

The 482nd Convocation

Address: "Could Morton Do It Today?"

By Dr. Jonathan Moss

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It is a rare privilege for an anesthesiologist to have the opportunity to give the convocation address at the University of Chicago. I suspect that there may have been some consternation among the administration about the choice of an anesthesiologist to address this audience. Because of the curious habit of speakers opining about their chosen area of knowledge, the President and Provost were concerned that I would put you to sleep. I assured them that could be done by virtually any professor at the University of Chicago, but my ability to wake up my subjects distinguished me from many of my peers. Hopefully you will find this true today, as I wish to consider a topic that has troubled me more and more—the impact of increased regulation on innovation and discovery.

As a practicing physician, one of the developers of a new class of drugs, and, for the past decade, chair of the Institutional Review Board for the Division of Biological Sciences, which oversees some two thousand human research studies, I have been afforded a unique perspective on the challenges of clinical research. The hypothesis I propose today is that the growing number and complexity of regulations surrounding clinical research, while well-intentioned, jeopardize the innovation we have come to expect from it. By way of illustration, I ask you to consider three medical miracles we take for granted: X-rays, cardiac catheterization, and general anesthesia. I contend all three would be stillborn if we tried to deliver them in 2005.

In December 1895, the German physicist Wilhelm Conrad Roentgen discovered a kind of ray that could travel through wood or tissue and yield photographs of living people's bones. Roentgen called these mysterious rays "X-rays," with X standing for the unknown. Just a few years later, a young Polish woman, Marie Sklodowska, more commonly known as Madame Curie, discovered radium and polonium, for which she was subsequently awarded two Nobel Prizes. With the onset of World War I, Madame Curie was called upon to develop radiology vehicles to transport X-ray apparatus to the battlefield. These were called Petite Curies. For her

first assistant, she chose her seventeen-year-old daughter, Irene. As Madame Curie observed, “The use of X-rays during the war saved the lives of many wounded men. It also saved many from long suffering and lasting infirmity.” It should be noted, however, that neither she nor her daughter was shielded from the radiation that saved these soldiers’ lives. Subsequently, they both developed some of the symptoms that have come to be associated with radiation overexposure.

Cardiac catheterization was first demonstrated by Werner Forssmann, a German surgical house officer. During experimentation on a human cadaver, he realized how easy it would be to guide a urologic catheter through a vein in the arm into the right side of the heart. He actually dissected the veins of his own forearm and guided the catheter into his right atrium. With the catheter in place, he walked to the X-ray room to have his chest X-rayed. In so doing, Forssmann discovered cardiac catheterization, which we now take for granted in the diagnosis and treatment of heart disease. Incidentally, Forssmann was fired from his position at the hospital, but subsequently was awarded the Nobel Prize in 1956.

While we celebrate these pioneers and recognize their work, it is my contention that both these epic discoveries would be impossible in the contemporary environment in which I practice and study. Self-experimentation such as that described in Lawrence K. Altman’s book *Who Goes First?* would never be permitted today. It would also be impossible because of a complex series of regulations, among them protection of human subjects, animal rights concerns, intellectual property rights, liability, and conflict-of-interest regulations. Although well-intentioned, each of these “protections” poses a potential barrier to the development of new knowledge. Cumulatively, the daunting regulatory burden imposed on creative researchers has a chilling effect. Brick by brick we have built a wall, a wall too high for those with new ideas to struggle over. While few can deny the importance of provisions to protect human subjects or regimens to assure animal welfare, I wonder how many revolutionary ideas are stillborn, untested, or unproven.

My own specialty, anesthesia, is a prime example. Could it be discovered today? Anesthesia is an American discovery. William T. G. Morton first demonstrated the effectiveness of ether as an anesthetic on October 16, 1846, at the Massachusetts General Hospital. Before then, modern surgery did not exist. The only surgeries involved amputations, trephining of the brain, and a few

other short procedures. The best surgeon was the fastest. The most important surgeon of the time was Lister. He held the record for limb amputation (under thirty seconds), but maintaining that record occasionally meant sacrificing the fingers of his assistants in the process. Hundreds of botanical agents and preparations were tried to relieve pain and to permit surgery; none succeeded.

Morton grew up in rural Massachusetts, trained as a dentist, and continued medical studies at Harvard University. Based on his experience as a dentist, Morton sought to develop a technique to facilitate the removal of teeth without pain. His tutor, an eminent chemist, suggested that perhaps applying ether to the gum might relieve some of the pain associated with tooth extraction. Morton went beyond that suggestion and undertook a series of experiments in which he administered ether to goldfish, pigeons, and even the family dog at his home in Wellesley, Massachusetts. For such an undertaking today, Morton would certainly have encountered problems with animal use regulations. Our society's well-intentioned desire to assure the humane treatment of animals has been co-opted by the animal rights movement, whose proponents have ransacked laboratories and threatened investigators. Many of the expensive and ill-considered regulations passed reflexly by the government make it increasingly complicated and costly to do research on animals. Rats at the University of Chicago have more rights than patients in most of the world. Although it would have been impossible to develop anesthesia without first experimenting with animal models, it is unlikely Morton's experiments would ever have been permitted by our animal use board today.

After performing his animal experiments, Morton actually inhaled ether himself, tested it on his two dental assistants, and then—recognizing that body constitutions and weights were different—administered it to a series of burly dockworkers. After his experiments on volunteers and with the advice of his tutor, Morton decided upon a preparation of pure, or rectified, ether. With ether he had purchased at the hardware store, he went back to his office where he maintained a small dental practice. When a patient arrived who had a painful toothache, Morton poured some ether on a handkerchief and anesthetized the man for the extraction. When it was all over, the patient promptly awoke. Morton asked him if he was ready to have his tooth out. When the patient said yes, Morton pointed to the floor and showed him the tooth. Shortly

afterwards, Morton approached one of the most renowned American surgeons of the time, John Collins Warren, professor of surgery at the Massachusetts General Hospital, to arrange a public demonstration of an ether anesthetic. In an event memorialized in the important painting by Reynolds, Morton successfully anesthetized Gilbert Abbott, a patient suffering from a neck tumor. When the operation was over, Warren asked the patient if he had felt any pain. Abbott replied he had not. Warren promptly proclaimed, “Gentlemen, this is no humbug.” Of that moment Oliver Wendell Holmes wrote, “The deepest furrow in the knotted brow of man has been smoothed forever.”

Morton’s research strategy, experimenting first on volunteers and later on patients, is very similar to what we do today. However, looking at Morton’s human experiments through my regulatory glasses, I see that his progression to human trials would never have been approved today. Absent detailed information on ether’s metabolism and toxicity, which may have taken several years to determine, we would not permit its use on volunteers or patients. In Morton’s time, there was no such process as informed consent. In our contemporary environment, the recruitment of subjects is a highly regulated process. Informing subjects of the purpose of a human trial and its potential risks and benefits is an important component of human subjects’ protection. Compensation and informed consent are carefully scrutinized for every study that is undertaken here and at any other university in the country.

If Morton had negotiated the animal and human studies issues, he would then have confronted a blizzard of bureaucracy to challenge his progress. Some elements of this blizzard are intellectual property rights, liability, and conflict of interest.

In 2005, Morton’s first challenge might be negotiation with Harvard about patents and commercialization. By custom and statute, a university shares the intellectual property associated with discoveries by its faculty. Although a university cannot prohibit the publication of ideas or inventions, the policy it adopts for technology transfer can profoundly impact an invention’s development directly and indirectly. Had technology transfer policies been in place in 1846, I suspect the miracle of anesthesia would have died on the desk of some Harvard University lawyer. In a remarkably contemporary action, Morton actually attempted to patent his invention.

He called his new anesthetic “letheon” without revealing what it actually was. At the time, however, the Boston Medical Society proclaimed that no individual could patent a product that was of such benefit to mankind. Because of public pressure, Morton was forced within a month to reveal that in fact the active agent was ether. One wonders whether this same pressure would prevail now for the various attempts to patent life forms or stem cell lines that are discovered in university research laboratories. When discovery means potential new income, a university’s technology transfer policy may directly conflict with its fundamental purpose—the development and dissemination of new knowledge.

Another issue is liability. Today there is considerable discussion about Vioxx, but consider the issues surrounding ether. I can hear our risk management lawyers now, “You want to do what, Dr. Morton, induce coma in patients?” Such liability issues have impinged recently on vaccine development. Because of liability concerns, some drugs and devices are available today only outside of the United States.

Finally, Morton would have encountered conflict-of-interest issues. In an environment in which active investigators are discouraged by the federal government and prohibited by their institutions from participation in the final human trials of a drug or device they have developed, it would not have been Morton administering anesthesia in the Ether Dome that day. The intent of conflict-of-interest regulations is to obviate perceptions of impropriety, yet there would have been a perverse reality in prohibiting Morton from demonstrating the drug he had developed or Madame Curie from going to the front. I submit that conflict of interest is not a bad thing per se. It can easily be managed by full disclosure of how the inventor is involved. Several years ago, our most prominent medical journals sought to exclude the editorial opinions of investigators sponsored by industry. Recently, some of these same journals have quietly reversed this policy, recognizing that these so-called “conflicted” researchers often have the most informed opinions. If evolution had been designed with this upside-down regulatory logic of punishing success, we would all be single-celled organisms.

While we can agree that the development of X-rays, heart catheterization, and anesthesia are sentinel events in medicine, I reluctantly conclude that the web of institutional and federal

regulations would make it very unlikely that these advances could be developed in 2005.

To be sure, there are very important benefits in the protections afforded by animal and human subject regulations, and there are legitimate concerns about conflict of interest, liability, and intellectual property. However, I have a growing concern about the barriers these regulations impose on new ideas—barriers that can be so daunting as to discourage innovation. As Institutional Review Board chair, I have seen many of our own young investigators drift away from clinical research because of these challenges. My experience is with medical research, but I suspect the problem of maintaining innovation in an increasingly regulated environment may well be a more general one.

On this wonderful day of your graduation, I do not want to convey a negative message. The best days of medical research are yet to come, but individual researchers such as Morton are becoming rare. The era in which a single individual can invent X-rays, heart catheterization, or anesthesia has passed. It now costs as much as \$1 billion to develop a new drug. Only 25 percent of that cost is attributable to the research itself, with most of the remainder going to legal and regulatory issues. The enormous financial rewards associated with drug and device discovery will likely propel the process forward, but research will be concentrated more and more in huge corporate or institutional bureaucracies that can overcome regulatory barriers. So this is my challenge to you—our newest graduates. You have proven your ability by virtue of your presence here today; but your diploma is only the admission ticket to a greater challenge. There is no doubt that the walls are higher and more difficult to climb, so it is now up to you to generate not only the ingenuity but also the enthusiasm and determination, to scale these walls and ultimately transform your chosen field.

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