolites of microorganisms. Many of these peptides are among the smallest nucleic acid-encoded translation products having defined conformations, and as such, they are somewhat unusual. Peptides in this size range normally equilibrate among many conformations. Proteins having a fixed conformation are generally much larger.

Web site: http://www.delphion.com/details?pn=US06172041__

Patent Applications on Morphine

As of December 2000, U.S. patent applications are open to public viewing.[10] Applications are patent requests which have yet to be granted. (The process to achieve a patent can take several years.) The following patent applications have been filed since December 2000 relating to morphine:

- **Detection of abused substances and their metabolites using nucleic acid sensor molecules**

  Inventor(s): Seiwert, Scott; (Pacifica, CA)

  Correspondence: Mcdonnell Boehnen Hulbert & Berghoff; 300 South Wacker Drive; Suite 3200; Chicago; IL; 60606; US

  Patent Application Number: 20030224435

  Date filed: May 16, 2003

  Abstract: Nucleic acid sensor molecules (allozymes, allosteric ribozymes, allosteric DNAzymes), aptamers and methods are provided for the detection and quantitation of small molecules, including drugs, drug analogs, and drug metabolites, for example recreational drugs, mood-altering drugs, and performance enhancing drugs such as 4-MTA (4-methylthioamphetamine), Alpha-ethyltryptamine, Amphetamine, Amyl nitrite, Benzocaine, Cocaine, Dimethyltryptamine, Ecstasy (MDA, MDMA, MDEA), Ephedrine, Erythropoietine (Epogen), Fentanyl, Gamma Hydroxybutyrate (GHB), GBL (Gamma butyrolactone), GHB (Gamma Hydroxybutyrate), Hashish, Heroin, Isobutyl nitrite, Ketamine, Lidocaine, LSD (Lysergic acid diethylamide), Mannitol, Marijuana (THC), Mescaline, Methadone, Methamphetamine, Methaqualone, Methcathinone, Methylphenidate (ritalin), **Morphine,** Nexus (2CB), Nicotine, Opium, Oxycodone, OxyContin, PCP (phencyclidine), Peyote, Phenobarbital, Procaine, Psilocybin, Psilocybin/psilocin, Pseudoephedrine, Rohypnol, Scopolamine, Steroids, Strychnine,

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

and Talwin. Also provided are kits for detection. The nucleic acid sensor molecules, methods and kits provided herein can be used in diagnositic applications for detecting drugs, analogs, and metabolites thereof.

Excerpt(s): This patent application claims the benefit of U.S. Ser. No. 60/381,006, filed May 16, 2002. This application is hereby incorporated by reference herein in its entirety including the drawings. This invention relates generally to the field of drug and drug metabolite detection in biological samples. More specifically, it provides a system for detecting or confirming the presence of a particular drug analyte in a sample that potentially contains interfering substances. This invention specifically relates to novel molecular sensors that utilize enzymatic nucleic acid constructs whose activity can be modulated by the presence or absence of signaling agents that include compounds and substances of abuse, such as recreational drugs, mood altering drugs, performance enhancing drugs, analgesics, and metabolites thereof. The present invention further relates to the use of the enzymatic nucleic acid constructs as molecular sensors capable of modulating the activity, function, or physical properties of other molecules useful in detecting compounds and substances of abuse and metabolites thereof. The invention also relates to the use of the enzymatic nucleic acid constructs as diagnostic reagents, useful in identifying such signaling agents in a variety of applications, for example, in screening biological samples or fluids for compounds and substances of abuse and metabolites thereof. The ability to perform rapid screening tests in diagnostic analysis of biological samples has been considerably facilitated by the evolving art of immunoassay. Antibodies can be raised that have exquisite specificity and sensitivity for small molecules of diagnostic interest, such as drugs and drug metabolites. In combination with other reagents that have a separating or labeling function, specific antibodies can be used as part of a rapid screening test for the presence of the small molecule in a clinical sample. Similarly, nucleic acid technology can be applied to develop polynucleotide based detection systems comprising nucleic acid molecules with high affinity for a particular small molecule target. Furthermore, the functionality of enzymatic nucleic acid molecules can be coupled with these recognition properties in the design of nucleic acid sensor molecules having both recognition and signal generating capability.

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

- **Histogranin-like peptides and non-peptides, processes for their preparation and uses thereof**

Inventor(s): Bernatchez-Lemaire, Irma; (Quebec, CA), Le, Hoang-Thanh; (Ottawa, CA), Lemaire, Simon; (Quebec, CA)

Correspondence: Gerald T. Shekleton, ESQ.; Welsh & Katz, LTD.; 22nd Floor; 120 S. Riverside Plaza; Chicago; IL; 60606; US

Patent Application Number: 20030176329

Date filed: February 7, 2002

Abstract: The invention relates to new basic amino acid derivatives of general formulae I, II and III, and the preparation and use thereof in treatment of pain. The compounds have histogranin-like antinociceptive, **morphine** potentiating and COX-2 induction modulating activities. 1wherein:A is -hydrogen, --(C.sub.1-C.sub.8)alkyl or --(C.sub.1-C.sub.8)alkyl substituted by hydroxy;B is --(C.sub.1-C.sub.6)alkylguanidino, --(C.sub.1-C.sub.6)alkyl(4-imidazo- lyl), --(C.sub.1-C.sub.6)alkylamino, p-aminophenylalkyl(C.sub.1-C.sub.6)--- , p-guanidinophenylalkyl(C.sub.1-C.sub.6)-- or 4-

pyridinylalkyl(C.sub.1-C.- sub.6)--;D is --(CO)--, --(CO)--(C.sub.1-C.sub.6)alkylene or --(C.sub.1-C.sub.6) alkylene;E is a single bond or --(C.sub.1-C.sub.6)alkylene;Z is --NH.sub.2, --NH--(C.sub.1-C.sub.6)alkylcarboxamide, --NH--(C.sub.1-C.sub.6)alkyl, --NH--(N-benzyl), --NH-cyclo(C.sub.5-C.sub.- 7)alkyl, --NH-2-(1-piperidyl)ethyl, --NH-2-(1-pyrrolidyl)ethyl, --NH-2-(1-pyridyl)ethyl, --NH-2-(morpholino)ethyl, -morpholino, -piperidyl, --OH, --(C.sub.1-C.sub.6)alkoxy, --O-benzyl or --O-halobenzyl;R.sup.1, R.sup.2 and R.sup.3 are, independent of one another, -hydrogen, -arylcarbonylamino, --(C.sub.1-C.sub.6)alkoylamino, --(C.sub.1-C.sub.6)alkylamino, --(C.sub.1-C.sub.6)alkyloxy, --(C.sub.1-C.sub.6)alkylaminocarbonyl, -carboxy, --OH, -benzoyl, -p-halogenobenzoyl, -methyl, --S-(2,4-dinitrophenyl), --S-(3-nitro-2-pyridinesulfenyl), -sulfonyl, -trifluoromethyl, --(C.sub.1-C.sub.6)alkylaminocarbonylamino, -halo or -amino;R.sup.4 and R.sup.5 are, independent of one another, -hydrogen, --(C.sub.1-C.sub.6)alkyl, -methyloxy, -nitro, -amino, -arylcarbonylamino, --(C.sub.1-C.sub.6)alkoylamino, --(C.sub.1-C.sub.6)alkylamino, -halo or --OH.

Excerpt(s): The present invention relates to pharmaceutical compounds for use in the management of pain. More particularly, it relates to histogranin-like peptides and non-peptides. Histogranin (HN, Scheme 1) (SEQ ID NO. 1), a pentadecapeptide whose structure presents 80% and 73% homologies with those of fragment-(86-100) of histone H4 (SEQ ID NO. 2) and osteogenic growth peptide (OGP) (SEQ ID NO. 3), respectively, was first isolated from extracts of bovine adrenal medulla (Lemaire, Eur. J. Pharmacol., 1993, 245, 247-256), a tissue recognized to contain various pain reducing substances, including the endogenous opioid peptides Met- and Leu-enkephalins and catecholamines (Boarder et al. J. Neurochem., 1982, 39, 149-154; Liston et al. Science, 1984, 225, 734-737). I.c.v. administration of HN (SEQ ID NO. 1) and related peptides in mice dose-and structure-dependently blocked writhing induced by i.p. administration of acetic acid and tail-flick induced by radiant heat (Lemaire et al., Soc. Neurosci. 1997, 23, 674., Ruan, Prasad and Lemaire, Pharmcol. Biochem. Behav. 2000, 66, 1-9). In addition, [Ser.sup.1]HN, a chemically stable analog of HN (SEQ ID NO. 1) (Shukla and Lemaire, Pharmcol. Biochem. Behav. 1995, 50, 49-54), blocked tonic pain in the rat formalin assay (Siegen and Sagan, Neuroreport. 1997, 8 1379-81) and attenuated hyperalgesia and allodynia caused by sciatic nerve injury (Siegan and Sagen, Brain Res. 1997, 755, 331-334) and intrathecal (i.t.) administration of N-methyl-D-aspartate (NMDA; Hama and Sagen, Pharmacol. Biochem. Behav., 1999, 62, 67-74).

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

- **Inhalable aerosol medicament for the treatment or prevention of pain**

  Inventor(s): Lecourt, Laurent; (Sevres, FR), Lemaire, Marc; (Paris, FR), Lescure, Franck; (Paris, FR)

  Correspondence: Young & Thompson; 745 South 23rd Street 2nd Floor; Arlington; VA; 22202

  Patent Application Number: 20020033174

  Date filed: August 3, 2001

  Abstract: The invention concerns the use of at least one gas in combination with at least one active product for manufacturing an inhalable medicament or part of an inhalable medicament intended for the treatment or prevention of pain in humans or animals. The gas is chosen from among helium, oxygen, nitrogen, xenon, hydrogen, carbon monoxide (CO), carbon dioxide (CO.sub.2), argon, krypton, nitrogen monoxide (NO), nitrogen protoxide (N.sub.2O), carbonated hydrocarbons, fluorocarbons and mixtures of several

of these gases. The active product is chosen from among paracetamol, acetylsalicylic acid, arylcarboxylic acid, corticosteroids, mineralosteroids, non-steroidal anti-inflammatory drugs and their derivatives, codeine and its derivatives, **morphine** and **morphine** mimetics.

Excerpt(s): The invention relates to the use of a gas or of a gas mixture, on the one hand, and of a therapeutically active product or substance, on the other hand, for manufacturing all or part of an inhalable medicament, in particular an aerosol, intended for the treatment or prevention of pain. At present, in order to fight pain, the analgesic medicament or medicinal substance is administered either by the enteral route or by the parenteral route so that it can act and either completely or partially alleviate the feeling of pain. The enteral route involves administering a product or an active substance via the patient's digestive tract, that is to say having the patient absorb or swallow by mouth the medicament, for example in the form of a powder, a pill, a tablet or a liquid; or introducing the active substance via the anus, for example in the form of a suppository.

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

- **Inhibition of betaarrestin mediated effects prolongs and potentiates opioid receptor-mediated analgesia**

  Inventor(s): Bohn, Laura M.; (Durham, NC), Caron, Marc G.; (Hillsborough, NC), Lefkowitz, Robert J.; (Durham, NC), Lin, Fang-Tsyr; (Durham, NC)

  Correspondence: Burns, Doane, Swecker & Mathis, L.L.P.; P.O. Box 1404; Alexandria; VA; 22313-1404; US

  Patent Application Number: 20030097671

  Date filed: January 3, 2003

  Abstract: The present invention provides a.beta.arrestin knockout mouse useful for screening compounds for efficacy in controlling pain, methods of controlling pain in subjects by inhibiting binding of.beta.arrestin to phosphorylated.mu. opioid receptors, and methods of screening a compound for activity in potentiating.mu. opioid receptor agonist activity (e.g., **morphine** activity) by determining whether or not said compound inhibits.beta.arrestin binding to a phosphorylated.mu. opioid receptor.

  Excerpt(s): The present invention concerns transgenic mice useful for screening compounds for their ability to control pain, methods of controlling pain in subjects in need thereof, methods of screening a compound for activity in controlling pain, and/or screening compounds for opioid receptor agonist activity. G protein coupled receptors (GPCRs) have important roles in mediating fundamental physiological processes such as vision, olfaction, cardiovascular function, and pain perception. Cellular communication through GPCRs requires the coordination of processes governing receptor activation, desensitization, and resensitization. However, the relative contribution of desensitization mechanisms to the overall homeostatic process still remains largely unexplored in vivo. GPCR kinases (GRKs) act to phosphorylate activated receptors and promote their interaction with.beta.arrestins. This, in turn, prevents further coupling with G proteins and disrupts normal activation of the second messenger signaling cascade. By this mechanism, GRKs and.beta.arrestins can act to dampen GPCR signaling, thereby leading to desensitization of the receptor (S. Ferguson, et al., Annu Rev Biochem 67, 653 (1998)). At least six GRKs (GRK1-6) and four arrestins (visual and cone arrestin,.beta.arrestin-1 and -2) have been discovered; however, the functional significance of such redundancy is unclear. Overexpression or inactivation of

certain GRKs leads to modulation of receptor responsiveness (W. Koch, et al., Science 268, 1350 (1995); H. Rockman et al., Proc Natl Acad Sci USA 93, 9954 (1996); D. Choi et al. J Biol Chem 272, 17223 (1997); G. Iaccarino et al., Am J Physiol 275, H1298 (1998); K. Peppel, et al., J Biol Chem 272, 25425 (1997); H. Rockman, et al., J Biol Chem 273, 18180 (1998). J. Walker et al., Am J Physiol 276, R1214 (1999)). In addition, mice that are deficient in.beta.arrestin-1 display increased cardiac contractility in response to.beta.-adrenergic receptor agonists (D. Conner et al., Circ Res 81, 1021 (1997)).

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

- **MC4-R as target for the identification of compounds used to treat drug addiction**

  Inventor(s): Duman, Ronald; (Guilford, CT)

  Correspondence: Anita L. Meiklejohn, PH.D.; Fish & Richardson P.C.; 225 Franklin Street; Boston; MA; 02110-2804; US

  Patent Application Number: 20030017966

  Date filed: August 23, 2002

  Abstract: The present invention relates to drug screening assays and therapeutic methods for the treatment of addictive behavior disorders, such as cocaine and **morphine** addiction utilizing the melanocortin 4-receptor (MC4-R) as the target for intervention. The invention also relates to compounds that antagonize the activity or expression of the MC4-R, and the use of such compounds in the treatment of addictive behavior disorders.

  Excerpt(s): The present invention is in the field of drug discovery to treat addictive behavior, particularly drug addiction. The present invention specifically provides drug screening assays and therapeutic methods for the treatment of addictive behavior, particularly drug addiction, involving the melanocortin 4-receptor (MC4-R). The invention also provides novel methods of using antagonists of the activity or expression of MC4-R to treat addictive disorders. It is well known that the chronic administration of opioids, cocaine and other drugs of abuse results in tolerance and, eventually, dependence. The use of cocaine, opiates, and alcohol are extremely widespread in many countries, despite the well known adverse effects of their use. Drug abuse endures as one of the major public health problems in the United States, and throughout the world. One of the core features of addictive disorders, in laboratory animals as well as in humans, is that drugs of abuse are acutely reinforcing and produce intense drug craving following chronic exposure. Behavioral and pharmacological studies have implicated the mesolimbic dopamine system (containing the ventral tegmental area [VTA] and its projections, e.g., the nucleus accumbens [NAc]) in the acute reinforcement and craving seen with opiates, cocaine, alcohol, and other drugs of abuse. An important goal of research in this area is to identify changes in this neural pathway that are caused by rugs of abuse and account for the intense craving seen with chronic drug use. Another critical goal is the identification of factors that can inhibit or reverse these changes to the neural pathway.

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

- **METHOD OF SIMULTANEOUSLY ENHANCING ANALGESIC POTENCY AND ATTENUATING DEPENDENCE LIABILITY CAUSED BY MORPHINE AND OTHER BIMODALLY-ACTING OPIOID AGONISTS**

  Inventor(s): Crain, Stanley M.; (Leonia, NJ), Shen, Ke-Fei; (Flushing, NY)

  Correspondence: Craig J. Arnold; Amster, Rothstein & Ebenstein; 90 Park Avenue; New York; NY; 10016; US

  Patent Application Number: 20020094947

  Date filed: January 3, 2002

  Abstract: This invention relates to a method for selectively enhancing the analgesic potency of a bimodally-acting opioid agonist such as **morphine** and simultaneously attenuating anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects associated with the administration of the bimodally-acting opioid agonist. The method of the present invention comprises administering to a subject an analgesic or sub-analgesic amount of a bimodally-acting opioid agonist such as **morphine** and an amount of an excitatory opioid receptor antagonist such as naltrexone or nalmefene effective to enhance the analgesic potency of the bimodally-acting opioid agonist and attenuate the anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects of the bimodally-acting opioid agonist.

  Excerpt(s): This is a continuation-in-part of copending application Ser. No. 08/276,966, filed Jul. 19, 1994, which is a continuation-in-part of application Ser. No. 08/097,460, filed Jul. 27, 1993, currently pending, which is a continuation-in-part of application Ser. No. 07/947,690, filed Sep. 19, 1992, now abandoned, the contents of which are hereby incorporated by reference in their entirety. This invention relates to a method of enhancing the analgesic (inhibitory) effects of bimodally-acting opioid agonists, including **morphine,** codeine and other clinically used opioid analgesics, while at the same time attenuating anti-analgesia, physical dependence, tolerance, hyperexcitability, hyperalgesia, and other undesirable (excitatory) side effects typically caused by chronic use of bimodally-acting opioid agonists. "Bimodally-acting opioid agonists" are opioid agonists that bind to and activate both inhibitory and excitatory opioid receptors on nociceptive neurons which mediate pain. Opioid analgesia results from activation by opioid agonists of inhibitory opioid receptors on neurons in the nociceptive (pain) pathways of the peripheral and central nervous systems. The undesirable side effects, including anti-analgesic actions, hyperexcitability and hyperalgesia, the development of physical dependence, and some types of tolerance result from sustained activation by bimodally-acting opioid agonists of excitatory opioid receptors on neurons in the nociceptive (pain) pathways of the peripheral and central nervous systems.

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

- **Method of treating pain using nalbuphine and opioid antagonists**

  Inventor(s): Levine, Jon D.; (San Francisco, CA)

  Correspondence: Townsend And Townsend And Crew; Two Embarcadero Center; Eighth Floor; San Francisco; CA; 94111-3834; US

  Patent Application Number: 20020016331

  Date filed: June 8, 2001

Abstract: Inflammatory or neuropathic pain in both men and women patients is treated by administering, sequentially or simultaneously, (a) nalbuphine and (b) an opioid antagonist selected from naloxone, naltrexone and nalmefene, or a salt or prodrug of nalbuphine and/or the opioid antagonist. Preferably, administration is made of (a) an amount of from about 3 to about 8 mg nalbuphine and (b) from about 0.2 to about 0.8 mg of an opioid antagonist selected from naloxone, naltrexone and nalmefene, or a salt and/or prodrug of either (in an amount that produces in a patient the same blood concentration of the compound in question as would administration of said amount of the nalbuphine or opioid antagonist itself).Treatment of both inflammatory and neuropathic pain can be achieved; side effects common with.mu.-opioids such as **morphine** were not observed.

Excerpt(s): This invention relates to methods and compositions for treating pain in humans using a combination of the kappa-opioid nalbuphine, in a relatively low dosage, with a low dosage of an opioid antagonist selected from naloxone, naltrexone, and nalmefene. Nalbuphine is a kappa-opioid, a member of the larger opioid group of agonists that includes many well-known agents used to relieve pain. The most well known member of this class is the mu-opioid **morphine.** Morphine, of course, is a widely known compound, administered for various purposes, including analgesia. **Morphine,** in fact, is the compound most often used to treat moderate to severe pain. However, it has known limitations. With time, patients can develop tolerance to it and/or become dependent on it or addicted to it. In addition, **morphine** can cause severe constipation.

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

- **Methods and compositions for treating addiction disorders**

  Inventor(s): Glick, Stanley D.; (Delmar, NY), Maisonneuve, Isabelle M.; (Delmar, NY)

  Correspondence: Braman & Rogalskyj, Llp; P.O. Box 352; Canandaigua; NY; 14424-0352; US

  Patent Application Number: 20020103109

  Date filed: January 18, 2002

  Abstract: A method for treating an addiction disorder (such as an addiction to or dependency on stimulants, nicotine, **morphine,** heroin, other opiates, amphetamines, cocaine, and/or alcohol) in a patient is disclosed. The method includes administering to the patient a first.alpha.sub.3.beta.sub.4 nicotinic receptor antagonist and administering to the patient a second.alpha.sub.3.beta.sub.4 nicotinic receptor antagonist. The second.alpha.sub.3.beta.sub.4 nicotinic receptor antagonist is different than the first.alpha.sub.3.beta.sub.4 nicotinic receptor antagonist, and the first.alpha.sub.3.beta.sub.4 nicotinic receptor antagonist and the second.alpha.sub.3.beta.sub.4 nicotinic receptor antagonist are administered simultaneously or non-simultaneously. Compositions which include a first.alpha.sub.3.beta.sub.4 nicotinic receptor antagonist and a second.alpha.sub.3.beta.sub.4 nicotinic receptor antagonist are also described. Examples of suitable.alpha.sub.3.beta.sub.4 nicotinic receptor antagonists for use in the present invention's methods and compositions include mecamylamine, 18-methoxycoronaridine, bupropion, dextromethorphan, dextrorphan, and phamaceutically acceptable salts and solvates thereof. A method of evaluating a compound for its effectiveness in treating addiction disorders is also described.

Excerpt(s): The present invention claims the benefit of U.S. Provisional Patent Application Serial No. 60/264,742, filed Jan. 29, 2001, which is hereby incorporated by reference. The present application relates, generally, to methods of treating addiction disorders using.alpha.sub.3.beta.sub.4 nicotinic receptor antagonists and to compositions useful in such treatments. Drug and alcohol addiction and/or abuse and/or dependency (collectively referred to herein as "addiction disorders") is extremely common. Individuals suffering from such addictions are generally subject to significant symptoms of withdrawal upon attempting to cease use of the addictive substance (whether alcohol or drugs such as cocaine, heroine, nicotine, painkillers, etc.). A number of medical therapies have been tried with differing levels of success. Unfortunately, to date, none of these methods of treatment have been very successful. For this and other reasons, a need exists for improved methods for treating addictive disorders.

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

- **MORPHINE-6-GLUCURONIDE SYNTHESIS**

  Inventor(s): Ewin, Richard Andrew; (Brighton, GB), Parsons, Philip James; (Heathfield, GB)

  Correspondence: Finnegan, Henderson, Farabow, Garrett &; Dunner Llp; 1300 I Street, NW; Washington; DC; 20006; US

  Patent Application Number: 20030083476

  Date filed: October 4, 2002

  Abstract: The invention provides a novel method for synthesising M6G, and intermediates therefor. In order to synthesise M6G the major problem to overcome is to obtain the glycoside linkage with very high.beta.-selectivity since prior methods produce the.alpha.-anomer. The invention provides a method for the preferential synthesis of the.beta.-anomer of M6G which includes the step shown in Scheme 6 wherein use of DMAP is optional.

  Excerpt(s): The invention provides a novel method for synthesising Morphine-6-Glucuronide (M6G) and intermediates therefor. Synthesis of M6G from 3-acetyl-morphine and-methyl2-.alpha.-bromo-3- ,4,5-tri-O-acetylgucuronate is described by Lacy, C., et al. (Tetrahedron Letters, 36 (22), (1995), 3949-3950). Hidetoshi, Y. er a!., (Chemical and Pharmaceutical Bulletin, JP, TOKYO, 16 (11), (1968), 2114-2119) describe synthesis of M6G by reaction of 3-acetyl-morphine with a bromo derivative of glucuronic acid to form a Methyl [3-acetyl-morphine-6-y1-2,3,4-tri-O-acetyl-.beta.-D-glucopyranosid-] uronate intermediate which is subsequently hydrolysed to M6G.

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

- **Multiple canopy**

  Inventor(s): Kazemzadeh, Farhad; (Bloomington, MN), Kriesel, Marshall S.; (St. Paul, MN), Langerud, Alan; (Plymouth, MN)

  Correspondence: James E. Brunton; Suite 860; 700 North Brand BLVD.; P. O. Box 29000; Glendale; CA; 91029; US

  Patent Application Number: 20020107480

  Date filed: December 18, 2000

  Abstract: A fluid delivery device having a self-contained stored energy membrane for expelling fluids at a precisely controlled rate, which is of a compact, laminate construction. The device is of very low profile so that it can conveniently be used for the precise delivery of a small volume of pharmaceutical fluids, such as insulin, **morphine** and the like, into an ambulatory patient at precisely controlled rates over extended periods of time. The device includes strategically configured, multiple fluid chambers to achieve the maximum possible average percent of extension of the membrane and thereby assure adequate fluid delivery pressure.

  Excerpt(s): The present invention relates generally to fluid delivery devices. More particularly, the invention concerns an improved, ultra-low profile, multiple chamber fluid delivery apparatus for precise subdermal delivery over time of medicinal liquids to an ambulatory patient, the device including novel reservoir filling means. A number of different types of liquid dispensers for dispensing medicaments to ambulatory patients have been suggested. Many of the devices seek either to improve or to replace the traditional hypodermic syringe that has been the standard for delivery of liquid medicaments such as insulin solution. Those patients that require frequent injections of the same or different amounts of medicament, find the use of the hypodermic syringe both inconvenient and unpleasant. Further, for each injection, it is necessary to first draw the injection dose into the syringe, then check the dose and, after making certain that all air has been expelled from the syringe, finally, inject the dose. This cumbersome and tedious procedure creates an unacceptable probability of debilitating complications, particularly for the elderly and the infirm.

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

- **OPIOID ANTAGONISTS AND METHODS OF THEIR USE**

  Inventor(s): BUNZOW, JAMES R.; (PORTLAND, OR), CIVELLI, OLIVIER; (IRVINE, CA), GRANDY, DAVID K.; (PORTLAND, OR), GRISEL, JUDITH E.; (PORTLAND, OR), MOGIL, JEFFREY S.; (VANCOUVER, WA), MONSMA, FREDERICK; (RIEHEN, CH), NOTHACKER, HANS-PETER; (IRVINE, CA), REINSCHEID, RAINER KLAUS; (ELLERAU, DE)

  Correspondence: Klarquist Sparkman Campbell; Leigh & Whinston Llp; One World Trade Center Suite 1600; 121 S W Salmon Street; Portland; OR; 972042988

  Patent Application Number: 20010010919

  Date filed: October 13, 1998

  Abstract: The present invention relates to a novel mammalian anti-opioid receptor protein (OFQR), peptide ligands (such as OFQ) that bind to OFQR, and methods of using the OFQ peptide and analogues to reverse the physiologic effects of opiates such as **morphine.** The isolation, characterization and pharmacological use of the

endogenous peptide ligand is described. A particular embodiment of the OFQ peptide is a heptadecapeptide having an FGGF aminoterminal motif. The peptide specifically binds to an OFQ receptor protein heterologously expressed in mammalian cells. The peptide does not bind with high affinity to.mu.,.delta. or.kappa. receptors, but it antagonizes opioid mediated effects (such as analgesia and hypothermia) without increasing nociceptive sensitivity. Tyrosine substitution variants of the peptide ligand specifically bind to the opioid receptor and can be radioiodinated. Also provided are methods of making such peptide ligands and OFQR antagonists, and methods of using the ligands for diagnostic and therapeutic uses and for the identification of other naturally-occurring or synthetic opioid receptor ligands.

Excerpt(s): This invention relates to receptors from mammalian species and ligands specific for such receptors, which are active in the antagonism of opioid action. Specifically, the invention relates to the isolation of an endogenous peptide ligand specific for a novel mammalian receptor, the recognition of its anti-opioid properties, and use of the ligand for reversing physiologic effects of opiates such as **morphine.** The invention also relates to the construction of analogues, derivatives and peptide mimetics of this endogenous mammalian receptor ligand, and their use as opiate antagonists. Specifically provided is a mammalian hypothalamus-derived endogenous opioid receptor ligand, synthetic embodiments and analogues thereof, and methods of making and using such ligands. The use (and abuse) of opiates, such as opium and **morphine,** have been known since antiquity (reviewed in Brownstein, 1993, Proc. Natl. Acad. Sci. USA 90: 5391-5393). Since the nineteenth century, chemical characterization and synthesis of many **morphine** analogues have been achieved in an effort to discover a compound having the analgesic effects of **morphine** but lacking its addictive potential. These efforts have heretofore been unsuccessful. The biology behind the reasons for the analgesic and addictive properties of **morphine** and morphine-like compounds was first elucidated by the discovery of endogenous morphine-like compounds termed enkephalins (see DiChara & North, 1992, Trends in Pharmacol. Sci. 13: 185-193 for review). Accompanying this finding of an endogenous opioid was the biochemical evidence for a family of related but distinct opiate receptors, each of which displays a unique pharmacological profile of response to opiate agonists and antagonists (see McKnight & Rees, 1991, Neurotransmissions 7: 1-6 for review). To date, four distinct opiate receptors have been described by their pharmacological profiles and anatomical distribution: these comprise the.mu.,.delta.,.kappa., and.sigma. receptors (the.sigma. receptor has been determined to be a non-opioid receptor displaying cross-reactivity with some opioid agonists).

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

- **Pharmaceutical composition for treating fecal incontinence and anal itch**

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  Patent Application Number: 20030216420

  Date filed: March 18, 2003

  Abstract: Fecal incontinence and anal itch can be treated by administration, more particularly by local application to the anus, of an a adrenergic blocker, nitric oxide synthase inhibitor, prostaglandin F.sub.2.alpha., dopamine, **morphine,**.beta.-blockers, and 5-Hydroxytryptamine. The patients who benefit most from the invention are those

who have a normal or low maximum anal resting pressure and a structurally intact internal anal sphincter muscle, and patients who have had major bowel resection and reanastomisis.

Excerpt(s): This invention relates to the treatment of relief of fecal incontinence and anal itch (pruritis ani), particularly for patients who have had a major bowel resection and reanastomosis. Anal or fecal incontinence is the inability to voluntarily control the passage of feces or gas through the anus. It may occur either as fecal soiling or as rare episodes of incontinence for gas or watery stools. It is a very distressing condition that can result in self-inflicted social isolation and despair. Conventional treatments for fecal incontinence include drug therapy to improve stool consistency, such as **morphine,** loperamide and codeine phosphate to reduce gut motility, and laxatives to soften stools and relieve constipation. Biofeedback training is another treatment which involves muscle strengthening exercises to improve anal canal resting pressure, and squeeze pressure, and to teach symmetry of anal canal function. The most common form of treatment however, is surgical repair, such as the creation of a neo-sphincter which involves grafting on muscle from other parts of the anus, or a colostomy. (Gastroenterology in Practice, Summer 1995, p18-21; Dig Dis 1990; 8:179-188; and The New England Journal of Medicine, April 1992, p1002-1004). In mild cases of anal leakage, the patient will often try and plug the anus with a ball of cotton wall.

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

- **Pharmaceutical compositions**

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  Correspondence: Mintz, Levin, Cohn, Ferris, Glovsky; And Popeo, P.C.; One Financial Center; Boston; MA; 02111; US

  Patent Application Number: 20030190290

  Date filed: May 28, 2003

  Excerpt(s): The present invention relates to compositions and dispensing devices for improved administration of fentanyl and other opioid analgesics, such as alfentanil, carfentanil, remifentanil, sufentanil, buprenorphine, **morphine,** diamorphine, and the like. Opioid analgesics are frequently used for the relief of moderate to severe pain, as well as in anaesthesia. The present invention relates primarily to the use of fentanyl and other opioid analgesics in pain management and in particular to the treatment of acute pain or "break-through" pain. Ideally, this type of pain relief has rapid onset. Fentanyl and other opioid analgesics have rapid effect following administration, making them particularly suited for the treatment of break-through pain. Nevertheless, onset of their analgesic effect can be slowed considerably if there is a delay between administration and uptake of the active agent into the blood. Such delay means that certain modes of administration are unsuitable for treatment requiring rapid onset and are therefore not to be used in the treatment of break-through pain. A particularly important consideration when administering opioid analgesics is that the doses are accurately controlled and are reproducible. Firstly, it is imperative that the patient does not over-dose. Large doses of opioid analgesics may lead to respiratory depression and some euphoric activity, which can lead to abuse and dependency. Secondly, it is undesirable for the patient to be provided with a dose which is too small, as such a dose is likely to provide inadequate pain-relief.

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

- **Pharmaceutical preparation for inhalation of an opioid**

  Inventor(s): Blom-Ross, Marianne E.; (Heemstede, NL), De Vos, Dick; (Oegstgeest, NL), Vandort, Karin; (Uithoorn, NL), Verkerk, Volcmar; (Amsterdam, NL)

  Correspondence: Browdy And Neimark, P.L.L.C.; 624 Ninth Street, NW; Suite 300; Washington; DC; 20001-5303; US

  Patent Application Number: 20010041164

  Date filed: June 11, 2001

  Abstract: The present invention relates to the inhalation of opioids, such as **morphine,** administered as a dry powder. Opioids administered as dry powder for inhalation are intended for local treatment in the respiratory tract, or for systemic treatment following absorption in the lungs and airways. Indications for opioids dry powder per inhalation include the treatment of dyspnoea and pain. Opioids as dry powder for inhalation may be administered with the use of an inhaler, which can be described as a multi-dose reservoir system such as the Cyclovent.TM., or a premetered single-dose system such as the cyclohaler.TM., or a premetered disposable system as the Disphaler.TM.

  Excerpt(s): The present invention relates to an improved pharmaceutical composition, in particular a powder composition suitable for inhalation. Numerous medicaments, especially those for the treatment of respiratory conditions such as asthma, are administered by inhalation. Since the drug acts directly on the target organ much smaller quantities of the active ingredient may be used, thereby minimising any potential side effects caused as a result of systemic absorption. The efficacy of this route of administration has been limited by the problems encountered in making appropriate and consistent dosages available to the lungs. The delivery systems currently available are pressurised metered dose inhalers, nebulisers and dry powder inhalers. Metered dose inhalers require good coordination of actuation and inhalation in order to achieve consistent dose administration; this coordination may be difficult for some patients. Nebulisers are effective but are relatively expensive and bulky and as a result are mainly used in hospitals. A variety of dry powder inhalers have been developed and, since dry powder inhalers rely on the inspiratory effect of the patient to produce a fine cloud of drug particles, the coordination problems associated with the use of metered dose inhalers do not apply.

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

- **PHARMACEUTICAL USES FOR NOS INHIBITORS**

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  Patent Application Number: 20020151572

  Date filed: August 11, 1999

  Excerpt(s): The present invention relates to new pharmaceutical uses for compounds that exhibit activity as nitric oxide synthase (NOS) inhibitors. Specifically, it relates to the use of NOS inhibitors, particularly selective neuronal NOS (N-NOS) inhibitors: (a) alone or in combination with another active agent for the treatment of psoriasis; (b) in combination with an antiinflammatory agent for the treatment of inflammatory

disorders; (c) in combination with a narcotic analgesic (e.g., opiates such as **morphine** or demerol) for the treatment of pain; (d) in combination with a serotonin-1D (5HT.sub.1D) agonist (e.g., eletriptan or sumatriptan) for the treatment of migraine, cluster or other vascular headaches; (e) alone or in combination with other active agents for the enhancement of cognition; and (f) alone or in combination with other active agents for the treatment of sleep disorders such as apnea, narcolepsy and insomnia. There are three known isoforms of NOS--an inducible form (I-NOS) and two constitutive forms referred to as, respectively, neuronal NOS (N-NOS) and endothelial NOS (E-NOS). Each of these enzymes carries out the conversion of arginine to citrulline while producing a molecule of nitric oxide (NO) in response to various stimuli. It is believed that excess nitric oxide (NO) production by NOS plays a role in the pathology of a number of disorders and conditions in mammals. For example, NO produced by I-NOS is thought to play a role in diseases that involve systemic hypotension such as toxic shock and therapy with certain cytokines. It has been shown that cancer patients treated with cytokines such as interleukin 1 (IL-1), interleukin 2 (IL-2) or tumor necrosis factor (TNF) suffer cytokine-induced shock and hypotension due to NO produced from macrophages, i.e., inducible NOS (I-NOS), see Chemical & Engineering News, December 20, p. 33, (1993). I-NOS inhibitors can reverse this. It is also believed that I-NOS plays a role in the pathology of diseases of the central nervous system such as ischemia. For example, inhibition of I-NOS has been shown to ameliorate cerebral ischemic damage in rats, see Am. J. Physiol., 268, p. R286 (1995)). Suppression of adjuvant induced arthritis by selective inhibition of I-NOS is reported in Eur. J. Pharmacol., 273, p. 15-24 (1995). NO produced by N-NOS is thought to play a role in diseases such as cerebral ischemia, pain, and opiate tolerance. For example, inhibition of N-NOS decreases infarct volume after proximal middle cerebral artery occlusion in the rat, see J. Cerebr. Blood Flow Metab., 14, p. 924-929 (1994). N-NOS inhibition has also been shown to be effective in antinociception, as evidenced by activity in the late phase of the formalin-induced hindpaw licking and acetic acid-induced abdominal constriction assays, see Br. J. Pharmacol., 110, p. 219-224 (1993). In addition, subcutaneous injection of Freund's adjuvant in the rat induces an increase in NOS-positive neurons in the spinal cord that is manifested in increased sensitivity to pain, which can be treated with NOS inhibitors, see Japanese Journal of Pharmacology, 75, p. 327-335 (1997). Finally, opioid withdrawal in rodents has been reported to be reduced by N-NOS inhibition, see Neuropsychopharmacol., 13, p. 269-293 (1995).

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

- **PRODUCTION OF THEBAINE AND ORIPAVINE**

  Inventor(s): Byrne, Christopher James; (Westbury, AU), Fist, Anthony John; (Norwood, AU), Gerlach, Wayne Lyle; (Killara, AU)

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  Patent Application Number: 20020106761

  Date filed: January 15, 2002

  Abstract: There is disclosed an improved poppy straw of a stably reproducing Papaver somniferum for the extraction of thebaine and/or oripavine, the threshed straw having thebaine and oripavine constituting about 50% by weight or greater of the alkaloid combination consisting of **morphine,** codeine, thebaine and oripavine.

Excerpt(s): The present invention relates to the improved production of thebaine and oripavine. More particularly, the present invention relates to the use of a mutagenized Papaver somniferum poppy plant to produce thebaine and oripavine in higher yield. In accordance with one conventional process, thebaine is oxidized to 14-hydroxycodeinone by use of m-chloroperbenzoic acid in an acetic acid/trifluoroacetic acid mixture or by a mixture of hydrogen peroxide and formic acid. 14-hydroxycodeinone is catalytically reduced to oxycodone. Oxycodone is a product sold for use as and analgesic and its production consumes large amounts of thebaine. Oxycodone can be, in turn, O-demethylated with boron tribromide to yield oxymorphone. After blocking of the hydroxyl groups with a suitable blocking agent, such as, acetyl groups, the oxymorphone derivative is reacted with cyanogen bromide in a von Braun demethylation to yield an N-cyanodihydronormorphinone derivative that is thereafter hydrolyzed to 14-hydroxydihydronormorphinone (noroxymorphone). Noroxymorphone can be readily converted to nal-compounds by N-alkylation with appropriate alkyl halide, or acylation with appropriate acyl halide or anhydride, followed by reduction. A more generally applicable process, converts the oxycodone of the above process to noroxycodone by the von Braun N-demethylation followed by conversion to a 3-O-methyl-nal-compound using N-alkylation with an appropriate alkyl halide, or by alkylation with an appropriate alkyl halide, or acylation with appropriate acyl halide or anhydride, followed by reduction. The 3-O-methyl-nal-compound is reacted to a nal-compound by O-demethylation.

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

- **PROKINETIC AGENTS FOR TREATING GASTRIC HYPOMOTILITY AND RELATED DISORDERS**

  Inventor(s): ANDREWS, PAUL L. R.; (LONDON, GB), WATSON, JOHN W.; (LEDYARD, CT), WOODS, ANTHONY J.; (LONDON, GB)

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  Patent Application Number: 20030176421

  Date filed: December 30, 1999

  Abstract: Stasis is treated or prevented in all or any part or parts of the stomach of a patient, especially a human patient, in need of such treatment, where said stasis results from hypomotility in the stomach, particularly gastric hypomotility with delayed emptying of the liquid and/or solid contents of the stomach. Gastric or gastrointestinal disorders are also treated which are characterized by one or more symptoms selected from pain, nausea, vomiting, heartburn, postprandial discomfort, indigestion and gastroesophageal reflux. Such treatment or prevention is achieved by administering to the patient a therapeutically effective amount of an inhibitor of phosphodiesterase-4 (PDE4), including isozyme subtypes thereof, sufficient to treat or prevent such hypomotility or gastric or gastrointestinal disorder in said patient. The PDE4 inhibitor comprises a compound of Formula (IA) or (IB): 1where in a preferred embodiment, R is cyclopentyl or cyclohexyl; R.sup.1 is (C.sub.1-C.sub.2) alkyl; one of R.sup.2.sub.a and R.sup.2.sub.b is hydrogen and the other is a substituent of partial Formula (1.0.0) above, where the dashed line represents a single bond, m is 0, R.sup.113 and R.sup.114 are in a cis relationship to each other, R.sup.113 is cyano, R.sup.115 is hydrogen, and R.sup.114 is carboxy, --CH.sub.2OH, or --CH.sub.2C(.dbd.O)NH.sub.2.Pharmaceutical compositions are also described which are useful for carrying out the above-mentioned

methods of treatment and prevention, and which are also useful in the treatment of a gastric or gastrointestinal disorder in a patient which comprises with respect to said patient, (i) a sign or concomitant of diabetic neuropathy, anorexia nervosa, achlorhydria, gastrointestinal surgery, post-surgical recovery in the period of emergence from general anesthesia; or the administration of **morphine** and morphine-like opioids; (ii) a secondary aspect of a primary disease or disorder in said patient which is organic, wherein said disease or disorder involves particularly a gastroenteric or gastroesophageal organ or tissue, or an organ or tissue of the central nervous system of said patient; or (iii) an adverse side effect of a different therapeutic agent administered to said patient in the course of treating another unrelated disease or disorder in said patient.

Excerpt(s): The method of treatment of the present invention involves a therapeutic agent having a prokinetic effect on, i.e., that promotes activity with regard to gastric motility. This type of drug is useful in treating gastric hypomotility with delayed gastric emptying of liquid and/or solid contents of the antrum (stomach), which is a component of a number of gastric or gastrointestinal disorders. The symptoms of such gastric or gastrointestinal disorders can be quite serious and include pain, nausea, vomiting, heartburn, postprandial discomfort, indigestion, and gastroesophageal reflux. In particular, the present invention relates to therapeutic agents which by various mechanisms are able to elevate cAMP in populations of neurons in the myenteric plexus, leading to release of excitatory transmitters, e.g., acetylcholine, and subsequent stimulation with resulting contraction of the smooth muscle of the antrum. The therapeutic compounds useful as active ingredients in the pharmaceutical compositions and methods of treatment of the present invention are closely related, in terms of their chemical structure and biological activity, to inhibitors of the phosphodiesterase-IV (PDE4) isoenzyme. However, to date the art has incorrectly taught that PDE4 inhibitors antagonize gastrointestinal contractile responses, suggesting their use as antikinetic agents for treating hypermotility disorders; rather than as prokinetic agents for treating gastric hypomotility, as surprisingly discovered in accordance with the present invention. The gastrointestinal system must preserve a proper balance between absorption and secretion of water and electrolytes in order to keep nutrients, wastes, electrolytes and water in a life-sustaining flux. Equally important to successful performance of this ongoing process is the maintenance along the gastrointestinal tract of the appropriate anterograde motility. Gastrointestinal motility is also known to be a key component of vomiting. This aspect of its role is important in light of the fact that some antiemetic agents have enhanced gastric emptying as a significant aspect of their actions.

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

- **Resin and its use in converting morphine to codeine**

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  Patent Application Number: 20020082357

  Date filed: October 5, 2001

  Abstract: A resin and its use as a methylating agent. One embodiment is a resin comprising a solid support and cationic methylated sulfonium, sulfoxonium, selenonium or phosphonium salts immobilized on the solid support. Another

embodiment is the use of the resin as a methylating agent, for example in the conversion of **morphine** to codeine.

Excerpt(s): This patent application claims the benefit of priority under 35 U.S.C.sctn. 119(e) to U.S. provisional application No. 60/238,697, filed on Oct. 6, 2000. The invention relates to a resin and its use as a methylating agent. One embodiment of the invention is a resin comprising a solid support and at least one cationic methylated sulfonium, sulfoxonium, selenonium or phosphonium salt immobilized on the solid support. Another embodiment of the invention is the use of the resin as a methylating agent, for example in the conversion of **morphine** to codeine. Methylation of the phenolic hydroxyl group of **morphine** produces codeine. Use of conventional methylating agents for that conversion, such as iodomethane and dimethylsulfate, suffers from the problem that the methylation may occur competitively at the nitrogen of the **morphine** molecule to give a quaternary ammonium salt. One method for avoiding this problem involves reacting **morphine** with a trimethylanilinium salt, for example in the salt's hydroxide form, to give the trimethylanilinium phenolate salt of **morphine.** Heating this salt leads to methylation of the phenolate with concomitant formation of dimethylaniline.

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

- **Sustained-release analgesic compounds**

Inventor(s): Ashton, Paul A.; (Boston, MA), Cynkowska, Grazyna; (Brookline, MA), Cynkowski, Tadeusz; (Brookline, MA), Mickunas, Edmund; (Holliston, MA), Smith, Thomas J.; (Weston, MA)

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Patent Application Number: 20030022876

Date filed: June 5, 2002

Abstract: A pharmaceutically active inventive compound comprises two independently active analgesic moieties covalently conjoined through a physiologically labile linker. A preferred embodiment comprises an opioid, such as **morphine,** covalently linked to at least one analgesic compound selected from the group consisting of an opioid or a non-opioid compound through a physiologically labile linker. Suitable covalent linkers are covalently bonded to the two independently active analgesic compounds through one or more lactone, lactam, or sulfonamido linkages. Suitable linkers include endogenous carboxylate, amido, and sulfonamido moieties, and exogenous moieties that form the aforementioned lactone, lactam or sulfonamido linkages.

Excerpt(s): The present invention relates generally to compounds, compositions, articles of manufacture and methods for treating acute or chronic pain in a mammal. In particular, the present invention relates to a sustained release system that relieves local pain, while reducing or eliminating adverse systemic side effects. The pain response is a protective reflex system, warning an individual of hostile situations and tissue injury. Although the following discussion focuses on pain management in humans, the person of skill in the art should appreciate that general concepts of pain are applicable to mammals in general, and that the concepts of pain management are applicable to veterinary medicine as well as to human medicine. Pain may be classified by etiology, duration and severity. Etiologically, pain may be classified as somatogenic (i.e. organic) or psychogenic (occurring without associated organic pathology sufficient to explain the severity and/or duration of the pain). Somatogenic pain may be further sub-classified as

nociceptive (arising out of stimulation of somatic or visceral pain-sensitive nerve fibers) or neuropathic (resulting from dysfunction of the nervous system).

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

- **System and method for intranasal administration of opioids**

  Inventor(s): Wermeling, Daniel P.; (Lexington, KY)

  Correspondence: Kalow & Springut Llp; 19th Floor; 488 Madison Avenue; New York; NY; 10022; US

  Patent Application Number: 20030077300

  Date filed: May 24, 2002

  Abstract: The invention relates to pharmaceutical drug compositions and preparations that are narcotic antagonists and analgesics, specifically opioids, more specifically **morphine** and its pharmaceutically active derivatives, analogues, homologues, and metabolites, and still more specifically hydromorphone and butorphanol. This invention also relates to pharmaceutical drug delivery devices, specifically to devices for the intranasal administration of drugs classified as controlled substances. The invention also relates to the field of acute pain management through pharmaceutical intervention, particularly as practiced in an institutional setting, such as a hospital.

  Excerpt(s): The invention relates to pharmaceutical drug compositions and preparations that are narcotic antagonists and narcotic analgesics, specifically opioids, more specifically **morphine** and its pharmaceutically active derivatives, analogues, homologues, and metabolites, and still more specifically hydromorphone and butorphanol. This invention also relates to pharmaceutical drug delivery devices, specifically to devices for the intranasal administration of drugs classified as controlled substances. The invention also relates to the field of acute pain management through pharmaceutical intervention, particularly as practiced in an institutional setting, such as a hospital. Marketers of opioids and other therapeutic compounds that act as systemic analgesics that have been approved by the U.S. Food and Drug Administration ("FDA") and long used for oral, intramuscular and/or intravenous administration, have generally not sought regulatory approval from the FDA for liquid compositions of the same therapeutic compound for intranasal administration. This is surprising since it is well-known from the literature that the intranasal administration of a pharmacologically active compound generally results in a more rapid bioavailability of the compound, or of its desired active metabolite than if the compound is administered orally. Moreover, the total quantitative dosage required to achieve the same concentration of the active compound in the bloodstream is generally less via the intranasal route compared to oral administration, because in oral administration a portion of the active compound is often converted to a non-active metabolite by passage through the GI tract and in the liver. The intranasal route of administration also provides numerous advantages over intravenous (IV) and intramuscular (IM) injections. One principal advantage of intranasal administration is convenience. An injectable system requires sterilization of the hypodermic syringe and in the institutional setting, leads to concerns among medical personnel about the risk of contracting disease if the they are accidentally stuck by a contaminated needle. Strict requirements for the safe disposal of the used needle and syringe must also be imposed in the institutional setting In contrast, intranasal administration requires little time on the part of the patient and the attending medical personnel, and is far less burdensome on the institution than injectables. There is no

significant risk of infection of medical personnel or others in the institutional setting that is associated with nasal spray devices.

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

- **Treatment of drug-induced sleepiness**

  Inventor(s): Esteve, Marc; (Saint-Maur Des Fosses, FR), Gertner, Jacques; (Paris, FR)

  Correspondence: Foley & Lardner; Washington Harbour; 3000 K Street NW Suite 500; PO Box 25696; Washington; DC; 20007-8696; US

  Patent Application Number: 20030008925

  Date filed: May 18, 2000

  Abstract: The invention concerns the use for making medicines with waking effect in conditions of disorders affecting wakefulness related to **morphine** treatment of sulphinyl benzhydryl compounds of formula (I) in which: each of the cycles is substituted by one or several groups F, Cl, Br, CF3 , NO2, NH2, C1-C4 alkyl, C1-C4 alkoxy, methylenedioxy; R is --OH, H, C1-C4 alkyl C1-C4 hydroxyalkyl, or R1R2N--Y--, where Y is a hydrocarbon radical in C1-C4 with linear or branched chain; n is a whole number equal to 1, 2 or 3; and their additive salts when R comprises a basic radical. Said medicines enable to reduce sleepiness in patients without affecting the antalgic effect of **morphine.**

  Excerpt(s): The invention relates to a new therapeutic use of benzhydrylsulphinyl derivatives. More particularly, it relates to the use of such derivatives in situations of disorders in vigilance associated with an anti-pain treatment as applied in cases of serious diseases such as cancer, or for the painful after-effects of serious conditions. About 40% of cancer patients have in fact to face pain in the course of the evolution of their disease.

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

- **Treatment of pain**

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  Correspondence: Marla J Mathias; Bristol-myers Squibb Company; Patent Department; P O Box 4000; Princeton; NJ; 08543-4000; US

  Patent Application Number: 20010016584

  Date filed: January 4, 2001

  Abstract: A method of treating pain with acetaminophen comprises the concurrent administration of buspirone. This combination of agents surprisingly results in a morphine-like analgesic response characterized by rapid onset, greater pain relief, and a longer duration of action.

  Excerpt(s): This continuation-in-part application claims priority from PCT/FR00/01817 filed Jun. 29, 2000 which claims priority from French patent application 99.08363 filed Jun. 30, 1999. This invention relates to the use of a therapeutic combination of two compounds to treat pain. The method of pain treatment comprises co-administration of buspirone with acetaminophen (paracetamol). This combination of agents produces a

more robust opioid-type analgesia providing more rapid onset and longer duration. Acetaminophen is an established analgesic agent having only weak anti-inflammatory activity and can be classified as a non-NSAID analgesic. Ibuprofen is an example of a non-steroidal analgesic having significant anti-inflammatory properties and is classified as a non-steroidal anti-inflammatory drug (NSAID). Acetaminophen is believed to relieve pain by elevation of the pain threshold and is generally given in amounts ranging from about 600 to 1300 mg per dose in humans.

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

- **USE OF MORPHINE DERIVATIVES AS MEDICAMENTS FOR THE TREATMENT OF NEUROPATHIC PROBLEMS**

  Inventor(s): Buschmann, Helmut; (Aachen, DE), Krueger, Thomas; (Langerwehe-Schlich, DE), Reiss-Mueller, Elke; (Bielefeld, DE), Strassburger, Wolfgang; (Wuerselen, DE), Wnendt, Stephan; (Aachen, DE)

  Correspondence: Crowell & Moring Llp; Intellectual Property Group; P.O. Box 14300; Washington; DC; 20044-4300; US

  Patent Application Number: 20020165247

  Date filed: February 15, 2002

  Abstract: A method for agonizing or antagonizing the ORL1 (opioid receptor-like) receptor of the nociceptin/orphanin FQ ligand ORL1 receptor system using a morphinan compound of the general formula I or derivatives thereof. Also disclosed are methods for treating neuropathic pain and/or anxiolysis and/or depression and/or diuresis and/or urinary incontinence and/or hypotension and or hypertension and/or senile dementia and/or Alzheimer's disease and/or general cognitive dysfunctions and/or tinnitus and/or impaired hearing and/or epilepsy and/or obesity and/or cachexia.

  Excerpt(s): The present application is a continuation of international patent application no. PCT/EP00/07585, filed Aug. 4, 2000, designating the United States of America, the entire disclosure of which is incorporated herein by reference. Priority is claimed based on Federal Republic of Germany patent application no. 199 39 044.4, filed Aug. 18, 1999. The present invention relates to the use of morphinan derivatives as well as their bases or salts of physiologically compatible acids as regulators for the nociceptin/orphanin FQ ligand ORL1 receptor system and for the production of a medicament. The heptadecapeptide nociceptin/orphanin FQ is an endogenous ligand of the ORL1 (opioid receptor-like) receptor (Meunier et al., Nature 377, 1995, pp. 532-535) that belongs to the family of opioid receptors and can be found in many regions of the brain and spinal cord (Mollereau et al., FEBS Letters, 341, 1994, pp. 33-38, Darland et al., Trends in Neurosciences, 21, 1998, pp. 215-221). The peptide is characterised by a high affinity, with a K.sub.d value of around 56 pM (Ardati et al., Mol. Pharmacol. 51, pp. 816-824), and by a high selectivity for the ORL1 receptor. The ORL1 receptor is homologous to the.mu.,.kappa. and.delta. opioid receptors, and the amino acid sequence of the nociceptin/orphanin FQ peptide has a strong similarity to those of the known opioid peptides. The activation of the receptor induced by nociceptin/orphanin FQ leads via the coupling with G.sub.i/o proteins to an inhibition of adenylate cyclase (Meunier et al., Nature 377, 1995, pp. 532-535) Also, at the cellular level there are functional similarities between the.mu.,.kappa. and.delta. opioid receptors and the ORL1 receptor as regards the activation of the potassium channel (Matthes et al., Mo. Pharmacol. 50, 1996, pp. 447-450; Vaughan et al., Br. J. Pharmacol. 117, 1996, pp. 1609-1611) and the

inhibition of the L, N and P/Q type calcium channels (Conner et al., Br. J. Pharmacol. 118, 1996, pp. 205-207; Knoflach et al., J. Neuroscience 16, 1996, pp. 6657-6664).

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

Keeping Current

In order to stay informed about patents and patent applications dealing with morphine, you can access the U.S. Patent Office archive via the Internet at the following Web address: **http://www.uspto.gov/patft/index.html**. You will see two broad options: (1) Issued Patent, and (2) Published Applications. To see a list of issued patents, perform the following steps: Under "Issued Patents," click "Quick Search." Then, type "morphine" (or synonyms) into the "Term 1" box. After clicking on the search button, scroll down to see the various patents which have been granted to date on morphine.

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

CHAPTER 7. BOOKS ON MORPHINE

Overview

This chapter provides bibliographic book references relating to morphine. In addition to online booksellers such as **www.amazon.com** and **www.bn.com**, excellent sources for book titles on morphine include the Combined Health Information Database and the National Library of Medicine. Your local medical library also may have these titles available for loan.

Book Summaries: Federal Agencies

The Combined Health Information Database collects various book abstracts from a variety of healthcare institutions and federal agencies. To access these summaries, go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. You will need to use the "Detailed Search" option. To find book summaries, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer. For the format option, select "Monograph/Book." Now type "morphine" (or synonyms) into the "For these words:" box. You should check back periodically with this database which is updated every three months. The following is a typical result when searching for books on morphine:

- **Drugs of Abuse, Immunity, and Infection**

  Contact: CRC Press, Incorporated, 2000 Corporate Blvd NW, Boca Raton, FL, 33431, (561) 994-0555.

  Summary: This book focuses on possible relationships among drugs of abuse, such as marijuana, **morphine,** cocaine, and alcohol, on immune response function and altered resistance to microorganisms, especially opportunistic ones. The book presents a number of literature reviews concerning various categories of drugs, immunity, and infectious diseases. The first series of chapters addresses the effects of marijuana on the immune response. The effects of opiates, including **morphine,** on infectious diseases, are described in the second set of reviews. Several reviews then describe the effects of ethanol on immunity, both in general and on bacterial infections. The final chapter explores the connection between psychiatric drugs and immunity.

Book Summaries: Online Booksellers

Commercial Internet-based booksellers, such as Amazon.com and Barnes&Noble.com, offer summaries which have been supplied by each title's publisher. Some summaries also include customer reviews. Your local bookseller may have access to in-house and commercial databases that index all published books (e.g. Books in Print®). **IMPORTANT NOTE:** Online booksellers typically produce search results for medical and non-medical books. When searching for "morphine" at online booksellers' Web sites, you may discover non-medical books that use the generic term "morphine" (or a synonym) in their titles. The following is indicative of the results you might find when searching for "morphine" (sorted alphabetically by title; follow the hyperlink to view more details at Amazon.com):

- **Advances in Morphine Therapy: The 1983 International Symposium on Pain Control** by International Symposium on Pain Control, Eric Wilkes; ISBN: 0199220077; http://www.amazon.com/exec/obidos/ASIN/0199220077/icongroupinterna
- **Chocolate to Morphine: Understanding Mind-Active Drugs** by Andrew Weil, Winifred Rosen; ISBN: 0395331900; http://www.amazon.com/exec/obidos/ASIN/0395331900/icongroupinterna
- **Drug Addiction I: Morphine Sedative-Hypnotic and Alcohol Dependence (Handbook Experimental Pharmacology Ser)** by W. R Martin; ISBN: 0387081704; http://www.amazon.com/exec/obidos/ASIN/0387081704/icongroupinterna
- **From Chocolate to Morphine : Everything You Need to Know About Mind-Altering Drugs** by Winifred Rosen (Author), Andrew T. Weil (Author); ISBN: 0395911524; http://www.amazon.com/exec/obidos/ASIN/0395911524/icongroupinterna
- **In the Arms of Morpheus: The Tragic History of Laudanum, Morphine, and Patent Medicines** by Barbara Hodgson (2001); ISBN: 1552975401; http://www.amazon.com/exec/obidos/ASIN/1552975401/icongroupinterna
- **Methods of Morphine Estimation in Biological Fluids and the Concept of Free Morphine** by J.F.B. Stuart (Editor); ISBN: 0127944354; http://www.amazon.com/exec/obidos/ASIN/0127944354/icongroupinterna
- **Micro-Dialysis As a Tool in Pharmacokinetic-Pharmacodynamic Studies Investigating the Brain Distribution and Effect Delay of Morphine and (Comprehensive Summaries of Uppsala Dissertations, 221)** by Marcel Rene Bouw (2000); ISBN: 9155446590; http://www.amazon.com/exec/obidos/ASIN/9155446590/icongroupinterna
- **Morphine** by Friedrich Glauser (Author); ISBN: 2070756122; http://www.amazon.com/exec/obidos/ASIN/2070756122/icongroupinterna
- **Morphine and Dolly Mixtures** by Carol-Ann Courtney; ISBN: 1870206096; http://www.amazon.com/exec/obidos/ASIN/1870206096/icongroupinterna
- **Morphine and the Relief of Cancer Pain: Information for Patients, Families and Friends** by Robert G. Twycross; ISBN: 0906584507; http://www.amazon.com/exec/obidos/ASIN/0906584507/icongroupinterna
- **Morphine, Ice Cream, Tears: Tales of a City Hospital** by Joseph Sacco, Sidney Williams; ISBN: 1558174397; http://www.amazon.com/exec/obidos/ASIN/1558174397/icongroupinterna
- **Oral Morphine in Advanced Cancer** by Robert Twycross (1997); ISBN: 0906584450; http://www.amazon.com/exec/obidos/ASIN/0906584450/icongroupinterna

- **Oral Morphine: Information for Patients, Families and Friends** by Robert Twycross FRCP, Sylvia Lack MB BS; ISBN: 0906584221; http://www.amazon.com/exec/obidos/ASIN/0906584221/icongroupinterna
- **The Incurable Cancer Patient at the End of Life: Medical Care Utilization, Quality of Life and the Additive Analgesic Effect of Paracetamol in Concurrent Morphine Therapy (Comprehensive Summaries of Uppsala Dissertations from the Faculty of mediciNe, 1013)** by Bertil Axelsson (2001); ISBN: 9155449689; http://www.amazon.com/exec/obidos/ASIN/9155449689/icongroupinterna
- **Year of Morphines: Poems (The National Poetry Series)** by Betsy Brown (2002); ISBN: 0807127833; http://www.amazon.com/exec/obidos/ASIN/0807127833/icongroupinterna

The National Library of Medicine Book Index

The National Library of Medicine at the National Institutes of Health has a massive database of books published on healthcare and biomedicine. Go to the following Internet site, **http://locatorplus.gov/**, and then select "Search LOCATORplus." Once you are in the search area, simply type "morphine" (or synonyms) into the search box, and select "books only." From there, results can be sorted by publication date, author, or relevance. The following was recently catalogued by the National Library of Medicine:[11]

- **Effect of biogenic amines and related drugs on morphine analgesia in rabbits** Author: Saarnivaara, Laila.; Year: 1940; Helsinki: [s.n.], 1969
- **Hair morphine concentrations of fatal heroin overdose cases and living heroin users** Author: Darke, Shane.; Year: 1954; [New South Wales, Aust.?]: National Drug and Alcohol Research Centre, c2000; ISBN: 0733406831
- **Methods of morphine estimation in biological fluids and the concept of free morphine** Author: Stuart, J. F. B. (James F. B.); Year: 1965; London: Royal Society of Medicine; New York: Grune; Stratton, 1983; ISBN: 0808915649 http://www.amazon.com/exec/obidos/ASIN/0808915649/icongroupinterna
- **Morphine & allied drugs [by] A. K. Reynolds [and] Lowell O. Randall.** Author: Reynolds, A. K.; Year: 1925; [Toronto] Univ. of Toronto Press [1957]
- **Morphine and cocaine produced by chemical synthesis; report to accompany H. R. 5561.** Author: United States. Congress. House. Committee on Ways and Means.; Year: 1953; [Washington, 1953]
- **Morphine cue saliency: limits of discriminability and third state perception by pigeons** Author: Swedberg, Michael D. B.; Year: 1965; Uppsala, Sweden: Dept. of Psychology, University of Uppsala, 1982

[11] In addition to LOCATORPlus, in collaboration with authors and publishers, the National Center for Biotechnology Information (NCBI) is currently adapting biomedical books for the Web. The books may be accessed in two ways: (1) by searching directly using any search term or phrase (in the same way as the bibliographic database PubMed), or (2) by following the links to PubMed abstracts. Each PubMed abstract has a "Books" button that displays a facsimile of the abstract in which some phrases are hypertext links. These phrases are also found in the books available at NCBI. Click on hyperlinked results in the list of books in which the phrase is found. Currently, the majority of the links are between the books and PubMed. In the future, more links will be created between the books and other types of information, such as gene and protein sequences and macromolecular structures. See **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books**.

- **Opioids and the guinea pig ileum: interrelations of calcium and endorphins with acute and chronic morphine actions** Author: Opmeer, Frederik Adriaan,; Year: 1965; [Netherlands: s.n., 1982?]
- **Oral morphine in advanced cancer** Author: Twycross, Robert G.; Year: 1936; Beaconsfield, Bucks, England: Beaconsfield Publishers, 1989; ISBN: 0906584272 http://www.amazon.com/exec/obidos/ASIN/0906584272/icongroupinterna
- **Pharmacokinetic aspects of spinal morphine analgesia** Author: Nordberg, Gunnar.; Year: 1960; Copenhagen: Munksgaard, 1984; ISBN: 8716062736
- **Stress antagonizes morphine-induced analgesia in rats. Final report** Author: Vernikos, J., Investigator, NASA center: ARC. Ames Research Center, Moffett Field, California, USA.; Year: 1983; Washington, DC: NASA Headquarters, 1981
- **The biological disposition of morphine and its surrogates [by] E. Leong Way & T. K. Adler.** Author: Way, E. Leong (Edward Leong); Year: 1962; Geneva, World Health Organization, 1962
- **The chemistry of the morphine alkaloids.** Author: Bentley, K. W. (Kenneth Walter); Year: 1957; Oxford [Eng.] Clarendon Press, 1954
- **The influence of morphine and several synthetic non-addicting morphine-like substances on pelvic colon motility in the dog and man.** Author: Wilkinson, George Richard,; Year: 1963; [Minneapolis] 1956
- **The morphine habit and its painless treatment.** Author: Scott, Frederick Gilbert Laughton,; Year: 1954; London, Lewis, 1930
- **The morphine habit, and its painless treatment.** Author: Scott, Frederick Gilbert Laughton,; Year: 1957; London, H. K. Lewis, 1937
- **Therapeutic effectiveness of methadone maintenance programs in the management of drug dependence of morphine type in the USA [by] Stephen S. Wilmarth and Avram Goldstein.** Author: Wilmarth, Stephen S.; Year: 1925; Geneva, World Health Organization, 1974; ISBN: 9241700033 http://www.amazon.com/exec/obidos/ASIN/9241700033/icongroupinterna

Chapters on Morphine

In order to find chapters that specifically relate to morphine, an excellent source of abstracts is the Combined Health Information Database. You will need to limit your search to book chapters and morphine using the "Detailed Search" option. Go to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find book chapters, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Book Chapter." Type "morphine" (or synonyms) into the "For these words:" box.

CHAPTER 8. MULTIMEDIA ON MORPHINE

Overview

In this chapter, we show you how to keep current on multimedia sources of information on morphine. We start with sources that have been summarized by federal agencies, and then show you how to find bibliographic information catalogued by the National Library of Medicine.

Video Recordings

An excellent source of multimedia information on morphine is the Combined Health Information Database. You will need to limit your search to "Videorecording" and "morphine" using the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find video productions, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Videorecording (videotape, videocassette, etc.)." Type "morphine" (or synonyms) into the "For these words:" box. The following is a typical result when searching for video recordings on morphine:

- **The AIDS Quarterly, Fall 1990: The Crisis in Poland; to Live With AIDS**

  Contact: WGBH Boston, Health Quarterly, 125 Western Ave, Allston, MA, 02134, (617) 492-2777. Public Broadcasting Service, PBS Video, 1320 Braddock Pl, Alexandria, VA, 22314-1698, (703) 739-5380.

  Summary: This videorecording, part of a series hosted by Peter Jennings, looks at the crisis in Poland due to the Acquired immunodeficiency syndrome (AIDS) epidemic. It says that Poland is a very traditional country, but that residents are being exposed to a new sight: that of Persons with AIDS (PWA's) living on the street. Most, it says, are Intravneous drug users (IVDU's). The videorecording explains that in Poland, hundreds of thousands of people are addicted to a homemade drug that is 25 percent heroin, 50 percent **morphine,** and 25 percent codeine; cheap; easy to make; and legal. However, needles are scarce, and usually shared. The Polish government doesn't allow treatment with methadone, and there are six-month waiting lists to get into "cold turkey" detoxification programs. The videorecording presents profiles of addicted and infected persons, portraying their lives as being bleak and devoid of hope. It also examines the

crisis in health care, where there is a shortage of health-care workers and little money to fund treatment for Human immunodeficiency virus (HIV) infection. It addresses issues of discrimiantion faced by PWA's and looks at the role the Catholic church in Poland plays in ministering to the epidemic. Children's views on the epidemic are studied. It also looks at the closeted lives of the country's homosexuals, who face much discrimiantion. The videorecording says that there are 10,000 registered prostitutes in Warsaw, but that many women who lose their jobs turn to prostitution without a license. Many of these people refuse to tell their clients about their HIV status. The presentation concludes with a brief meditation on living with AIDS by Edmund White, a prominent gay American writer.

Bibliography: Multimedia on Morphine

The National Library of Medicine is a rich source of information on healthcare-related multimedia productions including slides, computer software, and databases. To access the multimedia database, go to the following Web site: **http://locatorplus.gov/**. Select "Search LOCATORplus." Once in the search area, simply type in morphine (or synonyms). Then, in the option box provided below the search box, select "Audiovisuals and Computer Files." From there, you can choose to sort results by publication date, author, or relevance. The following multimedia has been indexed on morphine:

- **First aid use of morphine [motion picture]** Source: U.S. Naval Photographic Center; Year: 1959; Format: Motion picture; United States: Dept. of the Navy, 1959
- **Morphine on trial [videorecording]** Source: produced by Canadian Broadcasting Corporation; Year: 2002; Format: Videorecording; [Toronto?]: Canadian Broadcasting Corp.; Boston, MA: Distributed by Fanlight Productions, c2002
- **The effects of morphine on learned adaptive behavior and experimental neuroses in cats [motion picture]** Source: from the Neurophysiological Laboratories of the Division of Psychiatry and of the Otho S.A. Sprague Memorial Institute, University of Chicago; Year: 1942; Format: Motion picture; [United States: Psychological Cinema Register of the Pennsylvania State College, 1942]
- **Use of large doses of morphine in anesthetic practice [videorecording]** Source: Video Digest, inc; Year: 1972; Format: Videorecording; [Cincinnati, Ohio]: Video Digest, c1972

CHAPTER 9. PERIODICALS AND NEWS ON MORPHINE

Overview

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

News Services and Press Releases

One of the simplest ways of tracking press releases on morphine is to search the news wires. In the following sample of sources, we will briefly describe how to access each service. These services only post recent news intended for public viewing.

PR Newswire

To access the PR Newswire archive, simply go to **http://www.prnewswire.com/**. Select your country. Type "morphine" (or synonyms) into the search box. You will automatically receive information on relevant news releases posted within the last 30 days. The search results are shown by order of relevance.

Reuters Health

The Reuters' Medical News and Health eLine databases can be very useful in exploring news archives relating to morphine. While some of the listed articles are free to view, others are available for purchase for a nominal fee. To access this archive, go to **http://www.reutershealth.com/en/index.html** and search by "morphine" (or synonyms). The following was recently listed in this archive for morphine:

- **Nastech intranasal morphine performs well in phase II**
  Source: Reuters Industry Breifing
  Date: December 10, 2002
- **Intranasal morphine performs well in phase II**
  Source: Reuters Medical News
  Date: December 10, 2002

- **Amarin partner files for once-a-day morphine formulation in Japan**
  Source: Reuters Industry Breifing
  Date: November 12, 2002
- **Drug lessens morphine withdrawal in mice**
  Source: Reuters Health eLine
  Date: July 02, 2003
- **Morphine may help HTLV-1 thrive in the presence of HIV-1**
  Source: Reuters Medical News
  Date: April 23, 2003
- **Morphine-like drugs ease nervous system pain**
  Source: Reuters Health eLine
  Date: March 26, 2003
- **New painkiller may be less addictive than morphine**
  Source: Reuters Health eLine
  Date: March 24, 2003
- **Enkephalin analogs more potent, less addictive than morphine**
  Source: Reuters Medical News
  Date: March 24, 2003
- **Brain receptor may be key to non-addictive morphine**
  Source: Reuters Health eLine
  Date: July 30, 2002
- **Marine snail's toxin more powerful than morphine**
  Source: Reuters Health eLine
  Date: July 12, 2002
- **Cone shell compound more powerful than morphine in rats**
  Source: Reuters Medical News
  Date: July 12, 2002
- **Generex wins US clearance for buccal morphine IND**
  Source: Reuters Industry Breifing
  Date: May 03, 2002
- **Accuracy of pediatric abdominal pain exam unaltered by morphine use**
  Source: Reuters Medical News
  Date: May 02, 2002
- **Generex wins Canadian clearance of IND for buccal morphine trials**
  Source: Reuters Industry Breifing
  Date: March 19, 2002
- **"Free" morphine in India not available to many who need it**
  Source: Reuters Industry Breifing
  Date: March 12, 2002
- **Role of morphine as long-term treatment for central pain appears limited**
  Source: Reuters Industry Breifing
  Date: March 05, 2002
- **Drug mix-up could lead to morphine overdose**
  Source: Reuters Health eLine
  Date: February 21, 2002

- **Recurring drug mix-up could lead to morphine overdose**
  Source: Reuters Industry Breifing
  Date: February 20, 2002
- **Compound may improve morphine's effectiveness**
  Source: Reuters Health eLine
  Date: January 25, 2002
- **Generex stock dips despite positive phase I buccal morphine study results**
  Source: Reuters Industry Breifing
  Date: January 16, 2002
- **Drug combination can reduce morphine use**
  Source: Reuters Industry Breifing
  Date: October 17, 2001
- **Progenics' methylnaltrexone stops morphine-induced side effects in phase II**
  Source: Reuters Industry Breifing
  Date: October 16, 2001
- **Pohl-Boskamp licenses EU rights to Nastech's intranasal morphine product**
  Source: Reuters Industry Breifing
  Date: September 26, 2001
- **Co-administration of morphine and packed red blood cells safe for children**
  Source: Reuters Medical News
  Date: September 11, 2001
- **Patients with chronic noncancer pain prefer transdermal fentanyl to oral morphine**
  Source: Reuters Industry Breifing
  Date: May 10, 2001
- **Pharmacia's IV COX-2 inhibitor superior to morphine in post-op pain control**
  Source: Reuters Industry Breifing
  Date: March 02, 2001
- **FDA approves Watson's morphine sulfate generic tablets**
  Source: Reuters Industry Breifing
  Date: February 01, 2001
- **Advanced Neuromodulation's morphine pump trial cleared by FDA**
  Source: Reuters Industry Breifing
  Date: January 17, 2001
- **Ultra-low-dose naltrexone allows low-dose morphine to exert analgesic effect**
  Source: Reuters Medical News
  Date: January 12, 2001
- **Shrinking morphine dose could reduce addiction risk**
  Source: Reuters Health eLine
  Date: January 11, 2001
- **SkyePharma begins phase III trial of DepoMorphine, secures funding**
  Source: Reuters Industry Breifing
  Date: January 10, 2001

The NIH

Within MEDLINEplus, the NIH has made an agreement with the New York Times Syndicate, the AP News Service, and Reuters to deliver news that can be browsed by the public. Search news releases at **http://www.nlm.nih.gov/medlineplus/alphanews_a.html**. MEDLINEplus allows you to browse across an alphabetical index. Or you can search by date at the following Web page: **http://www.nlm.nih.gov/medlineplus/newsbydate.html**. Often, news items are indexed by MEDLINEplus within its search engine.

Business Wire

Business Wire is similar to PR Newswire. To access this archive, simply go to **http://www.businesswire.com/**. You can scan the news by industry category or company name.

Market Wire

Market Wire is more focused on technology than the other wires. To browse the latest press releases by topic, such as alternative medicine, biotechnology, fitness, healthcare, legal, nutrition, and pharmaceuticals, access Market Wire's Medical/Health channel at **http://www.marketwire.com/mw/release_index?channel=MedicalHealth**. Or simply go to Market Wire's home page at **http://www.marketwire.com/mw/home**, type "morphine" (or synonyms) into the search box, and click on "Search News." As this service is technology oriented, you may wish to use it when searching for press releases covering diagnostic procedures or tests.

Search Engines

Medical news is also available in the news sections of commercial Internet search engines. See the health news page at Yahoo (**http://dir.yahoo.com/Health/News_and_Media/**), or you can use this Web site's general news search page at **http://news.yahoo.com/**. Type in "morphine" (or synonyms). If you know the name of a company that is relevant to morphine, you can go to any stock trading Web site (such as **http://www.etrade.com/**) and search for the company name there. News items across various news sources are reported on indicated hyperlinks. Google offers a similar service at **http://news.google.com/**.

BBC

Covering news from a more European perspective, the British Broadcasting Corporation (BBC) allows the public free access to their news archive located at **http://www.bbc.co.uk/**. Search by "morphine" (or synonyms).

Newsletter Articles

Use the Combined Health Information Database, and limit your search criteria to "newsletter articles." Again, you will need to use the "Detailed Search" option. Go directly

to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. Go to the bottom of the search page where "You may refine your search by." Select the dates and language that you prefer. For the format option, select "Newsletter Article." Type "morphine" (or synonyms) into the "For these words:" box. You should check back periodically with this database as it is updated every three months. The following is a typical result when searching for newsletter articles on morphine:

- **Cause and Treatment of Pain in Chronic Intestinal Pseudo-Obstruction**

  Source: ASAP Forum Journal. 2(1): 7-10. May 1995.

  Contact: Available from American Society of Adults with Pseudo-Obstruction (ASAP). 19 Carroll Road, Woburn, MA 01801. (617) 935-9776. Fax (617) 933-4151.

  Summary: This newsletter article addresses the cause and treatment of pain associated with chronic intestinal pseudo-obstruction (CIP). The author defines the current knowledge on the cause of pain, discusses the results obtained with the use of various medications and procedures, including surgical procedures, and provides thoughts on future developments for pain control. The author notes that although CIP produces numerous symptoms and problems, the subjective complaint that most patients have is that of abdominal pain. Specific drug agents covered include antacids; histamine blockers, such as Tagamet, Zantac, and Pepcid; Prilosec, an acid pump inhibitor; Carafate; nonsteroidal anti-inflammatory agents (NSAIDs), including ibuprofen, Motrin, or Orudis; antibiotics including Flagyl and Bactrim; antidepressants, including Librax, Ativan, and Paxil; pain inhibitors, including Darvon, Vicodin, and Lortab; Codeine; Percocet; Demerol; **Morphine;** Buprenex; Stadol; and Dilaudid.

- **Drug Therapy of Chronic Pain**

  Source: Lifeline: The Newsletter of the National Chronic Pain Outreach Association. p. 6-8,10-12. Fall 1998.

  Contact: Available from National Chronic Pain Outreach Association. P.O. Box 274, Millboro, VA 24460. (540) 862-9437. Fax (540) 862-9485. E-mail: NCPOA@CFW.COM.

  Summary: This newsletter article provides health professionals and people who have chronic pain with information on the main classes of drugs used to treat pain. Medications are usually taken orally in the form of a pill, capsule, tablet, or liquid, but some may be delivered through creams, skin patches, inhalers, injections, spinal catheters, and rectal suppositories. The main drugs used to treat pain are the nonsteroidal antiinflammatory drugs (NSAIDs), opioids, and a group referred to as adjuvant analgesics. NSAID classes include salicylates, propionic acids, acetic acids, fenamates, and oxicams. Opioid analgesics have long been an accepted therapeutic modality in the treatment of acute and chronic pain; however, concerns about dosage increases and addiction have lead to controversy over their use. Evidence indicates that these concerns are unfounded, so opioids are appropriate for pain management. **Morphine** and fentanyl are two opioid formulations uniquely made for management of chronic pain. Adjuvant analgesics are a mixed class of medications that may be used to provide additive analgesic effect and to counteract the side effects of more traditional analgesics. Adjuvant analgesics include tricyclic antidepressants, anticonvulsants, benzodiazepines, antihistamines, stimulants such as caffeine and dextroamphetamine, steroids, phenothiazines, oral local anesthetics, sympatholytics, sumatriptan, and topical capsaicin. The article discusses the rationale for selecting particular drugs over others, their mechanism of action, and their common side effects. 3 tables and 17 references.

Academic Periodicals covering Morphine

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to morphine. In addition to these sources, you can search for articles covering morphine that have been published by any of the periodicals listed in previous chapters. To find the latest studies published, go to **http://www.ncbi.nlm.nih.gov/pubmed**, type the name of the periodical into the search box, and click "Go."

If you want complete details about the historical contents of a journal, you can also visit the following Web site: **http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi**. Here, type in the name of the journal or its abbreviation, and you will receive an index of published articles. At **http://locatorplus.gov/**, you can retrieve more indexing information on medical periodicals (e.g. the name of the publisher). Select the button "Search LOCATORplus." Then type in the name of the journal and select the advanced search option "Journal Title Search."

CHAPTER 10. RESEARCHING MEDICATIONS

Overview

While a number of hard copy or CD-ROM resources are available for researching medications, a more flexible method is to use Internet-based databases. Broadly speaking, there are two sources of information on approved medications: public sources and private sources. We will emphasize free-to-use public sources.

U.S. Pharmacopeia

Because of historical investments by various organizations and the emergence of the Internet, it has become rather simple to learn about the medications recommended for morphine. One such source is the United States Pharmacopeia. In 1820, eleven physicians met in Washington, D.C. to establish the first compendium of standard drugs for the United States. They called this compendium the U.S. Pharmacopeia (USP). Today, the USP is a non-profit organization consisting of 800 volunteer scientists, eleven elected officials, and 400 representatives of state associations and colleges of medicine and pharmacy. The USP is located in Rockville, Maryland, and its home page is located at **http://www.usp.org/**. The USP currently provides standards for over 3,700 medications. The resulting USP DI® Advice for the Patient® can be accessed through the National Library of Medicine of the National Institutes of Health. The database is partially derived from lists of federally approved medications in the Food and Drug Administration's (FDA) Drug Approvals database, located at **http://www.fda.gov/cder/da/da.htm**.

While the FDA database is rather large and difficult to navigate, the Phamacopeia is both user-friendly and free to use. It covers more than 9,000 prescription and over-the-counter medications. To access this database, simply type the following hyperlink into your Web browser: **http://www.nlm.nih.gov/medlineplus/druginformation.html**. To view examples of a given medication (brand names, category, description, preparation, proper use, precautions, side effects, etc.), simply follow the hyperlinks indicated within the United States Pharmacopeia (USP).

Below, we have compiled a list of medications associated with morphine. If you would like more information on a particular medication, the provided hyperlinks will direct you to ample documentation (e.g. typical dosage, side effects, drug-interaction risks, etc.). The

following drugs have been mentioned in the Pharmacopeia and other sources as being potentially applicable to morphine:

Narcotic Analgesics for Pain Relief

- **Systemic - U.S. Brands:** Astramorph PF; Buprenex; Cotanal-65; Darvon; Darvon-N; Demerol; Dilaudid; Dilaudid-5; Dilaudid-HP; Dolophine; Duramorph; Hydrostat IR; Kadian; Levo-Dromoran; M S Contin; Methadose; MS/L; MS/L Concentrate; MS/S; MSIR; Nubain; Numorphan; OMS Concentrate; http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202390.html

Narcotic Analgesics for Surgery and Obstetrics

- **Systemic - U.S. Brands:** Alfenta; Astramorph; Astramorph PF; Buprenex; Demerol; Duramorph; Nubain; Stadol; Sublimaze; Sufenta; Ultiva http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202391.html

Commercial Databases

In addition to the medications listed in the USP above, a number of commercial sites are available by subscription to physicians and their institutions. Or, you may be able to access these sources from your local medical library.

Mosby's Drug Consult™

Mosby's Drug Consult™ database (also available on CD-ROM and book format) covers 45,000 drug products including generics and international brands. It provides prescribing information, drug interactions, and patient information. Subscription information is available at the following hyperlink: **http://www.mosbysdrugconsult.com/**.

PDR*health*

The PDR*health* database is a free-to-use, drug information search engine that has been written for the public in layman's terms. It contains FDA-approved drug information adapted from the Physicians' Desk Reference (PDR) database. PDR*health* can be searched by brand name, generic name, or indication. It features multiple drug interactions reports. Search PDR*health* at **http://www.pdrhealth.com/drug_info/index.html**.

Other Web Sites

Drugs.com (**www.drugs.com**) reproduces the information in the Pharmacopeia as well as commercial information. You may also want to consider the Web site of the Medical Letter, Inc. (**http://www.medletter.com/**) which allows users to download articles on various drugs and therapeutics for a nominal fee.

If you have any questions about a medical treatment, the FDA may have an office near you. Look for their number in the blue pages of the phone book. You can also contact the FDA through its toll-free number, 1-888-INFO-FDA (1-888-463-6332), or on the World Wide Web at **www.fda.gov**.

APPENDICES

APPENDIX A. PHYSICIAN RESOURCES

Overview

In this chapter, we focus on databases and Internet-based guidelines and information resources created or written for a professional audience.

NIH Guidelines

Commonly referred to as "clinical" or "professional" guidelines, the National Institutes of Health publish physician guidelines for the most common diseases. Publications are available at the following by relevant Institute[12]:

- Office of the Director (OD); guidelines consolidated across agencies available at **http://www.nih.gov/health/consumer/conkey.htm**
- National Institute of General Medical Sciences (NIGMS); fact sheets available at **http://www.nigms.nih.gov/news/facts/**
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines: **http://www.nlm.nih.gov/medlineplus/healthtopics.html**
- National Cancer Institute (NCI); guidelines available at **http://www.cancer.gov/cancerinfo/list.aspx?viewid=5f35036e-5497-4d86-8c2c-714a9f7c8d25**
- National Eye Institute (NEI); guidelines available at **http://www.nei.nih.gov/order/index.htm**
- National Heart, Lung, and Blood Institute (NHLBI); guidelines available at **http://www.nhlbi.nih.gov/guidelines/index.htm**
- National Human Genome Research Institute (NHGRI); research available at **http://www.genome.gov/page.cfm?pageID=10000375**
- National Institute on Aging (NIA); guidelines available at **http://www.nia.nih.gov/health/**

[12] These publications are typically written by one or more of the various NIH Institutes.

- National Institute on Alcohol Abuse and Alcoholism (NIAAA); guidelines available at **http://www.niaaa.nih.gov/publications/publications.htm**
- National Institute of Allergy and Infectious Diseases (NIAID); guidelines available at **http://www.niaid.nih.gov/publications/**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); fact sheets and guidelines available at **http://www.niams.nih.gov/hi/index.htm**
- National Institute of Child Health and Human Development (NICHD); guidelines available at **http://www.nichd.nih.gov/publications/pubskey.cfm**
- National Institute on Deafness and Other Communication Disorders (NIDCD); fact sheets and guidelines at **http://www.nidcd.nih.gov/health/**
- National Institute of Dental and Craniofacial Research (NIDCR); guidelines available at **http://www.nidr.nih.gov/health/**
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); guidelines available at **http://www.niddk.nih.gov/health/health.htm**
- National Institute on Drug Abuse (NIDA); guidelines available at **http://www.nida.nih.gov/DrugAbuse.html**
- National Institute of Environmental Health Sciences (NIEHS); environmental health information available at **http://www.niehs.nih.gov/external/facts.htm**
- National Institute of Mental Health (NIMH); guidelines available at **http://www.nimh.nih.gov/practitioners/index.cfm**
- National Institute of Neurological Disorders and Stroke (NINDS); neurological disorder information pages available at **http://www.ninds.nih.gov/health_and_medical/disorder_index.htm**
- National Institute of Nursing Research (NINR); publications on selected illnesses at **http://www.nih.gov/ninr/news-info/publications.html**
- National Institute of Biomedical Imaging and Bioengineering; general information at **http://grants.nih.gov/grants/becon/becon_info.htm**
- Center for Information Technology (CIT); referrals to other agencies based on keyword searches available at **http://kb.nih.gov/www_query_main.asp**
- National Center for Complementary and Alternative Medicine (NCCAM); health information available at **http://nccam.nih.gov/health/**
- National Center for Research Resources (NCRR); various information directories available at **http://www.ncrr.nih.gov/publications.asp**
- Office of Rare Diseases; various fact sheets available at **http://rarediseases.info.nih.gov/html/resources/rep_pubs.html**
- Centers for Disease Control and Prevention; various fact sheets on infectious diseases available at **http://www.cdc.gov/publications.htm**

NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.[13] Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic citations, full-text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine:[14]

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

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

[14] See **http://www.nlm.nih.gov/databases/databases.html**.

- **Toxicology and Environmental Health Information (TOXNET):** Databases covering toxicology and environmental health: **http://sis.nlm.nih.gov/Tox/ToxMain.html**
- **Visible Human Interface:** Anatomically detailed, three-dimensional representations of normal male and female human bodies: **http://www.nlm.nih.gov/research/visible/visible_human.html**

The NLM Gateway[15]

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.[16] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type "morphine" (or synonyms) into the search box and click "Search." The results will be presented in a tabular form, indicating the number of references in each database category.

Results Summary

Category	Items Found
Journal Articles	39927
Books / Periodicals / Audio Visual	309
Consumer Health	498
Meeting Abstracts	44
Other Collections	3
Total	40781

HSTAT[17]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[18] These documents include clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.[19] Simply search by "morphine" (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

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[15] Adapted from NLM: **http://gateway.nlm.nih.gov/gw/Cmd?Overview.x**.

[16] The NLM Gateway is currently being developed by the Lister Hill National Center for Biomedical Communications (LHNCBC) at the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

[17] Adapted from HSTAT: **http://www.nlm.nih.gov/pubs/factsheets/hstat.html**.

[18] The HSTAT URL is **http://hstat.nlm.nih.gov/**.

[19] Other important documents in HSTAT include: the National Institutes of Health (NIH) Consensus Conference Reports and Technology Assessment Reports; the HIV/AIDS Treatment Information Service (ATIS) resource documents; the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Treatment Improvement Protocols (TIP) and Center for Substance Abuse Prevention (SAMHSA/CSAP) Prevention Enhancement Protocols System (PEPS); the Public Health Service (PHS) Preventive Services Task Force's *Guide to Clinical Preventive Services*; the independent, nonfederal Task Force on Community Services' *Guide to Community Preventive Services*; and the Health Technology Advisory Committee (HTAC) of the Minnesota Health Care Commission (MHCC) health technology evaluations.

Coffee Break: Tutorials for Biologists[20]

Coffee Break is a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. Here you will find a collection of short reports on recent biological discoveries. Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.[21] Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.[22] This site has new articles every few weeks, so it can be considered an online magazine of sorts. It is intended for general background information. You can access the Coffee Break Web site at the following hyperlink: **http://www.ncbi.nlm.nih.gov/Coffeebreak/**.

Other Commercial Databases

In addition to resources maintained by official agencies, other databases exist that are commercial ventures addressing medical professionals. Here are some examples that may interest you:

- **CliniWeb International:** Index and table of contents to selected clinical information on the Internet; see **http://www.ohsu.edu/cliniweb/**.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see **http://www.mwsearch.com/**.

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[20] Adapted from **http://www.ncbi.nlm.nih.gov/Coffeebreak/Archive/FAQ.html**.

[21] The figure that accompanies each article is frequently supplied by an expert external to NCBI, in which case the source of the figure is cited. The result is an interactive tutorial that tells a biological story.

[22] After a brief introduction that sets the work described into a broader context, the report focuses on how a molecular understanding can provide explanations of observed biology and lead to therapies for diseases. Each vignette is accompanied by a figure and hypertext links that lead to a series of pages that interactively show how NCBI tools and resources are used in the research process.

APPENDIX B. PATIENT RESOURCES

Overview

Official agencies, as well as federally funded institutions supported by national grants, frequently publish a variety of guidelines written with the patient in mind. These are typically called "Fact Sheets" or "Guidelines." They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. Since new guidelines on morphine can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

Patient Guideline Sources

The remainder of this chapter directs you to sources which either publish or can help you find additional guidelines on topics related to morphine. Due to space limitations, these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

The National Institutes of Health

The NIH gateway to patients is located at **http://health.nih.gov/**. From this site, you can search across various sources and institutes, a number of which are summarized below.

Topic Pages: MEDLINEplus

The National Library of Medicine has created a vast and patient-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are "health topic pages" which list links to available materials relevant to morphine. To access this system, log on to **http://www.nlm.nih.gov/medlineplus/healthtopics.html**. From there you can either search using the alphabetical index or browse by broad topic areas. Recently, MEDLINEplus listed the following when searched for "morphine":

- Other guides

  Amphetamine Abuse
  http://www.nlm.nih.gov/medlineplus/amphetamineabuse.html

  Prescription Drug Abuse
  http://www.nlm.nih.gov/medlineplus/prescriptiondrugabuse.html

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

The Combined Health Information Database (CHID)

CHID Online is a reference tool that maintains a database directory of thousands of journal articles and patient education guidelines on morphine. CHID offers summaries that describe the guidelines available, including contact information and pricing. CHID's general Web site is **http://chid.nih.gov/**. To search this database, go to **http://chid.nih.gov/detail/detail.html**. In particular, you can use the advanced search options to look up pamphlets, reports, brochures, and information kits. The following was recently posted in this archive:

- **Interaction of Prescription Drugs With Commonly-Abused Drugs Among Dialysis Patients**

  Source: American Kidney Fund Newsletter for Health Professionals. 7(1): [p. 9-14]. 1990.

  Summary: This article consists of a comprehensive chart detailing the effects of commonly abused drugs on dialysis patients. This chart is intended as a reference guide, and pulls together information heretofore unavailable in a single place. For each of fifteen drugs, the common name, generic name, class of drug, actions, indictions, methods of abuse, side effects, signs and symptoms of overdose, interactions, capability of dialyzing (if known), addictive potential, and signs and symptoms of withdrawal are provided. The fifteen drugs covered are: heroin; **morphine;** Demerol; codeine; Talwin; Quaalude; Nembutal; Seconal; phenobarbital; Restoril (temaepam); alium (diazepam); Dalmane (flurazepam); crank and ice (amphetamine, methamphetamine); cocaine; and crack (cocaine).

- **Sickle cell disease related pain: Assessment and management: A guide for patients and parents**

  Source: Mount Desert, ME: New England Regional Genetics Group. 1994. 25 pp.

  Contact: Available from Victoria Odesina, New England Regional Genetics Group, P.O. Box 670, Mt. Desert, ME 04660. Telephone: (207) 288-2704 / fax: (207) 288-2705 / e-mail: nergg@acadia.net / Web site: http://www.acadia.net/nergg. Available at no charge.

  Summary: This pamphlet gives information for parents and patients in lay language about managing the pain of sickle cell disease. It discusses the onset and types of pain; pain medications from aspirin to **morphine;** other ways to manage pain, such as

massage, and acupuncture; the relationship with the doctor; advocacy; and gives references and resources. [Funded by the Maternal and Child Health Bureau].

The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is "crawled" and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to morphine. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for professionals and patients. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: **http://search.nih.gov/index.html**.

Additional Web Sources

A number of Web sites are available to the public that often link to government sites. These can also point you in the direction of essential information. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=168&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/specific.htm**
- Google: **http://directory.google.com/Top/Health/Conditions_and_Diseases/**
- Med Help International: **http://www.medhelp.org/HealthTopics/A.html**
- Open Directory Project: **http://dmoz.org/Health/Conditions_and_Diseases/**
- Yahoo.com: **http://dir.yahoo.com/Health/Diseases_and_Conditions/**
- WebMD®Health: **http://my.webmd.com/health_topics**

Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to morphine. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with morphine.

The National Health Information Center (NHIC)

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about morphine. For more information, see the NHIC's Web site at **http://www.health.gov/NHIC/** or contact an information specialist by calling 1-800-336-4797.

Directory of Health Organizations

The Directory of Health Organizations, provided by the National Library of Medicine Specialized Information Services, is a comprehensive source of information on associations. The Directory of Health Organizations database can be accessed via the Internet at **http://www.sis.nlm.nih.gov/Dir/DirMain.html**. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. To access DIRLINE directly, go to the following Web site: **http://dirline.nlm.nih.gov/**. Simply type in "morphine" (or a synonym), and you will receive information on all relevant organizations listed in the database.

Health Hotlines directs you to toll-free numbers to over 300 organizations. You can access this database directly at **http://www.sis.nlm.nih.gov/hotlines/**. On this page, you are given the option to search by keyword or by browsing the subject list. When you have received your search results, click on the name of the organization for its description and contact information.

The Combined Health Information Database

Another comprehensive source of information on healthcare associations is the Combined Health Information Database. Using the "Detailed Search" option, you will need to limit your search to "Organizations" and "morphine". Type the following hyperlink into your Web browser: **http://chid.nih.gov/detail/detail.html**. To find associations, use the drop boxes at the bottom of the search page where "You may refine your search by." For publication date, select "All Years." Then, select your preferred language and the format option "Organization Resource Sheet." Type "morphine" (or synonyms) into the "For these words:" box. You should check back periodically with this database since it is updated every three months.

The National Organization for Rare Disorders, Inc.

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by health topic. You can access this database at the following Web site: **http://www.rarediseases.org/search/orgsearch.html**. Type "morphine" (or a synonym) into the search box, and click "Submit Query."

APPENDIX C. FINDING MEDICAL LIBRARIES

Overview

In this Appendix, we show you how to quickly find a medical library in your area.

Preparation

Your local public library and medical libraries have interlibrary loan programs with the National Library of Medicine (NLM), one of the largest medical collections in the world. According to the NLM, most of the literature in the general and historical collections of the National Library of Medicine is available on interlibrary loan to any library. If you would like to access NLM medical literature, then visit a library in your area that can request the publications for you.[23]

Finding a Local Medical Library

The quickest method to locate medical libraries is to use the Internet-based directory published by the National Network of Libraries of Medicine (NN/LM). This network includes 4626 members and affiliates that provide many services to librarians, health professionals, and the public. To find a library in your area, simply visit **http://nnlm.gov/members/adv.html** or call 1-800-338-7657.

Medical Libraries in the U.S. and Canada

In addition to the NN/LM, the National Library of Medicine (NLM) lists a number of libraries with reference facilities that are open to the public. The following is the NLM's list and includes hyperlinks to each library's Web site. These Web pages can provide information on hours of operation and other restrictions. The list below is a small sample of

[23] Adapted from the NLM: **http://www.nlm.nih.gov/psd/cas/interlibrary.html**.

libraries recommended by the National Library of Medicine (sorted alphabetically by name of the U.S. state or Canadian province where the library is located)[24]:

- **Alabama:** Health InfoNet of Jefferson County (Jefferson County Library Cooperative, Lister Hill Library of the Health Sciences), **http://www.uab.edu/infonet/**
- **Alabama:** Richard M. Scrushy Library (American Sports Medicine Institute)
- **Arizona:** Samaritan Regional Medical Center: The Learning Center (Samaritan Health System, Phoenix, Arizona), **http://www.samaritan.edu/library/bannerlibs.htm**
- **California:** Kris Kelly Health Information Center (St. Joseph Health System, Humboldt), **http://www.humboldt1.com/~kkhic/index.html**
- **California:** Community Health Library of Los Gatos, **http://www.healthlib.org/orgresources.html**
- **California:** Consumer Health Program and Services (CHIPS) (County of Los Angeles Public Library, Los Angeles County Harbor-UCLA Medical Center Library) - Carson, CA, **http://www.colapublib.org/services/chips.html**
- **California:** Gateway Health Library (Sutter Gould Medical Foundation)
- **California:** Health Library (Stanford University Medical Center), **http://www-med.stanford.edu/healthlibrary/**
- **California:** Patient Education Resource Center - Health Information and Resources (University of California, San Francisco), **http://sfghdean.ucsf.edu/barnett/PERC/default.asp**
- **California:** Redwood Health Library (Petaluma Health Care District), **http://www.phcd.org/rdwdlib.html**
- **California:** Los Gatos PlaneTree Health Library, **http://planetreesanjose.org/**
- **California:** Sutter Resource Library (Sutter Hospitals Foundation, Sacramento), **http://suttermedicalcenter.org/library/**
- **California:** Health Sciences Libraries (University of California, Davis), **http://www.lib.ucdavis.edu/healthsci/**
- **California:** ValleyCare Health Library & Ryan Comer Cancer Resource Center (ValleyCare Health System, Pleasanton), **http://gaelnet.stmarys-ca.edu/other.libs/gbal/east/vchl.html**
- **California:** Washington Community Health Resource Library (Fremont), **http://www.healthlibrary.org/**
- **Colorado:** William V. Gervasini Memorial Library (Exempla Healthcare), **http://www.saintjosephdenver.org/yourhealth/libraries/**
- **Connecticut:** Hartford Hospital Health Science Libraries (Hartford Hospital), **http://www.harthosp.org/library/**
- **Connecticut:** Healthnet: Connecticut Consumer Health Information Center (University of Connecticut Health Center, Lyman Maynard Stowe Library), **http://library.uchc.edu/departm/hnet/**

[24] Abstracted from **http://www.nlm.nih.gov/medlineplus/libraries.html**.

- **Connecticut:** Waterbury Hospital Health Center Library (Waterbury Hospital, Waterbury), **http://www.waterburyhospital.com/library/consumer.shtml**
- **Delaware:** Consumer Health Library (Christiana Care Health System, Eugene du Pont Preventive Medicine & Rehabilitation Institute, Wilmington), **http://www.christianacare.org/health_guide/health_guide_pmri_health_info.cfm**
- **Delaware:** Lewis B. Flinn Library (Delaware Academy of Medicine, Wilmington), **http://www.delamed.org/chls.html**
- **Georgia:** Family Resource Library (Medical College of Georgia, Augusta), **http://cmc.mcg.edu/kids_families/fam_resources/fam_res_lib/frl.htm**
- **Georgia:** Health Resource Center (Medical Center of Central Georgia, Macon), **http://www.mccg.org/hrc/hrchome.asp**
- **Hawaii:** Hawaii Medical Library: Consumer Health Information Service (Hawaii Medical Library, Honolulu), **http://hml.org/CHIS/**
- **Idaho:** DeArmond Consumer Health Library (Kootenai Medical Center, Coeur d'Alene), **http://www.nicon.org/DeArmond/index.htm**
- **Illinois:** Health Learning Center of Northwestern Memorial Hospital (Chicago), **http://www.nmh.org/health_info/hlc.html**
- **Illinois:** Medical Library (OSF Saint Francis Medical Center, Peoria), **http://www.osfsaintfrancis.org/general/library/**
- **Kentucky:** Medical Library - Services for Patients, Families, Students & the Public (Central Baptist Hospital, Lexington), **http://www.centralbap.com/education/community/library.cfm**
- **Kentucky:** University of Kentucky - Health Information Library (Chandler Medical Center, Lexington), **http://www.mc.uky.edu/PatientEd/**
- **Louisiana:** Alton Ochsner Medical Foundation Library (Alton Ochsner Medical Foundation, New Orleans), **http://www.ochsner.org/library/**
- **Louisiana:** Louisiana State University Health Sciences Center Medical Library-Shreveport, **http://lib-sh.lsuhsc.edu/**
- **Maine:** Franklin Memorial Hospital Medical Library (Franklin Memorial Hospital, Farmington), **http://www.fchn.org/fmh/lib.htm**
- **Maine:** Gerrish-True Health Sciences Library (Central Maine Medical Center, Lewiston), **http://www.cmmc.org/library/library.html**
- **Maine:** Hadley Parrot Health Science Library (Eastern Maine Healthcare, Bangor), **http://www.emh.org/hll/hpl/guide.htm**
- **Maine:** Maine Medical Center Library (Maine Medical Center, Portland), **http://www.mmc.org/library/**
- **Maine:** Parkview Hospital (Brunswick), **http://www.parkviewhospital.org/**
- **Maine:** Southern Maine Medical Center Health Sciences Library (Southern Maine Medical Center, Biddeford), **http://www.smmc.org/services/service.php3?choice=10**
- **Maine:** Stephens Memorial Hospital's Health Information Library (Western Maine Health, Norway), **http://www.wmhcc.org/Library/**

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

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

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

ONLINE GLOSSARIES

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

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

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

- **Basic Guidelines for Morphine**

  Morphine overdose
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002502.htm

- **Signs & Symptoms for Morphine**

  Bluish colored fingernails and lips
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003215.htm

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

  Constipation
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003125.htm

  Difficulty breathing
  Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003075.htm

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

Low blood pressure
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003083.htm

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

No breathing
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003069.htm

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

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

Weak pulse
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003078.htm

- **Diagnostics and Tests for Morphine**

Gastric lavage
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/003882.htm

- **Background Topics for Morphine**

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

Intravenous
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002383.htm

Labored breathing
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000007.htm

Respiratory
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/002290.htm

Shallow breathing
Web site: http://www.nlm.nih.gov/medlineplus/ency/article/000007.htm

Online Dictionary Directories

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

- Medical Dictionaries: Medical & Biological (World Health Organization): **http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical**

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

MORPHINE DICTIONARY

The definitions below are derived from official public sources, including the National Institutes of Health [NIH] and the European Union [EU].

Abdomen: That portion of the body that lies between the thorax and the pelvis. [NIH]

Abdominal: Having to do with the abdomen, which is the part of the body between the chest and the hips that contains the pancreas, stomach, intestines, liver, gallbladder, and other organs. [NIH]

Abdominal Pain: Sensation of discomfort, distress, or agony in the abdominal region. [NIH]

Acceptor: A substance which, while normally not oxidized by oxygen or reduced by hydrogen, can be oxidized or reduced in presence of a substance which is itself undergoing oxidation or reduction. [NIH]

Acetaminophen: Analgesic antipyretic derivative of acetanilide. It has weak anti-inflammatory properties and is used as a common analgesic, but may cause liver, blood cell, and kidney damage. [NIH]

Acetic Acids: Acetic acid and its derivatives which may be formed by substitution reactions. Mono- and di-substituted, as well as halogenated compounds have been synthesized. [NIH]

Acetone: A colorless liquid used as a solvent and an antiseptic. It is one of the ketone bodies produced during ketoacidosis. [NIH]

Acetylcholine: A neurotransmitter. Acetylcholine in vertebrates is the major transmitter at neuromuscular junctions, autonomic ganglia, parasympathetic effector junctions, a subset of sympathetic effector junctions, and at many sites in the central nervous system. It is generally not used as an administered drug because it is broken down very rapidly by cholinesterases, but it is useful in some ophthalmological applications. [NIH]

Achlorhydria: A lack of hydrochloric acid in gastric juice despite stimulation of gastric secretion. [NIH]

Acyl: Chemical signal used by bacteria to communicate. [NIH]

Acylation: The addition of an organic acid radical into a molecule. [NIH]

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

Adaptation: 1. The adjustment of an organism to its environment, or the process by which it enhances such fitness. 2. The normal ability of the eye to adjust itself to variations in the intensity of light; the adjustment to such variations. 3. The decline in the frequency of firing of a neuron, particularly of a receptor, under conditions of constant stimulation. 4. In dentistry, (a) the proper fitting of a denture, (b) the degree of proximity and interlocking of restorative material to a tooth preparation, (c) the exact adjustment of bands to teeth. 5. In microbiology, the adjustment of bacterial physiology to a new environment. [EU]

Adduct: Complex formed when a carcinogen combines with DNA or a protein. [NIH]

Adduction: The rotation of an eye toward the midline (nasally). [NIH]

Adenine: A purine base and a fundamental unit of adenine nucleotides. [NIH]

Adenocarcinoma: A malignant epithelial tumor with a glandular organization. [NIH]

Adenosine: A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA

and RNA. Adenosine itself is a neurotransmitter. [NIH]

Adenosine Monophosphate: Adenylic acid. Adenine nucleotide containing one phosphate group esterified to the sugar moiety in the 2'-, 3'-, or 5'-position. [NIH]

Adenylate Cyclase: An enzyme of the lyase class that catalyzes the formation of cyclic AMP and pyrophosphate from ATP. EC 4.6.1.1. [NIH]

Adjustment: The dynamic process wherein the thoughts, feelings, behavior, and biophysiological mechanisms of the individual continually change to adjust to the environment. [NIH]

Adjuvant: A substance which aids another, such as an auxiliary remedy; in immunology, nonspecific stimulator (e.g., BCG vaccine) of the immune response. [EU]

Adrenal Cortex: The outer layer of the adrenal gland. It secretes mineralocorticoids, androgens, and glucocorticoids. [NIH]

Adrenal Medulla: The inner part of the adrenal gland; it synthesizes, stores and releases catecholamines. [NIH]

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

Adrenergic Agents: Drugs that act on adrenergic receptors or affect the life cycle of adrenergic transmitters. Included here are adrenergic agonists and antagonists and agents that affect the synthesis, storage, uptake, metabolism, or release of adrenergic transmitters. [NIH]

Adrenergic Agonists: Drugs that bind to and activate adrenergic receptors. [NIH]

Adrenergic Antagonists: Drugs that bind to but do not activate adrenergic receptors. Adrenergic antagonists block the actions of the endogenous adrenergic transmitters epinephrine and norepinephrine. [NIH]

Adverse Effect: An unwanted side effect of treatment. [NIH]

Aerosol: A solution of a drug which can be atomized into a fine mist for inhalation therapy. [EU]

Afferent: Concerned with the transmission of neural impulse toward the central part of the nervous system. [NIH]

Affinity: 1. Inherent likeness or relationship. 2. A special attraction for a specific element, organ, or structure. 3. Chemical affinity; the force that binds atoms in molecules; the tendency of substances to combine by chemical reaction. 4. The strength of noncovalent chemical binding between two substances as measured by the dissociation constant of the complex. 5. In immunology, a thermodynamic expression of the strength of interaction between a single antigen-binding site and a single antigenic determinant (and thus of the stereochemical compatibility between them), most accurately applied to interactions among simple, uniform antigenic determinants such as haptens. Expressed as the association constant (K litres mole -1), which, owing to the heterogeneity of affinities in a population of antibody molecules of a given specificity, actually represents an average value (mean intrinsic association constant). 6. The reciprocal of the dissociation constant. [EU]

Agonist: In anatomy, a prime mover. In pharmacology, a drug that has affinity for and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances. [EU]

Agoraphobia: Obsessive, persistent, intense fear of open places. [NIH]

Airways: Tubes that carry air into and out of the lungs. [NIH]

Aldehydes: Organic compounds containing a carbonyl group in the form -CHO. [NIH]

Aldosterone: (11 beta)-11,21-Dihydroxy-3,20-dioxopregn-4-en-18-al. A hormone secreted by the adrenal cortex that functions in the regulation of electrolyte and water balance by increasing the renal retention of sodium and the excretion of potassium. [NIH]

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

Alfentanil: A short-acting opioid anesthetic and analgesic derivative of fentanyl. It produces an early peak analgesic effect and fast recovery of consciousness. Alfentanil is effective as an anesthetic during surgery, for supplementation of analgesia during surgical procedures, and as an analgesic for critically ill patients. [NIH]

Algorithms: A procedure consisting of a sequence of algebraic formulas and/or logical steps to calculate or determine a given task. [NIH]

Alimentary: Pertaining to food or nutritive material, or to the organs of digestion. [EU]

Alkaline: Having the reactions of an alkali. [EU]

Alkaloid: A member of a large group of chemicals that are made by plants and have nitrogen in them. Some alkaloids have been shown to work against cancer. [NIH]

Alkylation: The covalent bonding of an alkyl group to an organic compound. It can occur by a simple addition reaction or by substitution of another functional group. [NIH]

Allergen: An antigenic substance capable of producing immediate-type hypersensitivity (allergy). [EU]

Allylamine: Possesses an unusual and selective cytotoxicity for vascular smooth muscle cells in dogs and rats. Useful for experiments dealing with arterial injury, myocardial fibrosis or cardiac decompensation. [NIH]

Alpha Particles: Positively charged particles composed of two protons and two neutrons, i.e., helium nuclei, emitted during disintegration of very heavy isotopes; a beam of alpha particles or an alpha ray has very strong ionizing power, but weak penetrability. [NIH]

Alpha-Linolenic Acid: A fatty acid that is found in plants and involved in the formation of prostaglandins. [NIH]

Alternative medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used instead of standard treatments. Alternative medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Alum: A type of immune adjuvant (a substance used to help boost the immune response to a vaccine). Also called aluminum sulfate. [NIH]

Alveoli: Tiny air sacs at the end of the bronchioles in the lungs. [NIH]

Ameliorating: A changeable condition which prevents the consequence of a failure or accident from becoming as bad as it otherwise would. [NIH]

Amenorrhea: Absence of menstruation. [NIH]

Amine: An organic compound containing nitrogen; any member of a group of chemical compounds formed from ammonia by replacement of one or more of the hydrogen atoms by organic (hydrocarbon) radicals. The amines are distinguished as primary, secondary, and tertiary, according to whether one, two, or three hydrogen atoms are replaced. The amines include allylamine, amylamine, ethylamine, methylamine, phenylamine, propylamine, and many other compounds. [EU]

Amino Acid Sequence: The order of amino acids as they occur in a polypeptide chain. This

is referred to as the primary structure of proteins. It is of fundamental importance in determining protein conformation. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Ammonia: A colorless alkaline gas. It is formed in the body during decomposition of organic materials during a large number of metabolically important reactions. [NIH]

Amnesia: Lack or loss of memory; inability to remember past experiences. [EU]

Amnestic: Nominal aphasia; a difficulty in finding the right name for an object. [NIH]

Amphetamine: A powerful central nervous system stimulant and sympathomimetic. Amphetamine has multiple mechanisms of action including blocking uptake of adrenergics and dopamine, stimulation of release of monamines, and inhibiting monoamine oxidase. Amphetamine is also a drug of abuse and a psychotomimetic. The l- and the d,l-forms are included here. The l-form has less central nervous system activity but stronger cardiovascular effects. The d-form is dextroamphetamine. [NIH]

Amygdala: Almond-shaped group of basal nuclei anterior to the inferior horn of the lateral ventricle of the brain, within the temporal lobe. The amygdala is part of the limbic system. [NIH]

Anaesthesia: Loss of feeling or sensation. Although the term is used for loss of tactile sensibility, or of any of the other senses, it is applied especially to loss of the sensation of pain, as it is induced to permit performance of surgery or other painful procedures. [EU]

Anaesthetic: 1. Pertaining to, characterized by, or producing anaesthesia. 2. A drug or agent that is used to abolish the sensation of pain. [EU]

Anal: Having to do with the anus, which is the posterior opening of the large bowel. [NIH]

Analgesic: An agent that alleviates pain without causing loss of consciousness. [EU]

Analog: In chemistry, a substance that is similar, but not identical, to another. [NIH]

Analogous: Resembling or similar in some respects, as in function or appearance, but not in origin or development;. [EU]

Analysis of Variance: A statistical technique that isolates and assesses the contributions of categorical independent variables to variation in the mean of a continuous dependent variable. [NIH]

Anaphylatoxins: The family of peptides C3a, C4a, C5a, and C5a des-arginine produced in the serum during complement activation. They produce smooth muscle contraction, mast cell histamine release, affect platelet aggregation, and act as mediators of the local inflammatory process. The order of anaphylatoxin activity from strongest to weakest is C5a, C3a, C4a, and C5a des-arginine. The latter is the so-called "classical" anaphylatoxin but shows no spasmogenic activity though it contains some chemotactic ability. [NIH]

Anatomical: Pertaining to anatomy, or to the structure of the organism. [EU]

Anemia: A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

Anesthesia: A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

Anesthetics: Agents that are capable of inducing a total or partial loss of sensation, especially tactile sensation and pain. They may act to induce general anesthesia, in which an unconscious state is achieved, or may act locally to induce numbness or lack of sensation at a targeted site. [NIH]

Angiogenesis: Blood vessel formation. Tumor angiogenesis is the growth of blood vessels from surrounding tissue to a solid tumor. This is caused by the release of chemicals by the tumor. [NIH]

Animal model: An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models. [NIH]

Anionic: Pertaining to or containing an anion. [EU]

Anions: Negatively charged atoms, radicals or groups of atoms which travel to the anode or positive pole during electrolysis. [NIH]

Annealing: The spontaneous alignment of two single DNA strands to form a double helix. [NIH]

Anode: Electrode held at a positive potential with respect to a cathode. [NIH]

Anorexia: Lack or loss of appetite for food. Appetite is psychologic, dependent on memory and associations. Anorexia can be brought about by unattractive food, surroundings, or company. [NIH]

Anorexia Nervosa: The chief symptoms are inability to eat, weight loss, and amenorrhea. [NIH]

Anoxia: Clinical manifestation of respiratory distress consisting of a relatively complete absence of oxygen. [NIH]

Antagonism: Interference with, or inhibition of, the growth of a living organism by another living organism, due either to creation of unfavorable conditions (e. g. exhaustion of food supplies) or to production of a specific antibiotic substance (e. g. penicillin). [NIH]

Anterior Cruciate Ligament: A strong ligament of the knee that originates from the posteromedial portion of the lateral condyle of the femur, passes anteriorly and inferiorly between the condyles, and attaches to the depression in front of the intercondylar eminence of the tibia. [NIH]

Anterograde: Moving or extending forward; called also antegrade. [EU]

Antibacterial: A substance that destroys bacteria or suppresses their growth or reproduction. [EU]

Antibiotic: A drug used to treat infections caused by bacteria and other microorganisms. [NIH]

Antibiotic Prophylaxis: Use of antibiotics before, during, or after a diagnostic, therapeutic, or surgical procedure to prevent infectious complications. [NIH]

Antibodies: Immunoglobulin molecules having a specific amino acid sequence by virtue of which they interact only with the antigen that induced their synthesis in cells of the lymphoid series (especially plasma cells), or with an antigen closely related to it. [NIH]

Antibody: A type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen. [NIH]

Anticoagulant: A drug that helps prevent blood clots from forming. Also called a blood thinner. [NIH]

Anticonvulsant: An agent that prevents or relieves convulsions. [EU]

Antidepressant: A drug used to treat depression. [NIH]

Antidiuretic: Suppressing the rate of urine formation. [EU]

Antiemetic: An agent that prevents or alleviates nausea and vomiting. Also antinauseant. [EU]

Antigen: Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

Antigen-Antibody Complex: The complex formed by the binding of antigen and antibody molecules. The deposition of large antigen-antibody complexes leading to tissue damage causes immune complex diseases. [NIH]

Anti-infective: An agent that so acts. [EU]

Anti-inflammatory: Having to do with reducing inflammation. [NIH]

Anti-Inflammatory Agents: Substances that reduce or suppress inflammation. [NIH]

Antineoplastic: Inhibiting or preventing the development of neoplasms, checking the maturation and proliferation of malignant cells. [EU]

Antineoplastic Agents: Substances that inhibit or prevent the proliferation of neoplasms. [NIH]

Antioxidant: A substance that prevents damage caused by free radicals. Free radicals are highly reactive chemicals that often contain oxygen. They are produced when molecules are split to give products that have unpaired electrons. This process is called oxidation. [NIH]

Antipruritic: Relieving or preventing itching. [EU]

Antipyretic: An agent that relieves or reduces fever. Called also antifebrile, antithermic and febrifuge. [EU]

Antiseptic: A substance that inhibits the growth and development of microorganisms without necessarily killing them. [EU]

Antispasmodic: An agent that relieves spasm. [EU]

Antitussive: An agent that relieves or prevents cough. [EU]

Antiviral: Destroying viruses or suppressing their replication. [EU]

Antiviral Agents: Agents used in the prophylaxis or therapy of virus diseases. Some of the ways they may act include preventing viral replication by inhibiting viral DNA polymerase; binding to specific cell-surface receptors and inhibiting viral penetration or uncoating; inhibiting viral protein synthesis; or blocking late stages of virus assembly. [NIH]

Anus: The opening of the rectum to the outside of the body. [NIH]

Anxiety: Persistent feeling of dread, apprehension, and impending disaster. [NIH]

Anxiolytic: An anxiolytic or antianxiety agent. [EU]

Aorta: The main trunk of the systemic arteries. [NIH]

Apnea: A transient absence of spontaneous respiration. [NIH]

Aponeurosis: Tendinous expansion consisting of a fibrous or membranous sheath which serves as a fascia to enclose or bind a group of muscles. [NIH]

Apoptosis: One of the two mechanisms by which cell death occurs (the other being the pathological process of necrosis). Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be intrinsically programmed. It is characterized by distinctive morphologic changes in the nucleus and cytoplasm, chromatin cleavage at regularly spaced sites, and the endonucleolytic cleavage of genomic DNA (DNA fragmentation) at internucleosomal sites. This mode of cell death serves as a balance to mitosis in regulating the size of animal tissues and in mediating pathologic processes associated with tumor growth. [NIH]

Applicability: A list of the commodities to which the candidate method can be applied as presented or with minor modifications. [NIH]

Aqueous: Having to do with water. [NIH]

Arachidonic Acid: An unsaturated, essential fatty acid. It is found in animal and human fat as well as in the liver, brain, and glandular organs, and is a constituent of animal phosphatides. It is formed by the synthesis from dietary linoleic acid and is a precursor in the biosynthesis of prostaglandins, thromboxanes, and leukotrienes. [NIH]

Arcuate Nucleus: A nucleus located in the middle hypothalamus in the most ventral part of the third ventricle near the entrance of the infundibular recess. Its small cells are in close contact with the ependyma. [NIH]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Argon: A noble gas with the atomic symbol Ar, atomic number 18, and atomic weight 39.948. It is used in fluorescent tubes and wherever an inert atmosphere is desired and nitrogen cannot be used. [NIH]

Aromatic: Having a spicy odour. [EU]

Arrestin: A 48-Kd protein of the outer segment of the retinal rods and a component of the phototransduction cascade. Arrestin quenches G-protein activation by binding to phosphorylated photolyzed rhodopsin. Arrestin causes experimental autoimmune uveitis when injected into laboratory animals. [NIH]

Arrhythmia: Any variation from the normal rhythm or rate of the heart beat. [NIH]

Arterial: Pertaining to an artery or to the arteries. [EU]

Arteries: The vessels carrying blood away from the heart. [NIH]

Arterioles: The smallest divisions of the arteries located between the muscular arteries and the capillaries. [NIH]

Arteriosclerosis: Thickening and loss of elasticity of arterial walls. Atherosclerosis is the most common form of arteriosclerosis and involves lipid deposition and thickening of the intimal cell layers within arteries. Additional forms of arteriosclerosis involve calcification of the media of muscular arteries (Monkeberg medial calcific sclerosis) and thickening of the walls of small arteries or arterioles due to cell proliferation or hyaline deposition (arteriolosclerosis). [NIH]

Arthroplasty: Surgical reconstruction of a joint to relieve pain or restore motion. [NIH]

Arthroscopy: Endoscopic examination, therapy and surgery of the joint. [NIH]

Articular: Of or pertaining to a joint. [EU]

Ascites: Accumulation or retention of free fluid within the peritoneal cavity. [NIH]

Aseptic: Free from infection or septic material; sterile. [EU]

Aspartate: A synthetic amino acid. [NIH]

Aspartic: The naturally occurring substance is L-aspartic acid. One of the acidic-amino-acids is obtained by the hydrolysis of proteins. [NIH]

Aspartic Acid: One of the non-essential amino acids commonly occurring in the L-form. It is found in animals and plants, especially in sugar cane and sugar beets. It may be a neurotransmitter. [NIH]

Asphyxia: A pathological condition caused by lack of oxygen, manifested in impending or actual cessation of life. [NIH]

Aspirin: A drug that reduces pain, fever, inflammation, and blood clotting. Aspirin belongs to the family of drugs called nonsteroidal anti-inflammatory agents. It is also being studied in cancer prevention. [NIH]

Assay: Determination of the amount of a particular constituent of a mixture, or of the biological or pharmacological potency of a drug. [EU]

Astrocytes: The largest and most numerous neuroglial cells in the brain and spinal cord. Astrocytes (from "star" cells) are irregularly shaped with many long processes, including those with "end feet" which form the glial (limiting) membrane and directly and indirectly contribute to the blood brain barrier. They regulate the extracellular ionic and chemical environment, and "reactive astrocytes" (along with microglia) respond to injury. Astrocytes have high- affinity transmitter uptake systems, voltage-dependent and transmitter-gated ion channels, and can release transmitter, but their role in signaling (as in many other functions) is not well understood. [NIH]

Atmospheric Pressure: The pressure at any point in an atmosphere due solely to the weight of the atmospheric gases above the point concerned. [NIH]

Atrial: Pertaining to an atrium. [EU]

Atrioventricular: Pertaining to an atrium of the heart and to a ventricle. [EU]

Atrium: A chamber; used in anatomical nomenclature to designate a chamber affording entrance to another structure or organ. Usually used alone to designate an atrium of the heart. [EU]

Attenuated: Strain with weakened or reduced virulence. [NIH]

Attenuation: Reduction of transmitted sound energy or its electrical equivalent. [NIH]

Atypical: Irregular; not conformable to the type; in microbiology, applied specifically to strains of unusual type. [EU]

Auditory: Pertaining to the sense of hearing. [EU]

Autoimmune disease: A condition in which the body recognizes its own tissues as foreign and directs an immune response against them. [NIH]

Autonomic: Self-controlling; functionally independent. [EU]

Autoradiography: A process in which radioactive material within an object produces an image when it is in close proximity to a radiation sensitive emulsion. [NIH]

Avoidance Learning: A response to a cue that is instrumental in avoiding a noxious experience. [NIH]

Axonal: Condition associated with metabolic derangement of the entire neuron and is manifest by degeneration of the distal portion of the nerve fiber. [NIH]

Axons: Nerve fibers that are capable of rapidly conducting impulses away from the neuron cell body. [NIH]

Babesiosis: A group of tick-borne diseases of mammals including zoonoses in humans.

They are caused by protozoans of the genus babesia, which parasitize erythrocytes, producing hemolysis. In the U.S., the organism's natural host is mice and transmission is by the deer tick ixodes scapularis. [NIH]

Baclofen: A GABA derivative that is a specific agonist at GABA-B receptors. It is used in the treatment of spasticity, especially that due to spinal cord damage. Its therapeutic effects result from actions at spinal and supraspinal sites, generally the reduction of excitatory transmission. [NIH]

Bacteremia: The presence of viable bacteria circulating in the blood. Fever, chills, tachycardia, and tachypnea are common acute manifestations of bacteremia. The majority of cases are seen in already hospitalized patients, most of whom have underlying diseases or procedures which render their bloodstreams susceptible to invasion. [NIH]

Bacteria: Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccal, rodlike or bacillary, and spiral or spirochetal. [NIH]

Bacterial Infections: Infections by bacteria, general or unspecified. [NIH]

Bacterial Physiology: Physiological processes and activities of bacteria. [NIH]

Bactericidal: Substance lethal to bacteria; substance capable of killing bacteria. [NIH]

Bacteriophage: A virus whose host is a bacterial cell; A virus that exclusively infects bacteria. It generally has a protein coat surrounding the genome (DNA or RNA). One of the coliphages most extensively studied is the lambda phage, which is also one of the most important. [NIH]

Bacterium: Microscopic organism which may have a spherical, rod-like, or spiral unicellular or non-cellular body. Bacteria usually reproduce through asexual processes. [NIH]

Barbiturate: A drug with sedative and hypnotic effects. Barbiturates have been used as sedatives and anesthetics, and they have been used to treat the convulsions associated with epilepsy. [NIH]

Basal Ganglia: Large subcortical nuclear masses derived from the telencephalon and located in the basal regions of the cerebral hemispheres. [NIH]

Base: In chemistry, the nonacid part of a salt; a substance that combines with acids to form salts; a substance that dissociates to give hydroxide ions in aqueous solutions; a substance whose molecule or ion can combine with a proton (hydrogen ion); a substance capable of donating a pair of electrons (to an acid) for the formation of a coordinate covalent bond. [EU]

Basophils: Granular leukocytes characterized by a relatively pale-staining, lobate nucleus and cytoplasm containing coarse dark-staining granules of variable size and stainable by basic dyes. [NIH]

Benign: Not cancerous; does not invade nearby tissue or spread to other parts of the body. [NIH]

Benzene: Toxic, volatile, flammable liquid hydrocarbon biproduct of coal distillation. It is used as an industrial solvent in paints, varnishes, lacquer thinners, gasoline, etc. Benzene causes central nervous system damage acutely and bone marrow damage chronically and is carcinogenic. It was formerly used as parasiticide. [NIH]

Benzhydryl Compounds: Compounds which contain the methyl radical substituted with two benzene rings. Permitted are any substituents, but ring fusion to any of the benzene rings is not allowed. [NIH]

Benzodiazepines: A two-ring heterocyclic compound consisting of a benzene ring fused to a diazepine ring. Permitted is any degree of hydrogenation, any substituents and any H-isomer. [NIH]

Beta-Endorphin: A peptide consisting of amino acid sequence 61-91 of the endogenous pituitary hormone beta-lipotropin. The first four amino acids show a common tetrapeptide sequence with methionine- and leucine enkephalin. The compound shows opiate-like activity. Injection of beta-endorphin induces a profound analgesia of the whole body for several hours. This action is reversed after administration of naloxone. [NIH]

Bicuculline: Isoquinoline alkaloid from Dicentra cucullaria and other plants that is a competitive antagonist at GABA-A receptors and thus causes convulsions. [NIH]

Bile: An emulsifying agent produced in the liver and secreted into the duodenum. Its composition includes bile acids and salts, cholesterol, and electrolytes. It aids digestion of fats in the duodenum. [NIH]

Bile Acids: Acids made by the liver that work with bile to break down fats. [NIH]

Bilirubin: A bile pigment that is a degradation product of heme. [NIH]

Binding Sites: The reactive parts of a macromolecule that directly participate in its specific combination with another molecule. [NIH]

Bioavailability: The degree to which a drug or other substance becomes available to the target tissue after administration. [EU]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

Biogenic Amines: A group of naturally occurring amines derived by enzymatic decarboxylation of the natural amino acids. Many have powerful physiological effects (e.g., histamine, serotonin, epinephrine, tyramine). Those derived from aromatic amino acids, and also their synthetic analogs (e.g., amphetamine), are of use in pharmacology. [NIH]

Biological Factors: Compounds made by living organisms that contribute to or influence a phenomenon or process. They have biological or physiological activities. [NIH]

Bioluminescence: The emission of light by living organisms such as the firefly, certain mollusks, beetles, fish, bacteria, fungi and protozoa. [NIH]

Biopsy: Removal and pathologic examination of specimens in the form of small pieces of tissue from the living body. [NIH]

Biosynthesis: The building up of a chemical compound in the physiologic processes of a living organism. [EU]

Biotechnology: Body of knowledge related to the use of organisms, cells or cell-derived constituents for the purpose of developing products which are technically, scientifically and clinically useful. Alteration of biologic function at the molecular level (i.e., genetic engineering) is a central focus; laboratory methods used include transfection and cloning technologies, sequence and structure analysis algorithms, computer databases, and gene and protein structure function analysis and prediction. [NIH]

Bipolar Disorder: A major affective disorder marked by severe mood swings (manic or major depressive episodes) and a tendency to remission and recurrence. [NIH]

Bivalent: Pertaining to a group of 2 homologous or partly homologous chromosomes during the zygotene stage of prophase to the first metaphase in meiosis. [NIH]

Bladder: The organ that stores urine. [NIH]

Blastocyst: The mammalian embryo in the post-morula stage in which a fluid-filled cavity, enclosed primarily by trophoblast, contains an inner cell mass which becomes the embryonic disc. [NIH]

Bloating: Fullness or swelling in the abdomen that often occurs after meals. [NIH]

Blood Coagulation: The process of the interaction of blood coagulation factors that results in

an insoluble fibrin clot. [NIH]

Blood Glucose: Glucose in blood. [NIH]

Blood Platelets: Non-nucleated disk-shaped cells formed in the megakaryocyte and found in the blood of all mammals. They are mainly involved in blood coagulation. [NIH]

Blood pressure: The pressure of blood against the walls of a blood vessel or heart chamber. Unless there is reference to another location, such as the pulmonary artery or one of the heart chambers, it refers to the pressure in the systemic arteries, as measured, for example, in the forearm. [NIH]

Blood vessel: A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

Blood-Borne Pathogens: Infectious organisms in the blood, of which the predominant medical interest is their contamination of blood-soiled linens, towels, gowns, bandages, other items from individuals in risk categories, needles and other sharp objects, and medical and dental waste, all of which health workers are exposed to. This concept is differentiated from the clinical conditions of bacteremia, viremia, and fungemia where the organism is present in the blood of a patient as the result of a natural infectious process. [NIH]

Blood-Brain Barrier: Specialized non-fenestrated tightly-joined endothelial cells (tight junctions) that form a transport barrier for certain substances between the cerebral capillaries and the brain tissue. [NIH]

Blot: To transfer DNA, RNA, or proteins to an immobilizing matrix such as nitrocellulose. [NIH]

Body Fluids: Liquid components of living organisms. [NIH]

Bolus: A single dose of drug usually injected into a blood vessel over a short period of time. Also called bolus infusion. [NIH]

Bolus infusion: A single dose of drug usually injected into a blood vessel over a short period of time. Also called bolus. [NIH]

Bone Marrow: The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells. [NIH]

Bone metastases: Cancer that has spread from the original (primary) tumor to the bone. [NIH]

Borates: Inorganic or organic salts and esters of boric acid. [NIH]

Boron: A trace element with the atomic symbol B, atomic number 5, and atomic weight 10.81. Boron-10, an isotope of boron, is used as a neutron absorber in boron neutron capture therapy. [NIH]

Boron Neutron Capture Therapy: A technique for the treatment of neoplasms, especially gliomas and melanomas in which boron-10, an isotope, is introduced into the target cells followed by irradiation with thermal neutrons. [NIH]

Bowel: The long tube-shaped organ in the abdomen that completes the process of digestion. There is both a small and a large bowel. Also called the intestine. [NIH]

Bowel Movement: Body wastes passed through the rectum and anus. [NIH]

Bradykinin: A nonapeptide messenger that is enzymatically produced from kallidin in the blood where it is a potent but short-lived agent of arteriolar dilation and increased capillary

permeability. Bradykinin is also released from mast cells during asthma attacks, from gut walls as a gastrointestinal vasodilator, from damaged tissues as a pain signal, and may be a neurotransmitter. [NIH]

Brain Stem: The part of the brain that connects the cerebral hemispheres with the spinal cord. It consists of the mesencephalon, pons, and medulla oblongata. [NIH]

Branch: Most commonly used for branches of nerves, but applied also to other structures. [NIH]

Breakdown: A physical, metal, or nervous collapse. [NIH]

Breast reconstruction: Surgery to rebuild a breast's shape after a mastectomy. [NIH]

Bronchial: Pertaining to one or more bronchi. [EU]

Bronchiseptica: A small, gram-negative, motile bacillus. A normal inhabitant of the respiratory tract in man, dogs, and pigs, but is also associated with canine infectious tracheobronchitis and atrophic rhinitis in pigs. [NIH]

Buccal: Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

Bupivacaine: A widely used local anesthetic agent. [NIH]

Buprenorphine: A derivative of the opioid alkaloid thebaine that is a more potent and longer lasting analgesic than morphine. It appears to act as a partial agonist at mu and kappa opioid receptors and as an antagonist at delta receptors. The lack of delta-agonist activity has been suggested to account for the observation that buprenorphine tolerance may not develop with chronic use. [NIH]

Bupropion: A unicyclic, aminoketone antidepressant. The mechanism of its therapeutic actions is not well understood, but it does appear to block dopamine uptake. The hydrochloride is available as an aid to smoking cessation treatment. [NIH]

Burns: Injuries to tissues caused by contact with heat, steam, chemicals (burns, chemical), electricity (burns, electric), or the like. [NIH]

Burns, Electric: Burns produced by contact with electric current or from a sudden discharge of electricity. [NIH]

Buspirone: An anxiolytic agent and a serotonin receptor agonist belonging to the azaspirodecanedione class of compounds. Its structure is unrelated to those of the benzodiazepines, but it has an efficacy comparable to diazepam. [NIH]

Butorphanol: A synthetic morphinan analgesic with narcotic antagonist action. It is used in the management of severe pain. [NIH]

Cachexia: General ill health, malnutrition, and weight loss, usually associated with chronic disease. [NIH]

Caesarean section: A surgical incision through the abdominal and uterine walls in order to deliver a baby. [NIH]

Caffeine: A methylxanthine naturally occurring in some beverages and also used as a pharmacological agent. Caffeine's most notable pharmacological effect is as a central nervous system stimulant, increasing alertness and producing agitation. It also relaxes smooth muscle, stimulates cardiac muscle, stimulates diuresis, and appears to be useful in the treatment of some types of headache. Several cellular actions of caffeine have been observed, but it is not entirely clear how each contributes to its pharmacological profile. Among the most important are inhibition of cyclic nucleotide phosphodiesterases, antagonism of adenosine receptors, and modulation of intracellular calcium handling. [NIH]

Calcium: A basic element found in nearly all organized tissues. It is a member of the

alkaline earth family of metals with the atomic symbol Ca, atomic number 20, and atomic weight 40. Calcium is the most abundant mineral in the body and combines with phosphorus to form calcium phosphate in the bones and teeth. It is essential for the normal functioning of nerves and muscles and plays a role in blood coagulation (as factor IV) and in many enzymatic processes. [NIH]

Calcium Channels: Voltage-dependent cell membrane glycoproteins selectively permeable to calcium ions. They are categorized as L-, T-, N-, P-, Q-, and R-types based on the activation and inactivation kinetics, ion specificity, and sensitivity to drugs and toxins. The L- and T-types are present throughout the cardiovascular and central nervous systems and the N-, P-, Q-, & R-types are located in neuronal tissue. [NIH]

Capillary: Any one of the minute vessels that connect the arterioles and venules, forming a network in nearly all parts of the body. Their walls act as semipermeable membranes for the interchange of various substances, including fluids, between the blood and tissue fluid; called also vas capillare. [EU]

Capsaicin: Cytotoxic alkaloid from various species of Capsicum (pepper, paprika), of the Solanaceae. [NIH]

Capsules: Hard or soft soluble containers used for the oral administration of medicine. [NIH]

Carbohydrate: An aldehyde or ketone derivative of a polyhydric alcohol, particularly of the pentahydric and hexahydric alcohols. They are so named because the hydrogen and oxygen are usually in the proportion to form water, (CH2O)n. The most important carbohydrates are the starches, sugars, celluloses, and gums. They are classified into mono-, di-, tri-, poly- and heterosaccharides. [EU]

Carbon Dioxide: A colorless, odorless gas that can be formed by the body and is necessary for the respiration cycle of plants and animals. [NIH]

Carboxy: Cannabinoid. [NIH]

Carboxylic Acids: Organic compounds containing the carboxy group (-COOH). This group of compounds includes amino acids and fatty acids. Carboxylic acids can be saturated, unsaturated, or aromatic. [NIH]

Carcinogen: Any substance that causes cancer. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs. [NIH]

Cardiac: Having to do with the heart. [NIH]

Cardiopulmonary: Having to do with the heart and lungs. [NIH]

Cardiopulmonary Bypass: Diversion of the flow of blood from the entrance of the right atrium directly to the aorta (or femoral artery) via an oxygenator thus bypassing both the heart and lungs. [NIH]

Cardiorespiratory: Relating to the heart and lungs and their function. [EU]

Cardiovascular: Having to do with the heart and blood vessels. [NIH]

Carrier Proteins: Transport proteins that carry specific substances in the blood or across cell membranes. [NIH]

Case report: A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some demographic information about the patient (for example, age, gender, ethnic origin). [NIH]

Case series: A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual

patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. [NIH]

Catalepsy: A condition characterized by inactivity, decreased responsiveness to stimuli, and a tendency to maintain an immobile posture. The limbs tend to remain in whatever position they are placed (waxy flexibility). Catalepsy may be associated with psychotic disorders (e.g., schizophrenia, catatonic), nervous system drug toxicity, and other conditions. [NIH]

Catalyse: To speed up a chemical reaction. [EU]

Catecholamine: A group of chemical substances manufactured by the adrenal medulla and secreted during physiological stress. [NIH]

Catheterization: Use or insertion of a tubular device into a duct, blood vessel, hollow organ, or body cavity for injecting or withdrawing fluids for diagnostic or therapeutic purposes. It differs from intubation in that the tube here is used to restore or maintain patency in obstructions. [NIH]

Catheters: A small, flexible tube that may be inserted into various parts of the body to inject or remove liquids. [NIH]

Caudal: Denoting a position more toward the cauda, or tail, than some specified point of reference; same as inferior, in human anatomy. [EU]

Caudalis: Brain region that controls singing processes. [NIH]

Caudate Nucleus: Elongated gray mass of the neostriatum located adjacent to the lateral ventricle of the brain. [NIH]

Cause of Death: Factors which produce cessation of all vital bodily functions. They can be analyzed from an epidemiologic viewpoint. [NIH]

Cell: The individual unit that makes up all of the tissues of the body. All living things are made up of one or more cells. [NIH]

Cell Adhesion: Adherence of cells to surfaces or to other cells. [NIH]

Cell Cycle: The complex series of phenomena, occurring between the end of one cell division and the end of the next, by which cellular material is divided between daughter cells. [NIH]

Cell Death: The termination of the cell's ability to carry out vital functions such as metabolism, growth, reproduction, responsiveness, and adaptability. [NIH]

Cell Degranulation: The process of losing secretory granules (secretory vesicles). This occurs, for example, in mast cells, basophils, neutrophils, eosinophils, and platelets when secretory products are released from the granules by exocytosis. [NIH]

Cell Differentiation: Progressive restriction of the developmental potential and increasing specialization of function which takes place during the development of the embryo and leads to the formation of specialized cells, tissues, and organs. [NIH]

Cell Division: The fission of a cell. [NIH]

Cell membrane: Cell membrane = plasma membrane. The structure enveloping a cell, enclosing the cytoplasm, and forming a selective permeability barrier; it consists of lipids, proteins, and some carbohydrates, the lipids thought to form a bilayer in which integral proteins are embedded to varying degrees. [EU]

Cell proliferation: An increase in the number of cells as a result of cell growth and cell division. [NIH]

Cell Respiration: The metabolic process of all living cells (animal and plant) in which oxygen is used to provide a source of energy for the cell. [NIH]

Cellobiose: A disaccharide consisting of two glucose units in beta (1-4) glycosidic linkage. Obtained from the partial hydrolysis of cellulose. [NIH]

Cellulose: A polysaccharide with glucose units linked as in cellobiose. It is the chief constituent of plant fibers, cotton being the purest natural form of the substance. As a raw material, it forms the basis for many derivatives used in chromatography, ion exchange materials, explosives manufacturing, and pharmaceutical preparations. [NIH]

Central Nervous System: The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [NIH]

Central Nervous System Infections: Pathogenic infections of the brain, spinal cord, and meninges. DNA virus infections; RNA virus infections; bacterial infections; mycoplasma infections; Spirochaetales infections; fungal infections; protozoan infections; helminthiasis; and prion diseases may involve the central nervous system as a primary or secondary process. [NIH]

Centrifugation: A method of separating organelles or large molecules that relies upon differential sedimentation through a preformed density gradient under the influence of a gravitational field generated in a centrifuge. [NIH]

Cerebellum: Part of the metencephalon that lies in the posterior cranial fossa behind the brain stem. It is concerned with the coordination of movement. [NIH]

Cerebral: Of or pertaining of the cerebrum or the brain. [EU]

Cerebral Arteries: The arteries supplying the cerebral cortex. [NIH]

Cerebrospinal: Pertaining to the brain and spinal cord. [EU]

Cerebrospinal fluid: CSF. The fluid flowing around the brain and spinal cord. Cerebrospinal fluid is produced in the ventricles in the brain. [NIH]

Cerebrovascular: Pertaining to the blood vessels of the cerebrum, or brain. [EU]

Cerebrum: The largest part of the brain. It is divided into two hemispheres, or halves, called the cerebral hemispheres. The cerebrum controls muscle functions of the body and also controls speech, emotions, reading, writing, and learning. [NIH]

Cerium: An element of the rare earth family of metals. It has the atomic symbol Ce, atomic number 58, and atomic weight 140.12. Cerium is a malleable metal used in industrial applications. [NIH]

Cervical: Relating to the neck, or to the neck of any organ or structure. Cervical lymph nodes are located in the neck; cervical cancer refers to cancer of the uterine cervix, which is the lower, narrow end (the "neck") of the uterus. [NIH]

Cervix: The lower, narrow end of the uterus that forms a canal between the uterus and vagina. [NIH]

Cesarean Section: Extraction of the fetus by means of abdominal hysterotomy. [NIH]

Chemokines: Class of pro-inflammatory cytokines that have the ability to attract and activate leukocytes. They can be divided into at least three structural branches: C (chemokines, C), CC (chemokines, CC), and CXC (chemokines, CXC), according to variations in a shared cysteine motif. [NIH]

Chemotactic Factors: Chemical substances that attract or repel cells or organisms. The concept denotes especially those factors released as a result of tissue injury, invasion, or immunologic activity, that attract leukocytes, macrophages, or other cells to the site of infection or insult. [NIH]

Chemotherapy: Treatment with anticancer drugs. [NIH]

Chest wall: The ribs and muscles, bones, and joints that make up the area of the body

between the neck and the abdomen. [NIH]

Chimeras: Organism that contains a mixture of genetically different cells. [NIH]

Chloroform: A commonly used laboratory solvent. It was previously used as an anesthetic, but was banned from use in the U.S. due to its suspected carcinogenecity. [NIH]

Cholecystokinin: A 33-amino acid peptide secreted by the upper intestinal mucosa and also found in the central nervous system. It causes gallbladder contraction, release of pancreatic exocrine (or digestive) enzymes, and affects other gastrointestinal functions. Cholecystokinin may be the mediator of satiety. [NIH]

Cholera: An acute diarrheal disease endemic in India and Southeast Asia whose causative agent is vibrio cholerae. This condition can lead to severe dehydration in a matter of hours unless quickly treated. [NIH]

Cholesterol: The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

Cholinergic: Resembling acetylcholine in pharmacological action; stimulated by or releasing acetylcholine or a related compound. [EU]

Chromaffin System: The cells of the body which stain with chromium salts. They occur along the sympathetic nerves, in the adrenal gland, and in various other organs. [NIH]

Chromatin: The material of chromosomes. It is a complex of DNA, histones, and nonhistone proteins (chromosomal proteins, non-histone) found within the nucleus of a cell. [NIH]

Chromosome: Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes. [NIH]

Chronic: A disease or condition that persists or progresses over a long period of time. [NIH]

Chronic Disease: Disease or ailment of long duration. [NIH]

Cinchona: A genus of rubiaceous South American trees that yields the toxic cinchona alkaloids from their bark; quinine, quinidine, chinconine, cinchonidine and others are used to treat malaria and cardiac arrhythmias. [NIH]

Circulatory system: The system that contains the heart and the blood vessels and moves blood throughout the body. This system helps tissues get enough oxygen and nutrients, and it helps them get rid of waste products. The lymph system, which connects with the blood system, is often considered part of the circulatory system. [NIH]

CIS: Cancer Information Service. The CIS is the National Cancer Institute's link to the public, interpreting and explaining research findings in a clear and understandable manner, and providing personalized responses to specific questions about cancer. Access the CIS by calling 1-800-4-CANCER, or by using the Web site at http://cis.nci.nih.gov. [NIH]

Cisplatin: An inorganic and water-soluble platinum complex. After undergoing hydrolysis, it reacts with DNA to produce both intra and interstrand crosslinks. These crosslinks appear to impair replication and transcription of DNA. The cytotoxicity of cisplatin correlates with cellular arrest in the G2 phase of the cell cycle. [NIH]

Clamp: A u-shaped steel rod used with a pin or wire for skeletal traction in the treatment of certain fractures. [NIH]

Clathrin: The main structural coat protein of coated vesicles which play a key role in the intracellular transport between membranous organelles. Clathrin also interacts with cytoskeletal proteins. [NIH]

Clear cell carcinoma: A rare type of tumor of the female genital tract in which the inside of the cells looks clear when viewed under a microscope. [NIH]

Clinical Medicine: The study and practice of medicine by direct examination of the patient.

[NIH]

Clinical study: A research study in which patients receive treatment in a clinic or other medical facility. Reports of clinical studies can contain results for single patients (case reports) or many patients (case series or clinical trials). [NIH]

Clinical trial: A research study that tests how well new medical treatments or other interventions work in people. Each study is designed to test new methods of screening, prevention, diagnosis, or treatment of a disease. [NIH]

Clone: The term "clone" has acquired a new meaning. It is applied specifically to the bits of inserted foreign DNA in the hybrid molecules of the population. Each inserted segment originally resided in the DNA of a complex genome amid millions of other DNA segment. [NIH]

Cloning: The production of a number of genetically identical individuals; in genetic engineering, a process for the efficient replication of a great number of identical DNA molecules. [NIH]

Coal: A natural fuel formed by partial decomposition of vegetable matter under certain environmental conditions. [NIH]

Coated Vesicles: Vesicles formed when cell-membrane coated pits invaginate and pinch off. The outer surface of these vesicles are covered with a lattice-like network of coat proteins, such as clathrin, coat protein complex proteins, or caveolins. [NIH]

Coca: Any of several South American shrubs of the Erythroxylon genus (and family) that yield cocaine; the leaves are chewed with alum for CNS stimulation. [NIH]

Cocaine: An alkaloid ester extracted from the leaves of plants including coca. It is a local anesthetic and vasoconstrictor and is clinically used for that purpose, particularly in the eye, ear, nose, and throat. It also has powerful central nervous system effects similar to the amphetamines and is a drug of abuse. Cocaine, like amphetamines, acts by multiple mechanisms on brain catecholaminergic neurons; the mechanism of its reinforcing effects is thought to involve inhibition of dopamine uptake. [NIH]

Cochlear: Of or pertaining to the cochlea. [EU]

Cochlear Diseases: Diseases of the cochlea, the part of the inner ear that is concerned with hearing. [NIH]

Cod Liver Oil: Oil obtained from fresh livers of the cod family, Gadidae. It is a source of vitamins A and D. [NIH]

Codeine: An opioid analgesic related to morphine but with less potent analgesic properties and mild sedative effects. It also acts centrally to suppress cough. [NIH]

Cofactor: A substance, microorganism or environmental factor that activates or enhances the action of another entity such as a disease-causing agent. [NIH]

Cognition: Intellectual or mental process whereby an organism becomes aware of or obtains knowledge. [NIH]

Coitus: Sexual intercourse. [NIH]

Collagen: A polypeptide substance comprising about one third of the total protein in mammalian organisms. It is the main constituent of skin, connective tissue, and the organic substance of bones and teeth. Different forms of collagen are produced in the body but all consist of three alpha-polypeptide chains arranged in a triple helix. Collagen is differentiated from other fibrous proteins, such as elastin, by the content of proline, hydroxyproline, and hydroxylysine; by the absence of tryptophan; and particularly by the high content of polar groups which are responsible for its swelling properties. [NIH]

Colorectal: Having to do with the colon or the rectum. [NIH]

Colorectal Surgery: A surgical specialty concerned with the diagnosis and treatment of disorders and abnormalities of the colon, rectum, and anal canal. [NIH]

Colostomy: An opening into the colon from the outside of the body. A colostomy provides a new path for waste material to leave the body after part of the colon has been removed. [NIH]

Combinatorial: A cut-and-paste process that churns out thousands of potentially valuable compounds at once. [NIH]

Comorbidity: The presence of co-existing or additional diseases with reference to an initial diagnosis or with reference to the index condition that is the subject of study. Comorbidity may affect the ability of affected individuals to function and also their survival; it may be used as a prognostic indicator for length of hospital stay, cost factors, and outcome or survival. [NIH]

Complement: A term originally used to refer to the heat-labile factor in serum that causes immune cytolysis, the lysis of antibody-coated cells, and now referring to the entire functionally related system comprising at least 20 distinct serum proteins that is the effector not only of immune cytolysis but also of other biologic functions. Complement activation occurs by two different sequences, the classic and alternative pathways. The proteins of the classic pathway are termed 'components of complement' and are designated by the symbols C1 through C9. C1 is a calcium-dependent complex of three distinct proteins C1q, C1r and C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names. Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

Complementary and alternative medicine: CAM. Forms of treatment that are used in addition to (complementary) or instead of (alternative) standard treatments. These practices are not considered standard medical approaches. CAM includes dietary supplements, megadose vitamins, herbal preparations, special teas, massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Complementary medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used to enhance or complement the standard treatments. Complementary medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Compress: A plug used to occludate an orifice in the control of bleeding, or to mop up secretions; an absorbent pad. [NIH]

Computational Biology: A field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make biological discoveries or predictions. This field encompasses all computational methods and theories applicable to molecular biology and areas of computer-based techniques for solving

biological problems including manipulation of models and datasets. [NIH]

Conception: The onset of pregnancy, marked by implantation of the blastocyst; the formation of a viable zygote. [EU]

Concomitant: Accompanying; accessory; joined with another. [EU]

Conditioned stimulus: A situation in which one signal, or stimulus, is given just before another signal. After this happens several times, the first signal alone can cause the response that would usually need the second signal. [NIH]

Cone: One of the special retinal receptor elements which are presumed to be primarily concerned with perception of light and color stimuli when the eye is adapted to light. [NIH]

Congenita: Displacement, subluxation, or malposition of the crystalline lens. [NIH]

Congestive heart failure: Weakness of the heart muscle that leads to a buildup of fluid in body tissues. [NIH]

Conjugated: Acting or operating as if joined; simultaneous. [EU]

Conjugation: 1. The act of joining together or the state of being conjugated. 2. A sexual process seen in bacteria, ciliate protozoa, and certain fungi in which nuclear material is exchanged during the temporary fusion of two cells (conjugants). In bacterial genetics a form of sexual reproduction in which a donor bacterium (male) contributes some, or all, of its DNA (in the form of a replicated set) to a recipient (female) which then incorporates differing genetic information into its own chromosome by recombination and passes the recombined set on to its progeny by replication. In ciliate protozoa, two conjugants of separate mating types exchange micronuclear material and then separate, each now being a fertilized cell. In certain fungi, the process involves fusion of two gametes, resulting in union of their nuclei and formation of a zygote. 3. In chemistry, the joining together of two compounds to produce another compound, such as the combination of a toxic product with some substance in the body to form a detoxified product, which is then eliminated. [EU]

Conjunctiva: The mucous membrane that lines the inner surface of the eyelids and the anterior part of the sclera. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Consciousness: Sense of awareness of self and of the environment. [NIH]

Constipation: Infrequent or difficult evacuation of feces. [NIH]

Constitutional: 1. Affecting the whole constitution of the body; not local. 2. Pertaining to the constitution. [EU]

Constriction: The act of constricting. [NIH]

Constriction, Pathologic: The condition of an anatomical structure's being constricted beyond normal dimensions. [NIH]

Consumption: Pulmonary tuberculosis. [NIH]

Contact dermatitis: Inflammation of the skin with varying degrees of erythema, edema and vesinculation resulting from cutaneous contact with a foreign substance or other exposure. [NIH]

Contamination: The soiling or pollution by inferior material, as by the introduction of organisms into a wound, or sewage into a stream. [EU]

Continuous infusion: The administration of a fluid into a blood vessel, usually over a

prolonged period of time. [NIH]

Contraceptive: An agent that diminishes the likelihood of or prevents conception. [EU]

Contractility: Capacity for becoming short in response to a suitable stimulus. [EU]

Contraindications: Any factor or sign that it is unwise to pursue a certain kind of action or treatment, e. g. giving a general anesthetic to a person with pneumonia. [NIH]

Control group: In a clinical trial, the group that does not receive the new treatment being studied. This group is compared to the group that receives the new treatment, to see if the new treatment works. [NIH]

Controlled study: An experiment or clinical trial that includes a comparison (control) group. [NIH]

Convalescence: The period of recovery following an illness. [NIH]

Convulsions: A general term referring to sudden and often violent motor activity of cerebral or brainstem origin. Convulsions may also occur in the absence of an electrical cerebral discharge (e.g., in response to hypotension). [NIH]

Coordination: Muscular or motor regulation or the harmonious cooperation of muscles or groups of muscles, in a complex action or series of actions. [NIH]

Copulation: Sexual contact of a male with a receptive female usually followed by emission of sperm. Limited to non-human species. For humans use coitus. [NIH]

Cor: The muscular organ that maintains the circulation of the blood. c. adiposum a heart that has undergone fatty degeneration or that has an accumulation of fat around it; called also fat or fatty, heart. c. arteriosum the left side of the heart, so called because it contains oxygenated (arterial) blood. c. biloculare a congenital anomaly characterized by failure of formation of the atrial and ventricular septums, the heart having only two chambers, a single atrium and a single ventricle, and a common atrioventricular valve. c. bovinum (L. 'ox heart') a greatly enlarged heart due to a hypertrophied left ventricle; called also c. taurinum and bucardia. c. dextrum (L. 'right heart') the right atrium and ventricle. c. hirsutum, c. villosum. c. mobile (obs.) an abnormally movable heart. c. pendulum a heart so movable that it seems to be hanging by the great blood vessels. c. pseudotriloculare biatriatum a congenital cardiac anomaly in which the heart functions as a three-chambered heart because of tricuspid atresia, the right ventricle being extremely small or rudimentary and the right atrium greatly dilated. Blood passes from the right to the left atrium and thence disease due to pulmonary hypertension secondary to disease of the lung, or its blood vessels, with hypertrophy of the right ventricle. [EU]

Cornea: The transparent part of the eye that covers the iris and the pupil and allows light to enter the inside. [NIH]

Coronary: Encircling in the manner of a crown; a term applied to vessels; nerves, ligaments, etc. The term usually denotes the arteries that supply the heart muscle and, by extension, a pathologic involvement of them. [EU]

Coronary Arteriosclerosis: Thickening and loss of elasticity of the coronary arteries. [NIH]

Coronary Artery Bypass: Surgical therapy of ischemic coronary artery disease achieved by grafting a section of saphenous vein, internal mammary artery, or other substitute between the aorta and the obstructed coronary artery distal to the obstructive lesion. [NIH]

Coronary Thrombosis: Presence of a thrombus in a coronary artery, often causing a myocardial infarction. [NIH]

Corpus: The body of the uterus. [NIH]

Corpus Luteum: The yellow glandular mass formed in the ovary by an ovarian follicle that

has ruptured and discharged its ovum. [NIH]

Corpus Striatum: Striped gray and white matter consisting of the neostriatum and paleostriatum (globus pallidus). It is located in front of and lateral to the thalamus in each cerebral hemisphere. The gray substance is made up of the caudate nucleus and the lentiform nucleus (the latter consisting of the globus pallidus and putamen). The white matter is the internal capsule. [NIH]

Cortex: The outer layer of an organ or other body structure, as distinguished from the internal substance. [EU]

Cortical: Pertaining to or of the nature of a cortex or bark. [EU]

Corticosteroids: Hormones that have antitumor activity in lymphomas and lymphoid leukemias; in addition, corticosteroids (steroids) may be used for hormone replacement and for the management of some of the complications of cancer and its treatment. [NIH]

Cortisone: A natural steroid hormone produced in the adrenal gland. It can also be made in the laboratory. Cortisone reduces swelling and can suppress immune responses. [NIH]

Cranial: Pertaining to the cranium, or to the anterior (in animals) or superior (in humans) end of the body. [EU]

Craniocerebral Trauma: Traumatic injuries involving the cranium and intracranial structures (i.e., brain; cranial nerves; meninges; and other structures). Injuries may be classified by whether or not the skull is penetrated (i.e., penetrating vs. nonpenetrating) or whether there is an associated hemorrhage. [NIH]

Crystallization: The formation of crystals; conversion to a crystalline form. [EU]

Cues: Signals for an action; that specific portion of a perceptual field or pattern of stimuli to which a subject has learned to respond. [NIH]

Curative: Tending to overcome disease and promote recovery. [EU]

Cutaneous: Having to do with the skin. [NIH]

Cyanogen Bromide: Cyanogen bromide (CNBr). A compound used in molecular biology to digest some proteins and as a coupling reagent for phosphoroamidate or pyrophosphate internucleotide bonds in DNA duplexes. [NIH]

Cyclic: Pertaining to or occurring in a cycle or cycles; the term is applied to chemical compounds that contain a ring of atoms in the nucleus. [EU]

Cyclosporine: A drug used to help reduce the risk of rejection of organ and bone marrow transplants by the body. It is also used in clinical trials to make cancer cells more sensitive to anticancer drugs. [NIH]

Cysteine: A thiol-containing non-essential amino acid that is oxidized to form cystine. [NIH]

Cytochrome: Any electron transfer hemoprotein having a mode of action in which the transfer of a single electron is effected by a reversible valence change of the central iron atom of the heme prosthetic group between the +2 and +3 oxidation states; classified as cytochromes a in which the heme contains a formyl side chain, cytochromes b, which contain protoheme or a closely similar heme that is not covalently bound to the protein, cytochromes c in which protoheme or other heme is covalently bound to the protein, and cytochromes d in which the iron-tetrapyrrole has fewer conjugated double bonds than the hemes have. Well-known cytochromes have been numbered consecutively within groups and are designated by subscripts (beginning with no subscript), e.g. cytochromes c, c1, C2, . New cytochromes are named according to the wavelength in nanometres of the absorption maximum of the a-band of the iron (II) form in pyridine, e.g., c-555. [EU]

Cytokine: Small but highly potent protein that modulates the activity of many cell types,

including T and B cells. [NIH]

Cytoplasm: The protoplasm of a cell exclusive of that of the nucleus; it consists of a continuous aqueous solution (cytosol) and the organelles and inclusions suspended in it (phaneroplasm), and is the site of most of the chemical activities of the cell. [EU]

Cytotoxic: Cell-killing. [NIH]

Cytotoxic chemotherapy: Anticancer drugs that kill cells, especially cancer cells. [NIH]

Cytotoxins: Substances elaborated by microorganisms, plants or animals that are specifically toxic to individual cells; they may be involved in immunity or may be contained in venoms. [NIH]

Databases, Bibliographic: Extensive collections, reputedly complete, of references and citations to books, articles, publications, etc., generally on a single subject or specialized subject area. Databases can operate through automated files, libraries, or computer disks. The concept should be differentiated from factual databases which is used for collections of data and facts apart from bibliographic references to them. [NIH]

Debrisoquin: An adrenergic neuron-blocking drug similar in effects to guanethidine. It is also noteworthy in being a substrate for a polymorphic cytochrome P-450 enzyme. Persons with certain isoforms of this enzyme are unable to properly metabolize this and many other clinically important drugs. They are commonly referred to as having a debrisoquin 4-hydroxylase polymorphism. [NIH]

Decarboxylation: The removal of a carboxyl group, usually in the form of carbon dioxide, from a chemical compound. [NIH]

Decidua: The epithelial lining of the endometrium that is formed before the fertilized ovum reaches the uterus. The fertilized ovum embeds in the decidua. If the ovum is not fertilized, the decidua is shed during menstruation. [NIH]

Defecation: The normal process of elimination of fecal material from the rectum. [NIH]

Degenerative: Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

Dehydration: The condition that results from excessive loss of body water. [NIH]

Deletion: A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [NIH]

Delirium: (DSM III-R) an acute, reversible organic mental disorder characterized by reduced ability to maintain attention to external stimuli and disorganized thinking as manifested by rambling, irrelevant, or incoherent speech; there are also a reduced level of consciousness, sensory misperceptions, disturbance of the sleep-wakefulness cycle and level of psychomotor activity, disorientation to time, place, or person, and memory impairment. Delirium may be caused by a large number of conditions resulting in derangement of cerebral metabolism, including systemic infection, poisoning, drug intoxication or withdrawal, seizures or head trauma, and metabolic disturbances such as hypoxia, hypoglycaemia, fluid, electrolyte, or acid-base imbalances, or hepatic or renal failure. Called also acute confusional state and acute brain syndrome. [EU]

Dementia: An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness. [NIH]

Demethylation: Process that releases substantial amounts of carbon dioxide in the liver. [NIH]

Denaturation: Rupture of the hydrogen bonds by heating a DNA solution and then cooling it rapidly causes the two complementary strands to separate. [NIH]

Dendrites: Extensions of the nerve cell body. They are short and branched and receive stimuli from other neurons. [NIH]

Dendritic: 1. Branched like a tree. 2. Pertaining to or possessing dendrites. [EU]

Density: The logarithm to the base 10 of the opacity of an exposed and processed film. [NIH]

Dental Caries: Localized destruction of the tooth surface initiated by decalcification of the enamel followed by enzymatic lysis of organic structures and leading to cavity formation. If left unchecked, the cavity may penetrate the enamel and dentin and reach the pulp. The three most prominent theories used to explain the etiology of the disase are that acids produced by bacteria lead to decalcification; that micro-organisms destroy the enamel protein; or that keratolytic micro-organisms produce chelates that lead to decalcification. [NIH]

Dental Waste: Any waste product generated by a dental office, surgery, clinic, or laboratory including amalgams, saliva, and rinse water. [NIH]

Dentate Gyrus: Gray matter situated above the gyrus hippocampi. It is composed of three layers. The molecular layer is continuous with the hippocampus in the hippocampal fissure. The granular layer consists of closely arranged spherical or oval neurons, called granule cells, whose axons pass through the polymorphic layer ending on the dendrites of pyramidal cells in the hippocampus. [NIH]

Dentifrices: Any preparations used for cleansing teeth; they usually contain an abrasive, detergent, binder and flavoring agent and may exist in the form of liquid, paste or powder; may also contain medicaments and caries preventives. [NIH]

Depolarization: The process or act of neutralizing polarity. In neurophysiology, the reversal of the resting potential in excitable cell membranes when stimulated, i.e., the tendency of the cell membrane potential to become positive with respect to the potential outside the cell. [EU]

Depressive Disorder: An affective disorder manifested by either a dysphoric mood or loss of interest or pleasure in usual activities. The mood disturbance is prominent and relatively persistent. [NIH]

Deprivation: Loss or absence of parts, organs, powers, or things that are needed. [EU]

Dermatitis: Any inflammation of the skin. [NIH]

DES: Diethylstilbestrol. A synthetic hormone that was prescribed from the early 1940s until 1971 to help women with complications of pregnancy. DES has been linked to an increased risk of clear cell carcinoma of the vagina in daughters of women who used DES. DES may also increase the risk of breast cancer in women who used DES. [NIH]

Desensitization: The prevention or reduction of immediate hypersensitivity reactions by administration of graded doses of allergen; called also hyposensitization and immunotherapy. [EU]

Detoxification: Treatment designed to free an addict from his drug habit. [EU]

Deuterium: Deuterium. The stable isotope of hydrogen. It has one neutron and one proton in the nucleus. [NIH]

Dexamethasone: (11 beta,16 alpha)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione. An anti-inflammatory glucocorticoid used either in the free alcohol or esterified form in treatment of conditions that respond generally to cortisone. [NIH]

Dexmedetomidine: A selective inhibitor of receptors, adrenergic alpha-2 that has analgesic and sedative properties. Medetomidine is the other racemic form. [NIH]

Dextroamphetamine: The d-form of amphetamine. It is a central nervous system stimulant and a sympathomimetic. It has also been used in the treatment of narcolepsy and of attention deficit disorders and hyperactivity in children. Dextroamphetamine has multiple mechanisms of action including blocking uptake of adrenergics and dopamine, stimulating release of monamines, and inhibiting monoamine oxidase. It is also a drug of abuse and a psychotomimetic. [NIH]

Dextromethorphan: The d-isomer of the codeine analog of levorphanol. Dextromethorphan shows high affinity binding to several regions of the brain, including the medullary cough center. This compound is a NMDA receptor antagonist (receptors, N-methyl-D-aspartate) and acts as a non-competitive channel blocker. It is used widely as an antitussive agent, and is also used to study the involvement of glutamate receptors in neurotoxicity. [NIH]

Dextrorphan: Dextro form of levorphanol. It acts as a noncompetitive NMDA receptor antagonist, among other effects, and has been proposed as a neuroprotective agent. It is also a metabolite of dextromethorphan. [NIH]

Diabetes Mellitus: A heterogeneous group of disorders that share glucose intolerance in common. [NIH]

Diagnostic procedure: A method used to identify a disease. [NIH]

Diarrhea: Passage of excessively liquid or excessively frequent stools. [NIH]

Diastolic: Of or pertaining to the diastole. [EU]

Diclofenac: A non-steroidal anti-inflammatory agent (NSAID) with antipyretic and analgesic actions. It is primarily available as the sodium salt, diclofenac sodium. [NIH]

Diclofenac Sodium: The sodium form of diclofenac. It is used for its analgesic and anti-inflammatory properties. [NIH]

Diencephalon: The paired caudal parts of the prosencephalon from which the thalamus, hypothalamus, epithalamus, and subthalamus are derived. [NIH]

Diffusion: The tendency of a gas or solute to pass from a point of higher pressure or concentration to a point of lower pressure or concentration and to distribute itself throughout the available space; a major mechanism of biological transport. [NIH]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Digestive system: The organs that take in food and turn it into products that the body can use to stay healthy. Waste products the body cannot use leave the body through bowel movements. The digestive system includes the salivary glands, mouth, esophagus, stomach, liver, pancreas, gallbladder, small and large intestines, and rectum. [NIH]

Digestive tract: The organs through which food passes when food is eaten. These organs are the mouth, esophagus, stomach, small and large intestines, and rectum. [NIH]

Dihydrotestosterone: Anabolic agent. [NIH]

Dilatation: The act of dilating. [NIH]

Dilation: A process by which the pupil is temporarily enlarged with special eye drops (mydriatic); allows the eye care specialist to better view the inside of the eye. [NIH]

Dimethyl: A volatile metabolite of the amino acid methionine. [NIH]

Diploid: Having two sets of chromosomes. [NIH]

Direct: 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

Discrimination: The act of qualitative and/or quantitative differentiation between two or more stimuli. [NIH]

Disease Progression: The worsening of a disease over time. This concept is most often used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis. [NIH]

Disinfectant: An agent that disinfects; applied particularly to agents used on inanimate objects. [EU]

Dislocation: The displacement of any part, more especially of a bone. Called also luxation. [EU]

Disorientation: The loss of proper bearings, or a state of mental confusion as to time, place, or identity. [EU]

Disposition: A tendency either physical or mental toward certain diseases. [EU]

Dissection: Cutting up of an organism for study. [NIH]

Dissociation: 1. The act of separating or state of being separated. 2. The separation of a molecule into two or more fragments (atoms, molecules, ions, or free radicals) produced by the absorption of light or thermal energy or by solvation. 3. In psychology, a defense mechanism in which a group of mental processes are segregated from the rest of a person's mental activity in order to avoid emotional distress, as in the dissociative disorders (q.v.), or in which an idea or object is segregated from its emotional significance; in the first sense it is roughly equivalent to splitting, in the second, to isolation. 4. A defect of mental integration in which one or more groups of mental processes become separated off from normal consciousness and, thus separated, function as a unitary whole. [EU]

Dissociative Disorders: Sudden temporary alterations in the normally integrative functions of consciousness. [NIH]

Distal: Remote; farther from any point of reference; opposed to proximal. In dentistry, used to designate a position on the dental arch farther from the median line of the jaw. [EU]

Distention: The state of being distended or enlarged; the act of distending. [EU]

Diuresis: Increased excretion of urine. [EU]

Dizziness: An imprecise term which may refer to a sense of spatial disorientation, motion of the environment, or lightheadedness. [NIH]

Dopa: The racemic or DL form of DOPA, an amino acid found in various legumes. The dextro form has little physiologic activity but the levo form (levodopa) is a very important physiologic mediator and precursor and pharmacological agent. [NIH]

Dopamine: An endogenous catecholamine and prominent neurotransmitter in several systems of the brain. In the synthesis of catecholamines from tyrosine, it is the immediate precursor to norepinephrine and epinephrine. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. A family of dopaminergic receptor subtypes mediate its action. Dopamine is used pharmacologically for its direct (beta adrenergic agonist) and indirect (adrenergic releasing) sympathomimetic effects including its actions as an inotropic agent and as a renal vasodilator. [NIH]

Dopamine Agonists: Drugs that bind to and activate dopamine receptors. [NIH]

Doping: The action of administering a drug to someone before a sports event (originally to a horse before a race); the substance thus administered. [EU]

Dorsal: 1. Pertaining to the back or to any dorsum. 2. Denoting a position more toward the back surface than some other object of reference; same as posterior in human anatomy; superior in the anatomy of quadrupeds. [EU]

Dorsum: A plate of bone which forms the posterior boundary of the sella turcica. [NIH]

Dosage Forms: Completed forms of the pharmaceutical preparation in which prescribed

doses of medication are included. They are designed to resist action by gastric fluids, prevent vomiting and nausea, reduce or alleviate the undesirable taste and smells associated with oral administration, achieve a high concentration of drug at target site, or produce a delayed or long-acting drug effect. They include capsules, liniments, ointments, pharmaceutical solutions, powders, tablets, etc. [NIH]

Dose-dependent: Refers to the effects of treatment with a drug. If the effects change when the dose of the drug is changed, the effects are said to be dose dependent. [NIH]

Double-blinded: A clinical trial in which neither the medical staff nor the person knows which of several possible therapies the person is receiving. [NIH]

Drug Design: The molecular designing of drugs for specific purposes (such as DNA-binding, enzyme inhibition, anti-cancer efficacy, etc.) based on knowledge of molecular properties such as activity of functional groups, molecular geometry, and electronic structure, and also on information cataloged on analogous molecules. Drug design is generally computer-assisted molecular modeling and does not include pharmacokinetics, dosage analysis, or drug administration analysis. [NIH]

Drug Interactions: The action of a drug that may affect the activity, metabolism, or toxicity of another drug. [NIH]

Drug Monitoring: The process of observing, recording, or detecting the effects of a chemical substance administered to an individual therapeutically or diagnostically. [NIH]

Drug Resistance: Diminished or failed response of an organism, disease or tissue to the intended effectiveness of a chemical or drug. It should be differentiated from drug tolerance which is the progressive diminution of the susceptibility of a human or animal to the effects of a drug, as a result of continued administration. [NIH]

Drug Tolerance: Progressive diminution of the susceptibility of a human or animal to the effects of a drug, resulting from its continued administration. It should be differentiated from drug resistance wherein an organism, disease, or tissue fails to respond to the intended effectiveness of a chemical or drug. It should also be differentiated from maximum tolerated dose and no-observed-adverse-effect level. [NIH]

Drug Toxicity: Manifestations of the adverse effects of drugs administered therapeutically or in the course of diagnostic techniques. It does not include accidental or intentional poisoning for which specific headings are available. [NIH]

Dry Eye Syndrome: A common condition that occurs when the eyes do not produce enough tears to keep the eye moist and comfortable. Common symptoms of dry eye include pain, stinging, burning, scratchiness, and intermittent blurring of vision. [NIH]

Duct: A tube through which body fluids pass. [NIH]

Duodenum: The first part of the small intestine. [NIH]

Dura mater: The outermost, toughest, and most fibrous of the three membranes (meninges) covering the brain and spinal cord; called also pachymeninx. [EU]

Dynorphins: A class of opioid peptides including dynorphin A, dynorphin B, and smaller fragments of these peptides. Dynorphins prefer kappa-opioid receptors (receptors, opioid, kappa) and have been shown to play a role as central nervous system transmitters. [NIH]

Dyspepsia: Impaired digestion, especially after eating. [NIH]

Dysphoria: Disquiet; restlessness; malaise. [EU]

Dyspnea: Difficult or labored breathing. [NIH]

Dyspnoea: Difficult or laboured breathing. [EU]

Dystonia: Disordered tonicity of muscle. [EU]

Ectopic: Pertaining to or characterized by ectopia. [EU]

Edema: Excessive amount of watery fluid accumulated in the intercellular spaces, most commonly present in subcutaneous tissue. [NIH]

Effector: It is often an enzyme that converts an inactive precursor molecule into an active second messenger. [NIH]

Effector cell: A cell that performs a specific function in response to a stimulus; usually used to describe cells in the immune system. [NIH]

Efficacy: The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized control trial. [NIH]

Elastin: The protein that gives flexibility to tissues. [NIH]

Elective: Subject to the choice or decision of the patient or physician; applied to procedures that are advantageous to the patient but not urgent. [EU]

Electroacupuncture: A form of acupuncture using low frequency electrically stimulated needles to produce analgesia and anesthesia and to treat disease. [NIH]

Electrode: Component of the pacing system which is at the distal end of the lead. It is the interface with living cardiac tissue across which the stimulus is transmitted. [NIH]

Electrolysis: Destruction by passage of a galvanic electric current, as in disintegration of a chemical compound in solution. [NIH]

Electrolyte: A substance that dissociates into ions when fused or in solution, and thus becomes capable of conducting electricity; an ionic solute. [EU]

Electrons: Stable elementary particles having the smallest known negative charge, present in all elements; also called negatrons. Positively charged electrons are called positrons. The numbers, energies and arrangement of electrons around atomic nuclei determine the chemical identities of elements. Beams of electrons are called cathode rays or beta rays, the latter being a high-energy biproduct of nuclear decay. [NIH]

Electrophysiological: Pertaining to electrophysiology, that is a branch of physiology that is concerned with the electric phenomena associated with living bodies and involved in their functional activity. [EU]

Emboli: Bit of foreign matter which enters the blood stream at one point and is carried until it is lodged or impacted in an artery and obstructs it. It may be a blood clot, an air bubble, fat or other tissue, or clumps of bacteria. [NIH]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Emesis: Vomiting; an act of vomiting. Also used as a word termination, as in haematemesis. [EU]

Emulsion: A preparation of one liquid distributed in small globules throughout the body of a second liquid. The dispersed liquid is the discontinuous phase, and the dispersion medium is the continuous phase. When oil is the dispersed liquid and an aqueous solution is the continuous phase, it is known as an oil-in-water emulsion, whereas when water or aqueous solution is the dispersed phase and oil or oleaginous substance is the continuous phase, it is known as a water-in-oil emulsion. Pharmaceutical emulsions for which official standards have been promulgated include cod liver oil emulsion, cod liver oil emulsion with malt, liquid petrolatum emulsion, and phenolphthalein in liquid petrolatum emulsion. [EU]

Encephalitis: Inflammation of the brain due to infection, autoimmune processes, toxins, and other conditions. Viral infections (see encephalitis, viral) are a relatively frequent cause of

this condition. [NIH]

Encephalitis, Viral: Inflammation of brain parenchymal tissue as a result of viral infection. Encephalitis may occur as primary or secondary manifestation of Togaviridae infections; Herpesviridae infections; Adenoviridae infections; Flaviviridae infections; Bunyaviridae infections; Picornaviridae infections; Paramyxoviridae infections; Orthomyxoviridae infections; Retroviridae infections; and Arenaviridae infections. [NIH]

Endemic: Present or usually prevalent in a population or geographical area at all times; said of a disease or agent. Called also endemial. [EU]

Endocrine Glands: Ductless glands that secrete substances which are released directly into the circulation and which influence metabolism and other body functions. [NIH]

Endocrine System: The system of glands that release their secretions (hormones) directly into the circulatory system. In addition to the endocrine glands, included are the chromaffin system and the neurosecretory systems. [NIH]

Endocytosis: Cellular uptake of extracellular materials within membrane-limited vacuoles or microvesicles. Endosomes play a central role in endocytosis. [NIH]

Endometrium: The layer of tissue that lines the uterus. [NIH]

Endorphin: Opioid peptides derived from beta-lipotropin. Endorphin is the most potent naturally occurring analgesic agent. It is present in pituitary, brain, and peripheral tissues. [NIH]

Endoscopic: A technique where a lateral-view endoscope is passed orally to the duodenum for visualization of the ampulla of Vater. [NIH]

Endosomes: Cytoplasmic vesicles formed when coated vesicles shed their clathrin coat. Endosomes internalize macromolecules bound by receptors on the cell surface. [NIH]

Endothelial cell: The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart. [NIH]

Endothelium: A layer of epithelium that lines the heart, blood vessels (endothelium, vascular), lymph vessels (endothelium, lymphatic), and the serous cavities of the body. [NIH]

Endothelium, Lymphatic: Unbroken cellular lining (intima) of the lymph vessels (e.g., the high endothelial lymphatic venules). It is more permeable than vascular endothelium, lacking selective absorption and functioning mainly to remove plasma proteins that have filtered through the capillaries into the tissue spaces. [NIH]

Endothelium, Vascular: Single pavement layer of cells which line the luminal surface of the entire vascular system and regulate the transport of macromolecules and blood components from interstitium to lumen; this function has been most intensively studied in the blood capillaries. [NIH]

Endothelium-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes it. [NIH]

Endotoxin: Toxin from cell walls of bacteria. [NIH]

Enhancer: Transcriptional element in the virus genome. [NIH]

Enkephalin: A natural opiate painkiller, in the hypothalamus. [NIH]

Entorhinal Cortex: Cortex where the signals are combined with those from other sensory systems. [NIH]

Environmental Exposure: The exposure to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals. [NIH]

Environmental Health: The science of controlling or modifying those conditions, influences, or forces surrounding man which relate to promoting, establishing, and maintaining health. [NIH]

Enzymatic: Phase where enzyme cuts the precursor protein. [NIH]

Enzyme: A protein that speeds up chemical reactions in the body. [NIH]

Eosinophils: Granular leukocytes with a nucleus that usually has two lobes connected by a slender thread of chromatin, and cytoplasm containing coarse, round granules that are uniform in size and stainable by eosin. [NIH]

Ependyma: A thin membrane that lines the ventricles of the brain and the central canal of the spinal cord. [NIH]

Epidemic: Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

Epidemiological: Relating to, or involving epidemiology. [EU]

Epidural: The space between the wall of the spinal canal and the covering of the spinal cord. An epidural injection is given into this space. [NIH]

Epidural block: An injection of an anesthetic drug into the space between the wall of the spinal canal and the covering of the spinal cord. [NIH]

Epidural Space: Space between the dura mater and the walls of the vertebral canal. [NIH]

Epinephrine: The active sympathomimetic hormone from the adrenal medulla in most species. It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is used in asthma and cardiac failure and to delay absorption of local anesthetics. [NIH]

Epithelial: Refers to the cells that line the internal and external surfaces of the body. [NIH]

Epithelial Cells: Cells that line the inner and outer surfaces of the body. [NIH]

Epithelium: One or more layers of epithelial cells, supported by the basal lamina, which covers the inner or outer surfaces of the body. [NIH]

Erythema: Redness of the skin produced by congestion of the capillaries. This condition may result from a variety of causes. [NIH]

Erythrocytes: Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [NIH]

Escalation: Progressive use of more harmful drugs. [NIH]

Esophagus: The muscular tube through which food passes from the throat to the stomach. [NIH]

Esotropia: A form of ocular misalignment characterized by an excessive convergence of the visual axes, resulting in a "cross-eye" appearance. An example of this condition occurs when paralysis of the lateral rectus muscle causes an abnormal inward deviation of one eye on attempted gaze. [NIH]

Estradiol: The most potent mammalian estrogenic hormone. It is produced in the ovary, placenta, testis, and possibly the adrenal cortex. [NIH]

Estrogen: One of the two female sex hormones. [NIH]

Estrogen receptor: ER. Protein found on some cancer cells to which estrogen will attach. [NIH]

Ethanol: A clear, colorless liquid rapidly absorbed from the gastrointestinal tract and

distributed throughout the body. It has bactericidal activity and is used often as a topical disinfectant. It is widely used as a solvent and preservative in pharmaceutical preparations as well as serving as the primary ingredient in alcoholic beverages. [NIH]

Ether: One of a class of organic compounds in which any two organic radicals are attached directly to a single oxygen atom. [NIH]

Ethnic Groups: A group of people with a common cultural heritage that sets them apart from others in a variety of social relationships. [NIH]

Ethylmorphine: A narcotic analgesic and antitussive. It is metabolized in the liver by ethylmorphine-N-demethylase and used as an indicator of liver function. [NIH]

Etorphine: A narcotic analgesic morphinan used as a sedative in veterinary practice. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

Euphoria: An exaggerated feeling of physical and emotional well-being not consonant with apparent stimuli or events; usually of psychologic origin, but also seen in organic brain disease and toxic states. [NIH]

Evacuation: An emptying, as of the bowels. [EU]

Evoke: The electric response recorded from the cerebral cortex after stimulation of a peripheral sense organ. [NIH]

Evoked Potentials: The electric response evoked in the central nervous system by stimulation of sensory receptors or some point on the sensory pathway leading from the receptor to the cortex. The evoked stimulus can be auditory, somatosensory, or visual, although other modalities have been reported. Event-related potentials is sometimes used synonymously with evoked potentials but is often associated with the execution of a motor, cognitive, or psychophysiological task, as well as with the response to a stimulus. [NIH]

Excipients: Usually inert substances added to a prescription in order to provide suitable consistency to the dosage form; a binder, matrix, base or diluent in pills, tablets, creams, salves, etc. [NIH]

Excitability: Property of a cardiac cell whereby, when the cell is depolarized to a critical level (called threshold), the membrane becomes permeable and a regenerative inward current causes an action potential. [NIH]

Excitation: An act of irritation or stimulation or of responding to a stimulus; the addition of energy, as the excitation of a molecule by absorption of photons. [EU]

Excitatory: When cortical neurons are excited, their output increases and each new input they receive while they are still excited raises their output markedly. [NIH]

Excitatory Amino Acid Agonists: Drugs that bind to and activate excitatory amino acid receptors. [NIH]

Excitatory Amino Acids: Endogenous amino acids released by neurons as excitatory neurotransmitters. Glutamic acid is the most common excitatory neurotransmitter in the brain. Aspartic acid has been regarded as an excitatory transmitter for many years, but the extent of its role as a transmitter is unclear. [NIH]

Excitotoxicity: Excessive exposure to glutamate or related compounds can kill brain neurons, presumably by overstimulating them. [NIH]

Exhaustion: The feeling of weariness of mind and body. [NIH]

Exocrine: Secreting outwardly, via a duct. [EU]

Exocytosis: Cellular release of material within membrane-limited vesicles by fusion of the vesicles with the cell membrane. [NIH]

Exogenous: Developed or originating outside the organism, as exogenous disease. [EU]

Exon: The part of the DNA that encodes the information for the actual amino acid sequence of the protein. In many eucaryotic genes, the coding sequences consist of a series of exons alternating with intron sequences. [NIH]

Exotropia: A form of ocular misalignment where the visual axes diverge inappropriately. For example, medial rectus muscle weakness may produce this condition as the affected eye will deviate laterally upon attempted forward gaze. An exotropia occurs due to the relatively unopposed force exerted on the eye by the lateral rectus muscle, which pulls the eye in an outward direction. [NIH]

Expiration: The act of breathing out, or expelling air from the lungs. [EU]

Extensor: A muscle whose contraction tends to straighten a limb; the antagonist of a flexor. [NIH]

Extracellular: Outside a cell or cells. [EU]

Extracellular Space: Interstitial space between cells, occupied by fluid as well as amorphous and fibrous substances. [NIH]

Extracorporeal: Situated or occurring outside the body. [EU]

Extraction: The process or act of pulling or drawing out. [EU]

Extrapyramidal: Outside of the pyramidal tracts. [EU]

Extremity: A limb; an arm or leg (membrum); sometimes applied specifically to a hand or foot. [EU]

Exudate: Material, such as fluid, cells, or cellular debris, which has escaped from blood vessels and has been deposited in tissues or on tissue surfaces, usually as a result of inflammation. An exudate, in contrast to a transudate, is characterized by a high content of protein, cells, or solid materials derived from cells. [EU]

Facial: Of or pertaining to the face. [EU]

Family Planning: Programs or services designed to assist the family in controlling reproduction by either improving or diminishing fertility. [NIH]

Fat: Total lipids including phospholipids. [NIH]

Fatal Outcome: Death resulting from the presence of a disease in an individual, as shown by a single case report or a limited number of patients. This should be differentiated from death, the physiological cessation of life and from mortality, an epidemiological or statistical concept. [NIH]

Fatigue: The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli. [NIH]

Fatty acids: A major component of fats that are used by the body for energy and tissue development. [NIH]

Fecal Incontinence: Failure of voluntary control of the anal sphincters, with involuntary passage of feces and flatus. [NIH]

Feces: The excrement discharged from the intestines, consisting of bacteria, cells exfoliated from the intestines, secretions, chiefly of the liver, and a small amount of food residue. [EU]

Feeding Behavior: Behavioral responses or sequences associated with eating including modes of feeding, rhythmic patterns of eating, and time intervals. [NIH]

Femoral: Pertaining to the femur, or to the thigh. [EU]

Femoral Artery: The main artery of the thigh, a continuation of the external iliac artery. [NIH]

Femoral Neck Fractures: Fractures of the short, constricted portion of the thigh bone between the femur head and the trochanters. It excludes intertrochanteric fractures which are hip fractures. [NIH]

Femur: The longest and largest bone of the skeleton, it is situated between the hip and the knee. [NIH]

Fentanyl: A narcotic opioid drug that is used in the treatment of pain. [NIH]

Ferrets: Semidomesticated variety of European polecat much used for hunting rodents and/or rabbits and as a laboratory animal. [NIH]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

Fibrin: A protein derived from fibrinogen in the presence of thrombin, which forms part of the blood clot. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

Fissure: Any cleft or groove, normal or otherwise; especially a deep fold in the cerebral cortex which involves the entire thickness of the brain wall. [EU]

Fixation: 1. The act or operation of holding, suturing, or fastening in a fixed position. 2. The condition of being held in a fixed position. 3. In psychiatry, a term with two related but distinct meanings : (1) arrest of development at a particular stage, which like regression (return to an earlier stage), if temporary is a normal reaction to setbacks and difficulties but if protracted or frequent is a cause of developmental failures and emotional problems, and (2) a close and suffocating attachment to another person, especially a childhood figure, such as one's mother or father. Both meanings are derived from psychoanalytic theory and refer to 'fixation' of libidinal energy either in a specific erogenous zone, hence fixation at the oral, anal, or phallic stage, or in a specific object, hence mother or father fixation. 4. The use of a fixative (q.v.) to preserve histological or cytological specimens. 5. In chemistry, the process whereby a substance is removed from the gaseous or solution phase and localized, as in carbon dioxide fixation or nitrogen fixation. 6. In ophthalmology, direction of the gaze so that the visual image of the object falls on the fovea centralis. 7. In film processing, the chemical removal of all undeveloped salts of the film emulsion, leaving only the developed silver to form a permanent image. [EU]

Flatus: Gas passed through the rectum. [NIH]

Flexion: In gynaecology, a displacement of the uterus in which the organ is bent so far forward or backward that an acute angle forms between the fundus and the cervix. [EU]

Flunitrazepam: Benzodiazepine with pharmacologic actions similar to those of diazepam. The United States Government has banned the importation of this drug. Steps are being taken to reclassify this substance as a Schedule 1 drug with no accepted medical use. [NIH]

Fluorescence: The property of emitting radiation while being irradiated. The radiation emitted is usually of longer wavelength than that incident or absorbed, e.g., a substance can be irradiated with invisible radiation and emit visible light. X-ray fluorescence is used in diagnosis. [NIH]

Fluorine: A nonmetallic, diatomic gas that is a trace element and member of the halogen family. It is used in dentistry as flouride to prevent dental caries. [NIH]

Flurazepam: A benzodiazepine derivative used mainly as a hypnotic. [NIH]

Flush: Transient, episodic redness of the face and neck caused by certain diseases, ingestion of certain drugs or other substances, heat, emotional factors, or physical exertion. [EU]

Fold: A plication or doubling of various parts of the body. [NIH]

Follicular Phase: The period of the menstrual cycle that begins with menstruation and ends with ovulation. [NIH]

Forearm: The part between the elbow and the wrist. [NIH]

Fourth Ventricle: An irregularly shaped cavity in the rhombencephalon, between the medulla oblongata, the pons, and the isthmus in front, and the cerebellum behind. It is continuous with the central canal of the cord below and with the cerebral aqueduct above, and through its lateral and median apertures it communicates with the subarachnoid space. [NIH]

Fovea: The central part of the macula that provides the sharpest vision. [NIH]

Fractionation: Dividing the total dose of radiation therapy into several smaller, equal doses delivered over a period of several days. [NIH]

Frontal Lobe: The anterior part of the cerebral hemisphere. [NIH]

Fructose: A type of sugar found in many fruits and vegetables and in honey. Fructose is used to sweeten some diet foods. It is considered a nutritive sweetener because it has calories. [NIH]

Functional magnetic resonance imaging: A noninvasive tool used to observe functioning in the brain or other organs by detecting changes in chemical composition, blood flow, or both. [NIH]

Fundus: The larger part of a hollow organ that is farthest away from the organ's opening. The bladder, gallbladder, stomach, uterus, eye, and cavity of the middle ear all have a fundus. [NIH]

Fungemia: The presence of fungi circulating in the blood. Opportunistic fungal sepsis is seen most often in immunosuppressed patients with severe neutropenia or in postoperative patients with intravenous catheters and usually follows prolonged antibiotic therapy. [NIH]

Fungi: A kingdom of eukaryotic, heterotrophic organisms that live as saprobes or parasites, including mushrooms, yeasts, smuts, molds, etc. They reproduce either sexually or asexually, and have life cycles that range from simple to complex. Filamentous fungi refer to those that grow as multicelluar colonies (mushrooms and molds). [NIH]

Gallbladder: The pear-shaped organ that sits below the liver. Bile is concentrated and stored in the gallbladder. [NIH]

Gamma Rays: Very powerful and penetrating, high-energy electromagnetic radiation of shorter wavelength than that of x-rays. They are emitted by a decaying nucleus, usually between 0.01 and 10 MeV. They are also called nuclear x-rays. [NIH]

Gamma-hydroxybutyrate: Anxiolytic. [NIH]

Ganglia: Clusters of multipolar neurons surrounded by a capsule of loosely organized connective tissue located outside the central nervous system. [NIH]

Ganglion: 1. A knot, or knotlike mass. 2. A general term for a group of nerve cell bodies located outside the central nervous system; occasionally applied to certain nuclear groups within the brain or spinal cord, e.g. basal ganglia. 3. A benign cystic tumour occurring on a aponeurosis or tendon, as in the wrist or dorsum of the foot; it consists of a thin fibrous capsule enclosing a clear mucinous fluid. [EU]

Ganglionic Blockers: Agents having as their major action the interruption of neural transmission at nicotinic receptors on postganglionic autonomic neurons. Because their actions are so broad, including blocking of sympathetic and parasympathetic systems, their therapeutic use has been largely supplanted by more specific drugs. They may still be used in the control of blood pressure in patients with acute dissecting aortic aneurysm and for the induction of hypotension in surgery. [NIH]

Gap Junctions: Connections between cells which allow passage of small molecules and electric current. Gap junctions were first described anatomically as regions of close apposition between cells with a narrow (1-2 nm) gap between cell membranes. The variety in the properties of gap junctions is reflected in the number of connexins, the family of proteins which form the junctions. [NIH]

Gas: Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

Gas exchange: Primary function of the lungs; transfer of oxygen from inhaled air into the blood and of carbon dioxide from the blood into the lungs. [NIH]

Gasoline: Volative flammable fuel (liquid hydrocarbons) derived from crude petroleum by processes such as distillation reforming, polymerization, etc. [NIH]

Gastric: Having to do with the stomach. [NIH]

Gastric banding: Surgery to limit the amount of food the stomach can hold by closing part of it off. A band made of special material is placed around the stomach near its upper end, creating a small pouch and a narrow passage into the larger remainder of the stomach. The small outlet delays the emptying of food from the pouch and causes a feeling of fullness. [NIH]

Gastric Emptying: The evacuation of food from the stomach into the duodenum. [NIH]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastroesophageal Reflux: Reflux of gastric juice and/or duodenal contents (bile acids, pancreatic juice) into the distal esophagus, commonly due to incompetence of the lower esophageal sphincter. Gastric regurgitation is an extension of this process with entry of fluid into the pharynx or mouth. [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal tract: The stomach and intestines. [NIH]

Gastrointestinal Transit: Passage of food (sometimes in the form of a test meal) through the gastrointestinal tract as measured in minutes or hours. The rate of passage through the intestine is an indicator of small bowel function. [NIH]

Gelatin: A product formed from skin, white connective tissue, or bone collagen. It is used as a protein food adjuvant, plasma substitute, hemostatic, suspending agent in pharmaceutical preparations, and in the manufacturing of capsules and suppositories. [NIH]

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

Gene Deletion: A genetic rearrangement through loss of segments of DNA or RNA, bringing sequences which are normally separated into close proximity. This deletion may be detected using cytogenetic techniques and can also be inferred from the phenotype, indicating a deletion at one specific locus. [NIH]

Gene Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Genetic Code: The specifications for how information, stored in nucleic acid sequence (base sequence), is translated into protein sequence (amino acid sequence). The start, stop, and order of amino acids of a protein is specified by consecutive triplets of nucleotides called codons (codon). [NIH]

Genetic Engineering: Directed modification of the gene complement of a living organism by such techniques as altering the DNA, substituting genetic material by means of a virus,

transplanting whole nuclei, transplanting cell hybrids, etc. [NIH]

Genetic testing: Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder. [NIH]

Genetics: The biological science that deals with the phenomena and mechanisms of heredity. [NIH]

Genomics: The systematic study of the complete DNA sequences (genome) of organisms. [NIH]

Genotype: The genetic constitution of the individual; the characterization of the genes. [NIH]

Germ Cells: The reproductive cells in multicellular organisms. [NIH]

Gestation: The period of development of the young in viviparous animals, from the time of fertilization of the ovum until birth. [EU]

Giant Cells: Multinucleated masses produced by the fusion of many cells; often associated with viral infections. In AIDS, they are induced when the envelope glycoprotein of the HIV virus binds to the CD4 antigen of uninfected neighboring T4 cells. The resulting syncytium leads to cell death and thus may account for the cytopathic effect of the virus. [NIH]

Ginseng: An araliaceous genus of plants that contains a number of pharmacologically active agents used as stimulants, sedatives, and tonics, especially in traditional medicine. [NIH]

Gland: An organ that produces and releases one or more substances for use in the body. Some glands produce fluids that affect tissues or organs. Others produce hormones or participate in blood production. [NIH]

Globus Pallidus: The representation of the phylogenetically oldest part of the corpus striatum called the paleostriatum. It forms the smaller, more medial part of the lentiform nucleus. [NIH]

Glomerular: Pertaining to or of the nature of a glomerulus, especially a renal glomerulus. [EU]

Glomerulus: A tiny set of looping blood vessels in the nephron where blood is filtered in the kidney. [NIH]

Glottis: The vocal apparatus of the larynx, consisting of the true vocal cords (plica vocalis) and the opening between them (rima glottidis). [NIH]

Glucocorticoid: A compound that belongs to the family of compounds called corticosteroids (steroids). Glucocorticoids affect metabolism and have anti-inflammatory and immunosuppressive effects. They may be naturally produced (hormones) or synthetic (drugs). [NIH]

Glucose: D-Glucose. A primary source of energy for living organisms. It is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement. [NIH]

Glucuronic Acid: Derivatives of uronic acid found throughout the plant and animal kingdoms. They detoxify drugs and toxins by conjugating with them to form glucuronides in the liver which are more water-soluble metabolites that can be easily eliminated from the body. [NIH]

Glucuronides: Glycosides of glucuronic acid formed by the reaction of uridine diphosphate glucuronic acid with certain endogenous and exogenous substances. Their formation is important for the detoxification of drugs, steroid excretion and bilirubin metabolism to a more water-soluble compound that can be eliminated in the urine and bile. [NIH]

Glucuronosyltransferase: A family of enzymes accepting a wide range of substrates, including phenols, alcohols, amines, and fatty acids. They function as drug-metabolizing

enzymes that catalyze the conjugation of UDPglucuronic acid to a variety of endogenous and exogenous compounds. EC 2.4.1.17. [NIH]

Glutamate: Excitatory neurotransmitter of the brain. [NIH]

Glutamic Acid: A non-essential amino acid naturally occurring in the L-form. Glutamic acid (glutamate) is the most common excitatory neurotransmitter in the central nervous system. [NIH]

Glutathione Peroxidase: An enzyme catalyzing the oxidation of 2 moles of glutathione in the presence of hydrogen peroxide to yield oxidized glutathione and water. EC 1.11.1.9. [NIH]

Glycoprotein: A protein that has sugar molecules attached to it. [NIH]

Glycoside: Any compound that contains a carbohydrate molecule (sugar), particularly any such natural product in plants, convertible, by hydrolytic cleavage, into sugar and a nonsugar component (aglycone), and named specifically for the sugar contained, as glucoside (glucose), pentoside (pentose), fructoside (fructose) etc. [EU]

Goats: Any of numerous agile, hollow-horned ruminants of the genus Capra, closely related to the sheep. [NIH]

Gonad: A sex organ, such as an ovary or a testicle, which produces the gametes in most multicellular animals. [NIH]

Gonadal: Pertaining to a gonad. [EU]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Gp120: 120-kD HIV envelope glycoprotein which is involved in the binding of the virus to its membrane receptor, the CD4 molecule, found on the surface of certain cells in the body. [NIH]

Graft: Healthy skin, bone, or other tissue taken from one part of the body and used to replace diseased or injured tissue removed from another part of the body. [NIH]

Grafting: The operation of transfer of tissue from one site to another. [NIH]

Granule: A small pill made from sucrose. [EU]

Granulocytes: Leukocytes with abundant granules in the cytoplasm. They are divided into three groups: neutrophils, eosinophils, and basophils. [NIH]

Granuloma: A relatively small nodular inflammatory lesion containing grouped mononuclear phagocytes, caused by infectious and noninfectious agents. [NIH]

Gravis: Eruption of watery blisters on the skin among those handling animals and animal products. [NIH]

Growth: The progressive development of a living being or part of an organism from its earliest stage to maturity. [NIH]

Guanethidine: An antihypertensive agent that acts by inhibiting selectively transmission in post-ganglionic adrenergic nerves. It is believed to act mainly by preventing the release of norepinephrine at nerve endings and causes depletion of norepinephrine in peripheral sympathetic nerve terminals as well as in tissues. [NIH]

Guanylate Cyclase: An enzyme that catalyzes the conversion of GTP to 3',5'-cyclic GMP and pyrophosphate. It also acts on ITP and dGTP. (From Enzyme Nomenclature, 1992) EC 4.6.1.2. [NIH]

Gynaecological: Pertaining to gynaecology. [EU]

Haematemesis: The vomiting of blood. [EU]

Half-Life: The time it takes for a substance (drug, radioactive nuclide, or other) to lose half of its pharmacologic, physiologic, or radiologic activity. [NIH]

Hallucinogen: A hallucination-producing drug, a category of drugs producing this effect. The user of a hallucinogenic drug is almost invariably aware that what he is seeing are hallucinations. [NIH]

Haloperidol: Butyrophenone derivative. [NIH]

Haploid: An organism with one basic chromosome set, symbolized by n; the normal condition of gametes in diploids. [NIH]

Haptens: Small antigenic determinants capable of eliciting an immune response only when coupled to a carrier. Haptens bind to antibodies but by themselves cannot elicit an antibody response. [NIH]

Headache: Pain in the cranial region that may occur as an isolated and benign symptom or as a manifestation of a wide variety of conditions including subarachnoid hemorrhage; craniocerebral trauma; central nervous system infections; intracranial hypertension; and other disorders. In general, recurrent headaches that are not associated with a primary disease process are referred to as headache disorders (e.g., migraine). [NIH]

Headache Disorders: Common conditions characterized by persistent or recurrent headaches. Headache syndrome classification systems may be based on etiology (e.g., vascular headache, post-traumatic headaches, etc.), temporal pattern (e.g., cluster headache, paroxysmal hemicrania, etc.), and precipitating factors (e.g., cough headache). [NIH]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Heart failure: Loss of pumping ability by the heart, often accompanied by fatigue, breathlessness, and excess fluid accumulation in body tissues. [NIH]

Heartbeat: One complete contraction of the heart. [NIH]

Heartburn: Substernal pain or burning sensation, usually associated with regurgitation of gastric juice into the esophagus. [NIH]

Heme: The color-furnishing portion of hemoglobin. It is found free in tissues and as the prosthetic group in many hemeproteins. [NIH]

Hemicrania: An ache or a pain in one side of the head, as in migraine. [NIH]

Hemoglobin: One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal conentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

Hemorrhage: Bleeding or escape of blood from a vessel. [NIH]

Hemorrhoidectomy: An operation to remove hemorrhoids. [NIH]

Hemorrhoids: Varicosities of the hemorrhoidal venous plexuses. [NIH]

Hemostasis: The process which spontaneously arrests the flow of blood from vessels carrying blood under pressure. It is accomplished by contraction of the vessels, adhesion and aggregation of formed blood elements, and the process of blood or plasma coagulation. [NIH]

Hepatic: Refers to the liver. [NIH]

Hepatitis: Inflammation of the liver and liver disease involving degenerative or necrotic alterations of hepatocytes. [NIH]

Hepatocytes: The main structural component of the liver. They are specialized epithelial cells that are organized into interconnected plates called lobules. [NIH]

Hepatotoxicity: How much damage a medicine or other substance does to the liver. [NIH]

Heptanes: Seven-carbon saturated hydrocarbon group of the methane series. Include isomers and derivatives. [NIH]

Heredity: 1. The genetic transmission of a particular quality or trait from parent to offspring. 2. The genetic constitution of an individual. [EU]

Heroin Dependence: Strong dependence, both physiological and emotional, upon heroin. [NIH]

Heterogeneity: The property of one or more samples or populations which implies that they are not identical in respect of some or all of their parameters, e. g. heterogeneity of variance. [NIH]

Heterotropia: One in which the angle of squint remains relatively unaltered on conjugate movement of the eyes. [NIH]

Hip Fractures: Fractures of the femur head, the femur neck, the trochanters, or the inter- or subtrochanteric region. Excludes fractures of the acetabulum and fractures of the femoral shaft below the subtrochanteric region. For the fractures of the femur neck the specific term femoral neck fractures is available. [NIH]

Hippocampus: A curved elevation of gray matter extending the entire length of the floor of the temporal horn of the lateral ventricle (Dorland, 28th ed). The hippocampus, subiculum, and dentate gyrus constitute the hippocampal formation. Sometimes authors include the entorhinal cortex in the hippocampal formation. [NIH]

Histamine: 1H-Imidazole-4-ethanamine. A depressor amine derived by enzymatic decarboxylation of histidine. It is a powerful stimulant of gastric secretion, a constrictor of bronchial smooth muscle, a vasodilator, and also a centrally acting neurotransmitter. [NIH]

Histidine: An essential amino acid important in a number of metabolic processes. It is required for the production of histamine. [NIH]

Homeostasis: The processes whereby the internal environment of an organism tends to remain balanced and stable. [NIH]

Homogenate: A suspension of animal tissue that is ground in the all-glass "homogenizer" described by Potter and Elvehjem in 1936. [NIH]

Homogeneous: Consisting of or composed of similar elements or ingredients; of a uniform quality throughout. [EU]

Homologous: Corresponding in structure, position, origin, etc., as (a) the feathers of a bird and the scales of a fish, (b) antigen and its specific antibody, (c) allelic chromosomes. [EU]

Hormonal: Pertaining to or of the nature of a hormone. [EU]

Hormone: A substance in the body that regulates certain organs. Hormones such as gastrin help in breaking down food. Some hormones come from cells in the stomach and small intestine. [NIH]

Hospice: Institution dedicated to caring for the terminally ill. [NIH]

Host: Any animal that receives a transplanted graft. [NIH]

Hybrid: Cross fertilization between two varieties or, more usually, two species of vines, see also crossing. [NIH]

Hybridization: The genetic process of crossbreeding to produce a hybrid. Hybrid nucleic acids can be formed by nucleic acid hybridization of DNA and RNA molecules. Protein hybridization allows for hybrid proteins to be formed from polypeptide chains. [NIH]

Hydration: Combining with water. [NIH]

Hydrochloric Acid: A strong corrosive acid that is commonly used as a laboratory reagent. It is formed by dissolving hydrogen chloride in water. Gastric acid is the hydrochloric acid component of gastric juice. [NIH]

Hydrocodone: Narcotic analgesic related to codeine, but more potent and more addicting by weight. It is used also as cough suppressant. [NIH]

Hydrogen: The first chemical element in the periodic table. It has the atomic symbol H, atomic number 1, and atomic weight 1. It exists, under normal conditions, as a colorless, odorless, tasteless, diatomic gas. Hydrogen ions are protons. Besides the common H1 isotope, hydrogen exists as the stable isotope deuterium and the unstable, radioactive isotope tritium. [NIH]

Hydrogen Peroxide: A strong oxidizing agent used in aqueous solution as a ripening agent, bleach, and topical anti-infective. It is relatively unstable and solutions deteriorate over time unless stabilized by the addition of acetanilide or similar organic materials. [NIH]

Hydrolysis: The process of cleaving a chemical compound by the addition of a molecule of water. [NIH]

Hydromorphone: An opioid analgesic made from morphine and used mainly as an analgesic. It has a shorter duration of action than morphine. [NIH]

Hydrophobic: Not readily absorbing water, or being adversely affected by water, as a hydrophobic colloid. [EU]

Hydroxylysine: A hydroxylated derivative of the amino acid lysine that is present in certain collagens. [NIH]

Hydroxyproline: A hydroxylated form of the imino acid proline. A deficiency in ascorbic acid can result in impaired hydroxyproline formation. [NIH]

Hyperalgesia: Excessive sensitiveness or sensibility to pain. [EU]

Hyperbaric: Characterized by greater than normal pressure or weight; applied to gases under greater than atmospheric pressure, as hyperbaric oxygen, or to a solution of greater specific gravity than another taken as a standard of reference. [EU]

Hyperbaric oxygen: Oxygen that is at an atmospheric pressure higher than the pressure at sea level. Breathing hyperbaric oxygen to enhance the effectiveness of radiation therapy is being studied. [NIH]

Hypersensitivity: Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that particular antigen. [NIH]

Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Hyperthermia: A type of treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anticancer drugs. [NIH]

Hypertrophy: General increase in bulk of a part or organ, not due to tumor formation, nor to an increase in the number of cells. [NIH]

Hypnotic: A drug that acts to induce sleep. [EU]

Hypodermic: Applied or administered beneath the skin. [EU]

Hypoglycaemia: An abnormally diminished concentration of glucose in the blood, which may lead to tremulousness, cold sweat, piloerection, hypothermia, and headache, accompanied by irritability, confusion, hallucinations, bizarre behaviour, and ultimately, convulsions and coma. [EU]

Hypoglycemic: An orally active drug that produces a fall in blood glucose concentration. [NIH]

Hypopharynx: The portion of the pharynx between the inferior portion of the oropharynx and the larynx. [NIH]

Hypotension: Abnormally low blood pressure. [NIH]

Hypothalamic: Of or involving the hypothalamus. [EU]

Hypothalamus: Ventral part of the diencephalon extending from the region of the optic chiasm to the caudal border of the mammillary bodies and forming the inferior and lateral walls of the third ventricle. [NIH]

Hypothermia: Lower than normal body temperature, especially in warm-blooded animals; in man usually accidental or unintentional. [NIH]

Hypoxia: Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood. [EU]

Hysterectomy: Excision of the uterus. [NIH]

Hysterotomy: An incision in the uterus, performed through either the abdomen or the vagina. [NIH]

Ibuprofen: A nonsteroidal anti-inflammatory agent with analgesic properties used in the therapy of rheumatism and arthritis. [NIH]

Id: The part of the personality structure which harbors the unconscious instinctive desires and strivings of the individual. [NIH]

Idiopathic: Describes a disease of unknown cause. [NIH]

Ileum: The lower end of the small intestine. [NIH]

Imipramine: The prototypical tricyclic antidepressant. It has been used in major depression, dysthymia, bipolar depression, attention-deficit disorders, agoraphobia, and panic disorders. It has less sedative effect than some other members of this therapeutic group. [NIH]

Immune function: Production and action of cells that fight disease or infection. [NIH]

Immune response: The activity of the immune system against foreign substances (antigens). [NIH]

Immune system: The organs, cells, and molecules responsible for the recognition and disposal of foreign ("non-self") material which enters the body. [NIH]

Immunity: Nonsusceptibility to the invasive or pathogenic effects of foreign microorganisms or to the toxic effect of antigenic substances. [NIH]

Immunization: Deliberate stimulation of the host's immune response. Active immunization involves administration of antigens or immunologic adjuvants. Passive immunization involves administration of immune sera or lymphocytes or their extracts (e.g., transfer factor, immune RNA) or transplantation of immunocompetent cell producing tissue (thymus or bone marrow). [NIH]

Immunoassay: Immunochemical assay or detection of a substance by serologic or immunologic methods. Usually the substance being studied serves as antigen both in antibody production and in measurement of antibody by the test substance. [NIH]

Immunodeficiency: The decreased ability of the body to fight infection and disease. [NIH]

Immunodeficiency syndrome: The inability of the body to produce an immune response. [NIH]

Immunofluorescence: A technique for identifying molecules present on the surfaces of cells or in tissues using a highly fluorescent substance coupled to a specific antibody. [NIH]

Immunogenic: Producing immunity; evoking an immune response. [EU]

Immunoglobulin: A protein that acts as an antibody. [NIH]

Immunohistochemistry: Histochemical localization of immunoreactive substances using labeled antibodies as reagents. [NIH]

Immunologic: The ability of the antibody-forming system to recall a previous experience with an antigen and to respond to a second exposure with the prompt production of large amounts of antibody. [NIH]

Immunology: The study of the body's immune system. [NIH]

Immunosuppressant: An agent capable of suppressing immune responses. [EU]

Immunosuppressive: Describes the ability to lower immune system responses. [NIH]

Immunotherapy: Manipulation of the host's immune system in treatment of disease. It includes both active and passive immunization as well as immunosuppressive therapy to prevent graft rejection. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

Impotence: The inability to perform sexual intercourse. [NIH]

In situ: In the natural or normal place; confined to the site of origin without invasion of neighbouring tissues. [EU]

In Situ Hybridization: A technique that localizes specific nucleic acid sequences within intact chromosomes, eukaryotic cells, or bacterial cells through the use of specific nucleic acid-labeled probes. [NIH]

In vitro: In the laboratory (outside the body). The opposite of in vivo (in the body). [NIH]

In vivo: In the body. The opposite of in vitro (outside the body or in the laboratory). [NIH]

Incision: A cut made in the body during surgery. [NIH]

Incompetence: Physical or mental inadequacy or insufficiency. [EU]

Incontinence: Inability to control the flow of urine from the bladder (urinary incontinence) or the escape of stool from the rectum (fecal incontinence). [NIH]

Incubation: The development of an infectious disease from the entrance of the pathogen to the appearance of clinical symptoms. [EU]

Incubation period: The period of time likely to elapse between exposure to the agent of the disease and the onset of clinical symptoms. [NIH]

Indicative: That indicates; that points out more or less exactly; that reveals fairly clearly. [EU]

Indigestion: Poor digestion. Symptoms include heartburn, nausea, bloating, and gas. Also called dyspepsia. [NIH]

Indomethacin: A non-steroidal anti-inflammatory agent (NSAID) that inhibits the enzyme cyclooxygenase necessary for the formation of prostaglandins and other autacoids. It also inhibits the motility of polymorphonuclear leukocytes. [NIH]

Induction: The act or process of inducing or causing to occur, especially the production of a specific morphogenetic effect in the developing embryo through the influence of evocators

or organizers, or the production of anaesthesia or unconsciousness by use of appropriate agents. [EU]

Infarction: A pathological process consisting of a sudden insufficient blood supply to an area, which results in necrosis of that area. It is usually caused by a thrombus, an embolus, or a vascular torsion. [NIH]

Infection: 1. Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response. The infection may remain localized, subclinical, and temporary if the body's defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute, or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system. 2. An infectious disease. [EU]

Infiltration: The diffusion or accumulation in a tissue or cells of substances not normal to it or in amounts of the normal. Also, the material so accumulated. [EU]

Inflammation: A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

Influenza: An acute viral infection involving the respiratory tract. It is marked by inflammation of the nasal mucosa, the pharynx, and conjunctiva, and by headache and severe, often generalized, myalgia. [NIH]

Infuse: To pour (a liquid) into something. [EU]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion. [NIH]

Infusion Pumps: Fluid propulsion systems driven mechanically, electrically, or osmotically that are used to inject (or infuse) over time agents into a patient or experimental animal; used routinely in hospitals to maintain a patent intravenous line, to administer antineoplastic agents and other drugs in thromboembolism, heart disease, diabetes mellitus (insulin infusion systems is also available), and other disorders. [NIH]

Ingestion: Taking into the body by mouth [NIH]

Inhalation: The drawing of air or other substances into the lungs. [EU]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

Innervation: 1. The distribution or supply of nerves to a part. 2. The supply of nervous energy or of nerve stimulus sent to a part. [EU]

Inorganic: Pertaining to substances not of organic origin. [EU]

Inotropic: Affecting the force or energy of muscular contractions. [EU]

Inpatients: Persons admitted to health facilities which provide board and room, for the purpose of observation, care, diagnosis or treatment. [NIH]

Insight: The capacity to understand one's own motives, to be aware of one's own psychodynamics, to appreciate the meaning of symbolic behavior. [NIH]

Insomnia: Difficulty in going to sleep or getting enough sleep. [NIH]

Instillation: . [EU]

Insulator: Material covering the metal conductor of the lead. It is usually polyurethane or silicone. [NIH]

Insulin: A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

Insulin Infusion Systems: Portable or implantable devices for infusion of insulin. Includes open-loop systems which may be patient-operated or controlled by a pre-set program and are designed for constant delivery of small quantities of insulin, increased during food ingestion, and closed-loop systems which deliver quantities of insulin automatically based on an electronic glucose sensor. [NIH]

Insulin-dependent diabetes mellitus: A disease characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both. Autoimmune, genetic, and environmental factors are involved in the development of type I diabetes. [NIH]

Intensive Care: Advanced and highly specialized care provided to medical or surgical patients whose conditions are life-threatening and require comprehensive care and constant monitoring. It is usually administered in specially equipped units of a health care facility. [NIH]

Intermittent: Occurring at separated intervals; having periods of cessation of activity. [EU]

Interneurons: Most generally any neurons which are not motor or sensory. Interneurons may also refer to neurons whose axons remain within a particular brain region as contrasted with projection neurons which have axons projecting to other brain regions. [NIH]

Interstitial: Pertaining to or situated between parts or in the interspaces of a tissue. [EU]

Intestinal: Having to do with the intestines. [NIH]

Intestinal Pseudo-Obstruction: Obstruction of the intestines that is functional, not mechanical. [NIH]

Intestine: A long, tube-shaped organ in the abdomen that completes the process of digestion. There is both a large intestine and a small intestine. Also called the bowel. [NIH]

Intoxication: Poisoning, the state of being poisoned. [EU]

Intracellular: Inside a cell. [NIH]

Intracellular Membranes: Membranes of subcellular structures. [NIH]

Intracranial Hypertension: Increased pressure within the cranial vault. This may result from several conditions, including hydrocephalus; brain edema; intracranial masses; severe systemic hypertension; pseudotumor cerebri; and other disorders. [NIH]

Intralaminar Thalamic Nuclei: Cell groups within the internal medullary lamina of the thalamus. They include a rostral division comprising the paracentral, central lateral, central dorsal, and central medial nuclei, and a caudal division composed of the centromedian and parafascicular nuclei. [NIH]

Intramuscular: IM. Within or into muscle. [NIH]

Intrathecal: Describes the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord. Drugs can be injected into the fluid or a sample of the fluid can be removed for testing. [NIH]

Intravenous: IV. Into a vein. [NIH]

Intrinsic: Situated entirely within or pertaining exclusively to a part. [EU]

Intubation: Introduction of a tube into a hollow organ to restore or maintain patency if obstructed. It is differentiated from catheterization in that the insertion of a catheter is usually performed for the introducing or withdrawing of fluids from the body. [NIH]

Invasive: 1. Having the quality of invasiveness. 2. Involving puncture or incision of the skin or insertion of an instrument or foreign material into the body; said of diagnostic techniques. [EU]

Involuntary: Reaction occurring without intention or volition. [NIH]

Ion Channels: Gated, ion-selective glycoproteins that traverse membranes. The stimulus for channel gating can be a membrane potential, drug, transmitter, cytoplasmic messenger, or a mechanical deformation. Ion channels which are integral parts of ionotropic neurotransmitter receptors are not included. [NIH]

Ion Transport: The movement of ions across energy-transducing cell membranes. Transport can be active or passive. Passive ion transport (facilitated diffusion) derives its energy from the concentration gradient of the ion itself and allows the transport of a single solute in one direction (uniport). Active ion transport is usually coupled to an energy-yielding chemical or photochemical reaction such as ATP hydrolysis. This form of primary active transport is called an ion pump. Secondary active transport utilizes the voltage and ion gradients produced by the primary transport to drive the cotransport of other ions or molecules. These may be transported in the same (symport) or opposite (antiport) direction. [NIH]

Ionization: 1. Any process by which a neutral atom gains or loses electrons, thus acquiring a net charge, as the dissociation of a substance in solution into ions or ion production by the passage of radioactive particles. 2. Iontophoresis. [EU]

Ionizing: Radiation comprising charged particles, e. g. electrons, protons, alpha-particles, etc., having sufficient kinetic energy to produce ionization by collision. [NIH]

Ions: An atom or group of atoms that have a positive or negative electric charge due to a gain (negative charge) or loss (positive charge) of one or more electrons. Atoms with a positive charge are known as cations; those with a negative charge are anions. [NIH]

Iop: Intraocular pressure: pressure of the fluid inside the eye; normal IOP varies among individuals. [NIH]

Iris: The most anterior portion of the uveal layer, separating the anterior chamber from the posterior. It consists of two layers - the stroma and the pigmented epithelium. Color of the iris depends on the amount of melanin in the stroma on reflection from the pigmented epithelium. [NIH]

Ischemia: Deficiency of blood in a part, due to functional constriction or actual obstruction of a blood vessel. [EU]

Isoenzyme: Different forms of an enzyme, usually occurring in different tissues. The isoenzymes of a particular enzyme catalyze the same reaction but they differ in some of their properties. [NIH]

Joint: The point of contact between elements of an animal skeleton with the parts that surround and support it. [NIH]

Kainate: Glutamate receptor. [NIH]

Kainic Acid: (2S-(2 alpha,3 beta,4 beta))-2-Carboxy-4-(1-methylethenyl)-3-pyrrolidineacetic acid. Ascaricide obtained from the red alga Digenea simplex. It is a potent excitatory amino acid agonist at some types of excitatory amino acid receptors and has been used to discriminate among receptor types. Like many excitatory amino acid agonists it can cause neurotoxicity and has been used experimentally for that purpose. [NIH]

Kb: A measure of the length of DNA fragments, 1 Kb = 1000 base pairs. The largest DNA fragments are up to 50 kilobases long. [NIH]

Ketamine: A cyclohexanone derivative used for induction of anesthesia. Its mechanism of action is not well understood, but ketamine can block NMDA receptors (receptors, N-

Methyl-D-Aspartate) and may interact with sigma receptors. [NIH]

Keto: It consists of 8 carbon atoms and within the endotoxins, it connects poysaccharide and lipid A. [NIH]

Ketone Bodies: Chemicals that the body makes when there is not enough insulin in the blood and it must break down fat for its energy. Ketone bodies can poison and even kill body cells. When the body does not have the help of insulin, the ketones build up in the blood and then "spill" over into the urine so that the body can get rid of them. The body can also rid itself of one type of ketone, called acetone, through the lungs. This gives the breath a fruity odor. Ketones that build up in the body for a long time lead to serious illness and coma. [NIH]

Ketoprofen: An ibuprofen-type anti-inflammatory analgesic and antipyretic. It is used in the treatment of rheumatoid arthritis and osteoarthritis. [NIH]

Ketorolac: A drug that belongs to a family of drugs called nonsteroidal anti-inflammatory agents. It is being studied in cancer prevention. [NIH]

Ketorolac Tromethamine: A pyrrolizine carboxylic acid derivative structurally related to indomethacin. It is a non-steroidal anti-inflammatory agent used for analgesia for postoperative pain and inhibits cyclooxygenase activity. [NIH]

Kinetic: Pertaining to or producing motion. [EU]

Krypton: A noble gas that is found in the atmosphere. It has the atomic symbol Kr, atomic number 36, atomic weight 83.80, and has been used in electric bulbs. [NIH]

Labile: 1. Gliding; moving from point to point over the surface; unstable; fluctuating. 2. Chemically unstable. [EU]

Lactation: The period of the secretion of milk. [EU]

Laparotomy: A surgical incision made in the wall of the abdomen. [NIH]

Large Intestine: The part of the intestine that goes from the cecum to the rectum. The large intestine absorbs water from stool and changes it from a liquid to a solid form. The large intestine is 5 feet long and includes the appendix, cecum, colon, and rectum. Also called colon. [NIH]

Larynx: An irregularly shaped, musculocartilaginous tubular structure, lined with mucous membrane, located at the top of the trachea and below the root of the tongue and the hyoid bone. It is the essential sphincter guarding the entrance into the trachea and functioning secondarily as the organ of voice. [NIH]

Laser therapy: The use of an intensely powerful beam of light to kill cancer cells. [NIH]

Latency: The period of apparent inactivity between the time when a stimulus is presented and the moment a response occurs. [NIH]

Latent: Phoria which occurs at one distance or another and which usually has no troublesome effect. [NIH]

Lavage: A cleaning of the stomach and colon. Uses a special drink and enemas. [NIH]

Laxative: An agent that acts to promote evacuation of the bowel; a cathartic or purgative. [EU]

Lectin: A complex molecule that has both protein and sugars. Lectins are able to bind to the outside of a cell and cause biochemical changes in it. Lectins are made by both animals and plants. [NIH]

Lens: The transparent, double convex (outward curve on both sides) structure suspended between the aqueous and vitreous; helps to focus light on the retina. [NIH]

Lesion: An area of abnormal tissue change. [NIH]

Leucine: An essential branched-chain amino acid important for hemoglobin formation. [NIH]

Leukemia: Cancer of blood-forming tissue. [NIH]

Leukocytes: White blood cells. These include granular leukocytes (basophils, eosinophils, and neutrophils) as well as non-granular leukocytes (lymphocytes and monocytes). [NIH]

Levo: It is an experimental treatment for heroin addiction that was developed by German scientists around 1948 as an analgesic. Like methadone, it binds with opioid receptors, but it is longer acting. [NIH]

Levodopa: The naturally occurring form of dopa and the immediate precursor of dopamine. Unlike dopamine itself, it can be taken orally and crosses the blood-brain barrier. It is rapidly taken up by dopaminergic neurons and converted to dopamine. It is used for the treatment of parkinsonism and is usually given with agents that inhibit its conversion to dopamine outside of the central nervous system. [NIH]

Levorphanol: A narcotic analgesic that may be habit-forming. It is nearly as effective orally as by injection. [NIH]

Library Services: Services offered to the library user. They include reference and circulation. [NIH]

Lidocaine: A local anesthetic and cardiac depressant used as an antiarrhythmia agent. Its actions are more intense and its effects more prolonged than those of procaine but its duration of action is shorter than that of bupivacaine or prilocaine. [NIH]

Life cycle: The successive stages through which an organism passes from fertilized ovum or spore to the fertilized ovum or spore of the next generation. [NIH]

Ligament: A band of fibrous tissue that connects bones or cartilages, serving to support and strengthen joints. [EU]

Ligands: A RNA simulation method developed by the MIT. [NIH]

Limbic: Pertaining to a limbus, or margin; forming a border around. [EU]

Limbic System: A set of forebrain structures common to all mammals that is defined functionally and anatomically. It is implicated in the higher integration of visceral, olfactory, and somatic information as well as homeostatic responses including fundamental survival behaviors (feeding, mating, emotion). For most authors, it includes the amygdala, epithalamus, gyrus cinguli, hippocampal formation (see hippocampus), hypothalamus, parahippocampal gyrus, septal nuclei, anterior nuclear group of thalamus, and portions of the basal ganglia. (Parent, Carpenter's Human Neuroanatomy, 9th ed, p744; NeuroNames, http://rprcsgi.rprc.washington.edu/neuronames/index.html (September 2, 1998)). [NIH]

Linkage: The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

Lipid: Fat. [NIH]

Lipid Peroxidation: Peroxidase catalyzed oxidation of lipids using hydrogen peroxide as an electron acceptor. [NIH]

Lipoid: The most common nephrotic syndrome disease of childhood. [NIH]

Lithium: An element in the alkali metals family. It has the atomic symbol Li, atomic number 3, and atomic weight 6.94. Salts of lithium are used in treating manic-depressive disorders. [NIH]

Lithotripsy: The destruction of a calculus of the kidney, ureter, bladder, or gallbladder by physical forces, including crushing with a lithotriptor through a catheter. Focused

percutaneous ultrasound and focused hydraulic shock waves may be used without surgery. Lithotripsy does not include the dissolving of stones by acids or litholysis. Lithotripsy by laser is laser lithotripsy. [NIH]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Liver cancer: A disease in which malignant (cancer) cells are found in the tissues of the liver. [NIH]

Liver Transplantation: The transference of a part of or an entire liver from one human or animal to another. [NIH]

Lobe: A portion of an organ such as the liver, lung, breast, or brain. [NIH]

Localization: The process of determining or marking the location or site of a lesion or disease. May also refer to the process of keeping a lesion or disease in a specific location or site. [NIH]

Localized: Cancer which has not metastasized yet. [NIH]

Locomotion: Movement or the ability to move from one place or another. It can refer to humans, vertebrate or invertebrate animals, and microorganisms. [NIH]

Locomotor: Of or pertaining to locomotion; pertaining to or affecting the locomotive apparatus of the body. [EU]

Locus Coeruleus: Bluish region in the superior angle of the fourth ventricle floor, corresponding to melanin-like pigmented nerve cells which lie lateral to the ponto-mesencephalic central gray (griseum centrale). It is also known as nucleus pigmentosus pontis. [NIH]

Long-Term Potentiation: A persistent increase in synaptic efficacy, usually induced by appropriate activation of the same synapses. The phenomenological properties of long-term potentiation suggest that it may be a cellular mechanism of learning and memory. [NIH]

Loop: A wire usually of platinum bent at one end into a small loop (usually 4 mm inside diameter) and used in transferring microorganisms. [NIH]

Loperamide: 4-(p-Chlorophenyl)-4-hydroxy-N.N-dimethyl-alpha,alpha-diphenyl-1-piperidine butyramide hydrochloride. Synthetic anti-diarrheal agent with a long duration of action; it is not significantly absorbed from the gut, has no effect on the adrenergic system or central nervous system, but may antagonize histamine and interfere with acetylcholine release locally. [NIH]

Lower Esophageal Sphincter: The muscle between the esophagus and stomach. When a person swallows, this muscle relaxes to let food pass from the esophagus to the stomach. It stays closed at other times to keep stomach contents from flowing back into the esophagus. [NIH]

Lumbar: Pertaining to the loins, the part of the back between the thorax and the pelvis. [EU]

Luteal Phase: The period of the menstrual cycle that begins with ovulation and ends with menstruation. [NIH]

Lutein Cells: The cells of the corpus luteum which are derived from the granulosa cells and the theca cells of the Graafian follicle. [NIH]

Luxation: The displacement of the particular surface of a bone from its normal joint, without fracture. [NIH]

Lymph: The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [NIH]

Lymph node: A rounded mass of lymphatic tissue that is surrounded by a capsule of

connective tissue. Also known as a lymph gland. Lymph nodes are spread out along lymphatic vessels and contain many lymphocytes, which filter the lymphatic fluid (lymph). [NIH]

Lymphatic: The tissues and organs, including the bone marrow, spleen, thymus, and lymph nodes, that produce and store cells that fight infection and disease. [NIH]

Lymphatic system: The tissues and organs that produce, store, and carry white blood cells that fight infection and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes and a network of thin tubes that carry lymph and white blood cells. These tubes branch, like blood vessels, into all the tissues of the body. [NIH]

Lymphocyte: A white blood cell. Lymphocytes have a number of roles in the immune system, including the production of antibodies and other substances that fight infection and diseases. [NIH]

Lymphocytic: Referring to lymphocytes, a type of white blood cell. [NIH]

Lymphoid: Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop. [NIH]

Macrophage: A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells. [NIH]

Magnetic Resonance Imaging: Non-invasive method of demonstrating internal anatomy based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy and emit them as radiowaves which can be reconstructed into computerized images. The concept includes proton spin tomographic techniques. [NIH]

Maintenance therapy: Treatment that is given to help a primary (original) treatment keep working. Maintenance therapy is often given to help keep cancer in remission. [NIH]

Malaise: A vague feeling of bodily discomfort. [EU]

Malignant: Cancerous; a growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malignant tumor: A tumor capable of metastasizing. [NIH]

Malnutrition: A condition caused by not eating enough food or not eating a balanced diet. [NIH]

Mammary: Pertaining to the mamma, or breast. [EU]

Mania: Excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization of behaviour, and elevation of mood. [EU]

Manic: Affected with mania. [EU]

Manifest: Being the part or aspect of a phenomenon that is directly observable : concretely expressed in behaviour. [EU]

Mastectomy: Surgery to remove the breast (or as much of the breast tissue as possible). [NIH]

Mastication: The act and process of chewing and grinding food in the mouth. [NIH]

Maxillary: Pertaining to the maxilla : the irregularly shaped bone that with its fellow forms the upper jaw. [EU]

Maxillary Nerve: The intermediate sensory division of the trigeminal (5th cranial) nerve. The maxillary nerve carries general afferents from the intermediate region of the face including the lower eyelid, nose and upper lip, the maxillary teeth, and parts of the dura. [NIH]

Maximum Tolerated Dose: The highest dose level eliciting signs of toxicity without having major effects on survival relative to the test in which it is used. [NIH]

Mecamylamine: A nicotinic antagonist that is well absorbed from the gastrointestinal tract and crosses the blood-brain barrier. Mecamylamine has been used as a ganglionic blocker in treating hypertension, but, like most ganglionic blockers, is more often used now as a research tool. [NIH]

Mechanical ventilation: Use of a machine called a ventilator or respirator to improve the exchange of air between the lungs and the atmosphere. [NIH]

Medial: Lying near the midsaggital plane of the body; opposed to lateral. [NIH]

Mediate: Indirect; accomplished by the aid of an intervening medium. [EU]

Mediator: An object or substance by which something is mediated, such as (1) a structure of the nervous system that transmits impulses eliciting a specific response; (2) a chemical substance (transmitter substance) that induces activity in an excitable tissue, such as nerve or muscle; or (3) a substance released from cells as the result of the interaction of antigen with antibody or by the action of antigen with a sensitized lymphocyte. [EU]

Medical Staff: Professional medical personnel who provide care to patients in an organized facility, institution or agency. [NIH]

Medicament: A medicinal substance or agent. [EU]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

Medullary: Pertaining to the marrow or to any medulla; resembling marrow. [EU]

Meiosis: A special method of cell division, occurring in maturation of the germ cells, by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species. [NIH]

Melanin: The substance that gives the skin its color. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

Membrane Glycoproteins: Glycoproteins found on the membrane or surface of cells. [NIH]

Membrane Proteins: Proteins which are found in membranes including cellular and intracellular membranes. They consist of two types, peripheral and integral proteins. They include most membrane-associated enzymes, antigenic proteins, transport proteins, and drug, hormone, and lectin receptors. [NIH]

Memory: Complex mental function having four distinct phases: (1) memorizing or learning, (2) retention, (3) recall, and (4) recognition. Clinically, it is usually subdivided into immediate, recent, and remote memory. [NIH]

Meninges: The three membranes that cover and protect the brain and spinal cord. [NIH]

Menopause: Permanent cessation of menstruation. [NIH]

Menstrual Cycle: The period of the regularly recurring physiologic changes in the endometrium occurring during the reproductive period in human females and some primates and culminating in partial sloughing of the endometrium (menstruation). [NIH]

Menstruation: The normal physiologic discharge through the vagina of blood and mucosal tissues from the nonpregnant uterus. [NIH]

Mental Disorders: Psychiatric illness or diseases manifested by breakdowns in the adaptational process expressed primarily as abnormalities of thought, feeling, and behavior producing either distress or impairment of function. [NIH]

Mental Health: The state wherein the person is well adjusted. [NIH]

Mental Processes: Conceptual functions or thinking in all its forms. [NIH]

Meperidine: 1-Methyl-4-phenyl-4-piperidinecarboxylic acid ethyl ester. A narcotic analgesic

that can be used for the relief of most types of moderate to severe pain, including postoperative pain and the pain of labor. Prolonged use may lead to dependence of the morphine type; withdrawal symptoms appear more rapidly than with morphine and are of shorter duration. [NIH]

Mesencephalic: Ipsilateral oculomotor paralysis and contralateral tremor, spasm. or choreic movements of the face and limbs. [NIH]

Mesolimbic: Inner brain region governing emotion and drives. [NIH]

Metabolite: Any substance produced by metabolism or by a metabolic process. [EU]

Metaphase: The second phase of cell division, in which the chromosomes line up across the equatorial plane of the spindle prior to separation. [NIH]

Methacrylate: A vinyl monomer. [NIH]

Methamphetamine: A central nervous system stimulant and sympathomimetic with actions and uses similar to dextroamphetamine. The smokable form is a drug of abuse and is referred to as crank, crystal, crystal meth, ice, and speed. [NIH]

Methionine: A sulfur containing essential amino acid that is important in many body functions. It is a chelating agent for heavy metals. [NIH]

Methylcellulose: Methylester of cellulose. Methylcellulose is used as an emulsifying and suspending agent in cosmetics, pharmaceutics and the chemical industry. It is used therapeutically as a bulk laxative. [NIH]

Metoclopramide: A dopamine D2 antagonist that is used as an antiemetic. [NIH]

MI: Myocardial infarction. Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

Microbe: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microbiology: The study of microorganisms such as fungi, bacteria, algae, archaea, and viruses. [NIH]

Microdialysis: A technique for measuring extracellular concentrations of substances in tissues, usually in vivo, by means of a small probe equipped with a semipermeable membrane. Substances may also be introduced into the extracellular space through the membrane. [NIH]

Microorganism: An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms. [NIH]

Microscopy: The application of microscope magnification to the study of materials that cannot be properly seen by the unaided eye. [NIH]

Microtubules: Slender, cylindrical filaments found in the cytoskeleton of plant and animal cells. They are composed of the protein tubulin. [NIH]

Midazolam: A short-acting compound, water-soluble at pH less than 4 and lipid-soluble at physiological pH. It is a hypnotic-sedative drug with anxiolytic and amnestic properties. It is used for sedation in dentistry, cardiac surgery, endoscopic procedures, as preanesthetic medication, and as an adjunct to local anesthesia. Because of its short duration and cardiorespiratory stability, it is particularly useful in poor-risk, elderly, and cardiac patients. [NIH]

Middle Cerebral Artery: The largest and most complex of the cerebral arteries. Branches of the middle cerebral artery supply the insular region, motor and premotor areas, and large

regions of the association cortex. [NIH]

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [NIH]

Mineralocorticoid: 1. Any of the group of C21 corticosteroids, principally aldosterone, predominantly involved in the regulation of electrolyte and water balance through their effect on ion transport in epithelial cells of the renal tubules, resulting in retention of sodium and loss of potassium; some also possess varying degrees of glucocorticoid activity. Their secretion is regulated principally by plasma volume, serum potassium concentration and angiotensin II, and to a lesser extent by anterior pituitary ACTH. 2. Of, pertaining to, having the properties of, or resembling a mineralocorticoid. [EU]

Miosis: Pupillary constriction. This may result from congenital absence of the dilatator pupillary muscle, defective sympathetic innervation, or irritation of the conjunctiva or cornea. [NIH]

Miotic: 1. Pertaining to, characterized by, or producing miosis : contraction of the pupil. 2. An agent that causes the pupil to contract. 3. Meiotic: characterized by cell division. [EU]

Mitochondrial Swelling: Increase in volume of mitochondria due to an influx of fluid; it occurs in hypotonic solutions due to osmotic pressure and in isotonic solutions as a result of altered permeability of the membranes of respiring mitochondria. [NIH]

Mitosis: A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

Mobility: Capability of movement, of being moved, or of flowing freely. [EU]

Mobilization: The process of making a fixed part or stored substance mobile, as by separating a part from surrounding structures to make it accessible for an operative procedure or by causing release into the circulation for body use of a substance stored in the body. [EU]

Modeling: A treatment procedure whereby the therapist presents the target behavior which the learner is to imitate and make part of his repertoire. [NIH]

Modification: A change in an organism, or in a process in an organism, that is acquired from its own activity or environment. [NIH]

Modulator: A specific inductor that brings out characteristics peculiar to a definite region. [EU]

Molecular: Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

Molecular Structure: The location of the atoms, groups or ions relative to one another in a molecule, as well as the number, type and location of covalent bonds. [NIH]

Molecule: A chemical made up of two or more atoms. The atoms in a molecule can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms. [NIH]

Monitor: An apparatus which automatically records such physiological signs as respiration, pulse, and blood pressure in an anesthetized patient or one undergoing surgical or other procedures. [NIH]

Monoamine: Enzyme that breaks down dopamine in the astrocytes and microglia. [NIH]

Monoamine Oxidase: An enzyme that catalyzes the oxidative deamination of naturally occurring monoamines. It is a flavin-containing enzyme that is localized in mitochondrial membranes, whether in nerve terminals, the liver, or other organs. Monoamine oxidase is

important in regulating the metabolic degradation of catecholamines and serotonin in neural or target tissues. Hepatic monoamine oxidase has a crucial defensive role in inactivating circulating monoamines or those, such as tyramine, that originate in the gut and are absorbed into the portal circulation. (From Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 8th ed, p415) EC 1.4.3.4. [NIH]

Monoclonal: An antibody produced by culturing a single type of cell. It therefore consists of a single species of immunoglobulin molecules. [NIH]

Monocytes: Large, phagocytic mononuclear leukocytes produced in the vertebrate bone marrow and released into the blood; contain a large, oval or somewhat indented nucleus surrounded by voluminous cytoplasm and numerous organelles. [NIH]

Mononuclear: A cell with one nucleus. [NIH]

Mood Disorders: Those disorders that have a disturbance in mood as their predominant feature. [NIH]

Morphine: The principal alkaloid in opium and the prototype opiate analgesic and narcotic. Morphine has widespread effects in the central nervous system and on smooth muscle. [NIH]

Morphine Dependence: Strong dependence, both physiological and emotional, upon morphine. [NIH]

Morphine Derivatives: Analogs or derivatives of morphine. [NIH]

Morphology: The science of the form and structure of organisms (plants, animals, and other forms of life). [NIH]

Motility: The ability to move spontaneously. [EU]

Motion Sickness: Sickness caused by motion, as sea sickness, train sickness, car sickness, and air sickness. [NIH]

Motor Activity: The physical activity of an organism as a behavioral phenomenon. [NIH]

Mucinous: Containing or resembling mucin, the main compound in mucus. [NIH]

Mucosa: A mucous membrane, or tunica mucosa. [EU]

Mucositis: A complication of some cancer therapies in which the lining of the digestive system becomes inflamed. Often seen as sores in the mouth. [NIH]

Multiple Myeloma: A malignant tumor of plasma cells usually arising in the bone marrow; characterized by diffuse involvement of the skeletal system, hyperglobulinemia, Bence-Jones proteinuria, and anemia. [NIH]

Multiple sclerosis: A disorder of the central nervous system marked by weakness, numbness, a loss of muscle coordination, and problems with vision, speech, and bladder control. Multiple sclerosis is thought to be an autoimmune disease in which the body's immune system destroys myelin. Myelin is a substance that contains both protein and fat (lipid) and serves as a nerve insulator and helps in the transmission of nerve signals. [NIH]

Multivariate Analysis: A set of techniques used when variation in several variables has to be studied simultaneously. In statistics, multivariate analysis is interpreted as any analytic method that allows simultaneous study of two or more dependent variables. [NIH]

Muscle relaxant: An agent that specifically aids in reducing muscle tension, as those acting at the polysynaptic neurons of motor nerves (e.g. meprobamate) or at the myoneural junction (curare and related compounds). [EU]

Muscle Relaxation: That phase of a muscle twitch during which a muscle returns to a resting position. [NIH]

Musculature: The muscular apparatus of the body, or of any part of it. [EU]

Musculoskeletal System: Themuscles, bones, and cartilage of the body. [NIH]

Myalgia: Pain in a muscle or muscles. [EU]

Myasthenia: Muscular debility; any constitutional anomaly of muscle. [EU]

Myelin: The fatty substance that covers and protects nerves. [NIH]

Myenteric: On stimulation of an intestinal segment, the segment above contracts and that below relaxes. [NIH]

Myocardial infarction: Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

Myocardial Ischemia: A disorder of cardiac function caused by insufficient blood flow to the muscle tissue of the heart. The decreased blood flow may be due to narrowing of the coronary arteries (coronary arteriosclerosis), to obstruction by a thrombus (coronary thrombosis), or less commonly, to diffuse narrowing of arterioles and other small vessels within the heart. Severe interruption of the blood supply to the myocardial tissue may result in necrosis of cardiac muscle (myocardial infarction). [NIH]

Myocardial Reperfusion: Generally, restoration of blood supply to heart tissue which is ischemic due to decrease in normal blood supply. The decrease may result from any source including atherosclerotic obstruction, narrowing of the artery, or surgical clamping. Reperfusion can be induced to treat ischemia. Methods include chemical dissolution of an occluding thrombus, administration of vasodilator drugs, angioplasty, catheterization, and artery bypass graft surgery. However, it is thought that reperfusion can itself further damage the ischemic tissue, causing myocardial reperfusion injury. [NIH]

Myocardial Reperfusion Injury: Functional, metabolic, or structural changes in ischemic heart muscle thought to result from reperfusion to the ischemic areas. Changes can be fatal to muscle cells and may include edema with explosive cell swelling and disintegration, sarcolemma disruption, fragmentation of mitochondria, contraction band necrosis, enzyme washout, and calcium overload. Other damage may include hemorrhage and ventricular arrhythmias. One possible mechanism of damage is thought to be oxygen free radicals. Treatment currently includes the introduction of scavengers of oxygen free radicals, and injury is thought to be prevented by warm blood cardioplegic infusion prior to reperfusion. [NIH]

Myocardium: The muscle tissue of the heart composed of striated, involuntary muscle known as cardiac muscle. [NIH]

Myotonia: Prolonged failure of muscle relaxation after contraction. This may occur after voluntary contractions, muscle percussion, or electrical stimulation of the muscle. Myotonia is a characteristic feature of myotonic disorders. [NIH]

Naive: Used to describe an individual who has never taken a certain drug or class of drugs (e. g., AZT-naive, antiretroviral-naive), or to refer to an undifferentiated immune system cell. [NIH]

Nalbuphine: A narcotic used as a pain medication. It appears to be an agonist at kappa opioid receptors and an antagonist or partial agonist at mu opioid receptors. [NIH]

Naloxone: A specific opiate antagonist that has no agonist activity. It is a competitive antagonist at mu, delta, and kappa opioid receptors. [NIH]

Naltrexone: Derivative of noroxymorphone that is the N-cyclopropylmethyl congener of naloxone. It is a narcotic antagonist that is effective orally, longer lasting and more potent than naloxone, and has been proposed for the treatment of heroin addiction. The FDA has approved naltrexone for the treatment of alcohol dependence. [NIH]

Narcolepsy: A condition of unknown cause characterized by a periodic uncontrollable tendency to fall asleep. [NIH]

Narcosis: A general and nonspecific reversible depression of neuronal excitability, produced by a number of physical and chemical aspects, usually resulting in stupor. [NIH]

Narcotic: 1. Pertaining to or producing narcosis. 2. An agent that produces insensibility or stupor, applied especially to the opioids, i.e. to any natural or synthetic drug that has morphine-like actions. [EU]

Narcotic Antagonists: Agents inhibiting the effect of narcotics on the central nervous system. [NIH]

Nasal Cavity: The proximal portion of the respiratory passages on either side of the nasal septum, lined with ciliated mucosa, extending from the nares to the pharynx. [NIH]

Nasal Mucosa: The mucous membrane lining the nasal cavity. [NIH]

Nausea: An unpleasant sensation in the stomach usually accompanied by the urge to vomit. Common causes are early pregnancy, sea and motion sickness, emotional stress, intense pain, food poisoning, and various enteroviruses. [NIH]

NCI: National Cancer Institute. NCI, part of the National Institutes of Health of the United States Department of Health and Human Services, is the federal government's principal agency for cancer research. NCI conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at http://cancer.gov. [NIH]

Necrosis: A pathological process caused by the progressive degradative action of enzymes that is generally associated with severe cellular trauma. It is characterized by mitochondrial swelling, nuclear flocculation, uncontrolled cell lysis, and ultimately cell death. [NIH]

Need: A state of tension or dissatisfaction felt by an individual that impels him to action toward a goal he believes will satisfy the impulse. [NIH]

Neonatal: Pertaining to the first four weeks after birth. [EU]

Neoplasm: A new growth of benign or malignant tissue. [NIH]

Neostigmine: A cholinesterase inhibitor used in the treatment of myasthenia gravis and to reverse the effects of muscle relaxants such as gallamine and tubocurarine. Neostigmine, unlike physostigmine, does not cross the blood-brain barrier. [NIH]

Neostriatum: The phylogenetically newer part of the corpus striatum consisting of the caudate nucleus and putamen. It is often called simply the striatum. [NIH]

Nephrotic: Pertaining to, resembling, or caused by nephrosis. [EU]

Nephrotic Syndrome: Clinical association of heavy proteinuria, hypoalbuminemia, and generalized edema. [NIH]

Nerve: A cordlike structure of nervous tissue that connects parts of the nervous system with other tissues of the body and conveys nervous impulses to, or away from, these tissues. [NIH]

Nerve Endings: Specialized terminations of peripheral neurons. Nerve endings include neuroeffector junction(s) by which neurons activate target organs and sensory receptors which transduce information from the various sensory modalities and send it centrally in the nervous system. Presynaptic nerve endings are presynaptic terminals. [NIH]

Nerve Fibers: Slender processes of neurons, especially the prolonged axons that conduct nerve impulses. [NIH]

Nervous System: The entire nerve apparatus composed of the brain, spinal cord, nerves and ganglia. [NIH]

Neural: 1. Pertaining to a nerve or to the nerves. 2. Situated in the region of the spinal axis, as the neutral arch. [EU]

Neuralgia: Intense or aching pain that occurs along the course or distribution of a peripheral or cranial nerve. [NIH]

Neuroblastoma: Cancer that arises in immature nerve cells and affects mostly infants and children. [NIH]

Neuroendocrine: Having to do with the interactions between the nervous system and the endocrine system. Describes certain cells that release hormones into the blood in response to stimulation of the nervous system. [NIH]

Neurogenic: Loss of bladder control caused by damage to the nerves controlling the bladder. [NIH]

Neuroleptic: A term coined to refer to the effects on cognition and behaviour of antipsychotic drugs, which produce a state of apathy, lack of initiative, and limited range of emotion and in psychotic patients cause a reduction in confusion and agitation and normalization of psychomotor activity. [EU]

Neurologic: Having to do with nerves or the nervous system. [NIH]

Neuromuscular: Pertaining to muscles and nerves. [EU]

Neuromuscular Junction: The synapse between a neuron and a muscle. [NIH]

Neuronal: Pertaining to a neuron or neurons (= conducting cells of the nervous system). [EU]

Neuronal Plasticity: The capacity of the nervous system to change its reactivity as the result of successive activations. [NIH]

Neurons: The basic cellular units of nervous tissue. Each neuron consists of a body, an axon, and dendrites. Their purpose is to receive, conduct, and transmit impulses in the nervous system. [NIH]

Neuropathy: A problem in any part of the nervous system except the brain and spinal cord. Neuropathies can be caused by infection, toxic substances, or disease. [NIH]

Neuropeptide: A member of a class of protein-like molecules made in the brain. Neuropeptides consist of short chains of amino acids, with some functioning as neurotransmitters and some functioning as hormones. [NIH]

Neuropharmacology: The branch of pharmacology dealing especially with the action of drugs upon various parts of the nervous system. [NIH]

Neuroprotective Agents: Drugs intended to prevent damage to the brain or spinal cord from ischemia, stroke, convulsions, or trauma. Some must be administered before the event, but others may be effective for some time after. They act by a variety of mechanisms, but often directly or indirectly minimize the damage produced by endogenous excitatory amino acids. [NIH]

Neurosecretory Systems: A system of neurons that has the specialized function to produce and secrete hormones, and that constitutes, in whole or in part, an endocrine organ or system. [NIH]

Neuroses: Functional derangement due to disorders of the nervous system which does not affect the psychic personality of the patient. [NIH]

Neurotoxic: Poisonous or destructive to nerve tissue. [EU]

Neurotoxicity: The tendency of some treatments to cause damage to the nervous system. [NIH]

Neurotransmitters: Endogenous signaling molecules that alter the behavior of neurons or

effector cells. Neurotransmitter is used here in its most general sense, including not only messengers that act directly to regulate ion channels, but also those that act through second messenger systems, and those that act at a distance from their site of release. Included are neuromodulators, neuroregulators, neuromediators, and neurohumors, whether or not acting at synapses. [NIH]

Neutrons: Electrically neutral elementary particles found in all atomic nuclei except light hydrogen; the mass is equal to that of the proton and electron combined and they are unstable when isolated from the nucleus, undergoing beta decay. Slow, thermal, epithermal, and fast neutrons refer to the energy levels with which the neutrons are ejected from heavier nuclei during their decay. [NIH]

Neutrophils: Granular leukocytes having a nucleus with three to five lobes connected by slender threads of chromatin, and cytoplasm containing fine inconspicuous granules and stainable by neutral dyes. [NIH]

Nicotine: Nicotine is highly toxic alkaloid. It is the prototypical agonist at nicotinic cholinergic receptors where it dramatically stimulates neurons and ultimately blocks synaptic transmission. Nicotine is also important medically because of its presence in tobacco smoke. [NIH]

Nitric Oxide: A free radical gas produced endogenously by a variety of mammalian cells. It is synthesized from arginine by a complex reaction, catalyzed by nitric oxide synthase. Nitric oxide is endothelium-derived relaxing factor. It is released by the vascular endothelium and mediates the relaxation induced by some vasodilators such as acetylcholine and bradykinin. It also inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium. Nitric oxide activates cytosolic guanylate cyclase and thus elevates intracellular levels of cyclic GMP. [NIH]

Nitrogen: An element with the atomic symbol N, atomic number 7, and atomic weight 14. Nitrogen exists as a diatomic gas and makes up about 78% of the earth's atmosphere by volume. It is a constituent of proteins and nucleic acids and found in all living cells. [NIH]

Norepinephrine: Precursor of epinephrine that is secreted by the adrenal medulla and is a widespread central and autonomic neurotransmitter. Norepinephrine is the principal transmitter of most postganglionic sympathetic fibers and of the diffuse projection system in the brain arising from the locus ceruleus. It is also found in plants and is used pharmacologically as a sympathomimetic. [NIH]

Normal Distribution: Continuous frequency distribution of infinite range. Its properties are as follows: 1) continuous, symmetrical distribution with both tails extending to infinity; 2) arithmetic mean, mode, and median identical; and 3) shape completely determined by the mean and standard deviation. [NIH]

Nortriptyline: A metabolite of amitryptyline that is also used as an antidepressive agent. Nortriptyline is used in major depression, dysthymia, and atypical depressions. [NIH]

Noscapine: A naturally occurring opium alkaloid that is a centrally acting antitussive agent. [NIH]

Nuclear: A test of the structure, blood flow, and function of the kidneys. The doctor injects a mildly radioactive solution into an arm vein and uses x-rays to monitor its progress through the kidneys. [NIH]

Nuclei: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nucleic acid: Either of two types of macromolecule (DNA or RNA) formed by polymerization of nucleotides. Nucleic acids are found in all living cells and contain the

information (genetic code) for the transfer of genetic information from one generation to the next. [NIH]

Nucleic Acid Hybridization: The process whereby two single-stranded polynucleotides form a double-stranded molecule, with hydrogen bonding between the complementary bases in the two strains. [NIH]

Nucleolus: A small dense body (sub organelle) within the nucleus of eukaryotic cells, visible by phase contrast and interference microscopy in live cells throughout interphase. Contains RNA and protein and is the site of synthesis of ribosomal RNA. [NIH]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nucleus Accumbens: Collection of pleomorphic cells in the caudal part of the anterior horn of the lateral ventricle, in the region of the olfactory tubercle, lying between the head of the caudate nucleus and the anterior perforated substance. It is part of the so-called ventral striatum, a composite structure considered part of the basal ganglia. [NIH]

Octanes: Eight-carbon saturated hydrocarbon group of the methane series. Include isomers and derivatives. [NIH]

Ocular: 1. Of, pertaining to, or affecting the eye. 2. Eyepiece. [EU]

Odour: A volatile emanation that is perceived by the sense of smell. [EU]

Oedema: The presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body; usually applied to demonstrable accumulation of excessive fluid in the subcutaneous tissues. Edema may be localized, due to venous or lymphatic obstruction or to increased vascular permeability, or it may be systemic due to heart failure or renal disease. Collections of edema fluid are designated according to the site, e.g. ascites (peritoneal cavity), hydrothorax (pleural cavity), and hydropericardium (pericardial sac). Massive generalized edema is called anasarca. [EU]

Ointments: Semisolid preparations used topically for protective emollient effects or as a vehicle for local administration of medications. Ointment bases are various mixtures of fats, waxes, animal and plant oils and solid and liquid hydrocarbons. [NIH]

Olfaction: Function of the olfactory apparatus to perceive and discriminate between the molecules that reach it, in gas form from an external environment, directly or indirectly via the nose. [NIH]

Oncogene: A gene that normally directs cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure to carcinogens. [NIH]

Oncology: The study of cancer. [NIH]

Ondansetron: A competitive serotonin type 3 receptor antagonist. It is effective in the treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs, including cisplatin, and it has reported anxiolytic and neuroleptic properties. [NIH]

Opacity: Degree of density (area most dense taken for reading). [NIH]

Ophthalmic: Pertaining to the eye. [EU]

Ophthalmology: A surgical specialty concerned with the structure and function of the eye and the medical and surgical treatment of its defects and diseases. [NIH]

Opioid Peptides: The endogenous peptides with opiate-like activity. The three major classes currently recognized are the enkephalins, the dynorphins, and the endorphins. Each of these families derives from different precursors, proenkephalin, prodynorphin, and pro-opiomelanocortin, respectively. There are also at least three classes of opioid receptors, but

the peptide families do not map to the receptors in a simple way. [NIH]

Opium: The air-dried exudate from the unripe seed capsule of the opium poppy, Papaver somniferum, or its variant, P. album. It contains a number of alkaloids, but only a few - morphine, codeine, and papaverine - have clinical significance. Opium has been used as an analgesic, antitussive, antidiarrheal, and antispasmodic. [NIH]

Optic Chiasm: The X-shaped structure formed by the meeting of the two optic nerves. At the optic chiasm the fibers from the medial part of each retina cross to project to the other side of the brain while the lateral retinal fibers continue on the same side. As a result each half of the brain receives information about the contralateral visual field from both eyes. [NIH]

Orbit: One of the two cavities in the skull which contains an eyeball. Each eye is located in a bony socket or orbit. [NIH]

Orbital: Pertaining to the orbit (= the bony cavity that contains the eyeball). [EU]

Organ Culture: The growth in aseptic culture of plant organs such as roots or shoots, beginning with organ primordia or segments and maintaining the characteristics of the organ. [NIH]

Organelles: Specific particles of membrane-bound organized living substances present in eukaryotic cells, such as the mitochondria; the golgi apparatus; endoplasmic reticulum; lysomomes; plastids; and vacuoles. [NIH]

Orofacial: Of or relating to the mouth and face. [EU]

Oropharynx: Oral part of the pharynx. [NIH]

Orthopaedic: Pertaining to the correction of deformities of the musculoskeletal system; pertaining to orthopaedics. [EU]

Osmosis: Tendency of fluids (e.g., water) to move from the less concentrated to the more concentrated side of a semipermeable membrane. [NIH]

Osmotic: Pertaining to or of the nature of osmosis (= the passage of pure solvent from a solution of lesser to one of greater solute concentration when the two solutions are separated by a membrane which selectively prevents the passage of solute molecules, but is permeable to the solvent). [EU]

Osteoarthritis: A progressive, degenerative joint disease, the most common form of arthritis, especially in older persons. The disease is thought to result not from the aging process but from biochemical changes and biomechanical stresses affecting articular cartilage. In the foreign literature it is often called osteoarthrosis deformans. [NIH]

Osteoporosis: Reduction of bone mass without alteration in the composition of bone, leading to fractures. Primary osteoporosis can be of two major types: postmenopausal osteoporosis and age-related (or senile) osteoporosis. [NIH]

Outpatient: A patient who is not an inmate of a hospital but receives diagnosis or treatment in a clinic or dispensary connected with the hospital. [NIH]

Ovary: Either of the paired glands in the female that produce the female germ cells and secrete some of the female sex hormones. [NIH]

Overdose: An accidental or deliberate dose of a medication or street drug that is in excess of what is normally used. [NIH]

Overexpress: An excess of a particular protein on the surface of a cell. [NIH]

Ovulation: The discharge of a secondary oocyte from a ruptured graafian follicle. [NIH]

Ovum: A female germ cell extruded from the ovary at ovulation. [NIH]

Oxidation: The act of oxidizing or state of being oxidized. Chemically it consists in the increase of positive charges on an atom or the loss of negative charges. Most biological oxidations are accomplished by the removal of a pair of hydrogen atoms (dehydrogenation) from a molecule. Such oxidations must be accompanied by reduction of an acceptor molecule. Univalent o. indicates loss of one electron; divalent o., the loss of two electrons. [EU]

Oxidative Stress: A disturbance in the prooxidant-antioxidant balance in favor of the former, leading to potential damage. Indicators of oxidative stress include damaged DNA bases, protein oxidation products, and lipid peroxidation products (Sies, Oxidative Stress, 1991, pxv-xvi). [NIH]

Oximetry: The determination of oxygen-hemoglobin saturation of blood either by withdrawing a sample and passing it through a classical photoelectric oximeter or by electrodes attached to some translucent part of the body like finger, earlobe, or skin fold. It includes non-invasive oxygen monitoring by pulse oximetry. [NIH]

Oxycodone: Semisynthetic derivative of codeine that acts as a narcotic analgesic more potent and addicting than codeine. [NIH]

Oxygen Consumption: The oxygen consumption is determined by calculating the difference between the amount of oxygen inhaled and exhaled. [NIH]

Oxygenase: Enzyme which breaks down heme, the iron-containing oxygen-carrying constituent of the red blood cells. [NIH]

Oxygenator: An apparatus by which oxygen is introduced into the blood during circulation outside the body, as during open heart surgery. [NIH]

Oxytocic: 1. Pertaining to, characterized by, or promoting oxytocia (= rapid labor). 2. An agent that hastens evacuation of the uterus by stimulating contractions of the myometrium. [EU]

Oxytocin: A nonapeptide posterior pituitary hormone that causes uterine contractions and stimulates lactation. [NIH]

Paclitaxel: Antineoplastic agent isolated from the bark of the Pacific yew tree, Taxus brevifolia. Paclitaxel stabilizes microtubules in their polymerized form and thus mimics the action of the proto-oncogene proteins c-mos. [NIH]

Paediatric: Of or relating to the care and medical treatment of children; belonging to or concerned with paediatrics. [EU]

Pain Threshold: Amount of stimulation required before the sensation of pain is experienced. [NIH]

Palate: The structure that forms the roof of the mouth. It consists of the anterior hard palate and the posterior soft palate. [NIH]

Palladium: A chemical element having an atomic weight of 106.4, atomic number of 46, and the symbol Pd. It is a white, ductile metal resembling platinum, and following it in abundance and importance of applications. It is used in dentistry in the form of gold, silver, and copper alloys. [NIH]

Palliative: 1. Affording relief, but not cure. 2. An alleviating medicine. [EU]

Panax ginseng: A Chinese herb (Panax schinseng) having 5-foliolate leaves and umbels of small greenish flowers succeeded by scarlet berries. [NIH]

Pancreas: A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the Islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

Pancreatic: Having to do with the pancreas. [NIH]

Pancreatic Juice: The fluid containing digestive enzymes secreted by the pancreas in response to food in the duodenum. [NIH]

Panic: A state of extreme acute, intense anxiety and unreasoning fear accompanied by disorganization of personality function. [NIH]

Panic Disorder: A type of anxiety disorder characterized by unexpected panic attacks that last minutes or, rarely, hours. Panic attacks begin with intense apprehension, fear or terror and, often, a feeling of impending doom. Symptoms experienced during a panic attack include dyspnea or sensations of being smothered; dizziness, loss of balance or faintness; choking sensations; palpitations or accelerated heart rate; shakiness; sweating; nausea or other form of abdominal distress; depersonalization or derealization; paresthesias; hot flashes or chills; chest discomfort or pain; fear of dying and fear of not being in control of oneself or going crazy. Agoraphobia may also develop. Similar to other anxiety disorders, it may be inherited as an autosomal dominant trait. [NIH]

Papaverine: An alkaloid found in opium but not closely related to the other opium alkaloids in its structure or pharmacological actions. It is a direct-acting smooth muscle relaxant used in the treatment of impotence and as a vasodilator, especially for cerebral vasodilation. The mechanism of its pharmacological actions is not clear, but it apparently can inhibit phosphodiesterases and it may have direct actions on calcium channels. [NIH]

Parasite: An animal or a plant that lives on or in an organism of another species and gets at least some of its nutrition from that other organism. [NIH]

Parenchyma: The essential elements of an organ; used in anatomical nomenclature as a general term to designate the functional elements of an organ, as distinguished from its framework, or stroma. [EU]

Parenteral: Not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc. [EU]

Paroxysmal: Recurring in paroxysms (= spasms or seizures). [EU]

Particle: A tiny mass of material. [EU]

Parturition: The act or process of given birth to a child. [EU]

Patch: A piece of material used to cover or protect a wound, an injured part, etc.: a patch over the eye. [NIH]

Pathogen: Any disease-producing microorganism. [EU]

Pathogenesis: The cellular events and reactions that occur in the development of disease. [NIH]

Pathologic: 1. Indicative of or caused by a morbid condition. 2. Pertaining to pathology (= branch of medicine that treats the essential nature of the disease, especially the structural and functional changes in tissues and organs of the body caused by the disease). [EU]

Pathologic Processes: The abnormal mechanisms and forms involved in the dysfunctions of tissues and organs. [NIH]

Patient Education: The teaching or training of patients concerning their own health needs. [NIH]

Patient Satisfaction: The degree to which the individual regards the health care service or product or the manner in which it is delivered by the provider as useful, effective, or beneficial. [NIH]

Pelvic: Pertaining to the pelvis. [EU]

Penicillin: An antibiotic drug used to treat infection. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Peptide T: N-(N-(N(2)-(N-(N-(N-(N-D-Alanyl L-seryl)-L-threonyl)-L-threonyl) L-threonyl)-L-asparaginyl)-L-tyrosyl) L-threonine. Octapeptide sharing sequence homology with HIV envelope protein gp120. It is potentially useful as antiviral agent in AIDS therapy. The core pentapeptide sequence, TTNYT, consisting of amino acids 4-8 in peptide T, is the HIV envelope sequence required for attachment to the CD4 receptor. [NIH]

Perception: The ability quickly and accurately to recognize similarities and differences among presented objects, whether these be pairs of words, pairs of number series, or multiple sets of these or other symbols such as geometric figures. [NIH]

Percutaneous: Performed through the skin, as injection of radiopacque material in radiological examination, or the removal of tissue for biopsy accomplished by a needle. [EU]

Perfusion: Bathing an organ or tissue with a fluid. In regional perfusion, a specific area of the body (usually an arm or a leg) receives high doses of anticancer drugs through a blood vessel. Such a procedure is performed to treat cancer that has not spread. [NIH]

Perinatal: Pertaining to or occurring in the period shortly before and after birth; variously defined as beginning with completion of the twentieth to twenty-eighth week of gestation and ending 7 to 28 days after birth. [EU]

Perineal: Pertaining to the perineum. [EU]

Perioperative: Around the time of surgery; usually lasts from the time of going into the hospital or doctor's office for surgery until the time the patient goes home. [NIH]

Peripheral blood: Blood circulating throughout the body. [NIH]

Peripheral Nervous System: The nervous system outside of the brain and spinal cord. The peripheral nervous system has autonomic and somatic divisions. The autonomic nervous system includes the enteric, parasympathetic, and sympathetic subdivisions. The somatic nervous system includes the cranial and spinal nerves and their ganglia and the peripheral sensory receptors. [NIH]

Peristalsis: The rippling motion of muscles in the intestine or other tubular organs characterized by the alternate contraction and relaxation of the muscles that propel the contents onward. [NIH]

Peritoneal: Having to do with the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). [NIH]

Peritoneal Cavity: The space enclosed by the peritoneum. It is divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the stomach. The two sacs are connected by the foramen of Winslow, or epiploic foramen. [NIH]

Peritoneum: Endothelial lining of the abdominal cavity, the parietal peritoneum covering the inside of the abdominal wall and the visceral peritoneum covering the bowel, the mesentery, and certain of the organs. The portion that covers the bowel becomes the serosal layer of the bowel wall. [NIH]

Peritonitis: Inflammation of the peritoneum; a condition marked by exudations in the peritoneum of serum, fibrin, cells, and pus. It is attended by abdominal pain and tenderness, constipation, vomiting, and moderate fever. [EU]

Periventricular Leukomalacia: Rare form of epilepsy. [NIH]

Peroneal Nerve: The lateral of the two terminal branches of the sciatic nerve. The peroneal (or fibular) nerve provides motor and sensory innervation to parts of the leg and foot. [NIH]

Peroral: Performed through or administered through the mouth. [EU]

Pertussis: An acute, highly contagious infection of the respiratory tract, most frequently affecting young children, usually caused by Bordetella pertussis; a similar illness has been associated with infection by B. parapertussis and B. bronchiseptica. It is characterized by a catarrhal stage, beginning after an incubation period of about two weeks, with slight fever, sneezing, running at the nose, and a dry cough. In a week or two the paroxysmal stage begins, with the characteristic paroxysmal cough, consisting of a deep inspiration, followed by a series of quick, short coughs, continuing until the air is expelled from the lungs; the close of the paroxysm is marked by a long-drawn, shrill, whooping inspiration, due to spasmodic closure of the glottis. This stage lasts three to four weeks, after which the convalescent stage begins, in which paroxysms grow less frequent and less violent, and finally cease. Called also whooping cough. [EU]

Petrolatum: A colloidal system of semisolid hydrocarbons obtained from petroleum. It is used as an ointment base, topical protectant, and lubricant. [NIH]

Phagocyte: An immune system cell that can surround and kill microorganisms and remove dead cells. Phagocytes include macrophages. [NIH]

Phallic: Pertaining to the phallus, or penis. [EU]

Pharmaceutical Preparations: Drugs intended for human or veterinary use, presented in their finished dosage form. Included here are materials used in the preparation and/or formulation of the finished dosage form. [NIH]

Pharmaceutical Solutions: Homogeneous liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents. For reasons of their ingredients, method of preparation, or use, they do not fall into another group of products. [NIH]

Pharmacodynamics: The study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure; also, such effects on the actions of a particular drug or drugs. [EU]

Pharmacokinetic: The mathematical analysis of the time courses of absorption, distribution, and elimination of drugs. [NIH]

Pharmacologic: Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

Pharynx: The hollow tube about 5 inches long that starts behind the nose and ends at the top of the trachea (windpipe) and esophagus (the tube that goes to the stomach). [NIH]

Phencyclidine: A hallucinogen formerly used as a veterinary anesthetic, and briefly as a general anesthetic for humans. Phencyclidine is similar to ketamine in structure and in many of its effects. Like ketamine, it can produce a dissociative state. It exerts its pharmacological action through inhibition of NMDA receptors (receptors, N-methyl-D-aspartate). As a drug of abuse, it is known as PCP and Angel Dust. [NIH]

Phenobarbital: A barbituric acid derivative that acts as a nonselective central nervous system depressant. It promotes binding to inhibitory GABA subtype receptors, and modulates chloride currents through receptor channels. It also inhibits glutamate induced depolarizations. [NIH]

Phenolphthalein: An acid-base indicator which is colorless in acid solution, but turns pink to red as the solution becomes alkaline. It is used medicinally as a cathartic. [NIH]

Phenotype: The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

Phenyl: Ingredient used in cold and flu remedies. [NIH]

Phenylalanine: An aromatic amino acid that is essential in the animal diet. It is a precursor of melanin, dopamine, noradrenalin, and thyroxine. [NIH]

Phosphates: Inorganic salts of phosphoric acid. [NIH]

Phosphodiesterase: Effector enzyme that regulates the levels of a second messenger, the cyclic GMP. [NIH]

Phospholipases: A class of enzymes that catalyze the hydrolysis of phosphoglycerides or glycerophosphatidates. EC 3.1.-. [NIH]

Phospholipids: Lipids containing one or more phosphate groups, particularly those derived from either glycerol (phosphoglycerides; glycerophospholipids) or sphingosine (sphingolipids). They are polar lipids that are of great importance for the structure and function of cell membranes and are the most abundant of membrane lipids, although not stored in large amounts in the system. [NIH]

Phosphorus: A non-metallic element that is found in the blood, muscles, nevers, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

Phosphorylate: Attached to a phosphate group. [NIH]

Phosphorylated: Attached to a phosphate group. [NIH]

Phosphorylation: The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

Phototransduction: The transducing of light energy to afferent nerve impulses, such as takes place in the retinal rods and cones. After light photons are absorbed by the photopigments, the signal is transmitted to the outer segment membrane by the cyclic GMP second messenger system, where it closes the sodium channels. This channel gating ultimately generates an action potential in the inner retina. [NIH]

Physiologic: Having to do with the functions of the body. When used in the phrase "physiologic age," it refers to an age assigned by general health, as opposed to calendar age. [NIH]

Physiology: The science that deals with the life processes and functions of organismus, their cells, tissues, and organs. [NIH]

Physostigmine: A cholinesterase inhibitor that is rapidly absorbed through membranes. It can be applied topically to the conjunctiva. It also can cross the blood-brain barrier and is used when central nervous system effects are desired, as in the treatment of severe anticholinergic toxicity. [NIH]

Pilot study: The initial study examining a new method or treatment. [NIH]

Pituitary Gland: A small, unpaired gland situated in the sella turcica tissue. It is connected to the hypothalamus by a short stalk. [NIH]

Placenta: A highly vascular fetal organ through which the fetus absorbs oxygen and other nutrients and excretes carbon dioxide and other wastes. It begins to form about the eighth day of gestation when the blastocyst adheres to the decidua. [NIH]

Plants: Multicellular, eukaryotic life forms of the kingdom Plantae. They are characterized by a mainly photosynthetic mode of nutrition; essentially unlimited growth at localized regions of cell divisions (meristems); cellulose within cells providing rigidity; the absence of organs of locomotion; absense of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plasma: The clear, yellowish, fluid part of the blood that carries the blood cells. The proteins that form blood clots are in plasma. [NIH]

Plasma cells: A type of white blood cell that produces antibodies. [NIH]

Plasma Volume: Volume of plasma in the circulation. It is usually measured by indicator dilution techniques. [NIH]

Plasticity: In an individual or a population, the capacity for adaptation: a) through gene changes (genetic plasticity) or b) through internal physiological modifications in response to changes of environment (physiological plasticity). [NIH]

Platelet Activation: A series of progressive, overlapping events triggered by exposure of the platelets to subendothelial tissue. These events include shape change, adhesiveness, aggregation, and release reactions. When carried through to completion, these events lead to the formation of a stable hemostatic plug. [NIH]

Platelet Aggregation: The attachment of platelets to one another. This clumping together can be induced by a number of agents (e.g., thrombin, collagen) and is part of the mechanism leading to the formation of a thrombus. [NIH]

Platelets: A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

Platinum: Platinum. A heavy, soft, whitish metal, resembling tin, atomic number 78, atomic weight 195.09, symbol Pt. (From Dorland, 28th ed) It is used in manufacturing equipment for laboratory and industrial use. It occurs as a black powder (platinum black) and as a spongy substance (spongy platinum) and may have been known in Pliny's time as "alutiae". [NIH]

Pleomorphic: Occurring in various distinct forms. In terms of cells, having variation in the size and shape of cells or their nuclei. [NIH]

Pleural: A circumscribed area of hyaline whorled fibrous tissue which appears on the surface of the parietal pleura, on the fibrous part of the diaphragm or on the pleura in the interlobar fissures. [NIH]

Pleural cavity: A space enclosed by the pleura (thin tissue covering the lungs and lining the interior wall of the chest cavity). It is bound by thin membranes. [NIH]

Plexus: A network or tangle; a general term for a network of lymphatic vessels, nerves, or veins. [EU]

Podophyllum: A genus of poisonous American herbs, family Berberidaceae. The roots yield podophyllotoxins and other pharmacologically important agents. The plant was formerly used as a cholagogue and cathartic. It is different from the European Mandrake (Mandragora). [NIH]

Poisoning: A condition or physical state produced by the ingestion, injection or inhalation of, or exposure to a deleterious agent. [NIH]

Polymerase: An enzyme which catalyses the synthesis of DNA using a single DNA strand as a template. The polymerase copies the template in the 5'-3'direction provided that sufficient quantities of free nucleotides, dATP and dTTP are present. [NIH]

Polymerase Chain Reaction: In vitro method for producing large amounts of specific DNA or RNA fragments of defined length and sequence from small amounts of short oligonucleotide flanking sequences (primers). The essential steps include thermal denaturation of the double-stranded target molecules, annealing of the primers to their complementary sequences, and extension of the annealed primers by enzymatic synthesis with DNA polymerase. The reaction is efficient, specific, and extremely sensitive. Uses for the reaction include disease diagnosis, detection of difficult-to-isolate pathogens, mutation analysis, genetic testing, DNA sequencing, and analyzing evolutionary relationships. [NIH]

Polymorphic: Occurring in several or many forms; appearing in different forms at different

stages of development. [EU]

Polymorphism: The occurrence together of two or more distinct forms in the same population. [NIH]

Polypeptide: A peptide which on hydrolysis yields more than two amino acids; called tripeptides, tetrapeptides, etc. according to the number of amino acids contained. [EU]

Polysaccharide: A type of carbohydrate. It contains sugar molecules that are linked together chemically. [NIH]

Pons: The part of the central nervous system lying between the medulla oblongata and the mesencephalon, ventral to the cerebellum, and consisting of a pars dorsalis and a pars ventralis. [NIH]

Posterior: Situated in back of, or in the back part of, or affecting the back or dorsal surface of the body. In lower animals, it refers to the caudal end of the body. [EU]

Postmenopausal: Refers to the time after menopause. Menopause is the time in a woman's life when menstrual periods stop permanently; also called "change of life." [NIH]

Postnatal: Occurring after birth, with reference to the newborn. [EU]

Postoperative: After surgery. [NIH]

Postoperative Complications: Pathologic processes that affect patients after a surgical procedure. They may or may not be related to the disease for which the surgery was done, and they may or may not be direct results of the surgery. [NIH]

Postoperative Period: The period following a surgical operation. [NIH]

Postprandial: Occurring after dinner, or after a meal; postcibal. [EU]

Postsynaptic: Nerve potential generated by an inhibitory hyperpolarizing stimulation. [NIH]

Post-synaptic: Nerve potential generated by an inhibitory hyperpolarizing stimulation. [NIH]

Potassium: An element that is in the alkali group of metals. It has an atomic symbol K, atomic number 19, and atomic weight 39.10. It is the chief cation in the intracellular fluid of muscle and other cells. Potassium ion is a strong electrolyte and it plays a significant role in the regulation of fluid volume and maintenance of the water-electrolyte balance. [NIH]

Potassium Channels: Cell membrane glycoproteins selective for potassium ions. [NIH]

Potentiate: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Potentiating: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Potentiation: An overall effect of two drugs taken together which is greater than the sum of the effects of each drug taken alone. [NIH]

Practice Guidelines: Directions or principles presenting current or future rules of policy for the health care practitioner to assist him in patient care decisions regarding diagnosis, therapy, or related clinical circumstances. The guidelines may be developed by government agencies at any level, institutions, professional societies, governing boards, or by the convening of expert panels. The guidelines form a basis for the evaluation of all aspects of health care and delivery. [NIH]

Precipitation: The act or process of precipitating. [EU]

Preclinical: Before a disease becomes clinically recognizable. [EU]

Precursor: Something that precedes. In biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another. [EU]

Predisposition: A latent susceptibility to disease which may be activated under certain conditions, as by stress. [EU]

Prednisolone: A glucocorticoid with the general properties of the corticosteroids. It is the drug of choice for all conditions in which routine systemic corticosteroid therapy is indicated, except adrenal deficiency states. [NIH]

Prednisone: A synthetic anti-inflammatory glucocorticoid derived from cortisone. It is biologically inert and converted to prednisolone in the liver. [NIH]

Prefrontal Cortex: The rostral part of the frontal lobe, bounded by the inferior precentral fissure in humans, which receives projection fibers from the mediodorsal nucleus of the thalamus. The prefrontal cortex receives afferent fibers from numerous structures of the diencephalon, mesencephalon, and limbic system as well as cortical afferents of visual, auditory, and somatic origin. [NIH]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

Presynaptic: Situated proximal to a synapse, or occurring before the synapse is crossed. [EU]

Prevalence: The total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time. [NIH]

Probe: An instrument used in exploring cavities, or in the detection and dilatation of strictures, or in demonstrating the potency of channels; an elongated instrument for exploring or sounding body cavities. [NIH]

Procaine: A local anesthetic of the ester type that has a slow onset and a short duration of action. It is mainly used for infiltration anesthesia, peripheral nerve block, and spinal block. (From Martindale, The Extra Pharmacopoeia, 30th ed, p1016). [NIH]

Prodrug: A substance that gives rise to a pharmacologically active metabolite, although not itself active (i. e. an inactive precursor). [NIH]

Progeny: The offspring produced in any generation. [NIH]

Progesterone: Pregn-4-ene-3,20-dione. The principal progestational hormone of the body, secreted by the corpus luteum, adrenal cortex, and placenta. Its chief function is to prepare the uterus for the reception and development of the fertilized ovum. It acts as an antiovulatory agent when administered on days 5-25 of the menstrual cycle. [NIH]

Progression: Increase in the size of a tumor or spread of cancer in the body. [NIH]

Progressive: Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

Projection: A defense mechanism, operating unconsciously, whereby that which is emotionally unacceptable in the self is rejected and attributed (projected) to others. [NIH]

Prolactin: Pituitary lactogenic hormone. A polypeptide hormone with a molecular weight of about 23,000. It is essential in the induction of lactation in mammals at parturition and is synergistic with estrogen. The hormone also brings about the release of progesterone from lutein cells, which renders the uterine mucosa suited for the embedding of the ovum should fertilization occur. [NIH]

Proline: A non-essential amino acid that is synthesized from glutamic acid. It is an essential component of collagen and is important for proper functioning of joints and tendons. [NIH]

Pro-Opiomelanocortin: A precursor protein, MW 30,000, synthesized mainly in the anterior pituitary gland but also found in the hypothalamus, brain, and several peripheral tissues. It incorporates the amino acid sequences of ACTH and beta-lipotropin. These two hormones, in turn, contain the biologically active peptides MSH, corticotropin-like intermediate lobe

peptide, alpha-lipotropin, endorphins, and methionine enkephalin. [NIH]

Prophase: The first phase of cell division, in which the chromosomes become visible, the nucleus starts to lose its identity, the spindle appears, and the centrioles migrate toward opposite poles. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Propionic Acids: 3-carbon saturated monocarboxylic acids. [NIH]

Propofol: A widely used anesthetic. [NIH]

Proportional: Being in proportion : corresponding in size, degree, or intensity, having the same or a constant ratio; of, relating to, or used in determining proportions. [EU]

Propoxyphene: A narcotic analgesic structurally related to methadone. Only the dextro-isomer has an analgesic effect; the levo-isomer appears to exert an antitussive effect. [NIH]

Prospective study: An epidemiologic study in which a group of individuals (a cohort), all free of a particular disease and varying in their exposure to a possible risk factor, is followed over a specific amount of time to determine the incidence rates of the disease in the exposed and unexposed groups. [NIH]

Prostaglandin: Any of a group of components derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway that are extremely potent mediators of a diverse group of physiologic processes. The abbreviation for prostaglandin is PG; specific compounds are designated by adding one of the letters A through I to indicate the type of substituents found on the hydrocarbon skeleton and a subscript (1, 2 or 3) to indicate the number of double bonds in the hydrocarbon skeleton e.g., PGE2. The predominant naturally occurring prostaglandins all have two double bonds and are synthesized from arachidonic acid (5,8,11,14-eicosatetraenoic acid) by the pathway shown in the illustration. The 1 series and 3 series are produced by the same pathway with fatty acids having one fewer double bond (8,11,14-eicosatrienoic acid or one more double bond (5,8,11,14,17-eicosapentaenoic acid) than arachidonic acid. The subscript a or ß indicates the configuration at C-9 (a denotes a substituent below the plane of the ring, ß, above the plane). The naturally occurring PGF's have the a configuration, e.g., PGF2a. All of the prostaglandins act by binding to specific cell-surface receptors causing an increase in the level of the intracellular second messenger cyclic AMP (and in some cases cyclic GMP also). The effect produced by the cyclic AMP increase depends on the specific cell type. In some cases there is also a positive feedback effect. Increased cyclic AMP increases prostaglandin synthesis leading to further increases in cyclic AMP. [EU]

Prostaglandins A: (13E,15S)-15-Hydroxy-9-oxoprosta-10,13-dien-1-oic acid (PGA(1)); (5Z,13E,15S)-15-hydroxy-9-oxoprosta-5,10,13-trien-1-oic acid (PGA(2)); (5Z,13E,15S,17Z)-15-hydroxy-9-oxoprosta-5,10,13,17-tetraen-1-oic acid (PGA(3)). A group of naturally occurring secondary prostaglandins derived from PGE. PGA(1) and PGA(2) as well as their 19-hydroxy derivatives are found in many organs and tissues. [NIH]

Prostate: A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]

Prostatectomy: Complete or partial surgical removal of the prostate. Three primary approaches are commonly employed: suprapubic - removal through an incision above the pubis and through the urinary bladder; retropubic - as for suprapubic but without entering the urinary bladder; and transurethral (transurethral resection of prostate). [NIH]

Prostitution: The practice of indulging in promiscuous sexual relations for money. [NIH]

Protease: Proteinase (= any enzyme that catalyses the splitting of interior peptide bonds in a protein). [EU]

Protein C: A vitamin-K dependent zymogen present in the blood, which, upon activation by thrombin and thrombomodulin exerts anticoagulant properties by inactivating factors Va and VIIIa at the rate-limiting steps of thrombin formation. [NIH]

Protein Conformation: The characteristic 3-dimensional shape of a protein, including the secondary, supersecondary (motifs), tertiary (domains) and quaternary structure of the peptide chain. Quaternary protein structure describes the conformation assumed by multimeric proteins (aggregates of more than one polypeptide chain). [NIH]

Protein Kinases: A family of enzymes that catalyze the conversion of ATP and a protein to ADP and a phosphoprotein. EC 2.7.1.37. [NIH]

Protein S: The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

Proteins: Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

Proteinuria: The presence of protein in the urine, indicating that the kidneys are not working properly. [NIH]

Proteolytic: 1. Pertaining to, characterized by, or promoting proteolysis. 2. An enzyme that promotes proteolysis (= the splitting of proteins by hydrolysis of the peptide bonds with formation of smaller polypeptides). [EU]

Protocol: The detailed plan for a clinical trial that states the trial's rationale, purpose, drug or vaccine dosages, length of study, routes of administration, who may participate, and other aspects of trial design. [NIH]

Protons: Stable elementary particles having the smallest known positive charge, found in the nuclei of all elements. The proton mass is less than that of a neutron. A proton is the nucleus of the light hydrogen atom, i.e., the hydrogen ion. [NIH]

Proto-Oncogene Proteins: Products of proto-oncogenes. Normally they do not have oncogenic or transforming properties, but are involved in the regulation or differentiation of cell growth. They often have protein kinase activity. [NIH]

Proto-Oncogene Proteins c-mos: Cellular proteins encoded by the c-mos genes. They function in the cell cycle to maintain maturation promoting factor in the active state and have protein-serine/threonine kinase activity. Oncogenic transformation can take place when c-mos proteins are expressed at the wrong time. [NIH]

Protozoa: A subkingdom consisting of unicellular organisms that are the simplest in the animal kingdom. Most are free living. They range in size from submicroscopic to macroscopic. Protozoa are divided into seven phyla: Sarcomastigophora, Labyrinthomorpha, Apicomplexa, Microspora, Ascetospora, Myxozoa, and Ciliophora. [NIH]

Proximal: Nearest; closer to any point of reference; opposed to distal. [EU]

Pruritus: An intense itching sensation that produces the urge to rub or scratch the skin to obtain relief. [NIH]

Psoriasis: A common genetically determined, chronic, inflammatory skin disease characterized by rounded erythematous, dry, scaling patches. The lesions have a predilection for nails, scalp, genitalia, extensor surfaces, and the lumbosacral region. Accelerated epidermopoiesis is considered to be the fundamental pathologic feature in psoriasis. [NIH]

Psychiatric: Pertaining to or within the purview of psychiatry. [EU]

Psychiatry: The medical science that deals with the origin, diagnosis, prevention, and treatment of mental disorders. [NIH]

Psychic: Pertaining to the psyche or to the mind; mental. [EU]

Psychogenic: Produced or caused by psychic or mental factors rather than organic factors. [EU]

Psychology: The science dealing with the study of mental processes and behavior in man and animals. [NIH]

Psychometric testing: Psychological and mental testing and quantitative analysis of an individual's psychological traits or attitudes or mental processes. [NIH]

Psychomotor: Pertaining to motor effects of cerebral or psychic activity. [EU]

Psychotomimetic: Psychosis miming. [NIH]

Puberty: The period during which the secondary sex characteristics begin to develop and the capability of sexual reproduction is attained. [EU]

Public Health: Branch of medicine concerned with the prevention and control of disease and disability, and the promotion of physical and mental health of the population on the international, national, state, or municipal level. [NIH]

Public Policy: A course or method of action selected, usually by a government, from among alternatives to guide and determine present and future decisions. [NIH]

Publishing: "The business or profession of the commercial production and issuance of literature" (Webster's 3d). It includes the publisher, publication processes, editing and editors. Production may be by conventional printing methods or by electronic publishing. [NIH]

Pulmonary: Relating to the lungs. [NIH]

Pulmonary Artery: The short wide vessel arising from the conus arteriosus of the right ventricle and conveying unaerated blood to the lungs. [NIH]

Pulmonary Embolism: Embolism in the pulmonary artery or one of its branches. [NIH]

Pulmonary hypertension: Abnormally high blood pressure in the arteries of the lungs. [NIH]

Pulse: The rhythmical expansion and contraction of an artery produced by waves of pressure caused by the ejection of blood from the left ventricle of the heart as it contracts. [NIH]

Pupil: The aperture in the iris through which light passes. [NIH]

Purifying: Respiratory equipment whose function is to remove contaminants from otherwise wholesome air. [NIH]

Putamen: The largest and most lateral of the basal ganglia lying between the lateral medullary lamina of the globus pallidus and the external capsule. It is part of the neostriatum and forms part of the lentiform nucleus along with the globus pallidus. [NIH]

Pyramidal Cells: Projection neurons in the cerebral cortex and the hippocampus. Pyramidal cells have a pyramid-shaped soma with the apex and an apical dendrite pointed toward the pial surface and other dendrites and an axon emerging from the base. The axons may have local collaterals but also project outside their cortical region. [NIH]

Pyridoxal: 3-Hydroxy-5-(hydroxymethyl)-2-methyl-4- pyridinecarboxaldehyde. [NIH]

Quality of Life: A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment. [NIH]

Quaternary: 1. Fourth in order. 2. Containing four elements or groups. [EU]

Quinidine: An optical isomer of quinine, extracted from the bark of the Cinchona tree and similar plant species. This alkaloid dampens the excitability of cardiac and skeletal muscles by blocking sodium and potassium currents across cellular membranes. It prolongs cellular action potential, and decreases automaticity. Quinidine also blocks muscarinic and alpha-adrenergic neurotransmission. [NIH]

Quinine: An alkaloid derived from the bark of the cinchona tree. It is used as an antimalarial drug, and is the active ingredient in extracts of the cinchona that have been used for that purpose since before 1633. Quinine is also a mild antipyretic and analgesic and has been used in common cold preparations for that purpose. It was used commonly and as a bitter and flavoring agent, and is still useful for the treatment of babesiosis. Quinine is also useful in some muscular disorders, especially nocturnal leg cramps and myotonia congenita, because of its direct effects on muscle membrane and sodium channels. The mechanisms of its antimalarial effects are not well understood. [NIH]

Race: A population within a species which exhibits general similarities within itself, but is both discontinuous and distinct from other populations of that species, though not sufficiently so as to achieve the status of a taxon. [NIH]

Radiation: Emission or propagation of electromagnetic energy (waves/rays), or the waves/rays themselves; a stream of electromagnetic particles (electrons, neutrons, protons, alpha particles) or a mixture of these. The most common source is the sun. [NIH]

Radical prostatectomy: Surgery to remove the entire prostate. The two types of radical prostatectomy are retropubic prostatectomy and perineal prostatectomy. [NIH]

Radioactive: Giving off radiation. [NIH]

Radioimmunoassay: Classic quantitative assay for detection of antigen-antibody reactions using a radioactively labeled substance (radioligand) either directly or indirectly to measure the binding of the unlabeled substance to a specific antibody or other receptor system. Non-immunogenic substances (e.g., haptens) can be measured if coupled to larger carrier proteins (e.g., bovine gamma-globulin or human serum albumin) capable of inducing antibody formation. [NIH]

Radioimmunotherapy: Radiotherapy where cytotoxic radionuclides are linked to antibodies in order to deliver toxins directly to tumor targets. Therapy with targeted radiation rather than antibody-targeted toxins (immunotoxins) has the advantage that adjacent tumor cells, which lack the appropriate antigenic determinants, can be destroyed by radiation cross-fire. Radioimmunotherapy is sometimes called targeted radiotherapy, but this latter term can also refer to radionuclides linked to non-immune molecules (radiotherapy). [NIH]

Radiolabeled: Any compound that has been joined with a radioactive substance. [NIH]

Radiological: Pertaining to radiodiagnostic and radiotherapeutic procedures, and interventional radiology or other planning and guiding medical radiology. [NIH]

Radiotherapy: The use of ionizing radiation to treat malignant neoplasms and other benign conditions. The most common forms of ionizing radiation used as therapy are x-rays, gamma rays, and electrons. A special form of radiotherapy, targeted radiotherapy, links a cytotoxic radionuclide to a molecule that targets the tumor. When this molecule is an antibody or other immunologic molecule, the technique is called radioimmunotherapy. [NIH]

Randomized: Describes an experiment or clinical trial in which animal or human subjects are assigned by chance to separate groups that compare different treatments. [NIH]

Reaction Time: The time from the onset of a stimulus until the organism responds. [NIH]

Reagent: A substance employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances. [EU]

Receptor: A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell. [NIH]

Receptors, Adrenergic: Cell-surface proteins that bind epinephrine and/or norepinephrine with high affinity and trigger intracellular changes. The two major classes of adrenergic receptors, alpha and beta, were originally discriminated based on their cellular actions but now are distinguished by their relative affinity for characteristic synthetic ligands. Adrenergic receptors may also be classified according to the subtypes of G-proteins with which they bind; this scheme does not respect the alpha-beta distinction. [NIH]

Receptors, Dopamine: Cell-surface proteins that bind dopamine with high affinity and trigger intracellular changes influencing the behavior of cells. [NIH]

Receptors, Serotonin: Cell-surface proteins that bind serotonin and trigger intracellular changes which influence the behavior of cells. Several types of serotonin receptors have been recognized which differ in their pharmacology, molecular biology, and mode of action. [NIH]

Recombinant: A cell or an individual with a new combination of genes not found together in either parent; usually applied to linked genes. [EU]

Recombination: The formation of new combinations of genes as a result of segregation in crosses between genetically different parents; also the rearrangement of linked genes due to crossing-over. [NIH]

Rectal: By or having to do with the rectum. The rectum is the last 8 to 10 inches of the large intestine and ends at the anus. [NIH]

Rectum: The last 8 to 10 inches of the large intestine. [NIH]

Recurrence: The return of a sign, symptom, or disease after a remission. [NIH]

Red blood cells: RBCs. Cells that carry oxygen to all parts of the body. Also called erythrocytes. [NIH]

Red Nucleus: A pinkish-yellow portion of the midbrain situated in the rostral mesencephalic tegmentum. It receives a large projection from the contralateral half of the cerebellum via the superior cerebellar peduncle and a projection from the ipsilateral motor cortex. [NIH]

Reductase: Enzyme converting testosterone to dihydrotestosterone. [NIH]

Refer: To send or direct for treatment, aid, information, de decision. [NIH]

Reflex: An involuntary movement or exercise of function in a part, excited in response to a stimulus applied to the periphery and transmitted to the brain or spinal cord. [NIH]

Reflux: The term used when liquid backs up into the esophagus from the stomach. [NIH]

Refraction: A test to determine the best eyeglasses or contact lenses to correct a refractive error (myopia, hyperopia, or astigmatism). [NIH]

Refractory: Not readily yielding to treatment. [EU]

Regimen: A treatment plan that specifies the dosage, the schedule, and the duration of treatment. [NIH]

Regurgitation: A backward flowing, as the casting up of undigested food, or the backward flowing of blood into the heart, or between the chambers of the heart when a valve is incompetent. [EU]

Relapse: The return of signs and symptoms of cancer after a period of improvement. [NIH]

Relaxant: 1. Lessening or reducing tension. 2. An agent that lessens tension. [EU]

Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete

remission, all signs and symptoms of cancer have disappeared, although there still may be cancer in the body. [NIH]

Renal failure: Progressive renal insufficiency and uremia, due to irreversible and progressive renal glomerular tubular or interstitial disease. [NIH]

Reperfusion: Restoration of blood supply to tissue which is ischemic due to decrease in normal blood supply. The decrease may result from any source including atherosclerotic obstruction, narrowing of the artery, or surgical clamping. It is primarily a procedure for treating infarction or other ischemia, by enabling viable ischemic tissue to recover, thus limiting further necrosis. However, it is thought that reperfusion can itself further damage the ischemic tissue, causing reperfusion injury. [NIH]

Reperfusion Injury: Functional, metabolic, or structural changes, including necrosis, in ischemic tissues thought to result from reperfusion to ischemic areas of the tissue. The most common instance is myocardial reperfusion injury. [NIH]

Replicon: In order to be replicated, DNA molecules must contain an origin of duplication and in bacteria and viruses there is usually only one per genome. Such molecules are called replicons. [NIH]

Resection: Removal of tissue or part or all of an organ by surgery. [NIH]

Respiration: The act of breathing with the lungs, consisting of inspiration, or the taking into the lungs of the ambient air, and of expiration, or the expelling of the modified air which contains more carbon dioxide than the air taken in (Blakiston's Gould Medical Dictionary, 4th ed.). This does not include tissue respiration (= oxygen consumption) or cell respiration (= cell respiration). [NIH]

Respirator: A mechanical device that helps a patient breathe; a mechanical ventilator. [NIH]

Respiratory Physiology: Functions and activities of the respiratory tract as a whole or of any of its parts. [NIH]

Response rate: The percentage of patients whose cancer shrinks or disappears after treatment. [NIH]

Retina: The ten-layered nervous tissue membrane of the eye. It is continuous with the optic nerve and receives images of external objects and transmits visual impulses to the brain. Its outer surface is in contact with the choroid and the inner surface with the vitreous body. The outer-most layer is pigmented, whereas the inner nine layers are transparent. [NIH]

Retinal: 1. Pertaining to the retina. 2. The aldehyde of retinol, derived by the oxidative enzymatic splitting of absorbed dietary carotene, and having vitamin A activity. In the retina, retinal combines with opsins to form visual pigments. One isomer, 11-cis retinal combines with opsin in the rods (scotopsin) to form rhodopsin, or visual purple. Another, all-trans retinal (trans-r.); visual yellow; xanthopsin) results from the bleaching of rhodopsin by light, in which the 11-cis form is converted to the all-trans form. Retinal also combines with opsins in the cones (photopsins) to form the three pigments responsible for colour vision. Called also retinal, and retinene1. [EU]

Retrograde: 1. Moving backward or against the usual direction of flow. 2. Degenerating, deteriorating, or catabolic. [EU]

Retrograde Amnesia: Amnesia extending backward, to include material antedating the onset of amnesia proper. [NIH]

Retropubic: A potential space between the urinary bladder and the symphisis and body of the pubis. [NIH]

Retropubic prostatectomy: Surgery to remove the prostate through an incision made in the abdominal wall. [NIH]

Reverse Transcriptase Polymerase Chain Reaction: A variation of the PCR technique in which cDNA is made from RNA via reverse transcription. The resultant cDNA is then amplified using standard PCR protocols. [NIH]

Rheumatism: A group of disorders marked by inflammation or pain in the connective tissue structures of the body. These structures include bone, cartilage, and fat. [NIH]

Rheumatoid: Resembling rheumatism. [EU]

Rheumatoid arthritis: A form of arthritis, the cause of which is unknown, although infection, hypersensitivity, hormone imbalance and psychologic stress have been suggested as possible causes. [NIH]

Ribose: A pentose active in biological systems usually in its D-form. [NIH]

Ribosome: A granule of protein and RNA, synthesized in the nucleolus and found in the cytoplasm of cells. Ribosomes are the main sites of protein synthesis. Messenger RNA attaches to them and there receives molecules of transfer RNA bearing amino acids. [NIH]

Rigidity: Stiffness or inflexibility, chiefly that which is abnormal or morbid; rigor. [EU]

Risk factor: A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

Ritalin: Drug used to treat hyperactive children. [NIH]

Ritonavir: An HIV protease inhibitor that works by interfering with the reproductive cycle of HIV. [NIH]

Rod: A reception for vision, located in the retina. [NIH]

Saccharin: Flavoring agent and non-nutritive sweetener. [NIH]

Salicylate: Non-steroidal anti-inflammatory drugs. [NIH]

Salicylic: A tuberculosis drug. [NIH]

Salicylic Acids: Derivatives and salts of salicylic acid. [NIH]

Saline: A solution of salt and water. [NIH]

Salivary: The duct that convey saliva to the mouth. [NIH]

Salivary glands: Glands in the mouth that produce saliva. [NIH]

Saphenous: Applied to certain structures in the leg, e. g. nerve vein. [NIH]

Saphenous Vein: The vein which drains the foot and leg. [NIH]

Saponin: A substance found in soybeans and many other plants. Saponins may help lower cholesterol and may have anticancer effects. [NIH]

Schizoid: Having qualities resembling those found in greater degree in schizophrenics; a person of schizoid personality. [NIH]

Schizophrenia: A mental disorder characterized by a special type of disintegration of the personality. [NIH]

Schizophrenia, Catatonic: A type of schizophrenia characterized by abnormality of motor behavior which may involve particular forms of stupor, rigidity, excitement or inappropriate posture. [NIH]

Schizotypal Personality Disorder: A personality disorder in which there are oddities of thought (magical thinking, paranoid ideation, suspiciousness), perception (illusions, depersonalization), speech (digressive, vague, overelaborate), and behavior (inappropriate affect in social interactions, frequently social isolation) that are not severe enough to characterize schizophrenia. [NIH]

Sciatic Nerve: A nerve which originates in the lumbar and sacral spinal cord (L4 to S3) and

supplies motor and sensory innervation to the lower extremity. The sciatic nerve, which is the main continuation of the sacral plexus, is the largest nerve in the body. It has two major branches, the tibial nerve and the peroneal nerve. [NIH]

Sclerosis: A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Second Messenger Systems: Systems in which an intracellular signal is generated in response to an intercellular primary messenger such as a hormone or neurotransmitter. They are intermediate signals in cellular processes such as metabolism, secretion, contraction, phototransduction, and cell growth. Examples of second messenger systems are the adenyl cyclase-cyclic AMP system, the phosphatidylinositol diphosphate-inositol triphosphate system, and the cyclic GMP system. [NIH]

Secretion: 1. The process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the elaboration of a new chemical substance. 2. Any substance produced by secretion. [EU]

Secretory: Secreting; relating to or influencing secretion or the secretions. [NIH]

Secretory Vesicles: Vesicles derived from the golgi apparatus containing material to be released at the cell surface. [NIH]

Sedative: 1. Allaying activity and excitement. 2. An agent that allays excitement. [EU]

Seizures: Clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganized discharge of brain cells. Clinical manifestations include abnormal motor, sensory and psychic phenomena. Recurrent seizures are usually referred to as epilepsy or "seizure disorder." [NIH]

Selenium: An element with the atomic symbol Se, atomic number 34, and atomic weight 78.96. It is an essential micronutrient for mammals and other animals but is toxic in large amounts. Selenium protects intracellular structures against oxidative damage. It is an essential component of glutathione peroxidase. [NIH]

Semen: The thick, yellowish-white, viscid fluid secretion of male reproductive organs discharged upon ejaculation. In addition to reproductive organ secretions, it contains spermatozoa and their nutrient plasma. [NIH]

Senile: Relating or belonging to old age; characteristic of old age; resulting from infirmity of old age. [NIH]

Senna: Preparations of Cassia senna L. and C. angustifolia of the Leguminosae. They contain sennosides, which are anthraquinone type cathartics and are used in many different preparations as laxatives. [NIH]

Sensibility: The ability to receive, feel and appreciate sensations and impressions; the quality of being sensitive; the extend to which a method gives results that are free from false negatives. [NIH]

Sensitization: 1. Administration of antigen to induce a primary immune response; priming; immunization. 2. Exposure to allergen that results in the development of hypersensitivity. 3. The coating of erythrocytes with antibody so that they are subject to lysis by complement in the presence of homologous antigen, the first stage of a complement fixation test. [EU]

Sensor: A device designed to respond to physical stimuli such as temperature, light, magnetism or movement and transmit resulting impulses for interpretation, recording, movement, or operating control. [NIH]

Septic: Produced by or due to decomposition by microorganisms; putrefactive. [EU]

Sequence Homology: The degree of similarity between sequences. Studies of amino acid and nucleotide sequences provide useful information about the genetic relatedness of certain species. [NIH]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [NIH]

Serologic: Analysis of a person's serum, especially specific immune or lytic serums. [NIH]

Serotonin: A biochemical messenger and regulator, synthesized from the essential amino acid L-tryptophan. In humans it is found primarily in the central nervous system, gastrointestinal tract, and blood platelets. Serotonin mediates several important physiological functions including neurotransmission, gastrointestinal motility, hemostasis, and cardiovascular integrity. Multiple receptor families (receptors, serotonin) explain the broad physiological actions and distribution of this biochemical mediator. [NIH]

Serous: Having to do with serum, the clear liquid part of blood. [NIH]

Serum: The clear liquid part of the blood that remains after blood cells and clotting proteins have been removed. [NIH]

Serum Albumin: A major plasma protein that serves in maintaining the plasma colloidal osmotic pressure and transporting large organic anions. [NIH]

Sex Characteristics: Those characteristics that distinguish one sex from the other. The primary sex characteristics are the ovaries and testes and their related hormones. Secondary sex characteristics are those which are masculine or feminine but not directly related to reproduction. [NIH]

Shock: The general bodily disturbance following a severe injury; an emotional or moral upset occasioned by some disturbing or unexpected experience; disruption of the circulation, which can upset all body functions: sometimes referred to as circulatory shock. [NIH]

Side effect: A consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration. [EU]

Signal Transduction: The intercellular or intracellular transfer of information (biological activation/inhibition) through a signal pathway. In each signal transduction system, an activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter) is mediated via the coupling of a receptor/enzyme to a second messenger system or to an ion channel. Signal transduction plays an important role in activating cellular functions, cell differentiation, and cell proliferation. Examples of signal transduction systems are the GABA-postsynaptic receptor-calcium ion channel system, the receptor-mediated T-cell activation pathway, and the receptor-mediated activation of phospholipases. Those coupled to membrane depolarization or intracellular release of calcium include the receptor-mediated activation of cytotoxic functions in granulocytes and the synaptic potentiation of protein kinase activation. Some signal transduction pathways may be part of larger signal transduction pathways; for example, protein kinase activation is part of the platelet activation signal pathway. [NIH]

Signs and Symptoms: Clinical manifestations that can be either objective when observed by a physician, or subjective when perceived by the patient. [NIH]

Skeletal: Having to do with the skeleton (boney part of the body). [NIH]

Skeleton: The framework that supports the soft tissues of vertebrate animals and protects many of their internal organs. The skeletons of vertebrates are made of bone and/or cartilage. [NIH]

Skull: The skeleton of the head including the bones of the face and the bones enclosing the

brain. [NIH]

Sleep Deprivation: The state of being deprived of sleep under experimental conditions, due to life events, or from a wide variety of pathophysiologic causes such as medication effect, chronic illness, psychiatric illness, or sleep disorder. [NIH]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Snails: Marine, freshwater, or terrestrial mollusks of the class Gastropoda. Most have an enclosing spiral shell, and several genera harbor parasites pathogenic to man. [NIH]

Sneezing: Sudden, forceful, involuntary expulsion of air from the nose and mouth caused by irritation to the mucous membranes of the upper respiratory tract. [NIH]

Social Behavior: Any behavior caused by or affecting another individual, usually of the same species. [NIH]

Social Conditions: The state of society as it exists or in flux. While it usually refers to society as a whole in a specified geographical or political region, it is applicable also to restricted strata of a society. [NIH]

Social Environment: The aggregate of social and cultural institutions, forms, patterns, and processes that influence the life of an individual or community. [NIH]

Social Isolation: The separation of individuals or groups resulting in the lack of or minimizing of social contact and/or communication. This separation may be accomplished by physical separation, by social barriers and by psychological mechanisms. In the latter, there may be interaction but no real communication. [NIH]

Social Support: Support systems that provide assistance and encouragement to individuals with physical or emotional disabilities in order that they may better cope. Informal social support is usually provided by friends, relatives, or peers, while formal assistance is provided by churches, groups, etc. [NIH]

Sodium: An element that is a member of the alkali group of metals. It has the atomic symbol Na, atomic number 11, and atomic weight 23. With a valence of 1, it has a strong affinity for oxygen and other nonmetallic elements. Sodium provides the chief cation of the extracellular body fluids. Its salts are the most widely used in medicine. (From Dorland, 27th ed) Physiologically the sodium ion plays a major role in blood pressure regulation, maintenance of fluid volume, and electrolyte balance. [NIH]

Sodium Channels: Cell membrane glycoproteins selective for sodium ions. Fast sodium current is associated with the action potential in neural membranes. [NIH]

Solid tumor: Cancer of body tissues other than blood, bone marrow, or the lymphatic system. [NIH]

Solvent: 1. Dissolving; effecting a solution. 2. A liquid that dissolves or that is capable of dissolving; the component of a solution that is present in greater amount. [EU]

Soma: The body as distinct from the mind; all the body tissue except the germ cells; all the axial body. [NIH]

Somatic: 1. Pertaining to or characteristic of the soma or body. 2. Pertaining to the body wall in contrast to the viscera. [EU]

Somatostatin: A polypeptide hormone produced in the hypothalamus, and other tissues and organs. It inhibits the release of human growth hormone, and also modulates important physiological functions of the kidney, pancreas, and gastrointestinal tract. Somatostatin

receptors are widely expressed throughout the body. Somatostatin also acts as a neurotransmitter in the central and peripheral nervous systems. [NIH]

Somnolence: Sleepiness; also unnatural drowsiness. [EU]

Sparteine: An alkaloid isolated from lupin beans, Lupinus luteus and Lupinus niger. It has been used as an oxytocic and an anti-arrhythmia agent. It has also been of interest because of genetic variation in its metabolism. [NIH]

Spasm: An involuntary contraction of a muscle or group of muscles. Spasms may involve skeletal muscle or smooth muscle. [NIH]

Spasmodic: Of the nature of a spasm. [EU]

Spasticity: A state of hypertonicity, or increase over the normal tone of a muscle, with heightened deep tendon reflexes. [EU]

Spatial disorientation: Loss of orientation in space where person does not know which way is up. [NIH]

Specialist: In medicine, one who concentrates on 1 special branch of medical science. [NIH]

Species: A taxonomic category subordinate to a genus (or subgenus) and superior to a subspecies or variety, composed of individuals possessing common characters distinguishing them from other categories of individuals of the same taxonomic level. In taxonomic nomenclature, species are designated by the genus name followed by a Latin or Latinized adjective or noun. [EU]

Specificity: Degree of selectivity shown by an antibody with respect to the number and types of antigens with which the antibody combines, as well as with respect to the rates and the extents of these reactions. [NIH]

Spectrum: A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

Sperm: The fecundating fluid of the male. [NIH]

Sphincter: A ringlike band of muscle fibres that constricts a passage or closes a natural orifice; called also musculus sphincter. [EU]

Spinal cord: The main trunk or bundle of nerves running down the spine through holes in the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]

Spinal Cord Ischemia: Reduced blood flow to the spinal cord which is supplied by the anterior spinal artery and the paired posterior spinal arteries. This condition may be associated with arteriosclerosis, trauma, emboli, diseases of the aorta, and other disorders. Prolonged ischemia may lead to infarction of spinal cord tissue. [NIH]

Spleen: An organ that is part of the lymphatic system. The spleen produces lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach. [NIH]

Stabilizer: A device for maintaining constant X-ray tube voltage or current. [NIH]

Stasis: A word termination indicating the maintenance of (or maintaining) a constant level; preventing increase or multiplication. [EU]

Statistically significant: Describes a mathematical measure of difference between groups. The difference is said to be statistically significant if it is greater than what might be expected to happen by chance alone. [NIH]

Steel: A tough, malleable, iron-based alloy containing up to, but no more than, two percent carbon and often other metals. It is used in medicine and dentistry in implants and

instrumentation. [NIH]

Sterile: Unable to produce children. [NIH]

Sterilization: The destroying of all forms of life, especially microorganisms, by heat, chemical, or other means. [NIH]

Steroid: A group name for lipids that contain a hydrogenated cyclopentanoperhydrophenanthrene ring system. Some of the substances included in this group are progesterone, adrenocortical hormones, the gonadal hormones, cardiac aglycones, bile acids, sterols (such as cholesterol), toad poisons, saponins, and some of the carcinogenic hydrocarbons. [EU]

Stimulant: 1. Producing stimulation; especially producing stimulation by causing tension on muscle fibre through the nervous tissue. 2. An agent or remedy that produces stimulation. [EU]

Stimulus: That which can elicit or evoke action (response) in a muscle, nerve, gland or other excitable issue, or cause an augmenting action upon any function or metabolic process. [NIH]

Stomach: An organ of digestion situated in the left upper quadrant of the abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

Stomatitis: Inflammation of the oral mucosa, due to local or systemic factors which may involve the buccal and labial mucosa, palate, tongue, floor of the mouth, and the gingivae. [EU]

Stool: The waste matter discharged in a bowel movement; feces. [NIH]

Strabismus: Deviation of the eye which the patient cannot overcome. The visual axes assume a position relative to each other different from that required by the physiological conditions. The various forms of strabismus are spoken of as tropias, their direction being indicated by the appropriate prefix, as cyclo tropia, esotropia, exotropia, hypertropia, and hypotropia. Called also cast, heterotropia, manifest deviation, and squint. [EU]

Strand: DNA normally exists in the bacterial nucleus in a helix, in which two strands are coiled together. [NIH]

Stress: Forcibly exerted influence; pressure. Any condition or situation that causes strain or tension. Stress may be either physical or psychologic, or both. [NIH]

Stria: 1. A streak, or line. 2. A narrow bandlike structure; a general term for such longitudinal collections of nerve fibres in the brain. [EU]

Striatum: A higher brain's domain thus called because of its stripes. [NIH]

Stroke: Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

Stroma: The middle, thickest layer of tissue in the cornea. [NIH]

Structure-Activity Relationship: The relationship between the chemical structure of a compound and its biological or pharmacological activity. Compounds are often classed together because they have structural characteristics in common including shape, size, stereochemical arrangement, and distribution of functional groups. Other factors contributing to structure-activity relationship include chemical reactivity, electronic effects, resonance, and inductive effects. [NIH]

Stupor: Partial or nearly complete unconsciousness, manifested by the subject's responding only to vigorous stimulation. Also, in psychiatry, a disorder marked by reduced responsiveness. [EU]

Subacute: Somewhat acute; between acute and chronic. [EU]

Subarachnoid: Situated or occurring between the arachnoid and the pia mater. [EU]

Subclinical: Without clinical manifestations; said of the early stage(s) of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests, or of a very mild form of an infection or other disease or abnormality. [EU]

Subcutaneous: Beneath the skin. [NIH]

Subiculum: A region of the hippocampus that projects to other areas of the brain. [NIH]

Sublingual: Located beneath the tongue. [EU]

Subspecies: A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

Substance P: An eleven-amino acid neurotransmitter that appears in both the central and peripheral nervous systems. It is involved in transmission of pain, causes rapid contractions of the gastrointestinal smooth muscle, and modulates inflammatory and immune responses. [NIH]

Substantia Gelatinosa: Gelatinous-appearing material in the dorsal horn of the spinal cord, consisting chiefly of Golgi type II neurons and some larger nerve cells. [NIH]

Substrate: A substance upon which an enzyme acts. [EU]

Subtrochanteric: Below a trochanter. [NIH]

Sudden death: Cardiac arrest caused by an irregular heartbeat. The term "death" is somewhat misleading, because some patients survive. [NIH]

Sufentanil: An opioid analgesic that is used as an adjunct in anesthesia, in balanced anesthesia, and as a primary anesthetic agent. [NIH]

Sulfur: An element that is a member of the chalcogen family. It has an atomic symbol S, atomic number 16, and atomic weight 32.066. It is found in the amino acids cysteine and methionine. [NIH]

Sulfur Dioxide: A highly toxic, colorless, nonflammable gas. It is used as a pharmaceutical aid and antioxidant. It is also an environmental air pollutant. [NIH]

Sumatriptan: A serotonin agonist that acts selectively at 5HT1 receptors. It is used in the treatment of migraines. [NIH]

Superoxide: Derivative of molecular oxygen that can damage cells. [NIH]

Supplementation: Adding nutrients to the diet. [NIH]

Suppositories: A small cone-shaped medicament having cocoa butter or gelatin at its basis and usually intended for the treatment of local conditions in the rectum. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in which the process of exclusion is not conscious. [NIH]

Supraspinal: Above the spinal column or any spine. [NIH]

Sympathetic Nervous System: The thoracolumbar division of the autonomic nervous system. Sympathetic preganglionic fibers originate in neurons of the intermediolateral column of the spinal cord and project to the paravertebral and prevertebral ganglia, which in turn project to target organs. The sympathetic nervous system mediates the body's response to stressful situations, i.e., the fight or flight reactions. It often acts reciprocally to the parasympathetic system. [NIH]

Sympatholytics: Drugs that inhibit the actions of the sympathetic nervous system by any mechanism. The most common of these are the adrenergic antagonists and drugs that deplete norepinephrine or reduce the release of transmitters from adrenergic postganglionic

terminals. Drugs that act in the central nervous system to reduce sympathetic activity (e.g., centrally acting alpha-2 adrenergic agonists) are included here. [NIH]

Sympathomimetic: 1. Mimicking the effects of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. 2. An agent that produces effects similar to those of impulses conveyed by adrenergic postganglionic fibres of the sympathetic nervous system. Called also adrenergic. [EU]

Symphysis: A secondary cartilaginous joint. [NIH]

Symptomatic: Having to do with symptoms, which are signs of a condition or disease. [NIH]

Synapses: Specialized junctions at which a neuron communicates with a target cell. At classical synapses, a neuron's presynaptic terminal releases a chemical transmitter stored in synaptic vesicles which diffuses across a narrow synaptic cleft and activates receptors on the postsynaptic membrane of the target cell. The target may be a dendrite, cell body, or axon of another neuron, or a specialized region of a muscle or secretory cell. Neurons may also communicate through direct electrical connections which are sometimes called electrical synapses; these are not included here but rather in gap junctions. [NIH]

Synapsis: The pairing between homologous chromosomes of maternal and paternal origin during the prophase of meiosis, leading to the formation of gametes. [NIH]

Synaptic: Pertaining to or affecting a synapse (= site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means); pertaining to synapsis (= pairing off in point-for-point association of homologous chromosomes from the male and female pronuclei during the early prophase of meiosis). [EU]

Synaptic Transmission: The communication from a neuron to a target (neuron, muscle, or secretory cell) across a synapse. In chemical synaptic transmission, the presynaptic neuron releases a neurotransmitter that diffuses across the synaptic cleft and binds to specific synaptic receptors. These activated receptors modulate ion channels and/or second-messenger systems to influence the postsynaptic cell. Electrical transmission is less common in the nervous system, and, as in other tissues, is mediated by gap junctions. [NIH]

Synaptic Vesicles: Membrane-bound compartments which contain transmitter molecules. Synaptic vesicles are concentrated at presynaptic terminals. They actively sequester transmitter molecules from the cytoplasm. In at least some synapses, transmitter release occurs by fusion of these vesicles with the presynaptic membrane, followed by exocytosis of their contents. [NIH]

Synaptosomes: Pinched-off nerve endings and their contents of vesicles and cytoplasm together with the attached subsynaptic area of the membrane of the post-synaptic cell. They are largely artificial structures produced by fractionation after selective centrifugation of nervous tissue homogenates. [NIH]

Synchrony: The normal physiologic sequencing of atrial and ventricular activation and contraction. [NIH]

Syncytium: A living nucleated tissue without apparent cellular structure; a tissue composed of a mass of nucleated protoplasm without cell boundaries. [NIH]

Synergistic: Acting together; enhancing the effect of another force or agent. [EU]

Synovial: Of pertaining to, or secreting synovia. [EU]

Systemic: Affecting the entire body. [NIH]

Systolic: Indicating the maximum arterial pressure during contraction of the left ventricle of the heart. [EU]

Tardive: Marked by lateness, late; said of a disease in which the characteristic lesion is late in appearing. [EU]

Telecommunications: Transmission of information over distances via electronic means. [NIH]

Temporal: One of the two irregular bones forming part of the lateral surfaces and base of the skull, and containing the organs of hearing. [NIH]

Temporal Lobe: Lower lateral part of the cerebral hemisphere. [NIH]

Terminalis: A groove on the lateral surface of the right atrium. [NIH]

Testis: Either of the paired male reproductive glands that produce the male germ cells and the male hormones. [NIH]

Testosterone: A hormone that promotes the development and maintenance of male sex characteristics. [NIH]

Tetanic: Having the characteristics of, or relating to tetanus. [NIH]

Tetanus: A disease caused by tetanospasmin, a powerful protein toxin produced by Clostridium tetani. Tetanus usually occurs after an acute injury, such as a puncture wound or laceration. Generalized tetanus, the most common form, is characterized by tetanic muscular contractions and hyperreflexia. Localized tetanus presents itself as a mild condition with manifestations restricted to muscles near the wound. It may progress to the generalized form. [NIH]

Tetrahydrocannabinol: A psychoactive compound extracted from the resin of Cannabis sativa (marihuana, hashish). The isomer delta-9-tetrahydrocannabinol (THC) is considered the most active form, producing characteristic mood and perceptual changes associated with this compound. Dronabinol is a synthetic form of delta-9-THC. [NIH]

Thalamic: Cell that reaches the lateral nucleus of amygdala. [NIH]

Thalamus: Paired bodies containing mostly gray substance and forming part of the lateral wall of the third ventricle of the brain. The thalamus represents the major portion of the diencephalon and is commonly divided into cellular aggregates known as nuclear groups. [NIH]

Therapeutics: The branch of medicine which is concerned with the treatment of diseases, palliative or curative. [NIH]

Thermal: Pertaining to or characterized by heat. [EU]

Thigh: A leg; in anatomy, any elongated process or part of a structure more or less comparable to a leg. [NIH]

Third Ventricle: A narrow cleft inferior to the corpus callosum, within the diencephalon, between the paired thalami. Its floor is formed by the hypothalamus, its anterior wall by the lamina terminalis, and its roof by ependyma. It communicates with the fourth ventricle by the cerebral aqueduct, and with the lateral ventricles by the interventricular foramina. [NIH]

Thoracotomy: Surgical incision into the chest wall. [NIH]

Thorax: A part of the trunk between the neck and the abdomen; the chest. [NIH]

Threonine: An essential amino acid occurring naturally in the L-form, which is the active form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

Threshold: For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [NIH]

Thrombin: An enzyme formed from prothrombin that converts fibrinogen to fibrin. (Dorland, 27th ed) EC 3.4.21.5. [NIH]

Thrombocytes: Blood cells that help prevent bleeding by causing blood clots to form. Also called platelets. [NIH]

Thromboembolism: Obstruction of a vessel by a blood clot that has been transported from a distant site by the blood stream. [NIH]

Thrombomodulin: A cell surface glycoprotein of endothelial cells that binds thrombin and serves as a cofactor in the activation of protein C and its regulation of blood coagulation. [NIH]

Thrombosis: The formation or presence of a blood clot inside a blood vessel. [NIH]

Thrombus: An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation. Some authorities thus differentiate thrombus formation from simple coagulation or clot formation. [EU]

Thyroid: A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

Tibial Nerve: The medial terminal branch of the sciatic nerve. The tibial nerve fibers originate in lumbar and sacral spinal segments (L4 to S2). They supply motor and sensory innervation to parts of the calf and foot. [NIH]

Tin: A trace element that is required in bone formation. It has the atomic symbol Sn, atomic number 50, and atomic weight 118.71. [NIH]

Tinnitus: Sounds that are perceived in the absence of any external noise source which may take the form of buzzing, ringing, clicking, pulsations, and other noises. Objective tinnitus refers to noises generated from within the ear or adjacent structures that can be heard by other individuals. The term subjective tinnitus is used when the sound is audible only to the affected individual. Tinnitus may occur as a manifestation of cochlear diseases; vestibulocochlear nerve diseases; intracranial hypertension; craniocerebral trauma; and other conditions. [NIH]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

Tissue Culture: Maintaining or growing of tissue, organ primordia, or the whole or part of an organ in vitro so as to preserve its architecture and/or function (Dorland, 28th ed). Tissue culture includes both organ culture and cell culture. [NIH]

Tolerance: 1. The ability to endure unusually large doses of a drug or toxin. 2. Acquired drug tolerance; a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response. [EU]

Tomography: Imaging methods that result in sharp images of objects located on a chosen plane and blurred images located above or below the plane. [NIH]

Tonic: 1. Producing and restoring the normal tone. 2. Characterized by continuous tension. 3. A term formerly used for a class of medicinal preparations believed to have the power of restoring normal tone to tissue. [EU]

Tonicity: The normal state of muscular tension. [NIH]

Tooth Preparation: Procedures carried out with regard to the teeth or tooth structures preparatory to specified dental therapeutic and surgical measures. [NIH]

Toothache: Pain in the adjacent areas of the teeth. [NIH]

Topical: On the surface of the body. [NIH]

Tourniquet: A device, band or elastic tube applied temporarily to press upon an artery to stop bleeding; a device to compress a blood vessel in order to stop bleeding. [NIH]

Toxic: Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects. [NIH]

Toxicity: The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. [EU]

Toxicology: The science concerned with the detection, chemical composition, and pharmacologic action of toxic substances or poisons and the treatment and prevention of toxic manifestations. [NIH]

Toxins: Specific, characterizable, poisonous chemicals, often proteins, with specific biological properties, including immunogenicity, produced by microbes, higher plants, or animals. [NIH]

Toxoplasmosis: The acquired form of infection by Toxoplasma gondii in animals and man. [NIH]

Trace element: Substance or element essential to plant or animal life, but present in extremely small amounts. [NIH]

Traction: The act of pulling. [NIH]

Tramadol: A narcotic analgesic proposed for severe pain. It may be habituating. [NIH]

Transaminase: Aminotransferase (= a subclass of enzymes of the transferase class that catalyse the transfer of an amino group from a donor (generally an amino acid) to an acceptor (generally 2-keto acid). Most of these enzymes are pyridoxal-phosphate-proteins. [EU]

Transcriptase: An enzyme which catalyses the synthesis of a complementary mRNA molecule from a DNA template in the presence of a mixture of the four ribonucleotides (ATP, UTP, GTP and CTP). [NIH]

Transcutaneous: Transdermal. [EU]

Transdermal: Entering through the dermis, or skin, as in administration of a drug applied to the skin in ointment or patch form. [EU]

Transduction: The transfer of genes from one cell to another by means of a viral (in the case of bacteria, a bacteriophage) vector or a vector which is similar to a virus particle (pseudovirion). [NIH]

Transfection: The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

Transfusion: The infusion of components of blood or whole blood into the bloodstream. The blood may be donated from another person, or it may have been taken from the person earlier and stored until needed. [NIH]

Translation: The process whereby the genetic information present in the linear sequence of ribonucleotides in mRNA is converted into a corresponding sequence of amino acids in a protein. It occurs on the ribosome and is unidirectional. [NIH]

Translocation: The movement of material in solution inside the body of the plant. [NIH]

Transmitter: A chemical substance which effects the passage of nerve impulses from one cell to the other at the synapse. [NIH]

Trauma: Any injury, wound, or shock, must frequently physical or structural shock, producing a disturbance. [NIH]

Tricuspid Atresia: Absence of the orifice between the right atrium and ventricle, with the presence of an atrial defect through which all the systemic venous return reaches the left heart. As a result, there is left ventricular hypertrophy because the right ventricle is absent or not functional. [NIH]

Tricyclic: Containing three fused rings or closed chains in the molecular structure. [EU]

Trifluoroacetic Acid: A very strong halogenated derivative of acetic acid. It is used in acid catalyzed reactions, especially those where an ester is cleaved in peptide synthesis. [NIH]

Trigeminal: Cranial nerve V. It is sensory for the eyeball, the conjunctiva, the eyebrow, the skin of face and scalp, the teeth, the mucous membranes in the mouth and nose, and is motor to the muscles of mastication. [NIH]

Trigeminal Nerve: The 5th and largest cranial nerve. The trigeminal nerve is a mixed motor and sensory nerve. The larger sensory part forms the ophthalmic, mandibular, and maxillary nerves which carry afferents sensitive to external or internal stimuli from the skin, muscles, and joints of the face and mouth and from the teeth. Most of these fibers originate from cells of the trigeminal ganglion and project to the trigeminal nucleus of the brain stem. The smaller motor part arises from the brain stem trigeminal motor nucleus and innervates the muscles of mastication. [NIH]

Tryptophan: An essential amino acid that is necessary for normal growth in infants and for nitrogen balance in adults. It is a precursor serotonin and niacin. [NIH]

Tubercle: A rounded elevation on a bone or other structure. [NIH]

Tuberculosis: Any of the infectious diseases of man and other animals caused by species of Mycobacterium. [NIH]

Tubocurarine: A neuromuscular blocker and active ingredient in curare; plant based alkaloid of Menispermaceae. [NIH]

Tumor Necrosis Factor: Serum glycoprotein produced by activated macrophages and other mammalian mononuclear leukocytes which has necrotizing activity against tumor cell lines and increases ability to reject tumor transplants. It mimics the action of endotoxin but differs from it. It has a molecular weight of less than 70,000 kDa. [NIH]

Tumour: 1. Swelling, one of the cardinal signs of inflammations; morbid enlargement. 2. A new growth of tissue in which the multiplication of cells is uncontrolled and progressive; called also neoplasm. [EU]

Tyramine: An indirect sympathomimetic. Tyramine does not directly activate adrenergic receptors, but it can serve as a substrate for adrenergic uptake systems and monoamine oxidase so it prolongs the actions of adrenergic transmitters. It also provokes transmitter release from adrenergic terminals. Tyramine may be a neurotransmitter in some invertebrate nervous systems. [NIH]

Tyrosine: A non-essential amino acid. In animals it is synthesized from phenylalanine. It is also the precursor of epinephrine, thyroid hormones, and melanin. [NIH]

Ulcer: A localized necrotic lesion of the skin or a mucous surface. [NIH]

Unconscious: Experience which was once conscious, but was subsequently rejected, as the "personal unconscious". [NIH]

Uracil: An anticancer drug that belongs to the family of drugs called alkylating agents. [NIH]

Ureter: One of a pair of thick-walled tubes that transports urine from the kidney pelvis to the bladder. [NIH]

Urethra: The tube through which urine leaves the body. It empties urine from the bladder. [NIH]

Uridine Diphosphate: A uracil nucleotide containing a pyrophosphate group esterified to C5 of the sugar moiety. [NIH]

Uridine Diphosphate Glucuronic Acid: A nucleoside diphosphate sugar which serves as a source of glucuronic acid for polysaccharide biosynthesis. It may also be epimerized to UDP

iduronic acid, which donates iduronic acid to polysaccharides. In animals, UDP glucuronic acid is used for formation of many glucosiduronides with various aglycones. [NIH]

Urinary: Having to do with urine or the organs of the body that produce and get rid of urine. [NIH]

Urinary Retention: Inability to urinate. The etiology of this disorder includes obstructive, neurogenic, pharmacologic, and psychogenic causes. [NIH]

Urinary tract: The organs of the body that produce and discharge urine. These include the kidneys, ureters, bladder, and urethra. [NIH]

Urinary tract infection: An illness caused by harmful bacteria growing in the urinary tract. [NIH]

Urinate: To release urine from the bladder to the outside. [NIH]

Urine: Fluid containing water and waste products. Urine is made by the kidneys, stored in the bladder, and leaves the body through the urethra. [NIH]

Uterine Contraction: Contraction of the uterine muscle. [NIH]

Uterus: The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a fetus develops. Also called the womb. [NIH]

Uveitis: An inflammation of part or all of the uvea, the middle (vascular) tunic of the eye, and commonly involving the other tunics (the sclera and cornea, and the retina). [EU]

Vaccination: Administration of vaccines to stimulate the host's immune response. This includes any preparation intended for active immunological prophylaxis. [NIH]

Vaccine: A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. [NIH]

Vacuoles: Any spaces or cavities within a cell. They may function in digestion, storage, secretion, or excretion. [NIH]

Vagina: The muscular canal extending from the uterus to the exterior of the body. Also called the birth canal. [NIH]

Valproic Acid: A fatty acid with anticonvulsant properties used in the treatment of epilepsy. The mechanisms of its therapeutic actions are not well understood. It may act by increasing GABA levels in the brain or by altering the properties of voltage dependent sodium channels. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vascular Headaches: A group of disorders characterized by recurrent headaches associated with abnormal dilation and constriction of cerebral blood vessels. Representative disorders from this category include migraine, cluster headache, and paroxysmal hemicrania. [NIH]

Vasoconstriction: Narrowing of the blood vessels without anatomic change, for which constriction, pathologic is used. [NIH]

Vasodilation: Physiological dilation of the blood vessels without anatomic change. For dilation with anatomic change, dilatation, pathologic or aneurysm (or specific aneurysm) is used. [NIH]

Vasodilator: An agent that widens blood vessels. [NIH]

VE: The total volume of gas either inspired or expired in one minute. [NIH]

Vector: Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

Vein: Vessel-carrying blood from various parts of the body to the heart. [NIH]

Venom: That produced by the poison glands of the mouth and injected by the fangs of poisonous snakes. [NIH]

Venous: Of or pertaining to the veins. [EU]

Ventilation: 1. In respiratory physiology, the process of exchange of air between the lungs and the ambient air. Pulmonary ventilation (usually measured in litres per minute) refers to the total exchange, whereas alveolar ventilation refers to the effective ventilation of the alveoli, in which gas exchange with the blood takes place. 2. In psychiatry, verbalization of one's emotional problems. [EU]

Ventilator: A breathing machine that is used to treat respiratory failure by promoting ventilation; also called a respirator. [NIH]

Ventral: 1. Pertaining to the belly or to any venter. 2. Denoting a position more toward the belly surface than some other object of reference; same as anterior in human anatomy. [EU]

Ventral Tegmental Area: A region in the mesencephalon which is dorsomedial to the substantia nigra and ventral to the red nucleus. The mesocortical and mesolimbic dopaminergic systems originate here, including an important projection to the nucleus accumbens. Overactivity of the cells in this area has been suspected to contribute to the positive symptoms of schizophrenia. [NIH]

Ventricle: One of the two pumping chambers of the heart. The right ventricle receives oxygen-poor blood from the right atrium and pumps it to the lungs through the pulmonary artery. The left ventricle receives oxygen-rich blood from the left atrium and pumps it to the body through the aorta. [NIH]

Ventricular: Pertaining to a ventricle. [EU]

Venules: The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

Vertebrae: A bony unit of the segmented spinal column. [NIH]

Vertebral: Of or pertaining to a vertebra. [EU]

Vestibulocochlear Nerve: The 8th cranial nerve. The vestibulocochlear nerve has a cochlear part (cochlear nerve) which is concerned with hearing and a vestibular part (vestibular nerve) which mediates the sense of balance and head position. The fibers of the cochlear nerve originate from neurons of the spiral ganglion and project to the cochlear nuclei (cochlear nucleus). The fibers of the vestibular nerve arise from neurons of Scarpa's ganglion and project to the vestibular nuclei. [NIH]

Vestibulocochlear Nerve Diseases: Diseases of the vestibular and/or cochlear (acoustic) nerves, which join to form the vestibulocochlear nerve. Vestibular neuritis, cochlear neuritis, and acoustic neuromas are relatively common conditions that affect these nerves. Clinical manifestations vary with which nerve is primarily affected, and include hearing loss, vertigo, and tinnitus. [NIH]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Vibrio: A genus of Vibrionaceae, made up of short, slightly curved, motile, gram-negative rods. Various species produce cholera and other gastrointestinal disorders as well as abortion in sheep and cattle. [NIH]

Vibrio cholerae: The etiologic agent of cholera. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

Viral Load: The quantity of measurable virus in the blood. Change in viral load, measured in plasma, is used as a surrogate marker in HIV disease progression. [NIH]

Viremia: The presence of viruses in the blood. [NIH]

Virulence: The degree of pathogenicity within a group or species of microorganisms or viruses as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. [NIH]

Virus: Submicroscopic organism that causes infectious disease. In cancer therapy, some viruses may be made into vaccines that help the body build an immune response to, and kill, tumor cells. [NIH]

Virus Diseases: A general term for diseases produced by viruses. [NIH]

Viscera: Any of the large interior organs in any one of the three great cavities of the body, especially in the abdomen. [NIH]

Visceral: , from viscus a viscus) pertaining to a viscus. [EU]

Viscosity: A physical property of fluids that determines the internal resistance to shear forces. [EU]

Vitro: Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

Vivo: Outside of or removed from the body of a living organism. [NIH]

Waiting Lists: Prospective patient listings for appointments. [NIH]

Wakefulness: A state in which there is an enhanced potential for sensitivity and an efficient responsiveness to external stimuli. [NIH]

Weight Gain: Increase in body weight over existing weight. [NIH]

White blood cell: A type of cell in the immune system that helps the body fight infection and disease. White blood cells include lymphocytes, granulocytes, macrophages, and others. [NIH]

Whooping Cough: A respiratory infection caused by Bordetella pertussis and characterized by paroxysmal coughing ending in a prolonged crowing intake of breath. [NIH]

Whooping Cough: A respiratory infection caused by Bordetella pertussis and characterized by paroxysmal coughing ending in a prolonged crowing intake of breath. [NIH]

Withdrawal: 1. A pathological retreat from interpersonal contact and social involvement, as may occur in schizophrenia, depression, or schizoid avoidant and schizotypal personality disorders. 2. (DSM III-R) A substance-specific organic brain syndrome that follows the cessation of use or reduction in intake of a psychoactive substance that had been regularly used to induce a state of intoxication. [EU]

Xenograft: The cells of one species transplanted to another species. [NIH]

Xenon: A noble gas with the atomic symbol Xe, atomic number 54, and atomic weight 131.30. It is found in the earth's atmosphere and has been used as an anesthetic. [NIH]

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

Zygote: The fertilized ovum. [NIH]

Zymogen: Inactive form of an enzyme which can then be converted to the active form, usually by excision of a polypeptide, e. g. trypsinogen is the zymogen of trypsin. [NIH]

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