Personal reminiscences about Morton Grossman and the founding of the Center for Ulcer Research and Education (CURE)

Paul H. Guth1 with the assistance of Jonathan D. Kaunitz1,2
1Greater Los Angeles Veterans Affairs Healthcare System and 2Department of Medicine, School of Medicine, Los Angeles, California

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Guth PH, Kaunitz JD. Personal reminiscences about Morton Grossman and the founding of the Center for Ulcer Research and Education (CURE). Am J Physiol Gastrointest Liver Physiol 294: G1109–G1113, 2008. First published March 20, 2008; doi:10.1152/ajpgi.00594.2007.—The Center for Ulcer Research and Education (CURE) from its onset was primarily the work of one man: Professor Morton Grossman, or “Mort” as he was known and called by all. Mort’s legacy includes a large body of scientific publications, the first National Institutes of Health Digestive Diseases Center (CURE), and, most importantly, a group of scientists who have become academic leaders and who have made important contributions in the fields of upper gastrointestinal (GI) tract secretion, hormones and receptors, mucosal defense mechanisms, the design and conduct of randomized clinical trials, and ulcer epidemiology. Indeed, Mort is considered to be a founding father of modern academic GI research. I was fortunate to have known and worked with Mort and would like to memorialize his contributions so that his memory can inspire the next generation of academicians.

FROM ITS ONSET the Center for Ulcer Research and Education (CURE) was primarily the work of one man: Morton Grossman, or “Mort” as he was known and called by all. I was fortunate to be a member of the gastroenterology service at the Wadsworth Veterans Administration Medical Center in Los Angeles during this period. Morton Grossman (Fig. 1) received his M.D. and Ph.D. degrees from Northwestern University in 1944. At Northwestern he had studied under Andrew Ivy, one of the world’s leading gastrointestinal physiologists. In 1946 he received an appointment at the University of Illinois, and he was promoted to Professor of Clinical Science in 1952 at the remarkably young age of 32. During the Korean conflict Mort served as Head of the Physiology Branch of the Medical Nutrition Laboratory, first in Chicago and then Denver, from 1951 to 1954. Mort became Chief of Gastroenterology at the Wadsworth VA Medical Center following his discharge from the army.

In the early 1960s, Mort was recruited to the University of California, Los Angeles (UCLA) as the Chairman of Physiology. Only after working 6 months in that position, he found that heavy administrative workload was not to his liking, and he rejoined the Wadsworth VA Medical Center with a lifetime research appointment from the Veterans Administration as a Senior Medical Investigator.

Mort was an internationally recognized investigator and educator. Consequently, there was a flux of trainees and visiting professors from the United States and abroad working in his laboratory. He was constantly pressured by requests from investigators wanting to come to his laboratory, which he limited to five or six to be able to provide appropriate supervision. Mort Grossman was considered to be one of the greatest gastrointestinal physiologists of his time. Although he could have built a large laboratory enterprise staffed with numerous trainees and junior scientists, he rather restricted his laboratory to a relatively small number of fellows and associates to preserve the close interactions he believed were essential for high-quality research and training.

The importance of Mort’s contributions to gastrointestinal physiology up to that time can be recognized by a brief review of some of his key research contributions. His interest in the production and regulation of upper gastrointestinal secretion was established with the publication of his first article in 1943, in which he was the first to show that dietary alteration changed pancreatic enzyme content (4). In a prolific period from the later 1940s to the mid 1960s, his annual publication output rivaled the number of abstracts presented at the American Gastroenterological Association’s early annual meetings. Examples of pioneer observations include the isolation of a gastrinlike substance from a Zollinger-Ellison tumor (8), the interrelationship between hormones and nervous reflexes in regulation of gastric (3) and pancreatic (1) secretion, and the original observation in 1961 that parenteral aspirin in humans increased fecal blood loss (6). This last finding opened a new line of investigation that eventually led to the discovery of the importance of cyclooxygenase in gastric mucosal protection. There are many articles addressing ongoing controversies in a definitive fashion. Examples include the relation between gastric secretion and mucosal blood flow (9), a large study of normal and peptic ulcer subjects demonstrating differences in basal and stimulated gastric acid secretion (5), one of the first and most often cited studies of peptic ulcer epidemiology (2), and an exhaustive 1948 study involving complex dog surgery showing that gastric distention remotely augmented gastric acid secretion, confirming that secretion is hormonally regulated (7). These observations, some made 60 years ago, helped establish a firm foundation upon which modern upper gastrointestinal secretory physiology was built.

In 1973, Mort called a meeting of a number of investigators from Wadsworth VA Hospital and from UCLA to respond to a National Institutes of Health announcement calling for letters of interest from those interested in establishing a peptic ulcer research center. He had already demonstrated his disinterest in

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administrative work by resigning as chairman of physiology at UCLA. Although developing a center would only increase his already considerable workload and responsibilities, Mort’s passion was to find a cure for peptic ulcer disease. Founding such a center would thus enable him to assemble the appropriate groups of scientists to eradicate this disease. At that time peptic ulcer disease, prior to the advent of potent and safe antisecretory compounds, was a serious medical problem involving not only severe patient distress and even death, but also substantial economic costs due to considerable loss of time from work plus medical and hospitalization costs. Treatment options then included antacids and atropine-like medications; when these failed, surgery was the main option.

Mort proposed a center encompassing a broad strategy for addressing ulcer disease that would include clinical and basic science research programs. The clinical research unit became the Ulcer Clinic, which, along with providing outstanding clinical care, served as a registry for clinical subjects. The clinic included a secretory laboratory and an endoscopy unit, both of which are currently active. At the time, one of the most powerful investigative tools was radioimmunoassay (RIA). The existing RIA laboratories would need expansion to accommodate blood hormone assays necessary for the anticipated basic science and clinical research programs, in addition to having the capability to develop new assays as new hormones were discovered. In time, antibody and molecular biology laboratories were added.

Mort’s genius was in recognizing the need for a multidisciplinary approach for studying peptic ulcer disease. Mort recognized the value of having scientists with differing backgrounds approach the same clinical problem. Their doing so created a symbiosis among the investigators, enhancing their creativity and productivity. For example, he recruited an epidemiologist to investigate why duodenal ulcer disease first became a problem around 1915–1920, reaching a peak around the 1940s and subsequently declining. In contrast, the incidence of gastric ulcer was static, suggesting that new immigrants formed a cohort with respect to duodenal ulcer disease; as they aged and died the incidence of duodenal ulcer decreased. Mort envisioned a statistician as part of the center, recognizing the importance of the appropriate use of statistics to both basic and clinical research. Mort assembled a committee to develop the grant, including Jon Isenberg, Chief of Gastroenterology at the Wadsworth VA Medical Center, and a brilliant young gastroenterologist named Richard Sturdevant who had recently joined the Wadsworth VA staff. Jon later became Chief of Gastroenterology at the University of California San Diego Medical School. Richard tragically died of cancer of the pancreas in 1978, four years after the peptic ulcer center was established.

In 1974 the National Institutes of Health grant to establish a peptic ulcer center was approved and funded. Suggestions for a name for the center were solicited, with the winning name, Center for Ulcer Research and Education, submitted by Dr. Edward Passaro, Chief of Surgery at Wadsworth. The term “education” was included because the aims of the center included the education of researchers, clinicians, and patients. A logo was then designed for the new institution.

Following his retirement from the Mayo Clinic, the world-renowned gastrointestinal physiologist Dr. Charles Code (Fig. 2A) joined CURE as Associate Director in the first year of its existence. I wondered how two such outstanding investigators and leaders could work together. My worries that serious conflicts would occur were for naught. Each respected the expertise of the other. Dr. Code, or “Charlie,” as he soon became known, was a successful administrator, something that Mort had decided earlier in his career was not for him. Charlie had been instrumental in the successful establishment of a school of medicine at the Mayo Clinic. Shortly after he arrived, Charlie identified problems with accounting, supply management, and secretarial functions at CURE. My understanding is that when Mort heard Charlie’s suggestions regarding how to deal with these problems, he gladly delegated that responsibility.

Charlie’s research involved esophageal and small bowel physiology and pathophysiology. Mort’s research was in gastric and duodenal physiology and pathophysiology. Thus there were no scientific conflicts between them. Where there was overlap, e.g., gastric mast cells, they developed a highly productive collaboration.

CURE’s most remarkable feature was its openness. When you walked through the halls of the research building almost all the laboratory doors were open. Researchers were openly, happily, and productively discussing their findings with one another. These collaborations were an aspect of research that Mort strongly encouraged. He would frequently send notes to
researchers telling them to contact a fellow investigator as the latter had findings in an area that might be interest to the former. The note would be very brief, e.g., “Paul—see Gordie [Kauffman] about his findings with cimetidine.” You would ignore such messages to your own detriment. Invariably the investigator Mort referred you to had findings that impacted upon yours and would be of interest to you. Productive collaborative research was often the final result.

Mort’s door was always open. When you telephoned to ask to see him about some findings, the invariable response was, “Can you come now?” When you came, you would show him the results in question. He would look over the data and make pertinent and remarkably insightful comments. Within 10 min of coming, you knew your time was up and you would leave. The 10-min exchanges with Mort were worth more than an hour or two with almost any other person.

Mort was a very hard worker. He would come to his office very early, 6 AM or even earlier, and worked all day. Irrespective of the demands for his time, he was always available for offering help. If you left a draft of a paper for him to critique, invariably it was in your mailbox the next day covered with helpful and perceptive remarks written clearly in red ink. You might be upset that he did not agree that your writing was the work of a genius, but you were never insulted, and you were always grateful for the criticisms and suggestions.

Another important aspect of Mort’s teaching was the monthly evening research meetings in his home that he held even well before CURE was established. Anyone conducting gastrointestinal research was welcome to attend. His living room was set up with a screen at one end, an overhead transparency projector, and 10–20 chairs. Coffee and snacks were available. There was no schedule. Anyone who wished to present data simply came with prepared transparencies. The presenter would take about 10–15 min to show his or her data and then an open discussion would follow. The comments, suggestions, or criticisms were constructive but never rude or argumentative. Although Mort invariably led the discussion there was open debate in which anyone could freely participate.

When I first started attending these meetings, I was amazed at how the young researchers would regularly present new data every month or two. I thought it would take 6 months or more to gather sufficient data to present. Then I realized that Mort’s approach was to break your larger project into smaller steps and present the data serially, a huge advantage for the researcher. The data you collected in one month usually carried through one step, however small, toward your goal. You then could present your data for critical analysis by Mort and your fellow researchers. Their judgments and thoughts were invariably helpful in either confirming your conclusions or pointing out alternative interpretations, changes, or additional work that was necessary. Another advantage of this approach was the stimulation of competition among the fellows. If your colleague could produce new data every month or two that was worthy of presentation to Mort, then you could also. As my laboratory gradually built up, I incorporated this research teaching technique within my own small group of fellows to the benefit of all. One of my former fellows commented that “nothing focuses the mind like a deadline!”

Another important lesson I learned was Mort’s approach to research planning. It involved first asking yourself three fundamental questions: 1) What is the question? Thinking you would “like to study this subject” is too vague. 2) Is this an important question? You will be spending considerable time, effort, and money on this research. Is the question important enough to warrant this expenditure? 3) Is the question answerable? “What is the cause of cancer?” is an important question, but it is not a currently answerable question.

Mort not only provided meaningful critiques of your work but provided invaluable practical help, when possible, in answering questions. Hiroshi Satoh (Fig. 2B), a visiting research fellow in my (Fig. 2C) laboratory, had developed a fasting-indomethacin gastric ulcer model in the rat in Japan and wanted to study it further. Since it was known that indomethacin-induced small bowel mucosal lesions were due to bacterial penetration, he wanted to determine whether antibiotics would also protect rats against antral ulceration in his model. When the results showed that neomycin did remarkably decrease the extent of antral ulceration, we excitedly presented the data to Mort. He calmly suggested we repeat the experiment in germ-free rats so that we could be sure we were dealing with an antibacterial and not some other possible protective effect of neomycin. I was flabbergasted when I heard this. Neither Hiro nor I had any experience working with germ-free animals, and my grant was inadequate to establish and maintain a germ-free laboratory. Mort, with one telephone call to his colleagues at the UCLA gnotobiotic animal facility, made all of the arrangements. Mort’s concern about our too-rapid conclusion was correct. Ulcer development in germ-free rats did not support the antibacterial effect of neomycin in mucosal injury pathogenesis.

CURE rapidly became a well-recognized research center of excellence throughout the world. Fellows and visiting scientists from many countries gave CURE the appearance of a United Nations research center. It is not difficult to understand the reasons behind CURE’s success, both in its ongoing research and in attracting scientists. With the establishment of...
the Center for Ulcer Research and Education, Mort was able to focus on the cause, treatment, and, optimistically, cure of peptic ulcer disease. The underlying concept of CURE was the multidisciplinary approach described above. A second important element in Mort’s approach was scientific rigor and honesty to improve techniques for both the collection and the evaluation of research data. In that era scientists were just starting to appreciate the importance of well-designed studies whose data could be analyzed in depth by the appropriate statistical techniques. This was essential both for basic science studies and for the burgeoning field of double-blinded randomized controlled trials in clinical studies. This approach produces research with greater impact and lasting results. Although the idea of such studies did not originate with Mort and they were starting to be done elsewhere, he became a leading advocate of them. The third element was the scientific education program at CURE. Scientific meetings with leading investigators were held several times a year, with a poster session sometimes added at which CURE investigators could present their findings for discussion with visiting scientists and colleagues.

A fourth and most important factor: Mort was actively involved in all of these activities. It sometimes was difficult to determine who should get the credit for the idea and the findings. For example, Mort had good evidence that histamine potentiated gastrin-stimulated acid secretion (10) and therefore suspected that the parietal cell might have separate receptors for histamine, gastrin, and cholinergic stimuli (as opposed to Charlie Code who believed histamine was the final common pathway for all three). Andrew (Drew) Soll took on the task of isolating the parietal cell and studying its receptors in vitro with Mort’s guidance. Drew quite properly received worldwide credit for his finding of the three parietal cell receptors that had been predicted and established this line of investigation. Behind this study, and studies by many others, was the essential presence and guidance of Mort. Equally important, all those involved deeply appreciated and acknowledged this.

One of Mort’s greatest contributions to gastrointestinal research (and perhaps to all research), was the demonstration of the value of multidisciplinary centers to solve major medical or research problems and the importance of proper leadership. CURE was among the first of such centers. The success of CURE, the success of its randomized double-blind clinical studies such as the first to show the efficacy of cimetidine in healing duodenal ulcers, the large number of important basic science findings such as Dr. Soll’s, and the education and research training of many scientists who later became leaders in their own right at universities and medical research centers throughout the world are all to Morton Grossman’s credit and significantly helped thrust research in gastrointestinal physiology and pathophysiology along the highly successful path it now enjoys. At the height of his career Mort was world renowned, playing a prominent role in numerous international symposia (Fig. 3).

Unfortunately, those fellows and visiting scientists coming after 1980 did not have the opportunity to interact with Dr. Grossman for he had become ill and died in 1981. Nevertheless, in his dying, as in his life, he had something to teach us.

Early one Monday morning in the fall of 1980 I found a brief handwritten note from Mort in my CURE mailbox. He wrote something to the effect that biopsies taken at UCLA over the weekend revealed he had carcinoma of the esophagus! Other tests were being performed and he would keep us informed about his condition. It was a shock, both to learn of his serious illness and his openness in letting others know. Then I noticed small pieces of paper in the other boxes. He was telling everybody! This is unusual, for when one becomes seriously ill, usually only the immediate family knows and others learn of it much later. Why did Mort take such an unconventional action? After a little thought and the unfolding of events in the coming weeks, his probable reasoning became clear. He knew how much all of us at CURE depended on his leadership. Rather than leaving us guessing, he wanted everyone to be aware of the situation. Just as facing research problems requires clear, rational thought, so does facing life problems. In the next few weeks we learned that Mort had inoperable cancer of the esophagus with metastases. A new therapeutic approach was tried without success. Mort recovered from the various tests and therapeutic efforts and returned to work. We then learned that Mort had gone to the Dean of the UCLA School of Medicine, Sherman Mellinkoff, and asked him to form a search committee to look for his successor as director of CURE! He did not want the many people working at CURE, and CURE itself, to suffer through a long period without a leader. Mort came to his office every day and worked for as many hours as he was able to in his ever-weakening condition. After learning the diagnosis, he faced the inevitable realistically.

A few months before he died, an evening celebrating Mort Grossman was held at UCLA. Many friends and colleagues came from around the world to honor him. It was not a sorrowful affair but, in a sense, a celebration of life. Mort was in a weakened condition. He wore loose-fitting blue denim overalls, possibly to help relieve discomfort from the very prominent ascites secondary to his malignancy. Toward the end of the evening Mort spoke to us. He was half reclining on a couch but his voice was clear. I do not recall his exact words, but he spoke about life, not about death. He was happy to exchange thoughts and greetings with his many friends (there were over 200 people in attendance). I happened to be standing next to the Chairman of Medicine at UCLA, David Solomon. He was smiling and turned to me and whispered, “Just as in life Mort taught us how to live, now facing death, he is teaching us how to die.”

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REFERENCES


