

Anesthesiology & Critical Care News

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Two Researchers Take Clinical Problems to the Laboratory

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The clinician-scientist model is exemplified in the two department faculty featured in this issue of the News. Dr. Charles Buffington, an anesthesiologist, and Dr. Robert Schlichtig, an intensivist, responded to challenging clinical problems by taking them to the animal laboratory, where they could apply systematic investigation in a well-controlled setting. Pilot studies and perseverance ultimately won federal funding for both: a National Institutes of Health (NIH) research project grant to Dr. Buffington and a Veterans Administration Merit Review award to Dr. Schlichtig. Their stories follow.

Anesthetic Influences on Cardiac Function

Dr. Buffington was recruited to Pittsburgh from the University of Washington, Seattle, in 1988. He brought to the department clinical experience in cardiac anesthesia and research experience focusing on the coronary circulation.

Dr. Buffington aims to bridge the gap between basic research in cardiovascular medicine and the clinical practice of anesthesiology. He trained for this role in the laboratory of Dr. Eric Feigl in

Seattle and was supported for five years by a clinical investigator award from NIH. He attributes his career as an independent scientist in anesthesiology to this extended time in a basic science laboratory, combined with course work in statistics, instrumentation, and writing.

Dr. Buffington's research focuses on problems in three areas and their intersections: coronary physiology, myocardial ischemia, and anesthetics. He is perhaps best known for his work demonstrating coronary steal with the anesthetic isoflurane, but remains proudest of his original studies on the effects of hemodynamics on myocardial ischemia when coronary flow is limited. Recent efforts defined the load-dependence of postischemic, or "stunned," myocardium. Dr. Buffington recently received a research project grant from the NIH to support investigations of transmural coronary steal in a

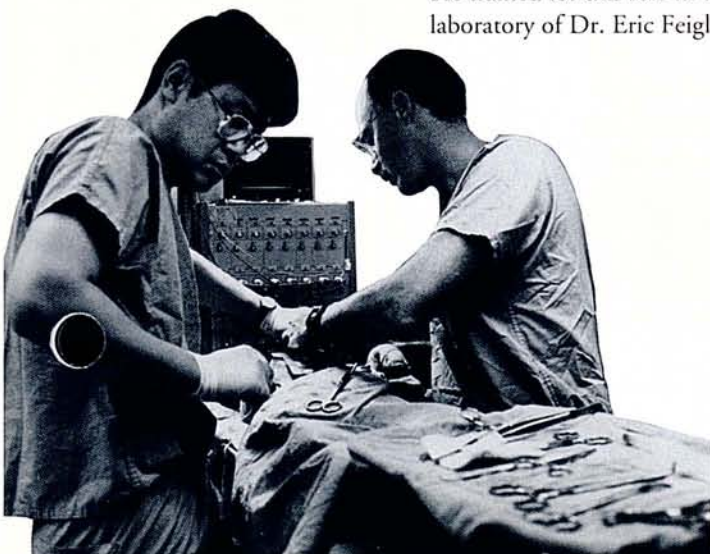
canine model and clinical studies comparing isoflurane and halothane in patients undergoing vascular surgery.

Collaborative work with Dr. David Strum has yielded exciting new information about myocardial energetics. This team postulated that ischemia, by reducing the contraction of the heart, would reduce oxygen demand and protect the myocardium, as occurs during cardioplegia. Surprisingly, recent studies have shown that when citrate is infused to stop contraction in regions of myocardium the oxygen demand of these regions remains high. These areas may be stretched by the surrounding regions with normal contraction.

Other research, with Dr. Seiji Watanabe, a visiting anesthesiologist from Kurume, Japan, has focused on the clinical observation of a "low-voltage electrocardiogram" in patients with a failing heart. Animal studies have revealed a close relation between reduced contraction and reduced electrical amplitude. Further, improved contraction during therapy with positive inotropic drugs is mirrored by increased electrical amplitude.

Dr. Buffington spends half of his time in the operating room, providing anesthesia for heart and lung operations. He welcomes the new challenges brought by the recent increase in lung transplantation at UPMC, crediting the expertise at UPMC in echocardiography and pathophysiology of the right ventricle and heart-lung interactions with enabling the successful management of these difficult cases.

Dr. Seiji Watanabe and
Dr. Charles Buffington in the laboratory.





Dr. Robert Schlichtig, left
Dr. Charles Buffington, right

Detecting Dysoxia in the Critically Ill

Dr. Schlichtig came to Pittsburgh by way of St. Louis University, where he trained in critical care medicine with Dr. Stephen Ayres. While in St. Louis he sought research experience in a physiology laboratory, where he "started measuring flows." In Pittsburgh his early inquisitiveness has evolved into sophisticated investigations of vascular control and oxygen transport. Dr. Schlichtig recently won a VA merit review award for this work.

Critical oxygen deprivation, or "dysoxia," is generally considered the final common pathway to organ failure in critically ill patients. However, clinicians have limited ability to detect dysoxia, particularly in nonvital organs. Thus, it can rarely be determined with certainty when resuscitation should begin and when it has met the needs of vulnerable organs.

A typical example of this dilemma is the patient with sepsis who sustains organ damage despite cardiac output that may be three times normal. Would resuscitation to an even higher cardiac output prevent such organ failure, or is organ-specific resuscitation needed? Over the last several years, Dr. Schlichtig and colleagues have used animal models to investigate methods to detect dysoxia in nonvital organs.

Many have believed that the biphasic oxygen consumption (VO_2)/oxygen delivery (DO_2) model could be used to detect dysoxia. According to this model, tissues are "well" as long as VO_2 remains constant with decreasing DO_2 (oxygen supply independence), and they are dysoxic when VO_2 decreases with decreasing DO_2 (oxygen supply dependence). Figure 1 shows this relation.

Inconsistent with this model, Dr. Schlichtig observed that kidney VO_2 , unlike that of liver or intestine, decreases in proportion to DO_2 as renal blood flow decreases. Realizing that this was not pathologic, but simply represented decreasing oxygen demand, he concluded that decrease in VO_2 alone cannot be used to detect dysoxia unless oxygen demand is known to be constant.

This principle illustrates one folly of trying to detect dysoxia using the VO_2/DO_2 model in critically ill patients, whose oxygen demand varies considerably from moment to moment because of marked variability in thermogenesis, work of breathing, alertness, and so on. In their search for new, organ-specific measures of dysoxia, Dr. Schlichtig and coworkers have examined two possible indicators: tissue redox state and tissue acidosis.

Tissue redox state (e.g., NADH/NAD) estimates the oxygen supply to demand ratio and thereby might overcome the problem of variable oxygen demand. As DO_2 decreases, NADH accumulates and NAD decreases (figure 2), because lack of oxygen prevents the transfer of fuel-derived energy to ATP. Dr. Schlichtig estimated mitochondrial redox state in intact liver in a canine model, and found that whole liver redox state was constant during oxygen supply independence but decreased during oxygen supply dependence. This finding suggested that decreasing redox state, which can be assessed noninvasively by a number of methods, might be used to detect dysoxia.

Tissue acidosis and hypercarbia are known to occur as blood flow decreases. However, many have considered these phenomena simply to represent stagnant carbon dioxide, which accumu-

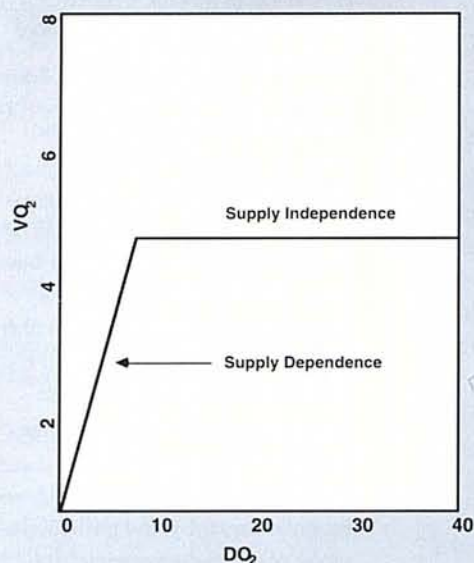


Figure 1

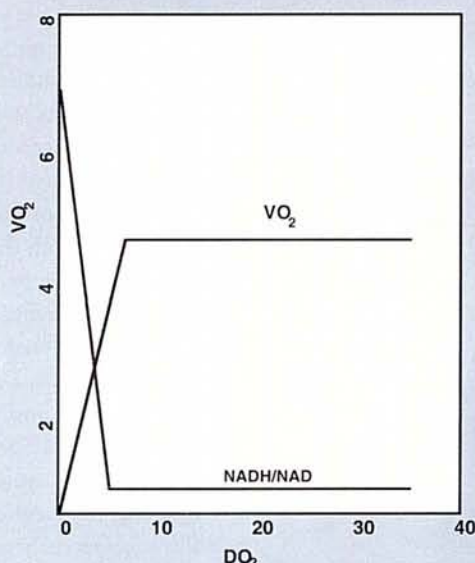


Figure 2

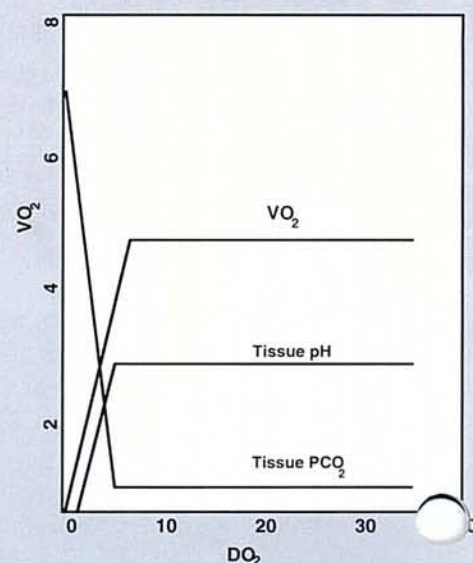


Figure 3

*From left to right:
Doctors James Krugh,
Paul Rogers,
and Kenneth Rothfield
distinguished
with awards.*



Dr. Michael DeVita

lates in tissues when flow is decreased, but not necessarily inadequate ("respiratory" acidosis). However, laboratory studies of Dr. Schlichtig and colleagues revealed that tissue acidosis and hypercarbia are only slight during oxygen supply independence and become extreme at the onset of supply independence (figure 3). Most important, these researchers used the concept of carbon dioxide titration to demonstrate that such extreme acidosis and hypercarbia represented "metabolic" acidosis, and therefore, dysoxia.

These studies led Dr. Schlichtig to suspect that the metabolic acid produced may derive from unreversed hydrolysis of ATP, a direct manifestation of dysoxia. Complete testing of this hypothesis will take several years of work. If it is confirmed, however, measurements of tissue pH or PCO_2 could be used to detect dysoxia in patients.

Although they have yet to develop a method that definitively detects dysoxia in nonvital organs, Dr. Schlichtig and his research group are optimistic that further testing of their hypotheses will ultimately lead to the development of useful clinical tools.

In the clinical arena, Dr. Schlichtig is codirector of the surgical ICU and medical director of the respiratory therapy department at the VA Medical Center.

Notes from the Residency Program...

July 1992 marked the beginning of the clinical anesthesia training for 18 new residents. The CA-1 class represents six southeastern universities, two midwestern institutions, and seven northeastern schools, including the University of Pittsburgh. In addition, three residents came from Belgium, Norway, and Riga, a former soviet socialist republic. Five other residents began their clinical base year in the department of medicine at Montefiore University Hospital. We welcome them all and wish them the best as they begin their training programs.

During the 1992-93 academic year, a fellowship (CA-4 year) in anesthesia for head and neck surgery will be developed by the anesthesiology faculty of the Eye & Ear Institute Pavilion, under the direction of Doctors Andrew Herlich and Robert Krohner. The unique caseload encountered at EEIP, ranging from routine myringotomies to complex cranial base tumors, should ensure an unusual and rewarding experience for an advanced trainee.

Welcome back to Dr. David Wilks, residency director, after a year-long sabbatic leave, and thanks to Dr. Andrew Herlich for his excellent service as acting director during the past year.

...and the Critical Care Training Program

The largest number of fellows in the history of the Multidisciplinary Critical Care Training Program joined the program in July. The first- and second-year fellows now include three anesthesiologists, four surgeons, and 20 internal medicine graduates. Four of the internists have already completed subspecialty training in pulmonary medicine and are taking one year of critical care training.

As usual, the fellows have broad experience and come from many parts of the world, as near as the University of Pittsburgh and as distant as Australia. Similarly, they represent a spectrum of seniority ranging from new residency graduates to a senior director of anesthesiology.

Teachers and Trainees Win Awards

For the second consecutive year, anesthesiology residents selected Dr. James Krugh to receive the Dr. Leroy Harris Award for Excellence in Teaching. In the critical care division, fellows chose Dr. Paul Rogers as Faculty of the Year, also for the second consecutive year.

Dr. Joel Kellner was voted best resident of 1991-92, and Dr. Kenneth Rothfield was selected as chief resident for 1992-93. CCM Fellow of the Year for 1991-92 was Dr. George Mazariegos.

Congratulations to all!

Ethics Committees Merge

A single ethics committee for the University of Pittsburgh Medical Center (UPMC) hospitals was formed on July 1 with the merger of the Presbyterian and Montefiore University Hospital ethics committees, directed by Doctors James Snyder and Michael DeVita, respectively. The two hospital committees had been collaborating closely for more than a year. Together, the committees had passed a new advance directive policy and a policy for organ donation following elective removal of life-supporting therapy. In addition, the committees worked together to revise and unite the two hospitals' guidelines on forgoing life-sustaining treatment and brain death policy.

Because of the close collaboration required by the ethics committees of these two closely affiliated hospitals, the medical executive committees recommended, and the ethics committees agreed to, forming a unified PUH/MUH ethics committee. The new committee's membership includes all members of the previous two committees and represents virtually all hospital departments. Chaired by Dr. DeVita, the ethics committee will continue to pursue its three main objectives: education of hospital personnel and patients about ethical issues; providing and supervising an ethics consultation service in concert with the UPMC Center for Medical Ethics; and reviewing and writing policies of ethical import.

To inquire about the ethics committee or to request an ethics consultation, call Dr. DeVita or Dr. Snyder.

Musings on Research

One purpose of this newsletter is to inform our faculty, trainees, and alumni about the department's research activities. In that tradition, this issue features work being done by Doctors Charles Buffington and Robert Schlichtig. Our department has been dramatically successful in its research endeavors. Objective

department's mission, in large measure, a department's national reputation is forged by its investigators. We are blessed with a large number of illustrious scientists. Their efforts have made material contributions to the fields of anesthesiology and critical care medicine, and, as a byproduct, to our growing national stature.

Our department has been dramatically successful in its research endeavors. Objective criteria for comparison across academic anesthesiology departments, based on the Society of Anesthesia Chairmen's administrative survey and other data, indicate that we are one of the foremost research departments in the country.

criteria for comparison across academic anesthesiology departments, based on the Society of Anesthesia Chairmen's administrative survey and other data, indicate that we are one of the foremost research departments in the country. We are, for example, among the top four or five departments in NIH funds generated by faculty efforts. We have the same status in papers published. In the number of abstracts accepted this year for presentation at the competitive American Society of Anesthesiologists' annual meeting, we are second only to Johns Hopkins. While this measure varies from year to year, our continued presence near the top of anesthesiology departments nationwide says a great deal about our collective productivity and national visibility. While outstanding clinician-teachers are central to our

Let me comment on the importance of federal research funding. All research takes money, some more than other. Anesthesiology research falls into two categories. The first consists of direct clinical questions, specific and circumscribed, generated by intellectually curious clinicians in the process of patient care. Most such ideas are unfundable by federal agencies as they are currently constructed. The second category consists of basic and complex conundrums, not necessarily generated by patient care, which, by vague but important criteria involving their importance, complexity, current sex appeal, and other factors, are judged to be of national import.

One can make a cogent argument that research in the first category has had as much or more impact on our field than the second. Examples that readily come to

mind are the advances in acute pain management, both obstetric and postoperative, the development of improved anesthetic agents and techniques, and the evolution of intraoperative and ICU monitoring, which have reduced morbidity and mortality so dramatically that even rapacious malpractice insurance carriers are acknowledging the change. Appallingly, despite the obvious importance of obstetric anesthesia research, only one investigator in the United States has federal funding to pursue it. Such clinically oriented research has been funded by two sources: industry and the few departments fortunate enough to be able to devote consequential resources to further their own research. Without a change in federal funding, the loss of either source would destroy our profession's capacity for direct, patient care-oriented problem solving.

The second category of research, that funded by federal agencies (the NIH, the NSF, the VA, the military), is more commonly directed at fundamental questions which may, but often do not, have direct relevance to patient care. Despite the current hysteria in these agencies about relevance, the crucial tradition of funding basic, unapplied science remains strong although threatened by cuts in resources. Past and current examples of such research in our field are the unraveling of the puzzle of gas exchange in health and disease, and the understanding of the mechanisms of action of inhaled anesthetics.

The reasons are in part important and in part silly. The ferocious competition for such funds has created a subculture of its own, with rigid rules of expression and a self-validating methodology—peer review.





While success in any research field leads to recognition for its investigator, success in the second category builds national reputations. The reasons are in part important and in part silly. The ferocious competition for such funds has created a subculture of its own, with rigid rules of expression and a self-validating methodology—peer review. The important part is that the methodology of the subculture assures that funded research is rigorously conceptualized and likely to prove successful. Indeed, it is now a

common prerequisite for funding to have already done at least some of the research. Elements of the silly part are the creation of a self-perpetuating bureaucracy that consumes research funds, and the limitation that the bureaucracy imposes on its own breadth of vision. Not uncommonly, truly important ideas are not funded, and thus not pursued, because they are really original, and there are no peers to review them. The peers in peer review often have their own vested agendas, one of which is to increase federal funding in their own arenas. An example of research impeded by this limitation of vision is the potentially crucial observation of Dr. Andrew Kofke, a member of our faculty, that high-dose opioids may cause brain damage. Despite excellent pilot data, high quality grant writing, and the obvious importance of the observation, funding has not yet been secured.

Why is the acquisition of federal research funds so important in academic life? In part, and obviously, it is often the only way for a scientist to do research, and thereby to fulfill his or her reason for being. In addition, although less important, it is recognition at a national level that one is a scientist of quality and consequence. Thus, medical schools commonly use federal funding as a measure of self-worth, and judge their departments and faculty by that standard.

This measurement, though it has limitations, is usually accurate. Thus, the two investigators highlighted in this issue, Doctors Buffington and Schlichtig, have produced outstanding science—


We have failed in another aspect, as well. Thanks to the creative efforts of many of our faculty, we have an outstanding residency program. Yet, with notable exceptions, few of our residents are

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clinically important, fundamental in its implications, and skillful in its methodology. Their success in attaining federal grants assures them of continuity of research support. Equally important, however, is that it acknowledges them as major players in one of the most important games of our time.

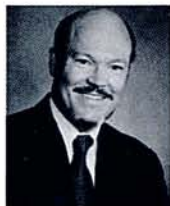
I would add another thought to this contemplation of department research. As I have noted, we have been outstandingly successful in many ways. In others, however, we have failed. Many faculty not only care nothing about doing research (a defensible position), but know little about our department's research endeavors (an indefensible position). The attendance at our research seminars is a disgrace. Intellectual understanding of what we do in research is a basic part of every faculty member's job.

involved in research, and fewer yet have made a commitment to pursue it. I find this incomprehensible. In part, I suspect, it is the fault of our training program—a problem that is being addressed and will be dealt with. In part, however, it is a result of the role models that we present to residents. Researchers commonly are absent from the residents' realm of activity, and clinicians often are uninformed, uninterested, or uninvolved. We're pretty good, but we have problems to solve.

 *Winter, M.D.*
Chairman, Department of Anesthesiology
And Critical Care Medicine



From left to right:
Doctors Sivam
Ramanathan,
W. David Watkins,
and Richard Bjerke



New Leadership

I am most pleased to announce the successful recruitment to leadership positions in three of our six hospitals. Dr. Richard Bjerke, previously associate chief of anesthesiology at PUH, assumed the chiefship of our group at the Oakland VA Medical Center last June. Under his leadership consequential steps have been taken to improve patient care and teaching, and three excellent faculty members have been recruited, two for this year and one for next July. Despite endless efforts by the VA to cut spending in accord with decreasing budgets, our group has been strengthened, new federal research funding has been acquired, and investigative programs are under way.

Dr. Sivam Ramanathan, formerly professor and vice chairman of anesthesiology at NYU, arrived in August to assume the chiefship at MWH. Dr. Ramanathan is a nationally respected senior figure in obstetric anesthesia, with an outstanding record as a clinical investigator in obstetric pain. Beginning his tenure at the same time as Dr. Richard Sweet, professor and chairman of the department of obstetrics, Dr. Ramanathan will bring both academic and clinical excellence to one of the largest obstetric anesthesiology programs in the country.

Dr. David Watkins, formerly professor and chairman of the department of anesthesiology at Duke University, began his new position of chief of anesthesiology at MUH in August. Dr. Watkins has an extensive research back-

ground, with a PhD in pharmacology. Following a residency at the MGH he remained a member of the Harvard faculty until his appointment at Duke in 1983. Over the next eight years, Dr. Watkins built an academic department of high quality. His research and leadership skills will benefit the faculty at MUH and the entire department, and will engender linkages with the new clinical pharmacology group under Dr. Robert Branch.

This new leadership is a source of great satisfaction to me, and is the result of intense effort by many people. It represents change and challenge for the department for many years to come—another example of the need to change while winning. My particular thanks for help in these matters go to Dr. Ryan Cook and the members of his search committee, who were instrumental in these recruitments. A measure of their success is the excitement expressed by the faculty of all three institutions about the changes already occurring.

Critical Care: How Effective Is It?

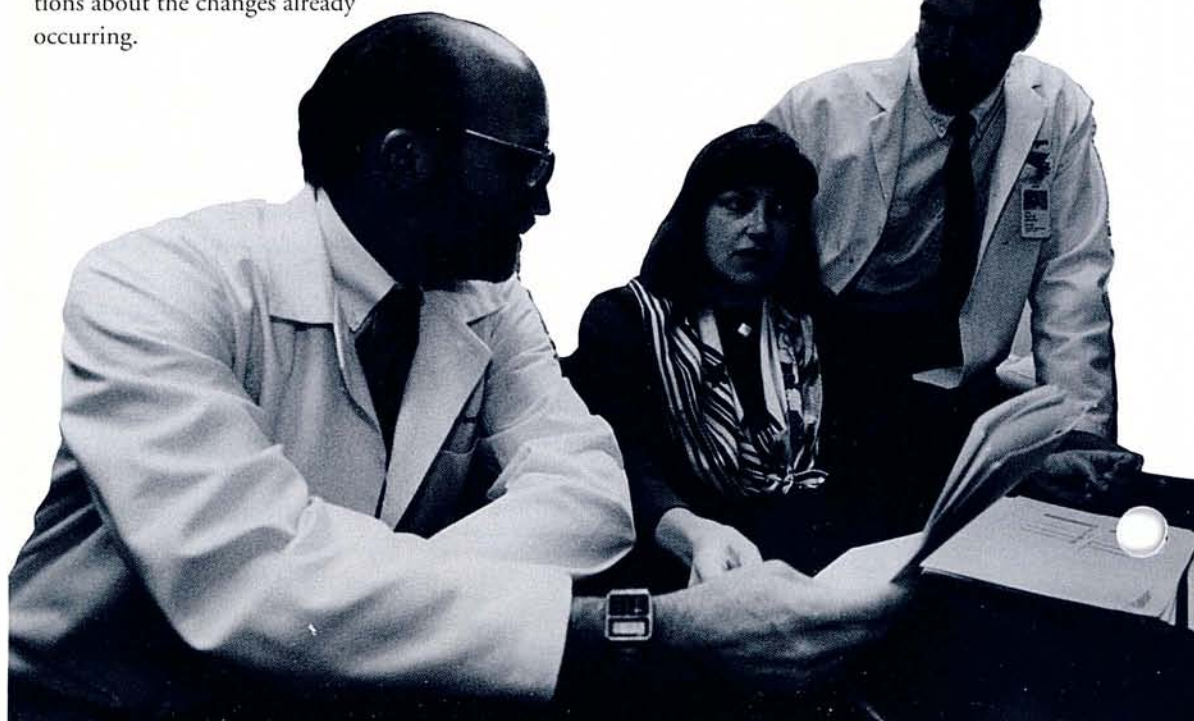
Three days after a cholecystectomy, a 43-year-old man develops a fever and a left shift, then shock with protracted hypotension, and finally multiorgan-system failure. The patient has now been in intensive care for three months, chronically on hemodialysis and mechanical ventilation. He is responsive, especially to his family, but appears not to think clearly and cannot communicate effectively. His total hospital and physician charges are up to \$943,000. Most of his insurance will run out in eight days, leaving the family equity—home, retirement savings, savings for children's education—at risk. What should be done? Who should decide?

Such ethical conundrums are not uncommon in critical care and have received considerable press. Cost evaluation of life and its quality may seem bizarre, but it is no longer a rare concern.

Less frequently, and even less well, addressed are such questions as, How did we get here? What could have been done better? What could have been done less expensively? Should other drugs or different drugs have been used? Fewer tests?

Helpful answers, answers that can alter management, are hard to find. To address these and related problems, the division of critical care has launched a multidisciplinary program to critically evaluate the application

Doctors James Snyder, Angela Colantonio, and Derek Angus review CCM data.





*Dr. Peter Safar, left,
Dr. Yung Shieh, right.*

of critical care practices. The program's goal is to promote and facilitate cost-effectiveness studies relating to all aspects of critical care. Important areas of study include survival and long-term quality of life after critical care, resource utilization and cost analysis, and detailed analysis of ICU practices. The program is a collaborative effort led by Doctors James Snyder, Luke Chelluri, and Derek Angus at PUH, Dr. John Hoyt, director of critical care at St. Francis Hospital, Dr. Edmund Ricci, chairman of the department of Health Services Administration in the Graduate School of Public Health, and Dr. Judith Lave, also of HSA and director of the UPMC Institute of Health Care Research.

To assist with population-based studies, including those evaluating critical care outcomes, the department recently recruited epidemiologist Dr. Angela Colantonio. After receiving her Ph.D. from Yale University, Dr. Colantonio completed a postdoctoral fellowship in the Department of Epidemiology here. Her previous research involved modeling outcomes of stroke and Alzheimer disease patients enrolled in large longitudinal studies. For the critical care evaluation program, she is investigating the research potential of existing patient data bases, including sources within the medical center as well as state and national patient registries. Future studies may use information extracted from these data bases to develop objective risk estimates, to monitor therapeutic processes and resource utilization, and to assess patient outcome.

Yung Shieh Delivers 13th Safar Lecture

May 21 marked the 13th Peter and Eva Safar Annual Lectureship in Medical Sciences and Humanities. Dr. Yung Shieh, Professor and Chairman of Anesthesiology and Deputy Director of the Institute of Clinical Medicine, Beijing Medical University, Beijing, China, was this year's esteemed lecturer. Dr. Shieh's long and distinguished career as an anesthesiologist parallels the growth of modern anesthesiology in China, the topic of his address. Dr. Shieh is largely responsible for the recognition of anesthesiology as an independent specialty in China, and he helped pioneer the establishment of modern intensive care units in China.

The Safar lectureship honors the professional and personal contributions of Dr. and Mrs. Safar to the scientific community. Dr. Safar, former chairman of this department, is Distinguished Service Professor of Resuscitation Medicine and Director of the International Resuscitation Research Center.

Grenvik Honored with New ICU

When the new 10-bed cardiothoracic surgical intensive care unit (CTICU) at PUH opened in March 1992, Dr. Keith Stein, medical director, and Dr. Bartley Griffith, chief of cardiothoracic surgery, wished to honor Dr. Ake Grenvik for his lifelong commitment to the critically ill. On April 20, the CTICU was formally dedicated to Dr. Grenvik for his outstanding contributions to the science, art, and humanitarian concerns of critical care.

At the ceremony, innumerable advances initiated by Dr. Grenvik were lauded by speakers including Dr. Thomas Detre, senior vice chancellor for the Health Sciences, and Doctors Peter Winter and

James Snyder, both long-time friends and collaborators in critical care. Notable among Dr. Grenvik's many accomplishments have been advances in the care of organ transplant recipients, the ethics of critical care, and appropriate care of the elderly, all of which have brought him international acclaim. His unceasing efforts as director of the multidisciplinary critical care training program, ensuring the continuing pursuit of excellence in patient care, were praised by the many current and former students and colleagues attending the ceremony. Dr. Grenvik was recognized as a visionary in his keen sense of the future needs of critical care.

Dr. Thomas Detre, right, congratulates Dr. and Mrs. Ake Grenvik.



Research Seed Grants Awarded

Once again, the department's biannual seed grant competition attracted a wide range of promising investigators and exciting proposals. Award winners announced in January were:

Dr. Stephen Bowles, for "The Effect of Sodium Bicarbonate on Systemic and Intestinal Critical Oxygen Delivery";

Dr. Peter Linden, for "A Prospective, Randomized, Double-blind Trial Comparing Selective Decontamination of the Digestive Tract Against Placebo in the Prevention of Postoperative Infection, Morbidity, and Mortality in Adult Orthotopic Liver Transplant Candidates and Recipients";

Dr. Patricia Dalby, for "Pregnancy and Chronic Pelvic Pain Effects on Peripheral Substance P Levels";

Dr. Alan Rosenbloom, for "Assay of Serum Cytokines and Leukocyte Surface Molecules in the Blood to Distinguish Infection, Rejection, and Other Complications After Liver Transplantation";

Dr. Peggy Seidman (the first Charles W. Schertz Research Fellow), for "Transforming Growth Factor Beta: Effects of Hypoxia";

Dr. Ippei Seki, for "Comparison of Flow Resistance and Viscoelastic Resistance in the Respiratory System in Infants and Children in Health and in Respiratory Failure with the Inspiratory Interrupter Technique"; and

Dr. Harvey Zar, for "Development of a Fiberoptic Biosensor for Oxygen Free Radicals."

Receiving grants in July were:

Dr. Morris Bierman, for "Variability of Bronchodilator Response in Critically Ill Patients";

Dr. Andrew Kofke, for "Opioid-induced Brain Damage";

Dr. Michael Pinsky, for "Aortic Pulse Pressure Variation During Positive-pressure Ventilation as an Index of Cardiovascular Instability";

Dr. Ernesto Pretto, for "The Study of Resuscitation Potentials Following the March 1992 Earthquake in Turkey";

Dr. Wolf Stapelfeldt, for "Effect of General Anesthetics on Neuropeptidergic Synaptic Transmission";

Dr. David Strum, for "Assessment of Left Ventricular Function During Regional Myocardial Dysfunction by Series and Contractile Element Analysis";

Dr. Shekhar Venkataraman, for "Age-related Differences in Endotoxic Shock in Rats"; and

Dr. Seiji Watanabe, for "Time Course of Electrical and Mechanical Events Following the Onset of Myocardial Ischemia."

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