

Abstracts of Current Research Grants (November 2007)

I. BASIC & CLINICAL PHARMACOLOGY OF ANESTHETICS & OTHER DRUGS

1. Modulation of Opioid Effects by Garlic Supplements

D. Shen, Ph.D., G.W. Terman, M.D., Ph.D.

Its overall objective is to explore whether a CYP3A- and Pgp-dependent interaction exists between garlic supplements and a commonly used oral opioid analgesics-oxycodone. The studies are designed to investigate the following hypotheses:

1. Garlic extract has the dual capability of inhibiting and inducing the activities of intestinal and hepatic CYP3A and intestinal Pgp, such that its effects on oxycodone pharmacokinetics vary over the course of garlic treatment (i.e., increased bioavailability and slowed clearance appear shortly after initiation of treatment with garlic supplement, and reduced bioavailability and accelerated clearance occur eventually at steady state during chronic treatment with garlic supplement).

2. Garlic-induced changes in oxycodone pharmacokinetics lead to significant changes in analgesic and side effects of oxycodone. In particular, we will assess whether the same degree of change in analgesia and side effects will result; in other words, whether there is a change in the therapeutic index. We will focus on the three most bothersome aspects of opioid side effects; i.e, the somatic, affective, and cognitive effects of oxycodone.

3. The magnitude and the time course of interaction differ between the two common types of garlic supplements, dried garlic powder and steam-distilled garlic oil, because of differences in their biologically active constituents.

These studies will allow us to assess the potential clinical significance of interactions between garlic and opioids and to elucidate the pharmacokinetic and pharmacodynamic basis of the observed interaction. They may point to the need for a more systemic investigation of potentially adverse interactions between garlic supplements and other opioid analgesics in use.

2. Garlic Metabolism and Cytochrome P450 Modulation

D. Shen, Ph.D., G.W. Terman, M.D., Ph.D.

There is growing concern over the quality, efficacy and safety of the many herbal products sold over the counter because of the increasing use of herbal medicine by Americans over the past decade and the current lack of stringent regulations governing the manufacturing and marketing of herbal products. A major safety concern is the potential for adverse interactions between herbs and drugs. At present, documentation of adverse herb-drug interactions relies mostly on clinical case reports, and studies in a small number of patients or healthy volunteers. This has led to conflicting reports, and debates over the reliability and clinical significance of the purported herb-drug interactions. Moreover, findings observed with one herbal product are often applied to all

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commercial products of that herb; such generalization warrants caution given the variation in the composition and strength of bioactive ingredients in many herbal medicines. Hence, carefully controlled and systematic studies must follow to confirm and clarify the initial clinical reports of potentially significant and widespread herb-drug interactions.

Americans frequently use garlic supplements; in 1998, garlic was the fourth best selling herbal product in the U.S. with an annual sale of \$84 million. In a recently completed VITamins And Lifestyle (VITAL) Study of 77,438 older (50-79 years) adults conducted at FHCRC, garlic supplements were amongst the top ten most used herbal supplements; 7.3% and 6.8% of men and women, respectively, took garlic supplements at least once a week for a year. In another earlier study from FHCRC, 27% of the cancer patients who admitted to using herbals were taking garlic supplements. Epidemiological evidence and findings from animal and in vitro studies suggest that garlic may prevent or halt cancer through multiple biochemical and cellular mechanisms, including inhibition of tumor promotion and proliferation, antioxidant actions, as well as suppression of carcinogen activation through inhibition of bioactivating enzymes (e.g. CYP1A1, 2E1 and epoxide hydrolase) and increase in expression of detoxification enzymes (e.g. glutathione S-transferase) The claims of immune enhancement and anticancer effects probably explain the frequent use of garlic in cancer patients with active disease or in remission.

The overall objective of this proposed research is to investigate the modulating effects of garlic supplements on the activity of several major drug-metabolizing cytochrome P450 enzymes (CYPs) and the membrane efflux transporter P-glycoprotein (Pgp) in healthy subjects. The studies are designed to investigate the pharmacokinetic mechanisms underlying several recently reported interactions between garlic supplements and drugs.

3. Subcellular Distribution & Regulation of α_1 -Adrenoceptors

D.A. Schwinn, M.D., A.Oganesian, Ph.D.

The long-term objective of this research is to understand the role of stress (acute and chronic) on perioperative outcome in humans. Within this context, our laboratory has focused on examining mechanisms underlying regulation of one of the stress hormone (catecholamine) binding receptor families, the alpha1-adrenergic receptors (alpha1 ARs). Our previous studies characterized subtype specific regulation of alpha1a AR transcription, desensitization, and internalization. One key finding that emerged was that alpha1a ARs have the unique ability to continuously signal in the presence of agonist in situations where alpha1b and alpha1dARs (and indeed many G protein-coupled receptors [GPCRs]) concurrently dampen (desensitize and/or downregulate) signaling. Indeed, our recent indicate that alpha1a AR trafficking mechanisms are distinct from other alpha1 AR subtypes since alpha1a AR displays a unique ability to constitutively recycle, independent of agonist stimulation. Underlying mechanisms remain unknown, but it is becoming increasingly clear that GPCRs are able to interact directly with an array of cytosolic that directly modulate receptor dimerization, trafficking, and transcription. The focus of this

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competitive renewal is to elucidate these processes with the overall hypothesis that alpha1a ARs couple to regulatory pathways distinct from other ARs. We propose two specific aims designed to identify novel alpha1a AR coupling (including clathrin, Gq-independent, and caveolin associated pathways). In the first aim we will investigate the ability of alpha1a ARs to interact directly with specific proteins in these pathways (e.g., beta-arrestins) using quantitative immunoprecipitation approaches in classic cellular models of both stably transfected rat-1 fibroblasts and neonatal cardiomyocytes. We will utilize novel soluble competitors that target intracellular loops to determine distinct alpha1a AR intracellular regions involved in alpha1a AR signaling and identify the proteins to which they bind using targeted proteomics. In a parallel second aim, we will examine mechanisms underlying both constitutive and agonist-induced alpha1a AR cycling using highly characterized functional and subcellular localization assays. Perturbation of model systems using engineered mutants for both alpha1a AR, as well as targeted factors within relevant pathways, be used to independently confirm results. Mutation of putative phosphorylation sites will be used to further mechanisms underlying alpha1a AR trafficking. Identification of alpha1a AR-responsive pathways is an important in understanding the role of catecholamines in stress responses with the ultimate goal of identifying novel designed to improve therapeutic strategies for acute and chronic disease.

4. Bladder Function During Thoracic Epidural Anesthesia and Analgesia(C)

D. J. Pavlin, M.D.

The purpose of this study is to investigate the effects of thoracic epidural anesthesia and analgesia on urinary bladder function, and determine the potential utility of ultrasound monitoring of bladder volume intra- and postoperatively in such patients, to diminish the incidence of painless urinary retention, bladder dysfunction, and urinary tract infection after surgery. Thoracic epidural analgesia is a method of pain control commonly used after thoracic or upper abdominal surgery. It is particularly advantageous for these types of operations (i.e. lung operations, gall bladder surgery, upper gastrointestinal surgery, colon surgery) because it has been shown to improve postoperative lung function when compared to use of pain medications without epidural analgesia.

We are proposing to study bladder function in patients who have a functioning thoracic epidural placed for management of postoperative pain. It will be studied in two groups of patients. **Group 1** will have bladder volume monitored by ultrasound with intermittent sporadic catheterization if indicated for urinary retention during surgery and in the first 5 days after surgery. **Group 2** will have continuous catheter drainage of the bladder for 24-48 hours after surgery, followed by non-invasive monitoring by ultrasound on day 3-5 with intermittent catheterization as required for retention.

Our expectation is that this study will allow us to (1) determine the need for continuous bladder catheter drainage or ultrasound monitoring in future in patients with a functioning thoracic epidural, (2) compare the risks/complications of continuous catheter drainage versus non-invasive

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monitoring with intermittent catheterization as required for retention, (3) identify risk factors for retention in patients with a functioning thoracic epidural. We will also evaluate the ability of patients and/or nurses to assess/estimate or guess bladder volume with and without the aid of an ultrasound scanner.

II. CARDIOVASCULAR AND RESPIRATORY PHYSIOLOGY

1. Hemoglobin, Nitric Oxide and the Pulmonary Circulation

S.A. Deem, M.D., E.R. Swenson, M.D., M.T. Gladwin, M.D.

Red blood cells (RBCs) have generally been thought to serve as mere carriers of oxygen and carbon dioxide between the lung and systemic tissues. However, recent studies indicate that RBCs are actively involved in the regulation of vascular tone, largely through their capacity to stimulate production of, inactivate, and transport the vasodilator substance nitric oxide (NO). In particular, the irreversible oxidation of NO to form metHb and nitrate, and the reversible reactions of NO with hemoglobin (Hb) to form S-nitrosoHb (SNO-Hb) and nitrosyl(heme)Hb are of potential major import. The interactions between RBCs and vascular tone appear to be particularly important during hypoxic conditions, wherein RBCs augment hypoxic pulmonary vasoconstriction and optimize regional ventilation-perfusion matching in the lung, and optimize oxygen delivery to systemic tissues. The Targeted Goals of the project are to: IA. Determine the effects of free and intraerythrocytic nitrosyl(heme)Hb and SNO-Hb on pulmonary pressure, HPV, and NO kinetics in an isolated lung model IB. Determine whether SNO-Hb and nitrosyl(heme)Hb have effects on pulmonary and systemic vascular resistance and HPV in vivo, using live anesthetized rats as a model. IC. Determine whether nitrite protects NO from oxidation by Hb and whether nitrite modulates HPV. IIA. Determine whether SNO-Hb and nitrosyl(heme)Hb relax pulmonary vascular smooth muscle (VSM) in vitro, and explore the mechanism of any different effects of these mediators on pulmonary vs. systemic VSM. In particular, we will determine effects on pulmonary VSM of the SNO-Hb/NO intermediate nitroxyl anion. IIB. Determine whether nitroxyl anion inhibits HPV in an isolated, perfused lung model, and determine whether nitroxyl may be produced from SNO-Hb in this model. Techniques used for all Targeted Goals will include measurement of physiologic variables and biomolecular markers of NO production and inactivation, including exhaled NO. The ultimate objectives of this project are to increase the understanding of how RBCs, Hb, and by extension anemia affect pulmonary and systemic oxygen exchange in health and disease. Ultimately, the information gained will allow refinement of blood transfusion practice during surgery and in critical illness. The potential clinical impact is large given the risk and cost associated with blood transfusion and world-wide shortage of blood products.

2. Red Blood Cells, Nitric Oxide and Pulmonary Circulation

S.A. Deem, M.D.

The long term objectives of this project are to elucidate the role of red blood cells (RBCs), hemoglobin (Hb), and nitric oxide (NO) in modulating pulmonary blood flow at the microvascular and macrovascular levels, and to

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thereby provide insight into the mechanisms by which RBCs affect pulmonary gas exchange.

The knowledge gained from this project will have health-related ramifications, in that it will allow more informed understanding and treatment of anemia, a common accompaniment of illness, and ultimately lead to improvements in patient care through the optimization of transfusion strategies and the development of hemoglobin-based oxygen carriers.

Dr. Deem has previously described the importance of RBCs in augmenting hypoxic pulmonary vasoconstriction through inactivation of NO by Hb, and has delineated the enhancement of pulmonary gas exchange by anemia under certain conditions. The current project will build on these findings in the following Specific Aims: I. Determine whether NO that is "biopreserved in the form of the oxidation product nitrite, or the NO-Hb products nitrosyl(heme)Hb and S-nitrosoHb can be released in the pulmonary circulation and result in vasodilation. The effect of these products on pulmonary artery pressure and NO production will be studied during normoxic and hypoxic conditions in an isolated, perfused rat lung model and in anesthetized rats. In addition, this aim will explore whether encapsulation of Hb within the red blood cell membrane alters the vasoactive properties of NO-Hb products. II. Determine the role of RBCs in determining microvascular hemodynamics using intravital microscopy in isolated, perfused rat lungs. This Aim will directly explore the rheology of the pulmonary microcirculation, help determine whether the RBC plays an active or passive role in determining pulmonary microvascular hemodynamics, and provide insights into the mechanisms by which RBCs alter pulmonary blood flow distribution and gas exchange.

3. Oxidative Inflammatory Mechanisms of Hypercapnia

J.D. Lang, Jr, M.D.

This project will define how hypercapnia (increased carbon dioxide concentrations) modifies oxidant-mediated inflammatory pathways with in vitro and in vivo models of inflammatory lung injury. Inflammatory-mediated lung injury often damages the air-blood barrier, impairing gas exchange and inducing hypoxemia. Recent innovative clinical strategies for resolving this pathologic process include the use of "protective" low tidal volume ventilatory strategies to retard ventilator-associated lung injury (VALI). There is an increasingly pervasive clinical perception that the allowance of hypercapnia is desirable and may be utilized as a strategy unto itself to retard lung injury. While there is modest clinical evidence that supports this approach, it remains biochemically unsubstantiated. In contrast, there is expanding evidence that CO₂ actively reacts with inflammatory oxidants, yielding products with altered oxidizing and nitrating capabilities. We have observed that carbon dioxide rapidly reacts with reactive oxygen species generated during systemic inflammation, forming reactive nitrating and oxidizing species, specifically nitrosoperoxocarbonate (ONOOCO₂⁻) a species capable of mediating further potent oxidation and nitration reactions. From this foundation of knowledge, it is hypothesized that hypercapnia amplifies inflammatory lung cell injury via modulation of oxidative

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injury and signaling pathways. To test this hypothesis, the following Specific Aims will be pursued: #1: Define the influence of hypercapnia on oxidant generation and cell signaling pathways in an in vitro model of lung epithelial and endothelial cell inflammation. #2: Investigate the contribution of mechanical stress, in conjunction with hypercapnia, on oxidative inflammatory and cell signaling events in an in vitro model of lung injury. #3: Delineate the consequences of concurrent hypercapnia, lung cell mechanical stress, and inhaled .NO in an in vivo model of critical illness. This proposed experimental plan advances recent investigation of CO₂ interactions with □NO-derived species by examining the influence of CO₂ on in vitro and in vivo models of inflammatory and ventilator-induced lung injury. The proposed research plan also provides a key element of the training platform that has been devised for the further development of the candidate as a physician-scientist and his pursuit to understand and improve issues of relevance to critical care medicine.

4. Early Antipseudomonal Therapy in Cystic Fibrosis

B. Ramsey, M.D., M. Treggiari, M.D.

The purpose of the present study is to determine the long-term microbiologic efficacy and safety of early intervention with antimicrobial therapy in infants and young children with cystic fibrosis (CF) and documented *Pseudomonas aeruginosa* (*Pa*) airway infection.

There is growing interest in investigating anti-pseudomonal therapies in very young children with the long-term goal of delaying or preventing chronic infection that contributes to irreversible lung disease. There has been minimal evaluation of either the clinical efficacy or safety of aggressive early intervention (i.e., intervention based on first isolation of *Pa* alone, in the absence of symptoms). While anti-pseudomonal therapy for first isolation of *Pa* will likely result in short-term eradication of *Pa* from respiratory cultures, it is not known whether it will improve clinical outcomes, be associated with unacceptable toxicities, or increase the rate of acquisition of resistant organisms. Young children with CF ranging in age from 6 months to 12 years will be enrolled at one of over 100 clinical centers nationwide to either a clinical trial (CT) that will include about 500 patients and/or an observational study (OS) that will include a total of about 3,500 CF children. The clinical trial is designed to allow randomized controlled evaluation of early intervention with inhaled antipseudomonal therapy in young patients with CF at first isolation of *Pa* from respiratory cultures. The observational study component will complement the clinical trial by assessing new risk indicators and biomarkers for disease, and observing the history of airway colonization with *Pa* in a large prospective cohort.

The primary outcome of the clinical trial is time to occurrence of a pulmonary exacerbation, comparing patients assigned to the three different treatment algorithms. The secondary outcomes will evaluate the effect of antibiotic therapy on safety (adverse events profile with particular reference to musculo-skeletal symptoms, renal function as measured by serum creatinine,

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hearing acuity, liver function tests, and complete blood count with differential), clinical variables (proportion of patients with pulmonary exacerbations, number of pulmonary exacerbations, linear growth, weight gain, FEV₁, total inpatient days, cough scores, and treatment failure), microbiology findings (time to first recurrence of *Pa* from oropharyngeal or sputum cultures, proportion of participants with respiratory cultures positive for *Pa* at the end of the study, presence and pattern of mucoid *Pa* isolates identified by colony morphology, changes in MICs of *Pa* isolates from oropharyngeal cultures, and changes in the genotype of *Pa* isolates from baseline to the end of the study), and *Pa* serology (changes and patterns in anti-pseudomonal antibody titers against exotoxin A, exotoxin S and elastase, and in inflammatory markers in blood from baseline to the end of study).

5. Does the vestibular organ play a role in the ventilatory response to hypercapnia during sleep?

D. Rubens, M.D.,

The purpose of the present study is to evaluate the role of the vestibular organ in the mediation of the ventilatory response to systemic hypercapnia during sleep. The ventilatory response of sleeping rodents with and without vestibular hair cell (vhc) impairment will be compared when both groups are exposed to increasing levels of carbon dioxide.

The primary goal of this study is to further the understanding of the relationship between vestibular function and ventilatory control. It may also help to establish a possible association between vestibular hair cell dysfunction and SIDS.

III. CEREBRAL FUNCTION AND CNS

1. Biomarkers of Hyperthermia in Sudden Infant Death

D. S. Jardine, M.D.

In 2002, the last year for which statistics are available, SIDS claimed the lives of 2295 infants (more infants died from SIDS than from accidents or congenital anomalies). The cause of SIDS remains unknown, but a group of factors that increase the risk of SIDS has been identified. Among these are prone sleeping, cold weather, and excessive sweating, to name only a few. Many of these risk factors appear to increase the risk of overheating (hyperthermia). Therefore, we hypothesize that lethal hyperthermia causes some (but not all) SIDS deaths. Consequently, we hypothesize that biomarkers of hyperthermia can be found in some SIDS victims.

In order to maintain thermal homeostasis, an infant must be able to transfer heat to the environment at a rate that equals heat production. Because a young infant lacks the motor coordination to remove blankets when he is too hot, he is at greater risk of overheating compared to an older child. An overheated, sweating infant is critically dependent upon evaporative losses, because the quantity of heat lost from evaporation is far greater than heat lost from

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convection, conduction and radiation. Blankets of modest thickness greatly reduce evaporative heat loss in a sweating infant, so the crucial factor determining heat loss is usually the quantity of uncovered skin rather than the thickness of the blankets. We have developed a mathematical model of heat balance which indicates that an infant's temperature may rise to injurious or lethal levels in as little as 90 minutes without excessively thick blankets.

Death from heat injury does not produce recognizable postmortem or histologic changes, so other evidence for overheating must be found in order to understand the role of hyperthermia in SIDS. Gene expression, which can be quantitated through microarray analysis, has great potential for this application, and to distinguish between SIDS caused by hyperthermia and SIDS caused by other stresses such as hypoxia.

If we can demonstrate that a substantial proportion of SIDS deaths are caused by hyperthermia, education and intervention could be directed at eliminating this problem by modifying bedding and sleep environments. This has the potential to be far more effective than public awareness campaigns aimed at avoiding risk factors that may contribute to hyperthermia.

2. CPP Management - Information Feedback and Nursing (C)

P. Mitchell, PhD, RN, FAAN, M. S. Vavilala, M.D., A.M. Lam, M.D.

This study is predicated on the assumption that there may be optimal levels of cerebral perfusion pressure (CPP) and systematic arterial blood pressure (ABP), that help prevent or reduce secondary brain injury in critically ill patients. Since CPP can be influenced by nursing care such as positioning, suctioning and the like, refining the ability for nurses to manage CPP on a minute-to-minute basis is currently being tested for the ability to demonstrate measurable improvement in short and long-term outcome for late adolescents and adults. We propose to extend the observation to children, for whom no adequate threshold has yet been determined, to examine complexity of physiologic waveforms to better understand the variations that may underlie clinical outcome differences or better predict outcome variation, and to conduct a cost-analysis of this improvement in technology. The specific aims are: 1) Determine if CPP threshold can be defined for children less than 16 years of age, based on 3, 6 and 12 month outcomes; 2) Characterize ICP and ABP complexity and HRV for both adults and children in relation to predicting outcome at discharge and 6 and 12 months (for children); 3) Estimate hospitalization cost across the life span for children, adolescents and adults monitored for CPP; 4) Estimate the value, in quality adjusted life years (QALY) for varying outcomes of care across the life span for children, adolescents and adults monitored for CPP.

Computer interfaces that provide visual information about CPP will be allocated to beds in each of the pediatric intensive care units used for children ages 1-16 years with traumatic injury, in whom ICP and blood pressure monitoring has been instituted as part of medical management. Data regarding CPP and 3, 6, and 12 month functional outcome will be evaluated to determine if a threshold for CPP can be determined for differing grades of outcome (from death to very good physical and social function). Continuous ICP, ABP and

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electrocardiographic data from these children and from the adults in the parent study will be analyzed using a variety of non-linear approaches to determine waveform factors that are predictive of outcome. Hospital data regarding costs and charges during acute care hospitalization will be examined in both children and adults to determine if the use of the computer interface is associated with greater or lesser acute care costs. Finally, a survey of survivors of acute brain injury and of community peers will be conducted to estimate the value (in quality adjusted life years) placed on differing outcomes states after both traumatic brain injury and aneurismal subarachnoid hemorrhage.

3. Hemodynamics and Outcome in Pediatric Brain Injury (C)

M. S. Vavilala, M.D.

Traumatic brain injury (TBI) is the leading cause of mortality in children over one year of age. Evidence suggests that hypotension after initial brain injury contributes to secondary brain injury and worsens outcome. Cerebral ischemia due to impaired cerebral autoregulation and hyperemia may both also contribute to poor outcome following pediatric TBI. Therefore, knowledge of optimal cerebral hemodynamics immediately following severe pediatric TBI is important. The objective of the proposed research is to describe the relationship between cerebral hemodynamics following severe pediatric TBI and outcome. The specific aims proposed here will provide new information regarding the early cerebral hemodynamic management of children with severe TBI. Therefore, we propose a logical series of investigations to: 1) determine the optimal blood pressure following severe pediatric TBI by examining the relationship between cerebral perfusion pressure (CPP) and outcome, 2) ascertain whether persistent impairment of cerebral autoregulation is associated with poor outcome, and 3) examine whether hyperemia is more common following severe TBI in children compared to adults.

It is important to conduct these studies in children of various ages because: 1) cerebral hemodynamics change significantly during development, 2) optimal cerebral hemodynamics following severe TBI may differ in young children compared to older children, 3) there is a paucity of physiologic data in children and 4) pediatric practice is currently extrapolated from adult practice,.

The results and experience gained in this research may aid in the future study of cerebral hemodynamics in children at risk of cerebral ischemia both with and without TB.

4. Cerebral Edema in Pediatric Diabetic Ketoacidosis (C)

M. S. Vavilala, M.D., A. M. Lam, M.D.

Nearly 22,000 children are hospitalized annually for complications of insulin dependent diabetes mellitus (IDDM). Diabetic ketoacidosis (DKA) is a life threatening condition and is the number one reason for IDDM related admissions. Cerebral edema occurs in 1-3% of pediatric DKA episodes and accounts for 30 - 90% of DKA deaths. Although several studies document cerebral edema in children with DKA, the cause of cerebral edema is unknown.

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The lack of understanding of the pathophysiology of cerebral edema leaves children with IDDM at risk for death or permanent disability, and health care providers without the necessary knowledge to prevent this complication. Epidemiologic data suggest an association between cerebral ischemia and cerebral edema in pediatric DKA. However, limited clinical studies document cerebral hyperemia NOT cerebral ischemia. Therefore, the overall goals of this study are to characterize cerebrovascular changes in children critically ill with DKA, and to determine the relationship between laboratory markers, cerebrovascular changes and the presence or absence of cerebral edema. To do this, we propose three specific aims: 1) To examine the relationship between cerebral hyperemia and cerebral edema in children with critical and severe DKA, 2) To determine the incidence of impaired cerebral autoregulation in critical and severe DKA and 3) To explore the relationship between potential clinical and laboratory predictors and cerebral hyperemia and cerebral edema in critical and severe DKA. The findings of this study will lead to: 1) a greater understanding of the pathophysiology of DKA related cerebral edema, 2) the innovative use of existing methodologies to examine cerebrovascular changes in pediatric DKA (new scientific area), and ultimately through further study, 3) the development of a clinically useful scoring system and screening program that identifies children at risk for cerebral edema, and 4) the identification of management strategies needed to prevent cerebral edema.

5. Determination of Risk Factors for Ischemic Optic Neuropathy After Spine Surgery

Lorri A. Lee, M.D., K. Domino, MD, MPH, K. Posner, PhD, et al.

One of the most devastating iatrogenic complications that can occur perioperatively is postoperative visual loss (POVL). Data from the American Society of Anesthesiologists (ASA) POVL Registry has provided important information on the perioperative characteristics of patients who developed ischemic optic neuropathy (ION) after spine surgery. However, it is unclear from these data if co-existing diseases, gender, hematocrit, blood pressure management, and other factors increase the risk of developing ION because there are no denominator data. We therefore propose to evaluate potential risk factors for ION after spine surgery using a multi-center randomized case control study in which patients with ION from the ASA POVL Registry (n = 80) will be compared to matched controls who did not develop ION after spine surgery. Determination of risk factors for perioperative ION after spine surgery could potentially identify 1) high risk pre-existing patient characteristics; and 2) perioperative events that may increase the risk of ION such as blood pressure management, type of fluid replacement, blood transfusion / hematocrit management, anesthesia / prone duration, or and use of vasopressors. These data could also be used to determine the odds ratio for developing ION for every additional hour of anesthesia and every liter of blood loss. These results could be used by both spine surgeons and anesthesiologists to improve patient safety by influencing appropriate patient selection and perioperative anesthetic and surgical management of prolonged spine operations with the goal of reducing the incidence of this devastating complication.

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6. Basal Ganglia Modulation of Trigeminal Intralaminar Nuclei Thalamic Activity

Eric Chudler, Ph.D., M. Byers, Ph.D.

The motor symptoms and underlying neuropathology resulting from damage to the basal ganglia such as that in Parkinson's disease (PD) have been described extensively. However, the basal ganglia role in somatosensory function, including that of pain and nociception, has been largely ignored. The proposed use electrophysiological methods to explore how the basal ganglia modulate the response of nociceptive neurons in the intralaminar nuclei of the thalamus to persistent trigeminal nociceptive stimuli. Our long range goal is to establish a framework to understand how the basal ganglia modulate nociceptive information. Dopaminergic degeneration of the nigrostriatal pathway is expected to enhance the response of thalamic neurons to persistent nociceptive trigeminal stimuli. The first specific aim is to analyze the connectivity between the caudate-putamen (CPu) and intralaminar nuclei of the thalamus by testing the effects of electrical CPu stimulation on the responsiveness of nociceptive neurons in the intralaminar nuclei of the thalamus. Activation of the CPu by electrical stimulation is expected to alter the discharge frequency of nociceptive thalamic neurons to noxious chemical and mechanical stimulation of the face. These electrophysiological experiments will also permit functional characterization of a nociceptive thalamostriatal pathway. This thalamostriatal pathway has not been described previously. The second specific aim is to test the effects of dopamine depletion on the responsiveness of trigeminal nociceptive neurons in the intralaminar nuclei of the thalamus and investigate how dopamine depletions affects pain behavior. Unilateral injection of 6-hydroxydopamine into the CPu to destroy dopamine-containing neurons is expected to alter the evoked discharge frequency of nociceptive neurons in the intralaminar nuclei of the thalamus and increase nociceptive behavioral responses. These experiments will provide new insights about the role of the basal ganglia in pain and nociception and will shed light on a new dopaminergic pain modulatory system. It is possible that damage to the basal ganglia, such as that which occurs in patients with PD, will cause an increase risk of pain because of the impairment of this pain modulatory system. These studies will help explain the complex sensory symptoms exhibited by patients with PD and may suggest new treatment strategies to alleviate such pain.

7. Pharmacokinetics of Intrathecal Drug Infusions

C.M. Bernards, MD, S. Flack, MBChB

Human clinical studies of intrathecal bolus drug distribution demonstrate that baricity (i.e., the density of the injected fluid relative to the density of CSF) is the most important determinant of drug distribution in CSF. However, the effect of baricity during very slow continuous drug infusions has never been studied in humans or animals. In vitro studies of drug distribution in the Medtronic spinal model suggest that baricity is also the overwhelming determinant of drug distribution during very slow chronic drug infusions. However, the in vitro model cannot account for the effects of drug clearance from CSF, which is a critical determinant of drug distribution during very slow continuous drug infusions. Consequently, to determine the effect of baricity on drug distribution

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during chronic slow intrathecal infusions it is necessary to study distribution in an animal model.

IV. PAIN

1. Regulation of Beta-Defensin Expression in Oral Epithelia

B. A. Dale-Crunk, Ph.D., M. R. Byers, Ph.D., et al.

Antimicrobial peptides of the human beta-defensin (hBDs) family are recognized as important components of the innate immune responses of oral epithelia as well as epithelia throughout the body. These peptides may be particularly important in the oral cavity where microbial flora are present in high numbers at all times. The overall working hypothesis for this project is that b-defensins, and other antimicrobial peptides, aid the oral health in two main ways, first, by their direct antimicrobial activity, and second, by their cytokine-like functions to stimulate other cells within the tissue to respond appropriately to the microbial challenge. Further, the innate immune mechanisms that function within the oral soft tissue are also reflected in the tooth pulp; that b-defensins are expressed in odontoblasts; that b-defensins expressed in oral epithelium vs. tooth pulp are different and reflect regional differences in their function; that b-defensins mediate communication between epithelial cells and dendritic cells in oral mucosa, the primary cells that bridge innate and adaptive immunity; and between odontoblasts and dendritic cells. The goal of this project is to put our work on b-defensin expression and regulation in oral epithelial cells into a more biological framework by taking advantage of two systems, cellular interactions in oral soft tissue and in tooth pulp. These studies will investigate expression of b-defensins and exploration of their role as functional mediators of cell interactions. Investigations include (1) influence of epithelial b-defensins on specific lineages of DCs; (2) co-culture of epithelial cells and dendritic cells, (3) characterization of b-defensin expression in an odontoblast cell line and (4) characterization of b-defensin expression in a dental pulp organ culture system.

2. Subgroups of FMS: Symptoms, Beliefs & Tailored Treatments (C)

D.C. Turk, Ph.D., J. Robinson, M.D., Ph.D.

Fibromyalgia syndrome (FMS) is a prevalent, chronic musculoskeletal pain disorder. Despite extensive research, the etiology and pathophysiologic mechanisms of FMS are not well understood, and no treatment has been shown to be universally effective. In this project, we propose that FMS is a complex disorder involving multiple factors, both physical and psychosocial-behavioral. In our previous research, we have demonstrated that FMS patients are heterogeneous in the psychosocial-behavioral axis and can be classified into three distinct subgroups on a basis of their psychosocial-adaptation to symptoms. In this project, we will extend our previous research and attempt to match treatments to patients' psychosocial-behavioral characteristics. Specifically, we will test the efficacy of uniquely tailored treatments for each psychosocial subgroup. Three groups of FMS patients will be treated with one of three treatment protocols with a standard physical therapy and varying psychological

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treatments. A total of 312 FMS patients will undergo a six half-day interdisciplinary treatment sessions consisting of physical therapy and psychological treatments. All protocols include a standardized physical therapy but include either cognitive-behavioral treatment outcome study, interpersonal skill training, or supportive counseling. In addition, to the treatment outcome study, various symptoms of FMS will be assessed prospectively in the patient natural habitats to better understand covariations of FMS symptoms. The repeated daily monitoring using the ratings compared to retrospective reports. Overall, the results of these studies should establish the benefit of matching treatments to subject characteristics, and enhance our understanding of the roles of cognitive-affective-behavioral adaptation of FMS patients.

3. Optimizing the Control of pain from Severe Burns (C)

D. Patterson, Ph.D.; S R. Sharar, MD; D. Heimbach, MD., J Doctor, Ph.D.

The primary long term objective of this project is to improve pain control and reduce resulting disability in all age groups of burn survivors (e.g., pediatric, adult, and elderly). This will be accomplished by determining the optimal combinations of Opioid analgesics, anxiolytics and psychological approaches, and matching treatments with patient characteristics that may predict therapeutic effects. Because extensive burn injuries are clearly an etiology of acute pain that produce substantial challenges in its treatment, the results will be generalizable to other causes of pain. A second primary objective will be to determine how pain and other factors related to burn injuries influence long term physical and psychological adjustment. To accomplish these objectives, the investigators will conduct six studies, of which four have randomized, controlled designs, one has an observational methodology and one uses longitudinal measurement. These studies will specifically 1) investigate the synergistic effects of a benzodiazepine (lorazepam) and a psychological technique (hypnosis) in reducing burn pain and stress level, relative to the individual use of such techniques, as well as opioid analgesics alone and 1a) introduce and test a new set of variables for their ability to predict the analgesic effects of the modalities used (e.g. Opioid analgesic, lorazepam, hypnosis, virtual reality), 2 provide the first controlled study of the use of virtual reality in reducing pain from skin graft dressing changes, 3) continue previous studies in order to gain a large enough sample to determine the effects that opioid pain medication scheduling has on acute pain levels in pediatric patients, 4) continue with previous studies in order to produce the first controlled pediatric burn pain study comparing the use of anxiolytics and Opioid analgesics, 5) perform the first even prospective analyses of the Opioid analgesic needs of elderly burn patients, and 6) test a predictive model for determining the longitudinal impact of burn injuries on psychological adjustment and health outcome. The anticipated benefits of this project will be that they will provide information enabling health care professionals to treat acute pain more effectively across the life span. This will not only reduce unnecessary suffering, but might improve health outcomes by minimizing the deleterious effects of acute pain.

4. Subjective and Neuroimaging Assessment of Combined Opioid and Virtual Reality Analgesia (C)

S. R. Sharar, M.D.T. Richards, Ph.D.

Painful medical procedures that do not warrant general anesthesia or deep sedation, yet require potent analgesia in awake and cooperative patients, are increasing in scope and number and exceed our specialty's resources to provide direct care. Awake patients undergoing painful procedures such as wound debridement, post-injury or post-operative physical therapy, cancer-related oncology procedures, or limited surgical procedures may benefit from the thoughtful combination of pharmacologic and non-pharmacologic analgesic techniques. Concrete evidence supporting this potentially widely applicable combined analgesic approach is lacking, but is best provided by anesthesiologists whose knowledge and training are best suited for such investigation. We propose to explore the efficacy, safety, and mechanism of one particularly promising combination -- systemic opioids + attentional distraction with immersive, interactive virtual reality (VR) - each of which alone can provide measurable analgesia for procedural pain. We propose to test the specific hypotheses: (1) that combined opioid + VR therapies act synergistically to effect clinically superior analgesia compared to either treatment alone, and (2) that functional neuroimaging of these therapies, alone and in combination, will demonstrate specific patterns of brain activation in the 'pain matrix' that explain their relative analgesic effects. Results from these studies will provide evidence for procedural analgesic strategies that maximize clinical and economic benefits, as well as provide valuable preliminary data for future clinical trials in procedural pain. Furthermore, these results will allow our specialty to positively impact conscious, procedural analgesic care outside of the operating room, whether or not we are directly involved in such patient care.

5. A Pilot Study of Virtual Reality Analgesia for Cancer Pain in the Elderly (C)

S. R. Sharar, M.D., H Hoffman, Ph.D

The proposed research -- investigating the potential clinical application of immersive virtual reality (VR) analgesia in the treatment of oncology procedure-related pain in the elderly -- directly addresses the Palliative Care, End-of-Life Care, Pain Relief. It also addresses overlapping issues in both (1) cancer pain management and (2) pain management in the aging population through the novel application of VR, a technique well-suited for short periods of cognitive distraction from pain (i.e., during procedural pain), but never before applied to elderly patients in any medical setting. The investigative approach utilizes a previously established protocol to study simulated lumbar puncture pain in healthy volunteers, and capitalizes on the strengths of a multidisciplinary team whose individual members are nationally recognized in their fields.

A comparative efficacy and safety of various types of audio/visual distraction analgesia techniques is requisite before a thoughtful clinical trial can commence. VR analgesia is an emerging technology, with the UW established as the field leader. To date, VR analgesia has been applied in experimental and clinical studies in pediatric, and to a lesser extent young adult, age groups, but

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never before in the elderly, who due to cognitive and sensory changes inherent to aging, may respond differently to VR. Thus, pilot project funding by SCAP will allow the first comprehensive study of pain modulation by VR and related distraction techniques in the previously neglected elderly population, and provide critical preliminary data requisite for future funding proposals (e.g., to NIH and AFAR) that will address its potential clinical use specifically in cancer, but also in other medical settings where pain is a daily challenge for this expanding demographic group and their care providers.

6. Assessment of Patient Recall/Awareness of Prehospital Endotracheal Intubation (C)

S. R. Sharar, M.D.

This application proposes performance of two related and complementary projects relevant to field airway management in critically ill patients. Both projects address endotracheal intubation issues (one in adults, one in children), both utilize unique and sizeable data available as a result of Medic One's proactive airway management policies, and both share budgeted resources in an efficient manner that allows completion of two projects for a cost similar to that for one project alone. Lastly, results from both proposed projects will have likely clinical application in establishing safe and effective airway management recommendations, both locally and nationally.

(1) Emergent endotracheal intubation is a painful, yet life-saving procedure that is often performed in the prehospital and emergency room settings without the benefit of adequate analgesic, sedative or amnestic medications because of cardiovascular side effects associated with these agents. Awareness (or recall) of pain or other unpleasant events associated with emergent intubation in these two settings has both potential psychologic and liability implications. However, the true incidence of this complication is unknown; hence, the indications and clinical guidelines for its prevention and treatment are undefined. Knowledge of its incidence and settings may alter prehospital care guidelines in a way that will improve patient care.

(2) Long-standing clinical practice teaches that children under ~10 years of age who require endotracheal intubation should receive an uncuffed tube, due to considerations of anatomy and potential complications unique to the pediatric age group. This practice has recently been questioned in the inpatient setting, due to increasing recognition of potential complications of uncuffed tubes in critically ill children, and has resulted in a change in clinical practice (i.e., placement of cuffed tubes) in the inpatient setting. However, the relative frequency and magnitude of complications related to cuffed v. uncuffed tubes placed in the prehospital setting is unknown. Knowledge of these relative complications may alter prehospital care guidelines in a way that will improve patient care.

7. Ketorolac in Surgical Infants: Pharmacokinetics/Analgesia (C)

A.M. Lynn, M.D.

The live birth rate in the United States in 1990 was 4,158,212. Major congenital defects that will require surgical corrections or palliation in the first year of life will affect 0.02% (for tracheoesophageal fistula) or 0.04% for imperforate anus as reported in the Congenital Malformations surveillance 1982-1985 from the Center for Disease Control (CDC) in 1988. Infants affected by

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these major congenital defects necessitating surgery in infancy comprise an orphan population of less than 100,000. For these infants, surgery offers the best (or only) potential for correction and a good quality of life. Postoperative pain control should be given to these infants, as it would be adults undergoing similar surgeries, despite their limited ability to communicate their needs.

Infants and children first received the label therapeutic orphans in 1968 when Shirkey pointed out they were excluded from the labeling of most drugs. Kauffman's editorial in 1991 presented the lack of rigorous study of drugs in infants and children as a continuing problem. More recently in 1996 Kauffman, Cote, and others anticipated the "adoption" of the pediatric therapeutic orphan, as the Food and Drug Administration implemented a more proactive stand encouraging pediatric investigation of pharmacologic agents.

V. HEALTH SERVICES

1. Closed Claims Project

F.W. Cheney, M.D., K. Domino, M.D., MPH, K. Posner, Ph.D.

The Closed Claims Project is a project sponsored and conducted by the Professional Liability Committee of the American Society of Anesthesiologists. The study involves an in-depth investigation of closed insurance claims resulting from anesthetic mishaps, with the goal of identifying major areas of loss in anesthesia practice. Data is gathered in the form of detailed case summaries collected by ASA member anesthesiologists from insurance company claim records. Claims for dental injury, a very common, well-understood, and in most cases minor injury, have been excluded from the study. Claims in which the basic sequence of events and/or nature of the injury could not be reconstructed from the information in the insurance files have also been excluded. This results in most cases being collected from mishaps resulting in lawsuits, as files these cases contain the most extensive information. Cases have been collected from throughout the United States. There are currently over 7,000 claims in the database.