ANESTHESIA

ITS MYSTERIES

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Gerald A. Gronert
March, 2008

I started 'moving on' even as a toddler, leaving my home in Chicago whenever I wasn't closely watched, and I even crossed a boulevard. After college and medical school in Chicago, I went to St. Louis, Missouri for my internship. Then on to Denver, Colorado for my two year anesthesia residency, which included four superb months at Los Angeles Children's Hospital. After five years' private practice in Denver, Colorado, during a visit to the Mayo Clinic at Rochester, Minnesota, I was enticed to begin a 20 year career in neuroanesthesia.

Within a year of moving there, I was drafted during the Viet Nam conflict and spent two years at the US Army Burn Unit in San Antonio, Texas. This fortuitously began my research career, with examination of the effect upon liver function of closely spaced multiple halothane anesthetics, and expansion into an entire series of patients of Tolmie, Joyce, and Mitchell's report of hyperkalemia after succinylcholine in a single burn patient.

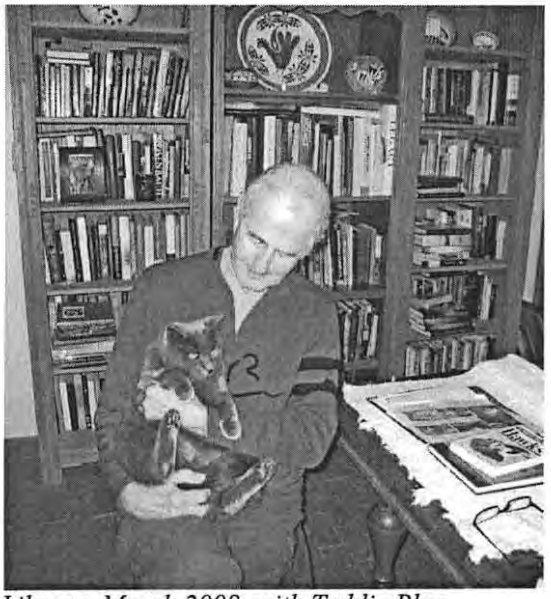
With my return to Mayo and neuroanesthesia clinical care and research, our research lab further investigated succinylcholine-induced hyperkalemia, first a study in swine with scald burns, and then a comprehensive canine study. One of our burned pigs developed malignant hyperthermia, great for future MH study, except that the successful resuscitation ended fatally when we mis-connected an oxygen source.

It took a while to determine how to finagle a source for MH susceptible swine from distrustful breeders, but we in time established barnyard testing, again with a beginning fatal mistake. Our very first barnyard tested pig was positive, with marked rigidity, tachypnea, and tachycardia, and we were eager to bring him to the laboratory. In our excitement, we didn't properly watch what was occurring until our swine breeder told us that he'd be dead within another minute or so. He was correct, and we thus learned to limit halothane exposure and to be ready to treat out-of-control responses.

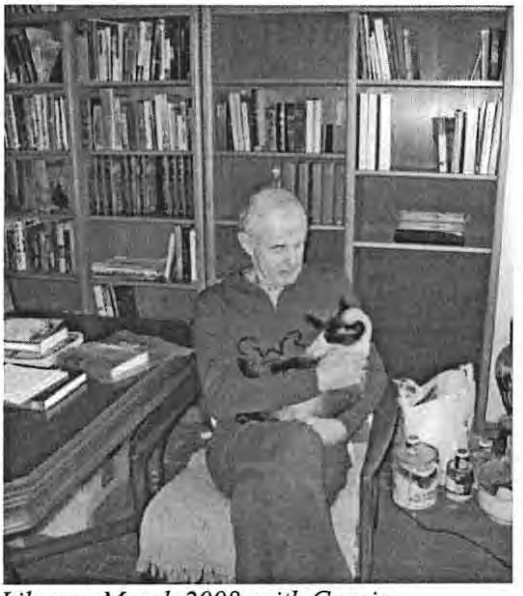
Third year Medical Student, autumn, 1956

With time, MH and other research systematically developed. After 20 years at Mayo, I moved to the University of

California at Davis for further research, in part with veterinary anesthesiologists. In addition, I set up another MH contracture testing laboratory. Disuse muscle atrophy was appealing because it occurred so extensively in burn patients. Advances in computer modeling and in detection of minute quantities of muscle relaxants in serum aided analysis. Furthermore, we compared relaxant responses in animals ranging in size from rat to horse, and had queries concerning species with rare and different muscle endplate receptors. These were exciting times. After 13 years at Davis, I retired as an emeritus professor to the high dry desert and forested mountains of New Mexico, living in Albuquerque. I am an adjunct professor in the Department of Anesthesiology, University of New Mexico.



Library, March 2008, with Teddie Blue



Library, March 2008, with Gracie

Dedication

Those who eased the work and added comfort and humor:

- ***Mayo:*** laboratory: Bill Gallagher, Dick Koenig, Jim Milde, Marilyn Oeltgen, Becky Wilson; secretary: Ann Tvedt.
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I carefully reviewed and re-reviewed this memoir, and my web advisor Luan Dinh helped immeasurably. For any reader, please contact me (gagronert@ucdavis.edu) if there are problems or errors.

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Introduction

This memoir recalls my development into a clinical and research anesthesiologist and my serendipitous focuses into succinylcholine-related hyperkalemia and malignant hyperthermia. When I started my residency, anesthesiology was in the throes of a new profession, with enormous progress and some turbulent years. This is a peripatetic wandering through my past, gathering together vital descriptions of principles, ideas, decisions, places, and people.

I reflect on things, some philosophy, a bit of history, advances, conflicts, disappointments, and immense satisfactions. My resident education and private practice coincided with the emergence of the anesthesiologist as partner with the surgeon, although some fought for years that loss of being 'captain of the ship.'

Surgeons needed to be that in early operating rooms, for virtually no one else had an education in medicine, and those providing anesthesia were sometimes non-medical personnel, even into the 1960s. Advances in surgery in part depend upon the development of sophisticated anesthesia that manipulates physiology to bring about the loss of sensation with or without the loss of consciousness via pharmacologic means using various drugs and equipment.

My sources are acts of memory, supported by my bibliography. Its contents, published, unpublished, and those unidentified, are in my files. I began my diary on the evening that I proposed to Pat in August 1957, and it is a valuable source. My somewhat random organization reflects a wandering memory according to impact. I'll try to keep the reader oriented.

Chapter One: Every Patient a Mystery

Every patient is a mystery until the anesthetic begins. Even though there is a pre-anesthetic workup, each patient's reactions vary during exposure to the stresses of anesthesia and surgery. How sound are physiological reflexes, and is s/he less fit or less healthy than seemed pre-op? Why do some steadily deteriorate? There are factors in anesthesia that mandate consideration and yet are unknown to the patient.

What makes some patients worse while under anesthesia? Which are resistant to the several anesthetic agents or muscle relaxants? Anesthetic agents put the patient to sleep, muscle relaxants do not. As derivatives of the curare plant, they merely paralyze. Which patients are sensitive to what will be administered? What are the clues? Does the patient have an unknown or unrecognized disorder? Has the patient taken medicines or perhaps illegal drugs that might complicate anesthesia, particularly amphetamines, cocaine, metabolic stimulants, or other 'uppers' that they were afraid to reveal? Such thoughts continually go through the anesthesiologist's mind, and that keeps the field ever fascinating. There are so many uncertainties during the beginning of an anesthetic that I preferred to anesthetize patients personally, as opposed to helping someone learn anesthesia, for only then could I understand the individual patient's physiologic responses. That feeling likely relates to my initial 5 years in private practice in Denver. Teaching and supervision of others guide them, but the teacher cannot feel the mask on the face, evaluate airway resistance and jaw tightness, measure tongue and throat reflexes, feel how tight or loose the chest is. Furthermore, you gain valuable information from the precordial or esophageal stethoscope, but must routinely listen to it to acquire the skill needed to detect altered sounds that someone might otherwise misinterpret or miss entirely.

Anesthesia is the middle ground between patient and surgeon: About 1990, I was anesthetizing an 11-year-old girl for surgery of her spine. Soon after the operation started, she began to deteriorate as her blood pressure dropped alarmingly, resistant to supportive drugs. Only epinephrine brought her blood pressure to a low normal level. We stopped the procedure, awakened her while resuscitating her, but could not determine what had caused the problem.

I contacted several friends, and one of them, the pediatric anesthesiologist Dr. Marilyn Larach instantly said, "She has a latex allergy."

I'd not heard of that. The girl's allergy was severe, as it caused an anaphylactic reaction, resistant to all but the most potent recuperative drugs. We re-did her a few days later, with non-latex rubber goods, and all went well.

A minor procedure with local anesthesia can become dangerous. A patient may be sedated while her/his condition may be monitored by persons not trained in anesthesia. Sedative drugs are a one way path to general anesthesia, and overdoses can easily occur if the patient is uncomfortable and those providing sedation try too hard to ease tension to facilitate the procedure.

Unfortunately, inexperienced or poorly educated personnel may not recognize early signs of an overdose and continue to push sedation. In fall 2006, a 4-year-old girl died following office dental care in Chicago, the city where I began my medical training. She was given repeated doses of sedatives to quiet her. Afterward, her mother told an aide in the dental office that her daughter wasn't breathing properly. The mother was reassured that all patients breathe that way, but awaken OK. Then the mother noted that the girl had stopped breathing. The dental personnel could not properly treat her, and she died, despite being rushed to a hospital. This is not a mystery. The girl's failure to breathe is easily treated by someone experienced in anesthesia, who would have had the proper equipment and medications set up and ready for just such a mishap.

Chapter Two: Anesthesia

Why did I choose anesthesia? I cannot explain it, but my choice was correct. My conscious interest began in 1956 with a lecture during my junior year by Herbert Natoff, a senior resident. He discussed cardiac arrest, its various causes during surgery, and how blame – personal or physiological - was assigned. He generated an awareness of the variations in physiology and pharmacology inherent in anesthesia, and the satisfaction in applying these to patients.

But what led me to the study of anesthesia? In 1956-8, my clinical years in medical school, I was intrigued by pediatric cardiology when Dr. Gazul of Chicago's Cook County Hospital demonstrated that improved techniques in cardiac catheterization solved auscultatory puzzles, e.g., heart sounds and murmurs that had confounded clinicians for decades. We medical students roamed the cardiac pediatric ward with him, and he taught us what the various heart sounds and murmurs signified as regards anatomical abnormalities.

Fig. 1a. There appears to be an inhalation apparatus at the patient's mouth.

I considered anesthesia in my senior year. Although I had anesthetized rats with ether as a research technician in endocrine physiology, this experience did not consciously lead me to anesthesia, and certainly not to surgery. I was open minded, and undecided, and then anesthesia simply fell in place.

A Bit on Development of Anesthesia

Fig. 1b. Close up.

The term 'anesthesia' or anaesthesia (as spelled in the Commonwealth), a state of insensitivity, was described in a thesis in Rostock, Germany in 1718 by JB Quistorp. His dissertation linked the concepts of anesthesia as mentioned by Greek and Latin authors (Wright et al, 2000). Genesis describes the deep sleep of Adam during which his rib was removed to form woman (Bible, Genesis 2:21). In the 15th century, Sabuncuoglu of Turkey described successful general anesthesia using mandrake root and almond oil (Basagaoglu et al, 2006). In 1513, several monks used what appears to be general anesthesia (Schilling, 1997). Fig. 1a, b. The monks were familiar with the

anesthetic action of "sleep"-drinks and were imprisoned by the city council of Berne for defrauding the clerus and the public. At trial, it was determined that the monks had permitted religious frauds to gain money for the monastery from pious people. Among other actions, they had manipulated a statue of the Holy mother Mary, causing her to apparently shed bloody tears. The city council asked the Pope for his verdict. The papal verdict was the rope around the neck till death occurs. (Fig: Schilling, Diebold: Schweizer Bilderchronik, 1513, Wie die Berner Predigermönche dem Laienbruder Hans Jetzer aus Zurzach in einer Narkose die Wundmale Christi mit Säure einätzten, figure 1-30, Seite 45-46. From: Brandt, Ludwig, Illustrierte Geschichte der Anäesthesia; Wissenschaftliche Verlagsgesellschaft Stuttgart 1997, used by permission.)

Ralph Waters, Initiator of Anesthesia Residencies

Dr. Robert Virtue was chair of the department at the University of Colorado, where I served my residency. He loved history and told us of the very first anesthesia residency program, initiated by Ralph M. Waters, about 1927 at the University of Wisconsin. Prior to that, he had been in private practice in Iowa. At Wisconsin, he had had to fight surgeons virtually constantly, with continuing frustrations. His routine fights with surgeon were much greater than our worst ones. Early surgeons were heavily dictatorial and did not take easily to others trying to change things. Waters was introducing applied physiology and pharmacology to anesthesia, training residents to become science-based.

As an example, M. Digby Leigh, who eventually gained fame as a pediatric anesthesiologist, visited Waters from Canada during his training, about 1937. As Leigh told us residents in 1960, Waters had an impressive department, and Leigh, never easy to impress, stayed some months. Surgeons, especially at that time, wanted results with their case now, without performing measurements or doing other things that distracted from or delayed their performance. Waters was so frustrated and disappointed with the surgeons at Madison that, when he retired to Florida to grow oranges, he vowed never to return to the hospital or to anesthesia meetings. When visiting Madison after retirement, he would come to the local drugstore across the street and phone over to the operating rooms so those who wished to see him could come over there. The only anesthesia meeting he ever attended during retirement was in Brazil (Parsloe, 2001).

Waters both started and aided academic anesthesia. When Emery Rovenstine finished Waters' residency, he left Madison to start the anesthesia program at Bellevue Hospital in New York City. Waters split his own group, and shared faculty and residents to begin that program (Morris, 2001) -- incredible unselfish generosity! Academic and private practice anesthesiologists that I met in my early anesthesia

years spoke reverently of Waters. At several conferences, I met Rovenstine – modest, quiet, and self-effacing.

Dangerous Application of Nitrous oxide

More from Dr. Virtue: While Waters was establishing quality educational policies, problems with nitrous oxide were occurring. It had been used for decades, but was weak, with borderline potency. It cannot maintain anesthesia deep enough to prevent awareness without also causing hypoxia. It can be used safely as a second gas with more potent agents, and enables use of lower concentrations of the potent agents. In the past, some used nitrous oxide alone, and pushed it so that the oxygen concentration was less than 20%. This was in part erroneously justified by the fact that nitrous oxide (N_2O) contains two molecules of nitrogen and one of oxygen. Some believed that this oxygen was available to the patient, but it was too tightly bound to nitrogen. In the 1960s, I recall discussing use of nitrous oxide with an anesthesia friend who admitted that he pushed the nitrous oxide concentration until the patient became slightly cyanotic. But this is asphyxia, which, if prolonged, can result in hypoxic brain damage.

E. I. McKesson, an early anesthesia pioneer, began an anesthetic with 100% nitrous oxide (O'Connor, 1990). The combination of the resulting brief anoxia with nitrous oxide rapidly induced anesthesia. He could then add oxygen and other agents. This approach was dangerous. The use of nitrous oxide in concentrations that limited oxygen to less than 20% was finally deterred after Courville (1939), a pathologist in Los Angeles, demonstrated that this resulted in catastrophic brain damage. Previously healthy patients who had received hypoxic concentrations of nitrous oxide for otherwise minor, safe procedures would suffer severe neurologic damage. Courville demonstrated microscopic areas in the brain of hypoxic destruction. His publication laid to rest arguments about the use of hypoxic concentrations of nitrous oxide.

Enough on early development of anesthesia and on to my early development.

Chapter Three: Run-away Toddler

Why did my active curiosity lead me into trouble as well as other directions? As I repeatedly discovered throughout my life, stimulation has been my ongoing motivation. Growing up in Chicago, at age 16 months, I began to run away from home. We lived in the 83d block on South Morgan St., a busy boulevard, and my family, including my two aunts (who lived with us during the depression in 1935) and my 5-year-old sister, kept a close watch on my wanderings. But I'd slip away, and someone would say, "He's gone again," and they'd start searching. They'd meet people on the street who'd say, "He went that way." I even crossed Morgan by myself -- unaware of traffic.

This behavior evolved as follows: my brother Don, 20 months older, developed a mild case of polio when he was three years old. His legs were weakened and he fell easily. I learned that I could give him a shove, he'd fall, and I'd take from him whatever I wanted. My father had had a tough, insecure life. He'd lost his mother at age 13, and quit school to support his work-injured father and younger brother. His present job as a printer was tenuous, saved in part by a depression craze for jigsaw puzzles. He was a strong Missouri Synod Lutheran and had been taught, as my siblings and I were later, that children's original sin needed to be punished, at times, harshly. So he began spanking me to correct my terrible behavior toward Don, to rid me of the 'evil.' Lutherans created rigid, strict responses. Later, I learned that Catholic kids had it easier, as the seven McCarthy's on our block put it:

"Do what you want, tell in confession, the priest takes care of it, and it's gone, no worries."

I began to leave whenever I could. I was subject to tough spankings for years, with resentment toward my father for decades. He used a bamboo stick when I was 5 to 10-years-old, terrifying me. My sister told me decades later that she and my two brothers told my father that this was overdone, but it didn't change things.

Migraine Headaches, Prostatectomy

At age ten, I developed migraine headaches. They begin as a scintillating scotoma next to the fovea, on either side. It's as though the sun is reflected off a rippling lake surface. If you close your eyes, it looks like a brilliant lightning flash that holds and holds. Most of mine affect the left visual field. A migraine's beginning is fascinating, except for the anticipation of pain. The beginning blind spot is small and next to the fovea. It can involve just one letter of a word, e.g., take the word 'date' --- you focus on the 'a' and the 'd' is obscured. You move your focus to the 't' and the 'd' reappears and the 'a' is

obscured. As the blind spot enlarges, entire words disappear. The scotoma gradually enlarges into a curvilinear shape, moves out to the farther reaches of that half of the visual field, and gradually fades. It's exactly the same in the visual field of each eye. The scotoma fades in about 45 minutes,. About 30 minutes later, the headache begins.

From my youth into my 30s, these headaches could be pounding and severe, on the side opposite that of the affected visual field, but sometimes central. I assume that this might be due to localized cerebral edema related to temporarily diminished blood flow. It lasted three to five hours or so, a crescendo-type of unbearable pain that broke dramatically with harsh retching and vomiting. It faded over the next two or three days.

As I aged, the emesis disappeared, and the headaches were generally less severe. These headaches occurred about five to seven times per year. I have had a few years in which I had no migraines at all, and they almost completely disappeared in my late 60s. I've thought over the years that emotions in part control these, as the abrupt release of suppressed feelings seemed to prevent a possible headache from occurring.

This was confirmed in fall, 2007: I developed localized prostate cancer and was scheduled for radical prostatectomy and pelvic lymph node dissection. I was fatalistic about it, and wasn't particularly disturbed, or so I thought. I hadn't had a migraine in a long time, but then had nine migraines in five weeks, six in the left visual field, more than I've ever had in a brief period. I've had none post surgery.

My migraines disturbed some of my youth and later life, but didn't prevent my achieving whatever I wished.

A Common Anesthesia Mystery

A common anesthesia mystery is simply how to control expected pain during emergence from anesthesia. When surgery is finished, respirations are depressed, to the point of apnea, and unconsciousness needs to be reversed, so that there is spontaneous adequate respiration, yet with minimal to no pain. The mystery is to judge when and how much pain-reliever to use: too little and the patient suffers, too much and the patient either doesn't breathe or cannot manage her/his airway. Furthermore, pain relievers are soon re-distributed from the blood to various tissues in the body, and their analgesic effect diminishes, requiring additional drug. This can be frustrating to those caring for the patient emerging from anesthesia.

As to my prostate surgery, my surgeon's analgesic approach eliminated immediate postoperative pain. I had opted for open prostatectomy for two reasons. First, the laparoscopic approach requires more time, and the elderly deteriorate during long anesthetics. Second, I wanted my surgeon to have a wide open view in case there was tumor spread. As to pain control, he introduced a new approach. He asked me to use Celebrex® the morning of surgery, and for four mornings thereafter, to diminish pain stimuli to the spinal cord. He also injected bupivicaine and epinephrine into the incision site prior to cutting, and again at wound closure. Now my anesthesiologist didn't need to consider the mystery of immediate pain control at emergence. Whenever I gave an anesthetic, I was personally always quite concerned at that point, because I prided myself on an awake comfortable patient at emergence. I awakened and my tracheal tube was removed in the operating room, although I don't remember it. I became aware immediately thereafter in the recovery room, and felt as though I was emerging from normal sleep. A wonderful emergence. I had no pain, was slightly hoarse, and didn't have a sore throat. Postoperative pain wasn't expected to be too severe, since my abdomen had not been opened nor my intestines explored. The incision was vertical, from below the umbilicus to just above the pubic area.

I did experience the vagaries of night-time hospital care. There is always concern about postoperative bleeding, so every four hours they checked my pulse and blood pressure, and every four hours they drew blood samples to check my hemoglobin. Unfortunately the sampling and pressure measurements were not coordinated, and occurred every two hours. In addition, the infusion pump for my intravenous fluids beeped a signal for air bubbles every 30 minutes or so, and, in between, my room-mates beeped. The charmer for fixing air bubbles was the nurse technician. This 20-year-old college student would answer our signal immediately, bubbling with good humor. With such irregular sleep, we talked. She was from a nearby small town. Her father was one of 18 children, and had married a woman with seven siblings. This charmer adored her family and said that family gatherings were just wonderful.

Sleep deprivation added up pretty quickly. On the day following surgery, I was really tired, and every time I closed my eyes, I saw a pattern on my eyelids that I'd never seen before. It looked like museum tapestry, gently fluctuating in and out. I went home the next afternoon, with just one night in the hospital. I hadn't needed any pain medicine. The museum tapestry pattern persisted for two days, as I caught up on sleep at home. How severe are the effects of sleep deprivation for long term patients?

I needed a mild opiate (Vicodin®) for pain relief the first morning at home (too much pain to get out of bed), and none thereafter. I hadn't been hospitalized since age 16, when I spent 122 days in bed for rheumatic fever, but that didn't involve pain or sleep deprivation.

Chapter Four: High School to College to Pre-med at the University of Illinois

During my sophomore year at Parker High School in Chicago, I was advised to take a competitive examination for the College of the University of Chicago. I was awarded a half-tuition scholarship and was a student there for two years, from 1949-1951. The college was the brainchild of Robert Maynard Hutchins, who mixed humanities, social sciences, science (physics and chemistry), and mathematics (analytic geometry and calculus) as a more or less standardized curriculum. Attendance to class was optional and not taken -- we had tests during the year, but our final grade depended entirely on the year-end comprehensive exam, three hours in the morning, and three in the afternoon. Our athletics involved beginning level gymnastics, and soccer on historic Stagg Field. We were warned to spend little time near the west stands (later removed), as the world's first atomic pile had been built under it in 1942, and residual low level radioactivity remained.

My grades were not good enough to maintain my scholarship and I switched to the University of Illinois Chicago branch on Navy Pier with about twelve hours of college credit, and started my pre-medical education. To help pay expenses, I worked part-time as an evening hospital orderly at Michael Reese Hospital.

Personal Values; Michael Reese Hospital, Chicago

I had begun working odd jobs at age 10. First was delivering Hunding Dairy milk with our neighbor, the wonderful Dan Herzel. I was hoping for more than the 10 cents/day that he offered, but I wanted to do it. I arose at 4-5 am, accompanied Dan to get the loaded milk truck at the dairy on east 71st St., and helped deliver the milk. On one occasion, while delivering to a delicatessen on 70th St. just east of Morgan, a horse-drawn open wagon stopped next to the milk truck. These wagons went up and down our alleys, and the driver repeatedly called out what sounded like "rags-a-lion" which was for 'rags and old iron.' Dan's door of the truck was open and, when the gelding peed gallons, it splashed on the pavement, into the truck, and behind Dan's seat onto the milk bottles. We returned to the dairy for a new truck and a day of delayed deliveries. Dan made a great impression on me, and I delighted in the fact that he valued me as a helper.

In time I realized that an extra-curricular education can be more valuable than a formal one. My further insight was that value is earned; you cannot chase it. At age 12, I delivered the Southtown

Economist, a non-daily neighborhood paper, to homes in the Englewood area. I was surprised how much I was paid, perhaps $15 a month. I set pins at the bowling alley of our St. Stephens church's recreation hall, not good pay. While at the University of Chicago, I worked as a clerk at the prestigious University Press, impressive, well run, with great concern for me and my education. My next job began my exposure to medicine.

Michael Reese hospital is at S. 29th St. and Ellis, one block east of Cottage Grove, just west of Chicago's Outer Drive along the lake front, and just south of what is now McCormick Place. The main red brick hospital, on the northeast corner, was about nine stories tall, with the entrance on its diagonal front facing the southwest. Meyer House, a several story red brick building across 29th St. and to the south, was the costly private hospital for the well-to-do.

My shift as an orderly was an adjustable 3-11 pm, and included preparation of all male patients scheduled for surgery on the following day. This included the surgical prep -- shaving of the prospective surgical skin area -- and enemas 'til clear -- soapsuds enemas until the fluid returned clear of pigment. My first surgical prep was to 'shave the perineum.' I'd never heard of that term. An intern explained where it was and that the prep needed to include a larger area for adequate cleanliness: shaving included the medial portions of the buttocks, scrotum, and sometimes the pubic area.

Another function was to move deceased patients to the morgue. I'd help a nurse's aide wrap the body and fasten ties to hold it securely, and then take it on a wheeled stretcher to the morgue refrigerator. Once, as I was transferring a patient onto the tray that slid into the refrigerator, I noted that his nose had bled sometime after we'd prepared him up in his room. I was shocked, wondered if he was truly deceased, and then relieved to learn that this was a not uncommon postmortem event. Interestingly, the seats for the morgue used for viewing an autopsy were accessed via an unmarked, unlocked door on the first floor, where anyone could wander in. I regularly watched when I could.

A polio epidemic in summer 1952 hit the Chicago area, and Michael Reese Hospital staffed a ward for patients needing a ventilator. We had an entire area of bulbar polio patients in iron lungs, 8 or 10 patients at a time. I delivered oxygen tanks and Drinker ventilators (iron lung). We didn't routinely wear masks or take undue precautions, although we did wash our hands. Amazingly enough, none of the orderlies or nurses caught polio, and, of course, none of us were immunized.

The Reese buildings had underground tunnels connecting them, for ease of transport of oxygen tanks, stretchers, iron lungs, and deceased to the basement morgue. Meyer House, as a preferred location, didn't move patients through basement tunnels. There was a second story passage way above

29th St. from Meyer House to the main hospital for transport to departments such as surgery or radiology. Main hospital's open unroofed four-east porch was great – four-east being the hospital area on that floor facing east toward Lake Michigan. Michael Reese was close to the Outer Drive going along Lake Michigan; the porch had a great view of the drive and the lake. We viewed the lake whenever we could, as the elevated open space promoted relaxation and ease.

As I was coming to Michael Reese one afternoon to start the 3 p.m. shift, and exited the Cottage Grove streetcar, I saw that there had been an accident. A well-dressed African-American woman had been hit by a streetcar. She had a head injury, was unconscious, and was being taken to the Michael Reese Emergency Room, one block away. I followed her there. The emergency room resident knew that I was a premedical student, and explained what was going on. The woman had recovered consciousness and now was sinking back into a coma. The resident said that this was classic for an acute epidural hematoma. She needed an emergency craniotomy as soon as possible

So I said, "Well, then she'll be going to surgery."

He said, "No, they won't care for her here. She'll be sent by ambulance to Cook County Hospital."

He added that the delay in transit meant that effective care would be late, but that was official policy. African Americans were routinely cared for at Reese, many as charity patients, but not for emergency surgery. I had had black friends for years and was appalled at this 'real world.' I played intra-mural basketball at school, and half our team was black. I didn't discuss this with anyone, and felt helpless. Things had to be better than that.

It's amazing how naïve I was then, and how little was known about homosexual contacts, precautions, and awareness. A Michael Reese pharmacist assistant was my first, me, unprepared and unsuspecting. When I walked past the pharmacy, he was overly friendly, and in time invited me to a movie. I declined. A few days later, he asked me to help lower a window blind that wouldn't move. While I fixed it, he stood behind me and pinched my buttock. That ended our communication.

One night, near the close of my shift about 11:30 p.m., I was paged. The paging system involved overhead screens in all wards and corridors so we could be contacted immediately, if we watched them. This was for emergency surgery on a man with penile bleeding, likely due to prostate problems. I went to his room and shaved the surgical area. That was the end of my shift, so I went to the operating room visitors' seats and watched the surgery. The surgeons were vocally amazed that anyone would watch

such routine surgery. They incised his lower abdomen, opened his bladder, and controlled the bleeding. Surgery finished well after 11 PM, when my shift generally ended.

I left Michael Reese about 1 a.m. and headed home. The Cottage Grove streetcar dropped me at 71st St. so I could head west to home on Princeton Avenue. However, the bus route on 71st had ended several hours earlier. I began to walk home along 71st St., a distance of about 1.5 miles. It's amazing now that I never considered phoning home for a ride.

Now began my only other homosexual encounter. Within a few blocks, a man offered me a ride. I was tired and took it. He was driving an older car in poor condition. He drove quite slowly, rather atypical. When we neared Princeton, he slowed even more, and said that we could get along fine and that he'd give me oral sex. I declined, and he continued past Princeton. I told him, no way, and he finally stopped by Stewart, because there was a stop sign. I told him, sorry (I can't imagine to this day why I said, sorry) and walked home. I was now beginning to recognize these unusual people and could more easily avoid such interactions. I told no one about these encounters.

This Michael Reese orderly position and my Navy Pier premedical education overlapped. When I applied to medical school, the nursing department at Michael Reese wrote me an excellent recommendation.

University of Illinois, Chicago, Navy Pier, 1951-1954

Can you imagine a college with a mile long single corridor with classrooms on either side? It was a wonderful solution for college for those who could not afford the downstate campus at Champaign/Urbana, or Northwestern University. Fig. 2. (Reprinted with permission from College History Series, The University of Illinois at Chicago, A Pictorial History, 2000, by Beuttler FW, Holli MG, Remni RV. Available from the publisher online at www.arcadiapublishing.com or by calling 888-313-2665), Figs 2-4 are from pages 49 (Fig. 2), 54 (Fig. 3), 16 (Fig. 4).

The college occupied the north, or left, half of the Pier. The south-half was for city functions and conventions. The restaurant convention was there every spring, and we students, not eligible to attend, did our best to invade their food exhibits. It's tough to describe Navy Pier as a college, and I borrow from a description by a former student, Wayne Klatt (2004). Navy Pier, the college, was a drab, cramped substitute for a Chicago campus of the University of Illinois. This $4 million freight terminal and exhibit hall was built by Mayor Big Bill "the Builder" Thompson and opened June 25, 1916. The pier itself was

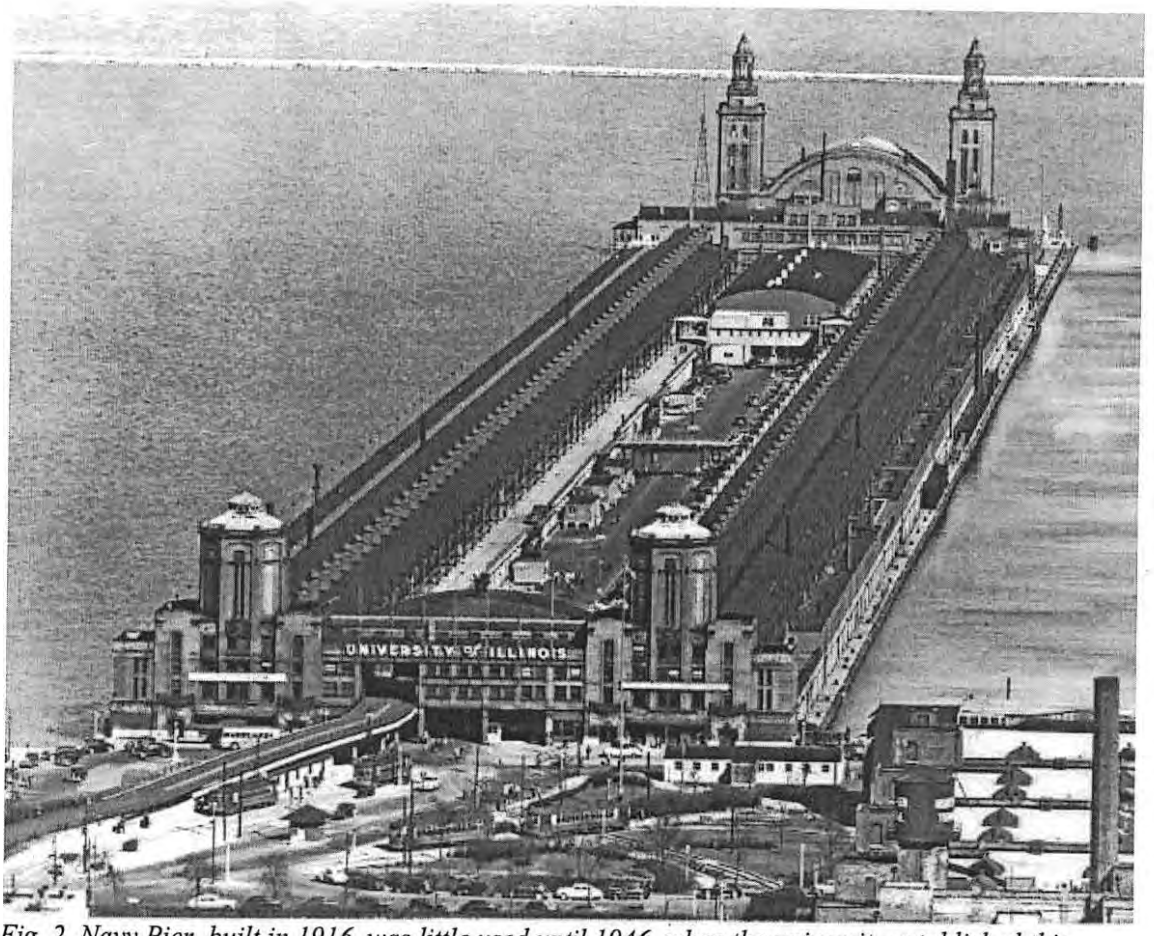

Fig. 2. Navy Pier, built in 1916, was little used until 1946, when the university established this branch. The present filtration plant (to the left) has not yet been built. The huge Quonset hut gymnasium is out of sight to the lower right.

renamed Navy Pier to match the newly built Soldier Field, but by 1921 the Chicago Tribune was calling it a "white elephant."

When World War II ended, thousands of young men and women across the country needed a university. The Illinois legislature, alarmed by severe overcrowding at the downstate campus, suddenly remembered that there were people in Chicago who also needed education. Workers sectioned off the northern tube of Navy Pier into 52 classrooms and 22 laboratories separated by Beaverboard (a variation of plywood) uniformly painted battleship gray. We were going to school in a long, narrow, one-and-half story human warehouse.

In the overcrowded years of the 1950s, there was no room to do anything except keep up with the crowd as students moved past the iron pillars like a slow-moving stampede that was set off every hour. There were no adornments, no hallway windows. The corridor ran between the long rows of classrooms; the north classrooms looked out on Lake Michigan (before the filtration plant was built); the

south windows looked out on the central roadway that serviced the north (university) and south (commercial) tubes. There was nothing to provide a distraction from the gray rooms and bland single corridor except a biology exhibit consisting of a glass-enclosed snake that was fed a mouse once a week. You could tell when the snake had eaten last by the location of the bulge in that coiled, scaly body. If the bulge was near the mouth, it was Monday; if at midpoint, Wednesday; if smaller and near the tail, Friday. Maybe that kept us in a morose mood.

During winter, the bitter cold of our classrooms was still better than braving that hellish wind off the lake. The wind off Lake Michigan also blew huge waves onto the faculty parking lot – whose privilege was to be closest to the entrance – this resulted in thick sheets of ice across the fronts of their cars, which couldn't be started or driven for several days until the weather warmed. The Pier was satisfying – we earned our way into higher education cheaper than any other way -- the students had a rare camaraderie working toward these goals. When we registered for classes, we used the massive Quonset hut-shaped gymnasium just southwest of the entrance to the Pier. Fig. 3. (See permission, Fig. 2; this figure is from page 54 of the source.)

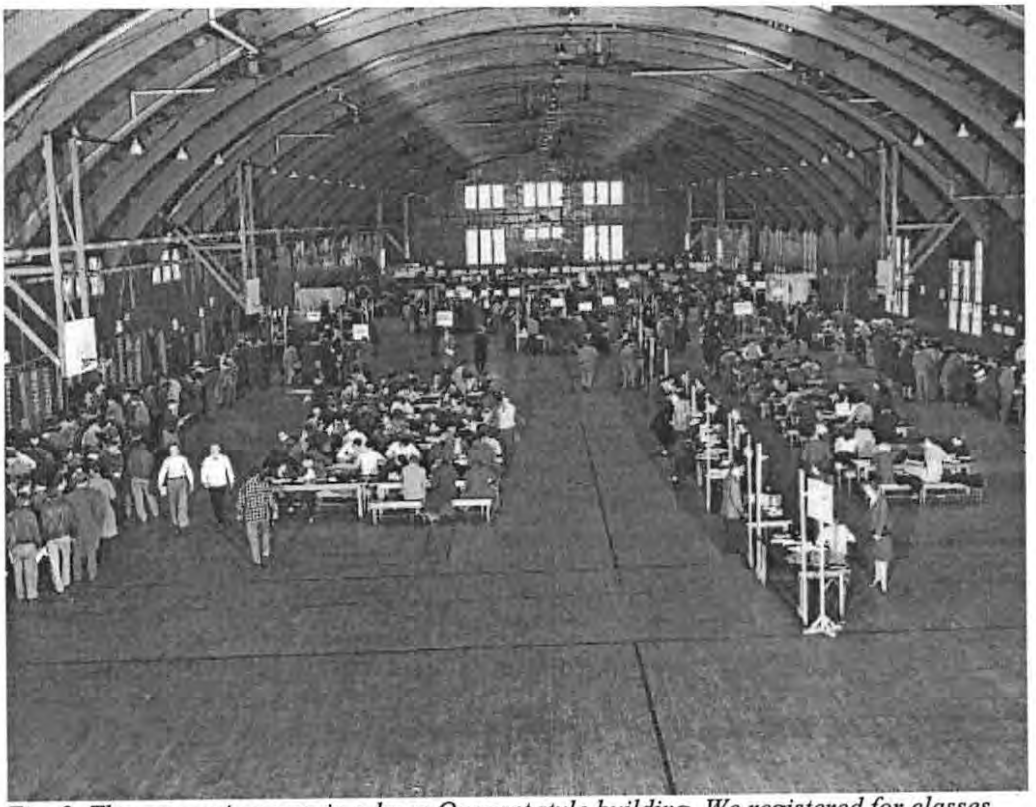

Fig. 3. The gymnasium was in a huge Quonset style building. We registered for classes, waiting in line for each specific class in a given subject. Once a class filled, we switched to another line for another class in the same subject.

When our orienting academic addressed our class of 400 premed students, he advised that 10%, or 40 of us, would eventually be admitted to medical school. This proved true. Navy Pier was not a major school and the student body not exceptional. There was a flood of veterans entering college under the GI Bill, eager for an education, but in general, not well prepared.

I had an introductory chemistry course in my first year. The lectures were enthusiastically and comprehensively presented by a retired chemist, whose name I cannot recall. He received royalties for techniques and procedures that he had developed and didn't need to work. His chauffeur dropped him off at the entrance to the Pier each lecture day and picked him up afterwards; it was elegant. I finished with a 4.58 grade average (5.0 was perfect), about 4th or 5th among premed students. I applied only to and was accepted by the University of Illinois College of Medicine at Polk and Wood Streets, near Cook County Hospital (3600 bed charity hospital) in Chicago.

I don't recall any family influence toward medicine. I had thought of being a teacher, which I later was, but the several teachers among my relatives suffered financially. I excelled at math and science, and believed that medicine would involve stimulation, satisfy curiosity, and be fulfilling.

I commuted by streetcar and the Englewood subway to downtown, and transferred to an elevated train above Chicago's loop that traveled west to the medical school. The loop, more or less a square, is formed by the dirty, soot-infested elevated rapid transit tracks above four streets: east-west Van Buren, north-south Wells, east-west Lake, and north-south Wabash. The major portion of the downtown businesses was included within the roughly mile square loop. It's a bit longer north to south than east to west. It includes the Board of Trade Building, Marshall Field's (now, disgustingly, Macy's), the Palmer House Hotel (now a Hilton), and the ancient Chicago Theater, south of Lake Street. The State and Lake Theater, directly across State Street to the west from the Chicago Theater, is long gone.

During college and medical school, outside jobs helped with expenses. US Steel South Works was another summer job during premed studies, which paid better than Michael Reese. My shift work hours, a week at a time, were rotated: 12 midnight to 8 am, 4 p.m. to 12 midnight, and 8 a.m. to 4 p.m. With this pattern, I didn't miss a day of work because of a shift change.

South Chicago Steel Mills

U.S. Steel South Works was a huge operation, located in far southeast Chicago on Lake Michigan. It began just south of 79th St. and extended for about two miles, to 95th St., and inland about ¾ mile. It used Calumet Harbor as a docking depot for iron ore ships from the Great Lakes and had about

17,000 workers on 3 shifts. There were blast furnaces for melting the ore and separating the steel, and rolling mills for rolling the resulting ingots into sheets of steel of varying quality. The quality was determined by a mix of elements in the molten steel to make various metals such as chrome and stainless steel.

I worked in the 44 inch (1.13 meter) slab mill, which rolled ingots of cheaper steel. Occasionally, it rolled chrome or other types, and that brought out the bosses, even in the middle of the night. They did not want expensive steel to crack in the rolling mill, which happened if the ingot wasn't evenly and deeply heated.

I had good pay, particularly on holidays. Regular employees wanted holidays free, so I worked a 16-hour shift on Memorial Day and Labor Day. I received double time for a holiday, and time and a half for the second eight-hour shift, which meant five days' pay for one 16-hour workday. The mill entrance was off 83d St., with of course a tavern within half a block. The crowd of men at each shift change was huge, and many stopped off at the tavern coming and going, particularly going, on payday. Occasionally, one could come to our shift drunk and all would cover for him, as mill workers were loyal to each other.

Our mill pit floor was oriented east-west, and the view of Lake Michigan from the east end was great, especially at sunrise near the end of a 12 midnight to 8 AM shift. The rolling mill was perpendicular to the pit floor, pointing south from its middle portion. Once ingots had been rolled into sheet steel, rollers moved it into the yards for cutting into lengths for shipment. The pit floor was about as large as a football field (100 yards by about 60 yards, or 92 by 55 meters).

There was an overhead roof with incomplete side walls extending down from it, to help dissipate heat; this open area provided our view of Lake Michigan. The pit floor had about eight or ten large gas oven pit furnaces imbedded in it, each with a sliding 30- by 40-foot cover on top. Each furnace could hold about 10 ingots. These furnaces were lined with coke, and heated to about 2500° F (1370° C) to re-heat ingots for milling. Red hot ingots from a blast furnace several blocks away were transported to the slab mill on an open flatbed train. They glowed brightly at night while in transit. These cooled once outside the blast furnace, and their outer edge formed a tough crust, so they were re-heated in the pit furnace until they had a uniformly even red hot appearance, to insure smooth milling without cracking.

I was a temperature recorder, and read ingot temperatures with an infrared device to determine even heating; I opened the pit furnace door several feet to view the ingots. To prevent skin burns from the intense radiant heat, we wore long sleeved flannel shirts and thick gloves, regardless of

the season. When the ingot was heated appropriately, the pit door was opened wide and an ingot transferred by a 50 ton overhead crane to the rollers taking it into the rolling mill. The ingots were about five feet tall and about three by four feet in width and depth. I remember one African American who worked one of the overhead cranes that moved ingots from the pit furnace to the rolling mill, a high paying job compared to most of the 44" slab mill jobs. While he was operating the crane, the other operators complained that his sweaty body odor left it overly 'smelly.' I argued that that was nonsense, that he didn't smell when he sat in the break room. These occasionally hostile ready-to-fight workers didn't regard me as competition and merely told me to quit being a college smart aleck, although their phrases were more colorful.

Two men, a roller and a manipulator, controlled the 20 ton rollers from a glassed-in observation room about 15 feet above the rollers. I went up there frequently to watch. The ingot's tough outer crust, now re-heated, was fragile, and literally exploded on its first pass through the rollers, spraying hot steel fragments 150 feet or so in every direction, some back onto the pit floor. When an ingot was entering the rolling mill, we took shelter behind human-sized curved steel shelters, and could hear the fragments bounce off the outside. My father had worked in the mills as an 18-year-old in 1923 and once had a red hot fragment land in the back of his shoe, burning his foot. Needless to say, all areas were always hot.

The red hot ingot was manipulated back and forth and side to side to stretch it out into a sheet of steel approximately ¼" thick, about eight feet wide, and 60 feet-80 feet long. Once evenly rolled, the sheet steel was transported by rollers into the next portion of the mill for cutting, stacking, and shipping.

Because of the heat and dryness, heat exhaustion was a constant risk. Fountains provided water, and we in addition could eat jelly candies containing salt and sugar. We were advised to take these candies at regular intervals or whenever we felt peculiar. These were effective, for, in a few minutes, we felt a sudden burst of energy. Regardless of the season, the pit floor was always hot and dry, with constant heat radiating from the pit furnaces. We wore heavy work shoes with wool socks.

I enjoyed these jobs; they were fascinating, helped pay for my education, oriented me toward medicine, and, in time, anesthesia.

Chapter Five: Medical School, University of Illinois, Chicago

As he began his presentation for our entering class of 160, our orienting professor said that a physiologist needed two students to work in her laboratory. Gerald Hammond and I agreed, and worked 20 hours per week in her laboratory the entire four years of medical school. Our work in the laboratory of the endocrinologist Neena B. Schwartz, Ph.D. in part involved anesthetizing rats with ether. In performing an experiment, we would place a rat in a closed beaker containing ether, transfer it to the laboratory table when asleep, and perform a tracheostomy. We would excise either the thyroid gland or the adrenals. Our research team reported responses with various drugs and with changes in temperature (Schwartz et al, 1957, 1960).

Fig. 4. Chicago's west side medical center, 1940s
#10 Cook County's Main Building, with 4 south-directed wings
#16 Contagious Diseases
#15 Medicine, 8 floors of 110 bed wards
#11 Pediatrics
Center of Photo: Power Plant – with smoke
#14 Tuberculosis
#13 Cook County Morgue
#12 Psychiatry
#1, 4-6 University of Illinois Medical School

Dr. Schwartz's research laboratory was on the second floor of the medical school building facing Polk Street, directly south of the city's Cook County Hospital grounds. The medical school teaching hospital, R&E (Research and Education), had some 300 beds (below and out of the picture in Fig. 4. (See Fig. 2 for

permission; this figure is from page 16 of the source). Cook County, or County, was the charity and emergency hospital for the city of Chicago. It had 3600 beds in separated buildings: the Main Hospital building (Obstetrics, operating rooms, Emergency Room), Internal Medicine, Pediatrics, Contagious Diseases, the Psychiatric unit, and the County Morgue. From our laboratory, we looked directly across at the morgue, and the Psychiatric Unit was to our right. The Psychiatric Unit was for temporary stays, while the patients were being evaluated regarding their more permanent disposition, e.g., returned home or committed to a psychiatric hospital.

County had underground tunnels connecting all the buildings. The tunnel going south from the main hospital building ended at the morgue, so, in bad weather, to leave County, we'd take the tunnels and exit through the morgue instead of walking outside. There was a Catholic chapel on an offshoot of one of the tunnels. It had all the required incense and mystery – incongruous in the setting of dirty poorly lit rough concrete walls. County at that time had no security guards, and people were all over it all the time, day and night. The pediatric building was restricted as to visiting hours, but no other wards. Elevator operators were there as political jobs --- the elevators were automatic. More on Cook County later, now back to the medical school.

In addition to my job as a laboratory technician, I supplemented my income by being a guinea pig. One experiment, for which I was paid $50, involved an examination of the efficacy of the common cold virus in a cold atmosphere. Ten of us sat on metal chairs for an hour in a room at 35-40° F, wearing a light sweater. Half were inoculated intranasally with the virus and half with saline. I eventually found out that I received saline. I don't know if the study was valuable but the money was.

I did this one other time, for $75, in an evaluation of the effectiveness of artificial ventilation in an anesthetized paralyzed human, using the then prevalent arm lift, back pressure technique. This discarded technique involved placing the victim in the prone position; the resuscitator knelt at the head and pulled both arms from the sides toward the head, then pushed both palms on the back of the lower chest, the former to aid in inspiration and the latter to aid expiration. Dr. Archer S. Gordon was the senior researcher. I received intravenous thiopental, had my trachea intubated, and had a steel needle placed into my femoral artery. They used an ear oximeter to evaluate the adequacy of oxygenation, as well as measured oxygen and carbon dioxide levels in my arterial blood.

When I emerged from the thiopental, I discovered firsthand the long tail of depression that results from large doses of thiopental. Despite being awake and intelligently responsive, I couldn't

prevent myself from falling back into intermittent deep sleep for 16-18 hours following emergence. My groin and trachea were quite sore.

The arm lift back pressure method of artificial resuscitation was discontinued in time for the improved mouth to mouth technique, but I'd seen its effectiveness prior to my being a guinea pig. In summer 1955, between my freshman and sophomore medical school years, I had taken my 5-year-old niece Phyllis to Lake Michigan near South 57th Street, walking along the large flat rocks at the water's edge. A passerby noticed that there was someone out in the lake, some 100 feet or so, flailing his arms. No lifeguard was near, so a teen and I swam out there after I'd stripped to my shorts. We pulled this man in his 50s to the rocks and discovered how difficult it was to lift a limp, soaked, dressed adult up out of the water to the rocks some 2 feet above water level.

With help from others, we finally lifted him onto the rocks, and I began arm lift back pressure resuscitation, realizing immediately that, for some reason, I wasn't moving any air at all. At that point a lifeguard dashed up and took over. First, he swept his hand inside the man's mouth and removed his false teeth. After that, ventilation was effective, the man awakened, and I was ashamed at my ignorance about airways. All my education toward care of people, and not yet any practical knowledge. Phyllis, meanwhile, was tugging at me, really wanting away from there, so we left.

I phoned the local hospital the next day to see how he was doing, and was told that he was quite upset because he'd been trying to commit suicide.

Research Chicanery – Polio Vaccine

Our chief of medicine Harry Dowling addressed our entire freshmen class in spring 1955. He began his presentation with the comment that there was developing a significant and major medical news item, for which we needed background information to provide balance to our opinions regarding this breakthrough.

He began with history: the National Institutes of Health had been funding a number of laboratories in the quest for a polio vaccine. He described an NIH coordinated effort planned by the virus scientist John Enders to perfect a polio vaccine. Preliminary studies had demonstrated a series of parallel avenues to pursue. These avenues, for efficiency, were cooperatively apportioned for NIH and the National Foundation for Infantile Paralysis by the internationally known epidemiologist Thomas Francis (Taber, 2005) as a mass search among ten capable laboratories, each qualified to identify an effective vaccine.

As Dr. Dowling told us, it would have been a waste of time and effort for each laboratory to follow each individual potential avenue. Therefore, the various laboratories were divided as to purpose and each was assigned a certain path, without knowing which lead was most likely to be successful. All were delighted that one laboratory was now successful in investigating its lead, and a news conference was planned for the next morning to announce this major advance and to delineate the results of a cooperative and unselfish effort among a number of laboratories. However, as Dr. Dowling solemnly told us, this news conference was now cancelled, as the single successful laboratory had scheduled its own news conference for this very afternoon, without consideration of the cooperative directed efforts among laboratories.

Thus Jonas Salk announced his discovery of the polio vaccine and how his laboratory had successfully achieved this. Dr. Dowling told us that we should form our own opinions in evaluating Salk's decision and that Salk's scientific honors would be somewhat limited. However he expected that Salk would be otherwise strongly rewarded (Oates, 1995). Salk's project was basic routine virus research, described by Salk's competitor, Sabin, as 'kitchen chemistry' (Obituary, Jonas Salk, 1995). Salk received neither a Nobel Prize nor election to the National Academy of Sciences, but did receive generous private funding for a well-regarded laboratory.

The Unforgettable Patient, Who Teaches You

Some patients you don't forget: "The career of every clinician is punctuated by a few formative cases" (Goldberg, 2001). I spent three months in a pediatric clerkship at R&E hospital during the spring of my junior year, 1957. During the first six weeks, while on the pediatric ward, a 20-month-old white boy was admitted for failure of mental and emotional development. This boy had an indelible effect on me as well as others.

Initially during his two week stay, he was quiet, virtually mute, and a loner. As nursing and medical personnel played with him, held him, and stimulated him, he began to blossom. By the end of the two week period, he was running around the ward, talking very well, laughing, and interacting. He was the star of the pediatric ward and obviously intelligent. We sent him home with great feelings of satisfaction.

Several weeks later, while I was in the outpatient clinic, his mother brought him back for his followup visit. He was a disaster, as he was now exactly as he had been when first admitted to the hospital. His home environment had prevailed. What was his later life like, and how did he eventually

use his intelligence? Had we wasted our time, or would the brief awakening of our ward life in time influence him beyond his home environment?

A Woman Dies

This 28-year-old woman entered the hospital with an infection that had turned into a raging sepsis. We could not find a cause and she swore that she knew of nothing that might be causing it. She died after several days of intensive treatment. Her autopsy disclosed a uterine infection related to a 'back room' abortion. Her husband related that they had three children and could not hope to afford another child. She apparently was psychologically unable to disclose what had happened, regardless of circumstances or outcome.

Cook County Hospital

Cook County Hospital was a parallel to Charity Hospital in New Orleans, the latter nicknamed the "Big Free". County was over-crowded and under-staffed and maintained through the efforts of dedicated nurses, residents, interns, medical students, teaching staff, and recovering patients.

For example, the eight floor building for internal medicine patients had a 110-bed ward on each floor. The beds were lined up side by side, 55 on each side of the ward, with two semi-private rooms near the nurses' station for sicker patients. By day, there was one nurse per ward; at night, there was one for the entire building. She did not have time for direct patient care, but could provide medications to those who needed them. We as medical students were impressed with the dedication of the nurses, as they stayed well past the end of their shift to finish giving meds or helping specific patients. Patients who were improving and ambulant routinely helped with nursing care. This is quite unusual now, but non-paying ward patients were grateful, friendly in general, and helpful. We medical students learned from the huge population and helped where we could.

One unique event involved an elderly Chinese patient, who spoke minimal English. He was recovering from an internal medicine disorder, and ambulatory, when his behavior changed. He continued to be his good-natured self, but now tried to give what little money he had, mainly change, to anyone who would accept it. We told him that he'd need it once he was again outside the hospital, but that didn't deter him. After he'd disposed of it, he lay down on his bed. Fifteen minutes later, he was dead, without evident cause.

Another example of Cook County's amazing health care was normal uncomplicated obstetrics, another 110-bed ward. Fifty women delivered every day, and, in two days, the ward was full. Those

doing well went home, and the others were transferred to a 'complications' ward. My 1957 summer job was as a 3-11 p.m. nurse technician in the fourth floor obstetrical delivery suite at Cook County Hospital. My function, not that of a nurse, was to facilitate where needed in the 50 deliveries per day, yes, 1500 per month, 18,000 per year.

There were four delivery tables in three delivery rooms, a totally inadequate number for that volume. With this incredible volume in a tiny facility, there were many urgent deliveries: in the hallway, coming off the elevator, and in the 'labor line' -- the 15-bed-room where the mothers waited until ready for delivery. We had occasional relief from obstetric stresses with our north-facing windows that overlooked the newly opened Eisenhower Expressway. After a severe June rainstorm, the freeway flooded, because leftover straw floated into and plugged the sewer system. We could see the tops of the stranded cars.

In these obstetric patients, pre-eclampsia was a frequent problem, with high blood pressure and various side effects. County treatment for pre-eclampsia was the Stroganoff method: morphine plus magnesium sulfate, given until the mother was groggily stuporous. This was effective because it kept blood pressure closer to normal limits, controlled muscle responses, and didn't require sophisticated equipment for administration. In that area, things moved quickly and nursing and physician staff had to make rapid decisions, as well as not be encumbered with equipment requiring close supervision. Their activities were directly focused on their patients.

The newborn infant of a Stroganoff-treated mother was opiate-obtunded, with markedly depressed respiration, and the obstetric resident would call for reversal with levallorphan (Lorfan®), then the popular reversing agent, to stimulate respiration. While awaiting the effects of Lorfan®, the resident used a slightly stiff brown woven tube to intubate the trachea tactilely (finger guidance – they did it impressively well), and gently breathed mouth to tube for the baby until the intra-muscular injection of levallorphan took effect. We flowed oxygen into the resident's mouth for expired gas enrichment.

A final Cook County example was a patient room in the eight floor pediatric building for babies with hydrocephalus. There were about 15-20 babies there, in individual cribs, with pumpkin-sized large heads, small faces, and tiny eyes. At that time, mid-1950s, this could not be treated, as shunt procedures were not yet developed. Without treatment, the babies' heads slowly enlarged. With their huge heads and tiny eyes, they could only lie on their backs, unable to lift their heads. They were given good care and feeding but in time could not survive. The skin on the back of the head developed bed

sores, and became infected. They were so inactive due to the weight of their heads that they were in poor condition to ward off any health stresses -- a tough ward to be on as a medical student.

Cook County Hospital is now closed. The replacement hospital, built several blocks southwest of the old one, has 464 beds, and is named for John Stroger, the present Democratic President of the Cook County Board -- typical Chicago politics.

During my summer as a nurse technician on the obstetrics labor line, I met Pat Sparlin, a student nurse on her evening teaching rotation. We were engaged within three weeks and married five months later, December 26, 1957. I first noticed her caring for patients in the labor line, attentive to patients, but also watchful of everything that went on. As was routine in the delivery area, she wore a full cap that hid her hair. Her face had a fabulous tan, which I later learned was due to a recent one week vacation in Salt Lake City with her widowed mother. Seeing her tan, I had decided that she was another of those young women with bleached blonde hair to go with the habit of soaking up sun on every possible day. To my surprise, when she took off her cap at the end of her shift, she had dark hair generously sprinkled with gray. I realized that this 5'3" 161 cm 21 y/o woman was remarkably attractive. At the first opportunity when our shift ended, I asked her to the Greek's, the hangout across Harrison Street from the hospital, for a hamburger. I learned that she was from Lewistown, Montana, and interested in everything about Chicago. Our first date was to the Indiana Dunes State Park at the southern tip of Lake Michigan, with its great beaches. We became serious rather soon.

Chapter Six: Medical Learning

Shifting Dullness, Twice a Diagnostic Tool, Not Pleasant

As a senior medical student on OB in January 1958, while caring for a mother in labor, I noticed via abdominal palpation that her uterus had become hard and rigid, and the baby's heart sounds had disappeared. I was pretty certain that it was *abruptio placenta*, with intense hemorrhage under the placenta and loss of blood and oxygen to the baby. My OB resident and faculty member confirmed this. I monitored her, expecting delivery in time of the dead fetus, repeatedly evaluating her abdomen and uterus by palpation. After several hours, I detected fluid between her uterus and her abdominal wall when she was lying on her side. She had shifting dullness, indicating free fluid in the peritoneal cavity.

After some disharmonious discussion among faculty, the decision was that this was blood and that surgery was necessary. There were two or three units of free blood in her abdominal cavity. She recovered physically without incident, and we counseled her as well as we could regarding the loss of her baby. My observations in her case earned me a grade of 'A' in OB. But within six months I had a grimmer case of shifting dullness, during my internship in St. Louis.

About 40 of my medical school classmates interned at St. Louis City Hospital. During my month in the emergency room, I saw a young woman; she and her husband were concerned because her skirts had been getting tighter and tighter, with no change in weight or eating habits. They had seen their family doctor who had said not to be concerned. She appeared healthy and there were no palpable masses. Examination in the supine and lateral positions disclosed shifting dullness, and I referred her as a patient with ovarian carcinoma and peritoneal metastases, later confirmed. A depressing evening!

City Hospital # 1 (Starkloff Memorial) was an older building, Catholic-oriented because St. Louis was. It had been built prior to use of antibiotics, so its wards were separated. While Cook County had separate buildings connected by tunnels, St. Louis City was on a smaller scale and had first floor connecting passageways between wings. The building was a darker red brick; seen from the south, there was a central building with 150 foot passageways going east and west to other portions. St. Louis was hot and humid, and the only air conditioning was in the hospital library. When we were scrubbed and gowned for surgical cases, we were incredibly uncomfortable in gowns and paper masks; nurses stuffed towels soaked in cold water down our backs.

The hospital has now been converted to condominiums (Greenfield, 2007). It's called the Georgian, with 104 condos ranging from $175,000 to $320,000. It was 75% sold as of October 2007, and a two-bedroom 1350 square foot unit sold for $240,000. A far cry from what it was like when I was there in 1958-1959.

Pat and I lived in a 9 story large reddish-tan brick building in the Pruitt-Igoe city housing at 1300 S. 14th, now gone, one block north of the hospital, on the east side of 14th. She worked as a pediatric nurse. I earned $150/month, Pat about $300/month, and we paid $40/month rent. Our 9th floor apartment, #903, is just above Pat's right shoulder, Fig. 5. We looked east toward the Mississippi River and August Busch's Budweiser brewery, which provided a constant strong beer processing 'fragrance' all year long. There were 4 apartments on our square of concrete right under the roof of the building.

Fig. 5. Pruitt-Igoe housing project in St. Louis in 1958

Our apartment was in the southeast corner, a white couple's was directly north of us on the northeast corner, a young black couple was just west of us, and a young black family was diagonally opposite us on the northwest corner. The latter family was particularly nice, and kept their ten children carefully distant from the rougher kids in the housing complex. The parents were our age; their tenth child was born about a month or so after we arrived. When Brian was born the next March, the mom was a 'pro' in aiding Pat with breast feeding.

We couldn't see the river, but we could see the Mac Arthur Bridge to the northeast, now closed. The St. Louis Arch was built years after we left there. The elevator serviced floors 1, 5 and 8, so moving

our furniture in and then out a year later, was mixed with carrying everything up or down one flight of stairs. We had no air conditioning (inadequate wiring) and modest heating. We used tepid water in the bathtub to cool us in summer and warm water to warm us in winter. The humid climate intensified both heat and cold.

Without a car, we walked all around our mixed racial neighborhood. While it wasn't a great area, all knew that local white people had medical functions and provided their medical care, so we were never bothered. Lafayette Park was nice with beautiful flowers in season. We took the Chouteau Avenue bus west to the wonderful Forest Park. St. Louis had a beautiful old fashioned railroad station, now remodeled. Since Pat's nursing school education finished 6 weeks later than the start of my internship on July 1, each week she took the train to Chicago on Sunday afternoon and returned on Friday evening. We walked the mile and a half to and from the station.

Measles-related Disaster: What Seemed Obvious Wasn't True

St. Louis had a serious measles epidemic in early spring 1959 and we saw several cases of measles encephalitis. We regularly performed spinal taps on measles patients so we wouldn't miss the easily treatable case of bacterial meningitis, but found none. When the next case came in, we decided against a spinal tap, since this boy was recovering from measles. He died of bacterial meningitis --- we had missed the diagnosis.

Emergency Room Drunks

Drunks were a logistical problem in the emergency room. There were quite a few and some were injured, although that wasn't always evident. They'd be brought in by the police for evaluation. If they weren't injured, they were taken to jail. If an injury was missed, and the drunk deteriorated in jail, the city could be sued. Yet, you couldn't do a complete physical on every drunk, or that was all you'd do for the night.

The emergency room protocol solved the problem: after 15-20 drunks had accumulated, we'd have them stand along the wall in a hallway, those that could stand. We instructed them to walk back and forth, raise their arms, bend over, reach to try to touch their toes, and other such routines to determine that they could stand without collapsing, meaning that they had no obvious injuries or malfunction. This ruled out serious problems and they were then turned over to the police. Some drunks were going into delirium tremens (DTs), and these had treatment in a specialized area.

Radical Application of a Potent Drug for Delirium Tremens

Psychiatry was the area for alcoholics with DTs. They were admitted directly from the emergency room because alcoholism was considered a mental disturbance. They were placed in padded cells so that they wouldn't injure themselves. They were wildly uncooperative, wouldn't eat or drink, and needed hydration with fluids. An intravenous was impossible to maintain, so the new tranquilizer Thorazine® (chlorpromazine) was used: 50 mg were injected intra-muscularly. This in part sedated them, but, more importantly, it produced vasodilation and diminished blood pressure in a fluid-deprived patient. If thrashing continued, it was repeated. With enough doses, the delirious patient recognized that he passed out every time he raised his head. He now tolerated an intravenous, his condition improved, and sedation/vasodilation was no longer needed. This radical approach would not be permitted today - an example of our changing medical ethics.

Chapter Seven: My Early Anesthesia

After medical school and internship, I began my residency in July 1959 at the University of Colorado in Denver. I had chosen this locale because I yearned to live near mountains. I had loved a vacation in Estes Park at age 17, and I'd married the Montana native Pat Sparlin. My residency included Colorado General Hospital, Denver General Hospital -- the city hospital for poor and trauma, National Jewish Hospital for lung and heart specialties, and Los Angeles Children's Hospital, for a valuable four month pediatric experience.

The University of Colorado department chair, Robert W. Virtue, Ph.D., M.D., was awkward with his hands, but he was intellectually stimulating and particularly admired scholarship. For example, he soon noted that I was co-author on two papers with Dr. Schwartz in the American Journal of Physiology and had me autograph copies. When John Severinghaus presented a departmental talk on morphine, Dr. Virtue told us of his exceptional abilities and promise. Dr. Virtue on another occasion told us to look into the medical library to see a young anesthesiologist spending the week there to prepare for his anesthesia oral board exams, with books and papers scattered all over the library table. This was Ted Eger, visiting his sister. Ted became an icon in anesthesia, for his research and his penetrating inexhaustible mind. He was also a Chicago product, and had attended Hyde Park High School, near the University of Chicago.

It is impossible to adequately explain the importance and significance of the contributions of Severinghaus and Eger to the development of modern anesthesia. They had phenomenal success in research and teaching and were pillars of strength in the academic world. Severinghaus was both an outstanding anesthesiologist and applied physiologist and a developer of the blood gas techniques used to track progress in ill patients. As residents, we knew just enough to be in awe with our exposure to them.

New Resident Training

There were two new residents each summer, at this time, Keith Preston and I. We new residents were tutored by all, but a resident a year ahead of me took me over from day one. Lou Lopez, five years older, showed me the ropes, what not to do, and how to learn through the system. He became my 'father figure' throughout my professional life. He had this easy relaxed approach to life and appreciated whatever came his way, but this came due to hard work.

Lou was born January 20, 1928 in Maxwell, New Mexico, population 400. When he was 7-years-old, his mother died, and his father, a mail carrier, placed his sister and him in a boarding school in Raton, New Mexico. His brother, Paul, was placed in the school for the blind in Alamogordo, New Mexico.

Lou served in the US Army from 1945 to 1948, and then attended Colorado College, the prominent school in Colorado Springs. He did this on the GI bill, the first in his family to earn a degree. He worked as a gardener in Englewood, Colorado to pay his way through medical school at the University of Colorado. He followed this with his residency, and a practice of anesthesia in Denver for more than 35 years. He helped and encouraged me throughout our lives, no matter where I lived or what I was doing.

As to beginning residency, he advised me to rely on the departmental nurse anesthetist, Casey, or Julia Kassanchuk, for the best clinical teaching. He warned me, "If you treat her as an underling, she will ignore you for your entire residency." She knew all the clinical tricks. For example, early in my residency, when we did a thoracic case, we intubated the trachea in the lateral position -- as she put it, if the tube comes out during the case, you'll have to replace it in that position anyway, so why not get some practice? It also confirmed what she said, "It's easy to intubate in that position; it's an almost straight line passage directly into the trachea."

This helped me greatly, later, in re-intubating patients in the prone position. None of my own patients were extubated prone (unless deliberately), but I did successfully re-intubate some five or six prone patients over the decades for other anesthesia people. These were ongoing operations with the patient face down for access to the site of surgery. When the tube in the patient's trachea becomes dislodged in the prone position, this is a terrifying situation: ventilation may be difficult to impossible, there may be loss of oxygen to her/him with total loss of ventilation, and turning the patient is a hazard because of the open surgical wound. Worse yet, there is decidedly no time to wait to solve this. The solution is a unique mystery in each particular patient, and a frightening challenge. It is valuable to re-intubate the trachea without turning the patient to the face up position. The approach is to lift one shoulder and turn the head a bit towards you. Intubation is then generally feasible, even though you sort of stand on your head to get a decent view into the back of the throat.

First Night Emergency Call

When I began night call, my tutor was the late Harvey Brown, an older (36) senior resident, who was to teach me judgment and proper decisions. He was unbothered by custom or tradition, had a great sense of humor, and couldn't be cajoled or threatened.

While on call, we slept in the daytime recovery room, which was used as a night-time recovery area for postoperative cardiac patients. If problems developed, it was easier to go to the operating room just down the hall, instead of crowding onto an elevator from the surgical intensive care unit up to the operating rooms. When stable, the patients were taken from the recovery room to the ICU. No emergencies were scheduled until after the cardiac patient was stable and in the ICU. After that, emergency cases could be scheduled. The temporarily closed operating room suite was not a serious problem because serious cases involving trauma or other problems generally went to Denver General Hospital or one of Denver's private hospitals.

One night, about 2 a.m., just after the cardiac case had been moved out, the chief surgical resident came loudly into the recovery room -- typical of the surgical ego then, he roared into the room, turned on the lights, and said, "Let there be light" -- and told us equally loudly that he had an appendectomy to perform. Harvey listened to the description of the modest findings in this patient, and told the resident that there was an unscheduled operating room at 7 a.m., and that the appendectomy could be done then. The surgical resident protested vehemently, eventually saying that the patient might die if not operated upon very soon.

Harvey responded, "Well, we won't do this one, but, if he dies, we'll do the next one." The patient was operated on in the morning and did just fine. A hilarious teaching experience.

Painful Learning Cases

In September 1959, now three months as a resident, I was gaining confidence but lost some of that with a case that so impressed a third year medical student that he too became an anesthesiologist. He and I were in the cystoscopy room on the first floor, below and isolated from the second floor main operating rooms at the old Colorado General Hospital. Once the case was started, our faculty went back upstairs, and was available if called. A 4-5 year old boy was undergoing circumcision, and a urology resident was the surgeon. We were using open drop ether on a gauze cone, and during the procedure, I was explaining that the pattern of breathing was typical of light anesthesia, and that we needed to deepen it. But I had misinterpreted the respiratory pattern, which actually was diaphragmatic tugging,

indicating deep anesthesia. So we dripped more ether, and the patient stopped breathing. Without respiration, the next stage would be cardiac arrest, at that time treated by incising the chest with a scalpel and performing open cardiac massage.

I said, "He's stopped breathing," and the student repeated, "He's stopped breathing."

The surgeon, understandably worried, said, "Is this a cardiac arrest?" He was worried that he might have to cut open the chest wall to manually massage the heart.

We all stared dumbfounded at this immobile child, and then he started breathing again -- while we were frozen in place, the ether was being re-distributed by the circulation from the brain and the respiratory center to other areas of the body. Once the ether levels in the brain decreased, the respiratory depression dissipated, and breathing re-started. I had known of this mechanism, but had not seen it before, and had not immediately thought of it when respiratory arrest occurred. I was now much more cognizant of the signs in anesthesia. Our patient had not actually been in trouble, as his apnea lasted about 20-30 seconds. In part, luck had prevented a catastrophe, and my medical student was dumbfounded at his new insight into physiological changes during anesthesia. Actually, so was I. But soon there was another lesson.

Laryngospasm is a potentially catastrophic complication of anesthesia. The patient cannot move air, nor can manual compression of the reservoir bag force oxygen into the lungs. It can be difficult to treat, and is easiest to break with the muscle relaxant succinylcholine. At Denver General Hospital, I anesthetized a 16-month-old infant for an eye examination. I was about nine months into my residency training and had not had much experience with small children. My faculty helped with induction and intubation, and then went to a lecture in our anesthesia conference room, about 150 feet down the hall. We were using cyclopropane, notorious for sensitizing the airway for laryngospasm.

After the eye examination, I waited until the baby seemed awake and reactive enough, and removed the endotracheal tube. I heard a slight high-pitched 'bleep' on the precordial stethoscope, and knew that laryngospasm had started. I could not break it with positive pressure. We did not have an intravenous, so I could not inject a relaxant to relax the vocal cords. The scene had been surreal. The ophthalmologists were talking quietly on the side of the operating room, the nurses were cleaning up, and none had any idea that there was a problem. They couldn't have helped anyway, and might have panicked.

Without saying anything, I was desperately trying to get oxygen into the baby's lungs with positive pressure by face mask. We had no quick method to get immediate help, as all anesthesia personnel were at the conference, and there was no direct alarm system. I could hear his heart rate slowing more and more. I continued in attempts to force oxygen past his tightly closed vocal cords and into his lungs. Perhaps a few small amounts got in, and helped. The laryngospasm finally broke at the time the heart rate reached about 40 beats per minute.

That reminded me of an old saying: "Laryngospasm breaks just before the heart stops" (including mine!). He survived uneventfully.

Clinical Research, Not to Boast of

The University of Colorado performed research in those earlier days when ethics were not yet clearly defined, i.e., specific directives limiting research on patients had not yet been applied. Our chair Dr. Virtue and a pulmonary physiologist-physician were conducting a research study at National Jewish Hospital to evaluate shunt factor during thoracotomy. Certain conditions exaggerate shunt, particularly operations with the chest open and compression of one of the lungs. Shunt is the deficiency of oxygen in arterial blood compared to the maximum possible at a given alveolar oxygen partial pressure.

For the study, Dr. Virtue specifically directed me to give a 30-year-old man an anesthetic consisting entirely of large doses of morphine and a tranquilizer plus a skeletal muscle relaxant so the patient would inspire only oxygen, thus ensuring accuracy for shunt measurements. This anesthetic is generally insufficient for adequate anesthesia without nitrous oxide, but they believed that greater morphine doses and the added tranquilizer would be satisfactory. No permission was requested from the patient, nor was he told that research would be performed on him during his lung surgery.

As soon as he was extubated at the end of the procedure, the patient complained bitterly about awareness -- he picturesquely described the knife cutting across his chest while muscle paralysis prevented voluntary movement. We tried to convince him that he had dreamed this, or that he was feeling chest pain during application of the chest dressing, but we couldn't make him think otherwise, and he was correct. Not a good moment. I had trusted my chief and his colleague and I now regretted it.

LA Children's Hospital

My pediatric anesthesia rotation at Los Angeles Children's Hospital involved four months with the formidable chief M. Digby Leigh. Pat was due to deliver our daughter Nancy while we were in LA, and we never considered that this might be an inconvenience, so we traveled, leaving Denver in August,

Fig. 6a. Colorado River from Toroweap Overlook

1960, during the second year of residency. Pat had no problems traveling. Sixteen month old Brian was a trooper and went along with whatever we arranged. We camped at national parks, sleeping in the back of our station wagon, and Pat cooked on the tailgate with a Coleman stove.

On the way, we decided to visit the Grand Canyon. The south rim was out of our way, so we chose the north rim, drove southeast to Colorado City and then about 60 miles on an unpaved road ("impassable when wet") to Toroweap Overlook. In our naïveté, we had not considered how isolated this could be. We saw no one, not even at a ranger station some 5 miles prior to the overlook, and found that the overlook had no railings, let alone facilities. We set things up for supper and sleeping, and I took photos of an uncomfortable Pat holding 16-month-old Brian, sitting near the edge. Fig. 6a, b. Again, we didn't worry about being isolated while Pat was pregnant. As she put it, Montanans were virtually always isolated.

After a bit, the ranger drove up, customarily friendly. He greeted us by our license plate, "Hi, Colorado," and said that no one comes to his area, and that even he doesn't try to drive that awful road. He routinely flew a small plane for shopping and local travel. Pat, Brian and I had a good meal and a quiet starlit night. In the morning we re-traced our steps (fortunately no rain).

In LA, as we were in the 'destitute' category of patients, Pat was delivered by the OB resident on the charity service of Hollywood Presbyterian Hospital. Nancy was born November 3, 1960, several weeks after Clark Gable had died there.

Fig. 6b. Pat and Brian at Toroweap Overlook

LA Children's was an active anesthesia group in a very large city, with the best and most challenging cases. The Canadian M. Digby Leigh was chair. Teaching and the variety of cases were excellent, with a push to all of us residents to assume the efficiency of private practice (this was seldom possible in academic teaching programs). One of the best locales was the heart/lung operating room for heart cases on cardiopulmonary bypass and various pulmonary procedures for congenital and acquired disorders. The second, and most useful for us going into more ordinary anesthesia practice, was the ENT room. We were taught to excel at anesthesia for tonsillectomy and adenoidectomy. In the past, most had used open drop and insufflated ether, without an endotracheal tube, and with a considerable risk of aspiration. Other great ENT cases were challenging problems of birth anomalies and other congenital disorders.

For T&As, we used the smooth agent halothane (plus nitrous oxide), breathing the child down, starting the intravenous, and intubating the trachea with deep halothane – no other drugs. We'd have the child deeply anesthetized for the adenoidectomy, as that's the most stimulating part of the procedure and requires deeper levels to prevent contraction of the pharyngeal muscles with the deeper dissection. We'd lighten the anesthetic for the more superficial part of the procedure, removal of the tonsils. As the surgeon was finishing, and drying up, we'd have the child at a light level of anesthesia, breathing on her/his own again. When the surgeon was finished, we'd turn the child on her/his side, for better drainage of secretions or blood from irritated tissues and slip out the endotracheal tube. With the smoothness of halothane, they didn't miss a breath. In the recovery area, we'd watch for a few minutes as they awakened, and had protective reflexes. As the child became reactive, we administered an opiate intravenously for comfort. These were wonderfully satisfying cases.

The toughest cases were repeated dilation of tracheal stenosis. These children had major breathing problems due to the great effort required to move air through the narrowed trachea. They periodically came in for tracheal dilation, which eased their breathing efforts. Unfortunately, with time, they re-stenosed, and thus had the procedure repeatedly. Because of the problems in their upper airway, at the end of the dilation, they all developed laryngospasm, far worse than what I'd seen in the baby in Denver after his eye examination. When the dilation was finished, we literally had to hold them and keep the endotracheal tube in their trachea until they were awake and could communicate. If we removed it even a tiny bit sooner, they had a laryngospasm that was impossible to treat with positive pressure or even with waiting until hypoxia and hypercarbia broke it. They'd need succinylcholine, and

then we'd have to resume anesthesia and start over again. We learned to wait until they removed their own tube. Even then, we had to watch them like a hawk.

These were wonderful cases for residents. As we finished the program at LA, we were capable at pediatric anesthesia, especially if Digby had given us extra time in these more demanding rooms. We had to prove ourselves to gain that blessing.

Digby Leigh, Fearless Commander

Digby was about 5' 5" tall (165 cm) and 160 lb (73 kg). He was fearless and innovative, had a penetrating acid voice, and a good academic department. He'd try anything that might smooth and aid in anesthesia. Babies coming to surgery sometimes cried endlessly, and the nurses' aides couldn't calm them. Digby approached this in his usual experimental way. He had the babies breathe cyclopropane by mask until they were just unconscious; he then stopped the cyclo and permitted them to awaken. After a few 'treatments' like that, most lay there rather groggily, and were quiet. Digby's fearlessness applied to surgeons, too. He certainly laid to rest at LA Children's the "Captain of the Ship" role that surgeons were slowly relinquishing.

One surgeon was a member of a long-standing well-known family. He complained during a case that my anesthetic was inadequate and demanded that the faculty attending come into the room to correct it. I don't recall the details of his complaint, but when Digby entered the room, the surgeon visibly blanched. Digby determined that the anesthetic was fine and then dismembered the surgeon. Digby told him that he came from a wealthy distinguished family, had no need to earn any money, and fumbled his way along as a pediatric specialty surgeon. He said that he was better off doing something else, and that he could learn medical expertise by watching this anesthesia resident perform superbly. Digby left, and I didn't hear anything from that surgeon ever again.

Some faculty don't effectively protect house staff. Digby never let even a supposed slight get by, and it was warming to us as temporary housestaff. It would have been easy for others to take advantage of our brief time there and our uncertainties, but there was never a hint of that with Digby around.

The recovery room at Children's was split between two floors, one part on the OR level for serious cases, and one a floor away for 'easy' cases. As one resident finished a case with Digby and removed the endotracheal tube, Digby injected a small amount of succinylcholine into the intravenous line and clamped off the flow. If an airway problem occurred after extubation of the trachea, the intravenous line would be unclamped, and the child could be quickly relaxed and treated promptly.

Everything went smoothly. The succinylcholine wasn't needed, but Digby was distracted and didn't tell the resident about it. The resident took the child onto the elevator to go to the secondary recovery room. On the elevator, he saw that the intravenous wasn't running, so he unclamped it. Next he saw fasciculations and paralysis, and realized what had happened. He ventilated the child from there to the recovery room, where the paralysis receded within a few minutes. Luckily no disaster occurred.

When the resident returned to the operating room suite, I was there in the hall when he told Digby that he should have been told about the succinylcholine. Digby's response was, "Aw, that was a good experience for you." Today, even Digby wouldn't consider doing that.

Needless Delay in Routine Clinical Use of End-expired Carbon Dioxide

Modern monitors routinely provide valuable information via measurement of carbon dioxide in the expired gases. We had occasionally seen an expired carbon dioxide monitor at Colorado, but Digby used it routinely for critical cases. By fall 1960, Digby wanted it introduced into routine anesthesia care, but there were scoffers who delayed its introduction some 20 years (Smith, 1996). This delay, lasting until the late 1970s to early 80s, likely and unfortunately, resulted in deaths during episodes of malignant hyperthermia or problems with airways, because of the associated delay in detection, or with difficulties in management.

Landmark: Closed Chest Cardiac Massage, No More Scalpels

While I was in LA, a Los Angeles County Anesthesiology meeting in the fall of 1960 introduced the Johns Hopkins landmark study of closed chest cardiac massage for treatment of cardiac arrest (Kouwenhoven et al, 1960). Until then, cardiac arrest had to be treated by open chest cardiac massage, and a sterile scalpel had to be available in all critical locations.

About a month prior to that, while I was on overnight call at Children's, a family physician brought his several month old son to the emergency room. He had been having apneic spells, recently more frequently, known to be cardiac in origin. The emergency call physicians – surgery, anesthesia (me), pediatrics – discussed this with the father. About 5 a.m., the boy had another arrest. At that time, I was doing routine 'checkup' rounds, to see that laboratory work was complete on the day's surgical patients. As I passed the ICU, a nurse called me in to check the baby. He was pulseless and apneic.

I opened his left chest with the ever available scalpel (careful not to sever an intercostal artery), and held a black rubber anesthesia mask to his face with my left hand. I performed cardiac massage right handed, while the ICU nurse manually ventilated his lungs. Within a minute, although his heart remained flaccid, he began to rouse and move around. Within another minute, the surgical resident appeared -- barely awake, disheveled, unshaven, in his scrub clothes. He took over the massage, while I intubated the trachea. The baby continued to respond physically, although his heart never contracted again. About 15 minutes after resuscitation began, the pediatric resident appeared -- clean shaven, hair combed, tie in place, white coat over his shirt. He looked a bit out of place, and even embarrassed. That response summarized a fundamental difference between medical- and surgical-related specialties. The latter routinely were forced to act quickly and be prepared for it. The former seldom had to 'jump' to a problem and didn't expect to on a routine basis.

Chapter Eight: Denver
Private Practice 1961-1966

The difference between academic teaching and private practice non-teaching hospitals is in part efficiency and that reflects income. The academic atmosphere focuses on the beginner in anesthesia to develop judgment, skills, and adaptation, especially with sudden changes in the patient or the anesthetic. The learning period is several years, with greater emphasis on complexities as skills and judgment develop. This takes time, and cases are generally longer. The non-teaching hospital focuses on efficiency and income, and that's become much more important with for-profit medicine, which is not a blessing. Even prior to the for-profit medicine era, as when I entered private practice, it was a considerable adaptation to be rapid and efficient, with cases immediately following one another.

I joined the Denver Anesthesiology Group, which consisted of Ed Heaton, Chuck McCrory, Lou Lopez, and me, a respected group among Denver anesthesia providers. We did pre and postop rounds on all our patients. We worked in multiple hospitals, and provided our own gas machines at each. We carried our own equipment, and washed it between cases --- laryngoscopes: several sizes for small and large patients, curved blade, straight blade; stylets and endotracheal tubes. I carried two sets of tubes, one set clear plastic, and the other, armored, in French sizes 12, 14, 16, ... 40. Pat sewed a roll-up cloth carrier for the tubes, with a slot for each size. When I started a case, I rolled out the carrier and selected the best size tube, with the others ready in case I needed a different size.

At that time, Denver anesthesia in the central hospitals included the Metz group, started by C. Walter Metz, the pioneer anesthesiologist in Denver, who was President in 1952 of the American Society of Anesthesiologists; the 'Girls' group', with Alice Smith, Katie Wood Payne, Margaret (Maggie) Mahowald, and Francie Sims; the group at Presbyterian Hospital, and other loosely organized or solo practitioners. The Girls' Group was an informal complimentary name that reflected their capability. They as individuals and as a group were respected for their consistent quality, and routinely provided some of the cardiac anesthesia for the strong group of cardiac surgeons, with John Grow, Art Prevedel, Chuck Demong, John 'Bud' Wilson, and Bob Maloney.

When I started in private practice, ventilators were not easily available or efficient, so we hand-ventilated all patients by squeezing the reservoir bag. If the patient's breathing was not too depressed, s/he could breathe spontaneously, without our helping each breath by squeezing the reservoir bag.

Most of the time, we assisted ventilation. If the patient's spontaneous breathing stopped, due to central nervous system depression or skeletal muscle paralysis, constant hand-ventilation was mandatory. When I needed both hands, as in pumping blood, or injecting extra drugs, I attached a length of breathing tube between gas machine and reservoir bag, and squeezed the bag either under an elbow, or between my knees. Later, mechanical ventilators permitted controlled ventilation in place of our hands and knees.

Obstetrical Salvation

In 1963, I provided general anesthesia with cyclopropane for a vaginal delivery at St. Joseph's Hospital, common practice at that time. When the baby was born, the excellent family practitioner, whom I knew, began the initial newborn care. I immediately observed, from chest movements, that the baby was trying to breathe but had a totally obstructed airway. The family practitioner suctioned the oral pharynx but knew no other methods of resuscitation. He recognized that he was in trouble, said that there was nothing else he could do, and could anyone help.

I told him to give me the baby, and set him on the tabletop of the Foregger anesthetic machine. Our chair in residency, Dr. Virtue, had triply emphasized to us in OB cases that we should always have infant resuscitation equipment set up in advance even if someone else was there to care for the newborn, for we were the best in airway management. This precaution paid off royally. I had an infant endotracheal tube and laryngoscope all ready. Direct laryngoscopy demonstrated a mucous plug totally occluding the opening of the trachea. It was easily suctioned. I ventilated the baby with oxygen (taken briefly from the mother), and there were no further problems. I had had to switch my anesthesia attention back and forth between mother and baby for several minutes. This cemented anesthesia relationships with that family practitioner and obstetrician.

Another birth, in December, was that of our daughter Gail Ann, at General Rose Hospital, always an exciting event.

Axillary Nerve Block with Brief Cardiac Collapse

I cared for a 17-year-old girl, providing an axillary nerve block via the peri-arterial injection of lidocaine for her surgery. Within less than a minute of finishing the injection, she began a high-pitched breathing sound, like laryngospasm. She lost her peripheral pulses, had no heart sounds, and looked gray. She did not convulse but did have cardiac arrest. I realized that she had lidocaine toxicity due to high blood levels.

I ventilated her by mask with 100% oxygen (the most important initial treatment) and the surgeon provided external cardiac massage --- thank God for Johns Hopkins research! She returned to consciousness and effective circulation within a minute or two, with amnesia for what had happened. She recovered quickly and had no complications.

Bier Block on the leg, with toxicity

While I was on call one winter night, a skier was brought to a Denver hospital for treatment of a fractured tibia. Until he fell, our patient had been drinking beer and eating hamburgers all afternoon during his ski runs. His stomach was therefore full of undigested food, and aspiration was a potential risk. Rather than use a general anesthetic, I decided to use a Bier block. After wrapping his leg from foot to groin, I inflated the tourniquet and injected lidocaine via an ankle vein.

After the orthopedist had reduced the fracture and placed the cast, it was time to deflate the tourniquet. Because the procedure had been brief, I was concerned that there might be too much remaining lidocaine in his leg veins, and that release of the full amount with tourniquet deflation might result in toxic blood levels. So I attempted to release small amounts at a time, by deflating the tourniquet for a minute or so. This was to let blood into the leg and wash some of the lidocaine into the general circulation, where it would in part be taken up by the liver and metabolized. I did this several times over, and then removed the tourniquet.

But I had missed an important consideration: even though the tourniquet was deflated, the firm wrapping around it prevented venous return to the general circulation. So he had arterial perfusion into his leg but essentially no venous drainage out of it, and no loss of lidocaine from his leg. When I removed the tourniquet, and a flood of lidocaine-containing venous blood roared into his general circulation, my patient suddenly changed.

He became apprehensive, and said, "Doc, I'm gonna die."

I knew immediately that this was lidocaine toxicity. Again, first was mask oxygen. His color, blood pressure and pulse were fine, and his EKG was normal. I repeatedly checked these. He continued stable, and after several minutes, he improved, but was still worried.

I asked him, "Do you need anything"? He said he really needed a cup of coffee. Against operating room regulations, I instructed the circulating nurse to bring a cup of hot coffee. That was a solid psychological boost, and from then on he did well.

These several cases underscore the need to monitor every case appropriately, have emergency equipment always set up for use, and take nothing for granted. The smoothest administration of anesthetic can lead to unexpected complications, and a disaster is generally due to not realizing the possibility and not anticipating such an event. These can start as mysteries and turn into disasters.

Heparin Failure on a Pump Case – Why?

During private practice in Denver, the cardiac surgeons were performing a mitral valve replacement on a 35-year-old woman. I injected the heparin into a peripheral intravenous line, and we started on cardiac bypass. Within a minute or two, the pump began to seize due to clotting of her blood. I injected more heparin, without correcting the problem. She was comatose afterwards due to blood clots in her brain, and died within a few days. We could not determine whether my injection missed the intravenous tubing, or whether the woman was resistant to heparin. I reviewed my approach to the injection into the peripheral line, but could not discover an error, as there was no fluid on the drapes under it.

Reflection

There must be many situations in which a physician performs a fatal error or comes close to it, saved only by pure luck, or by skilled help that wonderfully just happens to be available. In private practice, I was alone most of the time – always at night, and regularly so even in the daytime, as other anesthesia providers were generally busy with their own cases. I had enough unpleasantness like this and was pleased at any time to help others in treating unexpected patient problems. When an error occurs, or almost occurs, the savvy physician must recognize it, and learn from it.

Denver Anesthesia Practice

Better surgeons knew good anesthesia providers, and each cultivated the other. We went to multiple hospitals to work with preferred surgeons, and thus were assured of good surgical practice and good collections. I performed 1000 anesthetics per year, and had collection problems with about 5 patients per year. We had perhaps 15% charity work --- if our regular surgeon had a patient who could not pay, neither of us billed. I consistently earned about $3000/month.

Part of our practice was to help other hospitals get started. When Lutheran Hospital on the northwest side of Denver opened in 1964, it had surgeons but no dedicated anesthesia providers. Each

week, one of our group (now up to six members with Ken Simpson and Joe Alanis) would provide anesthesia there for a day.

On one occasion, my operating room was diagonally across the hall from another case. Since the doors of both rooms were open, I could see some of what was going on over there. An older obese woman was having a vaginal hysterectomy. Her legs were in stirrups, and the operating table was tilted head down. The general practitioner anesthetist was giving open drop ether on a cone-shaped cotton mask with spontaneous respiration. Even then, that was an unbelievably outmoded approach. Trained anesthesia providers would have used an endotracheal tube and controlled the patient's ventilation. It was obvious from her chest and belly movements that her airway was partially obstructed. This was a formidable stress to her heart and lung function.

Fortunately the surgery was not prolonged. When I arrived in the recovery room a bit later, she was there, in florid pulmonary edema, with a cardiologist treating her. I knew the cause -- prolonged partial obstruction to her airway, so she needed much extra effort to breathe. The extra effort created a greater negative pressure in her lung's airways, leading to fluid movement from blood vessels into the air passages. Fortunately, she was recovering.

Another case: a 10-year-old boy at Lutheran Hospital underwent an evening appendectomy. I used mask anesthesia with nitrous oxide-halothane since he had been vomiting, as we then generally assumed that his stomach was close to empty, and, even if not totally, without increased pressure within it. As he began to emerge from anesthesia near the end of the procedure, he began to swallow. I knew that this meant gastric contents, so I deepened him, passed a stomach tube (an adult tracheal suction catheter #18 works best in this size patient), and suctioned liquid material. I pulled the suction catheter, awakened him, saw the usual smooth emergence of halothane, and had no problems.

However, a similar Lutheran Hospital case was a disaster, and there but for the grace of God ... Several weeks later, another anesthesiologist cared for a 10-year-old boy for an appendectomy using mask anesthesia for the same reasons that I had. At emergence, the boy either vomited or regurgitated solid material that obstructed his upper trachea, but low in the neck so that not even a tracheotomy was helpful. They could not restore an airway and he did not survive.

Art Prevedel – Astute Surgeon and My First Hero

Art Prevedel was particularly gifted: fast when needed, deliberate when the situation demanded, comprehensive, and not ego oriented. He and I did pediatric bronchoscopies together, and

he arranged us as an efficient team after he saw how quickly I intubated the trachea. As he put it, why should he fumble around to get the bronchoscope into the trachea when I could do it in seconds?

I'd breathe the baby down with halothane to a deep level, spray the vocal cords and down the trachea with a 4% lidocaine spray to prevent laryngospasm and reflexes, expose the trachea, and place the tip of the bronchoscope into the top of the trachea. He'd take it from there. I'd ventilate via the oxygen flush button on the anesthesia machine to add positive pressure via the bronchoscope side arm, but carefully and just enough to gently raise the chest. If the procedure took a while, I'd add small doses of intravenous succinylcholine or have him quit for a few minutes to add more halothane. These cases did well, and I loved working as a team with him.

Art Prevedel saved the life of my patient at old Mercy Hospital when I introduced a potentially fatal air embolism. At that time, intravenous fluids were in glass bottles, and hurried infusion required increased pressure via the air vent to force fluid more quickly. Once the fluid was gone, the air pumped into the bottle could enter the patient's vein if you didn't stop the infusion. Art's procedure was a gastrectomy on a 37 year-old-man for carcinoma.

I fell behind on fluid replacement and added a pressure bulb that pumped air into the glass bottle of lactated ringer's solution to speed the infusion, confident that I would control the situation. Something distracted me and I suddenly heard the sound of air as coarse bubbling through the esophageal stethoscope. The bottle had emptied, and air was being pumped into the vein and on into the heart. I released the pressure and clamped the tubing, and warned Art that cardiac arrest was imminent. The heart was abruptly filled with air with an effect sort of like vapor lock in the carburetor of an old car. Effectively no blood can get through the heart and out to the body.

Art felt the heart through the diaphragm and noted the arrest. He incised the diaphragm and started manually pumping the heart, but said that it was empty --- the air in it created an empty bag, so that squeezing didn't push blood through. He needed added liquid within the heart. I hung another bottle of lactated ringers solution and again pumped it with a pressure bulb! Art felt the heart fill, he massaged it, and he felt it begin to beat strongly. Our patient had no complications and survived at least 15 years, apparently cancer free. My role postop, Art said, was to explain to the patient why he was in an ICU.

Art Prevedel was thoughtful and perceptive. Our daughter Mary was born seven weeks premature, a bit over 5 lbs., on May 21, 1965. She became jaundiced because her immature liver could

not metabolize her extra bilirubin. The treatment of choice at that time was exchange transfusion to dilute the blood hemoglobin level.

There was a recognized mortality to this procedure, as the babies were delicate and stressed, the blood was cooler, and it was difficult to maintain the baby's normal body temperature. Art interrupted his clinical day to stay with Mary and her pediatricians during the exchange transfusion. Her pediatricians knew Art well and trusted him as a colleague. With his routine experience in hypothermia and cardiac surgery, he knew what to avoid and how to treat any problems. I didn't learn of his action until well afterwards. He didn't broadcast. Soon after this, fluorescent light on the skin was shown to diminish bilirubin, thus eliminating exchange transfusion as a treatment.

Home Care: Caudal Anesthesia

I cannot believe what we sometimes accomplished, more or less fearlessly, but prepared and safe. An anesthesia friend had just had a hemorrhoidectomy and was home, with terrible suffering, attempting that first bowel movement. My desperate friend asked me to relieve the pain for that first attempt with a caudal anesthetic. It was decidedly not routine to give anesthesia at a home, but we were accustomed to bringing anesthesia machines and other anesthetic paraphernalia to various hospitals and some dental offices. As routine precautions, that evening I brought a small oxygen tank and a means to ventilate the patient if necessary, various drugs, and monitoring apparatus. I placed the caudal solution into a most cooperative patient, and had excellent analgesia around the buttocks. Function was temporarily painless and things improved from then on.

Prolonged apnea with succinylcholine

In 1963, in private practice in Denver, I anesthetized a teen-aged girl on vacation from North Dakota. She was healthy and needed an appendectomy. At 10 p.m., I gave her thiopental and succinylcholine, and intubated her trachea. The case was finished in 45 minutes, but she wouldn't breathe on her own. I soon realized that she had the rare prolonged apnea following succinylcholine, due to absence of pseudocholinesterase. That meant that I had to hand-ventilate her until she spontaneously recovered muscle strength.

At that time there was no night time recovery room, no intensive care unit, and no automatic ventilator. So the surgeon, nurses, and I stayed in the operating room until she again breathed, about 5 a.m. There was no risk to her health as long as we maintained respiration and kept her warm in the cool operating room. When she suddenly moved and awakened at 5 a.m., she had no memory of the

postoperative events, even though she had breathed nothing but oxygen, and the anesthetic drugs had easily been dissipated by midnight.

Awareness during anesthesia can be a problem --- in our Denver practice we tried to avoid awareness by partially but not totally paralyzing a patient during surgery. Thus, if the patient moved in any way, we knew that the level of anesthesia needed to be deepened. Even now I don't know why there was no awareness during the long wait, and am still surprised that she didn't remember at least something. We hadn't greatly hyperventilated her, as near as I could determine.

Practice in Denver had been interesting, varied, and at times unusual, but then my practice changed to Minnesota and the Mayo Clinic.

Travels with Art Prevedel – Move from Denver to Rochester

Art Prevedel and I traveled together on several occasions to visit practices in various areas around the country, to improve our approaches on heart cases that required perfusion pump bypass machines.

On one of our trips, in February 1966, we visited the Mayo Clinic in Rochester, Minnesota, for a meeting on cardiac surgery and visits to their surgical suite. Mayo was impressive, well organized, and productive. John Kirklin and Dwight McGoon were famous for Mayo Clinic's enviable success in open heart surgery.

During our visit, Emerson Moffitt, then chief of anesthesia at St. Mary's Hospital offered me an academic position, with the potential for teaching and research. Our entire family visited in the spring, by train from Denver (a wonderful way to travel), and stayed at Martha and Alan Sessler's home in northeast Rochester. Pat and I moved there in August 1966.

Mayo was a solid introduction to academia within a super organized large group practice. I began a 20 year career in neuroanesthesia, with every day challenges of placing a patient in the sitting position for surgery on the back of the skull or neck, carotid endarterectomies with measurements of regional cerebral blood flow and 16 lead EEG, intracranial aneurysms, and enough routine craniotomies to satisfy anyone. But, within 8 months, I was drafted for the Viet Nam conflict, a serendipitous move that began and focused my research future. Research, however, requires a mentor and control of ego.

Chapter Nine: Anesthesia Practice, Mentors, Ego

Mentors

As an academic at Mayo, teaching residents and nurse anesthetist students was rewarding (I was voted Teacher of the Year), but never as much as personally providing a patient's anesthesia. An anesthesiologist eases stresses, treats or prevents pain, and, in addition, participates in research that helps further understanding of the complexities. But few of today's graduate residents have the skills to perform worthwhile research, as there simply isn't time and a mentor available to educate them. In the absence of a mentor, initial efforts are wasted and their efforts rejected. Nothing kills their enthusiasm as totally as rejection, for that undercuts ego.

Ego Controls, Not the Person

Ego is peculiar. Those who strive for great ego support in medicine, perhaps most commonly surgeons, lose effectiveness once they achieve a measure of success. This is because ego, like gravity to the out-of-control downhill bicycle rider or skier, takes over, and from then on, control and judgment are lost. This is obvious in entertainers, academics, politicians, writers -- you name it. In some, it's tolerable, because of their gifts or talent. In those with modest gifts, they revel in it and misjudge their limitations, which is unbearable. It's important to control ego and to decide things rationally. A mentor is invaluable in preventing a crushed ego and the associated loss of esteem due to poor decisions or actions.

Whether in academia or private practice, all newcomers need a mentor. This provides a basis for rational attempts at success, and limits errors in judgment. A mentor helps you avoid minor to major mistakes, and aids in working out practical solutions prior to exposing your ideas to the sometimes confidence-destroying critiques of others. You need to be methodical and careful, but especially, disciplined, and ease into the awareness of others by letting your results or skills speak for themselves. Mentors tend to eat their young, if the mentor is not properly motivated. I saw that on several occasions in ego-driven mentors totally focused on self, or in young who did not develop an area of interest separate from that of their mentor.

Some self-motivated mentors appear to help their young, but caustically expose them to early mistakes without guidance. This guarantees failure in early research, and loss of confidence. A mentor is not a part-time or multi-person function. You need a mentor who is available virtually every day, and

who can focus on you personally and perhaps you alone (Kahn, 1994). You need the mentor's unselfish experience and generosity. Private practice and academic persons in clinical areas, and especially academics in beginning research, can fail utterly because their supposed mentor left them afloat, for whatever the reason. Some mentors are vulnerable, and become mentors because they can eliminate someone who might in time threaten them. It's an effective way to suppress potential competition. In virtually everything, once you show signs of succeeding and begin to do well, there are those eager to bolster their challenged ego by undercutting your progress. This has been a recurring lesson.

My mentors were valuable. Neena B. Schwartz, Ph.D., hired me during my first week of medical school to a 20-hour per week job in her endocrine physiology laboratory for the entire four years. Robert Virtue, Ph.D., M.D., Chair in Anesthesiology at the University of Colorado, had a focused interest in science and excellence. Lou Lopez, M.D. was my friend and godfather in residency and private practice. Julia Kassanchuk – aka "Casey" – was our University of Colorado phenomenal nurse anesthetist in teaching clinical anesthesia. Dick Theye, M.D., research, and Jack Michenfelder, M.D., neuroanesthesia and research, were two mentors at Mayo. Yet my two heroes in life, not specifically mentors, were surgeons: Art Prevedel in Denver, and Thor Sundt at Mayo.

While I was curious, loved stimulation, worked hard, and developed research in depth as much as possible, I was really just plain lucky and recognize that much of my success was in finding things I had not sought. It included the move from an excellent private practice to Mayo, the Viet Nam draftee stationed at the army burn unit, the savvy, direct, and at times painful mentor Dick Theye, and the realization of research ideas, at Mayo and again at UC Davis.

I can't consciously explain why I moved on these several occasions, I just knew that it was time. I couldn't know how things would work out, and simply adapted to the new situation. At certain times, you must leave wherever you are, and the US Government arranged my next move.

Chapter Ten: US Army Burn Unit, Fort Sam Houston, San Antonio, Texas

The Army drafted me in spring 1967. I had been continuously deferred during my education, but as a physician was eligible for the draft until age 35. The Viet Nam conflict was escalating and the military was drastically short of physicians. I had graduated medical school in 1958, and at basic training in September 1967 amazingly met ten of my fellow medical school graduates at Fort Sam Houston's . Military Field Service School in San Antonio where we were taught how to wear uniforms and salute.

We bivouacked at nearby Camp Bullis to learn compass maneuvering, and to crawl under barbed wire while 50 caliber machine guns fired 18" over our heads. We did this first in the afternoon, and again after dark when we could see the tracers just above our heads. Interestingly, while waiting for the evening strafing, we saw something high in the sky reflecting sunlight and moving progressively across the sky. It was neither a plane nor a planet; it was a satellite.

At Fort Sam, by the cannons in front of headquarters, a bugler played Reveille in the morning as the flag was raised, and Retreat at 5 p.m. as the flag was lowered. All local traffic halted, and drivers and passengers exited and stood at attention. Our daughter Mary kept track of the cannons. Fig. 7. Brooke's main hospital, then the site of the burn unit, is above her head in the background (arrow).

Fig. 7. Mary checks the cannons. The burn unit was located at Brooke Main Hospital, arrow.

Class 3 Institution in a Class 3 Military Hospital

My initial orders (we wondered why I received 50 copies, but found out in time that we gave one to every place or person we dealt with) included assignment to Viet Nam for a year after basic training. This was changed during basic to the U.S. Army Burn Unit at Fort Sam Houston, due to the excessive amount of burn trauma and the need for experienced anesthesiologists.

I had finished residency in 1961 and been in practice for 6 years, a greater experience than virtually all drafted anesthesiologists. The Burn Unit was unique: Military facilities were one of three categories of classes. Class 3 was the most restrictive: a major care and teaching institution serving major needs. Brooke Army Medical Center on the grounds of Fort Sam Houston in San Antonio, Texas was a huge Class 3 facility with multiple large buildings and care for orthopedic problems, eye injuries, and other major specialty categories.

The Burn Unit, a Class 3 institute, rented space in the Class 3 Brooke Hospital, occupying a relatively small area – two wards, one operating room in the Brooke surgical suite, and a separate building for its recognized burn research. Two anesthesiologists were assigned to this class 3 facility and were independent of the anesthesia program at Brooke. Marvelous Max Mendenhall was chief of anesthesia at Brooke Army Hospital and was supportive and encouraging to all we did in anesthesia at the burn unit, even though he had no official responsibility or involvement with us. His wife Rita and he had anesthesia parties at his home on post for everyone in anesthesia, regardless of affiliation, particularly when there was a visiting professor, e.g., Art Keats.

The two anesthesiologists assigned to the burn unit did have occasional periodic temporary rotations of residents or nurse anesthesia students from the Brooke program as part of the teaching program, but, in general, we personally provided virtually all the burn anesthesia. When we had really tricky cases, Max had someone from his department check on us, just in case. We were never offended, as he was not ever a competitor.

Jack Moncrief was chief, a major person in burn care, and a formidable and respected leader. He had a deep measured voice, and our 9-year-old son Brian called him "Gunsmoke," for in that he resembled James Arness of the TV program. When I was promoted, he agreed to pin my Captain's bars

on Brian. Fig. 8. The burn unit had its own dedicated medical personnel, including internists, nephrologists, general and thoracic surgeons, anesthesiologists, occupational and physical therapists, and various other specialty services. Unit capacity was perhaps 20 for acute burns, and 120 for ward patients.

Respiratory care as a specialty was in its infancy, and we in anesthesia provided some of the expertise. Since we worked with the airway in any anesthetic, we understood the early ventilators, because most were ward applications of equipment regularly used in the operating rooms. Each day, one of the anesthesiologists provided anesthesia for surgery, while the other made rounds with the surgeons and internists, and helped on those patients with respiratory problems, providing ventilator skills, and helping with tough intravenous or arterial lines.

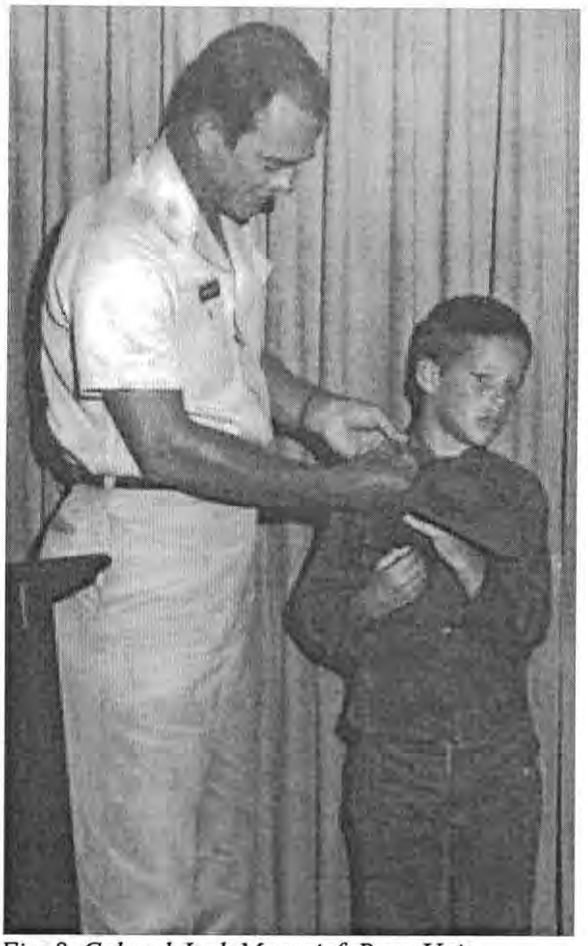

Fig. 8. Colonel Jack Moncrief, Burn Unit Commander, pins my Captain's bars on Brian's fatigues.

Burn patients had constant severe pain, and regularly told us in anesthesia that the only pain-free experience they had was during anesthesia. For minor procedures in the Hubbard tank, e.g., superficial debridement and dressing changes, we provided added analgesia at times with the methoxyflurane plastic whistle. This was a cigar-shaped white plastic tube, much like a whistle, with an internal wick. We poured the recommended amount (can't remember how much) into it, and the burn patient inhaled on it, more vigorously as debridement progressed. Methoxyflurane (Penthrane®) is no longer in use due to renal toxicity. The Hubbard tank is a large curved 6 foot by 10 foot metal warm water structure for soaking a patient in warm water for comfort, easier debridement, and other care. Modest debridement could involve considerable pain and analgesia was important. The plastic whistle temporarily magnified the effect of parenteral analgesics.

Many patients had other serious injuries in addition to their burns, e.g., fractures, loss of a limb, or an eye. In 1968, the unit cared for 389 burn patients, most there for two to four months, with 259 receiving 794 anesthetics. The average burn was 30%, and 38 died (Annual Report of the Burn Unit, 1969). In 1969, there were 309 patients, with 189 receiving 662 anesthetics. The average burn was 36%, and 70 died (Annual Report of the Burn Unit, 1970). Part of our burn care was to sing happy birthday to recuperating patients. This added some solace and support during their terrible suffering. While the wish was that there would be many more, we realized at times that this was a happy last birthday party.

Transport of Burn Patients from Viet Nam and Japan

Our patient sources were active duty military, dependents, and Native Americans, including Alaskan Inuits and Aleuts. At that time, we could not properly distinguish Alaskan tribes, and, furthermore, nomenclature varies. They are now described as three distinct racial groups: Aleut, Indian, and Eskimo – now Inupiat and Yupik. They do not like being confused with one another. These distinctions exist because they are alike with one exception – their languages are mutually unintelligible. Recently, an Inupiat visited Greenland and was amazed that he could talk to people there – Yupik are Siberian (Longenbaugh 2007).

Most of our patients were from Viet Nam. After they were stabilized there, usually within several days, they were transferred to the 106th General Hospital at Kishine Barracks, Yokahama, Japan. Averaging twice per month, we sent a burn team (one physician, two medical corpsmen) for the purpose of safe evacuation on a military jet of some 30-40 patients with thermal injury, back to Fort Sam, with re-fueling at Travis Air Force Base, southwest of Davis, CA. We never had a fatality on these prolonged evacuation flights. I never flew on these nor did I go to Viet Nam.

One source of patients was 'friendly napalm.' Planes targeting the enemy lines dropped napalm, prematurely, on our own troops. They were saturated with this clinging combination of gasoline and a jelly-like substance that burned deep and couldn't be wiped or scraped off. Phosphorous grenades were another terrible weapon. Phosphorous burns under water or in tissue because it combines with oxygen to combust in solution, so the grenades were particularly damaging to deep structures. Both of these produced horrible wounds with prolonged convalescence and deep scarring.

Scars due to thermal injury gradually contract over the years and restrict movement, so burn patients repeatedly return for plastic surgery to open these scars and add in new skin grafts, so-called 'scar swapping.'

For drafted military personnel sent to Viet Nam, the experience was crippling to their ego and sense of well being, with immense frustration. As a result, many became pre-occupied with drugs or alcohol. In part due to this, half of the casualties in Viet Nam (military records) were related to non-hostile action, e.g., drunk or drugged and disorderly conduct, or such things as unsuccessful attempts to fly a plane under a bridge. Some became our burn patients.

At this time, the Viet Nam military budget was $2.5 billion/month. Some of the funds were richly spent at Fort Sam. We had marvelous entertainment on the Parade Ground on the Fourth of July, with bands, sophisticated marching units, parachutists, and horses. At Thanksgiving, the hospital mess prepared a complete meal for all military and families, charging about $1.50/person. The Officers' Club and Non-commissioned Officer's Clubs were prosperous and tastily decorated throughout the year, with excellent food at reasonable prices. This benefited those who needed a quiet relaxing break from tensions.

Thermal Trauma in Families of Conservative Religion

One disturbing aspect of the burn unit population was the attitude of seriously burned children from families of some conservative and/or fundamentalist religions. These children were extremely depressed, with no desire to live, even though the causes of their burns were accidental. It took a major effort of many personnel to help them see that it was worth it to survive.

Finally, one of them described what was wrong: they had been told since their earliest years that, whenever they were hurt, it was God punishing them for misbehavior, and that, the more serious the injury, the more serious had been their misbehavior. A serious burn indelibly etched them with the idea that they were terrible human beings and that they shouldn't survive. Some of these parents even had difficulty supporting such a 'terrible' child.

Lyndon Baines Johnson and Brooke Army Medical Center

We lived on post among other officers' homes about ¾ mile from the hospital, at 125 Lang Road, with close contact to army activities, people, rules, and regulations. Many of our burn patients were draftees, primarily young men who lacked much education. As infantry, 'grunt' soldiers, and point men, they were more subject to injury or death. They had an almost child-like attitude while recuperating, with a teen's preoccupation with comic books.

Pat and I had supported the war effort until I was drafted, but now became anti-war. Hostility to the war was fairly widely seen at Fort Sam and toward our president, Lyndon Baines Johnson. This

hostility occurred in some regular army personnel, draftees, inpatients, recuperating ambulant patients, and post personnel. LBJ would come by helicopter from his ranch for checkups at Brooke's Main hospital. Pat could tell when he was about to arrive, although it was never announced. Military Police would start searching our neighborhood, lifting sewer covers, checking on who was around. The helicopter would land at varying locations, never the same, and LBJ would be driven to Brooke. On those days, we saw sharpshooters posted on the roofs of the buildings around the semicircular drive approaching Brooke Main.

Pat would phone to tell me he was coming, and, if I was not in the operating room, I would watch him enter the hospital from my second floor office overlooking the entrance.

We officers were periodically ordered to attend receptions at the Officers' Club or elsewhere, with a relaxed review by high ranking officers. Most interesting was how seriously their wives regarded their station in the military. The women introduced themselves, either by card, or directly, as "Mrs. Colonel Jones" or "Mrs. General Smith." They avoided any chance that their status might be missed. I entered as a Captain, was promoted to Major in nine months, based on my time out of college, and to Lieutenant Colonel six months after that, based upon my time out of medical school (by order of W.C. Westmoreland, Chief of Staff). I was now the ranking junior officer in the burn unit, second in command to the burn unit chief surgeon.

Chapter Eleven: Begin Research

The U.S. Army Burn Unit set the stage for several decades of research. Only years later did I realize that I'd properly approached research, perhaps due to the laid back influence of my medical school mentor, Neena B. Schwartz. Much later I read the following: 'Success must come gently, with a great deal of effort, but with no stress or obsession' (Carlos Castenada). I didn't realize that that's what I was doing. The Brooke Army anesthesia resident Bob Gunther and my burn unit colleague Paul Schaner were co-authors of our first research paper, in which we described the use of the volatile anesthetic halothane in burn patients (Gunther et al, 1969). Our next report evaluated liver function in patients exposed to halothane on multiple occasions, without evidence of hepatic damage, (Gronert, Schaner et al, 1968). Reports in the early 1960s had incriminated halothane as a liver toxin, and our article indicated that there was no evidence for that in burn patients anesthetized by it on 15 or more occasions in a two month period. This in a sense confirmed the findings of the National Halothane Study (Seeley, 1966; National Halothane Study, 1969), which showed that fatal necrosis after halothane was rare. Mortality after halothane anesthesia was overall 1.87%, and for all agents, 1.93%. There were 856,515 estimated administrations of anesthesia in the study and 254,898 involved halothane. There were nine unexplained cases of necrosis in the entire group, seven after halothane and 2 after cyclopropane or other anesthetics. Thus, if halothane was a factor, its incidence was less than 1:100,000 administrations.

Our next burn unit project had more than the usual significance.

Succinylcholine-induced Hyperkalemia

A seminal paper on hyperkalemia in burn patients, published in spring 1967 (Tolmie et al), opened an entire field involving upregulatory changes in skeletal muscle nicotinic acetylcholine receptors, although at that time, we didn't know of upregulation. I had been impressed with this article when I first read it, and, when I was assigned to the US Army Burn Unit, I jumped at the chance to pursue that lead.

A seemingly minor article had been published in 1964 (Bush). I had reviewed it when evaluating the literature concerning cardiac arrests in burn patients, but missed the point that there was resistance to the muscle relaxant curare. This, although I didn't realize it at the time, demonstrated the yin and yang between succinylcholine and non-deplarizing muscle relaxants. Non-depolarizers act by directly blocking acetylcholine in a competitive manner, and Bush's was the first report of simultaneously increased sensitivity to succinylcholine and resistance to the non-depolarizer, curare. This resistance

occurs for the same reason that excess potassium is released, namely, that there are greater numbers of acetylcholine receptors in the muscle membrane, resulting in supersensitivity. Thus, a depolarizer, e.g., succinylcholine, has many more receptors to act upon. Each receptor releases a small amount of potassium, but now, with the many extra receptors, there is a cumulatively greater release of potassium. Supersensitivity means that even very small doses of succinylcholine, e.g., 10% of the usual dose, release excessive amounts of potassium, due to the extra receptors (Gronert, Lambert et al, 1973). This is also an example of upregulation.

A non-depolarizing relaxant, e.g., curare, loses potency in paralyzing skeletal muscle because there are so many extra receptors to interact with the acetylcholine released from the motor nerve, and therefore more relaxant is required before it is blocked. The numbers of acetylcholine and non-depolarizer molecules classically compete for the acetylcholine receptor. We could have improved our early research goals had we realized the implications of Bush's paper.

Burn Patient Potassium Changes after Receiving Succinylcholine

We conducted a series of human studies. While Tolmie et al had potentially opened an entirely new field of investigation, which seemed to explain why any burn patient might arrest during anesthesia, we needed to confirm their single patient study. At that time, typical for the period, the burn unit research committee approved the study without requiring informed consent. I doubt that our very ill patients from the Army, Air Force, and Navy would have been able to provide a rationally informed consent. By today's standards, the study was likely unethical. When we did observe phenomenal increases in potassium after use of succinylcholine, we didn't stop the study (Fig. 9). We did not have a cardiac arrest in any study patient. Had one occurred, it's likely that we would have discontinued the project. Arrest was entirely possible had we done enough burn patients, but despite study of more than 60 patients, we saw none, in spite of high potassium levels, and abnormal EKGs (Fig. 10). Perhaps no patient had arrested because they were young and still fit as regards their cardiovascular system. We continued the study so that we could define the hyperkalemic response to succinylcholine as completely as possible, given our unique patients. We ended it after two groups of patients, given two differing doses of succinylcholine, which demonstrated that smaller and larger doses had similar results. We had examined soldiers and sailors recovering from burn injuries suffered in Viet Nam. We measured changes in plasma potassium after injection of succinylcholine at varying times after their thermal injury, and correlated them with EKG changes. (Gronert, Dotin et al, 1969).

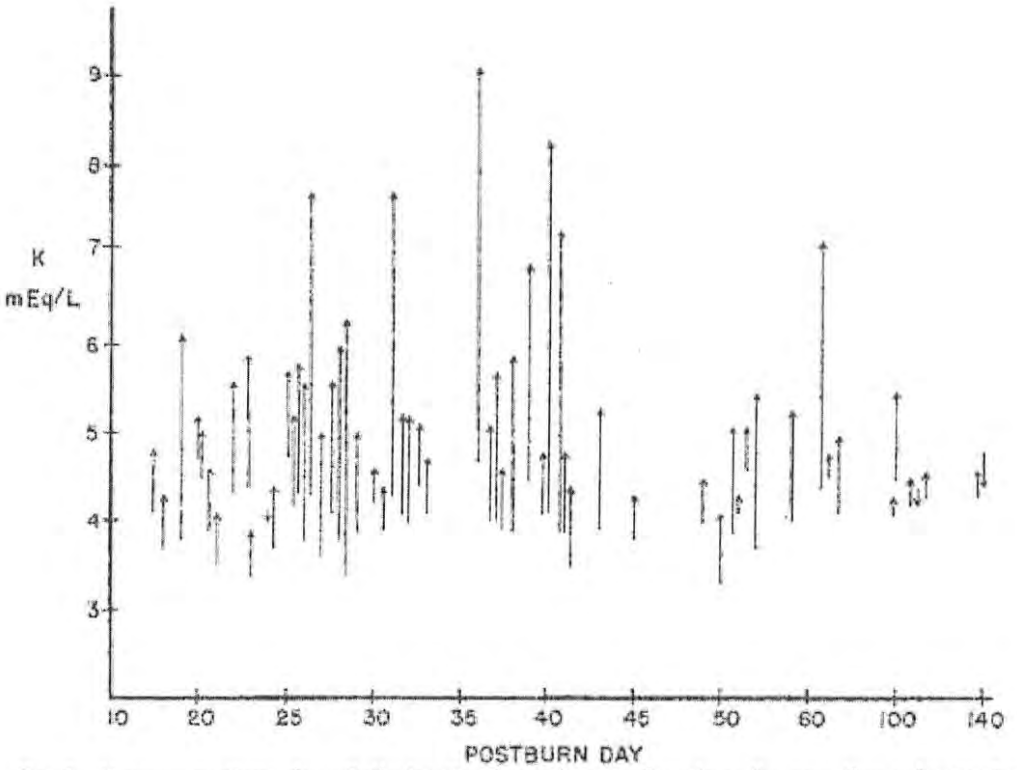

FIG. 2. Abscissa: postburn day. Ordinate: the change in potassium from the zero time value to the maximum value following the injection of succinylcholine.

Fig. 9. Note that the potassium value on day 36 increased from a baseline of 4.7 to 9.1 mEq/L. (Reprinted with permission from Succinylcholine-induced hyperkalemia in burned patients – II, by Gronert GA, Dotin LN, Ritchey CR, Mason AD Jr, Anesthesia Analgesia, November-December, 1969; 48:958-62, figures 2, 3, copyright owner Lippincott, Williams & Wilkins, www.LWW.com (for figures 9 and 10 of this memoir).

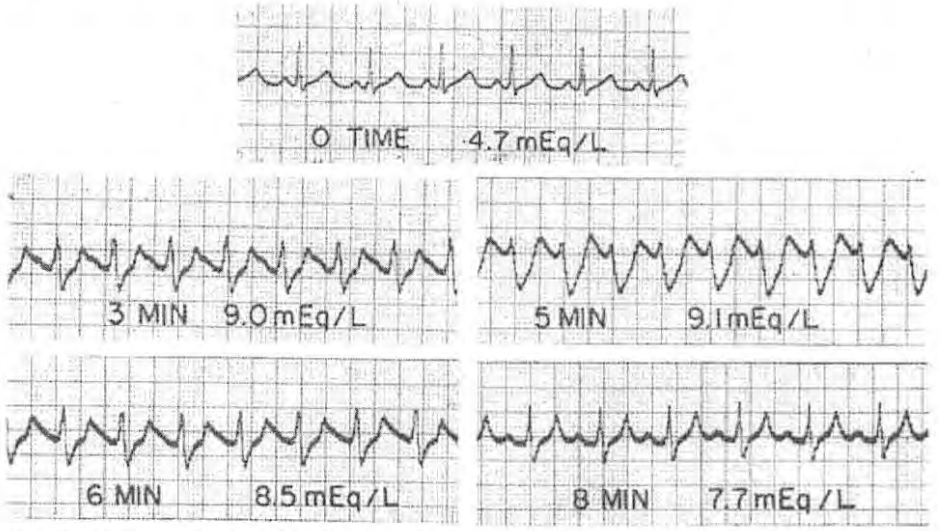

FIG. 3. Continuous tracing of lead II in patient with burn involving 25 percent of body surface area, 12 percent of which was 3rd degree, given 24 mg. of succinylcholine (0.4 mg./kg.) intravenously. 0 time: normal sinus rhythm. 3 min.: widened QRS, peaked widened T-waves; P-wave no longer evident. 5 min.: further widening of QRS and T-waves; pattern similar to ventricular tachycardia. 6 min.: slight narrowing of QRS and T-waves; QRS more recognizable. 8 min.: normal sinus rhythm with slight widening of QRS, and marked peaking of T-wave. (This is the usual pattern in an electrocardiogram diagnostic of hyperkalemia; it progresses into the above patterns with serum potassium above about 8.5 mEq./L.).

Fig. 10. The prior Fig. includes the entire group of study patients. (See Fig. 9 for permission.)

The hyperkalemic response begins in burn patients about one week post-burn, and diminishes when the patient has good skin graft coverage, becomes active and mobile, begins eating well, and is gaining weight. We further noted that non-depolarizing relaxants do not result in hyperkalemia (Carr et al, 1969).

My colleague Paul Schaner was to present an abstract of our early burn succinylcholine data at the 1968 annual meeting of the American Society of Anesthesiologists in Washington DC, but a family emergency called him home. This was my first presentation at a professional meeting (Schaner, Gronert et al, 1968). It was at that meeting that Hermann Rahn, the magnificent physiologist from the State University of New York at Buffalo, presented his concepts of relative alkalinity with the best Rovenstine Memorial Lecture I have ever heard. It complemented much of what I'd learned of acid-base considerations in medical school, internship, and residency.

Late summer 1969 ended my military commitment and I returned to Mayo. Using vacation time on our way home, we traveled via Washington, DC and were at services in the National Cathedral, where we watched our astronaut walk on the moon, and heard the striking comment: "One small step for mankind."

Chapter Twelve: Mayo Clinic -- Neuroanesthesia

Mayo is unique: isolated, organized better than most, productive, adaptable, and supportive. It is a small city in southeastern Minnesota, 75 miles south of Minneapolis/St. Paul, and about 350 miles northwest of Chicago. It is a company town, originally only with Mayo, and later, an added IBM development plant. We initially lived in Rochester, but later moved to a small farm, near the village of Pine Island.

Mayo Clinic has large outpatient, administrative, and research buildings in addition to its two hospitals. Its anesthesia group included staff physicians, nurse anesthetists, residents, and nurse anesthetist students. At that time, there were 75 operating rooms in the two hospitals: Methodist, across the street from the downtown clinic buildings, and St. Mary's, a mile west on Second Street. Each specialty area, consisting of anywhere from four to 15 operating rooms, had its own anesthesia physicians, supervisory nurse anesthetists, staff nurse anesthetists, and rotating residents and student anesthetists. With this arrangement, there was virtually no poor anesthesia care, because several persons checked on each case. Most areas had good care, and some superb care. The system's main strength was in its long term people. These upper mid-westerners were serious and conscientious about the quality of their work. They virtually never missed work, no matter how severe the Minnesota weather.

In Rochester, an individual's balance and ego support were sometimes tenuous because of the number of capable people. There was the feeling that this was a large pond in a small place, with only a few big fish. Mayo took very good care of its physicians (described by some in maternal terms). It provided a decent salary and comprehensive family health care. It did your income taxes, granted generous vacation and professional absences, and supported your practice with capable aides, technicians, and nurses.

Mayo did well for medicine, and capable people were enticed to work there. The organization of record keeping and its efficiency was and is phenomenal. The Mayo ego manifested itself in those who took it seriously, and that, at times, offended others. But that could be neutralized. On one occasion, I rented a car at O'Hare airport in Chicago.

The clerk asked me where I was employed; I replied, 'Mayo Clinic."

He said, "Is that spelled m-a-l-e?"

That broke me up and reminds me of Bill Clinton's experience at a home for old people with Alzheimer's. He was walking along a corridor, caught up with an older man, walked with him, held his hand, and asked, "Do you know who I am?"

The man replied, "No, but ask the woman at the desk, she'll tell you."

Neuroanesthesia

Neuroanesthesia, with colleagues Jack Michenfelder and Kai Rehder, involved four neurosurgical operating rooms until 1981, when a new wing expanded it to six rooms and two induction rooms (each placed between a pair of operating rooms). Annual case numbers included about 500 craniotomies; there were an additional 250 sitting-position procedures (posterior fossa exploration, cervical spine procedures), craniotomies for vascular cases and tumors; 150 trans-sphenoidal hypophysectomies; 150 carotid endarterectomies by the vascular neurosurgeons (vascular surgeons had their own carotids), and lumbar laminectomies.

Each surgeon operated every other day, and saw patients in clinic on alternate days. Internists, neurologists, and pediatricians evaluated patients in addition to surgeons. If they had a surgical problem, they were placed on the next day's schedule, no matter how full it was. There could be long days in the operating rooms.

It was only a few years before I began my neuroanesthesia career that neuroanesthesia was updated at Mayo, when they switched from ether to halothane. Many patients were operated on in the prone or face down position, particularly for operations opening the back of the head or neck. An experienced and capable senior nurse anesthetist I worked with, Bernadine McGovern, who celebrated her 90th birthday a few years ago, vividly described that experience. Supervised by an anesthesiologist, she sat on a small stool under the head of the operating table, poured ether into a cloth, and held it up to the face of the intubated patient to maintain anesthesia. She stayed that way for several hours at a time, with periodic relief. As she put it, she was determined to make this anesthetic the best possible. This approach would be unbelievable in this day and age. She was breathing fumes almost as much as the patient was! Wonderful stamina, but she was steady and reliable and a wonder to work with. One particular aggressive neurosurgeon insisted on use of ether, because it was the only agent and technique that he'd seen. He finally changed when he saw that patients given the new agent halothane didn't lie in the recovery room retching and vomiting. This was so routine with ether that he believed that this was part and parcel of all anesthesia.

Dave Dahlin, the Mayo pathologist with expertise in bone diseases, and I became handball partners and good friends. He added much to my adaptation to Mayo life, as he was practical, unaffected although famous for his contributions to diseases of bone, and didn't suffer fools. He was a South Dakota farm boy who decided to go to medical school. As he put it, when plowing a field, he sat on the plow behind the harnessed mare. Going into the wind on a hot summer day, when she had to pee, the warm shower all over him was easily the best promoter of a field other than farming. He and I graduated from the same medical school, although he preceded me by 20 years.

Thor Sundt, My Second Hero in Life

Thor Sundt was a parallel in character and personality to Art Prevedel. They were selfless and always providing for others, hard workers, and as surgically skilled as any I have seen. I've already described Art's performance under unexpected pressure. Thor was a vascular neurosurgeon who behaved similarly when confronted with unexpected major challenges. He performed carotid endarterectomies, and became Mayo's leading surgeon for ruptured aneurysms. He earned grant support for laboratory research and had collaborative projects with Jack Michenfelder, due to their combined interests in the metabolism and circulation of the brain. He was well respected and had his ego well under control, despite his fame in neurosurgical practice and research. He supported his staff and was beloved by his patients.

Lois and Thor Sundt had a bull mastiff, Winston, who resembled the historical Winston Churchill. One day he bit down so hard on a bone that he locked his jaws on it. I came over to their home, and injected thiopental, intravenously. He slept easily. Thiopental doesn't relax muscles very well, even though the patient is deeply asleep, and we had to pry Winston's jaws open with a crowbar to remove the bone.

Thor developed multiple myeloma in the 1980s and continued to work throughout. CBS' 60 Minutes devoted a program to him, helping to document his contributions and his continued clinical and research productivity despite his disease. He died in 1992. Art had died in 1989, several years after developing metastatic colon carcinoma, and the loss of them both was indeed great.

Impressive Talent in Anesthesia at Mayo

When I became faculty at Mayo in August 1966, several other anesthesia people entered the picture. Roy Cucchiara (later chair of the anesthesia departments at Mayo and then the University of Florida, Gainesville) came from New Orleans as a six week medical student preceptor in anesthesia, and

I was his mentor. Joe Messick (a solid contributor for Mayo's anesthesia department and its teaching) came from a Navy residency, and Sheila Muldoon (later chair of the department at the Uniformed Services School of the Health Sciences, Bethesda) came from anesthesia training in Ireland, both for anesthesia fellowships.

Dick Theye was the chief of anesthesia research, with Kai Rehder and Jack Michenfelder starting their own programs at Mayo. Kai, a former Mayo research fellow, had just returned from Germany to stay in the U.S. He had fought in World War II as an artillery gunner helping to protect Hamburg, and was in terrifying situations for a teenager. When he emigrated from Germany and was questioned about military service, he said that he'd served, and nothing more was asked, even though he'd fought for the opposing side!

German academic anesthesia practice had frustrated him. As he described it, the surgeon was the dictator: at the end of a case, he not only decided whether the anesthesiologist could bill the patient, he determined the amount.

Theye was discerning, tough, clever, and coldly objective. He could be supportive or unfairly damning. He respected those who would stand up to him and his abuse. He was a member of the American Board of Anesthesiology and an emotionally mutilating examiner to candidates taking the oral examination for certification. John Kampine (former Chair, Department of Anesthesiology, Medical College of Wisconsin, Milwaukee) was a junior examiner with Theye, and said that his behavior could at times be awful. Cucchiara took his boards in Minneapolis and was waiting in the hotel corridor with other candidates outside their respective examining rooms. Roy knew Theye well, since he had performed research in his laboratory. (The board examination comes in for greater detail later on.)

The door of the room next to his opened and Theye's voice boomed out, "OK, come in here – let's see what you can do to kill your patient!"

His candidate's nervousness prior to entering the room was nothing in comparison to how much worse it was after this diatribe. Joe Garfield, an anesthesiologist colleague of mine at the burn unit in San Antonio, had Theye as an examiner in spring, 1969. Joe, who passed, described Theye as a first rate agent for the FBI. His questions were deliberate, defined, pointed, and without a single unnecessary word. Theye was tough but not unfair to him.

Theye told me a story of Nick Greene and the first edition of his landmark monograph on spinal anesthesia (Greene, 1958). The late Dr. Greene, later my good friend and an overall excellent influence,

was a well regarded academic anesthesiologist. He had trained at Harvard, been chair at Yale, and edited two major anesthesia journals – *Anesthesiology* and *Anesthesia Analgesia*. But his first edition on spinal anesthesia had a major error in physiology, because he had mis-interpreted what took place after a spinal anesthetic took effect.

Theye corrected Greene's error in physiology. Greene had stated that the sympathetic block and vasodilation of spinal anesthesia would lead to a greater volume of blood in contact with cells, and a greater uptake of oxygen (Greene, pp 52, 54). However he failed to assess this in terms of reality: tissue oxygen consumption increases only with increased muscle tone or activity, increased temperature, or in the situation of prior inadequate blood flow, as is sometimes seen in septic shock (Bihari et al, 1987). Oxygen consumption of a tissue (or the leg) is the product of blood flow and the difference between arterial oxygen content and that of venous outflow. Greene saw increased blood flow in the leg, but that only implied greater oxygen availability to the tissue, not increased consumption. In actuality, venous oxygen levels increased, because extraction was unchanged, while flow had increased.

Greene appeared to be confused with the increased whole body extraction of oxygen and the resulting diminished mixed venous oxygen content, due to the well documented diminution in cardiac output during spinal anesthesia (Greene, pp 52, 67). In the leg, since overall tissue oxygen consumption is unchanged, there is less oxygen extraction from the blood, and femoral venous oxygen content increases (p 54). At that time, there was little data reporting increased femoral venous oxygen levels, and Greene had questioned the results of the single study reporting it. He corrected his error in later editions.

Theye discussed the great variations in academic mortality uncovered by the National Halothane Study (National Halothane Study, 1969). The study estimated unexplained mortality after halothane anesthesia, since there was an onus on halothane as a hepatic toxin. There were fewer than ten unexplained deaths following its use among some 900,000 anesthetics in 35 hospitals, documenting the safety of halothane (see prior discussion of our early US Army Burn Unit publication).

Surprisingly though, there was a ten fold difference in mortality among academic centers in healthy patients undergoing surgery that was unlikely to have significant mortality. This dramatic disparity has never been explained, and, as Theye stated, no one has investigated it.

Academics Can Be Nasty

Theye wasn't the only academic who showed nastiness. At a meeting in the 1970s of the Association of Academic Anesthesiologists (AUA) --- the honor society of academic anesthesiology --- some expressed concern regarding the increased numbers of foreign medical school graduates entering anesthesia. A clever, articulate, humorous U.S. academic chair, an immigrant himself from an English-speaking country, rose to speak at a floor microphone. He said that this influx was an embarrassment, and described these immigrants in colorful, insensitive, racially-insulting terms. My recollection is that some thought these comments were hilarious in context, but others properly and strongly criticized the speaker.

Theye as Mentor

Theye was a potent and capable investigator and administrator. He was my mentor in research and provided sound support and advice. He knew what to avoid and how to gain the most benefit in planning a series of studies. He realized the dictum, that mentoring has to be performed consistently over a sustained period of time and preferably one on one. I appreciated his example when I began to mentor others.

Mayo encouraged research and directly supported it. For each dollar of an individual's NIH funding, Mayo provided matching funds, a generous practice virtually unheard of in other academic institutions. Mayo recognized the value of research in maintaining reputation and standing. In my research, I had the additional funds and 50% non-clinical time. Theye loosened his oversight as I progressed. After his death in 1977, I became principal investigator of our NIH grant, and renewed the five year grant in 1979. After 1984, my numerous grant proposals were not funded. An NIH grant is invaluable in support of research, as it provides money from the federal government rather than drain the lesser reserves of a university or clinic. It automatically provides non-clinical time for research, which many institutions don't provide unless you have outside funding. However mentoring was not easily productive.

At the University of California at Davis, I mentored five potential researchers in anesthesia. To begin studies, and to maintain the effort, requires a certain fire and drive, and perhaps a more effective mentor. Several of my young researchers were but briefly effective. Joe Antognini persisted and succeeded. He was a bright and inquisitive senior resident when I arrived at Davis, and, after finishing, was in private practice for four years before returning to academia. He had always wanted to study

mechanisms of anesthesia and had determination. He initiated his research while still in private practice, and found it fascinating.

Joe needed minimal mentoring, but he needed it immediately when he did need it, and I was always available. Once started, he simply soared into productivity and earned NIH grants. I did direct him to his goat model of cerebral vascular isolation for study of spinal cord vs. brain mechanisms of anesthesia; once involved with that, his mentoring needs were minimal.

Eulogy – Best to Just Sit Down

Theye died of the bulbar form of amyotrophic lateral sclerosis in fall 1977. He was Jack Michenfelder's mentor and close friend. At the next AUA meeting after Theye's death, the president asked Jack to provide a eulogy. Jack agreed, since he knew that if he refused, the president would ask someone else. At the meeting, Jack stood up and said, "For those of you who knew Dick, the most appropriate thing I can do is sit down," which he did. Jack unfortunately died in May 2004 of a self-inflicted cranial gunshot wound.

Dick, Jack, and Kai furiously guarded their research commitment and non-clinical time, and could be nasty about it. They were all more or less fascinating, but at times inconsiderate and harsh to others. Their defects reflected their ambition and intense drive. Kai had the Teutonic-directed superior ego. Jack was quite an actor and assumed roles depending upon need and goals. He could be friendly or otherwise, and acted within the rules, but barely. He was more talented than most at discerning the essence of a problem. He had a great sense of humor, and was clever, but on occasion characterized hard working people with such cutting sarcasm and biting humor that it became awkward and uncomfortable.

Others laughed, but the victims, even years later, never forgot. Jack spared no one and challenged anyone. He didn't follow diplomacy, or any rules except his own, and those were sometimes difficult to identify. There were three women on the anesthesia faculty, and he characterized the most successful and conscientious as the 'best of a bad lot.' Her hard feelings were not expressed to him until years later, during a private discussion. She described it to me, and said that even afterward it was a bitter memory.

At this time, the old theory that surgeons were captain of the ship was being balanced by the role of the anesthesiologist. As Jack put it, when one neurosurgeon claimed that we worked for him: "We don't work *for* the surgeon; we work *with* the surgeon *for* the patient." When that wasn't strong

enough, he said that if the surgeons ran the ship, then they had to go to court in our place for any lawsuits. That ended arguments between them and us. Besides, they soon realized that we offered far more than they could in patient management during a difficult procedure. The solution to this problem had started for me in private practice.

In general, surgeon-anesthesia relationships were easy and respectful at Mayo. One contribution to overall neuro specialty rapport was the monthly good-natured poker games organized by Jack. It included anesthesiologists - Jack, Brian Dawson, me – and neurosurgeons - Ed Laws, Sundt, Burt Onofrio, and George Baker – sometimes a pathologist, sometimes a radiologist. These games rotated among the various homes, with food and liquid refreshments provided by the host. They started about 8 p.m. and ended promptly at midnight. They were frequently hilarious and effective in easing working relationships. About $25-30 per person, at most, changed hands.

In fall 1966, Kai, Jack, and I began writing a review on neuroanesthesia, perhaps the first comprehensive one on that topic, published in Anesthesiology (Michenfelder et al, 1969). I prepared and wrote 1/3 of the manuscript with guidance from Jack and Kai, an in depth learning experience. The title's brevity (Neuroanesthesia) was unfortunately ignored when the neuroanesthesia subspecialty group began its own journal several years later, with its wordy title.

About this time, our chair Albert Faulconer and I discussed my possibilities for non-clinical research time supported by Mayo until I earned an outside grant. I cited Theye's change from private practice to research and wished to do the same. Faulconer was not particularly encouraging or supportive. He reminded me that Theye had been first in his class in medical school at the University of Indiana, and that I had not, at the University of Illinois. I didn't argue about my relative merits, nor my concomitant jobs, but waited until later. At that time at Mayo, I was trying to advance my academic standing.

Chapter Thirteen: Mayo post U.S. Army – Neuroanesthesia, Research

In September 1969, I returned to Mayo neuroanesthesia and a quest for research time to investigate succinylcholine-induced hyperkalemia. Additional reports now documented similar hyperkalemia in patients with direct muscle trauma (Birch et al, 1969), upper motor neuron lesions such as cord section (Cooperman et al, 1970) or stroke, and lower motor neuron lesions such as peripheral motor nerve dysfunction, poliomyelitis, or Guillain-Barré syndrome (Case History, 1971).

One report suggested that pre-treatment with curare prior to use of succinylcholine prevented dangerous potassium efflux (Birch et al, 1969), but the response of one of our burn patients contradicted this interpretation (Gronert, 1970). Later reports confirmed its ineffectiveness.

Neuroanesthesia Publications

My role in neuroanesthesia involved both clinical care and clinical research. We had multiple projects, with fine leadership from Michenfelder.

Cucchiara documented 3827 sitting position cases at Mayo from 1966 through 1983 (average number of sitting cases per year was 240), with no intra-operative deaths, and just 2 major complications, incidence 0.05% (Cucchiara, 1984). The only death due to air embolism occurred during a prone position patient of mine, in the 15-20º head up position (Gronert, Messick et al, 1979). This case occurred prior to use of the Doppler. The neurosurgeon, Colin McCarty, was removing a meningioma from the posterior dura mater. He tented up the dura to clip a bleeding vessel. The dura mater at that point overlay the trigone, and the hole in the dura permitted massive entry of air into the venous channels.

In that position, with the head close to being level with the body, we did not suspect the possibility of air embolism. The heart sounds abruptly disappeared and the arterial monitoring trace went flat. The EKG appeared normal for about two minutes. Resuscitation was unsuccessful. I attended the autopsy that afternoon; there were several hundred ml of air in the patient's superior vena cava and right heart, with air in the coronary arteries via a patent foramen ovale.

In our experience, air embolism of greater danger was more likely to occur in posterior fossa cases, rather than cervical spine cases. For the latter, the sitting position provides superior advantages:

less venous pooling, less tissue swelling, less blood loss, and easier visibility than the prone position. I have worked with enough neurosurgeons - some preferring the prone position, some preferring sitting - to be convinced that the sitting position is preferred for cervical spine surgery if the anesthesia-surgical team is experienced in that approach.

Vascular neurosurgery was prominent at Mayo, with cooperative operating room contributions of neurosurgeons, neurologists, and anesthesiologists. There were several areas of interest. One continuous ongoing project involved multi-monitoring of patients undergoing carotid endarterectomy. Inherent in carotid surgery is the threat of inadequate regional cerebral blood flow with carotid occlusion, as this affects flow in the middle cerebral artery. The surgery is a serious risk and success depends in large part on a long-term well-functioning operating team that routinely works together, and is aware of the problems that can need immediate attention.

One approach utilizes regional anesthesia, e.g., deep cervical block; the anesthesiologist monitors the patient's level of consciousness, and ability to move the contralateral arm and leg. While in private practice in Denver, I performed deep cervical block for a number of awake carotid endarterectomies with one of the vascular surgeons, and it worked well. However, several demands must be satisfied for this risky procedure in an awake patient: for the patient, the proper personality and disposition during stress; for the nurses, everyday routine experience in the demands of carotids; for the anesthesiologist, skill in the nerve block and ease in communicating with the patient; for the surgeon, one who will not panic when something goes wrong. We did not use regional anesthesia in carotid surgery at Mayo, and this was not due to surgeons' factors.

The surgeon Thor Sundt and the neurologist Frank Sharbrough monitored regional cerebral blood flow with a collimator outside the skull, aimed at the area perfused by the middle cerebral artery. To measure regional cerebral blood flow in the middle cerebral distribution, Sundt injected small amounts of ^{133}Xenon prior to carotid occlusion, at the moment of occlusion, and during surgery on the occluded carotid. Sharbrough used a 16 lead EEG to monitor electrical activity over the entire brain surface. Sundt measured internal carotid artery shunt pressure during occlusion. These extraordinary approaches evaluated effects with varied monitoring and various anesthetic agents in carotid endarterectomy (McKay et al, 1976). Measurements of regional cerebral blood flow and the multi-lead EEG were of value in determining ischemia during occlusion and indications for an internal shunt. Stump pressure was of value only with critical value adjustments related to arterial PaCO2, and with the type of

anesthetic, e.g., volatile vs. narcotic based. The latter increased the critical value for stump pressure compared to that associated with halothane.

Some intra-cranial aneurysms are difficult to treat because they are deep within brain tissue and there can be substantial blood loss. This obstructs the surgeon's vision, particularly when using a mounted microscope for closer views of the deep, tiny field. A combined approach with Mayo cardiac surgeons was the application of profound hypothermia, utilizing surface hypothermia supplemented by a cardiac pump-oxygenator-heat exchanger. In patients with normal heart function, temporary cardiac arrest at a diminished body temperature (12□C, 53.6□F) permitted bloodless access for some 30-40 minutes while the neurosurgeon clipped the aneurysm. Bypass cannulas were inserted into major vessels in the groin in readiness for bypass. The chest was not opened. Bypass was not started until the head was open, the surgeon had dissected the aneurysm, and s/he was ready to clip it (Sundt et al, 1972). Once the aneurysm had been clipped, the heat exchanger in line with the bypass pump rapidly warmed the patient. Circulating water blankets with warm water continued to supply heat to the external body after the bypass pump was discontinued. Review of a large group of Mayo's profound hypothermia patients revealed that results were no better than a parallel group of patients having surgery at normal body temperature. After that, profound hypothermia was used only in very difficult-to-expose aneurysms.

An early neurosurgeon, Temple Fay (1959) of Philadelphia, applied hypothermia beginning in the 1930s in treatment of brain tumors, since the lowered temperature slowed tumor growth. He used two approaches: hypothermia via cooling the entire body, and localized hypothermia. Fay noted that whole body hypothermia, prolonged for several days, had an associated mortality rate. For localized hypothermia, he placed catheters within the brain, and cooled just that portion. At least one patient did not seem particularly bothered. Fig. 11. (Fig. 8, in: Fay T, Early experiences with local and generalized refrigeration of the human brain, Journal of Neurosurgery, May, 1959, number 3; 16:239-260, used with permission. www.thenjs-net.org)

Fig. 11. See text

In one complex case, June, 1981, Mayo neurosurgeons, anesthesiologists, obstetricians, and pediatricians combined Caesarean section delivery with clipping of an intracranial aneurysm (Lennon et al, 1984). The patient's family and I have remained in contact ever since. In spring 2007, the patient's husband surprised me by providing for the first time his specific recollections and impressions about his interactions with me prior to surgery. The reader needs to interpret this story in terms of the stresses this family suffered, their terrible expectations – beginning as soon as someone told them about the ruptured aneurysm – and the realization that, while the risks were considerable, the procedure went well. The family graciously permitted me to include their story here, based on how they recall it:

The patient, a 35-year-old nursing school teacher, and her husband had been anticipating an August delivery of their second child and were on vacation near Brownsville, Texas, about 200 miles from home. Her aneurysm ruptured early on a Sunday morning and she was admitted to a local hospital. Her condition, especially in light of the pregnancy, was critical and called for intervention beyond the resources available. Based on the recommendation of the attending neurosurgeon, she was transferred by air ambulance on Tuesday afternoon to Mayo, about a 1300 mile flight. Her husband and a friend flew commercially, and had departed Houston before his wife had arrived in Rochester. He couldn't find out whether his wife or child had survived the flight until after he landed. On arrival in Chicago, he anxiously phoned St. Mary's hospital in Rochester. Without identifying himself or his wife, he told the operator that he was seeking information on an emergency patient from Texas. The operator immediately said, "I'll connect you to her room." Which she did.

The husband and his friend were trial lawyers and long time acquaintances, both knowledgeable about medicine. The husband had once been a surgical technician. In Texas, they had been advised that the patient could die at any moment, and that the baby gave every indication of being healthy and viable. They had been in a strange place for less than 18 hours when the aneurysm had ruptured and he had authorized transfer of his wife to Mayo without having ever talked to anyone at Mayo. Furthermore, he had no idea how his wife was doing, nor the future plans for her care. He knew nothing about Dr. Sundt or me, except that the Mayo staff said that Dr. Sundt and I had worked there a number of years.

Her husband was apprehensive about meeting the physicians; the consultation took place at 11 a.m., adjacent to the ICU, in a large room reserved for family meetings or physician conferences. All that her husband knew was that they would meet with "the doctor." I had been chosen to discuss the surgery with them, as I was the only involved physician who had direct and active experience with the

combination of neurosurgery, obstetrics, and newborn resuscitation. I arrived in my scrub suit, and we huddled in a corner of the room, speaking in hushed tones since another family was being counseled at the other end of the room. Although not mentioned, they were concerned why, in a crisis of this magnitude, the initial contact doctor was the anesthesiologist and not the surgeon.

As he wrote in his letter, "it is very difficult to describe Dr. Gronert as he appeared to us. It is even more difficult to describe the conversation." He didn't specifically remember much of what was said, but what he does recall is that he received "a powerful lesson in communication." What I said in words was one thing. What he heard by way of communication was different and so important.

After short pleasantries and a brief summary of the backgrounds of Dr. Sundt and me, I began with the obvious facts and risks: his wife was gravely ill, and her not-yet-born baby was doing fine. Her angiogram showed two aneurysms, one of which was leaking or had leaked. Surgery would be the next day, and I explained that Dr. Sundt would operate on the aneurysm after the obstetrical surgeon performed a Caesarean Section and delivered the baby. I would provide anesthesia. The surgery was urgent, and required a team approach. I described how important it was for this dual surgical team to function cooperatively. I stated that the anesthetic would need to be balanced. For example, his wife's blood pressure could not increase during the C section, or it could force the clot off the aneurysmal opening and a re-bleed was potentially disastrous. Yet her blood pressure needed to be high enough to supply the uterine artery, or the baby would lack oxygen. I described a litany of risks and the percent likelihood of disability or death in mother and child.

I explained that I would control her blood pressure at the start and make certain before surgery commenced that I had enough control of her blood pressure to make it go up and down as needed during the C section and the craniotomy. I told them that the baby would be a bit depressed from medication his mother would receive that would cross the placenta into the baby, but that there would be doctors present to ventilate him to remove anesthetic gases and to reverse depressants.

These were the objective realities that I knew were true and which had to be covered. Her husband and friend with whom I was sharing this information received and processed these same facts. From their perspective, however, I was, with my own presence and personality, conveying another and probably far more important message on a different level. What occurred with this family is a profound lesson about doctor patient communications on life and death issues and proof that a physician's words may sometimes be only part, and perhaps a less important part, of the ultimate message that is conveyed.

The conversation, viewed as a whole, was, according to the husband, "... absurd from an intellectual perspective." He recalls it this way:

"Here my friend and I were, in a room speaking with you, someone we had never heard of and never met, a long way from home, and in a very few minutes and with minimal preliminaries you just rolled out one after another of several possible fatal scenarios. As you were speaking, I was doing calculations in my head. The totals for these percentages meant that the probability of my wife being dead the next day were substantially above 50%. My mind was reeling as I tried to contemplate in just seconds these awful possibilities. Then, in a somewhat rapid fire fashion, you told us that you, Dr. Sundt, and the other physicians would be ready for whatever might happen. Then Dr. G said the most *incredible* thing, "Don't worry, I think that she'll do as well as we can ever expect." In what seemed like just a few minutes more, you were gone.

My friend and I were then alone in the big silent room, the other family having left while we were talking with you. Any rational view of what just had transpired would conclude that now we would be ever more fearful than we were before we met you since now we had replaced anxious speculation with medical fact as to what might happen to my wife and baby.

But, the minute you left the room, my friend and I looked at one another in dumbfounded amazement. We were not despairing. On the contrary, we felt relief and a kind of paradoxical euphoria in that we now felt, after being in your presence, that we had done the best we could ever have done for my wife and baby in getting them to you and Dr. Sundt."

In these few moments together, and in the face of their quite rational apprehension and fear, as her husband put it, my words alone were about risk and matters of practice and technique. But, as her husband reported, the deeper message I communicated was something else: "What we really felt in that brief visit, was your persona, your spirit and humanity, and, above all, your optimism. The real message was that you and Dr. Sundt and the entire team would do as much as humanly could be done for my wife and baby, and that we could trust you for that. Your spirit allowed us to let go of the elephant of fear on our back. Nothing objectively had changed. The risks were the same. But because of you everything was different due to our decision made then and there to simply have faith in you and Dr. Sundt."

Something in my spirit and optimism and in the equivalence of trust that arose in that brief moment together led to his willingness to let go of morbid fear. In retrospect, I don't know how I did it.

The next morning, the husband recalled, I came 'flying' down the hall with a surgical stretcher to take his wife to surgery. There was no time for any conversation that morning. But he reported that he felt complete confidence in me and gratification that I had personally come to reassure his wife and be with her from start to finish on what would be a momentous and life-changing journey. Only after I had taken his wife to surgery did he meet Dr. Sundt for the first time and only for a brief moment. But it didn't matter --- he now had seen the Master, Dr. Sundt, and that was enough. Even to this day, he and his family remain in touch with Dr. Sundt's family. (Dr. Sundt was perhaps shy with families; on another occasion, he told this same family that he had stopped doing pediatric surgery because he could not take the emotions of dealing with kids, kids who put 100% faith in him at times when he knew that the outcome would be fatal.)

The New Yorker: Report on a New Anesthetic Agent

Because of concerns about volatile anesthetic agents, e.g., halothane and isoflurane, in increasing intracranial pressure, we measured spinal fluid pressure in craniotomy patients who did not have direct or indirect evidence of increased intracranial pressure (Adams et al, 1972, 1981). We noted that prior hyperventilation was needed to minimize ICP changes with halothane, but was not necessary with isoflurane. We postponed submission for publication of the isoflurane report – it was published 9 years later, because its introduction into clinical use was delayed due to the need for rebuttal of a scare concerning potential carcinogenic effects of isoflurane (Eger et al, 1978). The story is fascinating.

Thomas Corbett, in Michigan, had preliminary research results suggesting that isoflurane could cause cancer in rodents. He presented his data, in part, at the May 1975 meeting in Atlanta of the Association of University Anesthesiologists, but there was considerable criticism of his research. Because of problems in acceptance for publication in an anesthesia journal and Corbett's frustration that the pharmaceutical company would release isoflurane to the market by fall 1975 anyway (to coincide with the annual meeting of the American Society of Anesthesiologists), he contacted the FDA (Brodeur, 1975).

Because the data seemed sufficiently suspicious, the FDA withheld approval and delayed the introduction of isoflurane. In time, Corbett's findings were not substantiated (he is a co-author of the rebuttal study, Eger et al, 1978) and the FDA approved isoflurane.

Brodeur's article in *The New Yorker* described the turmoil. Corbett had been understandably concerned with potential long term toxic effects of anesthetic agents and that some of these might

involve carcinogenesis. He and his wife had noted that the odors of whatever agent he had used during the day were obvious upon his return home, even on his breath. What long term effects might accrue from this?

Corbett's fascinating distractions occurred during our investigation of the puzzles of hyperkalemia after use of succinylcholine.

Hyperkalemia Research – a Blank Beginning

Non-clinical time for laboratory research was finally mine. Theye and I planned further study of the hyperkalemic response to succinylcholine in patients with thermal trauma. The main question now was: why did hyperkalemia after administration of succinylcholine occur in burn patients who had no evidence of muscle damage? Why should burned tissue be involved with this?

After evaluating the literature and various animal models, I proposed a swine model. A deep thermal burn that did not affect muscle would eliminate damaged muscle as a potential potassium source. Also, a full thickness burn would be painless if its border had minimal second degree burn. That's because the skin's nerve endings in a third degree burn are destroyed. We could produce this by briefly dipping anesthetized swine into boiling water. There would be a sharp demarcation between burned and normal skin, thus no pain.

A major problem was to convince the Mayo animal care committee to permit this sort of destructive, disturbing, and, to some, alarming study. Here Theye was invaluable; the protocol had been approved, but on the first day of study, several investigators assembled outside the laboratory to protest and hopefully block this new inexperienced investigator from starting. Theye profanely raged like a wounded bull out there in the corridor and that ended any and all protests.

The study went fine. The pigs were anesthetized with halothane by mask, their tracheas intubated, and thermal trauma produced by holding them upside down and dipping their backs into a trough of 95º C, 203º F, water for 20 secs (Fox et al, 1947). I personally cared for these swine, much as we had for the U.S. Army burn patients: individual pens, supplemental feedings, twice daily baths followed by Sulfamylon (mafenide) ointment, and close attention for signs of superficial or systemic infection (there were none). The pigs were healthy and maintained their weight. Sulfamylon had been used in thermal trauma for only a few years, and it was a virtual miracle drug in its efficiency in controlling infection.

We anesthetized these swine each week while they were recuperating and injected succinylcholine. None developed hyperkalemia. We either had too small a burn, or the wrong species. To confirm that swine did develop this problem, we additionally examined succinylcholine-related potassium changes after sciatic nerve section, thus denervating the muscle. This confirmed that swine were an appropriate species (Gronert, Theye, 1971).

While the model was inadequate for study of burns and hyperkalemia, it did provide departmental barbecues at our farm home. These barbecues used pork that had not been damaged in a study. The National Institutes of Health banned this approach a few years later. On one occasion, I used our horse trailer to bring home the last pig from a study. When our eight-year-old Mary asked about it, I said that this was Esmeralda. She thought that it was neat to have a pig, until the next morning, when I took Esmeralda to the Pine Island Meat Market for slaughter.

Our First Porcine MH Episode, Death Due to an Open Oxygen Valve

One pig was unique in our burn/hyperkalemia study: after receiving succinylcholine, it developed MH (malignant hyperthermia), with acidosis, rigidity, and pronounced fever. We routinely measured esophageal temperature and serial arterial and mixed venous blood gases in these animals, valuable aids when MH started. With rigorous symptomatic treatment, we saved this pig. When we could finally relax our efforts, we took him off the ventilator for spontaneous breathing and attached a plastic tube to the endotracheal tube for added oxygen. When we opened the high pressure valve on the G tank of oxygen, the flowmeter had unfortunately been left full on. There was a large poof as the high pressure (2000 lb/in^2) oxygen ruptured the lungs, stomach, and diaphragm, and the pig turned into a true pigskin, or American shaped football.

We regretfully lost our first MH research pig, but we now knew that we could study MH, as Theye had already designed the methodology for studying specific organ metabolism during anesthesia (Theye et al, 1975). This was perfect for investigation of MH, but that was postponed until later.

Hyperkalemia Research Is First

We examined the release of potassium after succinylcholine, and quantitified canine potassium efflux from gastrocnemius muscle during four states that reflect varying muscle abnormalities. Its blood supply is simple, and we could totally isolate the venous drainage that enters the general circulation. We

collected and measured total blood flow of the muscle and its venous potassium and oxygen contents for comparison to the blood arterial content. General anesthesia was used in all investigations.

Our four conditions were: 1) normal muscle in active healthy dogs; 2) denervated muscle, a lower motor neuron lesion due to section of the sciatic nerve (Gronert, Lambert et al, 1973); 3) disuse atrophy related to cast immobilization of the pelvis and one hind limb (Gronert, Theye, 1974); 4) an upper motor neuron lesion produced by section of the spinal cord at the level of the sixth thoracic vertebra (Gronert, Theye, 1975). The last three conditions were studied in the laboratory one month after onset.

Denervation of the sciatic nerve eliminates muscle stimulation by halting release of acetylcholine from the motor nerve ending to its site of action at the muscle endplate receptor sites. Extra acetylcholine receptor sites now develop all across the muscle membrane. Succinylcholine, composed of two acetylcholine molecules connected by an ester linkage, acts as a long-duration acetylcholine. Succinylcholine, like acetylcholine, stimulates individual receptor sites to release small amounts of potassium. The circulation carries succinylcholine to the entire muscle membrane, and thus stimulates potassium release at the added receptors, with cumulative greater amounts.

We measured several effects of succinylcholine in the denervated state, condition 2 (see above): Ed Lambert, the pioneer in electromyography, brought electromyographic equipment to our laboratory and demonstrated in canine denervated muscle the silent muscle uncoordinated stiffening (contracture) concomitant with depolarization and exaggerated potassium efflux. This is a supersensitivity response. We were excited about these supposedly new and unique experimental findings until we found Brown's 1937 paper with similar findings in denervated muscle exposed to acetylcholine. Brown injected minute quantities of acetylcholine to examine the response in the laboratory. That exposed the entire muscle membrane to the acetylcholine. So, almost 40 years before, he had accomplished exactly what we had, and we no longer thought that we were wonderful. We again learned that few findings are new.

Quantitation involved measurement of venous blood flow, to estimate total blood flow through the muscle, and of the amounts of venous and arterial potassium and oxygen. The Fick equation permitted calculation of gastrocnemius potassium efflux and oxygen consumption after administration of succinylcholine:

quantity of substance produced (potassium) or consumed (oxygen) =

[blood flow X (difference between arterial content and venous content)]

This equation is accurate only if there is a steady state as regards blood flow, metabolism or excretion, perfusion pressure, etc. Otherwise we estimate values; we know whether there has been an increase or decrease, but the precise magnitude is uncertain. Our 1975 Medical Intelligence article summarized the field of succinylcholine-induced hyperkalemia (Gronert, Theye). Fig. 12. Note that potassium changes following succinylcholine are miniscule in the normal dog, are modestly increased during disuse atrophy, and reach toxic levels during upper and lower neuron lesions. (Fig 1, in: Gronert GA, Theye RA: Pathophysiology of hyperkalemia induced by succinylcholine, Anesthesiology 1975, July, vol. 43, number 1, pp 89-99, copyright owner Lippincott, Williams & Wilkins, www.LWW.com, used with permission.)

Human findings (Schaner et al, 1969; Gronert, Dotin et al, 1969; Viby-Mogensen et al, 1975) show that succinylcholine, because of the risk of cardiac arrest due to hyperkalemia, is contra-indicated in patients with serious burns between about one week post burn and about two months post burn, if healing is then complete as to skin coverage, and the patient is mobile and gaining weight. Canine results in conjunction with human findings demonstrated: 1) skeletal muscle disuse atrophy alone, unless marked over the entire body, does not contra-indicate use of succinylcholine, and 2) a

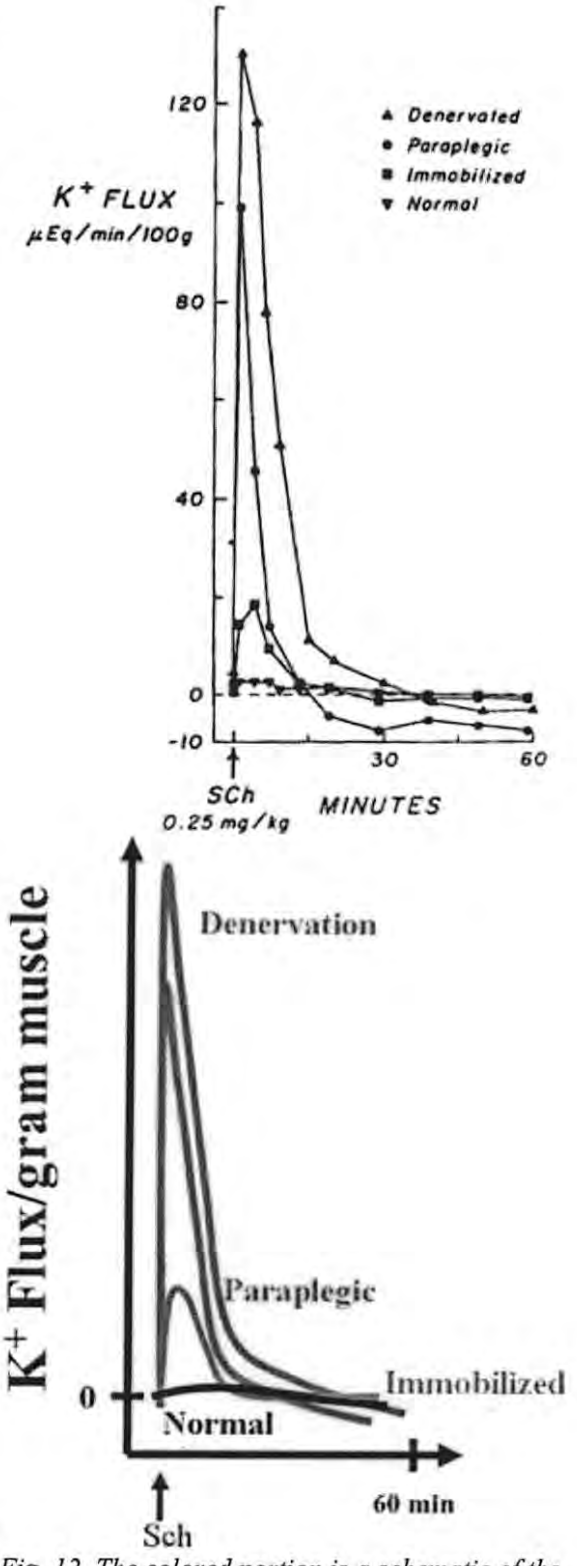

Fig. 12. The colored portion is a schematic of the upper portion

denervation lesion involving more than one hind leg, e.g., Guillain Barré, paraplegia or worse (quadriplegia), or stroke contraindicates succinylcholine. Furthermore, direct muscle trauma acts similarly to denervation and succinylcholine is not safe.

Other Muscle Relaxants and Abnormal Muscle

In 1985, two new shorter acting non-depolarizing muscle relaxants were introduced, vecuronium and atracurium. They would not produce exaggerated potassium release, since they did not depolarize muscle membranes, and thus were candidates for replacement of succinylcholine in patients who were at risk for hyperkalemia. However, they required greater doses than usual for rapid intubation. We investigated these in normal humans; the drugs were useful for that purpose, although their usual prolonged duration was exaggerated, and histamine side effects were pronounced with atracurium (Lennon et al, 1986). These side effects could be modified (Hosking et al, 1988).

LBJ and Mayo Conservatives

It's interesting that LBJ became a Mayo trustee at this time, the 1970s. Mayo is conservative and had never served alcohol at its dinners or meetings. When LBJ was told that, he said that they'd be serving it if they wanted him at any meetings. And they did. One of our conservative plastic surgeons said that he planned to push LBJ hard when they got together, socially, that evening, at the Mayo Foundation House. The morning after, the surgeon told us that that was impossible. LBJ walked into the room and effortlessly dominated it the entire time he was there. He controlled every conversation he was involved with, and countered anyone even before they began to express ideas. Our conservative surgeon was astounded, for he was himself accustomed to pushing others.

Tragic Anaphylaxis

Until 1981, the Mayo neuroradiology suite at St. Mary's Hospital was located on the floor just above the four neurosurgical operating rooms, directly accessible by a stairway. As the associated anesthesia team, we also covered this area, via a call light for aid and an alarm system for acute emergencies. A woman about 30-years-old received dye for a diagnostic study and immediately went into shock. The nurse anesthetist who monitored her called for help while she and the radiologist began therapy. When we arrived upstairs, we noted that she had hives on her skin, was loudly wheezing, was unable to breathe effectively, and had both a low blood pressure and an irregular heart beat. We intubated her trachea, and tried to ventilate her with oxygen, but this was ineffective, as her airways had shut down so completely that effective ventilation was not possible. Next her pulses disappeared,

and her heart sounds were gone. We performed external cardiac massage, but her bronchospasm was so tight that we couldn't force oxygen into her lungs. The entire process had been quick and nothing worked. This was no mystery but a terrible event. We had the proper drugs, experienced personnel, and appropriate equipment immediately available --- and we were helpless. How much frustration can one have?

Chapter Fourteen: Malignant Hyperthermia, Eerie Erratic Metabolic Mayhem

Now we began research into MH. This is an inherited disorder of skeletal muscle that occurs in swine and humans. Susceptible patients who appear perfectly normal, given a typical anesthetic, abruptly and disastrously change. They develop muscle rigidity, tachycardia, increased expired carbon dioxide, profound acidosis, and a rapid increase in temperature. These changes quickly result in heart failure, a shock-like blood pressure, and demise, with temperatures greater than 106º F, or 41º C. This is due to anesthetic-invoked increases in metabolism of skeletal muscle, which acts as though the patient is performing exhaustive full-scale exercise, such as finishing a marathon.

There is production of heat and acid, release of toxic intracellular substances, and fatal increases in acidosis and temperature if untreated. For the anesthesia provider, the typical safe anesthetic abruptly triggers this explosive alteration in vital signs and a devastating destruction of the normal state. The resulting alterations push the patient's tolerance to stress to an extreme. Dantrolene (reported in a swine study in 1975 (Harrison) and approved by the FDA in 1979) reverses these changes, but anesthetic agents must be quickly discontinued and dantrolene given before MH becomes uncontrolled. Because it can kill quickly, MH, although rare, even now continues to be a major consideration in the field of anesthesia. Effectiveness in porcine MH, almost identical to human MH, provided confidence that dantrolene would be effective in humans. It was a challenge to confirm dantrolene's effectiveness in human MH, since episodes occur in only about one in 50,000 general anesthetics. Efficacy was confirmed in a cooperative study involving 65 hospitals in the US and Canada in which dantrolene was stocked and ready to go, and given to those patients who unexpectedly developed an MH episode (Kolb et al, 1982).

I say 'confirmed,' although a statistical expert who analyzed the data said that the results merely 'whispered' efficacy (Forrest, 1982). Whisper or not, dantrolene is now, after years of use in treatment, fully recognized as the unique miracle drug in treating MH. The present mortality rate is estimated as less than 5%.

During my first year at Mayo in 1966-67, Kai Rehder, in a discussion in our then joint office, introduced me to MH. He had seen a few cases in Germany and was overwhelmed with their disastrous course. It was documented in humans in a 1960 case report from Australia (Denborough, Lovell). The

anaesthetist was Jim Villiers, who displayed admirable judgment in preventing a catastrophe (Ball, 2007). Prior to that, there had been subtle evidence about what, in time, was identified as MH, because there had been unusual familial fatal anesthetic responses.

As a teen, John Kampine, chair of anesthesia for many years at the Medical College of Wisconsin in Milwaukee, made rounds with his family doctor father in Wausau, Wisconsin. He'd see someone on the street, and tell John that that's a family whose members die during anesthesia. George Locher (Rockford, 1977) later practiced anesthesia in Wausau and was bothered by these unusual deaths. When he contacted the Department of Anesthesiology at the University of Wisconsin, Professor Karl Siebecker told him to return for updating his practice. That really irritated George, for he knew that these deaths were not the fault of his care, and were decidedly unusual.

As to the Denborough-Lovell case report, Villiers (Ball, 2007) was to anesthetize a 20-year-old man with a broken leg. The young man didn't fear surgery, but was terrified about anesthesia because ten of his relatives had died while anesthetized. The patient had had an appendectomy at age 12, and his anesthetic was infiltration of local anesthetic into his abdominal wall to avoid a general anesthetic. Villiers calmed him by saying that they'd use the new volatile anesthetic halothane. The young man had told Villiers that some of his relatives had died with high temperatures during anesthesia, so they measured it as they began anesthesia. A few minutes after starting anesthesia, the young man's limbs became stiff and rigid and his temperature increased, so the surgeon quickly finished and Villiers discontinued the anesthetic. This halted the MH episode before it could advance. It was later learned that halothane was a prime and potent trigger of MH.

The article by Denborough and Lovell opened a new field of research into abnormal metabolism, genetic analysis, and effects of anesthetics on skeletal muscle. In the 1960s and 70s, the mortality rate was greater than 70%. These patients could not be diagnosed as MH susceptible in the absence of anesthesia, as they appeared normal, and only certain stresses would trigger an episode. In addition, their muscle did not show abnormalities on histological examination under a microscope, as the abnormality is not structural, but functional. Biochemical processes became markedly abnormal once an MH episode began. This mandated development of a valid test for its detection. As with progress in emotional areas of medicine, MH testing has had an uneven course, with tests sometimes supported by enthusiastic investigators' faith rather than discipline and objectivity.

Muscle contraction occurs with a greater than 1000 fold increase in intracellular calcium concentration, and relaxation occurs when the extra free unbound ionized calcium is re-bound within

the cell, mainly by the sarcoplasmic reticulum (SR). This control of calcium concentration is normally tight. SR function is lost during an MH episode, and calcium concentration increases out of control.

With this uncontrollable increase in free ionized unbound intracellular skeletal muscle calcium concentration, there is an exaggeration of what happens during normal contraction. With this increase in calcium, metabolism of mitochondria is dramatically stimulated, to provide additional ATP for energy. During an MH episode, energy demands explode and oxygen consumption increases, with a related increase in carbon dioxide production, and a resulting respiratory acidosis. It's fascinating that oxygen consumption does not increase during MH near as much as with severe exercise, likely related to some sort of malfunction in the overall response to increased oxygen demand. There is also increased production of lactate, again to produce added ATP. This results in a metabolic acidosis, which is buffered in the body by bicarbonate, and excreted by the kidneys. Some of the bicarbonate is converted to carbon dioxide, again cleared by the lungs.

The intracellular SR stores huge amounts of calcium and rapidly releases and re-binds it during muscle contraction and relaxation. Furthermore, the mitochondria of muscle, by producing ATP, provide the energy needed for these muscle actions; mitochondria secondarily, during extreme stress, can store calcium. Finally, sarcolemma, the surface membrane of the muscle cell, is important, as there is a constant flux towards entrance of calcium from outside the muscle cell into its interior. Thus there is a constant metabolic energy use by all three components: sarcoplasmic reticulum, mitochondria, and sarcolemma, to maintain the calcium gradient even in the normal state, whether resting or during exercise.

Muscle Types

Some muscle has a greater blood supply (crudely, red muscle), with continuing renewal of oxygen, and does not rapidly lose energy stores during increased production of carbon dioxide. This is muscle typical of the distance runner, or distance cyclist, who relies on oxygen metabolism to maintain a prolonged effort. Other muscle has less vascularity (crudely, white muscle), with a lesser blood supply. It relies on glycogen stores within muscle. This muscle, during an MH episode, produces greater amounts of lactate, and a metabolic acidosis. This muscle is typical of the sprinter, or short distance cycling racer (or lizard or alligator), who can maintain immense energy expenditure for brief periods, until glycogen stores within muscle have been consumed. At that point, they 'hit the wall' and are unable to be competitive. Thus, the degree and type of acidosis during MH depends in part upon the type of affected muscle. However most muscular people do not have muscle diseases.

Example of a Normal Muscular Person

In the mid 1980s, at Mayo, I provided anesthesia to a retired former star of the Chicago Bears professional football team. He was about 6 feet tall, some 250 pounds, seemingly none of it fat. He was an example of a highly muscular person who had no abnormalities related to being muscular and had been a superbly coordinated athlete. He needed carpal tunnel releases on both wrists, as he had compression of the median nerve. He was uncomplaining, gentle, nice, and easy to care for. His hands and wrists were huge and highly muscular, and it wasn't surprising that he had finally developed a compression-type carpal tunnel syndrome.

His head, neck, and face were likewise large and muscular, and managing his airway under anesthesia appeared challenging. I did the anesthetic myself, and chose to use a mask without tracheal intubation. It was tricky to hold the mask but things went smoothly. As I was trained, and as I preferred, I didn't use a head strap to hold the mask in place, only my left hand. The head strap, as Dr. Virtue always hounded us, pushes the jaw back and helps obstruct the airway. This was a satisfying experience, to care for a retired professional athlete, who appreciated whatever we did. Would I do that by mask now? An LMA was not then available, and probably would have worked well. I was an expert at holding a mask for prolonged periods, and, even now, I might use it. I have more confidence than many providers in mask anesthesia; most change to an LMA early in the anesthetic if the case isn't too long.

Not very long afterwards, this athlete and one of our Mayo nurse anesthetists had abdominal surgery and awakened in the recovery room still mostly paralyzed from the non-depolarizing muscle relaxant. Contrary to almost everyone's usual practice, the senior staff anesthesiologist, per his habit, avoided reversal of curare-type muscle relaxants at the end of a procedure. This led to a sedated but in time aware patient who realized that effective movement was not possible and that tracheal extubation was not yet feasible. They each had to wait an hour or so until the effect wore off. Both were vocally unhappy, and rightly so. Further, our nurse anesthetist knew that this unpleasant episode was unnecessary.

Cycling the Douglas Trail

While at Mayo, I began to commute by bicycle, using an abandoned railroad that had been re-worked to a gravel surface (now paved), the Douglas Trail, connecting Pine Island to Rochester via Douglas. The trail is picturesque, avoids roads, and winds its way among the fields and woods and a few modest hills, a 17-mile-ride each way. The trail was safe, whether dark or light, as traffic was never a

challenge. In tolerable temperatures it was rejuvenating. Minnesota thunderstorms were a hazard, as the lightning could be vicious. You had to temporarily abandon your metallic bike and crouch under bushes until these passed. The other hazard was skunks. I'd come upon one walking along the trail ahead of me; when I'd attempt to pass, s/he would aim her/his tail at me and I'd retreat. I'd finally take a detour through the woods.

Chapter Fifteen: Evolution of MH Tests and Frustrations

The patterns of test development varied over the years until the principal focus zeroed in on skeletal muscle. MH tests in time established precision and accuracy. Kalow et al (1970) introduced what became the gold standard for testing of MH susceptibility, namely exposure of excised small skeletal muscle strips from the thigh to caffeine and halothane in a body temperature 37º C (98.6º F) tissue bath. They demonstrated that susceptible muscle responded with contractures (literally a muscle cramp). Ellis et al (1971) added halothane, without caffeine, as a test substance. Normal muscle doesn't develop a contracture until greater concentrations of drug are added to the muscle bath. In muscle susceptible to MH, contractures occur with much lower concentrations. This sensitivity to lower concentrations of test substance is the basis of contracture diagnosis, and is the clinical surrogate of MH.

For muscle biopsy testing, the patient needs anesthesia, either a general anesthetic that won't trigger MH, or a regional anesthetic such as a spinal, epidural, or specific nerve block in the leg. The muscle has to be carefully handled during excision so that it is viable in the laboratory, i.e., it responds with a twitch to electrical stimulation. It is dissected into thin strips and mounted in a tissue bath containing usual body saline solutions, attached to a strain gauge, to measure muscle contractile activity.

As time has passed, a variety of substances has been introduced to produce muscle contractures on biopsy specimens, thinking that the unique most accurate substance might be discovered and thus perfect the process of contracture testing. These include, in addition to the classic halothane and caffeine, ryanodine, 4-chloro-m-cresol, and potassium.

Various MH work demonstrated that porcine red blood cells showed changes that predicted MH susceptibility in pigs (Andresen, 1971; Hojny, 1973; Rasmusen et al, 1976). Further studies demonstrated muscle abnormalities in patients and families (Britt, Kalow et al, 1973: Isaacs et al, 1973; King et al, 1972; Kelstrup et al, 1974).

A more detailed early history of MH and its investigations can be accessed in other sources (Gronert, 1980; Gronert, Pessah, et al, 2005).

MH: Exaggeration of Normal Responses

Moulds (1975) presented still the best definition of an MH episode as an exaggeration of normal physiological responses rather than different or new responses, whether human or porcine.

The MH susceptible pig has a single point genetic mutation in all muscular breeds throughout the world (Fujii et al, 1991). This is an amazing finding: a single mutation explains their MH susceptibility. Since it is unlikely that this mutation arose *de novo* in swine of muscular build throughout the world, it is likely that potent breeding stock were shared via shipping sows or boars to various countries some 150 years ago. While humans share many mutations, the single point porcine mutation permits identification of muscular litters that lack the mutation. Testing of swine litters is valuable in controlling breeding, saving millions in pork losses at slaughter. Even normal swine become over-active with stress, and stressed MH susceptible swine can respond with an MH episode.

Abattoir (slaughterhouse) Triggering of MH and Major Pork Losses

Swine losses in North America during slaughter were as much as several hundred million dollars annually prior to identification of the MH mutation. At the abattoir, after stunning and exsanguination, the carcass was suspended from a hook, skinned, gutted, and cleaned while moved along an overhead track to the cooling room. Susceptible swine had a huge increase in metabolism related to the stresses of slaughter, and, in the 45 minutes or so needed to reach the cooler, the meat became hot, edematous, oozed water, and spoiled.

Testing litters for the single point mutation minimizes these losses by permitting breeding of muscular swine without the MH mutation. The laboratory director and the technical transfer person at the University of Toronto described application of the test program for screening of swine litters, using porcine muscle obtained from the University of Guelph. The test was patented, and assigned to the University of Toronto Innovations Foundation for licensing worldwide. Commercial testing began in a number of laboratories.

Summary of MH Testing

My reconsideration of MH testing, as a Monday morning quarterback, has the advantage of knowing that contracture responses are reliable and have genetic confirmation. The rigidity of an MH episode and the concomitant increase in serum creatine phosphokinase (CK) values suggested that the

origin of MH was directly related to skeletal muscle (Britt et al, 1973). Family evaluations implied that plasma CK values might aid in detection of susceptible persons (King et al, 1972; Isaacs et al, 1973; Kelstrup et al, 1974), but values in non-stressed susceptible humans were inconsistent and inaccurate (Paasuke et al,1986). CK, myoglobin, and potassium are released from muscle during extreme stress. Large increases in CK are not in themselves harmful, and indicate that the external membrane of the muscle is more porous. Myoglobin and potassium, respectively, are toxic to kidney and heart function. Back to MH testing: Once skeletal muscle contracture responses gained value in a few laboratories, they were evaluated by others in succeeding years.

After 1980, there was solid evidence that contracture responses were a valid determination of susceptibility. But these findings originated in a few university laboratories, and each had slightly varying protocols for study of porcine and human susceptible and non-susceptible muscle (Gronert, 1979, 1980; Gronert, Thompson et al, 1980). It was mandatory that all centers use standardized protocols, so that threshold responses for development of muscle contracture could be compared everywhere. After several years of conferences, contracture protocols were standardized (Ellis, 1984; Larach, 1989) and the revised protocol was studied in a few individual centers to confirm accuracy (Melton et al, 1989). But all centers had to be involved in such confirmation, and, a few years later, multi-center studies across Europe and North America provided acceptable sensitivity and specificity (Ording et al, 1997; Allen et al, 1998).

Genetic analysis of patients with clinical problems confirms the validity of contracture studies (Tobin et al, 2001; Girard et al, 2001; Kraev et al, 2003; Loke et al, 2003). The research into contracture testing illustrates Sir Karl Popper's dictum that a theory can be refuted but not verified, i.e., you cannot prove that it is true (Pollock et al, 1985). With time and multiple unsuccessful attempts at refutation, the theory, in this case contracture testing, is considered established. Other MH tests failed scrutiny.

Mayo MH Research

We developed a series of comprehensive multi-organ studies to quantitate alterations in MH. The porcine model, with its purebred approach to inbreeding for muscularity, hybrid vigor, and sensitivity to stress, results in marked stress susceptibility. Anesthetics trigger MH with the potent volatile agents such as halothane, isoflurane, sevoflurane, desflurane, and/or the muscle relaxant succinylcholine. Non-anesthetic MH occurs in swine exposed to environmental stress, fighting, shipping, coitus, or slaughter. It also rarely occurs in humans.

The exaggerated porcine response to anesthesia was first reported in 1966 (Hall LW et al). Others followed, analyzing its patterns: Harrison et al, 1969; Berman et al, 1970; Nelson et al, 1973; Lister et al, 1974; Hall GM et al, 1975; Gronert, Milde et al, 1976; Gronert, Theye, 1976, 1976; Hall GM et al, 1976, 1976, 1976; van den Hende et al, 1976; Lucke et al, 1976; Wood et al, 1977; Gronert, Heffron et al, 1977; Gronert, Milde et al, 1977; Hall GM et al, 1977, 1977; Gronert, Theye et al, 1978; Hall GM et al, 1978; Gronert, Milde et al, 1980; Hall GM et al, 1980; Hall GM et al, 1982; Gronert, White, 1988. While swine and human MH episodes are similar in many ways, porcine data can only with caution be transferred to humans.

The porcine feature of MH was identified as the Porcine Stress Syndrome, well reviewed (Topel et al, 1968; Cassens et al (1975). For our studies, we needed purebred swine, such as Poland China, Pietrain, or Landrace.

Tricks in Obtaining MH Susceptible Swine

When we wished to begin porcine MH research, we needed a reliable source of MH susceptible swine, and this proved tricky. Our prior single MH pig from the burn study was perhaps a single exception among his litter, and we didn't even know where he'd come from. In our search for suitable pigs, we quickly discovered that pig farmers don't want visitors, particularly investigators. Swine are susceptible to infection and strangers can introduce problems. Even normal swine are excitable and panic when confronted. We began our search by visiting the University of Wisconsin in Madison in early 1973. Their muscle laboratory was generously funded by royalties from sales of warfarin (Coumadin®), now widely used to diminish blood clotting in prevention of strokes and heart attacks.

Some years prior, their scientists had noted that cows that ate spoiled hay developed a bleeding disorder, and that the responsible substance was warfarin, leading the way to applied human anticoagulant use. The university had a swine herd reportedly susceptible to MH. Pat and I drove there, towing our horse trailer for bringing swine home. I spoke on hyperkalemia to the anesthesia department and met the MH researcher Charles Williams. He and I had vigorous arguments concerning our contradictory opinions regarding MH at the welcoming anesthesia department dinner. Williams, a biochemist, concerned with intra-cellular reactions, and I, an applied physiologist --- that's what anesthesia is --- had differing perspectives.

We tested the Wisconsin pigs by restraining them and giving them halothane to breathe. None tested positive. We brought several back to Minnesota, but they were not appropriate for MH research.

I contacted the swine caretaker at Madison and asked why they had not tested positive. He told me that they'd bred it out of their herd by noting which sow or boar produced susceptible litters, and controlled breeding now produced muscular pigs without the MH gene.

He advised us to visit a local swine breeder in Minnesota who prided himself on his highly muscular animals. He said to never admit that we're looking for animals with problems, as no breeder would admit to that, ever.


Fig. 13. Poland China swine

The Wisconsin swine breeder was correct. It was difficult to gain the confidence of purebred swine breeders. A local Poland China breeder agreed to permit testing if we paid twice the market price for any pigs that we either killed or decided to take for study. His pigs were appropriately muscular: Fig. 13: note the developed hams (and the 14 gauge ear veins). We did not specify why we were testing. The farmer was suspicious and didn't become friendly until we'd visited him on several occasions.

He soon realized that we wanted to study stress susceptibility in his pigs, as that was a recognized problem in muscular breeds. He frankly told us that it would be useless, since he'd never ever seen a sign of it in any of his pigs. For access, he had us wear clean jeans and wash our boots doubly in pans of cleaner at the barn door. We had to be quiet and move slowly and easily in getting near the pigs. Even normal swine are easily spooked.

We brought to the barnyard a G tank of oxygen (a cylinder about five feet tall, weighing some 80 pounds), a halothane vaporizer, and a plastic mask formed from a Clorox bleach bottle. We had cut out the bottom of the bottle and lined it with soft rubber to fit around the pig's snout, and drilled the stopper for flowing oxygen-halothane into the bottle, with a reservoir bag between gas supply and mask. The first pig breathed the mixture while restrained, and within three minutes developed pronounced hind limb rigidity, indicative of MH susceptibility. Fig. 14.


Fig. 14. Note the stiff limbs, off the ground, in the air.

We stopped the administration of anesthetic, and congratulated ourselves on our success. About 8-10 minutes later, during this self-congratulation, the farmer called our attention to the fact that the pig had rolled its eyes back up into its head, and said, "When they do this, they die." (This from someone who had never seen a stress pig death)

Sure enough, the pig died within a minute or so. We checked a rectal temperature; it was 112º F (44.4º C). We had now identified two MH pigs for research and prematurely killed them both (remember, we had a pig in the hyperkalemic study who surprisingly developed MH, which we successfully treated; we then lost him due to high pressure blowout of his lungs). Fortunately, further barnyard testing was more successful. The barnyard death occurred in 1973, but, once we knew of dantrolene (Harrison, 1975), we brought both a homemade intravenous preparation of dantrolene and bicarbonate to the barnyard.

Development of Dantrolene

Dantrolene has an unusual history. Keith Ellis, Ph.D., then of Norwich Eaton Laboratories in upper New York state, helped evaluate it. It was originally designed to replace Furadantin as a new urinary antibiotic. In initial toxicity studies in rats --- toxicity studies require huge doses --- they observed that the rats were blitzed. They lay around the cage without moving, their muscles were relaxed, and yet they breathed just fine. Their respiration was unaffected, and yet all other muscles appeared very weak. What was going on? Might this be an unanticipated property that could be effective in muscle disorders?

These findings mandated studies of the site of action in muscle. Keith and colleagues determined that dantrolene altered excitation-contraction coupling within skeletal muscle, and that it didn't alter cardiac function (Ellis et al, 1974, 1976, 1976). Dantrolene is a miracle drug for an MH episode (Harrison, 1975; Gronert, Milde et al, 1976; Hall, 1980).

Until the FDA approved dantrolene for human use in 1979, we developed our own preparation for emergency use, as approved by the Mayo Human Subjects Committee. Since Mayo had about 70,000 surgeries annually, and the incidence of MH was about 1/50,000, we expected to see MH episodes, and wanted to be prepared. Sterile dantrolene crystals for use in an intravenous solution for MH therapy were prepared by Ed Mansfield of the Mayo Clinic Pharmacy (Gronert, Mansfield et al, 1978). This preparation proved useful for a boy with a rapidly progressing episode of MH (Gronert, 1983). We performed contracture studies in the boy's father, which were positive for MH, and later an MH

mutation was detected in him and his two sons. This family and I have maintained contact since that episode.

Water solubility of the lipid soluble dantrolene is pH dependent, requiring an alkaline medium, and the oral capsule contains the usual excipients, e.g., starch, talc, magnesium stearate, and lactose. Mr. Mansfield dissolved the dantrolene at pH 10.3, and filtered the non-soluble excipients. He sterilized the resulting solution by passing it through a 0.45 μ millipore filter. He re-precipitated dantrolene by lowering the pH to 3.0. The resulting crystals were dried in a laminar flow hood and aseptically weighed into 500 mg lots. Dantrolene crystals are re-dissolved when needed by adding sodium hydroxide (for alkalinity, pH 9) and mannitol (to make the solution isotonic – otherwise it's hypotonic and may hemolyze red blood cells).

Each Mansfield-prepared 500 mg bottle cost us $10. We had originally requested dantrolene crystals from the pharmaceutical company for our research, but this was denied because we had no track record in dantrolene or MH research. Our own preparation eased the problems of our porcine MH research and our clinical care prior to NIH approval.

Research Approaches

We reviewed prior studies of MH in pigs (above) and began our own. Using pigs that tested either normal or susceptible, we first defined the response to halothane alone (Gronert, Theye, 1976) and then to succinylcholine alone (Gronert, Theye, 1976). The former approach showed that halothane gradually and progressively increased oxygen consumption and carbon dioxide production to a considerable degree, although not to as great a degree as is possible in extreme exercise. The latter approach – succinylcholine – showed that it affected the muscle immediately, with a sharp increase in oxygen consumption. This increase was brief and not great, as the action of succinylcholine is brief; circulation to muscle washes succinylcholine away from the muscle and it's hydrolyzed. However, a second dose of succinylcholine increases the likelihood of serious reaction from MH and death (Lucke et al, 1976).

The use of halothane and succinylcholine together acutely triggered MH. Fig. 15 - 17. (Figs. 1, 3, 4, in: Gronert GA, Milde JH, Theye RA: Dantrolene in porcine malignant hyperthermia. Anesthesiology 1976, June, number 1; 44:488-495, copyright owner Lippincott, Williams & Wilkins, www.LWW.com, used with permission.) We confirmed Harrison's 1975 article on the efficacy of dantrolene in treating porcine MH, with a broader study of al, 1976). Figs. 15-17 demonstrate this effectiveness in normalizing

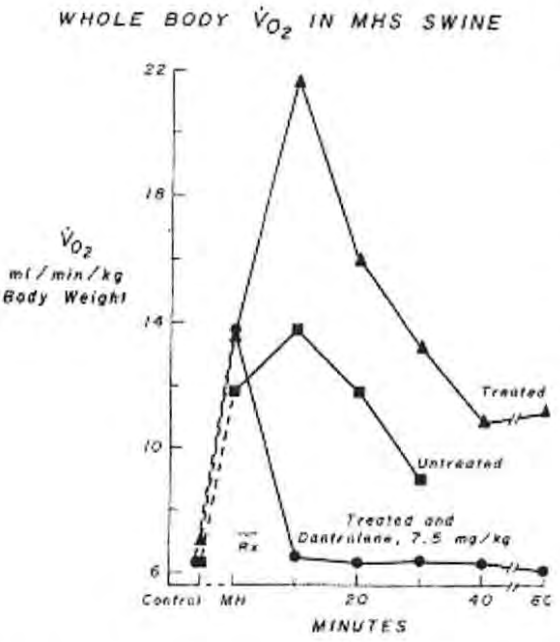

Fig. 15. Whole body oxygen consumption during MH triggered by halothane and succinylcholine; top line: symptomatic treatment; middle line: no treatment; bottom line: symptomatic treatment plus dantrolene.

whole body oxygen consumption, lactate production, and plasma potassium values. These three figures illustrate the curative response to dantrolene in swine triggered into MH by halothane and succinylcholine. The three treatment groups are: Untreated, Treated - symptomatic treatment only, and Treated – symptomatic therapy plus dantrolene. Horizontal axis: time in mins; vertical axis: **Fig 15**: whole body oxygen consumption ($\dot{V}_{O2}$); **Fig 16**: arterial lactate values; **Fig 17**: arterial K+ values. Symptomatic treatment included hyperventilation with oxygen, discontinuation of halothane, sodium bicarbonate to reverse metabolic acidosis, volume loading with cold fluids, and surface cooling. Pigs treated symptomatically or untreated died.

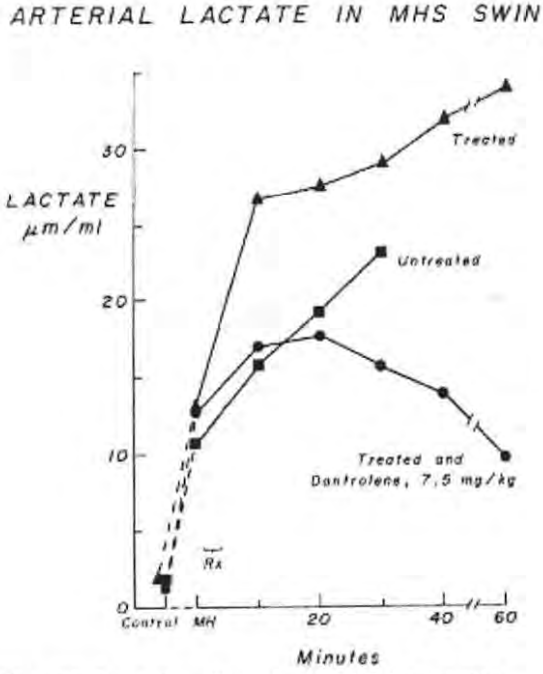

Fig. 16. Lactate values during MH; pigs not receiving dantrolene died.

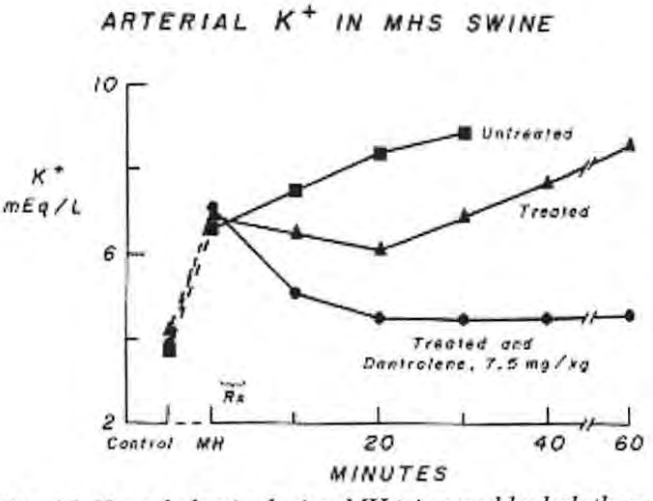

Fig. 17. Hyperkalemia during MH triggered by halothane and succinylcholine. Untreated and symptomatically treated pigs died.

We delved into the mysteries of MH; various organ systems needed to be analyzed as to possible roles in MH. The sympathetic nervous system plays a significant part in an MH episode, with rapid heart rate and elevated blood levels of sympathetic amines; some investigators felt that it was a vital factor in starting an MH episode. The sympathetic system in a stress and/or emergency situation invokes the exaggerated fight, fright, or flight response that prepares you for battle, brings out fear, and/or has you ready to run. MH susceptible swine can be triggered into an episode, awake, while not anesthetized, during extreme excitement, and even normal swine are grossly excitable. We needed to know, however, whether the sympathetic response is essential for an MH episode to develop.

Chapter Sixteen: Other MH Studies

Sympathetic Nervous System

Our sympathetic nervous system investigation included: blockade of its nerves, injection of its agonists, and use of drugs that blocked its responses. Sympathetic nerves can be anesthetized within the spinal canal. A total spinal anesthetic blocks all sympathetic responses. In this situation, the patient, in our case a pig, needed to be supported by artificial respiration via an endotracheal tube, and by volume loading to maintain adequate blood pressure and overall body perfusion.

We showed that a total spinal anesthetic did not alter an MH episode triggered by halothane (Gronert, Milde et al, 1977). We followed this with several other studies showing that sympathetic drugs did not trigger a porcine MH episode (Gronert, Milde et al, 1980, Gronert, White, 1988). Further evidence was that blockers of sympathetic responses did not alter an MH episode (Gronert, 2000).

Heart, Liver, Brain Function in MH: No Primary Abnormalities

The heart has intracellular organelles, including SR, similar to skeletal muscle. Myocardial sarcolemma and SR govern fluxes of calcium. SR does not play a role in liver or brain. Since SR is the seat of MH reactions in skeletal muscle, some felt that the heart muscle could actively participate in an MH reaction. We examined this in porcine heart muscle - with pigs on cardiac bypass - so we could measure cardiac metabolic responses during an MH episode. We found that the cardiac response during MH was due to recognized sympathetic reflexes that did not involve active MH involvement (Gronert, Theye et al, 1978).

Furthermore, we observed that responses of skeletal muscle accounted for the increase in whole body oxygen consumption during MH and that the splanchnic system and liver were not actively participating (Gronert, Heffron et al, 1977). Last, as regards study of organ systems in intact pigs during MH episodes, brain metabolism was not abnormal during an MH episode (Artru et al, 1980). Thus other elements of the body do not contribute to MH episodes and have normal responses, sometimes exaggerated due to the usual reflex responses of severe stress.

We also demonstrated that depressants and non-depolarizing relaxants delayed the onset of an MH episode. Depressants included barbiturates, opiates, sedatives, or tranquilizers (Gronert, Milde, 1981). Perhaps these directly or indirectly affect calcium fluxes within muscle cells. However, there are

major obstacles to study of what's going on within a cell. The very act of penetrating one to evaluate function can alter that function and may ruin the project.

Mayo Human MH Cases

In addition to the boy who developed MH during anesthesia at Mayo, described above, Mayo had a 50-year-old patient referred who had had febrile episodes for most of his life. With fatigue or stress or other problems, he would feel ill and have fevers that would not respond to aspirin or other drugs. He didn't sleep well and would take cold showers to counteract the fevers. The Mayo infectious disease specialist, Dr. Rodney Thompson, referred him because the episodes resembled what he and I had discussed regarding awake porcine episodes of MH. His biopsy was positive, and the article regarding him helped to raise awareness of rare human awake episodes (Gronert, Thompson et al, 1980).

A bit later, we cared for a 4-year-old boy with both a glycogen storage disease and acute leukemia who had developed intussusception. After surgical reduction, and beginning with recovery from the triggering anesthetic drugs enflurane and succinylcholine, he developed an MH reaction manifested by fever, tachycardia, tachypnea, mottled skin, and cyanosis. Laboratory values were typical of MH. He responded to dantrolene and improved, and then MH recurred, several times over. During the next several hours, he needed 16 mg/kg dantrolene to reverse this, a dose about seven fold greater than usual.

He unfortunately succumbed after a series of complications related to his multi-system diseases. Lymphoma patients have had a series of anesthetic responses remarkably similar to MH (Simmons et al, 1984).

Frances Foldes - a Wonderful Research Experience

The late anesthesiologist Frances Foldes was a gifted indefatigable muscle researcher. He helped introduce succinylcholine into use for clinical paralysis in the early 1950s and earned major awards in anesthesia, including the 1972 Distinguished Service Award and the 1988 Excellence in Research Award.

Early in my career, I heard him stand up to speak at our various anesthesia meetings and wondered about his work. He frequently had worked in the area being discussed and added information, although not always published. I was, frankly, skeptical. I found out in due time that he really had 'done it all' and had universal respect.

He believed a calcium antagonist might control an MH episode, so he proposed a study to examine this theory during a visit to our laboratory. He, at 75 years old, wanted to supervise it. Most interesting was that he crosschecked every protocol, plan, and calculation (in his head) that we performed, and followed every moment of study in every animal. He delighted everyone in our laboratory. The drug he was interested in is verapamil, a calcium antagonist. Dantrolene is a calcium antagonist, and he believed that other such antagonists may aid in preventing or treating MH. But dantrolene is lipid soluble, soluble in cellular membranes, so it easily enters the interior of the cell. Other calcium antagonists are generally water soluble, do not easily penetrate a cell's outer membrane, and thus cannot interact within the cell to diminish harmful reactions.

Unfortunately, verapamil was no help in treatment of porcine MH (Gallant, Foldes, et al, 1985). Foldes was disappointed in the result, but realistic.

As he put it, "I have had two goals in life, to win a medal in the 1500 meters at the Olympics, and to win a Nobel (he pronounced it, with his accent, as 'noble') Prize. Well, back to the 1500 meters."

As I say, we loved him. He stimulated our research program.

Ongoing MH Research

Ongoing research showed that electrical stimulation (Ahern et al, 1985), much like porcine stressful exercise or injection of either succinylcholine (Gronert, Theye, 1976) or carbachol (Gronert, Milde et al, 1980) also triggered MH. Carbachol is a drug useful only in laboratory studies. It matches the action of acetylcholine, but is long lasting - many minutes - and not practical for MH studies in intact animals. We used it in a porcine muscle preparation (Gronert, Milde et al, 1980). In evaluation of the progress of MH or its treatment, it is necessary to remember that lactate ion does not easily cross cellular membranes, as movement of substances across cell membranes is favored by lipid solubility and an unionized state. Thus the measured extracellular deficit may not reflect true intracellular lactate levels (Gronert, Ahern et al, 1986).

Finally, skeletal muscle in MH susceptible swine (and by inference, the human) is abnormal at a basic level of response, as, due to the mutation, exposure to heat by itself triggers exaggerated metabolism (Gronert, Milde et al, 1980). This has also been reported by Ording et al, 1985 and Denborough et al, 1994, 1996.

Several other factors that had been incriminated as triggers in porcine MH included carbon dioxide, calcium, digitalis preparations, and potassium. We evaluated these in separate studies (Gronert,

Ahern et al, 1986). The lungs of paralyzed anesthetized pigs were ventilated with sustained concentrations of 17% carbon dioxide. This did not trigger MH. Examination of exaggerated amounts of calcium, digitalis, and potassium would result in total depression of cardiac function, so we placed anesthetized pigs on cardiac bypass, using a pump-oxygenator-heat exchanger system. Calcium and digitalis in large doses did not trigger MH responses in skeletal muscle.

Potassium, however, decidedly triggered skeletal muscle, an expected result since we knew that muscle strips in tissue baths responded to potassium with muscle contractures typical of MH. In 1996, Isaac Pessah of UC Davis, Carl Lynch of the University of Virginia, and I wrote an editorial regarding the advances in determining the role of the ryanodine receptor in MH (Pessah et al). The ryanodine receptor is the connecting link to the SR in skeletal muscle and conveys information to the SR to release calcium and begin muscle contraction. With a genetic abnormality related to MH, the ryanodine receptor begins an MH episode.

Chapter Seventeen: Problematic MH Research: Muscle Calcium Uptake

An article on a case of human MH and its successful treatment via cardiac bypass began a sad era in testing a person for susceptibility (Ryan et al, 1974). This paper proposed measuring calcium uptake from muscle strips as a test for detecting MH susceptibility (Mabuchi et al, 1978). However there was a major contradiction to its use in MH testing: the test was positive immediately after the MH episode while the patient was still recovering, and normal later, when the patient had recovered more fully. Little did we know that this application was the beginning of a wayward path into MH testing.

Muscle calcium uptake did not have publications supporting its application in MH. MH experts became aware of calcium uptake as a test primarily via diagnostic letters to patients, signed by John Ryan, an anesthesiologist at Harvard's Massachusetts General Hospital. Ryan et al initially reported cardiopulmonary bypass as a treatment of acute MH (Ryan et al, 1974). As mentioned above, the problem was that calcium uptake had been abnormal immediately after the MH episode, but normal in the same patient several months later, i.e., poor evidence for reliability.

Letters to patients (personal files) who had been tested by calcium uptake did not include evidence supporting its validity. Their impact could not be ignored, as the test came from the muscle research laboratory of Harvard University. It utilized thin strips of muscle from a small biopsy that were frozen and shipped to Boston. It was easier and more convenient than the contracture test, which utilized viable twitching muscle specimens and therefore required the patient to travel to the test center for careful dissection during surgery and immediate delivery to the muscle laboratory.

The Harvard laboratory had several publications concerning muscle calcium uptake, but none directly supportive of its use as an MH diagnostic test (Sreter et al, 1964, 1966; Sreter, 1969; Mabuchi et al, 1978). Many involved in MH doubted the efficacy of the calcium uptake test. It is an in vitro measure of total calcium bound to muscle tissue, not isolated portions. It is not as sensitive as calcium binding, a measure of calcium taken up into isolated SR, and it did not distinguish normal humans from MH susceptible humans (Blanck et al, 1981). Next was an abortive attempt to compare contracture testing and muscle calcium uptake.

Initial Comparative Contracture-calcium Uptake Study, Unilaterally Cancelled

In an effort to document the accuracy of muscle calcium uptake, Henry Rosenberg, then of Philadelphia, began a joint study with the Harvard laboratory to compare MH patient contracture test results with those of calcium uptake, in the same patients. Dr. Rosenberg's laboratory performed contracture studies on a patient sample and forwarded an unused portion of that sample to Dr. Ryan's laboratory for study of calcium uptake. When six patients had been studied, the results disagreed, and Ryan, despite Rosenberg's protests, unilaterally discontinued the study. Ryan believed that the test was accurate despite the conflicting contracture results.

This vexing decision by Ryan was disturbing and I discussed this with my chair at Mayo, and with the chair at Harvard in fall 1983, at the annual meeting in Atlanta of the American Society of Anesthesiologists, and the oral examinations of the American Board of Anesthesiology in Albuquerque. Both supported a cooperative study between their two institutions, that would be blinded, and that would be finished.

Harvard/Mayo Contracture-calcium Uptake Study that could Not be Cancelled

The two chairs, Ryan, and I planned and approved a double blind study similar to that of Rosenberg and Ryan, in which no one would know results until the study was completed. Furthermore, an outside academic, with no knowledge of the study until requested to become involved, would supervise breaking the code. After the study was completed, the chair of anesthesia at Columbia University, agreed to break the code, and in a letter confirmed his role (personal files).

The study went smoothly. We biopsied thigh muscle on patients with questions regarding susceptibility to MH. My Mayo laboratory measured muscle contractures, and saved a portion for shipment to Ryan, both sets of samples coded as to identity. He didn't know our contracture results, and we didn't know his calcium uptake results. When eight or ten samples had accumulated, a technician blinded to the code shipped these to Harvard for muscle calcium uptake.

When finished, we had 29 joint samples, 28 suitable for publication. No results were known until we broke the code in a conference telephone call with the anesthesia chair at Columbia. The results did not support the accuracy of muscle calcium uptake, which had false positive results. Ryan was disturbed

that conflicting results had again occurred, this time in a completed protocol. He and I began to prepare a manuscript for publication. After several unproductive efforts to consolidate our differences in writing the manuscript, I submitted our individual efforts to a journal, with a letter explaining the problems, and requested the aid of the editor-in-chief.

The editor was supportive and attempted to consolidate our differences, but was not successful. He described Ryan's draft as unsuitable for a peer-review journal. I knew now that I needed to consult someone for advice who had no knowledge of the situation, and phoned my friend Arthur Keats, now deceased, a former editor-in-chief of the journal, Anesthesiology, who was noted for his common sense and straightforward approach. He had tutored me as a junior examiner on the anesthesia boards, and I knew I could trust in an objective opinion that favored no one. He said that this was a sad story, but, when you lose a colleague, you lose a colleague's data, so forget it. Arthur had quite a formidable presence but a subtle sense of humor and used it in the board examination system. I provide an example later in this memoir when describing the American Board oral examination.

A Direct Contact from Harvard

During our efforts on the calcium uptake manuscript, the late senior Harvard Anesthesia Professor, Aaron Gissen, phoned. He was chair of an ad hoc Harvard committee examining the validity of the muscle calcium uptake test. Controversies concerning the test had prompted the university to establish his committee. Gissen informed me that a professor from another institution (personal files), a former President of the American Society of Anesthesiologists, had advised him to contact me. Gissen said that two members on the ad hoc committee (identities, personal files) were involved with the calcium uptake project, but that neither had mentioned the Mayo-Harvard study. He learned of it only after talking to me, during the several conversations in which we had phoned each other, and in which I described the study and our results.

Once the entire project was finished, in part because of the Ryan-Rosenberg brouhaha, I reviewed my records of letters, phone calls, and other related sources. My files relating to this specific study include more than 65 letters, phone calls, and other material involving members of both anesthesia departments, present and former officers of the American Society of Anesthesiologists, and others. Some who contacted me were concerned with success in publication, some with a major public relations problem for our specialty, and others with legal ramifications, institutional and personal. Those active in MH testing were vitally interested in this study and were disturbed to see its publication fail, particularly since it duplicated the results of the Rosenberg-Ryan study.

In June 1986, the Harvard investigators promoting calcium uptake testing published an article describing results in 121 patients, 76 of whom had survived unequivocal episodes as diagnosed by standard criteria (Allen et al, 1986).

They concluded: "... the decreased SR Ca2+ uptake correlates so well with MH that it clearly may provide a valuable diagnostic tool."

But the test involves thin strips of muscle, not isolated SR, and they provided no details justifying these 76 'unequivocally' susceptible patients. This appears to be enthusiasm untempered by discipline, and in part led to calcium uptake being applied in determining care of patients (Schwartz et al, 1984; Watson et al, 1986), although that was strongly criticized (Ellis et al, 1986).

Unexpected: Harvard Abandons the Calcium Uptake Test

Then, a surprise: Harvard abandoned the test in late 1986. The Pathology Department representative commented in the MHAUS (Malignant Hyperthermia Association of the United States) *Communicator* that they were abandoning the calcium uptake test (spring and fall issues, 1987). They had performed the assay since fall 1985, and could not discriminate between normal and abnormal patients.

In the spring issue, Ryan stated that he was at a loss concerning the results of the Pathology Department, and that his group had successfully distinguished between patients with positive histories and normal controls for 12 years. They had examined more than 1200 muscle specimens and counseled more than 600 families. Laboratories could duplicate contracture test results, but not those of calcium uptake.

Verification of the Failure of the Calcium Uptake Test

In April, 1987, Muldoon's laboratory in the Department of Anesthesiology at the Uniformed Services University of the Health Sciences published a comprehensive refutation of the calcium uptake test (Nagarajan et al, 1987). It had performed contracture tests for diagnosis in 51 patients in the preceding years, and had frozen extra tissue. Her colleagues had now performed calcium uptake measurements on the preserved muscle tissue. Calcium uptake values had not declined in specimens stored up to 5 years at -70° C, -94° F. There was no correlation with any accepted prognosticators of MH

susceptibility. They stated that calcium uptake data also may fail to correlate with results from isolated fragments of sarcoplasmic reticulum. Finally, re-biopsy of a patient originally tested by calcium uptake confirmed its unreliability (Jaffe et al, 1991). Experts in MH could now focus comfortably on promising tests.

Chapter Eighteen: Maturity in MH Testing

To summarize, contracture testing in muscle strips from the vastus muscle in the thigh is accepted as the Gold Standard and as the putative clinical surrogate. This is because it mimics a direct anesthetic challenge in a human, somewhat similar to the actual challenge in swine. Genetic analysis of DNA further matured MH testing: the polymorphic ryanodine receptor gene has more than 170 missense mutations (Robinson et al, 2006), but just 21 are known to cause MH (Girard et al, 2008). Once DNA analysis detects an MH mutation, blood samples from relatives can be tested for that mutation. If it is found, susceptibility is confirmed; if not, contracture testing on biopsied vastus muscle is desirable to confirm normality (Rueffert et al, 2001; Urwyler et al, 2001; Pollock et al, 2002; Jurkat-Rott et al, 2000; Curran et al, 1999).

The multiple MH mutations are grouped by locus, the location on a chromosome: MHS-1, on chromosome 19q, encodes the ryanodine receptor, the primary MH site. Secondary sites include MHS-2, on chromosome 17q, the voltage dependent sodium channel of skeletal muscle, MHS-3, on chromosome 7q, the dihydropyridine receptor, MHS-4, on chromosome 3q, MHS-5, on chromosome 1q, MHS-6, on chromosome 5p. The equivalent porcine chromosome for MH susceptibility is number 6, and is a single mutation accounting for MH susceptibility in all swine.

Other advances in MH testing that may obviate contracture testing include micro-injection of caffeine or halothane into human quadriceps muscle to measure exaggerated CO2 responses (Anetseder et al, 2002; Schuster et al, 2006, 2007; Bina et al, 2006), and advanced application of leukocyte DNA analysis, since skeletal muscle RYR mutations also appear in leukocytes (Sei et al, 1999; Girard et al, 2001; Kraev et al, 2003; Loke et al, 2003). Micro-injection is explained next.

Adaptation of Isolated Perfused Caudal Pig Preparation to an in Vivo Test

At the invitation of the senior researcher, Dr. Edmund Hartung, I had visited the anesthesia department at the University Hospital in Wurzburg, Germany in 1993, where micro-injection was later developed, and discussed our perfused isolated caudal pig preparation, in which MH could be triggered (Gronert, Milde et al, 1980). This study involved complete section of the body of a pig just below the umbilicus, with perfusion via a cannula in the aorta going to the legs, and another in the inferior vena cava going away from the legs. Dr. Hartung told me in summer 2005 in Stralsund, Germany that my

presentation of this technique stimulated his consideration of the possibility of micro-injection of MH triggers, and he began the study. It was further developed after he left Wurzburg. The approach in pigs and humans involves placing a microdialysis catheter into a thigh muscle and adding tiny amounts of MH triggers such as caffeine or halothane. A second catheter is inserted to measure changes in pH, lactate, or CO2 in the region of the injecting catheter. MH susceptible swine or humans safely respond with exaggerated acid production, limited to just that area, i.e., a whole body MH response does not occur. This has developed into a fertile approach toward identification of MH susceptible persons (Anetseder et al, 2002; Schuster et al, 2006, 2007; Bina et al, 2006). Dr. Hartung has been a co-author of two abstracts (Anetseder et al, 2000).

Another minimally invasive non-destructive test is electrical stimulation of a muscle to produce a twitch in susceptible swine that produces a pattern different from that in normal swine. The altered pattern presents an *in vivo* differentiating test to detect MH susceptibility in swine, but requires sophisticated stimulating equipment. Examination of this approach in susceptible humans was unsuccessful in detecting MH susceptible humans, as their responses were weakened by heterogeneity, e.g., the varied mutations resulted in excessive variability in response to electrical stimulation (Quinlan et al, 1986; Quinlan et al, 1989). Interpretation of human test results and their variations, coordination with clinical findings if a suspected MH episode has occurred, and further MH research are aided by a standardized clinical grading scale, for use in a patient who has had an episode suspicious of MH (Larach et al, 1994). The scale evaluates changes in vital signs and laboratory data and scores them by degree of abnormality. Various case reports of human MH rely upon background information of abnormal physiology, genetics, contracture testing, and altered drug responses (Simmons et al, 1984; Lee et al, 1994; Ogletree et al, 1996; Albrecht et al, 1997; Melton et al, 1999).

Worldwide Human MH Testing

Where is human MH testing in 2008? Major achievements lie with researchers in the European MH Group, South Africa, Japan, China, the United States, and Australia/New Zealand. The United States lags in this area because of our inefficient and fragmentary profit-based health care system. In the U.S., a muscle biopsy and contracture studies costs more than $5000 per patient, and few health care organizations pay for much of that, as opposed to the willingness of medical insurance companies in years past. MH experts are now obtaining Medicare support. Also, there are only about five centers in the US and Canada, and costly travel is involved for testing.

In Europe, where there are more centers, the cost per patient, to the family, is small and the additional amount is subsidized by the government and the university testing center. So, in the U.S., few are tested, while in Europe entire families are routinely tested. Once contracture studies confirm MH susceptibility, genetic analysis can determine the presence of mutations. If a mutation responsible for MH is detected, additional family members can be examined for that specific mutation without need for the invasive muscle biopsy. In time, it may be that relatives who lack the mutation can be considered not susceptible but more patients must be evaluated before making this conclusion.

DNA analysis is usually performed on blood samples. The U.S. MH interests are expanding DNA analyses with in depth analysis of affected families, with modest financial support.

Other Species and MH Susceptibility

Both at UC Davis and Mayo, we analyzed responses of species other than swine that were considered potentially susceptible to MH, particularly wild animals that suffered capture stress or were super athletes. Capture stress occurs in wild animals captured after a prolonged chase or by a net dropped from a helicopter chasing the animal. The clinical picture, as you might expect, resembles an MH episode, rapid pulse rate, trembling in muscles, high temperature, acidosis, and systemic acidosis.

Species sometimes suspected of MH include wild deer, myotonic goats, and greyhound dogs. None demonstrated MH susceptibility, based upon anesthetic exposure and contracture testing (Antognini et al, 1996; Newberg et al, 1983; Cosgrove et al, 1993). Roberts et al have confirmed MH and ryanodine mutations in some dogs, although the canine MH reaction is qualitatively different (Roberts et al, 2001).

Chapter Nineteen: Risks, Drugs, Upset at a University Residency

Wrong Way Drivers

On Saturday December 31, 1960, Pat and I had finished my four months at LA Children's Hospital and began the drive back non-stop to Denver. While driving in the right lane on a divided four lane highway in western New Mexico, as we reached the crest of a hill, a car flashed by, driving the wrong way in the left lane. We were lucky that we didn't have a head-on collision.

This near tragedy occurred once more in our lives, in 1968. We were in the army, in San Antonio, driving on a Sunday afternoon on Interstate 10 on the east side of town, in a van, with our four children. A car suddenly came over the crest of a small hill toward us, in the left lane, going the wrong way. It passed us almost before we realized it. In another mile or so, the driver swerved into an oncoming car, a head-on fatal collision, a suicide.

Tragic Drug Addictions

One University of Colorado anesthesia resident rotated at LA Children's after I did, but returned to Denver addicted to drugs – Demerol® and pentobarbital. At that time, I was at Denver General Hospital. During night call, he'd periodically come into the operating room suite. I saw him at least twice when I was doing cases in the late evening. We'd see him because the OR doors were kept open. He explained that his child was ill, and needed some sedation. Addictive drugs were freely accessible on the anesthesia carts. A week or so later, our chair, Dr. Virtue said at conference that addictive drugs were missing. Several residents remembered these visits, and he was caught. Despite rehabilitation, after residency, he was dead by fall 1962. He was found one morning in his car with an empty syringe by his side.

In 1986, I became Vice Chair in the Department of Anesthesiology at the University of California, Davis and Director of Research. My clinical work and night call were at the hospital in Sacramento. In late 1989, a senior resident and I were on call together on a Wednesday night. I covered the several busy operating rooms and he covered the out-of-the-operating room calls, e.g., obstetrics, problems in patient rooms, or critical events in the Emergency Room. He was capable and quite intelligent. We routinely had anesthesia parties at our home near Woodland and knew the residents. It was 7 miles

from our home to my research lab in Davis, and another 13 to the hospital, on a bike path paralleling the freeway I 80 across the causeway to Sacramento. This resident and another once cycled from Sacramento to our home for an afternoon pool party.

He was a critical intellect, and a talented young anesthesiologist. He and several of our other residents were the greatest of friends. When we parted the morning after that Wednesday night call, we'd both been up all night. During the night, he had routinely described what he'd been covering. I could help residents on out-of-the-OR cases when necessary but he hadn't needed it.

Residents had the day off after call, this time a Thursday, to rest and recuperate. However he didn't come to the late afternoon regular anesthesia conference, which was an automatic, for his friends and he got together after conference. After this day's conference, several went to his apartment and found him dead. They all swore that it couldn't have been drug related, but autopsy confirmed that it was. Smart as he was, I concluded that he was accustomed to controlling doses. That casual confidence led to an overdose, a loss of consciousness before he realized it, and suppression of breathing to apnea. We were all stunned at this useless loss.

Almost a Barbiturate Suicide

In the 1960s, one Denver private practice anesthesiologist was found in his bathroom by his wife, while trying to make himself vomit. When queried, he admitted taking one hundred 100 mg pentobarbital (Seconal®) tablets. He had abruptly re-considered suicide and told her to bring him to an emergency room as soon as possible. When they arrived there some 15 minutes later, he was deeply cyanotic, a deep blue color, like a tank of nitrous oxide. His trachea was intubated, his lungs were mechanically ventilated, and he remained deeply comatose for about a week, as pentobarbital is not easily removed by dialysis.

After recovery, he seemed normal, and resumed practice in another state.

Cyclopropane Addiction

There was a Denver senior anesthesiologist in private practice who sneaked sniffs of cyclopropane, a potent volatile anesthetic. He'd sit on his anesthesia stool at the head of the operating table, behind the drapes, and open the popoff valve slightly for occasional repeated sniffs. Some had noted his bright red countenance during cases and wondered what was going on. Finally, during one case, he fell off the stool, obviously obtunded. He was rehabilitated into the public health arena.

Upset at Denver's Residency

Fifteen years after finishing my residency at the University of Colorado, I returned in February 1976 as a visiting professor, speaking on neuroanesthesia, MH, induced hypotension, and succinylcholine-induced hyperkalemia. It was quite a visit. The anesthesia chair, an intellect but not a strong administrator, had left for a Midwestern university at the end of 1975, with harsh feelings between him and the surgeons. As a 'going away gift', he found new positions for most faculty and residents at other programs. The talented Carol Hirshman went to the University of Oregon (Wood, 2000).

In the turmoil, they had forgotten that I was arriving. There were two faculty and two residents remaining. One, a North Dakota native, who later moved to an eastern university, was the sole faculty at the VA Hospital, directly across 9th street to the north from the university hospital. The late wonderful Katie Wood, who literally saved the University of Colorado program over the next few years, managed academic anesthesia at Colorado General Hospital. Nurse anesthetists flew in from the adjacent plains states for a week at a time to bolster coverage. Recovery was slow, but the University of Colorado effectively did so and has done well.

Chapter Twenty: University of California, Davis

After 20 years at Mayo, in part because of the harsh winters, Pat and I decided to move if I found a decent position. Our last child had graduated high school, so we searched a number of places, several as potential chair: George Washington University (they selected Burt Epstein, a good decision); the University of Chicago (I withdrew and they selected Mike Roizen, another good decision) and the University of Colorado (I withdrew and they selected Charles Gibbs, again a good decision). Over the years, I had seen enough picky problems for department chairs that my enthusiasm for it was limited.

UC Davis, with its veterinary school, veterinary anesthesia residency, and veterinary anesthesiologists, provided a broadening of research questions. I became Vice Chair of the human Anesthesia Department, and organized a laboratory for diagnosis of and research into MH. Also, at that time, I became Founding Chair of the Board of Directors of the North American Malignant Hyperthermia Registry, an association of the directors of the MH biopsy centers in the US and Canada. This, as a professional extension of the Malignant Hyperthermia Association of the United States (MHAUS), provided professional direction and coordination for standardization of biopsy protocols. At UC Davis, I taught or provided anesthesia in the operating rooms about 50% of the time.

Foundation for Anesthesia Education and Research

In 1987, I was appointed to the Board of Directors of the newly established Foundation for Anesthesia Education and Research (FAER), and was elected founding Secretary-Treasurer, a non-funded position I held through 1992. I maintained the financial data and secretarial information, countersigned the checks, and reported personally at the board meetings. FAER is the independent non-profit research arm of the American Society of Anesthesiologists, a separate entity, since political donations by the Society made it impossible for it to be a charitable concern. FAER fulfilled this role and funded deserving researchers.

Greg LeMond, Shot

A dramatically unusual experience at UC Davis, covered in newspapers worldwide in those countries in which cycling was popular: in the spring following his first Tour de France win in 1986, Greg LeMond was hunting wild turkeys in the California Sierra's, east of Sacramento, wearing camouflaged clothing. His companion unintentionally shot him with a shotgun, with severe hemorrhaging in his chest and abdomen. An urgent helicopter rescue brought him to UC Davis for dramatic and bloody life-saving

emergency surgery, his identity unknown. He was lucky to survive, to have a helicopter arrive soon after the shooting, and to go to a hospital experienced in trauma and equipped for it. As the Level One Trauma Center serving central California and its 7 million people, UC Davis saw many patients like this and had outstanding emergency doctors and nurses.

He stayed in the ICU a few days, and then recovered in a private room adjacent to it. His recovery among the other ICU patients was without regard to international status (or lack thereof), income, sex, or other factors. At least one of his fellow patients was a prisoner from Folsom, the prison south of Sacramento.

Beginning about his second or third postoperative day, I was the faculty anesthesiologist on pain rounds. He and I discussed bikes, and my solo cycling trip in 1983 from London to Heidelberg in which I passed through Kortrijk, Belgium, where he had owned a home. A lengthy recuperation caused him to miss the next two Tours. After that, he won the next two Tours, against virtually all expectations. Without those health crises, he might have won at least five Tours.

UC Davis Research Projects

One project was factual support of the inaccuracy of muscle calcium uptake as an MH diagnostic test (Jaffe et al, 1991). Another project involved the 'final common path' phenomenon in apparent clinical MH episodes in muscle disorders such as Duchenne Dystrophy. The lesion in Duchenne's is lack of dystrophin, a substance that stabilizes the permeability of the surface muscle membrane, the sarcolemma. Duchenne muscular dystrophy is an X-linked chromosomal disorder, which means that it's carried by the mother and mostly passed on to boys. It seldom occurs in girls because the second normal X chromosome overpowers the effect of the abnormal X chromosome. In boys, the 'puny' ineffective Y chromosome can not counteract the abnormal X chromosome, and Duchenne's appears. The skeletal muscles are abnormal at birth although that may not be apparent even during activity. However a muscle abnormality can be detected at birth because CK can be increased some 10 fold.

Because of evidence suggesting that MH can occur in a patient with Duchenne's, we performed muscle biopsy and contracture responses on two 2-year-old boys. The test for dystrophin showed that one boy had Duchenne's and the other, Becker Dystrophy, a weaker form of Duchenne's. The Duchenne weakened muscle membranes lose integrity when stressed and thereby promote compensatory hypermetabolism, resembling an MH episode (Gronert, Fowler et al, 1992). Our results helped demonstrate that this hypermetabolism is a resemblance to MH, unrelated to genetic MH and not an

episode. Treatment with dantrolene may be indicated, to relieve the stresses and toxicity affecting the patient.

We assisted in evaluating California's Fish and Game transfer of wildlife to aid declining populations, and evaluated stress responses during capture, handling, and transfer of Bighorn sheep (Martucci et al, 1992).

We updated the MH field with chapters in monographs (Gronert, 1994; Gronert, Brandom 2002; Gronert, Pessah et al, 2005), plus an annual update article (Adnet et al, 1999). Pascal Adnet, first author, unfortunately met with disaster; this native Belgian died in Africa while working with Doctors Without Borders. In addition, I helped prepare chapters for monographs, on the effect of general anesthesia in modifying the effects of muscle relaxants (Gronert, 2003), guidance in animal research (Gronert, Antognini, 2001), and malignant hyperthermia as a pediatric neuromuscular disorder (Gronert, Brandom, 2002).

During testing on a patient's muscle specimen on one of our laboratory's contracture test days, we observed a bath temperature that was greater than the normal of 37□C (98.6□F). This mishap was due to an error in the temperature control of our muscle baths. Because we were concerned that this could alter contracture test results, we studied the effects of variations in temperature, and observed few problems, none great enough to alter a diagnosis (Antognini et al, 1997).

Publication of a fatal case of apparent awake MH in association with quite mild exercise (Ryan et al, 1997) prompted journal editors to request an editorial from Joe Antognini and me (Antognini et al, 1997). This well conditioned runner was running easily at a moderate pace on a track, when he collapsed and died. Our editorial discussed the implications of this tragedy, for his degree of activity was not sufficient to explain why he collapsed.

Computer Programs for Analysis of Muscle Relaxant Responses

Additional research at UC Davis included pharmacokinetic and pharmacodynamic analysis to quantitate altered muscle responses to non-depolarizing skeletal muscle relaxants (Gronert, Matteo et al, 1984). These non-depolarizers include curare, vecuronium, rocuronium, and metocurine. These studies were finally possible because of advances in laboratory-based muscle relaxant analysis and computer-directed determination of the relationship between plasma drug concentration and degree of paralysis. Plasma concentrations of relaxants are tiny, and newer developments in analysis made these studies possible. They could as of recently be measured accurately. In addition, mathematical analysis of

plasma concentration, drug doses, time, and degree of paralysis could now be modeled via computer programs. The formula, the Hill equation, for the 50% paralyzing plasma concentration is

$$\text{Degree of paralysis} = (1.0 * Ce^{\gamma}) / IC_{50}^{\gamma} + Ce^{\gamma})$$

Where 1.0 is the maximal effect (100% paralysis), Ce is the estimated plasma concentration in the theoretical effect compartment, IC_{50} is the effect compartment concentration at 50% paralysis, and γ is the slope factor of the sigmoidal concentration-response curve (Shafer et al, 1989). The effect compartment is the site at which the drug interacts with the receptor.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics refers to how the body handles the drug, and pharmacodynamics refers to how the drug acts on the body. For example, succinylcholine is inactivated as it is hydrolyzed by plasma cholinesterase, but hydrolysis is slowed or halted when there is abnormal or absent cholinesterase, thereby leading to a greatly prolonged action, i.e., from about ten minutes to about six hours. This is a pharmacokinetic effect, because the body cannot break down the molecule.

When there is upregulation of acetylcholine receptors, the agonist effect of succinylcholine is exaggerated at the receptor site due to undue depolarizing sensitivity, and hyperkalemia results. This is a pharmacodynamic effect, i.e., a normal amount of drug acts on receptors that over-respond. Succinylcholine depolarizes the additional receptors, with an extraordinary extra release of potassium, because, while each receptor releases approximately a set amount of potassium, the greater numbers of receptors releasing potassium lead to a magnified cumulative increase in its amount.

The opposite effect occurs with downregulation, when there are fewer numbers of functional receptors. In myasthenia gravis, there are fewer receptors to respond to succinylcholine, so there is a modest and not dangerous resistance to succinylcholine, well demonstrated by Eisenkraft et al (1988). This is also a pharmacodynamic effect.

Exercise and Disuse Atrophy: Effects of Non-depolarizing Relaxants

Using these more sophisticated pharmacokinetic and pharmacodynamic analyses, we evaluated effects of cast immobilization disuse atrophy as a milder form of upregulation in altering the potency of succinylcholine (Fung et al, 1991), and of non-depolarizing relaxants (Fung et al, 1995). We evaluated the effects of conditioning equine exercise (running on a giant treadmill) in increasing the potency of

metocurine, as down regulation (White et al, 1992), such as we had seen in dogs (Gronert, White et al, 1989). While there was a trend toward a difference, it was not significant (White et al, 1992).

It's amazing to see horses run on James Jones' treadmill; it's set up in a large room in a laboratory building and the noise is akin to that in a boiler factory. The horse wears a face mask to permit measurement of total body oxygen consumption for associated studies, so virtually everything about the experiment is weird. Horses adapt to the face mask and running in place more easily than you might expect.

Jeeva Martyn and several others of us wrote an article on up- and downregulation of acetylcholine receptors, and also discussed another risk of succinylcholine-induced hyperkalemia, namely those patients having long term intensive care unit immobilization and confinement to bed (1992). These exaggerated responses were likely due to receptor upregulation of skeletal muscle disuse atrophy and of denervation-related receptor changes secondary to patients receiving long term non-depolarizing relaxants, sometimes accentuated by steroids. These relaxants pharmacologically block the acetylcholine receptor and essentially chemically denervate the muscle, i.e., deprive it of its nerve impulses. These are vital to maintain a normal distribution of endplate receptors.

Chapter Twenty-One: World Congress of Anaesthesiology, den Haag, 1992

In October 1983 I flew with my bike to London and cycled – solo – from there to Dover, ferried across the channel, on to Köln, and up the Rhine River, eventually to Heidelberg, with help from Kit and Bob Lennon on the last segment from Frankfurt. For Fig. 18, I set my camera on the roof of a car to take this photo, just east of Lo, Belgium; note that I carried maps, slides, valuables, bicycle parts, and 'dress clothes' in the handlebar and rear carrier bags. During the trip, I read "A Bridge Too Far" about the Market Garden offensive of World War II, and decided that it would be worthwhile to trace the movements, since they followed Holland's canals. In 1992, Pat and I flew with our bikes to London, cycled there a few days to orient ourselves, and then traveled by train to the coast. Next, the ferry to Oostende, and cycling into Bruges: so wonderfully gracious: the hospitality --- the superb hotel kept our bicycles in its formal dining room, the food, the canals at midnight. Then to Antwerp, eastern Belgium and into Holland, where we visited some of the routes and battlefields. Various areas were vital to success or failure. Dutch intelligence was not always trusted, because of possible Nazi infiltration, but the Allies apparently erred in ignoring the small ferry at Driel, a few miles west of the main bridge crossing of the Rhine River at Nijmegen. The simple ferry crossing might have saved the offensive, and the failure of the 'bridge too far.'

Fig. 18. Solo bike trip just east of Lo, Belgium

We particularly enjoyed the efficient cross country Dutch cycling routes. We visited the Kröller-Müller Museum and also found by accident a great restaurant, the Herberg de Schutter, in Woerden. We stayed overnight in Delft, then on to den Haag, its Mauritshuis, and the World Congress of Anaesthesiology, where I spoke on malignant hyperthermia. We stayed at the meeting-related tall

Promenade Hotel, and stored the bikes in an underground store room. We hung out our clothes – the first time my suit had been out of my Robert Beckman pannier in two weeks – and washed our dirty laundry. The next morning we visited the Floriade (national flower celebration held every ten years) with the Dutch native Abraham van der Spek of the Children's Hospital, University of Michigan, Ann Arbor, and his family.

Origin of the Succinylcholine Regulatory Furor

The best part of the Congress (for me) was a symposium reviewing recent advances in MH, held in Amsterdam and published in several languages as a teaching videotape, distributed worldwide ("Understanding Malignant Hyperthermia" 1992). I took the train to Amsterdam, but needed a taxi to the meeting as it was in an obscure area. This was an educational program for Proctor and Gamble, not commercially overdone.

The panel included Henry Rosenberg, Philadelphia, chair, Helle Ording, Denmark, Richard Ellis, Leeds, Uwe Schulte-Sasse, Heilbronn (near Heidelberg), Jens Peter Jensen, Mainz, Vincenzo Tegazzin, Padua Italy, and me. Rosenberg, Schulte-Sasse, and I discussed episodes of succinylcholine related cardiac arrest in young children. Until then, most cases like this had been regarded as aberrant MH episodes. But this had been a mistake. We now realized that these were due to acute rhabdomyolysis and hyperkalemia related primarily to other myopathies, such as Duchenne muscular dystrophy. In many children, there may be no obvious sign of a myopathy, which does not mean that they're normal, or that their muscles would respond normally to anesthetic drugs. Some might develop MH, some might develop that other terrible problem, rhabdomyolysis: muscle breakdown and loss into the blood stream of potassium, myoglobin, and CK.

Necessary Warning Sparks the Anesthesia Furor

This conference generated a letter to the journal, Anesthesiology (Rosenberg et al,), published in December 1992, a review by the National Institutes of Health, and review of relevant publications (Delphin et al, 1987; Larach et al, 1997; Schulte-Sasse, 1993). After the publication of the material relating to sudden cardiac arrest in children given succinylcholine, the FDA and one of the pharmaceutical companies re-wrote the succinylcholine drug label to better define the problem, and recommended that succinylcholine be used in children only in emergencies or airway challenges. Furor resulted as pediatric (and other) anesthesiologists vehemently protested these restrictions. The label was modified but with essentially the same overall cautionary guidelines (Bedford et al, 1995).

Fifty- year Review of Succinylcholine Cardiac Arrests

In 2001, I published an analysis of cardiac arrests following use of succinylcholine, including all cases I could find over the prior fifty years since it had been introduced in clinical practice (Gronert, 2001). Arrests related to use of succinylcholine in myopathies were more difficult to successfully resuscitate; an added difficulty is that many of these children appear normal and show no sign of myopathy prior to anesthesia. Resuscitation following hyperkalemic cardiac arrest related to upregulation of skeletal muscle acetylcholine receptors was generally 90% successful, while resuscitation in cases involving rhabdomyolysis was about 70% successful. Statistical analysis of these results is not possible because the data are uncontrolled, representing a 50 year historical collection of case reports. The poorer result in myopathies was likely due to ongoing potassium release from damaged muscle membranes, a less fit patient due to restrictions of activity related to the myopathy, or myopathic deterioration of cardiac muscle function. The upregulatory arrest was limited in time and amount because the extra potassium channels closed again within a few minutes.

The total amount of circulating plasma potassium is small, about 12 mEq in adults. This is calculated as follows: an average adult has a five liter blood volume and hematocrit 40%. Since 40% is the volume of red cells, then 40% of the five liter blood volume equals two liters of red cells. That leaves three liters for the plasma volume, the source of potassium to the coronary arteries. Multiply the 3 liter volume of plasma by the normal concentration of potassium in that plasma, or 4 mEq/l --- 3 X 4 = 12 mEq of potassium total in the circulating plasma. The rapid release of just 12 mEq of potassium from muscle tissue into the blood stream will double the plasma potassium, from 4 to 8 mEq/l, a toxic cardiac level (Gronert, Theye, 1975; Gronert, 2001). Ordinarily, potassium is re-distributed from plasma into tissue, particularly liver, but rapid release of potassium from tissues will increase the concentration to toxic levels before re-distribution can relieve the stress.

Muscle Receptor Responses in Various Mammals

Later, at den Haag, during the meeting, I discussed some research data in several mammalian species given a single non-depolarizing muscle relaxant with the renowned muscle researchers Francis Foldes (it was his 82d birthday during the meeting) and Bill Bowman. Foldes didn't think that the receptor area for relaxants was the same in various species, could be, or should be. He cited rat data that curare-type drugs are modestly effective, and that steroid types are fifty times more effective.

However we had an interest regarding the relationship of the skeletal muscle nicotinic acetylcholine receptor and varying animal responses. And our data showed a relationship among higher mammals, perhaps supporting the belief that muscle receptors for relaxants are relatively uniform among many species (Gronert, Fung et al, 1995). This was an interesting project. We – and veterinary anesthesiologists – anesthetized various healthy species, sometimes for elective surgery, ranging in size from horse to rat, and determined their response to gradual paralysis by metocurine, much as we'd done in study of disuse atrophy.

Since the acetylcholine receptor is highly conserved among species, our simple theory was that, if receptor density and amount are similar among species, then the potency of a competitive antagonist, e.g., a non-depolarizing skeletal muscle relaxant, might be similar among species. We examined seven mammals: rat, cat, dog, sheep, pig, horse (Gronert, Fung et al, 1995), and goat (Antognini et al, 1995). We observed a correlation between size and potency of metocurine, for all but three of the mammals we examined. There was a linear relationship between the plasma concentration at 50% blockade of the muscle twitch and body mass.

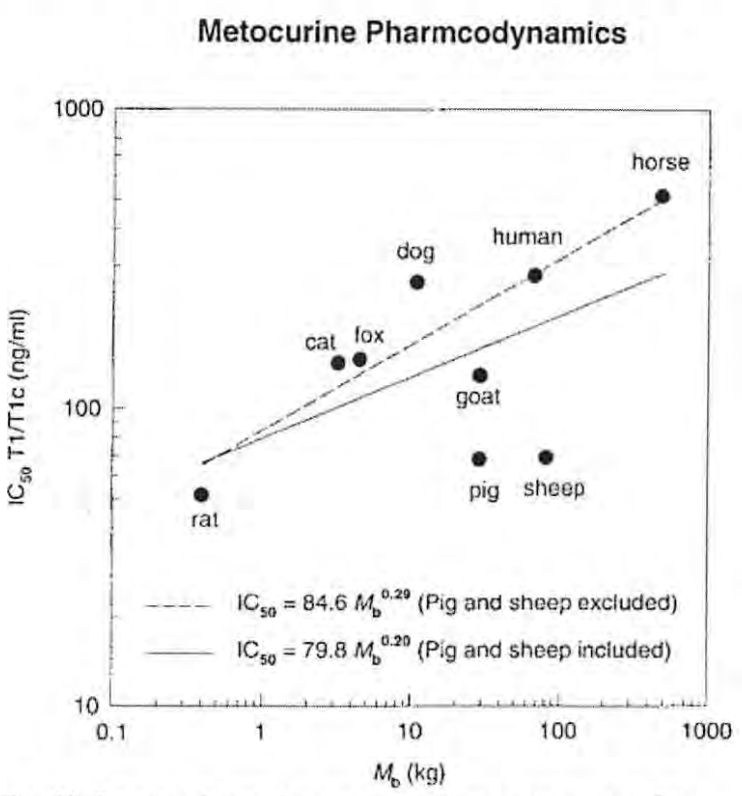

Fig. 19. Linear relationship among various species regarding potency of the non-depolarizing muscle relaxant metocurine.

Fig. 19 (modified with permission --- by the addition of the goat point --- from Fig. 5, in Allometry of pharmacokinetics and pharmacodynamics of the muscle relaxant metocurine in mammals, Gronert GA, Fung DL, Jones JH, Shafer SL, Hildebrand SV, Disbrow EA, American Journal of Physiology, 1995; 268:R85-R91, used with permission, The American Physiological Society, www.the-aps.org; goat data point, Antognini JF, Wood R, Gronert GA, Metocurine pharmacokinetics and pharmacodynamics in goats, J Vet Pharmacol Therap 1995; 18:464-467, used with permission, Wiley-Blackwell Publishing, www.blackwellpublishing.com).

From den Haag, we cycled to Vlissingen, took the ferry to Sheerness, and cycled via Greenwich to our Crescent Hotel in London. After a day or so we flew to San Francisco. Customs x-rayed our bicycles in the boxes, and asked us where we'd last been on a foreign trip.

We said, "Germany in 1990."

Customs said, "What about Canada a month ago?"

We'd been there to celebrate the 50th anniversary of the introduction of curare into anesthesia and forgotten that, but we also didn't think that Canada was a foreign country.

Chapter Twenty-Two: Non-MH Research

Barbiturate Tolerance

Research ideas sometimes apparently came out of nowhere. Part of our care for patients undergoing neurosurgery involved prevention or treatment of diminished blood flow --- ischemia --- to areas of the brain, with the possible problem of a stroke. Barbiturates such as thiopental (Sodium Pentothal®) were being used for these purposes because they suppressed metabolism in the brain and constricted blood vessels, theoretically improving the chances for success. But, with greater doses and prolonged use, their therapeutic effect waned, due to tolerance to the drug. So we investigated this in dogs, examining responses of the whole body as well as individual organs.

Barbiturates were valuable in cerebral protection during brain ischemia, but what were the limitations? Tolerance might mitigate protection, and there could be unexpected specific organ damage with time. Tolerance could be related to enzyme induction of metabolism, where metabolism increases due to enzyme stimulation, or to receptor changes.

With the latter, greater blood concentrations are needed for a similar effect. We did not observe this. We examined multi-organ system responses via Theye's approach: isolate organ venous drainage and use the Fick equation to determine individual organ metabolism (Theye et al, 1975). Dogs developed tolerance within the brain within three hours, manifested as an increase in cerebral oxygen consumption with constant blood levels of pentobarbital (Gronert, Michenfelder et al, 1981). Similar findings were noted in other systems: whole body, gastrocnemius muscle, kidney, splanchnic region, and heart, without evidence for toxicity (Gronert, Michenfelder et al, 1983).

It was surprising, and remains unexplained, that tolerance occurred as a change in metabolism and not as a need for greater blood concentrations of depressant. In addition, there was no apparent toxicity of barbiturates when used in these large doses, and for at least three hours. We confirmed what Theye had postulated: changes in whole body oxygen consumption during general anesthesia are due to the sum of events in individual organs and tissues, and an anesthetic-induced change in function correlates with a change in metabolic requirements (Theye et al, 1975). These metabolic events were observed when tolerance developed, where the change in requirement is not due to an increase in function (Gronert, Michenfelder et al, 1981, 1983).

Upregulation of AChRs --- Downregulation of AChRs
Study of Muscle Disuse Atrophy

Back to our considerations of disuse activity: from our early studies, we knew that burn patients had an agonist sensitivity, observed as an exaggerated potassium efflux after receiving succinylcholine (Tolmie et al, 1967; Schaner et al, 1969; Gronert, Dotin et al, 1969), a response also observed in patients with denervated muscle (Birch et al, 1969; Cooperman et al, 1970; Case History, 1971; Gronert, 1970). We wondered why inactive muscle not directly involved in burns would also have altered responses to a muscle relaxant.

Since all burn patients suffer muscle disuse atrophy from confinement to bed, and great weight loss, we believed that disuse might be a vital factor. Our canine studies of immobilization disuse atrophy ruled out disuse as the sole factor because the extra potassium efflux after succinylcholine was only slightly greater than normal, about 10% of the quantitated denervated response (Gronert, Lambert et al, 1973; Gronert, Theye, 1975).

But then another milestone was reached: resistance to non-depolarizing muscle relaxants was reported in patients with upper motor neuron lesions (Graham, 1980; Moorthy et al, 1980) and in burn patients (Martyn et al, 1980). These confirmed the earlier observation of resistance to curare noted years earlier (Bush, 1964). It could not be an unrelated coincidence that these disparate lesions imposed an exaggerated response, i.e., sensitivity to succinylcholine, and a diminished response, resistance, to non-depolarizing relaxants. We therefore examined qualitatively the response of canine gastrocnemius muscle suffering immobilization disuse atrophy to the non-depolarizing skeletal muscle relaxant pancuronium, and observed resistance (Gronert, 1981). This resistance was confirmed with a more sophisticated quantitative study (Gronert, Matteo et al, 1984). On a hunch, because exercise is the opposite of disuse, we examined metocurine pharmacodynamics in exercise conditioned dogs, and observed sensitivity (Gronert, White et al, 1989). This all began prior to our awareness of receptor theory and up- and downregulation of nicotinic acetylcholine receptors (Kenakin et al, 1992).

My reading began to clarify this area (Kenakin, 1989), and this, in time, resulted in an article on up- and downregulation of skeletal muscle nicotinic acetylcholine receptors with various disorders (Martyn et al, 1992).

Anti-epileptic Drugs and Resistance to Non-depolarizing Relaxants

In addition to skeletal muscle disuse atrophy, resistance to non-depolarizing muscle relaxants occurs in patients treated with anticonvulsants, drugs used to treat convulsive disorders, or epilepsy. These act in multi-synaptic areas to control seizures and have a spillover effect at the neuromuscular junction, a facet of their structure-activity relationship in blocking synaptic transmission (Alderice et al, 1980). This attenuation of the effect of acetylcholine results in a weak non-depolarizing blockade, of which patients seem unaware.

When the anticonvulsant is first started, this weak blockade potentiates the potency of non-depolarizers. If surgery is needed during this period, non-depolarizers or curare type drugs would be needed in lesser amounts. After about two weeks, this weak blockade results in proliferation, or upregulation of acetylcholine receptors, with resistance to non-depolarizers, manifested in part as a shorter duration of action (Messick et al, 1982). In further research, as a manifestation of this upregulation of receptors during anticonvulsant therapy, we observed the typical accompanying sensitivity to a cholinergic agonist, e.g., succinylcholine, as prolonged action (Melton et al, 1993). Newer anti-convulsant drugs do not seem to have this property (Audu et al, 2006). All these considerations led to a complex study of sedated dogs.

Canine Intensive care: three weeks, 24 hours/day, Sedated Ventilated

I had wondered for some years about the effects of muscle disuse atrophy, skeletal muscle that is forced to rest, and never contract, but with no lesion that could cause direct damage, e.g., denervation or other abnormality. I'd performed some studies regarding this, but still had puzzles: How much alteration is there in responses of muscle that is without activity, but no other problems? I followed this for some years, beginning with my years at the burn unit in San Antonio, for burn patients had peculiar alterations in muscle function despite having only a burn injury on the skin. I had superficially pursued the literature regarding disuse, beginning early with a monograph from a 1962 symposium (Gutmann et al, 1963). We had over the years performed several studies of casted leg immobilization but wished to expand to a study of leg muscle disuse, or total inactivity, with no physically restricting immobilization. My experience at an NIH meeting expanded my interest and this led to this next study.

Background: FDA Meeting in Bethesda

The FDA Advisory Committee Meeting on Anesthetic and Life Support Drugs convinced me that additional study of ICU-related immobilization was warranted (FDA Advisory, 1992). At that meeting, we discussed problems in ICU patient weakness (FDA Advisory, 1992: Summary, Appendix #5). On page 2 of Appendix #5, Drs. Miller (Chair, UCSF), Roizen (Chair, U Chicago), Hoyt (U Pittsburgh), and Gronert discuss the difficulties in evaluating ICU complications and some concluded that in depth prolonged ICU studies would be impossible. This 'impossible' conclusion bothered me, and I mulled it over during the trip back to UC Davis.

I decided to study dogs in an intensive care unit with collaborators from the UC Davis medical and veterinary schools. This is a hugely difficult study, for it requires skilled monitoring, 24 hours a day, for 21 straight days. A variety of experiences had prepared our laboratory for planning and arranging this study of extended prolonged animal care. My past studies had included porcine thermal trauma, with debridement and cleansing twice per day during a six week period, and anesthesia once per week (Fox et al, 1947; Gronert, Theye, 1971), tolerance in dogs during a 24 hour period of pentobarbital anesthesia (Gronert, Michenfelder et al, 1981; 1983), and close observation of 48 hour studies by Michenfelder et al of cerebral ischemia plus five day follow-up (Michenfelder et al, 1976).

All of these prior studies involved cooperation, organization, a well equipped laboratory, planning, and reliable skilled technicians. We fortunately had skilled colleagues at UC Davis: veterinary anesthesiologists with ICU experience, and experienced capable full time technicians in our laboratory. When I returned to UCD, I discussed these factors with two colleagues, and we formulated a protocol.

The Study Itself

Previously healthy active dogs, two or three at a time, were heavily sedated, and their tracheas intubated, with mechanical ventilation. This labor intensive study required direct skilled personal care 24 hours per day for the three weeks of the study, with immediate presence or immediate backup by faculty for problems. The worst problem was a power failure in the middle of the night, handled magnificently. The lone veterinary student managed to ventilate both dogs via reservoir bags, and simultaneously call the emergency phone number (911) for aid. Both dogs survived uneventfully.

Strict careful handling and intensive unit care was maintained for three weeks, for fluids, gastric feedings, change of position, temperature control, and bowel and bladder function (Gronert, Haskins et

al, 1998). Each week, all dogs were challenged with a brief infusion of the non-depolarizing relaxant metocurine, with measurement of degree of paralysis, time, and plasma levels of metocurine.

Pharmacokinetic and pharmacodynamic analysis (Shafer et al, 1989; Fung et al, 1995) estimated the degree of resistance to metocurine with time, and thereby estimated the degree of upregulation from total disuse atrophy due to heavy sedation without exposure to skeletal muscle relaxants.

These dogs showed greater upregulation with disuse atrophy than previously observed, e.g., resistance to the test non-depolarizing relaxant, metocurine, Fig. 20 (Fig 1, in Gronert GA, Fung DL, Haskins SC, Steffey EP, Deep sedation and mechanical ventilation without paralysis for 3 weeks in normal beagles, Anesthesiology 1999, June, number 6, 90:1741-5, copyright owner Lippincott, Williams & Wilkins, www.LWW.com, used with permission.)

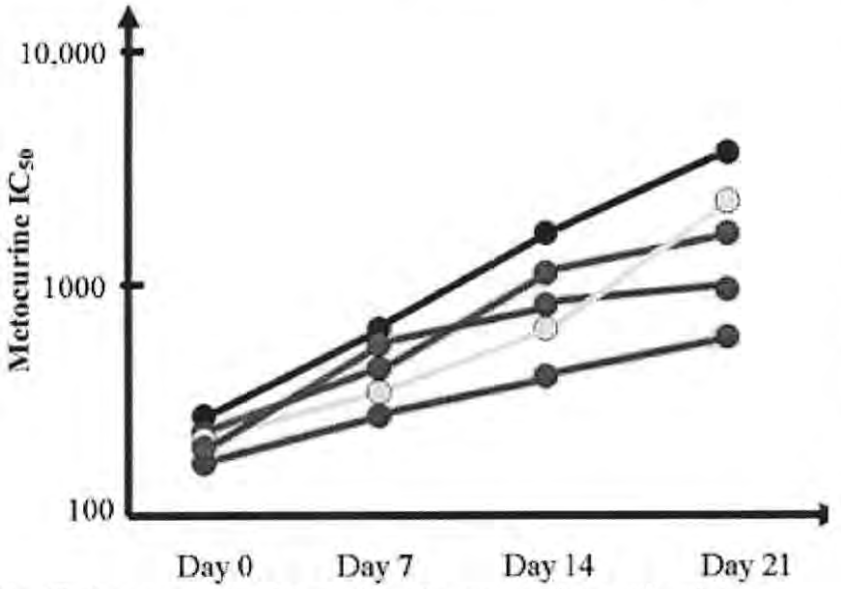

Fig. 20. Exaggerated resistance to metocurine in dogs with sedation-related muscle disuse atrophy. Normal canine IC_{50} is about 250 ng/ml.

This confirmed our suspicion that a total loss of volitional muscle activity would greatly exaggerate the increase in potency of metocurine that we had reported during immobilization disuse atrophy. With casted immobilization, volitional movement is still possible, and likely, within the cast.

Relationship of Exercise and Graded Muscle Disuse

Because we had used the same protocol involving the skeletal muscle relaxant metocurine in a series of canine studies for some years, and our approaches regarding drugs and study analyses were similar, we compared the results. Chronic conditioning exercise resulted in sensitivity to metocurine (smaller doses than normal produced the same degree of paralysis) and graded amounts of disuse resulted in graded degrees of resistance to metocurine. Thus there is a gradation, depending upon the primary stress upon muscle, and presumably related to numbers of functioning acetylcholine receptors.

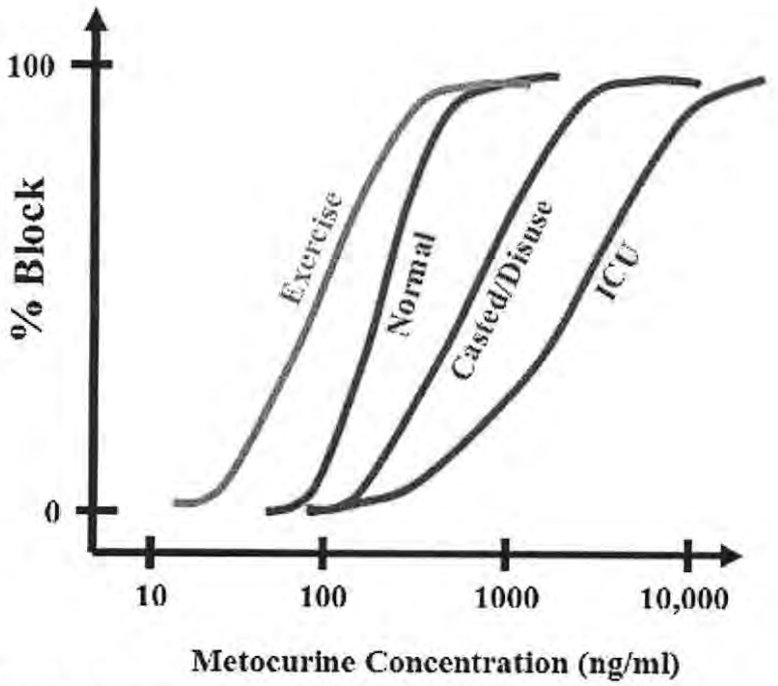

Fig. 21. Comparison of sensitivity to metocurine with varying degrees of exercise or disuse atrophy

Fig. 21. (Fig 2, in Gronert GA, Fung DL, Haskins SC, Steffey EP, Deep sedation and mechanical ventilation without paralysis for 3 weeks in normal beagles, Anesthesiology 1999, June, number 6, 90:1741-5, copyright owner Lippincott, Williams & Wilkins, www.LWW.com, used with permission.) The figure showing our results summarizes some relationships regarding skeletal muscle function in several situations: exaggerated use such as conditioning exercise, normal use, modest disuse atrophy from cast immobilization, and total muscle disuse with intense sedation.

Our canine extreme example of ICU sedation and marked paralysis mirrors the human situation in which very ill ICU patients have been given large doses of non-depolarizers to aid in management of their ventilation. These patients would also have increased numbers of functioning acetylcholine receptors, and cause them to potentially react to succinylcholine with dangerous hyperkalemia. Case reports support this conclusion (Bolton CF, 2005; Martyn et al, 2006). All these data support Kenakin's statements (1989; 1992) that the skeletal muscle motor nerve-endplate represents a classic competitive agonist/antagonist system. Acetylcholine and non-depolarizing muscle relaxants compete at the endplate receptor. When there are more acetylcholine molecules (the agonist) than relaxant molecules (the competitive antagonist), the muscle contracts when a nerve impulse arrives. When there are more relaxant molecules, acetylcholine released by the nerve impulse cannot reach the endplate receptor, and there is paralysis.

Ironically, while two of my colleagues participated in planning the ICU protocols, neither were co-authors on the published material. One withdrew in the early stages, due to his own research projects. The other had participated in depth, but disagreed on an approach that involved two separate

papers. I felt that we needed a basic article on "how to" as regards the challenging animal care and its success, and a clinical paper describing the exaggerated upregulation demonstrated by the muscle relaxant metocurine.

He declined co-authorship on both papers; he did not complain after the first paper appeared, but did so vigorously after the second. We exchanged letters concerning this conflict with the journal editor and the UC Davis Administrative Offices. He and I disagree as to precisely how this all happened (Letters, Beagle study, 1999). This unfortunate interaction rigorously reinforced my awareness that planning should be confirmed in writing, signed by all.

Species with Unique Muscle Receptor Responses

An interesting species is the pronghorn (antelope), an astounding athlete. It can continuously run 40 miles per hour or so, for relatively long distances (Lindstedt et al, 1991). With this degree of exercise conditioning, would the antelope have greater sensitivity to a non-depolarizing relaxant, i.e., be down-regulated, similar to our exercised dogs (Gronert, White et al, 1989; Martyn et al, 1992)? We had several pronghorns for potential study via the veterinary physiologist Jim Jones at UC Davis, but problems developed, and we could not pursue their relaxant studies.

Another example is the mongoose. It is resistant to poisoning by α-bungarotoxin of snake venom, yet it is a mammal with apparently normal functioning skeletal muscle nicotinic acetylcholine receptors (Keller et al, 1995). How different is the blocking effect of a non-depolarizing relaxant in the mongoose from the various mammals we studied? What might that hint at regarding structure-activity relationships?

Unfortunately, despite continued attempts, we could not secure any for study. The response may be instructive in determining structure-function relationships in a variety of situations of varying activity and innately altered receptor responses.

Chapter Twenty-Three:
Presentations, Unique Anesthesia

My formal speaking career began when I briefly presented at our annual anesthesia meeting in Boston in 1972, on our early hyperkalemic studies (Gronert, Theye, 1972). My first comprehensive presentation was a refresher course on neuroanesthesia in San Francisco in 1973, at the annual meeting of the American Society of Anesthesiologists. I was so concerned about an adequate performance that, on our drive to California from Minnesota, I rehearsed the talk every evening in our motel room with my wife Pat as audience, and even described sounds of air embolism while playing an audio tape. After that trip, Pat said that she would never again listen to me give a talk, formally or informally, and she never has.

Followed were invitations to a series of regional refresher courses around the country during the next few years, topics being neuroanesthesia, sitting position and air embolism, succinylcholine-induced hyperkalemia, other issues relating to muscle relaxants and muscle disorders, and various facets of malignant hyperthermia. Professional travel elsewhere included Canada, England, Ireland, Belgium, The Netherlands, France, Germany, Italy, Switzerland, Denmark, Sweden, and Japan.

Presidential Anesthesia

My family and I visited Walter Reed Army Hospital in Bethesda Maryland in summer 1974. We'd begun this eastern trip with anesthesia refresher course lectures at the Great Gorge Playboy Club in New Jersey, now defunct. Walter Reed was next --- I lectured and taught in the operating rooms. By chance, this was during the several days leading to Nixon's resignation. We visited the Senate floor on the day prior, and saw Dan Rather on the sidewalk outside the White House. We saw Nixon's resignation at the home of an anesthesia friend, Dutch Lichtmann.

At Walter Reed, one of the army personnel told me of surgery for President Eisenhower in the 1950s. He was given intravenous thiopental in his hospital room for quick easy sedation to calm him during the transfer to the operating suite. But he developed laryngospasm. Ike was unconscious, unable to move air into his lungs, and began to get cyanotic. Unfortunately a reservoir bag, mask, and oxygen were not available. As I was told, it was quite a sight to see a blue President Eisenhower being wheeled down the corridor at a dead run to the operating suite for ventilation with oxygen via bag and mask.

On another occasion, LBJ had surgery in Washington with a team composed essentially of Mayo personnel. The late Paul Didier had provided anesthesia, and vividly described it all to us when he returned to Rochester. The operation went fine, but, in the immediate postoperative period, he incurred LBJ's wrath when he attempted to re-start an intravenous line. The nurse in LBJ's room had been with the family for decades, as the Johnson family felt more comfortable with her there. Paul had injected local anesthetic into LBJ's forearm to prevent the pain of insertion of a larger needle. As he began to insert the IV needle, the nurse was fussing with the bed, and pushed the button to elevate it. LBJ's arm rose as Paul began the insertion, and the needle went into soft tissue instead of the vein. LBJ was not one to tolerate even minor irritants and colorfully banished Paul from his presence. Later, the entire Mayo team received White House letters of appreciation. Paul's envelope contained a blank sheet of White House stationery.

Chapter Twenty-Four: Overview

Once I became known via research publications, clinical articles, presentations on neuroanesthesia, succinylcholine/hyperkalemia, and MH, my evaluation was requested for various clinical problems and legal cases. Attorneys needed a recognized expert in a given area who was believable in testimony, consistent in responses, honest, and durable under pressure. Some, with opposing attorneys, or a judge guiding them in court, became confused and uncertain, and undercut their effectiveness. But all they had to do was not be greedy, and participate only in those areas in which they had expert information. Their expertise needed to be confirmed by their testimony, and they needed to be consistent, i.e., not have to remember what they'd said before. They had to be straight forward without pretensions. Following are some situations that I experienced in evaluations as an expert, some were legal.

Drug Error

This involved the injection of excess epinephrine into the back of an anesthetized patient undergoing lumbar laminectomy. The surgeon was given 7 ml pure 1:1000 epinephrine instead of the usual dilute solution. About five minutes later, a nurse notified the surgeon of the error. Unfortunately, anesthesia personnel were not informed. About 10-15 minutes later, pronounced hypertension and tachycardia occurred, findings similar to those of a pheochromocytoma. The patient suffered a cardiac arrest, and despite resuscitation, a poor result. The problem was directly treatable if the anesthesiologist had known the cause. It would have been difficult for anyone to imagine the need for symptomatic treatment of symptoms of a pheochromocytoma in that situation.

MH Sidelight

This involved a teen who had suffered in the past from what might have been an MH episode and now needed another operation. The parents interviewed two anesthesiologists at the local university hospital, and were assured that no MH triggers would be used. The anesthesiologists together anesthetized the boy, and prepared to intubate his trachea.

To eliminate noxious reflexes related to tracheal intubation in someone who had not been paralyzed, they sprayed his vocal cords with 2% procaine. I was taught as a resident that procaine is not effective for that because of poor mucosal absorption. Lidocaine 4% or cocaine 5% would have been more appropriate. The procaine spray resulted in pronounced laryngospasm, and the boy could not be

ventilated. To alleviate this and prevent dangerous hypoxia, they injected a small dose of succinylcholine to relax his cords, knowing full well that it is an MH trigger. They were worried about problems related to the hypoxia caused by the inability to ventilate him. The boy did just fine, despite use of the trigger.

The parents sued, because the anesthesiologists had virtually guaranteed a trigger-free anesthetic, and had violated that promise. They further said that their son now had severe headaches. When the case came to trial, the plaintiff's Canadian expert witness testified that use of succinylcholine in MH susceptible patients resulted in long term debilitating headaches. I testified that I had never heard of such a thing, that the plaintiff's expert, whom I knew well, had not published these results in the scientific literature, nor had it been mentioned at meetings related to MH.

After I testified, the university offered to settle for much less than the plaintiff's request of $500,000. There seemed to be little value for my testimony. The plaintiff's lawyer scoffed at this and refused to consider it. Later, the jury awarded the plaintiff $75,000. I told the defense attorneys that I should share in the amount that I'd saved the university, but their reply was not humorous.

Expert Witness?

Here an expert witness testified in an area in which s/he had minimal expertise. An experienced neurosurgical/anesthesia team had a serious non-fatal neurologic complication related to air embolism during surgery in the sitting position and was sued. The plaintiff's anesthesia 'expert', from a major academic center, was known to have decidedly modest experience in sitting position cases. When asked by the defense attorney about these types of cases, the response was, "Yes, I do neuroanesthesia."

The confident 'expert' testimony was that the anesthesia-surgical team was excellent, but, so was Babe Ruth. Babe Ruth occasionally struck out, and that's what the team had done in this case. The jury was convinced, but the 'expert' had now defined a reputation among peers.

Child with Unpredicted Hyperkalemia Due to Rhabdomyolysis

A boy approximately 20-months in age was anesthetized using halothane and succinylcholine for tracheal intubation. He immediately suffered acute rapid rhabdomyolysis and cardiac arrest. Despite rapid and successful resuscitation, he was brain damaged and the family sued.

I testified that the doctors had not been negligent in the care of this boy, had used typical agents and techniques for his surgery, and that his problem could not have been predicted. However I observed that the jury paid little attention to any testimony or to my defense of the defendant

anesthesiologist. At the end of the trial, the jury awarded the boy and his family $3,000,000. After he had interviewed members of the jury, the defense lawyer explained that the jury knew that the anesthesiologist had done nothing wrong, and they were sympathetic. But this was a poor local rural family, with major challenges in caring for their son. They would need the funds, and the university could afford it, especially since the university's supporting state taxes would help ease the financial strain on the university.

Legal Finagling Regarding Use of Succinylcholine

I was a consultant in two lawsuits involving complications related to use of succinylcholine in patients with upregulation of acetylcholine receptors, and testified in one trial. Because the malpractice coverage of the individual anesthesiologists was considered insufficient for proposed damages, the plaintiff's attorneys also sued the pharmaceutical company that manufactured the succinylcholine, alleging that the package insert did not clearly state the risks. But succinylcholine is a commonly used drug right from the start in anyone's residency, and anesthesiologists do not need to read its package insert, nor do they, in general. The risks are clearly known throughout one's career, and mishaps sometimes occur because of multiple interacting factors.

I believed that adding the pharmaceutical company to the suit was inappropriate and nonsense. In one of these cases, the jury increased the award to the plaintiff significantly because of this approach.

Peri-tonsillar Abscess, a Major Challenge

This problem involved a teen with a peri-tonsillar abscess. Rapid sequence anesthesia accomplished a secure airway and the oral surgeon drained the abscess.

Unfortunately, while moving to the recovery room after surgery, the patient semi-awakened and thrashed around, pulling out the intravenous catheter and the endotracheal tube. Swelling inside the mouth prevented successful ventilation, and life saving drugs could not be administered intravenously, resulting in a disaster. The failure in care occurred during transit, due to the impossibility of rapid venous access, and not having adequate restraint during emergence.

Plagiarism – Actual?

A university attorney requested evaluation of a journal article and its author as regards plagiarism. The author of the article, the department chair, was accused of publication without due credit, and the investigation involved the author, the accuser, who was a research advisee, and the

editor-in-chief of the journal. The latter and I discussed this a few months later at an anesthesia meeting.

The author sued the university, because it was discrediting him, and the university counter-sued. The research advisee and I discussed this directly. There had been eight drafts of the material. It was difficult to analyze the manuscript's progress and confirm plagiarism. The case was ultimately settled. Several years later, I met a Ph.D. who was a former member of the department, who told me that he had evidence regarding preparation of the drafts that would conclusively settle the question regarding plagiarism. He refused to share the information except off the record, verbally.

Athlete's Heat Stroke

I evaluated a case of heat stroke death. This was a young healthy athlete weighing more than 280 pounds. Successful highly competitive athletes take care of themselves and pride themselves in keeping fit and not having difficulties in front of others. Elite athletes have a warrior mentality, in part in not letting anyone know they're tired, frightened, or hurt. This attitude develops early in their lives, once they became competitive. It becomes a stable part of their competitive nature.

Two factors appeared to play roles in this heat stroke death: acclimatization vs. conditioning. Acclimatization is adaptation to a different climate or differing environmental conditions such as hot humid vs. hot dry vs. cold humid, or higher altitude. Acclimatization requires several days to weeks, depending upon the degree of difference from the original environment. It is less of a stress in someone who has been conditioned prior to experiencing the new environment.

Conditioning implies physical fitness, particularly with aerobic exercises, although non-aerobic exercise, such as workout with weights, is also a form of conditioning. Someone conditioned to a specific type of exercise is less bothered by it, and has lesser changes in heart rate and body temperature, less fatigue, and lessened other physiological responses as opposed to someone who is not conditioned.

This athlete was not strongly conditioned when this episode occurred. The weather was hot and humid and he lacked acclimation for working out in it. This athlete's heavy muscular build impeded heat loss, as there is greater insulation, and cooling is difficult. During harsh exercise, the athlete produces considerable body heat, and the marked increase in metabolism produces even more heat, and with an increase in body temperature due to insulation and accompanying dehydration.

In mammals, metabolism increases 7% per centigrade degree increase in body temperature. Since normal body temperature is 37º C, an increase to, say, 42º C is five degrees above normal, and

thus there is an increase in whole body metabolism of 35%. This can occur during a period of exercise, wherein metabolism is already increased, due to the exercise.

If an athlete uses energy enhancing drugs -- the information is frequently incomplete regarding this -- there is added a drug-related stimulation of metabolism and heat production, and cutaneous vasoconstriction, further limiting heat loss. These drugs may also inhibit gastric emptying and limit some aspects of digestion. Nausea and vomiting may occur. These factors cyclically further stress the entire body milieu, with catecholamine release, hypoxia, serious acidosis, and circulatory problems such as hypotension, low cardiac output, renal failure, muscle breakdown.

Pride and leadership responsibilities in this athlete apparently led him to conceal his problems. His coaches and teammates had difficulty in determining how serious his situation was, and were unable to easily halt his efforts and prevent him from overdoing it. He needed massive fluid loads and cooling. These were delayed because the severity of his problems was not realized in due time. His condition moved rapidly from severe to virtually moribund. Survival was unlikely once he was well into the final episode of his heat illness.

There is controversy concerning the effectiveness of dantrolene in a case like this. Dantrolene diminishes energy metabolism in skeletal muscle, and, therefore, heat production (Lin et al, 2004). Skeletal muscle is about 40% of body weight, and dantrolene could markedly diminish overall heat production, and conceivably tide the patient over until other measures take effect.

Oral Examinations by the American Board of Anesthesiology

For 20 years, I was an associate examiner for the American Board of Anesthesiology oral examination, the final step in the ladder of academic success for a budding anesthesiologist. It is the end of the beginning of the anesthesiologist's career, and s/he now can proceed to the middle ground, whether private practice or academia, and begin a mature stage of development.

Candidates must first pass a computerized written cognitive exam immediately following their residency. A year later, they take the oral exam, which is a measure of applied judgment in varying clinical situations rather than cognition. The most effective way to pass is for the candidate to imagine that the patient is directly in front of the candidate, lying on an operating room bed, and that s/he is providing the best possible comprehensive care, with detailed explanations of interpretation and the care that is provided. Examiners interrupt or alter the exam's progress as they see fit to determine the candidate's ability to adapt.

The exam period is a week, and takes place each six months in varying areas of the country, with several hundred candidates each time. Each candidate's examination consists of two 35 minute periods, with a 10 minute break in between. Two examiners in each room, four different examiners total, grade independently. Since perhaps 60 hotel rooms may be needed for the exam, at least 120 examiners are needed, plus extras in case of illness. The exams take place in the hotel rooms of the examiners.

Examiners are not given their questions until the evening prior to the exam day, and are not to discuss these with other examiners more expert in the exam's topics than they may be. At the end of each 35-minute portion of the exam, a monitor in the hall knocks on the door, the candidate leaves, and the two examiners grade the candidate's performance. The sheets are handed to the hall monitor and only then can they discuss their grades. They cannot alter grades because of this discussion.

Early in my career as a board examiner, there was tolerance for smoking, the policy being that if the candidate wished to smoke, then so could an examiner, but otherwise examiners were not to smoke. Arthur Keats, my senior examiner, was a smoker, and directly solved the problem: As the candidate was ready to begin the exam, Arthur would ask, in a harsh tone,

"Do you mind if I smoke?"

No candidate ever said yes, but, if one had, Arthur would have respected her/him and perhaps gone a slight bit easier.

This examination is a serious stress to candidates, and their nervousness is palpable. Two examples: a department chair, who is now a former President of the Association of University Anesthesiologists, and I had a candidate who collapsed at the end of the examination. At the knock on the hotel room door, he dropped his head sharply onto the table, broke his glasses, and sobbed uncontrollably. We tried to reassure him and ease his overwhelming discomfort. As senior examiner, I wrote the report to the board.

Candidates have three opportunities to pass each phase of the exam, each opportunity a year apart. If they fail the oral exam on all three attempts, they must re-take the written to again be eligible for the oral exam. Generally, more than 90% pass within the three year period. I counseled one candidate who had failed the oral exam on eight occasions, and passed it on his ninth. He was an excellent clinician, but, for him, the exam pressure was unreal. On one occasion his senior examiner, Jack Michenfelder, asked him what drug he would use to begin anesthesia in the proposed patient (I was not present).

The candidate said, "I could use drug A or drug B or drug C."

That's an ungradeable answer, since no judgment is involved. Jack slammed his fist on the table and said, "I don't care what you could do, I want to know what you will do."

The candidate was unable to respond to any question thereafter, so the two examiners and he sat in silence until the exam ended with the knock on the door.

Book Reviews – the Same Review, Twice

I found it fascinating that, in checking my records after retirement, there were two book reviews of works by Stanley A. Feldman, the British anaesthetist, who twice published monographs reflecting his continued interest in muscle relaxants. My first review was when I was a beginner in study of relaxants (Gronert, 1974). I did not remember the initial review when I did the second review (Gronert, 1996).

It was my opinion that in both, he was careless, error-prone, and poorly organized. The second review was requested by Jim Eisenach, book reviewer for Anesthesiology and now Editor-in-Chief. When I realized the number of careless errors, I sent Jim detailed notes of the errors (not to be published) to support my critical review, which Jim accepted. The then Editor-in-Chief of Anesthesiology suggested that my review was overly brusque and might offend our overseas friends. Jim in turn said that the Editor-in-Chief had no say in the decision to accept my review. The review was published unchanged. Feldman's opening statement in his preface was apropos: 'Academia should encourage debate on established thought. It should strip away covering veneer of certainty and lay bare illusion' (Feldman, 1996).

Chapter Twenty-Five: Rewards of an Anesthesia Career

Anesthesia appealed because it involved ongoing manipulations of physiology and pharmacology, with adaptations according to disease factors. It stimulated thinking and creativity, even prior to my research career. It was always fun to administer anesthesia, whether general or regional. I missed some things I shouldn't have, some regarding patients, and some regarding research. I didn't recognize Bush's observation that burned patients are resistant to curare at the same time that they're sensitive to succinylcholine. He wrote this before hyperkalemia to succinylcholine was recognized; it would have advanced the field two decades sooner.

Over the years, I have erred at times in providing patient care, and regretted that I hadn't been more observant. And I was ineffective in continuing my research grant support after several renewals. Perhaps I had too weak an insight into what I could have done next. I didn't think so, but I've noticed that most researchers go through this waning of successful grant proposals. The late pioneer B. Raymond Fink, initially a neuroanesthesiologist at Columbia University, re-located to the University of Washington in Seattle, and didn't fade at all even into his 80s, with ongoing grant renewals. He and I discussed our two careers, and my attempts. I always admired his findings, respected his work, and would love to have been as successful.

A Special Emergency Case

After 45 years, I vividly remember this case, and how gratifying it was. It's helped to remember it. When I've been challenged with tough stressful problems, I try to focus an enormous effort into practical straightforward solutions without becoming overly obsessed. In private practice in Denver, about 1963, I needed to anesthetize a 15-month-old baby with a hand laceration. This could have been a challenging emergency, and I needed to waste no time in deciding the best anesthetic approach. An intravenous line was already in place, and I administered small doses of demerol and pentobarbital for light sedation. Then, instead of a general anesthetic (I always prepared for that possibility), I performed an axillary block. The skin wheal provoked only a slight wince and the baby slept thereafter. I placed the needle around the arteries without searching for paresthesias, and, with the baby's thin build, blockade of the nerves was easy, and the case went well. This was satisfying because of its simple successful approach.

Academia, a great choice

My dictum still holds: In anesthesia, we make possible tolerance of stressful situations, even though they may not be painful. And the motivation to find out or discover what's behind what's going on has led to satisfying experiences in a wonderful variety of places.

Academia was my choice after five years' private practice. I don't know if I would have switched if I hadn't been asked to join the Mayo Clinic, as I wasn't thinking of change. The combination of research and clinical care at Mayo and in the army was intoxicating. This was furthered at UC Davis.

In time, I became a visiting professor at various universities, lectured at regional, national, and international meetings, and was an associate examiner for the oral board examinations of the American Board of Anesthesiology. These examinations provided the best anesthesia refresher course. You can scarcely match the breadth of knowledge of a well prepared candidate, for s/he covers wider aspects than any single person's specific and focused anesthesia knowledge. In general, all of these experiences have led to friends and contacts that I would not have otherwise known. I finish with a brief description of our 1985 cycling trip with Pat and our daughter Gail (Fig. 22) to several pilgrimage churches in France: Cluny, Autun, Vézelay, Auxerre. We had flown to Zurich with our bikes and traveled by train to Mâcon. We would not have attempted this if Gail hadn't been fluent in French. She used the formalities that the French prefer. For example, lunch in a village we were passing through: She'd enter the restaurant while Pat and I waited outside. In her proper French, and her open easy smile, she'd ask if the proprietor was there; then, are you serving lunch; then, may we partake with you? With her healthy appearance, red hair, and shorts, she made what could be difficult approaches for us wonderfully easy. The rural French meals were marvelous.

Fig. 22. Daughter Gail on our cycling trip from Mâcon to Cluny, Autun, Vézelay, Auxerre, and Pontigny.

The church at Cluny, by 1150, had become the center of the universe of 300 monasteries, located across Europe, England, Scotland, Poland, and the Holy Land. Its abbot Odo had developed religious studies, traveled extensively, and organized beliefs. Pilgrims traveling to Santiago de Compestella in northwest Spain used the various pilgrimage churches as stopping points.

We didn't know where we'd stay each night, and we enjoyed simple wonderful meals. Pontigny, on a side trip east of Auxerre, was marvelous: it had a nondescript quiet cafe. Gail made the customary formal requests about lunch and we ordered in the bar area. We thought we'd eat in one of the booths, which were much like those in an American restaurant. Thank goodness for Gail's facility.

After fifteen minutes, two beers each, we were asked to come back and eat. We walked directly through the kitchen into a large dining room where they were serving about 25 customers – all working men. They shared rectangular tables that seated eight, in a room five tables wide, and six tables long, all this totally unexpected. The salad was, again, good, but mysterious, with finely meshed celery or sauerkraut in long strands, cucumber, and sausages. The main course was lean circular ham and thick short noodles that were very good. We had no cheese or dessert. The bottle of red table wine was good, simple, and smooth, no label, no cork. 210 ff ($25) for 3 meals, ½ bottle red wine, four beers, three cokes -- a wonderful meal. We have reminisced about that unique experience.

Fig. 23. Pascha, the Great Dane at L'Hotel de la Tête Noir in Autun. He owned the hotel.

Our trip prize was Pascha: in Autun, during its 2000th anniversary, we stayed at L'Hotel de la Tête Noir. It had this quiet Great Dane, Pascha, who patrolled the lobby, laid his chin on your table at breakfast --- he never tried to get food --- so of course you gave him a croissant. The lobby had his personal chair. Fig. 23.

There was much to be grateful for in my professional life: probes of questions, research, travel. I tried to work gently with a great deal of effort, to avoid stress or obsession, to work to a feeling of value, yet be satisfied with simple pleasures: Pascha underlined that.

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Permanent Record Keeping

How should you maintain records and what do you do with them in retirement? Should you dispose of them? Dick Theye of Mayo taught me how to file research articles: 3x5 file cards, later computerized, and keyed by authors, titles, journal, citation, and abstract; each card (later, each as an individual computer reference) is numbered consecutively, and the articles are filed consecutively in file drawers. The filing system is thus ordered numerically, and easy to search by key words. I now have about 7000 references, and continue to collect data. I maintain them because I remain active in my areas of interest, some are historical and difficult to find, and I can immediately look up any when there's a query. A research friend at retirement destroyed slides, papers, and references, as they were now 'out of date.' While published papers remain, the history of involvement and the development of ideas and projects are otherwise evanescent sources. I saved these records separate from my reference file system, in individual file folders, beginning with my first research projects, and proceeding chronologically to my last projects. This material is important to those interested in the field.