Roger A. Moore, M.D., President
American Society of Anesthesiologists

The past year has been filled with many advocacy successes for ASA. These successes are not due to ASA leadership alone, but also the result of strong partnerships with both private practice anesthesiologists and academic anesthesiologists working toward common goals. Our major success on behalf of all anesthesiologists was the acceptance by the Centers for Medicare & Medicaid Services (CMS) of a request by the Relative Value Scale Update Committee (RUC) for a 32-percent increase in work value for anesthesia services. In itself, this was a major accomplishment; but placed in the context that the RUC recommendation had to be budget neutral – requiring any increase in anesthesia reimbursement to be compensated by a decrease in payment to other physicians – this achievement was close to a miracle. Obviously, this successful advocacy was not the work of one person, but rather years of effort by the ASA Committee on Economics. The final result was an increase in the ASA conversion factor to over $19 a unit for the first time since 1991. For the naysayers who might argue that getting back to 1991 payment levels for the conversion factor was a hollow victory, I would remind them that without the intervention of ASA and its involved membership, our conversion factor would now be $8 a unit.

Another equally important success for all anesthesiology, but particularly academic anesthesiology, was our final passage of the anesthesia teaching rule. As many of you are quite aware, the voyage to get the teaching rule overturned, thereby allowing payment to an anesthesiologist supervising two residents, has been long and turbulent. The initial teaching rule, limiting payment to supervising anesthesiologists, came into effect in 1994 with the advent of the Resource-Based Relative Value Scale (RBRVS). This rule only applied to anesthesiology teaching programs (surgical teaching programs were unaffected) and cost each academic anesthesiology department an estimated $400,000 a year. ASA leadership worked hand-in-hand with academic anesthesiology departments and state components in order to get this unfair rule overturned. After repeated efforts spanning many years, we finally succeeded. The result will be some half a billion dollars infused into anesthesiology academic programs over the next 10 years. Though this important accomplishment should be celebrated, it should also serve as a point of reflection. The passage of this bill required a concerted effort year after year with failure after failure. Many began to lose heart after the first few failures when they were asked once again to participate in letter writing campaigns and visits to their legislators. However, by keeping our eye focused on our ultimate goal and remaining undeterred by repeated failures, we did finally succeed. The lesson to be learned is that if something is worth doing, one must keep the passion, the persistence and the patience to stay the course, through thick and thin, until the goal is reached. OUR success, and I emphasize the word “our,” was a direct result of academic anesthesiologists partnering with ASA’s advocacy efforts. I think we can all be gratified by the result of our combined efforts.

Though we have had tremendous success in advocacy, there are many clouds on the horizon that bear watching. One of the key concerns expressed by Ronald D. Miller, M.D., when giving his 2008 Rovenstine Memorial Lecture was whether anesthesiology of the future would be a trade or a profession. A trade is

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Nanotechnology is widely recognized as an emerging discipline that may have important implications for medicine. But another emerging science receiving less attention in the popular science journals is changing the way research is performed throughout biology and medicine — systems biology. The new systems biology emerges from systems science, and its elements were elegantly described by Bertalanffy decades ago (General Systems Theory: Foundations, Development, Applications). Very simplistically, systems science developed because complex systems (such as a cell or an organism) cannot be described adequately by simply cataloguing all the parts of the system. Systems science focuses on the organizational principles that control the behavior of the entire system. In modern systems biology, these organizational principles are identified in the form of protocols (rules that determine interactions of parts of a system), and the overall organization of protocols is the system architecture. The necessary elements of study using systems approaches were put forward by Kitano in an article in Science: a) The structure of the system has to be identified (such as a biochemical pathway or gene network); b) dynamics (behavior over time); c) control elements (methods to maintain behavior and function); and d) design principles (the protocols and architecture).

Where systems biology gets difficult for those of us trained in medicine is in the math. And, in fact, it is the math that divides the systems biology community. Mathematical disciplines are as different from each other as medical disciplines, maybe more so because they do not necessarily share a common language. The mathematical background of any individual systems biology group largely informs the kinds of analytic approaches they will take and also constrains the analyses. The world of ‘omics (genomics, proteomics, metabolomics) is now fairly mainstream in medicine, but ‘omics is not systems biology (though the high-throughput data are useful ingredients for statistical analysis). In general, high-throughput data are fairly static, and systems biology emphasizes behavior, which requires time series data — expensive to do in a high-throughput way. When physicists come to the study of biology, they bring a completely different mathematical toolbox than when engineers come to the study of biology. Kitano’s view of the necessary areas of study emphasizes control, and mathematical tools from control engineering are proving to be the most powerful ones for getting to the heart of describing biology. For those of us trained in medicine and familiar with complex feedback loops of hormones that govern daily and monthly cycles, a control engineer’s view of a system – with sensors and actuators and feedback – makes sense.2

Recently, mathematicians interested in control of complex systems have pointed to the common organizational and control features of complex technologies and biological systems. In particular, the Internet and its engineered control system (TCP/IP) have been intensively studied by computer scientists and engineers3 and compared to biological systems. The shared features of robustness (maintenance of behavior in the face of perturbations) and evolvability across these complex systems can be described using similar mathematical principles. This is good news for systems biology. Biologic experiments yield a bewildering amount of data that are impossible to interpret without a mathematical framework. If the analytic tools used to dissect engineered systems can be shared with biology, the insights from experiments can be significantly enhanced. Progress in systems biology is also good news for medicine. For medicine, a deep understanding of the features that make patients robust to perturbations (disease) is a holy grail of a systems approach. Understanding robustness implies an understanding of the fragilities inherent in a systems design. Systems approaches hold promise that the fragilities identified in analyzing complex, designed engineered systems will contribute to identification of the fragilities underlying complex, evolved biologic systems.

References:
Seeking Venture Capital for the Next Big Thing

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It’s the question I hear most often as a venture capitalist (VC):
“I have an idea for a new medical device. How do I get some venture capital?”

For starters, most good ideas come to market without a dollar of venture capital money. They are usually developed in collaboration with an existing medical device company. So what types of new technologies are VCs looking for? Product ideas that have the potential to become big companies. These company-starting ideas have three things in common:

- A large market opportunity — is there sufficient demand for a device that will result in hundreds of millions of dollars in sales in a given year?
- A meaningful unmet need — will the device satisfy an unmet clinical need that doctors care about passionately?
- Unique and patentable concepts — is the device truly new and different, and can it be well protected by patents?

Those are big shoes to fill, and most ideas fall short of one or more of those criteria. But if your idea satisfies all three elements, seeking venture capital may just be the answer to how to get your idea on the market. The next question to ask yourself: “Are you committed to starting a company?” You will become deeply immersed in things you probably never thought about before — finance, human relations and lots and lots of legal issues, even if you bring on a partner to help you start the company.

Assuming you have decided to take the start-up plunge, a VC will want to see “proof of concept.” That means you will have done some experiments that show the technology is feasible, that the device has a high chance of achieving the desired patient outcomes and that someone — you or someone else — doesn’t have to invent something more to make your device a reality.

Your idea will be much more attractive to a VC if you already have your patents in place. And you should be able to show a VC a well-developed “pitch” that addresses why this opportunity is attractive — how many patients this device will help, the size of the potential market, why it will help the patient, the doctor and the hospital, what will be required in terms of FDA approval, and whether reimbursement is in place.

Once you have your ducks in a row, you can begin to look for a VC. Venture capitalists come in at least three flavors: seed stage, early stage and late stage. Seed-stage VCs are willing to invest in new ideas and will help form the initial company to carry out the project. Early-stage VCs want the company and its key management team to be in place before they become involved. Late-stage VCs are looking for companies that are already up and running and showing signs of gaining traction. Keep in mind that relatively few VCs operate in the seed stage these days.

Having said all that, you still need to know how to find the VC who can help finance your dream into a reality. To do that, you’re going to have to engage in lots of networking. VCs rarely invest in ideas that walk in off the street or come in the form of unsolicited e-mails. A venture capitalist is making a commitment to spend millions of dollars and years of his/her life on an idea. He only wants to make that commitment to someone he knows directly or has been connected to by someone else he knows and trusts. The best place to start probably is your patent attorney. You want a patent attorney who does a lot of work with start-up companies and their venture capitalists. You’re going to need the patents anyway, so you might as well get double duty out of those big legal bills. You might also get a lead to a VC from friends or colleagues who have started their own companies.

In the end, you are looking for a partner. Good VCs provide more than just capital. They become a company builder alongside you by providing guidance, contacts and as much help as is necessary to make the company successful.

“A venture capitalist is making a commitment to spend millions of dollars and years of his/her life on an idea. He only wants to make that commitment to someone he knows directly or has been connected to by someone else he knows and trusts.”
On April 23, 2008, the FDA approved methylnaltrexone (MNTX), administered subcutaneously to treat opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. This approval, obtained by Progenics Pharmaceuticals, Inc., represented the culmination of more than 20 years of research by the Department of Anesthesia and Critical Care at the University of Chicago, and more specifically, Drs. Joe Foss, Chun-Su Yuan, Michael Roizen, and myself. Although trials leading to its approval were in palliative care patients, other studies using MNTX allowed us to discriminate between the central and peripheral effects of opioids, including effects on gastric emptying, nausea and vomiting, pruritus, and urinary retention. Further studies undertaken by our group included an elucidation of some of the cellular mechanisms of opioids on HIV penetration, tumor angiogenesis, vascular permeability and bacterial virulence. While the details of the development process have been presented at the AUA and recently published by ourselves and others (Moss J, Rosow CE. Mayo Clin Proc. 2008; 83:1116; Kharasch ED, Mayo Clin Proc. 2008; 83:1083), our experiences may be of interest to other members involved with drug development. In an era when molecular design and high-throughput screening are increasingly used to develop drugs, our experience suggests that there can be a meaningful role for clinical scientists throughout the development process.

Methylnaltrexone was first identified in 1979 by Professor Leon Goldberg, who was chair of the Clinical Pharmacology Department at the University of Chicago. Dr. Goldberg was presented with the conundrum of a colleague with advanced cancer receiving opiates but whose constipation was so troubling he could not receive adequate analgesia. Reasoning that charged molecules would not easily penetrate membranes, Dr. Goldberg set about synthesizing charged versions of naltrexone, which would, in theory, not cross the blood-brain barrier and therefore selectively reverse the peripheral effects of opiates. Unfortunately, initial studies with rodents were not successful. Subsequently, Dr. Goldberg discovered that rodents possessed a demethylylating enzyme that converted a fraction of the MNTX to naltrexone, making it difficult to use these animal models. An important lesson for those developing new compounds is that animal studies may not adequately represent human pharmacology. Dr. Goldberg himself developed cancer and died in 1989. His last fellow, Dr. Joe Foss, worked on MNTX. Upon his death, the Department of Anesthesia and Critical Care undertook development of MNTX as a project to bring Dr. Goldberg’s work to the clinic.

While we had initially believed MNTX would be well suited to treat PONV, the introduction of propofol and ondansetron led us back to develop it for its originally intended use, to treat opioid-induced constipation in patients receiving palliative care. In early 1993, when Dr. Chun-Su Yuan entered his clinical pharmacology fellowship at the University of Chicago, we went back to the laboratory and utilized the hanging gut model developed by Professor Paton at Oxford in the 1950s. *We showed that MNTX was equally effective – although substantively less potent than naloxone – in reversing the effect of opiates on isolated human and guinea pig smooth muscle.*

Recognizing that there was equal efficacy, we reasoned that we would be able to utilize MNTX in a clinical setting. We demonstrated in human volunteers that there was a 97-percent reversal of the effect of morphine on oral-cecal transit time (OCTT), a surrogate for motility approved by the FDA for use in this study. While reversal of OCTT would occur with any of the tertiary opiate antagonists, as measured by a cold pressor test, morphine analgesia was not reversed in patients receiving MNTX. *This study, completed in 1996, was the first demonstration in humans that the constipation associated with opioids was peripherally-based.* We subsequently repeated this investigation with an oral formulation of MNTX that required a substantively larger dose, i.e., 20-40 times the I.V. dose, in order to achieve the same effect on OCTT.

Although we had proposed to treat palliative care patients with opioid-induced constipation, as Dr. Goldberg had originally intended, the FDA required a proof-of-concept trial in methadone-maintenance subjects. These subjects are very challenging, as many have a history of multiple drug use, and there were real questions of patient reliability. The very question of how to compensate subjects who are addicted to opiates and other drugs is ethically challenging. *When MNTX was given intravenously, laxation occurred immediately, and there was a dramatic reduction in OCTT.* Importantly, no subjects exhibited symptoms of opioid withdrawal, and all were satisfied, confirming the selective peripheral antagonism of MNTX. We also determined that the gut, like the brain, becomes supersensitive to antagonists in these subjects who were receiving chronic opiates. We repeated this study in 2000 in methadone-maintenance subjects with an oral formulation of MNTX, using reduced doses.
based on our studies with intravenous methylnaltrexone. In this case, laxation took hours, not minutes.

As clinicians, we recognized that the route of administration would be key in terms of facilitating patient use and acceptance. While the intravenous route was very efficient, many patients at home would not have intravenous access. We also recognized that the oral preparation that we had formulated took several hours before onset and required substantively larger doses. Because the pattern of palliative care in the United States often utilizes visiting nurses who come in for two or three hours a day to tend to patients, we sought a route of administration that would be more useful for the population we intended to serve. For that reason, we developed a subcutaneous formulation. On the basis of volunteer studies, we predicted an onset within 30 minutes at the same concentrations as we had used with the I.V. infusion.

Our studies in methadone-maintenance subjects drew the interest of Progenics Pharmaceuticals, Inc., who subsequently licensed the drug from representatives of the Goldberg estate and the University of Chicago in 2001. Progenics conducted a phase 2b dose-ranging study and then two phase 3 studies of subcutaneous MNTX. The data that were developed during these phase 3 studies (the first phase 3 registration studies of any drug in palliative care) largely conformed to the expectations that we had predicted in our volunteer trials. Doses of subcutaneous MNTX (0.15 mg/kg, 0.3 mg/kg) were given to patients in advanced illness receiving palliative care who exhibited opioid-induced constipation that was refractory to laxatives. Most patients had advanced cancer, although some had chronic obstructive pulmonary disease, ALS or AIDS. In one study, 62 percent of the patients laxated within four hours of the first 0.3 mg/kg MNTX injection as compared to 13 percent of patients given placebo. These reactions occurred within a median of about 30 minutes of treatment.

The side effects of the drug included flatulence and abdominal cramping. No patients experienced symptoms of opioid withdrawal. The results of a second phase 3 trial completed in 2005 using the lower dose of 0.15 mg/kg were very similar [Thomas J. et al. N Engl J Med. 2008; 358(22):2332-2343].

Progenics and its co-development partner Wyeth conducted trials studying postoperative bowel function. While the initial small phase 2 trials were successful, two subsequent larger phase 3 trials failed to reach statistical significance. A recent phase 3 trial of subcutaneous MNTX has also shown significant improvement in OIC patients with chronic non-malignant pain, although the data are not yet fully analyzed, and an oral formulation is in early clinical trials of this indication.

The lessons we learned from this long course of drug development are multiple, but perhaps the key message is that there is a very real advantage to early and sustained participation by clinicians in drug development. Because we demonstrated that MNTX is active in volunteers and compassionate-use patients, we were encouraged to interpret the animal/in vitro experiments not only to design appropriate dose and route of administration studies, but also to explore other potential clinical uses of MNTX. As clinicians routinely using opioids in our practice, we were well aware of other potential side effects. In addition to the work for the intended uses of the drug, several other research aspects have been explored. These aspects include human studies on pruritus, gastric emptying, nausea and vomiting, and urinary retention, all of which appear to have a peripheral component. Although these findings are preliminary, they may prove to be clinically important as MNTX is used in clinical practice.

Finally, studies with opioid antagonists may provide new insights into the clinical role of peripheral opioid receptors and shed light on why endogenous opioids exist. Cellular studies of the effects of opioids (and MNTX) on HIV penetration, vascular permeability, angiogenesis and bacterial virulence suggest other effects of opioids that had not been previously recognized. Some of these effects that we observed with opioid antagonists occur at concentrations well below their ability to reverse GI effects. Thus our journey, in all likelihood far from being complete, is poised to continue.

“Cellular studies of the effects of opioids (and MNTX) on HIV penetration, vascular permeability, angiogenesis and bacterial virulence suggest other effects of opioids that had not been previously recognized.”
# 56th Annual Meeting

## PROGRAM SCHEDULE

### Thursday, April 2, 2009

5-7 p.m.  Registration

7-9 p.m.  Welcome Reception at the Moody Gardens Hotel

### Friday, April 3, 2009

6:30 a.m.-5:30 p.m.  Registration

7-8 a.m.  Continental Breakfast and Poster Viewing

8-8:15 a.m.  Introductions and Welcome  
Donald S. Prough, M.D.  
Marie E. Csete, M.D., Ph.D.

8:15-10:15 a.m.  Oral Presentations

- **Nano-Medicine Meets Critical Care. Mapping Cell Surface Biomechanics of the Lung Endothelial Glycocalyx: Implications for Mechano-Transduction and Barrier Regulation**  
  Randal O. Dull, M.D., Ph.D.

- **Mechanism of Anesthetic-Mediated Neurodegeneration and Cognitive Dysfunction: Role of Inositol 1,4,5-Trisphosphate Receptors**  
  Huafeng Wei, M.D., Ph.D.

- **Immune-to-Brain Signalling Mediates Cognitive Dysfunction Following Surgery in Mice**  
  Niccolo Terrando, B.Sc.

- **MOC-Etomidate: A Novel Rapidly Metabolized and Ultra-Short-Acting Etomidate Analogue**  
  Douglas E Raines, M.D.

- **Race and Variations in Operative and Non-Operative Treatment for Hip Fracture**  
  Mark D. Neuman, M.D.

- **Metabolomic Serotypes of Perioperative Myocardial Infarction Following Cardiac Surgery with Planned Myocardial Ischemia-Reperfusion — Resident Travel Award**  
  Robert L. Lobato, M.D., M.S.

- **Hypothalamic Knockout of Leptin Receptor in a Murine Model Leads to Early Obesity and Diabetes Resident Travel Award**  
  Laurence E. Ring, M.D.

10:15-10:20 a.m.  Presentation of Resident Travel Awards  
Marie E. Csete, M.D., Ph.D.

10:20-10:45 a.m.  Break and Poster Viewing

10:45-11:45 a.m.  SAB Session — The History of Safety in Anesthesiology  
Jeffrey B. Cooper, Ph.D.

11:45 a.m.-1 p.m.  Group Luncheon and Resident/Fellow Luncheon

1-1:45 p.m.  ASA Update  
Roger A. Moore, M.D.

1:45-3 p.m.  EAB Session, Part 1 — Fellowship Opportunities for Faculty Career Development in Anesthesiology  
Moderator: Robert E. Shangraw, M.D., Ph.D.

- **Overview — Catalog of Opportunities for Clinician-Educators**  
  Robert E. Shangraw, M.D., Ph.D.

- **The Harvard-Macy Fellowship Programs**  
  Lindsey C. Henson, M.D., Ph.D.

- **The Robert Wood Johnson Programs**  

3:30 p.m.  Break and Poster Viewing

3:30-4:45 p.m.  EAB Session, Part 2 — Subspecialty Certification in Anesthesiology: Progress or Exclusivity?  
Moderator: Sulpicio G. Soriano, M.D.

- **Historical Background/Setup**  
  Sulpicio G. Soriano, M.D.

- **The Case for Certification in Pediatric Anesthesiology**  
  Francis X. McGowan, M.D.

- **Why Subspecialty Certification in Anesthesiology Is Not a Good Idea**  
  Steven J. Barker, Ph.D., M.D.

- **Potential Impact of Subspecialty Certification on an Academic Department**  
  Neal H. Cohen, M.D.

4:45-5:45 p.m.  NIH Session: Research Perspectives from the NINDS  
Walter Koroshetz, M.D.

6:30-9 p.m.  Evening Reception at the Aquarium Pyramid®, Moody Gardens
Saturday, April 4, 2009
7 a.m.-5:30 p.m. Registration

7-8 a.m. Continental Breakfast

8-9:45 a.m. Host Program Introductions
Donald S. Prough, M.D.
Edward R. Sherwood, M.D., Ph.D.

Host Program, Part 1
Global Health/Pandemics
James LeDuc, Ph.D.

From Bench to Bedside — Translational Research
Csaba Szabo, M.D., Ph.D.

9:45-10 a.m. Break and Poster Viewing

10-11:45 a.m. Host Program, Part 2
Breaking Down Barriers to Health: Telehealth and Access to Care
Ben Raimer, M.D.

Recovery of UTMB from Hurricane Ike
David Callender, M.D.

11:45 a.m.-1 p.m. Luncheon

1-1:45 p.m. AUA Business Meeting

1:45-3:45 p.m. President’s Panel — Industry Support for Academic Anesthesia — Research, Lunches, and CME: Who’s Helping Whom?
Moderator: Ronald G. Pearl, M.D., Ph.D.
Panelists: Howard Brody, M.D., Ph.D.
Avi Markowitz, M.D.

3:45-4 p.m. Break and Poster Viewing

4:5:30 p.m. Moderated Poster Session

6:15-10 p.m. Reception and Dinner at Moody Gardens Hotel

Sunday, April 5, 2009
7 a.m.-noon Registration

7-8 a.m. Continental Breakfast

8-10:30 a.m. Oral Presentations

Hypoxia-inducible Factor-dependent Induction of Netrin-1 Dampens Inflammation Caused by Hypoxia
Holger K. Eltzschig, M.D., Ph.D.

Transient Limb Ischemia in Humans Induces Ischemic Preconditioning in Skeletal Muscles by Protein Kinase Translocation
Mali Mathru, M.D.

Cardiomyocytes Derived From Human Embryonic Stem Cells as a Model of Anesthetic Preconditioning
Zeljko J. Bosnjak, Ph.D.

Protective Effect of Erk5 Mitogen Activated Protein Kinase Against Renal Ischemia Reperfusion Injury
Tomoko Kawakami, M.D., Ph.D.

Role of Neutrophil Collagenase (MMP-8) in Murine Model of Sepsis
A. Murat Kaynar, M.D.

Strain-specific Differences in Murine Sepsis-Induced Cardiac Dysfunction: A Physiologic and Genomic Analysis
Andrew J. Patterson, M.D., Ph.D.

Identification and Characterization of a Fluorescent General Anesthetic
Roderic G. Eckenhoff, M.D.

Quantitative Imaging of the Distribution of Proteins at a Gas Liquid Interface
David M. Eckmann, Ph.D., M.D.

For complete meeting and registration information visit www.auahq.org
Responding to the Challenge

Continued from page 1

something one learns as an apprentice and then simply seeks employment for in providing that service. Cookbooks are good for trades, since they allow for consistency and a limitation of original thought or experimentation. The difficulty with a trade is that it is prone to stagnation, and there is often active suppression of innovation. A profession also requires the learning of a specific body of knowledge as well as its applications. However, what defines a profession is the continued advancement of that knowledge base through research and the application of the results of that research into clinical practice. Therefore, my challenge to academic anesthesiology is to ensure that anesthesiology in the United States remains a profession and does not slide into trade status. I have concerns looking at the number of original research papers submitted to the journal Anesthesiology from the United States compared to those from foreign countries. For the past decade, there has been an unabated fall in U.S. manuscript submissions to the point that foreign submissions not only outnumber U.S. submissions, but continue to widen the gap. The only way this trend can be reversed is for academic departments to make a concerted effort to carve out the time and resources to support research. Though grants from ASA foundations such as the Foundation for Anesthesia Education and Research and the Anesthesia Patient Foundation have dramatically increased, dependence on foundation funding is limited and narrow. There must be a transition from foundation grants to National Institutes of Health grants (NIH) in order for academic anesthesiology research programs to remain solvent and credible. Compared to other medical specialties, anesthesiology has severely lagged in obtaining NIH funding. My challenge to academic departments is to use the extra payments from the reversal of the teaching rule to solidify anesthesiology’s standing as a profession.

There has never been a better time in the history of medicine than right now to be an anesthesiologist. As a member of ASA, anesthesiology is a profession that each of us can be proud to be a part of. However, we will need to work together in order to ensure that anesthesiology continues to maintain this status in the years ahead.

Impact of the economic stimulus package on health care