CLEVELAND CLINIC JOURNAL OF MEDICINE

PROCEEDINGS OF THE

ETHICAL CHALLENGES IN SURGICAL INNOVATION SUMMIT

MAY 8–9, 2008 • CLEVELAND CLINIC, CLEVELAND, OH

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Thanks and Acknowledgments

There are many people to thank for their help in making this summit possible. We would like to thank Delos Cosgrove, MD, CEO of Cleveland Clinic, and Joseph Hahn, MD, Chief of Staff of Cleveland Clinic, for the tremendous support they gave us from the beginning that made this conference possible. We are grateful to Jamie Belkin and the staff of Jamie Belkin Events for planning and running the summit; to Shelley Freed for assistance with marketing; to Barb Goulden, Department of Bioethics administrator, and Beverly Himelfarb, secretary to the Ethics Committee, for providing excellent administrative assistance; and to all of the outstanding faculty and summit attendees. We thank Glenn Campbell and Brian Mandell, MD, of the *Cleveland Clinic Journal of Medicine* for their excellent work in preparing this proceedings supplement, and we extend a special thanks to James Young, MD, for his insights early on and for supporting production of these proceedings through the Cleveland Clinic Division of Medicine Humanities in Medicine Research and Education Fund.

— *Allen Bashour, MD, and Eric Kodish, MD*
Summit Directors and Supplement Editors

From the summit directors

Surgical innovation lives on the border between tradition and regulation in a vaguely defined frontier. Over the course of many centuries, a framework for clinical medical ethics has developed with broad consensus regarding fiduciary obligations between patient and doctor, the principles of beneficence and nonmaleficence, and, more recently, respect for persons and autonomy. During the past century, a parallel set of ethical and regulatory norms has developed surrounding the ethics of research involving human subjects. While both sets of frameworks—those governing clinical ethics and those governing research ethics—contribute to understanding the ethical challenges that arise in the course of surgical innovation, neither is alone sufficient to provide clear guidance.

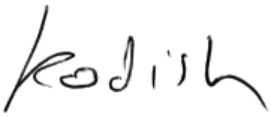
We decided that further discourse would help resolve some of the ambiguity that exists between the frameworks of clinical ethics and research ethics, and we set out to convene a summit meeting to provide a forum for this discourse. It was our hope that bringing together some of the nation's foremost surgical innovators with leading bioethicists would catalyze a series of presentations and discussions to create a meaningful ethical framework for thinking about surgical innovation. The summit took place May 8–9, 2008, at Cleveland Clinic, and we were not disappointed. We now have the pleasure of presenting the proceedings in text form.

The summit's five panel presentations and discussions and two keynote addresses shared the objective of educating participants about moral dilemmas that often arise in the conduct of device development and other innovations in surgery. Panelists suggested potential solutions to the challenges of protecting patients from risk without hindering creativity and progress.

The ethical challenges faced by surgical innovators will not go away. As we develop and refine technology, including new devices, procedures, and transplants, new problems will arise. Two examples of complicated issues on the horizon are robotic surgery and natural orifice transluminal endoscopic surgery (NOTES). While the specific developments will change, the ethical basis of our actions should remain constant. We need to always ask the same questions:

- Is this in the best interests of the patient?
- Have we been thoughtful and effective in the process of informed consent?
- Will our actions be consistent with our own professional integrity?

Our hope is that these proceedings will prompt the necessary next steps: further development of these ideas, writing of papers and convening of more meetings, and, most importantly, further innovation to continue helping patients.



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AMM Association of Medical Media

Keynote Address

Panel 3: Inside the Operating Room

Keynote Address

Panel 4: Outside the Operating Room

Panel 5: New Surgical Devices and Ethical Challenges

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DELOS M. COSGROVE, MD
Cleveland Clinic

Ethics in surgical innovation: Vigorous discussion will foster future progress

Welcome to Cleveland Clinic. We are delighted to have you here, and I am sure this is going to be a very interesting and provocative meeting.

In 1873 Sir John Eric Erichsen, surgeon to Queen Victoria, wrote that "although methods of practice may be modified and varied, and even improved to some extent," "the knife cannot always have fresh fields for conquest." How wrong he was.

Surgical innovation has continued without a break from Erichsen's day to ours. In 1873 only 2.5% of the population survived to age 65. Over the past 100 years, surgical innovation has helped to extend the average life expectancy to 76 years.

AN UNRULY TRADITION

Surgical innovation has happened largely without rules and by its own unruly tradition. In some ways, it is the last frontier in medicine. Today surgical innovation is arguably defined and barely regulated. Technical variation is the norm, and every patient is different. The boundary between taking an alternative approach and embarking on a novel human experimentation may be finely shaded. No surgical equivalent to the Food and Drug Administration monitors the operating room. Professional ethics and common sense guide routine intraoperative intervention.

Formal research projects are carried out in compliance with the institutional review board (IRB) and the usual ethical and regulatory standards for human subjects research. Between these two posts lies a large, vaguely defined field. That is where this symposium will be spending the majority of its time.

Surgical progress is problem-driven and rarely planned. It has often taken place under stress or in response to contingent need or opportunity.

In our own lifetimes we have seen the development of cardiac surgery in a virtually rule-free environment. Surgery for coronary artery disease did not develop out of a surgical protocol but arose out of new knowledge of the disease mechanism and improvements in imaging, anesthesia, extracorporeal oxygenation, and a combination of gifted surgeons and experienced surgical teams. It was immediately accepted as therapy. There are similar examples in every surgical field.

Over the past 40 years only 10% to 20% of surgical techniques have undergone clinical trials. Transplant is a classic example. Cardiac transplant moved forward without clinical trials, and it is unlikely that clinical trials will ever be done. The laparoscopic revolution came about in the same way.

A REGULATORY BALANCING ACT

Regulation is necessary, but where and how much? In a recent speech here at Cleveland Clinic, Anne Mulcahy, chief executive officer of Xerox, said, "Most great things happen by accident and experimentation. The moment you try to streamline and keep everything captive to very focused and disciplined outcomes, you lose your ability to really invent."

On the other hand, we cannot let surgery devolve into what a past president of the Canadian Medical Association called "a chaos of techniques devoid of moral purpose."

Finding the right balance will be difficult. All of this makes this symposium on ethics in surgical innovation relevant, necessary, and likely to be of interest well beyond these rooms. The profession of surgery has everything to gain from a frank discussion of the issues surrounding innovation. A solid grasp of ethics will improve our practice, protect our patients, and foster progress and innovation as we go forward.

You have a wonderful opportunity to discuss with some of the finest innovators in surgery—who are here in this room—the ethical and moral dilemmas of innovation. We cannot, on the one hand, proceed completely without plan; on the other hand, we cannot regulate innovation out of existence. In the end, it is about our patients, and their interest has to be placed first.

Thank you for joining us. I am sure you are going to have an excellent symposium.

Dr. Cosgrove is Chief Executive Officer and President of Cleveland Clinic and former Chairman of its Department of Thoracic and Cardiovascular Surgery.

Dr. Cosgrove reported that he has no financial interests or relationships that pose a potential conflict of interest with this article.

This article was developed from an audio transcript of Dr. Cosgrove's address. The transcript was edited by the *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness, and was then reviewed, revised, and approved by Dr. Cosgrove.

JOSEPH J. FINS, MD
Weill Cornell Medical College

Surgical innovation and ethical dilemmas: Precautions and proximity

No! I am not Prince Hamlet, nor was meant to be;
Am an attendant lord, one that will do
To swell a progress, start a scene or two…
—T.S. Eliot, *The Love Song of J. Alfred Prufrock*

Let me start by thanking the organizers for their invitation to be here and to start this off. I am not sure if that invitation was an act of kindness or of throwing a fellow bioethicist to the lions, as we will be addressing a complicated set of issues upon which well-intentioned folks disagree and sometimes disagree with a passion.

What I would like to do is to lay out some of the inherent ethical problems related to surgical innovation. I will argue that some of these problems are unique to surgery and that others relate to how we have chosen to define categories like research and practice. Other problems involve how we view the proportionality of risks and benefits in surgical research. I will argue that we have falsely analogized surgical progress to progress made in other areas of biomedical research and misunderstood the highly personal, or proximate, nature of surgical inquiry. Without appreciating the import of what I will call "surgical proximity," we will be unable to adequately address ethical issues in surgical innovation.

In a surgical trial, the therapeutic impact has to be larger than in a drug trial to warrant ongoing study. This burden of scale increases the probability of reciprocally large adverse effects.

PROBLEMS OR DILEMMAS?

So let me begin with the title of our session, "Surgical Innovation and Ethical Dilemmas," and why this juxtaposition is counterproductive. A colleague long ago taught me to distinguish problems from dilemmas—the former being resolvable, the latter intractable, often involving a choice between two equally unfavorable choices.

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Dr. Fins reported that he is an unfunded co-investigator of the use of deep brain stimulation in the minimally conscious state funded by Intelect Medical Inc.

Although I may be making too much of the semantics, I do think the title betrays a presumption that surgical innovation invariably forces adversarial choices. It tends to dichotomize ethical reflection, pitting those who favor prudence against those who endorse progress, or it creates too stark a difference between ethical issues in surgical practice and those encountered in the conduct of surgical research.

Even therapeutic, validated surgery in many ways has the potential to become innovative, if not outright experimental. Patients may have anatomical differences that require surgical improvisation, or complications may arise during "routine" surgery, creating the need for an imaginative response.[1] At what point do these departures from expected care become novel interventions, innovative or even experimental? A routine case with an unexpected turn can even become a case report opening up a new field of endeavor.

For instance, the field of stereotactic functional neurosurgery was born out of a "routine" case of ablative surgery for Parkinson's disease in the 1980s, when the French neurosurgeon Alim Benabid was using electrodes to determine which areas of the brain should be destroyed. As he was mapping the thalamus, he noted that the tremor of his patient abated. This led him to wonder if one could treat drug-resistant Parkinson's with electrical stimulation instead of destructive lesioning.[2] Benabid's translational insight during an ordinary case led to the development of the rather extraordinary field of stereotactic functional neurosurgery and neuromodulation.[3,4]

Another example from an earlier era comes from the life work of neurosurgeon Wilder Penfield, who did pioneering work in the surgical treatment of epilepsy. Here, the accumulation of experience from "routine care" led to generalizable knowledge, much like hypotheses are validated in experimental work. In Penfield's case, his clinical use of electrical stimulation to plan resections of scar tissue causing epilepsy led him to map the human homunculus, a magnifi-

cent achievement of profound importance.[5,6]

So let us avoid simplistic and confounding demarcations. Instead of dichotomizing innovation and prudence—or surgical research and surgical practice—let us try to start our deliberations with an eye toward a more synthetic approach. Like most things in nature and in biology, ethics too is on a continuum with gradations that can fit into an Aristotelian taxonomy. Let us emulate what Aristotle called *phronesis*, or practical wisdom, these next 2 days so that we achieve constructive outcomes, or what the pragmatists would call instrumental goods.[7]

If we are successful in laying out the ethical issues in this clinically pragmatic fashion, we can turn intractable "dilemmas" into problems amenable to resolution through the particularistic invocation of ethical principles as they relate to the surgical context.[8] If we follow this inductive method of moral problem solving, we will avoid sweeping ethical generalizations, or categoricals, that can misrepresent the complexity of innovative research and deprive society of its benefits.[9]

INNOVATION VS PRUDENCE: A FALSE DICHOTOMY

So let us start by understanding the presuppositions that led to the expectation that *dilemmas* will descend upon those who engage in surgical innovation. In my view, this expectation begins with what is called the precautionary principle, a concept with some currency in the realm of environmental ethics.[10]

History tells us, as contemporary assessments of current research cannot, that only Harvey Cushing could achieve Cushingoid results.

The precautionary principle urges caution and prudence when facing unknowns and is an antecedent sort of utilitarianism. One makes judgments about the advisability of actions based on a prior assessment of foreseeable risks and benefits. If the risks are excessive or exceed benefits, the precautionary principle urges care, caution, and even avoidance of a given course of action.

When the precautionary principle is implicitly invoked in making judgments about research, the objective is to pursue a degree of safety that is comparable to that of established therapy. But interventions that have progressed to being deemed "therapeutic" have of course achieved a requisite degree of both safety and efficacy—that is what makes them therapeutic, as opposed to investigational, interventions. One cannot know before one has conducted a clinical trial, and completed statistical analysis, whether a new surgical advance or device meets these expectations. Because of this lack of knowledge, there is an inherent degree of risk in any novel intervention.

The challenge posed by innovation or novelty creates the possibility of untoward events. It leads to invocation of the precautionary principle, which, echoing the admonitions of the philosopher Hans Jonas, urges us to "give greater weight to the prognosis of doom than to that of bliss."[11,12]

This is not a bad way to go through life, assuming one wants to emulate T.S. Eliot's J. Alfred Prufrock, who lamentably "measured out my life with coffee spoons."[13] Unlike the surgeon, who must make decisions in real time, Eliot's protagonist could not move forward. Despite his desire to avoid the indecision of Prince Hamlet, alluded to in this paper's epigraph, Prufrock was paralyzed by doubts and fears, with "time yet for a hundred indecisions, and for a hundred visions and revisions."[13]

Despite Eliot's invocation of "a patient etherised upon a table,"[13] the poem shares little with the surgical life. It has much more in common with the precautionary principle. Like Prufrock, the precautionary principle favors what is known—the status quo—as what is unknown is invariably more risky than the familiar. Needless to say, this is antithetical to innovation because discovery invariably requires scenarios that involve novelty and unknown risks. When faced with the certain security of stasis or the potential dangers of innovation, the precautionary principle will invariably choose stasis, leading us, as the legal scholar Cass Sunstein notes, "in no direction at all."[14]

Seen through the prism of the precautionary principle, then, surgical innovation invariably presents a dilemma. Discovery and innovation are fundamentally at odds with the precautionary principle, because of their potential for risk.[15]

The challenge posed by the precautionary principle—which, to be fair, is seen in all areas of clinical research—becomes even more pronounced in surgical research because of the size and scope of clinical trials. As is well appreciated here, compared with drug trials, surgical trials are small. Sometimes they can involve a single subject, whereas drug trials may include thousands of participants. Because of drug trials' large volume of subjects, therapeutic effects can be small to justify ongoing research. In a surgical trial or a device trial, the number of subjects is smaller, so the therapeutic impact has to be larger to warrant

further development and ongoing study. This burden of scale increases the probability of reciprocally large adverse effects. This potential for disaster magnifies the impact of the precautionary principle and may lead to a distortion in ethical judgment along the lines of Hans Jonas' admonition.[12]

By all of this I am not suggesting that we abandon precautions and prudence. Instead, my point is to explicate the additional challenges faced by surgical research and the sway of the precautionary principle over this area of inquiry and innovation. By being explicit about the impact of this principle, we can be cognizant of its potential to distort judgments about risks and benefits. Only then can we hope to balance the pursuit of progress with that of safety.

SURGICAL RESPONSIBILITY

These distortions also need to be recognized, and made explicit, because surgical research, more so than pharmacologic research, is much more personal and intimate. This point becomes clear if we consider a surgical trial that does not succeed.

In the surgical arena, such failures are taken to heart and personalized. Unlike trials that involve drugs, surgical research is more proximate. It is not just the failure of a drug or of pharmacology; it is also possibly the failure of the operator, the surgeon who did not achieve the desired goal because of poor execution of surgical technique.

Even the great Harvey Cushing perceived the weight of surgical burdens, suggesting that any effort to depersonalize the ethics of surgical innovation would be naïve.

This crucial difference in medical versus surgical cultures is captured by Charles Bosk in his magisterial sociological study of surgery, *Forgive and Remember: Managing Medical Failure*. In a discussion of morbidity and mortality rounds, Bosk writes:

> The specific nature of surgical treatment links the action of the physician and the response of the patient more intimately than in other areas of medicine.... When the patient of an internist dies, the natural question his colleagues ask is, "What happened?" When the patient of a surgeon dies, his colleagues ask, "What did you do?"[16]

As in clinical surgical practice, in surgical research, it is the personal and individualized mediation of the surgeon that is central to the intervention. Here the intermediary is neither a drug nor its bioavailability; rather, it is the operator's technique plus or minus the operative design and the reliability of an instrument or a device. In either case, the contribution is more proximate and personal, stemming from the actions of individual surgeons and the work of their hands.

History is instructive on this theme of surgical causality and personal culpability if we consider the life of Harvey Cushing, a Cleveland native whose ashes are buried nearby in Lake View Cemetery.[17] Cushing was a gifted and innovative surgeon whose technique handling tissues changed how the brain was approached operatively. He is acknowledged as the father of neurosurgery, having created a professional nexus to institutionalize and carry on his innovative work.[18]

Cushing's greatest innovation was probably in his individual efforts as a working surgeon. Over the course of his lifetime, he made the resection of brain tumors a safe and sometimes effective treatment for an otherwise dread disease. Michael Bliss, Cushing's most recent biographer, reports mortality data from more than 2,400 surgeries done by Cushing during his operative lifetime.[17] Early in his career (from 1896 to 1911), while he was at Johns Hopkins, Cushing's case mortality rate was 24.7%. During his later years at the Brigham Hospital, it was 16.2%. By 1930–1931 it was down to 8.8%.

These were extraordinary statistics: no one matched Cushing's numbers, or his ability to do what he did. Bliss cites mortality data from his surgical contemporaries in the late 1920s as ranging from approximately 35% to 45%. By the numbers Bliss compares Cushing's talent—his truly brilliant outlier performance—to that of his Jazz Age contemporary, Babe Ruth, who also had outsized talent compared with his peers.[17]

Cushing himself, a collegiate second baseman at Yale, linked sport and statistics in a most telling way. Documenting his ongoing surgical progress was a hedge against failure and lightened the emotional burdens of the surgical suite. Cushing observed: "A neurosurgeon's responsibilities would be insufferable if he did not feel that his knowledge of an intricate subject was constantly growing—that his game was improving."[17]

This quote and Cushing's operative statistics point to his nascent effort to engage in evidence-based research and speaks to the spectacular difference that a surgical innovator can make. The extraordinary results achieved by Cushing in his day also suggest that surgeons are not fungible at the vanguard of discovery. History tells us, as contemporary assessments of current research cannot, that only Harvey Cushing could achieve Cushingoid results.

A second point that stems from Cushing's comment about the burdens of operative work and surgical research is how personally taxing that responsibility can be. Without making progress, he said, the "*responsibilities would be insufferable*"[17] (my italics).

Even the great Harvey Cushing perceived the weight of these burdens, suggesting that any effort to depersonalize the ethics of surgical innovation would be naïve. The singularity of Cushing's surgical accomplishments (his operative excellence as compared with his peer group) and the felt weight of these achievements suggest that surgical innovation is highly personal and proximate to the surgical researcher in a way that is distinct for surgical innovation. This relationship of operative causality and personal culpability can be subsumed under what I will call *surgical proximity*.

SURGICAL PROXIMITY

Surgical proximity has several implications for the conduct of research. In this section I will address two issues: conflicts of interest and clinical equipoise.

Surgical proximity and conflicts of interest

As the Cushing example illustrates, at least at the outset of a clinical trial the surgeon himself is part of the actual design of the trial. The same surgical method in the hands of one of his contemporaries would have led to a dramatically different result. The surgeon who is at the forefront of innovation becomes an experimental variable until the methods can be generalized.

The importance of the operator as an essential ingredient in early surgical research points to a key difference with pharmaceutical trials, where the purity of the drug-based intervention can be maintained. This difference has implications for the "rebuttable presumption" stance promulgated by the Association of American Medical Colleges (AAMC), which looks askance at innovators conducting clinical trials if they have a conflict of interest, such as intellectual property rights for their discoveries.[19,20]

In many cases, the work that surgical innovators do, as in the case of device development, could not be done without collaborations with industry. Taking the surgical talent of the potentially conflicted—but highly talented—innovator out of the equation may be counterproductive.

Time does not allow me to fully address the conflict-of-interest issue in this forum; suffice it to say that the differential knowledge, skill, and talent of early surgical innovators may be the difference between a trial's early success or failure. The role of such innovators should neither be truncated or precluded nor be viewed a priori in a prejudicial fashion. Instead, their talents and vision should be welcomed as instrumental to the potential success of the work, managed of course with the proper degree of transparency and disclosure.

As I have noted previously,[4,21] if the rationale for a conflict of interest is to allow laudable work to continue that otherwise could not occur without the personal intervention, and talents, of a surgical innovator, it seems prejudicial to view the conflict of interest as disqualifying until proven otherwise. This view is consistent with the legal framework of the US Constitution, which explicitly authorizes Congress "to promote the Progress of Science and the useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."[22] It is also embedded in the Patent Act of 1790,[23] which balances the patent's period of exclusivity against the inventor's obligation to share and disseminate expertise. This role for the innovator is also consistent with the intent and incentives within the framework of the Bayh-Dole Act of 1980,[24] which was passed with the expectation that industrial partnerships would move ideas from the bench to the bedside.

Taking the talent of the potentially conflicted—but highly talented—surgical innovator out of the equation may be counterproductive.

I hope that others at this conference will be able to return to the issue of conflicts of interest and how the question of surgical proximity may, or may not, alter our ethical judgments about the surgeon's role in research where there may be a conflict of interest.

Surgical proximity and equipoise

Surgical proximity also has an impact on clinical equipoise, the ethical neutrality about outcomes felt necessary for the conduct of clinical trials.[25] The surgeon's sense of causality and proximity to the operative act makes surgical research different because the equipoise, which exists objectively about the research questions at hand, may not exist in the mind of the surgical researcher. Let me explain.

Taking a patient to surgery is highly consequential. As we have seen from Bosk's work,[16] surgeons feel a sense of responsibility for their operative acts and surgical work. This felt responsibility, inculcated in surgical training and surgical culture, obligates the surgeon to make a

proportionality judgment about bringing a patient to the operating room, be it for research or for clinical practice. In this way, surgical investigators have determined, at least in their own minds, that net benefits outweigh net risks, thus breaching clinical equipoise.

It is hard for a surgeon to commit to an operative procedure—be it for clinical care or for research—with all its attendant risks if he or she does not believe that the intervention is safe and effective. We can appreciate the importance of the surgeon's perspective on the utility of any proposed operation if we consider the opposing question of futility in clinical practice.[26] Whereas internists or intensivists might be compelled by families to continue aggressive intensive care, surgeons cannot be compelled to take a patient to the operating room when they deem that the risks outweigh the benefits. Because the surgeon is such a proximate moral agent, he or she will be held culpable for the actions that occur in theater. This degree of responsibility is accompanied by a retained degree of discretion—an almost old-world paternalistic discretion[27]—to counter the demands for disproportionate care.

This same sense of culpability and responsibility informs the surgeon's willingness to take any patient to the operating room. In the case of research, this willingness becomes an issue of concern because it means that in the surgeon's mind, favorable operative proportionality has been achieved.

This process of self-regulation[28] can have implications for the informed-consent process because surgeons believe in their work and can exert a strong dynamic transference on subjects who may be desperate for cure.[29] Because of this potential bias, surgical research may become especially prone to a therapeutic misconception. That is, if the surgeon is willing to take the risks of doing an innovative procedure in the operating room, then it has crossed some sort of internal threshold of proportionality in which the risks, whatever they are, have become acceptable given the putative benefits. Given what Bosk has written about surgical failure,[16] a high bar is crossed when a surgeon takes a patient to the operating room for a novel procedure, even though motivations at that bar may occasionally be mixed.*

Surgical investigators have determined, at least in their own minds, that net benefits outweigh net risks, thus breaching clinical equipoise.

FROM SURGICAL RESEARCH TO EDUCATION

This leads to my closing observations about transitions in surgical research, when the work of the pioneering surgeon is bequeathed to the broader surgical community to pick up the torch—or scalpel—and expand the work.

This takes me away from research and, fittingly here at a medical school dedicated to research training, brings me to medical education. To transcend the personal dimensions of surgical innovation—and the courage and vision of the founders—and sustain it more broadly, innovators also have to become educators of future surgeons, organizers of talent, and moral exemplars for the next generation. They have to appreciate that the work that they started, if it is important, will not be completed during their tenure but that future generations will carry it forward and expand upon it. They also have to prepare the next generation with the tools and orientation to appreciate their vision and to embrace what Thomas Kuhn might call new scientific paradigms.[30]

On several occasions Wilder Penfield, who founded the Montreal Neurological Institute, wrote with regret about Victor Horsley, the neurosurgeon at Queens Square in London. Penfield viewed Horsley as the founder of his field, but Horsley left no disciples. In his autobiography, fittingly entitled *No Man Alone*, Penfield noted that Horsley, "the most distinguished pioneer neurosurgeon, had died in 1916 without having established a school of neurosurgery."[5] This is in contrast to the discipline-building work of Cushing.

It is not an accident that Dr. Cushing founded a field full of trainees and protégés, of which my copanelists are descendants. It was intentional and part of his ethos of being truly innovative. And it is not an accident that the distinguished surgical innovators at this symposium have also created institutional structures to continue their work for decades to come. Their achievements have transcended the individual innovator and have become systematic. It is said that Dr. Thomas Starzl launched a field.[31] Dr. Denton Cooley founded the Texas Heart Institute.[32] Dr. Thomas Fogarty started the Fogarty Institute for Innovation, whose mission statement explicitly notes that it is "an educational non-profit that mentors, trains and inspires the next generation of medical innovators."[33]

*Lest I be misconstrued as too idealistic, this burdens-vs-benefits equation may be fueled by a complex mosaic of motivations and may not always be informed fully by patient-centered benefits. If the surgeon is the innovator and the inventor, these benefits may be for the pursuit of a hypothesis and associated with potential fame or fortune. But even in these cases, judgments about proportionality are informed by surgical proximity. (For more on the ethics of conflicts of interest, see references 4 and 21.)

Each of these pioneers, I believe, appreciates the need for continuity and dissemination.

But even here there is something that we nonsurgeons need to understand: although the work transcends the individual surgeon, the ties remain personal and linked to the impact and legacy of founders. Take, for example, highly prized membership in the Denton A. Cooley Cardiovascular Surgical Society.[34] This too is about the importance of individuals and surgical proximity, but here it is transgenerational.

CONCLUSION

If we truly want to continue the dialogue begun here today, we need to understand these social and professional networks and the importance of surgical proximity in transmitting both methods and values. The proximate nature of surgical research—and the causality and responsibility that accrues to the surgeon—makes surgical research different than other areas of biomedical inquiry. This difference has implications for risk-benefit analysis, conflicts of interest, and clinical equipoise. I hope that my colleagues return to these themes in the coming days so that the regulation of this important area of research can be informed by a deeper understanding of the ethics of surgical discovery and innovation.[35]

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Surgical innovation and ethical dilemmas: A panel discussion

END RESULTS: WHY SO ELUSIVE STILL?

Dr. Isador Lieberman, Moderator: Let me begin this discussion with a 1910 quote from Ernest Codman, a general surgeon at Massachusetts General Hospital, who stated:

> In 1900 I became interested in what I called the "end result" idea, which was merely the commonsense notion that every hospital should follow every patient it treats long enough to determine whether or not the treatment has been successful, and then should inquire, "If not, why not?" with a view to preventing similar failure in the future.

My questions to the panel are: What has changed in the last 100 years? Are we documenting our end results? Have we gone wrong and, if so, where have we gone wrong?

Surgical training is now so oriented to operative techniques that residency programs have difficulty dealing with other important issues, such as evaluating outcomes.
—Dr. James Herndon

Dr. James Herndon: Although Codman's ideas in this area were not well received at the time, today we do have some "end result" ideas. We have outcomes data, but I would argue that they are far too limited and not to the level required in the 21st century. I have asked myself many times why the surgical profession has not focused on this issue more than it has. I agree with Dr. [Joseph] Fins' comments in his presentation [see previous article in this supplement] that it would be nice to have a bottom-up approach rather than a top-down approach, but I do not see a change until we as physicians step up to the plate and make a change.

Why haven't we? There are a number of reasons. The malpractice climate in the United States has been one major factor. Surgeons fear disclosure. The relationship between a surgeon and the patient is professional and private, and physicians do not want transparency—they do not want their patient or anyone to know that an adverse event or bad outcome has occurred.

Also, doctors, especially surgeons, are reluctant to use guidelines or follow protocols. I participated a number of years ago in an American Academy of Orthopaedic Surgeons project called MODEMS; it was an attempt to set up guidelines for orthopedic surgeons to manage back pain, shoulder pain, and other orthopedic conditions. By the time we finished we had accomplished nothing, because the protocols and guidelines were so extensive that almost any type of management for any patient would be compliant.

Additionally, hospitals in the United States have become more like for-profit businesses, with a focus on short-term profits and with short tenures for their chief executive officers (CEOs)—4 or 5 years, on

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average. With nearly 50% of US hospitals bordering on bankruptcy, they are not able or willing to invest in major patient safety protocols and guidelines because the CEOs do not see a short-term benefit to them. Witness the fact that only 15% of US hospitals have computerized physician order entry systems and electronic medical records. From what I have read, it takes about 5 years before a hospital recoups such investments from the resulting safety improvements and efficiencies.

These are some, but by no means all, of the reasons we do not have appropriate outcomes in all specialty fields. My plea is that physicians lead the effort to measure and report outcomes down the road.

Dr. Lieberman: Dr. Hahn, why do you think we have not kept up with Dr. Codman's premise from 100 years ago?

Dr. Joseph Hahn: We hold a yearly Medical Innovation Summit at the Cleveland Clinic, and what has emerged from many of those meetings is a lack of interest in paying for outcomes analyses. The providers, the government, and industry all say that they do not have the money for these analyses. So the first reason that Codman's premise has not been lived up to is that the source of funding remains undetermined. Second, most surgical innovations have been geared toward inventing devices to overcome very specific problems that arise during or following surgery rather than toward substantiating the worth of a procedure through collection of evidence. A third reason involves the pressure that investors place on industry to make money, which tends to lead to investments in getting products to market rather than outcomes research. With all of these factors and the pressures from so many directions, the surgical profession hasn't stepped back to thoroughly consider what we are doing to our patients and just how worthwhile it is.

As innovations develop, we have to ensure that the new technology is matched by the operator's skill.
—Dr. Joseph Fins

Dr. Lieberman: Who do you think should be paying for outcomes analyses?

Dr. Hahn: I think the government should. The role of government is to take care of its citizens. The Centers for Medicare and Medicaid Services (CMS) does its best with the information it has, but it admits that it pays for some procedures without knowing whether or not they are truly worthwhile. An example is the use of artificial discs in the cervical spine. I am sure that the artificial disc manufacturers made a case for their product to CMS by claiming it was associated with less pain and resulted in a superior outcome compared to fusion using bone from the hip, regardless of whether they had the scientific evidence to prove it.

Dr. Lieberman: Dr. Fins, would you like to weigh in on Codman's "end result" premise?

Dr. Joseph Fins: I would just point out that the history is not homogeneous. I have been involved in deep brain stimulation work, and the legacy of psychosurgery has been an egregious lack of outcomes studies, but now we do have outcomes studies and scales. For example, there is now the Yale-Brown Obsessive Compulsive Scale to rate the severity of symptoms in obsessive-compulsive disorder. In our deep brain stimulation study,[1] we are using a coma recovery scale, and the Food and Drug Administration's (FDA's) investigational device exemption (IDE) process requires us to produce outcomes data to protect potential subjects. It may be an example of neuropsychiatric exceptionalism that neurology and psychiatry are areas of increased focus while somatic therapies are somehow presumed to be okay.

Dr. Hahn: FDA may be requiring the outcomes data, but I have not heard that they are willing to pay for it.

Dr. Fins: You are correct.

Dr. Ali Rezai: Part of the problem is the translation of rapid scientific discoveries and technological advances into the field, and education has a role here. Surgeons' reluctance to integrate guidelines and outcomes measures into practice must be addressed very early in their training—in medical school—and then continued throughout residency and fellowship programs. The same early and continuing approach should be taken with respect to how to conduct and properly interpret a clinical trial.

Dr. Herndon: That is a good point. Surgical education programs have slipped a bit in the past 5 to 10 years, at least in orthopedics. With the reductions in residents' work hours and the fast pace of residency programs, our residents spend most of their time in the operating room, struggling to master the multitude of procedures in orthopedics. As a result, they are not discussing outcomes or adequately following patients long-term after surgery. I have a hard time getting our faculty to bring residents into their offices so that the residents can examine patients and see why they are operating on certain kinds of patients, as well as the

types of follow-up information that can and should be obtained from patients. Training today is so oriented to operative techniques that residencies have difficulty dealing with these other important issues.

WHO DEFINES THE INDICATIONS?

Dr. Lieberman: As new devices and new techniques emerge, who defines their indications? The inventor of the device, a government authority that may or may not have the medical background, patient advocacy groups, or the device manufacturer? And how should we regulate those indications?

Dr. Fins: I would echo Dr. Wilder Penfield's words, "No man alone." The orthopedic surgeon or neurosurgeon does not have to do this alone; it is really about teams. And those teams can and should include biostatisticians, recognizing that the biostatistician needs to fully understand what the surgeon is doing. There also has to be attention given to patients' individualistic outcomes. I recently met with some FDA staff and learned that the FDA is very interested in novel methodologies to better understand what counts as an outcome for individual patients. So I think indications should be guided by individualistic outcomes coupled with the surgical possibilities and with the rigorous biostatistical methods that are now evolving. A conference like this represents an opportunity to generalize the conversation and support more collaboration on indications going forward.

It is important to try new technologies because the failure or complication rates may be reduced over time, but only if you evaluate the failures and then restrategize.
—Dr. Ali Rezai

Dr. Rezai: Indications should be defined using a team-oriented approach. Part of the problem of psychosurgery in the past was that the surgeon was defining indications without collaborating with the psychiatrist. In my field of deep brain stimulation and brain pacemakers, everything we have done for the past 20 years—surgery for Parkinson's disease, depression, obsessive-compulsive disorder, traumatic brain injury, epilepsy—has involved working closely with neurologists, epileptologists, brain injury specialists, psychiatrists, and psychologists to agree on indications. These teams also need to have close partnerships with ethicists. Teamwork is a vital aspect of proper development of an indication.

Dr. Hahn: It has to be the clinicians who set forth the indications. Of course, that may be done by a team of clinicians, but as a surgeon I certainly do not want the manufacturers of an artificial disc telling me what they think the indications for an artificial disc are.

As for the role of patients, some of them are very well informed about their problem. I cannot tell you how many have shown up in my office with reprints of articles I have written. This is a trend that has really mushroomed over the past 10 years. But even though patients are catching up, they are still at a disadvantage. Patients are going to have a say, but it is still the clinicians whose role is to decide the indications and then provide patients with a risk-benefit analysis.

Dr. Herndon: I agree. Although patients are becoming more involved in the process, real shared decision-making has not yet happened in my field.

More broadly, I feel that our professional organizations have to become more actively involved in the process of defining indications. Otherwise, after the innovators develop a device or procedure that will significantly change the approach to a particular problem, it will enter the market at large without any critical assessment of the technology involved and without accounting for the learning curve for each individual surgeon.

Take the example of minimally invasive total hip replacement, which involves a 1-inch incision in the front of the hip and a 1-inch incision in the back of the hip. The learning curve for this procedure appears to be about 40 cases, based on the opinion of experts around the country. Yet when this minimally invasive approach emerged, every surgeon who had been performing total hip replacements wanted this new operation at his or her fingertips because patients were demanding it. Some surgeons adopted it too quickly, without adequate training. I know one distraught surgeon who abandoned the procedure because of numerous failures during his first 100 cases. He returned to the standard hip replacement approach.

Our profession cannot let this experience continue or proliferate. Yet the professional organizations in orthopedics have walked away from technology assessment because industry does not want it; technology assessment is not in industry's best interest. We have had a number of conflicts in our professional organizations when attempting to move technology assessment forward. It is also very expensive to do.

Finally, indications can sometimes be governed more by economics than by science. I was asked to

write a letter to the editor about two technologies for managing intertrochanteric fractures of the hip that were recently featured in the *Journal of Bone and Joint Surgery*.[2,3] One technology involves a compression screw that has been shown to be effective in outcomes studies. The other is an intramedullary nail that has not been well studied and has no proven benefit over the compression screw. In doing research for my letter,[4] I found that Medicare assigns more relative value units (RVUs) for the intramedullary nail than for the compression screw. In Boston, the total dollar difference in RVUs between the two is $300: the surgeon makes $1,500 for the procedure that involves the intramedullary nail versus $1,200 for using the compression screw. Not surprisingly, use of the intramedullary nail has been climbing rapidly in the United States without any evidence to justify its use over the other, less expensive technique.

CREDENTIALING: CAN IT KEEP PACE WITH INNOVATION?

Dr. Fins: I agree that surgical competence and regulation—self-regulation or professional regulation—are big issues. One of my greatest fears is that surgeons will do procedures they are not trained to do, and cause great harm as a result. We are hearing about this now with the resurgence of psychosurgery in China.

It strikes me as interesting that the field of neurosurgery is as yet undifferentiated and that there is no subspecialty certification in stereotactic neurosurgery. This is in contrast to invasive cardiology on the medical side, where physicians who do catheterizations and electrophysiologic studies have special additional training.

There is a learning curve for every operation, and learning on one's own, at the expense of patients, is not appropriate.
—Dr. James Herndon

As innovations develop, we have to track qualifications and credentialing along the way. There should be provisions to grandfather surgeons in if they are in a post-training point in their career, but we have to ensure that the new technology is matched by the operator's skill. This is particularly pertinent in light of the concept of "surgical proximity"[5] and the importance of the individual operator; this is not comparable to just disseminating a new drug.

Dr. Lieberman: Who should do the credentialing? Should it be the government or our profession?

Dr. Fins: Recertification or credentialing should be by peers—the American College of Surgeons and the surgical boards. Of course, funders or payors may request an additional level of certification to do certain procedures, which I would endorse as a safety measure and to help ensure a minimal standard of care for innovative interventions.

Dr. Hahn: But it is not so simple. There is a blurring of surgical expertise once surgeons complete their training. Spine surgery used to be done by either neurosurgeons or orthopedic surgeons; now we have spine surgeons. What we neurosurgeons started to see with that change was that our neurosurgery trainees were being told they could not get on hospital staffs because they did not have credentials in spine surgery or, to take another example, in pediatric surgery. Well, the neurosurgery board made a conscious decision to not offer certificates of added qualification (CAQs). We challenged the hospitals in court and won. But the overriding message is that it is all about economics.

Dr. Herndon: In orthopedics we now have two CAQs—one in hand surgery and one (starting in 2009) in sports medicine. The hand surgeons have not noticed any adverse effect because they do not generate as much revenue as the spine surgeons do. Most orthopedic surgeons start as general orthopedists and then change their practice characteristics as their practices mature. Over time they may focus on one particular area, such as arthroscopic knee surgery or total hip or knee replacement, which makes it difficult for them to pass a general orthopedic examination. Our board recognized this trend and developed oral and written board exams with case reviews concentrating on the surgeon's self-chosen specialty. We do not need the CAQs because they have been misused, and we as a profession have been letting others misuse them. Again, I think we need to get back to controlling the process ourselves.

Dr. Hahn: What do you do when a surgeon has finished training and then becomes interested in performing a new procedure developed since the time of his or her training? This can really be a challenge when the surgeon hears of a new procedure, goes and takes a 3-day training seminar on it, and comes back believing that he or she is ready to perform the procedure. I have had creative surgeons on staff who want to try a new procedure but have never done any cases, believing that the new technology alone will suffice. What we finally decided to do in these instances was

to put in place other staff to proctor these cases to ensure that no harm was coming to patients.

Dr. Herndon: I admire that approach, because we as a profession have to educate our colleagues about whatever new procedures they are about to use in their practice. There is a learning curve for every operation, and learning on one's own, at the expense of patients, is not appropriate. Should we have experienced colleagues work with surgeons on new procedures until they have performed the 40 or so cases necessary to be proficient? Should we send surgeons to other institutions to do their 40 cases under experienced supervision? I am not sure what the best approach is, but this is a question that a forum like this should begin to address.

HOW MUCH RISK IS ACCEPTABLE?

Dr. Lieberman: Let's build on this issue of credentialing by turning to the concept of risk. What is an acceptable level of risk with a new device? Is a 50% risk of an adverse outcome appropriate? What about 10%? And who determines the acceptable risk? The profession? The regulatory bodies? Patients?

Dr. Fins: Our expectation about risks in clinical practice should evolve from what was anticipated and actually observed in the clinical trial of an intervention. Adverse events should be envisioned prospectively in the design of a trial, with the magnitude of risks delineated in the protocol. Any unexpected risks that occur, even if small, could be a major reporting issue.

Beyond that, it is difficult to say what an acceptable level of risk is without a particularistic clinical trial. Whatever the risk of an intervention, the assessment of the risk must account for regional variation, variation among surgeons, and also systems issues.

The Institute of Medicine report, *To Err is Human*, attributed medical errors to faulty systems, processes, and conditions. So when we think about errors and risk, we have to consider more than just the individual operator. Just as *To Err is Human* analogized medical errors to airplane crashes, we might think of surgical retraining in the context of how pilots get retrained using flight simulators. If pilots have not flown a particular aircraft in a long time, they lose their flight certification for that type of craft and then must be retrained to operate it.

As surgical technology gets more advanced, specific, and nuanced, the discordance between one's training and the potential things one can do becomes greater. Paradoxically, innovation can at least potentially make situations more dangerous in that the operator may not be able to perform the task with the improved technology. For example, pilots who know how to fly a Cessna can fly another simply constructed plane, but if they attempt to fly a higher-technology aircraft, like an F-16, they have a greater risk of having a catastrophic event even though the F-16 flies better, faster, and higher.

Dr. Lieberman: But are you willing to identify a level of acceptable risk?

Dr. Fins: It is based on the patient's preference, after informed consent. An acceptable level of risk is the level that people are willing to accept. What I am concerned about is the variance around a known risk, whatever it may be, that is attributable to human errors that may be preventable through training or by solving systems problems.

Industry may try to convince us to use its innovations without our input, as opposed to working with us to identify a clinical problem and trying to solve it together.
—Dr. Joseph Hahn

Dr. Lieberman: Dr. Rezai, you place needles into the brain. Who should decide the risk of that action? You? The patient? And what do you feel is an acceptable risk level?

Dr. Rezai: It is a complex question, of course, and a number of variables come into play. Whether or not the patient's condition is life-threatening or disabling is a very important factor in the risk-benefit ratio. Regulatory guidance from the FDA is strong with respect to defining device-related adverse effects as serious or nonserious, and our peers, both surgeons and nonsurgeons, help to further dictate the risk and tolerability of a procedure and its alternatives. For example, in considering a surgical procedure, one must weigh its risk against the risks of medications to treat the disorder, such as side effects, the ease of medication adherence, and the number of emergency room visits that may result from adverse effects of the medications.

Determining acceptable risk rests fundamentally and first with the patient and then with the surgeon and his or her peers (surgeons and nonsurgeons) in conjunction with regulatory components and oversight. All of these factors contribute.

In my field of deep brain stimulation, the threshold for acceptable risk can be high since we see patients

with chronic conditions in whom all previous medication attempts have failed, many of whom are disabled, intractable to current therapies, and with a significant compromise of quality of life. Examples include wheelchair-dependent patients with severe Parkinson's disease, severely depressed patients who will not leave the house and have attempted suicide, and obsessive-compulsive disorder patients who need 10 hours just to take a shower. This type of intractability to current therapies and the suffering of patients and families with limited options and little hope influence assessments of procedural risk.

Dr. Hahn: Performing a controlled clinical trial of a surgical procedure is difficult at best. I recall a clinical trial in which patients with parkinsonism were to be randomized either to have stem cells implanted in their brain or to undergo a sham operation with no stem cells. Well, very few patients signed up for the trial because everyone wanted the stem cells. So, obtaining a large enough denominator to define the risk of, for example, hemorrhage from sticking a needle into a vessel is almost impossible.

Dr. Herndon: Except when there are risks of serious life-threatening events, I believe the patient is the one who makes the decision after having the risks fully explained to him or her. Surgeons are educated in a system in which we learn to accept complications. It is the risk of doing business. We have not learned very well how to differentiate a complication from an adverse event or an error. We must learn to do that. We live with complications every day. Those complications must be conveyed to patients so that they understand what they are about to undergo, what can happen, and what cannot happen. The patient is the ultimate decider, in my opinion.

Investigators and innovators must use their roles to leverage industry resources to perhaps pay for some of the care that innovative devices make possible.
—Dr. Joseph Fins

Dr. Lieberman: That reminds me of something one of my mentors often said: "If you are going to run with the big dogs, expect to get bitten in the butt once in a while."

ETHICAL DILEMMAS ARISING FROM NEW OPTIONS

Question from audience: In my specialty, we have a non-life-threatening condition with a well-established 25% recurrence rate after traditional surgery with sutures, and a 25% rate of reoperation. A device comes along and it improves the outcomes so that the recurrence rate declines to 10%, but along with the extra costs of doing the procedure with the device, there is also a complication rate of about 10% that requires reoperation with the device, and a few of those patients actually end up worse. Ethically, how should the clinician proceed in this situation? The old way, or the new way that improves outcomes but at a higher cost and risk?

Dr. Fins: Based on the size of the populations, is the difference in the combined rates of recurrence and complications between the traditional and new methods (25% vs 20%) statistically significant?

Response from questioner: The difference is probably not statistically significant.

Dr. Fins: Okay, so you are saying that the numbers are basically equal. That is the first consideration, but there is a nuance to one of the variables, and that is an improvement in quality of life with one of the treatments. Measuring its significance is subjective. A patient may place greater emphasis on quality of life than would somebody who is not a beneficiary of the operation. That is why I said before that biostatistical input that goes beyond crude measures of mortality or reoperation rates can be very helpful. The risk of reoperation may be one that the patient is willing to take for a chance at an improvement in quality of life.

There is a wonderful book by Howard Brody called *The Healer's Power*[6] in which he writes about the physician's power to frame a question so as to engineer outcomes. While that is not something that Brody endorses, he does endorse the use of the physician's power to guide patients using good informed consent, providing direction without being so determinative that patients feel compelled to choose the physician's recommendation. Patients should be able to decline your recommendation while still having the benefit of your counsel. And in a case like this, your counsel should include variables that may seem "softer" or more difficult to quantify than crude measures such as mortality or reoperation rates.

Dr. Rezai: You have to compare multiple outcomes between the two approaches—surgical time, recovery time, patient quality of life (as assessed by scales), family quality of life, time to return to work, etc. I think it is important to try new technologies because the failure rate or the complication rate may be reduced over time, but only if you evaluate the

failures and then restrategize. Only in doing so can you reduce risk, and if the benefit profile and the risk profile prove to be good, then the new technology should be pushed forward.

Dr. Herndon: If the volume of procedures performed by the surgeon is important with respect to outcomes with either one of these two procedures, that should be taken into account. Also, if a new procedure carries a higher complication rate than the traditional procedure, I think that more cohort studies from large centers are needed to gauge the true complication rate before the new technology enters the general market. Continued surveillance, such as with a postmarket registry of outcomes with these procedures, would also be helpful to make adjustments in the future if necessary.

Dr. Hahn: If you looked at the early experience of Medtronic with pacers, you would be amazed at the number of deaths and complications that occurred during the first 3 years. But we do not even think about that now.

CAN INNOVATION HAPPEN WITHOUT INCENTIVES?

Question from audience: Dr. Hahn alluded earlier to the influence of money. All of you on the panel are institutionally based, and you are used to practicing with colleagues. I would suggest that surgery today is really not an individual sport, but that is the way it is practiced in much of the nation. Would we be better off if we developed a system that removed us from direct financial influence? Can we get the money out of the equation so that people have motives other than direct personal gain?

Dr. Hahn: I went to an institutional review board (IRB) retreat that included, of course, some IRB members who were not clinicians. They asked the same question that you just did: Why would you even expect to get anything for what you invent? I think that is naïve. People who work hard and invent things deserve to reap a reward. The challenge lies in working with industry, which may try to convince us to use its innovations without our input, as opposed to working with us to identify a clinical problem and trying to solve it together. In that way, the end product and the logic behind its use will be better.

I will give you an example from when I was head of surgery here. A company made a voice-activated table that would obey the surgeon's commands, such as "left," "right," "up," or "down." I asked the representative why such a product was needed, and he responded that the surgeon wants to be in total control of the operating room. I told him we do not change the position of the table very often. After a 2-week trial, the table was a dud. He fired the entire group that was working on the project. It was a case of a company simply trying to come up with a product it could sell.

The opposite scenario is if I invent the latest and greatest stent for the carotids and I want to use it. The question becomes how to strike a balance: how to protect the patients while at the same time rewarding the inventor. Another challenge is that device companies want you to stay on their scientific advisory board and they will pay you for it.

We owe it to our patients to work on their problems. We also owe it to them to tell them when we are working with industry on a product and explain why we think it would work in their case, if we think it would.

—Dr. Joseph Hahn

These questions are a big concern, and we have spent a lot of time on these issues at Cleveland Clinic. In fact, we held our own conference on biomedical conflicts of interest in September 2006 with attendees from around the country to discuss the necessary firewalls for ensuring that data are not contaminated, that the surgeon-inventor does not fudge data so that his innovation will make it to the marketplace, etc. At that conference, a number of people spoke about Vioxx. I am a surgeon, and my take on the COX-2 inhibitors is that a lot of my patients take these drugs and think they are wonderful, but there are some problems and risks. What is wrong with explaining to patients the risks and complications of these drugs, making your own recommendation about their use (unless you are receiving money from their manufacturers, which you would need to disclose to patients), and then letting patients make their own informed decisions? Personally, I was on Bextra for 3 years and was furious when it was pulled from the market because nobody gave me a choice whether or not to continue using it.

Dr. Lieberman: Let's explore this concept a little deeper. We know that innovation is so important, but how do we encourage clinicians to innovate in this environment? Dr. Hahn, you served as chairman of CC Innovations, which is Cleveland Clinic's technology commercialization arm. What were some of the strategies you came across in that role?

Dr. Hahn: We look for creative staff. We tell them up front that we want them to come to Cleveland Clinic and invent things. Our mission is literally to work on problems and take solutions to our patients. The culture here is meant to be creative. As a part of that culture, we welcome working with industry, as opposed to industry thrusting its innovations on us.

We are averaging more than 200 invention disclosures per year. More than 500 of our staff are involved with various industrial partners, and we are not going to hide that. In fact, we are going to make it public. The thought is that we owe it to our patients to work on their problems. At the same time, we owe it to our patients to say when we are working with industry on a particular product and explain to them why we think it would work in their case, if we think it would. While doing so, we need to make it clear that we will be happy to refer them for a second opinion if they would like. If I have a patient who wants a second opinion, I will offer to make the phone call for them and get them in. I think that is an advantage of the model we have here.

The reality is that there are some procedures that can only be done by one surgeon here, a surgeon who may have helped develop the procedure or some technology involved in it. Are we going to tell that surgeon that he or she cannot perform the procedure on anyone? That does not make sense. So you need to have a management plan that puts in place firewalls to protect the data on that procedure from any possible contamination.

So yes, we do reward staff who are doing innovation, and we do work with industry, and we do tell our patients we are doing it, and we do build firewalls to protect the data.

Dr. Lieberman: How about the rest of the panel? What are your thoughts on providing incentives for innovation?

Dr. Fins: Money is a key issue. The way the landscape is now structured, collaborations with industry are part of the mix. Under the Bayh-Dole Act of 1980, institutions are granted intellectual property rights to ideas or inventions developed by their researchers, and then the institutions can enter into contracts with industry to move the innovations forward. If industry support of research were removed, we would have to double the budget of the National Institutes of Health to compensate.

On the other hand, industry support can sometimes prove to be a disincentive to innovation in that it may engineer certain kinds of research or deprive investigators of tools they may need to do more basic science types of research. It is an academic freedom issue. At a translational level, industry may be helpful and catalytic. But sometimes it pushes an investigator to work for a short-term innovative application at the expense of a more speculative, riskier innovation.

We need to acknowledge that industry collaborations are part and parcel of the universe and focus on working with industry to moderate its influences. At the same time, we must use our leverage on the investigative side of the equation to pursue academic freedom and to leverage industry resources to perhaps pay for some of the care that innovative devices make possible. For example, contracting agreements could be drawn up so that money came back to the populations that participated in a clinical trial, or to a community that otherwise may need the device but cannot afford it. I think we have to create some type of charitable impulse to moderate the excesses of the profits and use them for the common good.

Most innovators have it in their genes and in their blood. They can be taught to innovate, but they have to have the intrinsic curiosity and the creative mind to be an innovator.
—Dr. Ali Rezai

Dr. Herndon: I would like to touch on disclosure. The orthopedic implant industry has been required by law to disclose its relationships with orthopedic surgeons, including the amount of money that surgeons may be getting from industry. This requirement has had unintended consequences that underscore the importance of disclosure. First, some of the monetary awards, whether market-driven or not, are quite excessive. Second, reviewing the contracts for royalties has led to the discovery that many are not supported by patents or intellectual property rights. Third, these disclosures have revealed that certain surgeons who work at major US institutions, and who thus have an obligation to pay the institution some of the monies from their research, have not disclosed their relationships for years and have kept those monies solely for themselves. So this disclosure requirement has brought many things to light.

Dr. Rezai: As long as there is human disease and suffering, innovation will continue. It has in the past and it will in the future. Most innovators have it in their genes and in their blood. They can be taught to innovate, but they have to have the intrinsic curiosity and the creative mind to be an innovator. Institutional support of innovation is important, as is respect for

the process that must be followed, including transparency and disclosure. If you put all these together, then innovation can be facilitated.

IF TESTING MOVES OFFSHORE, CAN ETHICS FOLLOW?

Dr. Lieberman: I am going to paint a scenario on which I would like each panelist to briefly comment. New Device X is backed by a big vendor. It is a great device, but because of all the regulatory issues in the United States, it is taken to China or South America and is being implanted there, where the regulatory environment is much more lenient. Can we rationalize this practice? How is it possibly ethical?

Dr. Fins: I can answer in 5 seconds: we shouldn't do it.

Dr. Rezai: This is a reality we are facing with increasing rules and regulations in the United States. You have to engage the process, and it takes time. If you have colleagues who can follow clinical trials outside the United States, you can have the device tested outside and then bring it back to the United States. Unfortunately, the reality is that the regulatory process can be slow, so more testing will be done abroad, in my opinion.

Dr. Hahn: I disagree with Dr. Fins. This may be the only way to get the trials started, and we then are able to use some of the offshore data to approach the FDA for approval. I do not think that it is taking advantage of anybody; it is a way of getting things through the system.

Dr. Herndon: The door has been opened, and it is only going to increase. My only request would be that the investigators who do this function as they would here in the United States, under IRB controls and the other kinds of oversight that they would expect and demand of themselves in their own institutions.

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PAULINE W. CHEN, MD
Transplant Surgeon and Author

Pushing the envelope in transplantation: Three lives at stake

Anyone involved in transplantation has witnessed the Lazarean awakening of many of our patients. On the verge of dying, these patients receive a transplant then go home to their loved ones, to their communities, and to the rest of their life.

Transplantation has always straddled the border between life and death; it has always pushed the biological envelope.

But it has also always pushed the ethical envelope.

How? In forcing all of us, not just transplant surgeons, to reconsider some of our most fundamental ethical dilemmas:

- What is death?
- Can we extend life?
- Whose life do we extend?
- At what price the extension of life?
- Just because we can extend life, *should* we?

There are always *three* patients to consider—the patient, the donor, and the person on the waiting list who likely died because the organ went to your patient.

And every one of these dilemmas is further complicated by another issue unique to transplantation. At stake in every transplant is not just the patient's life, but *three* lives—the patient, the donor, *and* the person on the waiting list who likely died because the organ went to *your* patient, not her or him.

While we are not focusing today on organ donation or allocation, let us not forget that transplantation is unique in this regard. There are always *three* patients to consider.

What we will focus on today are transplant and post-transplant innovations. To help introduce the discussion, I would like to share a narrative that I believe illuminates ethical dilemmas that go hand-in-hand with transplantation's innovations.

THE STORY OF MAX

Max was the tiny embodiment of a biological keystone cop. In utero he had developed a gaping defect of his abdominal wall. His intestines twisted around themselves, and the obstetricians had to deliver Max emergently. The pediatric surgeons immediately removed the gangrenous remnants of nearly his entire bowel.

At 10 months, Max received a liver and small bowel transplant. The transplanted organs worked initially; with a small feeding tube inserted directly into his gut, Max digested for the first time in his life tablespoons of food, albeit a chalky liquid supplement.

But Max, within 2 months of his transplant, had again become a permanent resident in the pediatric intensive care unit. Achieving the right balance of immunosuppression so Max could keep the transplanted organs and yet maintain sufficient immunity to fight off infection had become an impossible task.

I was in my fellowship at the time of Max's transplant; and Eric, an attending surgeon with a square jaw and dark Dick Tracy looks, led the surgical team's management of Max's case.

As Max became sicker, Eric spent more hours with his tiny patient. I found him by Max's bedside at 3:00 in the morning and then at 7:00 the next night, his hair, clothes, and personal aura in a state that reflected obliviousness to his own care. Just by being with Max so much, Eric knew all the particularities of that baby, all his idiosyncratic reactions, every significant lab result of Max's entire life.

At first I found Eric's dedication inspiring, almost thrilling in a martyred saint kind of way. And Max seemed to call out to any of us who hoped to be divinely touched. During rounds, Max giggled at me, as if he understood that playing with him was infinitely more interesting than arguing over doses of medication with other doctors. Spurred on by Max's cause, I raced to uncover test results before Eric, as if my quicker response would translate into an equal or greater enthusiasm for Max's plight. I nagged the radiology technicians to give me Max's x-rays hot off the presses. I set the alarms on my beeper to see Max in the middle of the night and on mornings long before any member of the surgical team, particularly Eric, arrived.

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Dr. Chen reported that she has no financial interests or relationships that pose a potential conflict of interest with this article.

Despite my enthusiastic attentions, Max became sicker. We gave Max higher doses of steroids, and his big, shiny black eyes turned into a pair of hyphens on the rolling swells of his face. His tiny body became engorged with fluid from repeated infections, and Max's once buttery skin slowly became the ridiculously inadequate biological grounding for monitors and catheters. The nurses took to using the bed around him to clip wires and anchor dressings, and they hung mechanized pumps on tall IV poles which stood like skeletal beasts of burden crowded around Max's bed.

Through all of Max's crises, Eric never let up. But Max was going to die soon if we could not find the source of his infections. Eric finally decided to take Max to the operating room, worried about a hidden infection around his transplanted intestines. "We've got to take him back to the OR," he said to us. Eric looked at us then asked rhetorically, "I mean, is there any other option?" We all understood what Eric was really asking. Were we doing enough? Was it our *fault?*

That trip to the OR would be the first of almost a dozen. Under searing heat lamps we snipped the sutures that held a plastic abdominal patch in place and uncovered the small cavity filled with congealed organs. We picked away at the block-like mass, terrified of inadvertently cutting a hole in his transplanted intestine and creating another source of infection. Then, finding nothing and too scared to cause any more damage, we whipstitched a piece of plastic back to the edge of Max's abdominal wall. Over time, it became harder and harder to find untouched flesh where we could place a new stitch.

Over a month later Max died of a massive fungal infection. I mentioned his death to Jaimie, a pragmatic and brilliant head nurse who possessed more insight into our patients and hospital politics than most of the physicians.

"Maybe it was a good thing, huh?" Jaimie responded flatly. She walked out of the room and I could hear her asking aloud, "I mean, how much can you do to a person?"

THE EARLY TRANSPLANT ERA, DESPITE BLEAKER OUTCOMES, HAS LESSONS TO TEACH

I grew up, surgically speaking, at a time when transplant science fiction had become standard of care, when patients transplanted a decade or more earlier would routinely drop by clinic to say hello, and when patients on the brink of death could expect a full recovery.

But it was not always this way. And it took courageous individuals navigating the difficult relationship between innovation and ethics to get us here.

What is extraordinary about this panel is that these surgeons not only were at the forefront of transplantation's history but also remain deeply involved in its future. Over the next hour roughly, they will give us an extraordinary look into the intersection of innovation and ethics in the past, present, and future of transplant surgery.

I hope you are eager as I am to hear what they have to share with us.

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Transplant innovation and ethical challenges: What have we learned?

A collection of perspectives and panel discussion

We have come far, but selecting organ recipients remains an ethical minefield

By Denton A. Cooley, MD

Only 40 years ago, on December 3, 1967, the world was electrified by news of the first cardiac transplantation, performed in Cape Town, South Africa, by the renowned Dr. Christiaan Barnard.

We have progressed considerably since that time, but not all issues have been settled. After several attempts by Dr. Norman Shumway and by Dr. Adrian Kantrowitz in this country, we in Houston performed the first successful cardiac transplantation in the United States in April 1968. Initially we were impressed with the results, and we embarked upon a very active cardiac transplant program, performing as many as had been done in total around the world. But after we had done some 15 or 20 cardiac transplants, the discouraging news began to emerge that the patients were not surviving long: our longest survived for only 2 years.

As a result, our group in Houston, like others, declared a moratorium on cardiac transplantation. The only group that continued throughout this era was at Stanford University under Shumway, who had some success with immunosuppressive drugs. In the early 1980s, a new immunosuppressant, cyclosporine, appeared that was used for kidney transplantation, which reinvigorated us and others to use this drug for cardiac transplantation. Since then, under the direction of my colleague, Dr. Bud Frazier, we have performed more than 1,000 cardiac transplantations at the Texas Heart Institute.

From the beginning, we were called upon to identify appropriate donors and suitable recipients. Although we rely on certain objective factors, such as age, weight, body size, gender, and blood type, many other issues must also be considered. Fortunately, the modern concept of brain death has now been accepted not only by the public and ethicists, but also by the legal community; in contrast, at one time it was considered homicidal to remove a beating heart. I credit Christiaan Barnard with having the courage to remove a beating heart from a 26-year-old donor who had suffered irreversible brain damage. Many of us had wanted to get into the transplant program, but we could not identify a donor.

The following case illustrates some of the other ethical complexities that we continue to struggle with today.

CASE STUDY: A 17-YEAR-OLD WITH HEART FAILURE AND A DESTRUCTIVE LIFESTYLE

Several years ago, a 17-year-old Latin American boy came to our clinic in heart failure. He was very disarming, but when we looked into his background we found that he had dropped out of high school after 1

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year and was living with a girlfriend who was 2 months pregnant by him and already had a 2-year-old child. The patient's cardiomyopathy was related to cocaine and alcohol abuse. Nevertheless, his stepfather was eligible for Texas Medicaid, and he was accepted for cardiac transplantation.

After the transplantation, he abided by the immunosuppressive drug regimen while he was under our care. Then he moved to Fort Wayne, Indiana, where Indiana Medicaid would not honor his Texas Medicaid coverage. So our hospital had to send him his immunosuppressive drugs, which he used rather sporadically.

While in Indiana, he was incarcerated for assault and battery on his girlfriend. He began to have heart failure but did not qualify to have the biopsies required for proper study of rejection of his heart. He returned to our clinic and was scheduled for catheterization the next day when he went into acute cardiac failure. He had emergency late-night implantation of a percutaneous ventricular assist device, which required catheterizing the left atrium by perforating the interatrial septum, taking the oxygenated blood out of the left atrium, and pumping it back into the aorta with a centrifugal pump. His heart began to recover, and the device was removed after 72 hours.

At this point he needed another transplantation. Our medical review board considered his eligibility and turned him down, citing that others on our waiting list were more deserving of a transplant and that retransplantation has a poorer success rate than initial transplantation.

EACH CASE POSES PROBLEMS, BUT A RECORD OF SUCCESS EMERGES

Although this patient could be viewed as a sort of sociopath, he nevertheless is a young man who is incapacitated and in need of heroic measures. His case illustrates the kind of nonmedical problems that face those of us who are actively involved in cardiac transplantation. It can be very difficult to find solutions to the myriad social, economic, legal, and ethical issues.

We perform about 50 transplants a year in our institution, and every one of them has some issue. Nevertheless, we just honored 25 patients who have survived more than 20 years with cardiac transplantation.

Despite the odds, the transplant field has progressed rapidly

By John J. Fung, MD, PhD

Dr. Pauline Chen's clinical vignette [see previous article in this supplement] unfortunately still typifies small bowel transplantation. One would not expect to hear that kind of story today for a kidney or liver transplant, but in the early 1970s it was typical.

'WHY WOULD ANY YOUNG PHYSICIAN WANT TO GET INVOLVED IN THIS?'

Dr. Cooley's comments about the moratorium on cardiac transplantation brought back memories for me, particularly from when I was studying liver transplantation in the 1970s. There was almost uniform mortality in transplants performed in the late 1960s and early '70s. One wonders why any young physician would have wanted to get involved in transplantation at that time. I was a fellow training with Dr. Thomas Starzl at the University of Pittsburgh and remember him saying, "Just make it work, then let everybody else figure out why." I think that typifies the surgical mentality.

If we had proceeded in a very stepwise manner, we probably would not be even a tenth as far along in the transplant field as we are now.

—Dr. John Fung

We perform transplantations because we know that the alternative is prolonged morbidity and death. Knowing that we can provide a touch of hope is why we move forward in this field.

The technology of transplantation has developed through aggressive scientific developments in the laboratory. It is fascinating that all this has developed in only 50 years. If we had proceeded in a very stepwise manner, we probably would not be even a tenth as far along in the field as we are now.

Heart, lung, liver, and kidney transplantation are now all pretty routine. Intestinal transplantation is in the developing phase. The Cleveland Clinic is currently involved in facial transplantation, which has some different ethical issues related to identity.

Everything in transplantation relates to ethics, from issues about using marginal donor grafts or using beating-heart donors when someone has not been declared brain dead, to issues in patient selec-

tion, which often depends on social, economic (ie, insurance coverage), and psychosocial factors such as substance abuse and nonadherence issues.

ETHICAL INSIGHTS FROM TRANSPLANTS IN HIV-POSITIVE PATIENTS

An ethical area of particular interest to me that the Cleveland Clinic has also been involved with is transplanting patients who are HIV-positive. This has always been an enigma: why would we want to transplant an HIV-positive patient? Before the advent of antiviral therapies for HIV in the mid-1990s, mortality rates were very high, with patients suffering miserable deaths from Kaposi sarcoma, the JC virus leukoencephalopathies, and other debilitating opportunistic infections.

When I first arrived at the University of Pittsburgh as a fellow, Dr. Starzl was telling us about this mystery virus disease; when they retrospectively analyzed specimens from organ recipients and donors, they realized that HIV was being transmitted to patients from donors as well as from blood transfusions. The exposure to health care providers was also substantial: an average of 20 to 30 units of blood was used for a liver transplant.

Patients who were HIV-positive were excluded from transplants even through the mid-1990s. I remember evaluating standard listing criteria for transplant recipients at a conference and hearing transplant surgeons say that HIV is an absolute contraindication to transplant. I said, "Wait a minute, this is 1997; you cannot say that. Given that attitude, patients with HIV will never be transplanted." The *New England Journal of Medicine* had just published a major paper about the extent of survival in patients being treated with highly active antiretroviral therapy.

So we then started a prospective study of transplantation in HIV-positive patients, and long-term follow-up has shown that these patients can do very well. Interestingly, transplantation offers a new approach to treating HIV-positive patients, in terms of immune reconstitution and the ability of immunosuppressive agents to restore immune competency by preventing the T-cell apoptosis initiated by HIV infection.

A continued need for evidence-based guidance

By James B. Young, MD

Speaking as the lone internist on this panel, and also as a clinical trialist and evidence-based clinical practitioner, the greatest ethical challenge I see for transplantation is how to move the field forward in terms of garnering evidence that can help us treat patients and keep them alive. Nobody will deny that heart transplantation is life-saving therapy: my patients with end-stage ischemic cardiomyopathy can be dramatically transformed by a heart transplant after being near death. The questions now are how best to gain the data to guide the next round of innovations in transplant medicine and how to know when the time is right to attempt those innovations.

Heart transplant is a bit of a boutique science, so questions arise about how to evaluate it with the rigor of regulatory authority.
—Dr. James Young

A HISTORICAL GLANCE AT HEART TRANSPLANTATION

Dr. Sharon Hunt, who was one of the first heart transplant cardiologists and worked with Dr. Norman Shumway, almost singlehandedly moved the field of cardiac transplantation forward. She recently chronicled its history,[1] and this sort of historical review yields a couple of insights. First, fewer heart transplants are being done in the United States in this decade than in the 1990s,[2] in large part because other effective interventions for heart failure have been developed. However, the number of heart transplants is in fact on the rise again.[2] Second, survival rates in heart transplant have improved substantially in recent years compared with earlier eras, as documented by registry data from the International Society for Heart and Lung Transplantation.[3]

Among other things, we have learned how to improve the operation, better choose and preserve hearts, and better match hearts to recipients. We now can use hearts from older donors and allow older patients to undergo transplantation. One of the keys to the better survival rates is a dramatic change in the use of medications. Cyclosporine allowed for successful heart transplantation in the 1980s, and we have since seen the advent of agents such as tacrolimus, rapamycin, and mycophenolate mofetil. We rely less on the early immunosuppres-

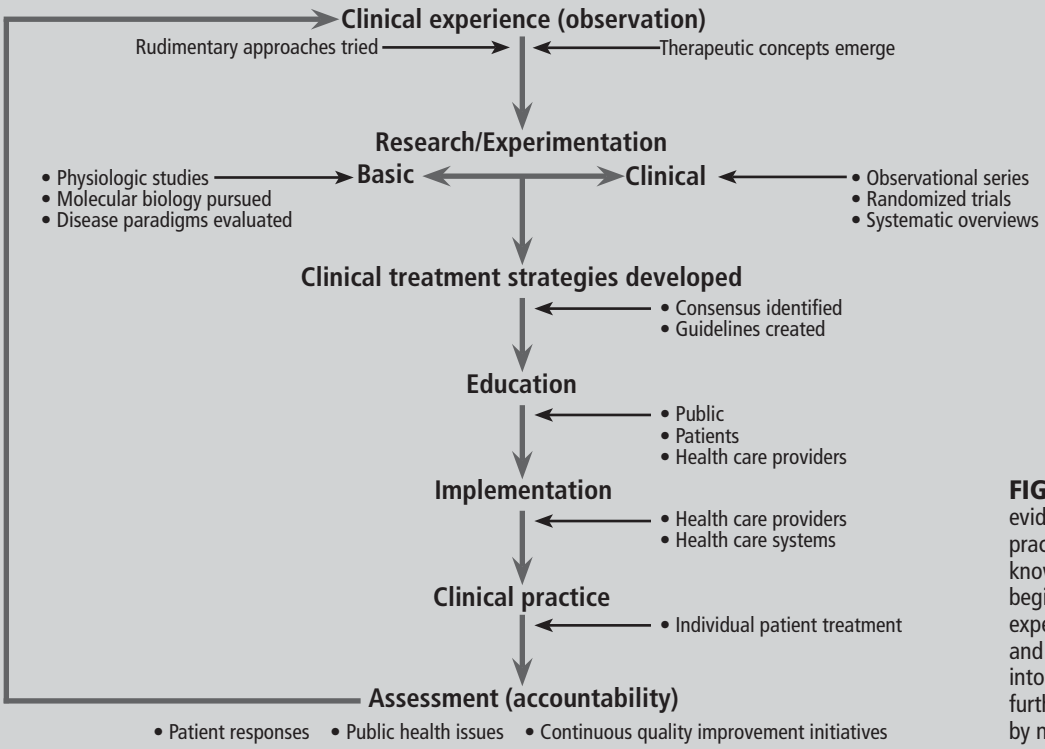

FIGURE 1. Flow chart of evidence-based medical practice. The drive for new knowledge is circuitous, beginning with clinical experience and observation and ultimately feeding back into clinical practice and further research prompted by new experience.

sants, such as prednisone and azathioprine.

Despite these successes from a survival standpoint, problems still need to be addressed. For instance, at 5 years, virtually every patient following a heart transplant develops hypertension and dyslipidemia, 1 in 3 has renal dysfunction (some requiring dialysis or transplant), 1 in 3 has diabetes, and some develop a strange allograft arteriopathy.[3]

THE CHALLENGE OF EVALUATING A BOUTIQUE SCIENCE

Heart transplantation is a bit of a boutique science. Although relatively few heart transplants are performed compared with liver or kidney transplants, heart transplantation is a dramatic operation limited by many ethical challenges surrounding organ donor supply and utilization.

As for any boutique science, questions arise about how to evaluate it with the rigor of regulatory authority—from both the Food and Drug Administration (FDA) perspective and the institutional review board (IRB) perspective—without large clinical trials. Suppose that Dr. Cooley wants to make a minor modification in his immunosuppressive protocol because of an observation of a high incidence of renal failure at the 5-year point; does that ethically demand a large randomized clinical trial?

How can we design clinical trials to help determine which direction to take in immunosuppression intensification or utilization protocols? Other challenges include evaluating outcomes (such as coronary artery vasculopathy) from databases, and then figuring out good and bad practices. For example, databases show us that a donor history of diabetes increases the recipient's long-term risk of developing coronary artery vasculopathy.[3] Receiving a heart from a male donor also increases risk.[3] Better understanding the panoply of adverse events and what leads to better outcomes will give us a sense of how to proceed and can drive the design of clinical trials.

OTHER ETHICAL CHALLENGES

From an ethical standpoint, how do we change practice? We have data on outcomes at 5, 10, and even 20 years. The half-life of a heart transplanted today is 12.5 years, whereas it used to be about 7 years.[3] Although it is clear that we have made progress, it is a challenge to determine exactly how to make subtle changes in practice, such as addressing polypharmacy post-transplant.

Developing schemes that enable major innova-

tion, particularly through coordination among medical and surgical teams, is another challenge. For example, we are working with preservation techniques that use a beating heart for transplantation. From solid evidence based on animal models, we believe this preparation can allow preservation of a heart for up to 12 hours. To some, that may beg a number of questions: Why do we need to do a clinical trial in humans? Why does the FDA need to regulate us? Why do we even need to answer to an IRB? Why not just make the change to alleviate the problem of donor organ supply?

My perspective is that I believe in evidence-based medicine and in clinical trials. I believe we should try to ethically move the field forward by taking a clinical experience or an observation and moving it through all the necessary elements of evaluation and treatment strategy development **(Figure 1)** to drive knowledge. I believe this applies to post-heart transplant patients as much as it does to patients with conditions such as heart failure or ischemic heart disease.

What does—and does not—spur innovation?

By Thomas E. Starzl, MD, PhD

LESSONS FROM THE CODMAN ANALYSIS OF FAILURES

Dr. Ernest Codman was a Harvard Medical School professor in the early 20th century who tried to introduce a system of analyzing failures at Massachusetts General Hospital and other Harvard-affiliated hospitals. As a result, he was metaphorically ridden out of town on a rail.

Codman recommended that complications and failures be classified as one of the following:

- An error in diagnosis
- An error in judgment
- An error in technique (if a surgical or a medical problem)
- An error in management.

Only one escape hatch existed that did not indict the surgical or medical team as culpable: the disease. At the time, nothing could be done for many diseases, including cancer, heart disease, renal failure, and bowel insufficiency.

This is a type of analysis that can be brought to a mortality and morbidity conference and will not accept a lot of alibis; it forces the group to always look at what could have been done to prevent a complication or death. Some practitioners always want to blame some factor other than themselves: sometimes the patient, by being deemed noncompliant, is even held responsible for his or her own complication or death.

I think the Codman analysis of failures is a good starting point for discussing innovations, especially since true breakthroughs come in those cases where the failure falls into the category of being caused by the disease itself, not by a medical or surgical error. And that is surely where transplantation falls.

PROGRESS DOES NOT ALWAYS REQUIRE FULL UNDERSTANDING

Transplantation was first successfully performed in the context of breaking through the donor-recipient genetic barrier on January 6, 1959, when Joseph Murray and his team at the the Brigham Hospital performed a kidney transplant using the patient's fraternal twin as a donor. This event was reproduced in Paris by Jean Hamburger and his team on June 14, 1959, and then on three or four other occasions in the next several years in patients who received sublethal total body irradiation. This was at a time when no pharmacological immunosuppression was available, so no follow-up treatment was offered.

Astoundingly, the first case—the fraternal twin—lived for more than 20 years, and the French case for 25 years, without ever being treated with immunosuppression. They were inexplicably tolerant. When immunosuppressive drugs were developed and survival rates improved, the questions around these early cases were never answered: Why did those transplantations work? What were the mechanisms of engraftment? What was the relationship of engraftment to tolerance? Without answering those questions, there was no way to make other big leaps in improvement of what was already proved in principle—that is, the feasibility of actually doing this kind of treatment. Improvements in patient and graft survival were dependent almost entirely on better drugs.

RANDOMIZED TRIALS HAVE A DUBIOUS RECORD IN TRANSPLANTATION

I know this will offend just about everyone here, but I have no confidence in evidence-based therapy if we are talking about randomized trials. None of the

great advances in transplantation has had anything to do with randomized trials. In my opinion, randomized trials in transplantation have done nothing but confuse the issue and have very nearly made it impossible for the better immunosuppressants to be brought on board. Cyclosporine offered a tremendous step forward, but the randomized trials, carried out mostly in Europe, did not reveal much difference in outcome from treatment with azathioprine, at least as assessed by patient and graft survival. The same thing occurred when tacrolimus emerged; randomized multicenter trials actually delayed the widespread use of this superior drug for at least half a dozen years.

IN THE BIG PICTURE, MONEY IS HOBBLING INNOVATION

Earlier it was debated whether money drives everything. I do not believe that money drives everything in medicine in Europe, and it certainly has little to do with driving improvements in Asia. But money does drive everything in the United States, although the real question is whether it has to be that way.

Randomized trials in transplantation have done nothing but confuse the issue and have very nearly made it impossible for the better immunosuppressants to be brought on board.
—Dr. Thomas Starzl

I believe that innovation is somehow built within our genome. Many of the great advances in transplantation, the elucidation of principles, and the relatively recent discovery of the mechanisms of alloengraftment were achieved without grant support. The researchers involved could not have asked for National Institutes of Health funding because their ideas were so far out of the box that they probably would have been rejected or stolen.

I wonder to what extent the vast amount of money available for research is actually a disincentive for genuine advancements. Part of the problem is that the power of allocation is put in the hands of anonymous peer-review committees. That system generates droves of people to pursue money allocated to a certain area to learn more and more about less and less, in the vague hope that acquiring enough details will result in a realistic concept. Sometimes the picture simply becomes more confused.

Another problem is that we have produced far more scientists than jobs, so that funding becomes the first priority because it is the only means of employment. In earlier days, what drove people more often was that they were confronted with a child who was dying and the central question was, "How can I treat this patient?" They did laboratory research on their own to produce evidence that a new innovative idea could work. I believe that if you have experiments that show that you can keep a heart beating on a preservation device for 12 hours, and you can put it in a dog and it works well, that is the evidence you need to proceed. How are you going to do a randomized trial—hang on to an organ and let it beat for 12 hours just so it conforms with some protocol? That is nonsense.

There was a period when clinical journals—*Surgery of Gynecology and Obstetrics*, *Annals of Surgery*, *Annals of Internal Medicine*, *New England Journal of Medicine*, and others—published front-running discoveries. That ended about 25 years ago when it became more important to learn about details. The journals then became superfluous, and for another reason as well: money drove the wheel more and more. Hospital and program administrators expected the publications to be advertisements, and the minute that articles started promoting something rather than reporting facts, they lost value. Today the impact factors of the surgical journals are at about 2 or 3, meaning that their articles are cited infrequently and have little real influence on the practice of medicine.

How did we reach this point where money drives everything? I think the page was turned in the very early 1990s, and it had to do with how medical practice is governed, especially in academic hospitals. Half of the health care in this country is now provided by hospitals that are associated with medical schools. Those hospitals and basic research laboratories are where our young people will assimilate their ideals. If that climate is not right, then we are raising the wrong kind of doctors.

Earlier researchers looked at a problem and thought, "Here's a question that has to do with this patient before my eyes, and I must find some way to solve it. Let's go to the laboratory." Today there is a real danger that they are thinking, "I need to advance my career, so let's see how I can get some money. A little research will be a stepping stone to my professional development." Our discussion of medical and surgical ethics today should take place within this framework.

Panel discussion

Moderated by Mark Siegler, MD

WERE FINANCES A DRIVER OF EARLY TRANSPLANT INNOVATION?

Dr. Mark Siegler: It is clear that there are more ethical and less ethical ways to introduce innovations. I am reminded of an article in *JAMA* by Francis Moore in the late 1980s in which he warned that one of the things to look at for any new innovation was the ethical climate of the institution.[4] He cautioned us to be very aware of the driving force behind an innovation. Is it to improve patient care? To save lives that otherwise would be lost? Or is it primarily for the self-aggrandizement of an investigator or the financial goals of an institution?

I also remember the chapter in Dr. Starzl's book *The Puzzle People*[5] about the anguish involved in introducing liver transplantation. It seems that financial considerations were not the driver of major steps forward in introducing liver transplantation, in Dr. Starzl's case, or heart transplantation, in Dr. Cooley's case. Would you comment?

Those of us privileged to spend our entire career in academic settings, with institutions to represent and protect us, have an obligation to become innovators.
—Dr. Denton Cooley

Dr. Thomas Starzl: Actually, not only were we not driven by economic gain, we expected financial penalty for focusing on transplantation. If ever there was a field that developed against the grain, that was costly to people who worked in it, whose engagement meant that for most of their career they would work for substandard income compared with their peers—even those peers in academic medicine, let alone those in private practice—it would be transplantation.

It was not until 1973, when the end-stage renal disease (ESRD) program began under Medicare, that cash for transplantation started to become available. The real cash streams did not start until the middle to late 1980s when nonrenal organs became the cash cows. To be fair, no new technology can be assimilated into the health care system unless it at least pays for itself. But you can go beyond that and create baronial kingdoms, and I think that is where you can go wrong.

Dr. Denton Cooley: I would add that those of us privileged to spend our entire career in academic settings have an opportunity that others may not have. A lot of brilliant people in private practice are capable of doing many things but do not have an institution to represent and protect them. I have also always felt that those of us in these positions have an obligation to become innovators. Surgeons who merely see how many appendectomies or cholecystectomies they can perform are being very derelict of their responsibility to the institution.

MEASURING SUCCESS IN HEART TRANSPLANTATION

Dr. Siegler: Dr. Cooley, what is the current success rate for heart transplants?

Dr. Cooley: Nationwide, around 90% of recipients survive 12 months. Of those, maybe half are still alive 5 years later. Of course, we do not know what the future will hold. It is interesting that the first sign of rejection seems to be coronary occlusive disease. It is a different type of coronary occlusive disease than is seen in atherosclerosis: it is diffuse, involving the entire extent of the coronary circulation, and is not really amenable to coronary bypass or other interventional procedures.

Dr. Siegler: We are now at about the 40th anniversary of the first human heart transplants, an extraordinary and historic innovation. Dr. Cooley, do you think the timing was right in 1968 when you did the first heart transplant in the United States? In retrospect, would you have done the first transplant sooner or maybe even a couple of years later?

Dr. Cooley: You can argue it both ways. Should we have waited for further developments? At the time, heart transplantation seemed to work fairly well in animals, but we never really know until it reaches the clinical level. It was probably as opportune a time as any. We knew something about organ rejection at the time, and we had immunosuppressive drugs, although they were not as effective as they are today. The news electrified the world. I think we were pretty well prepared for this spectacular event.

Dr. Siegler: When would have been the optimal time to do a clinical trial in order to achieve evidence-based medicine in heart transplantation? Would it have been during the big breakthroughs of Shumway, Barnard, and Cooley, or now, when we have the general strategy and can find out how we can do better?

Dr. James Young: I would not have done a randomized trial at that time. The patients who were getting transplanted then were nearly dead; all other management was futile. In 1970, *Life* magazine listed the 102 heart transplants that had been done around the world up to that point, and maybe only 2 or 3 of the patients were still alive. That prompted the moratorium that Dr. Cooley referred to.

As ethical clinicians, we are supposed to do our best to make our patients feel better and make them live longer. Sometimes you have to do something radical. On that basis, one can argue that we should not transplant "the walking wounded," that instead we should save organs for patients who are truly terminal without some sort of ventricular replacement therapy. But today we are getting away from transplanting only dying patients, so we need randomized trials to find out how we are doing in transplanting outpatients. That is the setting in which trials are now needed.

THE ETHICS OF 'LETTING GO'

Question from audience: Dr. Chen's story [see previous article] raised the issue of the ethics of "letting go" of one's patient. I wonder if in transplantation, especially when innovative procedures are involved, a commitment to the procedure itself might sometimes conflict with the need to let go of the patient.

Dr. John Fung: In the United States, we measure efficacy and benefits in different ways than people do in other parts of the world. Here, for a child with a biliary atresia—the most common reason for liver transplantation—we expend hundreds of thousands of dollars for a liver transplant, which is usually able to save the child's life. But in China, a severely ill child is viewed as a medical and economic liability and will be allowed to die so the family can have another child.

It is also not only the ethics of letting go. We all deal with letting go, not just in transplant medicine. It is also the ethics of actually getting a patient into the system. In the case of transplanting a newborn, as in Dr. Chen's narrative, should they even have embarked on that?

Dr. Pauline Chen: For me, the story illustrates the remarkable connection and profound attachment between a surgeon and his or her patient. The fact that three patients are really involved in transplantation—the donor, the recipient, and the patient still on the waiting list because the organ went to the recipient instead—also motivates the team with a sense of obligation to the two unseen patients.

If there is a lesson about the ethics of letting go, I think it is that we often fail to talk about these issues among ourselves. Perhaps if we had discussed end-of-life care or palliative care in Max's case, we might have had more insight into the pressures we felt in considering the lives of three separate people. And those discussions might have—or might not have—changed the situation.

Dr. Starzl: I agree completely with the preceding comments. All kinds of motivations might cause a surgeon to cling too long—the ones that were mentioned as well as some ignoble ones, such as vanity, in terms of looking at one's survival numbers.

For my vintage of transplant surgeons, death and failure are rarities and are truly a sort of enemy, whereas prior generations of surgeons are wiser and perhaps have a better sense of when it is time to stop intervening.

—Dr. Pauline Chen

I would also like to take a much larger view. Some years ago in Colorado, the governor at the time, Richard Lamm, thought that intensive care units (ICUs) were harmful—that they were economically draining, did not serve society, and prolonged suffering. My position, which was really the opposite, was that maybe he was right in his philosophy but transplantation had, in a sense, changed all that. Transplantation took desperate people who were in the ICU, with no chance of coming out, and dramatically returned them to wonderful health.

As procedures get better, this scenario happens more and more often. I agree that there is a time when you realize that no intervention will work and you should stop treatment. That is a bitter pill. But it is very hard to define when that moment occurs.

Dr. Chen: There also may be somewhat of a generational difference in approach.

Most surgeons will fully acknowledge that they stand on the shoulders of giants, and that holds particularly true in a field like transplantation. When I was training in liver transplantation, for example, 80% to 90% of the patients could fully expect to survive 5 years. For my vintage of surgeons, then, death and failure were rarities and they were truly a sort of enemy, whereas surgeons like Dr. Starzl and Dr. Cooley have seen so much more and are far more used to all the variations of outcomes. Because of that breadth of experience that you have, I think you are wiser than

my generation of surgeons, for whom death often has to be ablated at all costs. I think it follows, then, that you would also have a better sense of when to stop.

Dr. Starzl: There is a generational change—there is no doubt about it.

IS TRANSPLANT ETHICAL WHEN A LIFE IS NOT AT STAKE?

Question from audience: What are the ethical implications of non-lifesaving transplants, specifically of the hand and face?

Dr. Young: I have been on many peer-review committees charged with looking at this issue. Although the ethics can be very troubling, I have resolved important questions in my mind by examining them through the context of human suffering. Our mission as physicians and caregivers is to relieve suffering, which can take the form of pain, a shortened lifespan, or even a debilitating disfigurement of the face or a severe limitation, such as after traumatic amputation. Looking at the issue this way, I am less troubled than I was initially, when I viewed these kinds of transplantations as simply altering physical appearance or extending ability.

Dr. Starzl: The next big movement in transplantation is going to be in composite tissue allotransplantation—that is, transplantation of the face, limbs, etc. Mechanisms of alloengraftment have recently been uncovered such that it is now possible to formulate protocols that use either very light immunosuppression (avoiding the 20% or 25% rate of renal failure at 5 years that we heard about from Dr. Young) or no immunosuppression at all.[6] Without the heavy burden of immunosuppression, this type of transplantation can become worthwhile. Putting a new hand or face on someone is astounding: it changes the morphology of the brain, which can be observed with functional magnetic resonance imaging. It changes the soul, if that is what you want to think of when talking about the brain. I think it will be very important.

Thomas Jefferson wrote, 'We should never return to earlier times when all scientific progress was proscribed as innovation.' His insight is still modern and relevant today.

—Dr. Mark Siegler

Dr. Siegler: This extraordinary panel has not only discussed events from 50 years ago; each of the panelists spoke of a future that is rich in promise and innovation—and in ethical issues. It reminds me of a remarkable letter written in 1794 by Thomas Jefferson to John Adams, which says, "We should never return to earlier times when all scientific progress was proscribed as innovation." More than 200 years later, Jefferson's insight remains modern and relevant.

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Medical professionalism in a commercialized health care market*

Medical professionalism in the United States is facing a crisis, just as serious as the crisis facing the health care system, and the two crises are interrelated.

To understand today's crisis in medical professionalism requires knowing what a profession is and what role it plays in modern society. Freidson[1] considered a profession to be one of three options modern society has for controlling and organizing work. The other two options are the free market and management by organizations such as government or private businesses. Freidson suggested that medical work was totally unsuited for control by the market or by government or business and, therefore, the practice of medicine could only be conducted properly as a profession.

According to Freidson,[1] a profession is highly specialized and grounded in a body of knowledge and skills that is given special status in the labor force, its members are certified through a formal educational program controlled by the profession, and qualified members are granted exclusive jurisdiction and a sheltered position in the labor market. Perhaps most important, professionals have an ideology that assigns a higher priority to doing useful and needed work than to economic rewards, an ideology that focuses more on the quality and social benefits of work than its profitability.

The fundamental ethos of medical practice contrasts sharply with that of ordinary commerce.

Although this ideology is the most important part of medical professionalism, it is what is now most at risk. The science and technology of medicine and the special place that medical practice holds in the labor market are not presently threatened. The expanding professional health care responsibilities of nurses and the increase in other health workers such as physician assistants and technicians are changing the mix of the health care workforce, but the central role of the physician as the manager and provider of medical services is not likely to be challenged.

Endangered are the ethical foundations of medicine, including the commitment of physicians to put the needs of patients ahead of personal gain, to deal with patients honestly, competently, and compassionately, and to avoid conflicts of interest that could undermine public trust in the altruism of medicine. It is this commitment, what Freidson called the "soul" of the profession,[1] that is eroding, even while its scientific and technical authority grows stronger. Ironically, medical science and technology are flourishing, even as the moral foundations of the medical profession lose their influence on the behavior of physicians.

This undermining of professional values was an inevitable result of the change in the scientific, economic, legal, and social environment in which medicine is now being practiced. A major reason for the decline of medical professional values is the growing commercialization of the US health care system.[2] Health care has become a $2 trillion industry,[2] largely shaped by the entry and growth of innumerable private investor-owned businesses that sell health insurance and deliver medical care with a primary concern for the maximization of their income. To survive in this new medical market, most nonprofit medical institutions act like their for-profit competitors, and the behavior of nonprofits and for-profits has become less and less distinguishable. In no other health care system in the world do investors and business considerations play such an important role. In no other country are the organizations that provide medical care so driven by income and profit-generating considerations. This uniquely US development is an important cause of the health cost crisis that is destabilizing the entire economy, and it has played a major part in eroding the ethical commitments of physicians.

Many physicians have contributed to this transformation by accepting the view that medical practice is also

Many of the ideas expressed herein were presented in a talk on medical professionalism before the President's Council on Bioethics, June 28, 2007, Washington, DC, and in *A Second Opinion: Rescuing America's Health Care*.[2]

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Dr. Relman reported that he has no financial interests or relationships that pose a potential conflict of interest with this article.

in essence a business. Medical practice is now widely viewed as a demanding and technical business that requires extensive, credentialed education and great personal responsibilities—but a business nevertheless. This change in attitude has important consequences. In business, increasing shareholder value through increased revenue and increased profit is the primary goal. However, medical professionalism requires that physicians give even greater primacy to the medical needs of patients and to the public health of the society in which their patients live. When physicians think of themselves as being primarily in business, professional values recede and the practice of medicine changes.

Physicians have always been concerned with earning a comfortable living, and there have always been some who were driven by greed, but the current focus on moneymaking and the seductions of financial rewards have changed the climate of US medical practice at the expense of professional altruism and the moral commitment to patients.[3] The vast amount of money in the US medical care system and the manifold opportunities for physicians to earn high incomes have made it almost impossible for many to function as true fiduciaries for patients.

The essence of medicine is so different from that of ordinary business that they are inherently at odds. Business concepts of good management may be useful in medical practice, but only to a degree. The fundamental ethos of medical practice contrasts sharply with that of ordinary commerce, and market principles do not apply to the relationship between physician and patient.[4] Such insights have not stopped the advance of the "medical-industrial complex,"[5] or prevented the growing domination of market ideology over medical professionalism.

Other forces in the new environment have also been eroding medical professionalism. The growth of technology and specialization is attracting more physicians into specialties and away from primary care.[6] The greater economic rewards of procedural specialties are particularly appealing to new graduates who enter practice burdened with large educational debts. Specialization is not necessarily incompatible with ethical professional practice, but it often reduces the opportunities for personal interactions between physicians and patients and thus weakens the bond between physicians and patients. It is too easy for even the best specialists to behave simply as skilled technicians, focused exclusively on their patients' narrow medical problems and unmindful of their professional obligations to the whole person they are serving.

The law also has played a major role in the decline of medical professionalism. The 1975 Supreme Court ruling that the professions were not protected from antitrust law[7] undermined the traditional restraint that medical professional societies had always placed on the commercial behavior of physicians, such as advertising and investing in the products they prescribe or facilities they recommend. Having lost some initial legal battles and fearing the financial costs of losing more, organized medicine now hesitates to require physicians to behave differently from business people. It asks only that physicians' business activities should be legal, disclosed to patients, and not inconsistent with patients' interests. Until forced by antitrust concerns to change its ethical code in 1980, the American Medical Association had held that "in the practice of medicine a physician should limit the source of his professional income to medical services actually rendered by him, or under his supervision, to his patients" and that "the practice of medicine should not be commercialized, nor treated as a commodity in trade."[8] These sentiments reflecting the spirit of professionalism are now gone.

Until 1980, the AMA held that a physician should limit the source of his professional income to medical services rendered to his patients.

Professionalism is also compromised by the failure of physicians to exercise self-regulation that would be supported by law. Many physicians are reluctant to identify incompetent or unethical colleagues. Such behavior also undermines the public's trust in the profession.

Yet another deprofessionalizing force has been the growing influence of the pharmaceutical industry on the practice of medicine. This industry now uses its enormous financial resources to help shape the postgraduate and continuing medical education of physicians in ways that serve its marketing purposes.[9] Physicians and medical educational institutions aid and abet this influence by accepting, sometimes even soliciting, financial help and other favors from the industry, thus relinquishing what should be their professional responsibility for self-education. A medical profession that is being educated by an industry that sells the drugs physicians prescribe and other tools physicians use is abdicating its ethical commitment to serve as the independent fiduciary for its patients.[10]

The preservation of independent professionalism and its ethical commitment to patients still are very important because physicians are at the center of the

health care system and the public must be able to depend on and trust physicians. There is currently much concern about the paternalism and elitism of medicine, and this concern is often used to justify policies seeking to establish so-called consumer-directed health care.[11] Although there undoubtedly is a need for patients to have more information and responsibility for their health care choices, without trustworthy and accountable professional guidance from physicians, the health care system could not function. In the absence of physicians' commitment to professional values, health care becomes just another industry that may, by continuing along its present course, be heading toward bankruptcy.

Physicians should not accept the industrialization of medical care, but should work instead toward major reforms that will restore the health care system to its proper role as a social service that society provides to all. Virtually every other advanced nation has achieved that goal. An essential part of the needed reforms is a rededication of physicians to the ethical professional principles on which the practice of medicine should rest. Such reforms will require public and political initiatives[12] and the active participation of the medical profession.

Medical professionalism cannot survive in the current commercialized health care market. The continued privatization of health care and the continued prevalence and intrusion of market forces in the practice of medicine will not only bankrupt the health care system, but also will inevitably undermine the ethical foundations of medical practice and dissolve the moral precepts that have historically defined the medical profession. Physicians who care about these values must support major reform of both the insurance and the delivery sides of the health care system.[2] It is the one policy option most likely to preserve the integrity and values of the medical profession.

In academic-industrial cooperation, any financial gains for the academic side should flow to institutions, not individuals, and should be strictly regulated by law.

ADDENDUM

The foregoing commentary, published last year in *JAMA*, explains why I am concerned about the "ethical challenges in surgical innovation," the subject of this conference. Although the legal status of patent applications for surgical methods ("process patents") has not yet been fully defined,[13] such applications fortunately are relatively rare. The great majority of surgical techniques are not patented and are freely available to surgeons—as they should be. However, the devices, equipment, and implants that may be an essential part of new surgical techniques can be and are patented, and may therefore be profitable. If these patented items are developed by a staff physician or are the product of collaboration between such a physician and a company, should financial benefits accrue to the physician involved? Some say yes. They seem convinced that without some sort of financial incentive—royalties, direct payments from the manufacturer, or equity interest in the manufacturer—physicians would simply not be motivated to do innovative work, and the "translational" research essential for medical progress would languish.

I strongly disagree with this view, but unfortunately it has gained considerable influence in academic medicine in recent years, despite the fact that it conflicts with medical professional ethics. Court interpretation of antitrust law in 1975[7] forced the American Medical Association to abandon its long-standing ethical injunction against practicing physicians earning income from financial interests in the medical products they use or prescribe. However, antitrust legislation is not relevant here, and no legal restraints prevent medical schools, teaching hospitals, and similar medical institutions from regulating or even prohibiting such outside earnings by their full-time salaried staff. These earnings constitute a clear conflict of interest, and there is a growing national consensus that such conflicts not only should be publicly disclosed but should be regulated by the institutions employing the physicians. If the institutions do not do this job, many now believe the government should.

What is the evidence that personal financial rewards are necessary incentives for physicians to work on "translational" research? I submit that there is little or none—only an assumption. But the fact is that even before commercialization began to transform health care 3 or 4 decades ago, and even before salaried academic physicians began to earn substantial outside income from their financial ties to device and drug manufacturers, "translational" research was thriving. In the 2 or 3 decades after World War II, salaried academic physicians conducted applied medical and surgical research, often in cooperation with industry but usually without any personal gain. It is true that today there is much more "translational" research going on, but that is probably explained by the greater number of researchers working now and the much greater

public and private investment in research. It does not follow that the recent growth in applied biomedical investigation would not have occurred without personal financial incentives to academic physicians and surgeons. Such an assumption not only ignores medical history but demeans the professional values that we physicians swear to live by.

If we continue to encourage, or even allow, practicing physicians and surgeons to be entrepreneurs and have financial interests in the products they use and prescribe, we will surely undermine the ethical traditions of our profession, as I have argued in the above *JAMA* commentary. But beyond this ethical catastrophe, such policy would surely destroy the credibility and integrity of the whole US medical research enterprise, with dire consequences for society. I believe it is time for our best clinical research institutions to insist that research cooperation with industry be conducted in a much more professional and controlled manner. Academic-industrial cooperation can often facilitate advances in research, but any financial gains for the academic side should flow to institutions, not individuals, and should be strictly regulated by law to ensure that the public interest is protected and the integrity of the medical profession preserved.

I refuse to believe that academic physicians will stop their search for innovative devices and methods for treating their patients if they are not given financial rewards beyond their salaries.

I refuse to believe that academic physicians will stop their search for innovative devices and methods for treating their patients if they are not given extra financial rewards beyond their salaries. Of course, they need to be paid well and they need the time and resources required for their research, but that should be the responsibility of their institutions, not of industry. The present shortage of time and resources for research in not-for-profit medical institutions must be addressed, but turning the responsibility over to the free market of medical entrepreneurialism is not the answer. It will lead only to a dead end for our profession and for the public stake in medical research. This is a challenge that the best and strongest US medical institutions must face up to, but government will also need to help. Our country depends on a vibrant but socially responsible and trustworthy medical research sector. That is an objective that unregulated commercial markets and private interests cannot achieve. We need academic institutions, supported by public policies, to lead the way.

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Inside the operating room—balancing the risks and benefits of new surgical procedures

A collection of perspectives and panel discussion

How should we introduce and evaluate new procedures?

By Joel D. Cooper, MD

Time magazine published an article in 1995 titled "Are Surgeons Too Creative?" that examined the question of whether operations should be regulated the way that medications are.[1] The piece featured two patients. One, a patient with emphysema who underwent lung volume reduction surgery at our institution during the early days of this procedure, had a good outcome. The other was a neurosurgical patient who had a bad outcome.

The public is somewhat sympathetic to this article's premise, which can be viewed as a call to require a similar level of evidence for surgical procedures as for new drugs. This sympathy arises from the expense of new technologies, pressure from payors to control costs and increase profits, hospital budget restraints, and the reality of increasingly well-informed patients.

Yet there are distinct differences between drugs and surgery. A new drug does not change over time. A new drug is associated with a variable biologic response whose assessment often requires large numbers of patients and considerable follow-up. And a new drug may manifest unforeseen late side effects and toxicities far removed from the time of initial use. In contrast, none of these characteristics applies to surgical procedures. A surgical intervention changes over time as the technique and experience evolve and as refinements are made in patient selection and in pre- and postoperative management. With this evolution comes a change in risk over time. Patient selection for surgery is as much an art as a science; each patient requires assessment of both the potential benefits and risks of the procedure, which argues against offering an operation by prescription. Moreover, with surgery, the facilities and the operator's skill and experience levels vary from one center to another.

INTRODUCTION OF NEW PROCEDURES: COVERAGE VS VALIDATION

Introduction of a new surgical procedure depends on the nature of the procedure and the other inter-

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ventions that may be available for the condition. In assessing how new procedures should be introduced, I believe we need to distinguish between coverage and validation. Coverage—ie, payment for the procedure—is an economic issue, whereas validation involves an ethical and scientific evaluation of the role of the procedure.

Coverage by an insurer should have at least theoretical justification and presumption of benefit. For instance, the rationale behind a heart transplant for a patient with a failing heart is obvious. Coverage generally requires preliminary evidence of efficacy, possibly in an animal model, although no animal models may exist for some conditions. Most important, a different standard for providing initial coverage should be applied if no alternative therapy exists for a condition that is severe, debilitating, and potentially life-threatening; if a new procedure treats a condition for which a standard therapy already exists, the standard for coverage must be higher. Finally, coverage in all cases should require ongoing reassessment of the procedure.

In contrast, validation is a scientific analysis of results over time, including long-term results, and can be accomplished by well-controlled case series, particularly if the magnitude of the benefit is both frequent and significant and especially if no alternative therapy exists. Randomized clinical trials are the gold standard for appropriate interventions but are not always applicable.

One of our duties when conducting studies is not just to answer unanswered questions but to question unquestioned answers.
—Dr. Joel Cooper

A 1996 study by Majeed et al[2] provides a good example of validation-oriented surgical research. In this blinded trial, 200 patients scheduled for cholecystectomy were randomized to either laparoscopic or open (small-incision) procedures. The study found no differences between the groups in terms of hospital stay or postprocedure pain or recovery. In an accompanying commentary,[3] *Lancet* editor Richard Horton praised the design and conduct of the study, noting that it was very much the exception in surgical research, which he argued was preoccupied with case series. Horton offered the following speculation about this preoccupation:

> Perhaps many surgeons do not see randomised trials as feasible strategy to resolve questions about surgical management. Cynics might even claim that the personal attributes that go to make a successful surgeon differ from those needed for collaborative multicentre research.[3]

IS THE 'SURGICAL SCIENTIST' AN OXYMORON?

Barnaby Reeves, writing in *The Lancet* 3 years later, offered a more diplomatic take on the difficulty of evaluating surgical procedures:

> What makes a surgical technique new is not always easy to define because surgical procedures generally evolve in small steps, which makes it difficult to decide when a procedure has changed sufficiently to justify formal evaluation.[4]

Reeves went on to argue that doing an evaluation too early may preclude acceptance, since the technique may not have evolved sufficiently and surgeons may not have mastered it; conversely, doing an evaluation too late may make the evaluation moot, since the technique may have already become established and withholding it may be deemed unethical. Additionally, he noted that the quality of surgical evaluation is complicated by the possibility that some surgeons have better mastery of—and therefore better outcomes with—one procedure while other surgeons have better mastery and outcomes with an alternative procedure.[4]

These concerns were well captured by the late Dr. Judah Folkman, whom I once heard say, "When a basic scientist is informed that another investigator cannot reproduce his work, it has a chilling effect; for the surgeon, however, it is a source of pride."

RANDOMIZED TRIALS VS CASE SERIES: A TIME AND PLACE FOR EACH

Even as we recognize these challenges specific to surgical evaluation, we are still left with the task of determining when a randomized controlled trial is appropriate and when a case-control series may suffice.

There are three broad sets of circumstances in which a randomized trial is essential:

- For preventive procedures, ie, when the operation is done to reduce the potential for a future adverse event. An example would be evaluating carotid endarterectomy to reduce the potential for stroke in asymptomatic patients with 60% or greater stenosis. Only a randomized trial could have shown a difference in favor of endarterectomy over aspirin plus best medical therapy.
- To compare a procedure with alternative medical or surgical interventions. I would argue that laparoscopic surgery should have been introduced with randomized trials, as it begs one to suspend judgment

and accept that small incisions are invariably and de facto better than a large incision.

- For trials in oncology, where the outcome depends on long-term results, such as survival or time to recurrence. Examples would include comparisons of surgery alone versus surgery plus chemotherapy for prevention of cancer recurrence.

Similarly, there are several scenarios in which a case-control series is appropriate and adequate:

- When no alternative therapy exists. Falling into this category, in my view, are lung transplant, which we introduced successfully at the University of Toronto in 1983, and lung volume reduction surgery, which we introduced in 1993.
- When the natural history of the condition is well documented and the impact of the intervention is obvious.
- When the magnitude of the procedure's effect is measurable, significant, and expected.

RANDOMIZED TRIALS IN SURGERY

Advantages of randomized trials

Randomized clinical trials confer a number of advantages. They eliminate bias. They ensure a balance between treatment groups in terms of known or unknown prognostic factors. And, importantly, they have a major impact on payors.

The application of new procedures should be restricted, for a time, to a limited number of centers of excellence that have appropriate resources and experience.

—Dr. Joel Cooper

A tale of two Medicare payment decisions

The impact of clinical trials on payors is exemplified by the contrasting stories of two procedures: transmyocardial laser revascularization and lung volume reduction surgery.

Transmyocardial laser revascularization (TMR) involves the creation of channels in the myocardium with a laser to relieve angina. Although TMR is a dubious intervention with no physiologic rationale (similar to internal mammary artery ligation for angina[5]) and no proven improvement in life expectancy (only a reduction in pain), it was approved for reimbursement by Medicare because it was investigated in a randomized trial.[6] However, the "randomized trial" was not truly a randomized investigation because the control patients received only medical therapy and did not go to the operating room to receive a sham operation.[6] Despite this flaw, the perceived authority of the trial was sufficient to influence Medicare.

In contrast, Medicare refused to pay for lung volume reduction surgery until it was subjected to a randomized trial, despite the fact that the procedure had produced tremendous benefit in hundreds of patients at multiple centers who otherwise could not have achieved such benefit. Only after $50 million was spent on a randomized controlled trial, the National Emphysema Treatment Trial (NETT),[7–9] did Medicare agree to pay for lung volume reduction surgery. The trial showed that over 5 years, the procedure was associated with significant improvements in life expectancy, exercise tolerance, and quality of life, but the study took 8 years to conduct and by then it was a bit too late, as detailed in the following section.

NETT: A case study in how a trial can be counterproductive

Lung volume reduction surgery is an operation based on the recognition that the crippling effects of emphysema are hyperinflation of the chest, flattening of the diaphragm, and inability to move air in and out of the chest. The notion that the chest can be reconfigured in the patient with emphysema by removing the distending overinflated emphysema led us to develop the volume reduction operation.

The NETT was initiated by Medicare, and the protocol denied compassionate crossover of patients.[7] In an attempt to establish clinical equipoise, surgeons who participated were not allowed to perform any volume reduction operations on non-Medicare patients or on Medicare patients not enrolled in the trial. After 2 years of slow patient enrollment, the clinical trial committee, in an effort to increase enrollment, eliminated the original entrance criteria specifying certain degrees of hyperinflation and diffusing capacity. An excess of mortality was discovered 2 years later in a subgroup randomized to volume reduction surgery;[8] not surprisingly, further analysis showed that the excess mortality was largely confined to patients who would have been excluded based on the original entrance criteria. This is a matter of public record but was never acknowledged in published reports of the trial. Final 5-year NETT results showed that in patients with upper lobe emphysema, lung volume reduction surgery improved survival, increased exercise capacity, and improved quality of life.[9] By the trial's completion, however, the procedure's reputation had been tarnished irreparably by bad publicity from the deaths attributable to the misguided changes to the original eligibility criteria.

Disadvantages of randomized trials

The NETT exemplifies many of the drawbacks of randomized trials in surgery, particularly the need to wait long periods while they are being conducted. During the 8 years in which the NETT was ongoing, the number of lung volume reduction operations declined, with the typical center performing fewer than 6 cases per year, on average. That limitation is certainly not conducive to the development of a new procedure for a disabling condition in patients with no ready alternative.

Other disadvantages of randomized trials in surgery are their considerable expense and the fact that they often are not generalizable and often are not appropriate. Moreover, when they are flawed, randomized trials propagate, sometimes for decades, misleading information that is nonetheless considered "authoritative." For instance, lung cancer kills more men and women in the United States than the next three cancers combined, yet, on the basis of a flawed randomized trial,[10] the American Cancer Society advises smokers to wait for symptoms before undergoing chest radiography, instead of recommending annual screening chest radiography. This is a major reason why two-thirds of lung cancer cases are discovered too late to save the patient.

'Better to know nothing than to know what ain't so'

Indeed, this potential for randomized clinical trials, when flawed, to propagate misleading information makes the perceived authoritativeness of randomized trials both an advantage and a disadvantage. As Berger and colleagues noted a few years ago, overuse of randomized trials for evaluating emerging operations could have led to the demise of heart transplantation, mechanical circulatory assist devices, cardiac valve procedures, coronary bypass grafting, and repair of congenital lesions.[11]

For this reason, one of our responsibilities when reading the literature and conducting studies is not just to answer unanswered questions but to question unquestioned answers. As 19th-century humorist Josh Billings put it, "It's better to know nothing than to know what ain't so."

A PERSONAL PERSPECTIVE

In my view, health care providers should restrict the application of new procedures to a limited number of centers of excellence that have appropriate resources and experience. Those centers should be required to document and report specified information regarding morbidity, mortality, and objective measures of outcome; if they do not comply, they should lose the privilege of doing such research. The data should be reviewed by an independent, nongovernmental scientific panel. In this way, the procedure can be offered to appropriate patients, insurers and patients can be protected against abuse, and the necessary data can be collected for objective analysis.

Idea to implementation: A personal perspective on the development of laparoscopic nephrectomy

By Ralph V. Clayman, MD

Change in the surgical world involves three aspects, which I refer to as the three Ds: discovery, development, and dissemination. Change requires proof that the new method is superior to the old. When we, as innovators, develop something "new," I believe that our immediate subsequent task is to do everything we can to prove that this "new" finding is of no value whatsoever before we determine that it is worth advancing.

Getting to Malcolm Gladwell's tipping point—the act or event after which nothing is ever the same—requires a team of people, usually from different disciplines, coming together to concentrate on a problem, or an individual whose experiences in different fields provides the ability to "see" the next level. In my opinion, one person working in one discipline rarely leads to breakthrough progress in medicine.

These observations about surgical innovation stem largely from my experience in the development of laparoscopic nephrectomy, in which I was privileged to play a role while at Washington University in St. Louis, which I will outline here.

THE HISTORY BEHIND LAPAROSCOPIC NEPHRECTOMY

After doing preliminary work in dogs, the German surgeon Gustav Simon performed the first human nephrectomy in 1869, in a woman with a ureteral vaginal fistula. The operation was a success: it took him 50 minutes to complete the procedure, and 6 months later the patient went home.

From that point in 1869 until 1990, progress in nephrectomy was minimal, with open surgery remaining the gold standard. While the surgeon's tools remained largely unchanged, the advances that did occur were in anesthesia, analgesia, and antibiotics, which allowed patients to better survive the onslaught of the operation.

In an unrelated arena, laparoscopy was developed in 1901 by another German surgeon, Georg Kelling, who pumped air into the peritoneal cavity of a dog in a successful effort to stop bleeding from the stomach. Within the pneumoperitoneum, Kelling was able to examine the canine organs with a cystoscope at pressures as high as 140 mm Hg. This discovery was not applied clinically, however, until 9 years later when the Swedish gastroenterologist H.C. Jacobeus used Kelling's pneumoperitoneum concept and a cystoscope to visualize the peritoneal cavity to search for cancer. The technique advanced little in the subsequent decades—apart from Semm's seminal laparoscopic removal of the appendix in the 1960s—until 1985, when the first laparoscopic gallbladder removal ignited the era of laparoscopic cholecystectomy.

When innovators develop something "new," our immediate subsequent task is to do everything we can to prove that it is of no value whatsoever before we determine that it is worth advancing.
—Dr. Ralph Clayman

Three technological developments spurred this recent surge in laparoscopy: (1) the ability to affix a camera to the endoscope, (2) the ability to display the camera's images on a video screen, and (3) the development of self-feeding clip appliers to allow occlusion of vascular or ductal structures.

THE EVOLUTION OF LAPAROSCOPIC NEPHRECTOMY

Discovery

I became interested in the possibility of laparoscopic nephrectomy during the laparoscopic cholecystectomy craze in the late 1980s. At that time, I was working with Dr. Nat Soper, performing laparoscopic cholecystectomies in pigs to show that the procedure could be done safely with electrocautery rather than a laser. As it turns out, the anatomy of the porcine kidney is such that the colonic reflection lies medial rather than lateral to the organ. As such, the kidney is quite visible as soon as one enters the abdomen. Indeed, the kidney seemed to be saying to us, "Hey, what about me? I could come out through that hole too." That is basically how the idea arose.

So, along with Dr. Lou Kavoussi and many others in our research team, we attempted laparoscopic nephrectomy in the pig and succeeded: the kidney could be removed through a small hole by entrapping it in a sack, breaking it up in the sack, and pulling it out.[12] The team involved in this discovery were specialists in urology and general surgery as well as biomedical engineers from industry, specifically a team from Cook Urological led by Mr. Fred Roemer.

After performing this technique numerous times in the laboratory, we reduced the operation's duration to 90 minutes, at which point we believed the procedure had advanced sufficiently to be considered for clinical use.

Development

The patient we selected for the initial clinical case was an 85-year-old woman with a 3-cm mass in her kidney. She was deemed to be "too sick to operate on," so she was presented to me as a candidate for the new laparoscopic procedure.

Amazing as it may seem in our current medical climate, at that time (1990) we were faced with the question of whether or not to seek institutional review board (IRB) approval. The argument could be made that since radical nephrectomy had been practiced for 120 years and laparoscopy had been around for nearly 100 years, the combination of these two well-accepted procedures might require nothing more than physician-patient informed consent. However, the concept of "informed consent" in this context was problematic: what could we tell the patient about a procedure that had never been done before except that if it was not working out we would convert to the standard open procedure?

A senior colleague—actually my boss at that time, Dr. Bill Catalona—sagely advised me to get IRB approval, noting, "If the operation works out well, you'll be fine, but if it doesn't work out well, they'll kill you if you don't have approval." So we fortunately ended up seeking (and receiving) IRB approval, as well as providing, as best we could, informed consent to the patient and her best friend.

Our next consideration was designating a team member to determine if and when conversion to open surgery would be necessary. We needed a "referee" to aid in objectively determining a point at which we should convert. For our team, that person was Dr. Teri Monk, our anesthesiologist, who had no previous experience with our laboratory work but understood

what we were attempting.

So we proceeded with the first clinical laparoscopic nephrectomy on June 25, 1990. The kidney was embolized the morning of the procedure. Five laparoscopic ports were placed. The clip appliers proved too small for renal vein occlusion, so the main renal vein had to be traced to its branches; in total we clipped five separate sets of renal vascular branches. The kidney was ensnared and morcellated, which took 7 minutes. Total operative time was 6.8 hours. The complications that arose were not anticipated:

- Intraoperative oliguria due to the prolonged pneumoperitoneum
- Fluid overload (postoperative congestive heart failure) due to providing fluids to the patient as though this were an open procedure
- Dilutional anemia, again due to providing excessive fluids for a closed procedure.

Postoperative pain medications consisted of one dose of morphine sulfate. The patient was discharged on postoperative day 6 and resumed normal activities by postoperative day 10.[13]

Dissemination

Before a new procedure is disseminated, evidence of the four Es—efficiency, effectiveness, equanimity, and economy—must be obtained. In retrospective reviews, laparoscopic removal was associated with a slightly longer operating time but much less blood loss, a shorter hospital stay, and fewer complications. The immediate cancer cure rate was the same for open and laparoscopic nephrectomy, and over time the laparoscopic procedure has been shown to be just as good as open surgery at 5 and now 10 years. Also, with time, laparoscopic nephrectomy was shown to reduce institutional costs.

The next question was the proper way to disseminate this knowledge. At Washington University we took the traditional route of providing courses, offering 17 courses on laparoscopic surgery to nearly 1,000 urologists from 1985 to 2002. But as Winfield and associates later showed, only 54% of urologists who completed a 2.5-day hands-on, laboratory-based laparoscopic course actually ended up introducing laparoscopy into their practice.[14]

The challenge of dissemination is still with us, and we need to find better methods of transferring new skills to our surgical colleagues. In this regard, longer experiences, such as weeklong mini-fellowships and the development of procedure-specific surgical simulators, hold great promise.

UNANSWERED CHALLENGES, UNMET NEEDS

With the advent of any technology comes a cornucopia of unanswered questions and challenges. In the areas of discovery and development, a key question is whether every procedure performed using a new Food and Drug Administration (FDA)-approved technology requires a separate approval by the IRB and ethics committee. For instance, if robotic prostatectomy is approved and performed, are separate approvals needed for robotic nephrectomy, robotic pyeloplasty, and robotic vasectomy? Where would or should the approvals end?

With respect to dissemination, many questions remain: How is a new technology taught effectively? How is surgical competency tested? How is clinical performance or proficiency evaluated?

One problem specific to dissemination is a lack of funding. While ample funding is available for discovery and development, as they bring prestige and profit, dollars are scarce for dissemination, or the teaching and testing of competency and proficiency with new procedures.

As a society, we need to find a way to fund the development of simulators for each surgical subspecialty and use these devices to objectively test surgeons' skills.
—Dr. Ralph Clayman

Evidence of our failure to educate the postgraduate surgeon abounds in terms of poor outcomes and malpractice suits. The response of government all too often is the knee-jerk reaction to protect (ie, regulate), not educate. To be sure, we can do better, but only if our society commits to the process—not with words, but with funded educational action.

With regard to the last, I believe there is an unmet need for the development of accurate, validated surgical simulators. As a society, we need to find a way to fund the development of simulators for each surgical subspecialty and then use these devices to objectively test an individual surgeon's manipulative skill as well as cognitive ability when he or she seeks certification or recertification—and perhaps, albeit in an abbreviated 5-minute format, before beginning each operative day. We owe this to ourselves, but most of all to our patients, who in all confidence place their lives in our hands.

Special perspectives in infants and children

By Thomas M. Krummel, MD

If we surgeons take a step back and consider for a moment what has changed in the operating room (OR) in the past 50 to 60 years, the clear answer is, "Just about everything." The monitors, pumps, transport devices, and OR tables and lights have all changed dramatically, as have the tools, catheters, sutures, energy sources, scopes, staplers, ports, valves, and joints. If we consider technologies outside the OR that guide what we do inside the OR, the changes are just as striking. Circulatory assist devices for the failing heart and widespread use of dialysis for the failing kidney postdate 1950, as does all of our modern imaging capability—ultrasonography, computed tomography, magnetic resonance imaging, positron emission tomography, functional imaging. As for pharmacotherapy in 1950, there were three antibiotics, no antivirals, one antifungal, and three chemotherapeutic agents. Open drop ether was the anesthetic of choice. Not only have the tools and technologies changed, but virtually every procedure has been changed. Both our profession and the industry that has developed these devices and tools can be rightfully proud.

Our patients have been partners in innovation. Many have given informed consent to undergo experimental procedures while expecting that the benefits might accrue only to future patients, not themselves.

—Dr. Thomas Krummel

It is likewise necessary to recognize that our patients have been partners in this innovation. Many of them have given informed consent to participate in research and experimental procedures with the expectation that the benefits might accrue only to future patients and not to themselves. That is a hell of a contribution, and we can be proud of our patients' partnership.

THE GOOD, THE BAD, AND THE UGLY OF INNOVATION

The history of progress in surgical care is always about innovation, and such progress almost always begins with an unsolved patient problem, regardless of the solution that is developed, be it a tool, a device, a technology, or a surgical procedure. At the same time, any discussion of the ethics of surgical innovation should recognize that while efforts to solve patient problems over the years have had many good results, they have also had some bad results and even the occasional ugly result.

This conference has already focused on much of the good that has come from surgical innovation, including transplantation, remarkable advances in cardiac and gastrointestinal surgery, a host of devices, and too many other benefits to list. Yet missteps have been made along the way, such as bloodletting, gastric freezing as a therapy for ulcer, and carotid denervation for treatment of asthma in children.

Then there are the ugly incidents, and these notably include a number of cases involving children, an issue of special interest to me as a pediatric surgeon. Consider the following examples:

- Edward Jenner's notorious cowpox experiment in the late 18th century was conducted in an 8-year-old boy.
- A well-documented literature shows that orphans were used as subjects for tuberculosis and syphilis inoculations.
- The more recent case of Jesse Gelsinger involved a teenager with a nonlethal condition who died in a clinical trial of gene therapy, after which an undisclosed financial interest on the part of one of the treating physicians was revealed.

It should give us pause to note that many of these practices that look foolish in hindsight probably seemed more rational at the time they were undertaken.

CHILDREN: THE ORPHANS OF INNOVATION

Children have been the orphans of innovation, as technology development specifically for children has traditionally been a low priority. There are several reasons for this:

- FDA standards for approving therapies in children are high. For instance, the vast majority of chemotherapeutic drugs are not approved for use in children because conducting a trial specifically in children is deemed too expensive.
- Pediatric markets for therapies are small.
- The payor mix is poor.

The benefits of duality

Nevertheless, children have benefited enormously from the duality of technology development, in which a technology developed for one population—either adult or pediatric—ends up benefiting both populations. For instance, no one would have invented the pulse oximeter to care for a child, yet now it is the

only device with which infants and children are monitored in the operating room and during transport.

Likewise, in some cases the solutions to pediatric problems have had reciprocal benefits in adults. Ligation of the patent ductus arteriosus and the Blalock-Taussig shunt for tetralogy of Fallot opened the door to our understanding of surgery on the great vessels and ultimately enabled the development of cardiac surgery. Similarly, the early impetus for Thomas Starzl's groundbreaking work in transplantation was focused on children with biliary atresia even though this work is now much more widely applied in adults.

ETHICAL PRINCIPLES APPLY EQUALLY TO ADULTS AND CHILDREN

The principles of medical ethics that began with Hammurabi in 1750 BC and progressed through Hippocrates' work circa 400 BC, the 1946 Nuremberg medical trial, the 1964 Declaration of Helsinki,[15] Henry Beecher's classic exposé in 1966,[16] and the 1979 Belmont Report[17] are just as valid for children as they are for adults.

Francis Moore, the great surgeon who created the environment and the team at Brigham and Women's Hospital that facilitated the first twin-twin transplant, identified six important components of ethical surgical innovation:[18,19]

- A solid scientific background (basic laboratory research)
- A skilled and experienced team ("field strength," as Moore called it)
- An ethical climate within the institution
- An open display for ongoing discussion
- Public evaluation
- Public and professional discussion.

The principles behind these components remain as true today as they were 20 years ago when Moore outlined them.

Many ethically ugly practices from the past look foolish in hindsight but probably seemed more rational at the time they were undertaken.
—Dr. Thomas Krummel

SPECIAL CONSIDERATIONS IN PEDIATRIC SURGERY: A CASE STUDY IN MATERNAL-FETAL MEDICINE

The Belmont Report, mentioned above, was developed by the US government in 1979 to form the basis of regulations for federally funded research involving human subjects.[17] The report identified three basic principles that must underlie such research:

- Respect for persons—protecting the autonomy of all subjects, treating them with courtesy, and allowing for informed consent
- Beneficence—maximizing benefits from the research initiative while minimizing risks to the subjects
- Justice—ensuring reasonable, nonexploitative, and well-considered procedures that are administered fairly.

In pediatric surgery, everyone agrees that the "best interests of the child" must be protected, but the issue of autonomy (a key element of the first Belmont principle) is more difficult to define, of course, when the patient is a child rather than an adult. The question of autonomy is especially tricky in the evolving field of maternal-fetal medicine: what if the patient is a fetus and the mother is an innocent bystander?

Over the past 20 years, tremendous progress has been made in our understanding of diseases of the fetus, particularly diseases that limit fetal viability and diseases that cause serious organ damage but which may be more responsive to postnatal therapy if they are treated prenatally. Michael Harrison, N. Scott Adzick, and a few of their disciples have laid the ethical groundwork for consideration of the fetus as a patient.

Considerations in maternal-fetal medicine

I will conclude with a case in maternal-fetal medicine for us to consider and perhaps debate in the panel discussion at the end of this session. As you consider this case, keep in mind several important observations relating to maternal-fetal medicine:

- The mother's health interests cannot be underestimated.
- Most "fixable" fetal lesions (ie, those that interfere with development and cannot be fixed postnatally, but for which intervention in utero may result in normal development) are very rare. They include obstructive uropathy, lung lesions causing hydrops, congenital diaphragmatic hernia, sacrococcygeal teratoma, hydrocephalus, twin-twin transfusion syndrome, congenital high airway obstruction, hydrothorax, myelomeningocele, and congenital heart disease.
- The field is evolving, and the efficacy of therapy is supported by variable level I, II, and III evidence.
- The law has not kept (and perhaps cannot keep) pace with developments in this field.

Case study

A 24-year-old healthy woman has a fetus of 28 weeks' gestational age with progressive lower urinary tract

obstruction with megacystis, bilateral hydronephrosis, and oligohydramnios. In other words, there is diminished volume in the uterine cavity that causes compression of the fetal chest and subsequent respiratory compromise that will be fatal if not addressed. The karyotype is a normal 46,XY male. Serial urine sampling reveals electrolyte and protein profiles with a good prognosis.

Prenatal counseling with fetal therapy specialists suggests that this is the "perfect case" for a vesicoamniotic shunt. This is the least invasive, most successful fetal surgical intervention. It is done under local anesthesia and involves transabdominal transuterine percutaneous placement of a double-lumen pigtail catheter in the fetal bladder. There has never been a reported maternal death, and morbidities have been minimal. Renal and pulmonary function both are improved by approximately 80% in fetuses treated with this intervention, and survival is improved.

The father is eager to proceed. The mother is ambivalent. Should the mother be pressured to proceed, for the good of the child?

Questions to ponder

The following questions are intended to be provocative, with no clear-cut answers:

- Should (or does) the fetus have independent moral status? Is it full, graded, or none? Does it matter?
- What are the beneficence-based obligations to the fetus? At 28 weeks' gestation, the fetus is viable outside the uterus. The fetus is otherwise well, without a lethal karyotype, and has currently good renal function.
- What are the beneficence-based and autonomy-based obligations to the mother? What are the mother's obligations to the fetus?
- What if the mother ultimately decides to proceed and the insurance company denies coverage? What are the social responsibilities to care, cost, and research?

These questions lend themselves to discussion. As much as we surgeons like to be certain about what we do, we would do well to heed the quote from Voltaire that the great surgeon Norman Shumway hung on his office door: "Doubt is not a very agreeable state, but certainty is a ridiculous one."

Bariatric surgery: What role for ethics as established procedures approach new frontiers?

By Philip R. Schauer, MD

Obesity is a staggering problem: 100 million Americans are overweight, 85 million more are obese, and another 15 million are morbidly obese (ie, ≥ 100 lbs above ideal body weight). The incidence of obesity is rising rapidly and threatens to shorten the life spans of today's young generations relative to their parents. Unlike other conditions, such as cardiovascular disease and cancer, obesity has seen no widespread progress in management in recent years.

Recognition of obesity as a medical problem is a challenge in itself. Many people consider obesity to be a character flaw or a behavioral issue and fail to recognize it as a disease entity. Yet obesity is the root cause of many metabolic conditions and diseases with metabolic components, including type 2 diabetes, heart disease, blood pressure, metabolic syndrome, acid reflux, gout, arthritis, and sleep apnea.

The approach to obesity treatment can be conceptualized as a pyramid, with the aggressiveness of the intervention based on the patient's body mass index (BMI). At the base of the pyramid, for patients with lower BMIs, are minimally invasive (and minimally effective) interventions involving changes in diet, physical activity, and other lifestyle factors. As BMI increases, so does the intensity of treatment, to include pharmacotherapy and eventually bariatric surgery. Traditionally, surgery has been considered only at the very top of the pyramid, for morbidly obese patients, and is usually not offered as an option for the vast majority of people with this condition.

The sad reality is that the various combinations of these therapies are effective in fewer than 1% of the approximately 100 million Americans who are obese. Because surgery has been shown to be the most effective therapy for obesity, the remainder of my discussion will focus on surgery, with an eye toward potential new indications for bariatric procedures and the questions they raise.

SURGICAL APPROACHES TO OBESITY

Bariatric surgery has evolved over the past 50 years. Although there are about a dozen different permutations of bariatric procedures performed in the United States today, they fall into one of three major types of operations, as outlined below:

Gastric banding reduces appetite and satiety by adjusting and tightening the gastric band. This procedure has been in existence for 10 to 15 years and represents about 25% of operations for obesity in the United States.

The biliopancreatic diversion procedure diverts most of the small bowel and radically reduces absorption of calories. Patients undergoing this procedure lose weight because few calories are absorbed into the body. This approach, while quite effective, is somewhat radical and represents only about 2% of the operations for obesity in the United States.

The Roux-en-Y gastric bypass procedure has been the dominant procedure over the past 15 to 20 years. A combination of the above two procedures, it involves reducing the gastric reservoir and bypassing the stomach and upper intestine. The reduction in gastric volume reduces calorie intake by enhancing satiety, and the limited foregut bypass moderately reduces absorption.

No randomized trials, but much support from observational studies

Virtually none of these procedures evolved with randomized controlled trials. Instead, they evolved incrementally, primarily on the basis of knowledge gained from case procedures. Despite the lack of randomized trials, these operations have been shown to be effective, particularly in patients with multiple metabolic abnormalities associated with severe obesity. A large body of data from case-control and cohort studies demonstrates not only dramatic improvement in metabolic abnormalities with the use of various bariatric procedures, but also improvements in quality of life and survival.[20–26] The two most recent of these studies, published in 2007, found reductions in mortality of 29% (adjusted) and 40% among surgical patients compared with well-matched obese controls during mean follow-up of more than 7 years.[25,26] Reductions in the incidence of cardiovascular mortality and, secondly, cancer-related mortality were the two major contributors to the overall mortality reduction in these two studies. Consistent with this latter finding, obesity is starting to be thought of as a disease that may lead to cancer.

The current indications for bariatric surgery have existed intact for about 25 years, and were based on limited evidence.
—Dr. Philip Schauer

NEW FRONTIERS FOR BARIATRIC PROCEDURES

The current indications for bariatric surgery have existed intact for about 25 years, and were based on limited evidence available at the time. They are basically as follows, assuming acceptable operative risk and appropriate patient expectations:

- BMI greater than 40 kg/m^2
- BMI greater than 35 kg/m^2 with significant obesity-related comorbidities.

Payors adhere strictly to these indications, such that they will not pay for bariatric surgery in a patient with a BMI less than 35 kg/m^2. This raises questions about the appropriateness of such a firm threshold and whether expansion of these strict indications may be reasonable.

Even without broadened indications, the volume of bariatric procedures in the United States has grown dramatically in recent years. Whereas only 10,000 to 20,000 of these operations were performed annually in the 1990s, approximately 200,000 such procedures were performed in 2007, and this number is expected to double over the next 5 years or so.

This growth in volume has been paralleled by burgeoning media interest in bariatric procedures, particularly in the last few years. More attention can be expected as we increasingly recognize the potential of bariatric procedures for indications beyond strictly the treatment of morbid obesity. At least two new frontiers loom: metabolic surgery and endoscopic surgery.

Metabolic surgery

Procedures that incorporate a bypass—the Roux-en-Y gastric bypass and the biliopancreatic diversion—have been associated with a reversal of metabolic diseases such as type 2 diabetes.[27–32] Many patients with type 2 diabetes who have undergone these procedures have been able to be weaned off insulin and insulin-sensitizing medications while maintaining normal blood glucose levels. The effect has been profound and immediate, occurring even before the patient loses weight. In one series of patients with type 2 diabetes who had undergone a bypass operation, 30% left the hospital in a euglycemic state.[29]

These observations have been made primarily in the morbidly obese population, who are the primary candidates for bariatric bypass procedures. However, because of the rapid improvement in metabolic abnormalities that has been observed, interest has arisen in applying these procedures to populations that are not morbidly obese. Bypassing of the foregut appears to be critical, perhaps because it tempers the release of hormonally active peptides from the gastrointestinal tract.[33] In any case, the gut is regaining recognition as a major metabolic organ.

In light of these hypotheses, the duodenal-jejunal bypass is a bariatric procedure that may be beneficial for a patient with type 2 diabetes who is not mor-

bidly obese. In this operation, the stomach volume is preserved but the foregut is bypassed. In a small experimental series from Brazil, patients with type 2 diabetes who were normal weight or only slightly overweight had resolution of their diabetes following this procedure, without any weight loss.[34]

New applications for endoscopy

Another area of development is endoluminal and transgastric bariatric surgery. Endoluminal surgery is performed entirely within the lumen of the gastrointestinal tract using flexible endoscopy. Transgastric surgery is performed within the peritoneal cavity, which is accessed via a hollow viscus. Both approaches use natural orifices to gain surgical access, thereby avoiding access incisions and scars.[35]

The benefits of such an approach are numerous: (1) fewer complications and side effects; (2) less invasiveness, and thus the ability to perform in the outpatient setting; (3) reduced procedure costs; and (4) better access to treatment. The implication in terms of indications is the potential to use such procedures to *prevent progression* to morbid obesity.

Examples of these procedures are proliferating:

Gastrojejunostomy reduction is an endoscopic procedure that involves reducing the dilated opening of the gastric pouch after gastric bypass surgery. New endoscopic suturing or stapling devices enable the outlet reduction without requiring surgery. The result is enhancement of weight loss without a major operation.

Endoluminal suturing uses endoscopic instruments to suture the stomach to reduce its volume. When this procedure is perfected, the patient should be able to leave the endoscopy suite and return home within a few hours.

The duodenal sleeve is an avant garde concept in which an internal sleeve is threaded into the stomach and down the intestines.[36] The sleeve covers the absorptive surface of the small bowel, preventing absorption of nutrients to cause weight loss. This procedure has been shown to have a strong antidiabetic effect as well.

Clinical applications of these operations are emerging. An endoluminal sutured gastroplasty procedure to shrink stomach volume has been shown in a small clinical trial to cause loss of significant excess body weight; the operation leaves no scars and is associated with a low risk of bleeding or any type of surgical complication.[37] A similar procedure is in development that involves staples instead of sutures.

How best to validate innovations moving forward?

As we move into these new eras of metabolic surgery and endoluminal and transgastric bariatric surgery, interesting questions arise. We as innovators and caregivers are ethically obligated to demonstrate reasonable safety and efficacy before such new procedures are performed widely. Although some of these emerging procedures involve new devices that will go through the FDA review process, many are existing procedures for which indications may be expanded, while others are permutations of existing procedures for which no formal rules for validation exist. For new procedures that differ substantially from existing proven procedures but which do not require new devices, should we not be ethically bound to demonstrate safety and efficacy even though they do not require FDA review? These are the challenges that await as innovation takes bariatric surgery to new frontiers.

Natural orifice transluminal endoscopic surgery: Too much too soon?

By Christopher Thompson, MD, MHES

Although the endoscope has changed very little since the first fiberscope was developed 50 years ago, the accessories and other instruments used in conjunction with the endoscope have changed remarkably. These include clips for hemostasis, ultrasonographic technology, and instruments for tissue dissection.

These advances in endoscopy, combined with advances in laparoscopic surgery, have led to the convergence of these two fields, culminating in the new field of natural orifice transluminal endoscopic surgery (NOTES). In NOTES, the surgeon enters a natural orifice and punctures through a viscus to perform surgery, removes the endoscope, and closes the area without leaving a scar.

HISTORY OF NOTES AT A GLANCE

NOTES was patented as a concept in 1992. Its first application was as an exploratory procedure in the pig in 2004.[38] Soon thereafter, therapeutic NOTES procedures in animals were reported, including tubal ligation, organ resection, cholecystectomy, and splenectomy.

Particularly notable in the development of NOTES is the extremely short interval between early animal experiments (2004) and the first human procedures, which took place as early as 2005 when surgeons in India used the technique to perform a human appendectomy. Since then, more than 300 NOTES procedures have been performed in humans throughout the United States, Europe, Latin America, and Asia, for

applications ranging from percutaneous endoscopic gastrostomy rescue to transvaginal cholecystectomy.

This rapid adoption of NOTES in humans is concerning, as it raises clear questions about whether there has been time for adequate oversight and safety assessment. For instance, at a surgical conference in April 2008, questions and debate swirled around whether a large Brazilian registry of more than 200 NOTES cases did or did not include two deaths. Other ethical issues raised by NOTES are discussed further below.

DRIVING FORCES BEHIND NOTES

The medical rationale

Abdominal wounds can cause pain, are unaesthetic, and are prone to wound infections, ruptures, and hernias. They sometimes cause adhesions or may lead to abdominal wall syndromes with scar neuromas that cause pain later. They also require general anesthesia. Beyond these shortcomings of incision-based procedures, NOTES offers potential reductions in length of stay and therefore in cost. Moreover, certain patient populations may specifically stand to benefit from NOTES, such as obese patients, those with abdominal mesh in place, and those undergoing palliative procedures. This is the essence of the medical rationale for NOTES, which is somewhat thin.

The fear of being left behind cannot be underestimated. Many surgeons fear they will lose their patient base if they do not adopt NOTES into their practices.
—Dr. Christopher Thompson

Professional organizations and courses

In July 2005, leaders from the American Society of Gastrointestinal Endoscopy and the Society of American Gastrointestinal and Endoscopic Surgeons convened a working group to support and plan for the responsible development of NOTES.[39] The group formed the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR), an organization that has since sponsored several conferences on NOTES and procured millions of dollars in grants for NOTES research in animals. (In the interest of full disclosure, I am one of the founding members of NOSCAR.)

Additionally, leading institutions in this field have held numerous hands-on courses on NOTES throughout the United States, Europe, Latin America, and Asia. These courses, including those held by my laboratory at Harvard University, are designed to teach colleagues at other institutions how to set up an appropriate animal laboratory and to promote and encourage proper research in NOTES. There have been unintended consequences, however, as we have learned that some course attendees have returned to their home countries and immediately started using the techniques in humans.

New technology

At the July 2005 working group meeting that launched NOSCAR, we determined that several technological advances were needed before NOTES could be safely applied to humans. These included development of multitasking platforms, better devices for tissue apposition and fixation, better imaging and spatial orientation, and improved means of retraction.[39] Industry responded with novel devices and end effectors such as guide tubes, direct drive systems, endoscopic suturing devices, magnetic retraction, devices for closing luminal defects, flexible staplers, and computerized robotics.

Other driving forces

Additional forces have undoubtedly contributed to the rapid development of NOTES:

- The slowdown in innovation in general surgery in recent years has left a vacuum to be filled.
- An abundance of venture capital has been available to rush into that vacuum.
- Perceived patient demand (owing to cosmetic advantages) has been a driver, especially in cities such as Rio de Janeiro, Milan, and New York.
- The fear of being left behind is a factor that cannot be underestimated. Surgeons who failed to convert to laparoscopic techniques from open techniques in the early 1990s for procedures such as cholecystectomy, fundoplication, and splenectomy were losing their patient bases. Many surgeons fear a similar phenomenon today if they do not adopt NOTES into their practices.

ETHICAL ISSUES RAISED BY NOTES

As NOTES moves toward further evaluation in humans, several ethical questions need to be grappled with:

- Must there be a significant potential for improvement in care before an innovation advances to human research?
- Is the cosmetic benefit of NOTES sufficient, considering the substantially increased risk? For instance, laparoscopic cholecystectomy is well estab-

lished, whereas NOTES cholecystectomy carries an increased risk of bile duct injuries and other injuries. Is NOTES worth the risk?

- What about the corporate agenda behind new technologies and its associated influence on the media?
- Are hospital IRBs adequate to the task of evaluating and monitoring these questions, and will they be independent of the impact of hospitals' larger agendas?

Finally, the problem of premature adoption of this technology is particularly concerning. I heard a surgeon explain at a course that he performed NOTES on a few pigs at a previous course and then returned home to Peru and immediately started performing it on patients at his ambulatory surgery center. There is also the temptation for well-respected surgeons to go to other countries to practice their NOTES skills before returning to the United States, in hopes that their experience will help them attain IRB approval. Practices like these raise questions about what ethical responsibilities lie with those of us who have pioneered the technology and are trying to develop and disseminate it responsibly. We can try to vigilantly watch course attendees from certain countries, but there is little we can do in the absence of regulation and enforcement in those countries. These are difficult ethical challenges.

Panel discussion

Moderated by Jonathan D. Moreno, PhD

Dr. Jonathan Moreno: I would like to begin with any questions that the panelists have for one another.

Dr. Philip Schauer: I would be curious to hear how my colleagues define incremental changes in a procedure. In other words, what constitutes a new procedure versus a modification of an existing one?

In bariatric surgery we are grappling with a procedure called the sleeve gastrectomy, which poses challenges comparable to lung volume reduction surgery as described by Dr. Cooper. Many of us believe that this procedure is just a slight modification of a gastroplasty, yet payors consider it an entirely different procedure, and some want 5 to 10 years of follow-up data before they will pay for the operation.

Dr. Joel Cooper: That is not an easy question, but I would approach it from the standpoint of what you would tell the patient. When we were first developing lung volume reduction, we performed it only in patients who had absolutely no other alternative. Only later in its development did we offer it as an alternative to transplantation. How do you approach the patient when you can already achieve a very good result with an existing procedure and you can tell the patient, with some assurance, what to expect with that procedure? In the case of NOTES, I do not think that the cosmetics are sufficient justification.

The second aspect is regulatory. I am not a supporter of the FDA's practices for the introduction of new procedures, but I believe strongly that universities have been derelict in setting the standard for the introduction of new procedures, particularly minimally invasive procedures. They have been using these procedures as marketing tools to vie with private hospitals for dollars and patients. I cannot say whether the rapid promulgation of these procedures at too early a stage actually can be prevented, but I do not recall the chairmen of major surgery departments getting together to issue public statements about the proper protocol for introducing new techniques. As Pogo said, "We have met the enemy and he is us."

This may not answer your question, but I believe there should be no payment for any new or novel procedure for a certain period after its introduction, and certainly the hospitals should not be able to profit from it, although the expenses of a new procedure may be recouped. That alone would perhaps put the brake on some of the marketing and the financial incentives, and it might separate, to some degree, the development of new procedures from economic interests.

WHO SHOULD OBTAIN INFORMED CONSENT?

Dr. Moreno: Should informed consent be obtained only by a knowledgeable third party rather than the surgeon-innovator?

Dr. Thomas Krummel: The question is whether there is a disinterested third party who truly is knowledgeable; in cases where there is such a person, I see no downside to having that person involved. However, the notion of having someone who is not associated with clinicians or surgeons obtaining informed consent makes me uncomfortable. Informed consent is not a piece of paper. It is a trust between physician and patient, and to ignore that could leave you in a heap of trouble.

Dr. Cooper: I agree, but another process is important as well. In proposing lung transplantation before

there had been any successful transplants, we defined in advance the standards, indications, and contraindications that we thought should apply. We did this in the absence of any particular patient, and it relieved us of the difficulty of making arbitrary decisions that may have led to unfairly accommodating one patient over another. Once the standards have been set in this way, they can be applied—whether by the investigator or by a committee—in an objective way to the group of patients that is most appropriate in the early phases of development.

Dr. Ralph Clayman: It is difficult for the inventors of an operation to dampen their enthusiasm for their creation to a point where they are as objective as they should be. Joel is bringing up situations for which there are no alternatives. My realm is an area in which there were well-established alternatives for everything we have done laparoscopically or percutaneously, and it was difficult to decide the indications or contraindications early on. Often, the early indications only had to clear the threshold of not seeming ridiculous.

The early development of percutaneous stone removal at the University of Minnesota took place entirely outside the purview of an IRB. Percutaneous nephroscopy had been around since 1955, and we extended it to plucking out a stone. That is how that entire field developed. Early on, we were not going to go after a stone that was as big as a fist because we did not have a way to break it up. As time went by, however, it evolved to the point where there was no stone in the kidney—regardless of its size, location, or hardness—that could not be removed through a small hole in the back. But that entire evolution proceeded without IRB approval.

Universities have been derelict in setting the standard for the introduction of new procedures. They have used these procedures as marketing tools to vie for dollars and patients.

—Dr. Joel Cooper

For laparoscopic nephrectomy, for which there were well-known alternatives, who should have obtained the informed consent? Should it have been me, bringing along the "white coat" factor and not being able to really explain the potential problems since nobody had yet gone there, despite my rapport with the patient? Or should it have been a third party with whom I had discussed the procedure and its possible problems? I do not know the answer, but it raises an interesting point, especially in this age of IRBs and ethics committees.

Dr. Krummel: It is not unlike what we have tried at Stanford when we are not sure of the boundary for IRB consultation. The surgical chairs are willing to convene and essentially police one another, so that when the neurosurgeon proposes a brain transplant, there probably will be a pretty interesting conversation before it gets the green light.

Dr. Cooper: My experiences with IRB involvement differed quite a bit between my work in lung transplantation and my work in volume reduction surgery, but the differences owe a lot to the countries where I was practicing at the time. I did my early work in transplantation in Canada, where I did ask for approval from my hospital's ethics committee and other relevant committees. In Canada, the hospital had a global budget, and it made a decision that it was willing to use part of its budget for transplantation. We received no fees for years, until the operation was proven to be effective, but that did not stop us from developing the procedure.

I had returned to the United States when I began my work with lung volume reduction, and I did not ask the IRB for permission to do that procedure. My justification was that, theoretically, volume reduction was similar to accepted practices for removal of nonfunctioning lung to improve respiratory mechanics (bullectomy) and that we would simply be applying the concept to a different group of patients. However, unlike in Canada, I did not have institutional financial support for doing this new procedure, so how was I going to do it if the hospital could not receive payment for it? I went to the IRB, but instead of asking for permission to do the procedure I asked for permission to study the procedure and to collect data on it. In that way, I was notifying the IRB of my action and thus giving it an opportunity to act. If I had gone to the IRB to approve the procedure, however, the operation would have been labeled experimental by insurance companies, who would have then found a way to deny payment. At least that was how it was in those days.

MARKETING OF MEDICINE: IS THERE NO TURNING BACK?

Question from audience: What makes you think that in 10 years there won't be 100 million obese Americans watching television ads for noninvasive bariatric surgery promising to rid them of their obesity problem? What will keep that from happening?

Dr. Krummel: Nothing. What makes you think it is not happening now? Just look at the ads for the Lap-Band in the lay press.

Dr. Clayman: We already have direct marketing of drugs and direct marketing of facilities. What Joel said is true: "the enemy is us." When I was in training, the idea that a physician would advertise was considered unethical. I still consider it thus. But everybody is doing it, so should that make it acceptable? I think not.

The same thing is true of the huge amount of money spent marketing drugs on television. Why should a single nickel be spent to advertise health care beyond generically informing the public of important health care issues and initiatives? You cannot go to an airport without seeing a surgical robotics program being advertised or a hospital being advertised. You cannot turn on National Public Radio without hearing well-financed spots touting the achievements of a hospital. You cannot watch television without seeing ads for erectile dysfunction medications or other new drugs. It is a waste of dollars. If we took all of that money and redirected it, we could probably solve much of the indigent health care problem, but we as a society have chosen not to do that.

Emerging procedures should be introduced in fellowship programs until they reach the point where they are so standardized that they become a major part of practice.
—Dr. Philip Schauer

SHOULD THE BAR BE RAISED FOR SURGICAL TRIALS?

Dr. Moreno: Let's consider some additional questions. Why shouldn't the government raise the bar on the level of evidence needed to gain regulatory approval for new devices? Why not require randomized trials, as is done for drugs?

Dr. Cooper: Procedures that lend themselves to a randomized trial should be studied at a limited number of centers with mandatory reporting and preset indications for promulgation and payment. I believe that universities have been derelict in their duty to require this level of evidence.

This question is always nuanced, however. Consider the case of laparoscopic procedures. They offer the advantage of smaller incisions, yet how many patients have had to die or suffer serious consequences for the sake of these smaller incisions? On the other hand, how many patients may have been saved from pulmonary embolism, wound infections, or a prolonged hospital stay as a result of laparoscopic techniques? Only a randomized trial could demonstrate whether or not there has been an overall payback from new procedures such as this, although even then the payback may be present for some types of patients but not others.

Dr. Schauer: The problem is expense. Perhaps it is all a matter of economics. Return on investment for the drug industry is something like 10 to 1, but return on investment for the medical device industry is generally much lower. Therefore, conducting large randomized controlled trials is extremely expensive and much more complicated for a device or procedure. This may explain why the standard for trials is different for the two industries.

Dr. Krummel: Virtually all fetal surgical procedures have been subjected to a trial, several of them randomized. The National Institutes of Health paid for many of these trials. One such study prevented rapid uptake of the congenital diaphragmatic hernia operation, which has never been proven in a randomized trial to be better than our current therapy. It is a good example of a randomized trial making a difference.

Dr. Clayman: As Joel pointed out, surgery is constantly evolving, whereas a drug remains unchanged throughout its lifespan. If we had started a prospective randomized trial after we had done our first laparoscopic nephrectomy, the procedure would have died because we were not nearly as facile with our first 10 as we were after our first 100. The technology continues to develop, and the surgeon continues to develop his or her skills, which makes a study of this nature overly dynamic. Perhaps the best you can do is a retrospective, matched, controlled study with the same surgeon, comparing his or her results after 40 or 50 laparoscopic procedures with results after his or her 50 most recent open procedures.

Dr. Cooper: How do you put a brake on the system? Would some sort of limited trial perhaps put a brake on the too-rapid promulgation that we often see?

Dr. Clayman: In the general surgery realm, laparoscopic cholecystectomy came out of private practice. It did not come out of the university with its faculty and laboratories dedicated to exploration and investigation. It never was properly vetted in the scientific realm but rather came to the light of day as an "economic" edge.

Dr. Krummel: I would not underestimate the talent and creativity of those that we train who go out into

private practice. Much innovation has come from very active practitioners.

Dr. Clayman: Right, but they do not have the infrastructure that we are blessed with at universities both to create and to validate.

Dr. Schauer: I agree that academia does not have a monopoly on creative ideas. But perhaps academia should play a major role in defining validation-type studies. That is one area where we may be especially well suited to meet an important need.

THE INNOVATION-TRAINING INTERFACE

Question from audience: I have a dilemma as a residency program director. Our residents want to learn the new technology—laparoscopic surgery, robotic surgery, etc—but we have them in our program for such a limited time. How do you justify teaching them new technology and at the same time still teach them basic, traditional surgical procedures, especially with the reduction in residents' hours? It is fine to be able to do a nephrectomy laparoscopically, but if you get in trouble, you still have to know how to do a good open nephrectomy. How do you address this?

Dr. Schauer: I think the answer largely is fellowship training. Emerging procedures probably should be introduced in fellowship programs until they reach the point where they are so standardized that they become a major part of practice. For example, cholecystectomy quickly became part of general surgery practice, but laparoscopic colectomy took several years to evolve and was taught primarily in fellowship or advanced training, after which it gradually filtered down to residency programs.

Some believe that we should not allow foreign physicians to come here to be trained in NOTES, for fear they will go back to their home countries and use it on humans.
—Dr. Christopher Thompson

Dr. Krummel: All of us who are responsible for training are wrestling with this problem. Residents are expected to learn more yet do so in less time. One approach would be early specialization, so that instead of 5 years of general surgery, you would have 3 years of general surgery and then 3 years of, for instance, thoracic surgery. Also, Ralph mentioned earlier the advantage of skills labs. We increasingly see that type of approach as a backbone for providing broad training without putting patients at harm.

As for teaching the use of new technology, first you have to teach the existing base of practicing surgeons. Here again there is much to be said for skills labs, and I give credit to the American College of Surgeons for its drive to establish and accredit centers around the country as a way to teach this base of surgeons.

Dr. Schauer: If I may expand this question beyond residency and fellowship training, how do we balance the desire to share new innovations with our colleagues against the need to temper their desire to prematurely jump into an area where they do not yet really belong? Chris, I know this applies to your challenges in disseminating knowledge about NOTES.

Dr. Christopher Thompson: Yes, courses on NOTES are also being held in conjunction with all the major society meetings, and we are seeing many enthusiastic trainees at these hands-on courses. The original intent was to give attendees instruction on setting up their own animal labs, yet some trainees took it beyond this limited purpose. As a result, some in our field believe that we should not allow foreign physicians to come here to be trained in NOTES, for fear they will go back to their home countries and use it on humans. I am not certain that that approach is the best way to go, but there has been much discussion about how to handle this. It is a real conundrum. Certainly there are a number of surgical residents and gastroenterology fellows who are clamoring to get into the lab right now and learn these techniques.

Dr. Clayman: This goes back to our earlier discussion about from where new technologies should emerge. What frightens me are the consequences of creative activity occurring outside the university, where there are no laboratories or animal or cadaver models for refining or testing a technique. To me, it was frightening to see laparoscopic cholecystectomy suddenly emerge as a craze without the proper animal and clinical studies having been done. That is not the way I believe clinical research should go forward. I once heard a prominent urologic surgeon say at a major surgical meeting, after a presentation on the impact of percutaneous stone surgery on the canine kidney, "Now that I've done a thousand of these in humans, it's reassuring to know that it's safe to do in dogs." That is not the way it should happen, and every time it does happen that way, we pay a large price, some of us as individuals and all of us as a society.

Dr. Cooper: The answer therefore is to use our academic facilities to facilitate the training of those in community

practice. We should continue to offer training because we have the resources to make it available.

Dr. Clayman: Yes, and this is why I emphasized earlier that support for surgical training centers is so essential. I see all the dollars spent on health care advertising and wonder why these dollars are not instead poured into surgical training, or research facilities, or training simulators.

The way we should train surgeons in new technologies is to train them on simulators equipped with a properly vetted curriculum. This is the future for training, because once you put instruments through small ports, everything becomes measurable—economy of motion, past pointing, and efficiency; simulators with a curriculum will also be able to assess the trainee's cognitive abilities. When an individual performs well on the simulator, he or she can then come into the operating room and work with surgeons experienced in the procedure. The use of simulators in this manner should ultimately improve the overall quality and safety of each surgical specialty.

RISE OF THE ROBOTS

Question from audience: I am curious how the panel members interpret early randomized trial data showing an increased cost without an improvement in care with the use of surgical robots in certain procedures. Should we persist or consider an investment in the future as robotic technology improves and surgeons further adapt to it?

The current robot is not an end device. We will see more. This theme of immediate benefit versus follow-on iterations is the story of device development in this country.

—Dr. Thomas Krummel

Dr. Cooper: I think the robot should be used only for those procedures for which it has unique capability and can perform a task better than we can. It appears that the robot performs better than the ear, nose, and throat surgeon for operations on the base of the tongue. The same may be true of prostate surgery, but I am not certain. But to do a laparoscopic Nissen repair with a robot…as Dr. Nat Soper of Northwestern University has said, "If I needed a robot, I shouldn't be doing laparoscopic Nissens."

The robot provides light, it gives you magnification, and it reduces tremor. We should concentrate on its use for operations where these attributes are particularly valuable. But we should be wary of its use as an expensive marketing tool.

Dr. Clayman: The robot provides you with superhuman capabilities: 10 to 30× magnification, no tremor, a 540-degree wrist, instrumentation with 6 degrees of freedom, and motion scaling. It allows you to be a better surgeon than you are without it. I agree that it is expensive. It is woefully overpriced at this point, but I believe the expense will come down with time. It is no different than the first computers, which were terribly expensive. The robot enables surgeons to do a better job than they would without it if we are talking about reconstructive-type surgery.

Ergonomically, the robot is very positive for the surgeon. For the first time, the surgeon is actually allowed to sit down in a comfortable environment and can work for 4 hours straight, get up at the end of the surgery, and feel fine. If you are older than 50 and you operate standing at the table staring at a television screen on the other side for 4 to 6 hours, you are going to ache afterwards. I believe surgeons work better if they are comfortable.

Dr. Schauer: At least within my field of general surgery, there has been no evidence that this superhuman ability has translated into superhuman results, in terms of reduced operating time, fewer complications, or better efficacy. We should probably develop the metrics to measure progress. How do the theoretical benefits translate into clinical benefit?

Dr. Clayman: It is not theoretical in radical prostatectomy if you look at the data. The potency rates for patients who undergo robotic surgery for these procedures are now almost 90%, which is something that no surgeon performing open prostatectomy has ever achieved. Fortunately, the continence mechanism is so strong in most adults that it does not matter whether prostatectomy is done with a robot or open surgery—patients are probably going to be all right. But the bottom line is that robotic surgery is a bit better. Most surgeons would use it if it were free. The problem is that it is so expensive right now and it is breaking the backs of many hospitals.

Dr. Schauer: You make a good point. Demonstrating metrics is important, and prostatectomy is a good example. But I am not aware of any other procedures for which benefit from robotic surgery has been documented.

Dr. Krummel: The history of robotic surgery is so interesting because the killer application was supposed to be coronary work—percutaneous bypass surgery. But then the heart port went to pot and patients with anterior wall lesions ended up not being a big

enough group. It turns out that it is still difficult to do and there is not a lot of room. So prostatectomy has ended up as the initial killer application.

Keep in mind that the current robot is not an end device. We will see more. There are now robotic steerable catheters that I think will be adopted into NOTES procedures. This theme of immediate benefit versus follow-on iterations is the story of device development in this country.

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THOMAS J. FOGARTY, MD
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Will the United States maintain its position as a world leader in medical technology?

Conflict-of-interest statement
I am seriously conflicted. You may assume that I have a financial interest and conflicts with any emerging med-tech company you choose. In addition, I actually take royalties when possible and encourage innovation and entrepreneurship in others.

As an inventor, my perspective on financial relationships with medical technology companies is quite different from the one presented by Dr. Arnold Relman in his earlier keynote address (see page S33). Although I agree with him that the state of medicine is indeed a mess, the mechanism by which that mess can be cleaned up is debatable. I believe strongly that the mechanism advocated by Dr. Relman—prohibiting financial rewards (outside of salaries) to physicians involved in innovation—will do nothing to benefit patients.

My assessment of the topic I am charged with addressing—will the United States maintain its preeminence in medical technology?—is that it will not. I will use this talk to present the reasons for that assessment in the hope that you will understand that we are going the wrong way in American medicine today.

Committees usually consist of a group of the unwilling picked from the unfit to do the unnecessary.

THE NATURE OF INNOVATION

True innovation requires broad acceptance

Innovation, invention, and technology development are not simple or single occurrences. They represent an iterative process requiring reduction to practice and, most important, acceptability by others. An inventor does not determine the worth of his invention; his peers do. Self-proclaimed inventors are numerous and multiple, and the technologies that they put forward rarely receive broad acceptance. Everybody wants to be an inventor, recognizing that it brings attention and reward, but it also brings a lot of baggage, which I will discuss shortly.

What's wrong with a medical-industrial complex?

Dr. Relman and others may object to the term "medical-industrial complex," but to do so is to deny reality, because health care in the United States simply is a medical-industrial complex, but one devoted to optimal patient care.

The process by which optimal patient care is delivered involves relationships among a whole host of people. In my view, the key players are the engineers and physicians coming together to develop a technology intended to benefit patients—this relationship is a critical element of invention and innovation. At the same time, patients are the most important individuals involved in any process of innovation. Without patients, we simply could not innovate. Of course, other players have roles as well: institutions, the government, industry, entrepreneurs, lawyers, payors, investors. And in the middle of this mix we have chief executive officers of industry, whose job is to make sure all these players are talking to one another and collaborating for the benefit of patients.

CHALLENGES TO INNOVATION

Challenges to innovation are abundant, and some of them have been with us for decades. I have outlined some major challenges below.

Technology evaluation

There are many ways that technology can be evaluated. We hear a lot about evidence-based medicine, which is ideal if used appropriately, yet too many people demand it in a knee-jerk way. In the field of surgery, level I evidence is often impractical, extremely costly, and sometimes not even possible, and attempts to use it may lead to inaccurate conclu-

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sions. If applied too broadly, the demand for level I evidence can impede innovation, so it is important to recognize that evidence-based medicine is only one way to get answers about a technology, especially in the surgical specialties.

Teaching and training

Teaching and training of new technologies is another challenge. The shelf life of a new surgical technology is approximately 5 years. Failure to recognize a new technology can lead to a loss of business, as in the case of cardiac surgeons who initially ignored catheter-mediated therapy. Other specialties are rarely willing to help surgeons adapt to new technology, for fear of losing business. So the issues at play can be pretty complex.

Who is to do the training? Because academic medical centers cannot afford to teach new technology, industry must take on this role. We need to recognize that industry offers a very valuable service in the process of teaching and training. As for potential downsides, surgeons should be smart and savvy enough to be able to evaluate whether a sales representative's presentation is solid or nothing more than marketing. If we cannot do that, our medical schools have egregiously failed in their mission.

If you do not have conflict of interest, you are not doing very much. It is impossible to get rid of conflict of interest if you are going to be a productive human being.

Cost

Cost is one of the most significant deterrents to innovation. The accelerating cost of innovation is difficult to imagine. For example, the first embolectomy catheter cost about $3,000 to develop back in the early 1960s. As its developer, I can tell you that it cost so little because I stole or borrowed—on a permanent basis—most of the equipment needed to make the catheter systems, which I sterilized in a preparation of glutaraldehyde (Cidex) and reused. Compare that cost to the cost of developing the drug-coated stent. If the costs of the drug, the device, and the clinical trials are all included, Johnson & Johnson's total cost of developing its drug-coated stent was more than $1 billion.

What is often not acknowledged, however, is that technology may be a solution to accelerating costs. Many startup companies fail to obtain funding simply because venture capitalists do not believe they will be able to make money based on the cost of product development and dissemination. Therefore, many potentially valuable technologies that could address large patient populations may never see the light of day. This is a very significant problem that must be addressed. Overregulation, when analyzed, is extremely expensive.

'Committeeism'

Another obstacle to innovation is likely to be familiar to all: what I call "committeeism," or the expansion or growth of multiple committees for multiple purposes. It is rampant not only among universities but within industry as well.

There is an overabundance of committees involved in technology evaluation and acceptance at hospitals in the United States, including the institutional review board (IRB), the conflict-of-interest committee, and committees in charge of everything from ethics to contracts to adjudication. The IRB is clearly the most valuable, but it is only as effective as its members. Through the *Federal Register*, the federal government has outlined what the functions of IRBs should be.[1] However, I have personally polled IRB members and found that very few are aware of these *Federal Register* guidelines for IRBs. As a result, individual IRBs come up with their own concepts for what they are supposed to do, and often they do not correlate with the *Federal Register*'s concepts, which obviously creates problems.

Of course, committees are necessary to some extent and they can bring value. In my experience, however, committees usually consist of a group of the unwilling picked from the unfit to do the unnecessary. Too often we come out of committee meetings with little more than the date and time of the next committee meeting—or perhaps with a newly created subcommittee, whose members are typically culled from those absent from the committee meeting. If we honestly reflect on the effectiveness of most committees, we will usually conclude that it is fairly marginal.

From the standpoint of the inventor or innovator, committees and consensus can constitute a significant deterrent. Invention is not done by committee. Patients are not treated by committee. Many committee members have never been involved in patient care, yet physicians are encumbered by committees and a point is often reached where the patient is not being served in the best way. Of course, oversight is needed, and we still need some committees, but the overall number and value of committees needs to

be reevaluated throughout the health care system. My experience suggests that fewer committees and smaller committees would serve us all better.

Conflict of interest

Conflict of interest represents yet another challenge to innovation. The dictionary definition of *conflict of interest* is "to be at odds." My practical definition is that it involves trying to serve more than one master.

Who has got conflict of interest? We all do. If you do not have conflict of interest, you are not doing very much. Should we get rid of our conflicts? We cannot—it is impossible to get rid of conflict of interest if you are going to be a productive human being.

Conflict of interest exists in practice. When a surgeon operates on a patient, is he or she doing it to benefit the patient or to make money? The honest answer is that it is probably for both reasons.

Likewise, conflict exists when physicians are involved in research, either basic or clinical. Why do we do research, and why do universities encourage it? In the case of basic research, is it done for discovery, or to pay for direct and indirect overhead? The reality is that it is done for both reasons. Similarly, clinical research is conducted for many reasons. One is to benefit patients. Another is to gain notoriety as someone who has benefited patients through innovation. A third reason is financial. In most cases, clinical research is probably done for all three reasons, and the particular emphasis will differ according to the individual.

In most cases, clinical research is probably done for all three reasons—to benefit patients, for notoriety, and for money—and the particular emphasis will differ according to the individual.

The concept of making money while benefiting patients is egregious to many academic medical centers today. But the reality is that if you develop useful technology, you will make money. That is just the American way. Should medical innovators start out with the motivation of making money? No, although some do. However, if their innovation provides a real service to humanity, there is nothing wrong with that approach, although financial rewards should come only as a byproduct of benefiting patients.

Institutional conflicts are present as well. Historically, institutions have had significant conflicts of interest, but only recently have these conflicts been scrutinized. Advertising of services is an example of an institutional conflict, with the goal being to attract patients to increase revenue. Whether or not this is bad depends on whether there is an overriding benefit to patients in the big picture, as well as on how the advertising is done.

Finally, there are personal conflicts as well. How much time do you spend at the institution? How much time do you spend seeing a patient? Doing clinical research? Spending time with your family? All of these things are technically in conflict with one another, and occasionally they can represent serious conflicts. Conflicts are inescapable, so to say that you do not have any is simply not consistent with reality.

Academia

The way that some major academic centers have responded to concerns about conflicts of interest has actually turned some of these academic centers—which are supposed to promote exploration and innovation—into deterrents to innovation. To innovate at these institutions has become extremely cumbersome, costly, and inefficient. I do not believe that these institutions—which include prestigious teaching centers such as my institution, Stanford University, and Harvard Medical School—really understand the effects that some of their policies are having. Nevertheless, these policies are taking a toll as these institutions do less and less in the way of medical innovation. In the process, the institutions are failing to fully serve their missions. An example of the mentality behind such policies is laid out in the following section.

A CLOSER LOOK AT CONFLICT: ONE WAY *NOT* TO GO

AAMC's 'rebuttable presumption' policy does not serve patients

The Association of American Medical Colleges (AAMC) is a group of academic institutions that helps to define policy for the conduct of research in academic medicine. A few years ago an AAMC task force came out with a policy for the oversight of financial interests in clinical research, which states the following: "Institutional policies should establish the rebuttable presumption that an individual who holds a significant financial interest in research involving human subjects may not conduct such research."[2]

This "rebuttable presumption" policy, which establishes the premise of guilt until innocence can be proven, is decidedly un-American. Although

patient harm or other abuses can occur when a physician performs clinical research using devices, procedures, or drugs in which he has a financial stake, such abuses are quite rare in my experience. This AAMC policy is not in the best interest of patients because it insists that innovators recuse themselves from research that involves the very technology in which they are the ones who are most expert and knowledgeable. As a result, patients who are candidates for a new procedure or a procedure that uses a new device will not be able to undergo the operation at the hands of the most capable person but must be sent to another surgeon. This is the case even if the patients are referred to the innovator by their own personal physician and even if another independent surgeon agrees that the proposed procedure makes sense.

The only party whose interest is served by this ridiculous policy is the institution, as the goal is to prevent potential adverse publicity. In this, too, the policy is misguided, since bad publicity for an institution can come from cases involving new procedures and old procedures alike.

The only party whose interest is served by the AAMC's "rebuttable presumption" policy is the institution, as the goal is to prevent potential adverse publicity.

Conflicts must be accepted and managed

The AAMC has come out with a related policy maintaining that conflicts of interest among researchers are to be avoided at all costs. I take that to mean that researchers are supposed to just die, since conflicts of interest are inherent in our existence and represent a critical element in all relationships. It is true that most routine daily conflicts are not serious, but to deny conflicts when they exist serves no useful purpose. We have conflicts and we have to learn how to manage them, consistent with protecting the interests of individuals. In the case of physicians, these individuals are our patients.

THE NECESSARY WORK OF DEFYING CONSENSUS

Much of what is done in health care—developing rules and regulations; issuing recommendations, standards, and guidelines; working to increase compliance—is aimed at creating order and consensus. While a certain degree of order and consensus is necessary, of course, these are not the factors needed to spur improvements and advances. Improvement requires people who are willing to challenge, who will defy consensus and tell us what we are doing that is not so good.

This is the natural tendency of the inventor and the innovator—to go against the grain, to go outside the standard of care and do something that is new, that is not in compliance, and that may or may not be accepted. This is why, in my view, it takes more courage than brains to be an innovator. No one likes to be ridiculed or to be told that they are not in compliance and are perhaps endangering patients' lives. Of course, inventors and innovators often do not help themselves in this regard, as they tend to be odd ducks by nature and do not always express themselves well. Still, their function of defying consensus is necessary to virtually all medical progress.

A WAKE-UP CALL FOR INNOVATION IN AMERICA

I will conclude by returning to my broad topic of whether the United States will maintain its preeminence in medical technology. As I said at the outset, I cannot answer that question in the affirmative, largely because of the breakdown in cooperation and collaboration among practitioners, academia, and industry for the reasons I have outlined above.

The signs of our waning preeminence cannot be missed. The manufacturing of medical technologies is going offshore, with significant economic implications. More importantly, clinical studies are now increasingly moving offshore. I was recently involved in 9 months of offshore clinical studies to collect the necessary data to submit a device for US approval, because the studies were prohibited from being performed in the United States. Despite this prohibition, it is these offshore studies that reveal any deficiencies in the technologies being assessed and that allow those deficiencies to be corrected for the benefit of US patients. And US patients themselves are increasingly going offshore for medical care—either to obtain medications or to undergo procedures that involve a device that cannot be used in the United States.

As a result of the above developments, significant investment is going offshore, taking with it a great deal of interest in innovation. Meanwhile, that interest in innovation is decreasing in the United States because it is being deterred, delayed, and encumbered by overregulation. This practice is not in the best interest of our economy and certainly not in the best interest of patients in this country, and not enough people are aware of this considerable problem.

I will be happy to take questions from the audience.

DISCUSSION

Question from audience: Is it possible that changing some laws could allow us to increase innovation and enable more clinical research?

Dr. Fogarty: I think it is possible, but laws cannot be changed unless people become aware of the issues. I want to spend the rest of my life making people aware of issues that deter innovation. That is the reason I started the Institute for Innovation: to create an environment in which innovation can take place efficiently, honestly, effectively, and with proper oversight to ensure consistency with the relevant rules and regulations. Many of the rules and regulations are self-imposed. Most of them are misunderstood by the people to whom they apply.

The rapidity of technologic change clearly outpaces the ability of the Food and Drug Administration (FDA) to keep up. The FDA has a difficult time attracting people who have the background and experience to assess the value of clinical investigation. My approach to the FDA is to be as collaborative as possible. I will approach the FDA and simply ask what they want me to do to support a submission for product approval and then assure them that I will do it if it is possible. That is a good way to make clear that your intent is to be collaborative for the benefit of the patient.

It takes more courage than brains to be an innovator.

Another problem is that regulatory and reimbursement approvals should be simultaneous and take parallel paths, but that is not the case. While the FDA covers the regulatory piece, the Centers for Medicare and Medicaid Services (CMS) covers the reimbursement piece, and it has a different charter and operates on a separate timetable. What happens is that old technologies are being rewarded by being reimbursed but new technologies are not being rewarded because they are not being cleared for reimbursement quickly enough. Ultimately CMS will pay for these new technologies, but if a product is a 510(k) submission (a premarket submission to the FDA to demonstrate that a new device is at least as safe and effective as an existing device),[3] the interval from the time of concept to implementation is usually 7 years. This delay cannot be tolerated, since it means that many patients are being deprived of the potential of effective technology as a result of regulation.

Question from audience: I agree with many of your criticisms and your concern about bureaucracy getting in the way of innovation. However, I really object to your use of the term "the American way," which implies that there is an "un-American way," which I guess is the way that is different from your way. Also, you seem to imply that the medical-industrial complex has as its primary purpose good patient care. But this complex does not have any fiduciary responsibility to patients, so what do you base your implication on?

Dr. Fogarty: Industry does not want a bad outcome, just as a physician does not want a bad outcome. If you have related to industry throughout your career, you will come to see that this is absolutely the case. Now, are there bad occurrences within the framework of industry? You bet there are, but they are not common and they are not intended.

Question from audience: Let me reframe the previous questioner's question. Companies have a fiduciary duty to stockholders to make a profit. The best way to do that is to develop good products that benefit patients. But when you have a product that is just as good as someone else's but you can find a way to sell more of it, you have a fiduciary duty to do that as well. Your duty is to make money, and if there are times when your product does not really benefit patients or is to the detriment of patients, your duty is still to make money. So to say, by definition, that all that people care about is maximizing patient care just doesn't make sense.

Dr. Fogarty: Let me ask you: how often have you related to and worked with industry?

Questioner: I don't think that is relevant.

Dr. Fogarty: It is very relevant. You have to know how other parties think and why they think that way. When responsible people in industry can identify a consistent occurrence of adverse events related to their technology, they do something about it. Now, some don't, and may hide it…

Questioner: And there have been multiple cases of that.

Dr. Fogarty: I am not denying that, because it is certainly true, and they have done so for bad reasons. But that does not mean all of industry functions that way, because it doesn't. It is the frequency that you have to look at. I would suggest that it is relatively infrequent, although sometimes it is very egregious. It is the same way with physicians.

Question from audience: Perhaps regulation is actually beneficial to industry, in that it creates a barrier

to entry. For example, when Johnson & Johnson has to spend a billion dollars to develop a drug-eluting stent, it can be highly confident that there are very few other entities capable of reproducing that feat. As a result, it will have a lot of market presence for many years to allow it to recoup its investment. How would you respond to that?

Dr. Fogarty: You are right—I have seen companies take products that obviously warrant a 510(k) submission and try to submit them as PMA (premarket approval) candidates for precisely the reason you suggest. That type of thinking does go on, but those who really understand economics recognize that that is not a good way to go. From my perspective, competition is good, and to eliminate it by any mechanism is not good. If you are going to have competition, you want to have good competition because you can learn from it. Overregulation that creates barriers to entry is not in the interest of patient care and it encumbers competitive companies, certainly from a time standpoint.

Comment from audience: I enjoyed Dr. Fogarty's talk, but I would like to add one comment: we should not confuse duty with ethics. One's duty is to make money, but one's ethics are to be honest, and we each have to decide what we are going to follow. That is true in industry, and it is true in medicine. I have worked with a lot of companies, and most of them are ethical and have the patient's best interest at heart. I have seen companies spend millions of dollars on products that never came into clinical use because clinical trials showed them not to have value. Most companies cannot sustain that because they will disappear. The bottom line is that I have seen very high ethics within industry, as I have in medicine. The problem is that when ethics are violated, it hits the news and then unfortunately gets generalized to the entire profession or industry.

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Outside the operating room—economic, regulatory, and legal challenges

A collection of perspectives and panel discussion

Preface

By Lawrence K. Altman, MD (Moderator)

Early in the history of the United States, physicians commonly discussed medical issues in newspapers and other public forums. But a remark attributed to Osler, "Never trust anything you read in a newspaper…and if you do, immediately doubt it at once," was used by the medical profession for decades to justify avoiding public discussion of medical issues. This retreat by physicians from the public discourse was particularly harmful in that it overlapped with the period when the public began paying for most medical research via federal research funding. Recently the medical profession has again started to discuss medical matters openly with the public, but this step has been taken reluctantly, in response to public pressure.

This resurgence in physicians' engagement with the public has come not a moment too soon, as factors and players outside the operating room—economic forces, regulators, legislators, lawyers, and others—today may have as much influence on what goes on in US operating rooms as do the surgeons, nurses, and technicians who work there. Our panel will address some of these influences on surgical innovation from outside the operating room, touching on historical and current examples of attempts to regulate innovation as well as the points of view of device companies, investors, lawyers, government, and health economists.

A device company perspective: Serving patients is the key to sustainable success

By Michael A. Mussallem

I am honored to be here to represent industry. Although medical technology companies compete fiercely with one another in the marketplace, we also have a broad common interest: we want to develop innovations to help patients.

DEVICE AND DRUG DEVELOPMENT DIFFER

Discussing ethical challenges involving industry is easier in the context of pharmaceutical development, for a number of reasons. The pharmaceutical industry is so large that it tends to dominate the discussion. But medical devices, which are primarily what is involved when we speak of surgical innovation, differ from pharmaceuticals in key ways.

The physician-company relationship is central

First, medical devices are not used directly by patients but are tools for physicians, which makes the relation-

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Mr. Mussallem reported relationships with Edwards Lifesciences (employment, ownership interest, board membership). All other authors reported no financial interests or relationships that pose a potential conflict of interest with this article.

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ship between industry and physicians more closely intertwined when devices are involved.

An iterative process by nature

Second, it takes years of development and enormous sums of money before a drug is finally approved. The final product then has a market life of 10 or 20 years. In contrast, device development is an inherently iterative process. After Thomas Edison developed the light bulb, attempts to improve the product were immediate and constant: "Can the light be made softer? The bulb smaller? Can it be turned off?" The same type of continuous improvement process happens with medical devices, which typically are refined every 12 to 18 months. Occasional breakthroughs occur and open up a whole new way of thinking, but far more often device innovation is about incremental modifications and improvements.

SUCCESS BREEDS CONFLICTS… AND REGULATION

The development of medical devices is an American success story; we tend to be better at it than any other country. Our system works well and rewards risks and innovation. When technology is racing forward to address an unmet patient need, a tremendous amount of value is created in the form of patients living longer and healthier lives. People pay for that value, which can create substantial payoffs for successful innovators and companies. I believe that six of the companies in the Fortune 500 are medical device companies, and the medical device industry has a $450 billion market capitalization in total.

I refuse to believe that raising ethical standards requires pulling apart companies, engineers, scientists, and physicians. Instead, we need to find ways for these various players to engage together.
—Michael Mussallem

The medical device business is like an ecosystem with many interacting components. Someone with a bright idea puts a physician and an engineer together, starts a company, attracts some capital, and develops a product. Because they need startup money for production, they might offer physicians a share of the company and some stock options, and immediately an opportunity for conflict of interest arises.

As a result of these many interacting components and the conflicts they can create, medical device companies today are highly regulated by a long list of entities, including the Securities and Exchange Commission, the Food and Drug Administration (FDA), the Department of Justice, the Internal Revenue Service, the Environmental Protection Agency, the New York and NASDAQ stock exchanges, the Office of the Inspector General, and the Foreign Practices Act. This degree of regulation makes every part of the medical device development process more time-consuming and expensive.

LONG-TERM SUCCESS REQUIRES THAT COMPANIES SERVE PATIENTS

The motivation of medical technology companies is often called into question. Medical device companies are certainly motivated to make money, and they certainly have obligations to shareholders. But for a company to be successful for many years, it cannot be single-minded about the constituencies that it serves. Great medical device companies have employees who want to work for them, physicians who want to buy products from them, communities that welcome them, and shareholders who want to own their stock, but the primary goal is always to serve patients: if that is done really well over the long term, the company can count on those other success factors being present. To have a sustainable competitive advantage, one must think beyond the next quarter and run a highly respectable business on an ongoing basis.

It is true that there are outlier medical device companies who do not always operate with full integrity, as there are in any industry. The challenge, both for the medical technology industry and for the broader health care community, is to raise the standards and encourage everyone to operate at a highly ethical level. I refuse to believe that doing so requires pulling apart companies, engineers, scientists, and physicians. Instead, we need to find ways for these various players to engage together.

A good start may be the revised Physician Payments Sunshine Act, proposed by US Senator Charles Grassley. This legislation, which is supported by the Advanced Medical Technology Association (AdvaMed), would establish a national registry of payments made to physicians by medical device, medical supply, and pharmaceutical companies, and seems to make a lot of sense. As we move forward on this and other efforts to raise the ethical bar in health care innovation, it is important that there be a place at the table for everyone involved.

A regulatory and legal perspective: Issues in off-label device use

By Rebecca Dresser, JD

My comments will focus on off-label use of medical devices, which is a topic rife with ethical questions. I will begin by reviewing recent experience with drug-eluting coronary stents, which are regulated by the FDA as Class III devices, as this experience touches on many of the challenges that arise from off-label product use.

CASE STUDY: DRUG-ELUTING STENTS

The earliest coronary stents were made of bare metal. Over time, arteries treated with these stents tend to become blocked again, requiring patients to return for repeat revascularization. Drug-eluting stents were developed to extend the time that the artery stays open.

Earlier this decade, a couple of device manufacturers sought FDA approval to market their drug-eluting stents. Each manufacturer submitted data from randomized clinical trials in otherwise healthy patients with small, newly diagnosed heart blockages. The trials showed that patients who had received drug-eluting stents had reduced reclogging rates after 9 months compared with those who had received bare metal stents. Risks appeared to be similar between the two types of stents. On the basis of this evidence, the FDA approved the initial drug-eluting stents for marketing in 2003 and 2004.[1]

The few courts that have addressed off-label use ruled that physicians have no obligation to specifically inform patients of off-label status.

—Rebecca Dresser

Soon after they were approved, drug-eluting stents were being used in about 80% of patients who received coronary stents. However, although these new stents had been tested and approved for use in otherwise healthy patients with small, newly diagnosed heart blockages, about 60% of their real-world use was off label—specifically, in patients with large blockages or additional health problems such as diabetes.

Reports of adverse events with drug-eluting stents began to emerge, so the FDA issued a statement of concern in September 2006 and subsequently convened an advisory panel of outside experts to review the data and make recommendations. In January 2007, that advisory panel concluded that off-label use of drug-eluting stents is associated with an increased risk of thrombosis, death, or myocardial infarction compared with on-label use. The panel noted, however, that data on off-label use were limited and that additional studies were needed to determine optimal treatments for more complex patients.[2]

So research on the safety of off-label use of drug-eluting stents continues. Recent data—including studies published in the *New England Journal of Medicine* and *JAMA* earlier this year[3,4]—suggest that some off-label uses are safe and effective, but much uncertainty remains.

PHYSICIANS SHOULDER THE ETHICAL BURDEN

The story of drug-eluting stents illustrates some of the issues that can arise with off-label use of devices. Currently, the FDA gives physicians discretion to prescribe approved products for uses that deviate from the products' FDA-approved package inserts. Although the FDA is imperfect, it provides the most thorough and systematic review we have of medical product safety and efficacy. However, an FDA review typically addresses the risks and benefits of a product in only one context or patient population, which might not apply to another context or population. For instance, children and the elderly are generally not well studied in clinical trials, so off-label use of therapies is particularly common in these populations. Of course, patients can be harmed if off-label use presents unappreciated risks or does not provide an adequate benefit. Even if no adverse effects result from off-label therapy, other harms are possible: an alternative therapy might have been superior or the treatment may simply be a waste of money.

In this absence of regulation, the questions of whether and when to prescribe off label—and what the guiding ethical standards should be—fall to physicians. A few professional groups provide some guidance. The American Medical Association states that off-label use is justified when "based upon sound scientific evidence and sound medical opinion."[5] The American Academy of Pediatrics (AAP) has issued what is perhaps the best statement[6] (although it focuses on drugs, its principles can be applied to devices as well). The AAP maintains that off-label use should be based on "sound scientific evidence, expert medical judgment, or published literature" and notes that physicians who prescribe off label have "a public and professional responsibility to assist in the systematic development of the information" about a particular off-label use. The AAP also advocates that prescribers consider discussing with patients (or their

parents) the off-label status of a therapy and the degree of the therapy's acceptance among physicians for the proposed off-label use.

SPECIFIC ETHICAL ISSUES

How to evaluate evidence about off-label use?

The justification for off-label use is not to advance knowledge but to best meet the needs of an individual patient. But how can a physician know that a therapy is best for a proposed use when it has not been through the FDA approval process for that use or for the particular type of patient at hand? Some off-label uses are supported by strong data while others are not. Physicians have the responsibility to evaluate the available evidence with integrity and to promote rigorous research when the available evidence is inadequate.

Healthy skepticism of industry promotion warranted

One problem is that the pharmaceutical and device industries are heavily involved in communicating about off-label uses of products. Since 1997, the FDA has permitted drug and device companies to engage in limited promotion of off-label product uses through distribution of "enduring materials" such as textbook chapters and peer-reviewed articles. Industry has also been allowed to sponsor education sessions about off-label uses so long as an independent continuing medical education provider is involved in planning the sessions. The authorization for such off-label promotion expired recently, however, and was not renewed in the FDA reauthorization law passed in the fall of 2007. The FDA has since proposed a similar rule regarding off-label promotion,[7] but it has been criticized for being a bit more lenient toward such promotion.

Concerns about off-label promotion and communication remain. Manufacturers sometimes violate the spirit of the rules that require independence, for example, through compensating physicians who speak favorably about off-label uses. Similarly, manufacturers sometimes design studies of off-label uses of therapies so that the results are especially likely to turn out favorably.

Data collection: Easier said than done

The aim of promoting information gathering and systematic research on off-label uses may be viewed as a professional duty,[6] but in practice this duty is complicated by the question of who will pay for it. Often product manufacturers are already making plenty of money from an off-label use and therefore have little financial incentive to conduct trials to obtain FDA approval to add a new indication or population to the label. At the same time, there is very little money available in the public sector for such studies.

No consensus on patient consent

The principle of informing patients about off-label use is also controversial. Not much litigation has been brought on this issue. The few courts that have addressed it have ruled that no obligation exists to specifically inform patients of off-label status and that physicians are obliged only to inform patients about risks, anticipated benefits, and alternatives to an off-label treatment. Some writers think that most patients do not understand the concept of off-label use and that informing patients will only confuse them. Others argue that off-label uses ought to be disclosed, especially in situations involving very innovative off-label applications or when insurers may not provide coverage. Interestingly, a recent Harris Interactive poll found that about half of the US public feels that doctors should only be allowed to prescribe drugs for diseases for which they are FDA-approved.[8]

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WHAT SHOULD BE DONE?

Some people argue that the regulatory approach to off-label use already works well. Others want more government oversight. Probably no one would argue that every variation from the label should be subjected to the FDA approval process. There is debate over exactly how to define an off-label use—ie, how different it must be from the approved use to legitimately warrant the "off label" title. This is similar to the question of how to define when a change in surgical technique is innovative enough to require formal evaluation.

Some argue that better postmarketing surveillance is needed to assess the effects of off-label device use in patients. Additional help could come from a 2007 amendment to federal law that strengthens requirements to make clinical trial information publicly available through clinical trial registries. This will make it difficult for sponsors to conceal unfavorable data from trials involving off-label uses. More information exchange and independent assessments of off-label uses are also needed to promote better and safer off-label use of medical devices.

A historical perspective: The more things change, the more they remain the same

By Paul A. Lombardo, PhD, JD

As a historian and a lawyer, I tend to look back to established precedents, a tendency that often leads to a conservative and cautious perspective. This kind of temperament is slow to reach sweeping conclusions, slow to push for change, and slow to believe that anything is really very new. This temperament is in stark contrast to that of the successful surgeon, who tends—again, speaking in stereotypes—to be aggressive, bold, courageous, pathbreaking, and, at the best moments, even heroic.

This contrast in temperaments may bring a different and perhaps helpful perspective to the task I have at hand—to look to the past for examples of ethical challenges in surgical innovation. In gathering these examples I was struck by how many of the foundational ethical issues that surgeons have faced over the years remain with us today.

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—Dr. Paul Lombardo

CASE 1, 1649: 'STANDARD OF CARE' CONCEPT ARTICULATED

In 1649, an ordinance passed by the Massachusetts Bay Colony made it a crime to operate on a person without consent. It also stated that no person employed as a surgeon may perform any act contrary to "the known approved rules of the art" as laid out by one's medical peers. The ordinance pointed out that this rule was meant not to discourage "the legal use of the skills of healers" but rather to inhibit those who might not be restrained from "the presumptuous arrogance of their own skill."

This law mandated three things that are a foundation of what we think of as surgical ethics today:

- The notion of a standard of care ("the known approved rules of the art")
- Peer review (the need to consult preoperatively with peers regarding that standard)
- Patient consent.

Interestingly, this ordinance was adopted at a time when most surgery was performed on visible pathologies or deformities, and elective surgery was all but unknown. Only about 150 years later did surgeons open a body cavity on a regular basis.

CASE 2, 1809: INNOVATION IN THE FACE OF CONDEMNATION

In 1809, Ephraim McDowell, a Kentucky surgeon, described the desperation of his patients as a motive for attempting a new procedure to fix a problem that was otherwise incurable. In his most famous case, McDowell reported visiting a woman some 60 miles from his home who thought she was pregnant but who actually had a large ovarian tumor. McDowell told her that there was no cure but invited her to come to his home if she were willing to undergo an experiment. He thought she would not make the trip, but, to his surprise, she arrived on Christmas Day in 1809.

As McDowell prepared for surgery, his nephew, who was a physician and his partner, argued that the procedure was a terrible thing to try. McDowell was also condemned from the pulpit by a preacher, who declared that the surgery was tantamount to murder if it failed.

While his patient recited psalms from the Bible, McDowell removed a 22-pound lump of tissue without anesthetic or antisepsis. The patient returned home about a month later and lived for more than 30 more years.

After having performed this oophorectomy procedure three times, McDowell deemed it less perilous than any other mode of treatment and the only certain cure for diseased ovaries. Later, surgeons in England who read about his work criticized McDowell for not explaining the operation sufficiently for others to replicate it, although he denied this charge.

In pioneering oophorectomy, McDowell did something quite innovative in the face of considerable professional and community opposition. Moreover, he took care to obtain patient consent and to include his patient in decision making.

CASE 3, MID-1800s: J. MARION SIMS AND 'THERAPEUTIC MISCONCEPTION'

J. Marion Sims, considered the father of American gynecologic surgery, is famous not only for his technique as a surgeon but also for inventing several instruments, including the speculum. Yet he is criticized by historians and ethicists, primarily because he often performed experimental procedures on slaves, who probably were not in a position to give true consent. He kept patients as boarders for many months, doing a variety of experiments on them, and described in his writings how much pain his patients endured from his mistakes or from the prolonged operations.

Sims' work is an example of "therapeutic mis-

conception": while he told his patients that he was going to cure them, he often had no idea whether he could. Thus, his patients believed that the operations were primarily for their benefit although he seems, as critical colleagues came to believe over time, to have sometimes been simply experimenting on patients who were uniquely vulnerable.

CASE 4, 1903: EARLY EXAMPLE OF MODERN INFORMED CONSENT

In contrast to the record of Sims, some 50 years later Dr. Franklin Martin described the painstaking approach he took to advising a patient who would undergo one of the first ovarian transplants, performed around 1903. Martin wrote:

> I carefully explained to her the difficulties which we had to surmount…. I also clearly informed her that the operation must be looked upon entirely in the light of an experiment, and that she must be prepared to assume all responsibility with regard to failure in the outcome. Being a woman of unusual intelligence and one who was thoroughly in earnest in her efforts to regain her normal condition, these preliminaries were very easily settled.[9]

Without being required to do so, 100 years ago Martin went through a process equal to any informed consent disclosure that one might encounter today.

Even a century ago, "giving the donors what they want" was seen as a prerequisite for hospitals' ability to raise the funds needed to care for the poor.
—Dr. Paul Lombardo

CASE 5, EARLY 1900s: A CALL FOR RESTRAINT IN EXPERIMENTATION

Around the same time, at the beginning of the 20th century, a surgeon writing in the *Boston Medical and Surgical Journal* condemned "over-confidence in the benefits to be derived from mechanical interference and an unrestrained enthusiasm for doing something tangible and heroic."[10] He urged his colleagues to "be brave enough to refrain from the mutilation and suffering caused by too late and hopeless operations."[10] He noted the habit of experimentation with new methods, arguing that advances in surgery led to a disproportionate focus on surgery as an art and too little attention to surgery as a science.

These arguments from a century ago make clear that today's debates about the evidence required to move forward with innovative procedures are certainly not new.

CASE 6, 1913: COMPLEX INSTITUTIONAL MOTIVATIONS

In his 1913 book, *The Modern Hospital: Its Inspiration, Its Architecture, Its Equipment, Its Operation*, Dr. John Allen Hornsby wrote:

> Benefactors of institutions, before giving their money, will want to know just what care the poor… are actually receiving at the hands of the institutions asking for their aid….Yet there must be a difference between the service given to a millionaire and a pauper, but that service should be wholly of the luxuries. The pauper need not have broiled quail and asparagus tips for dinner, and he need not have a private room with adjoining bath, with roses on every stand and the odor of perfumes scenting the room; but these extras should be the only ones that the man of millions should have that the pauper should not have; and patrons of wealth and refinement and of humanitarian instincts will give thousands annually to the institution where they know the poor are getting everything a rich man can get that is needful, where they will give begrudgingly a few paltry dollars to the institution that they know is neglecting the wants and welfare of the poor.[11]

While this excerpt is notable for Hornsby's eloquence in arguing for meeting a standard of care for the poor, it is just as notable for demonstrating how complex Hornsby's motivations were. Not only should we care for the poor, but we have to do it right or the institution will not get money from the rich. In other words, "give the donors what they want." Then, as now, it took large sums of money to run institutions, as well as to put new innovations in place. And then, as now, institutions had to grapple with complicated motives.

SAME ISSUES, NEW CONTEXTS

This historical review makes clear that the ethical issues we face today are not new. The foundational questions about the ethics of biomedical research as applied to surgery consistently revolve around consent, how thoroughly to inform patients, the use of vulnerable populations as research subjects, distinguishing between experimentation and therapy, and, of course, money and the best use of resources. Variations on these questions continue to loom for surgeons and other physicians.

An economic value perspective: Setting limits on health care can be ethical

By Peter A. Ubel, MD

I am a fan of innovation: my patients benefit from it every day. But I am also concerned about the cost of health care. In the Veterans Affairs health system, I see patients who cannot afford their medications and who cannot afford to get private insurance; such problems are largely due to the high cost of health care.

As an example, consider a new pharmaceutical innovation, bevacizumab (Avastin), which costs approximately $106,000 per year when used to treat lung cancer.[12] On average, the treatment leads to a 2-month increase in survival, making the cost of this intervention more than $600,000 per quality-adjusted life-year. Or consider the use of a left ventricular assist device rather than medical management for patients with congestive heart failure who are not eligible for transplantation. The estimated cost is approximately $900,000 per quality-adjusted life-year.

These examples illustrate that some benefits to patients can come at a very high cost. For this reason, I believe that we need to set limits in (ie, ration) health care. I will outline here why we need to do so and why third-party payors—both government and private insurance companies—need to consider the cost-effectiveness of health care interventions in deciding whether to pay for them. In the process, I will discuss common thresholds for defining the price of life and explore whether special moral considerations are required for life-saving treatments—ie, whether the price of life should be higher for severely ill patients.

We hate making difficult decisions, both as individuals and as a society.
—Dr. Peter Ubel

WHY IS IT TIME TO RATION MEDICAL CARE?

Spending on health care in the United States has risen steadily in the last few decades both in real dollars and as a percentage of the gross domestic product. One important reason for setting limits on health care spending is that we have other things to spend our money on. Medicare budgets compete with tax cuts, education, military spending, homeland security, and many other national interests. Economics teaches us that we have to make difficult choices: when we spend more on health care, we have less money to spend on other things.

Cost-effectiveness analysis provides insight on why it is important to set limits. When I trained at the Mayo Clinic, we used to send patients home with six fecal occult blood test cards to screen for colon cancer. (Patients smear stool on a card and mail it to the laboratory, where it is tested for blood; if blood is present, the patient needs a colonoscopy. The six card samples are taken and mailed at periodic intervals to maximize sensitivity.) What is the cost-effectiveness of the sixth card? The answer is surprising: although the cards cost only a couple of dollars, the cost per life saved is an estimated $26 million, which most would agree is more than we can afford to spend to save a life from cancer.

Why is the sixth card so expensive? If any of the first five cards shows blood, the sixth card is worthless, as it provides no new information. On the other hand, if none of the first five cards shows blood, the chance is minuscule that the sixth card will show blood that actually comes from a precancerous lesion that can be removed and save a person's life.

This example illustrates that cost-effectiveness does not apply only to expensive new therapies like Avastin; it also applies to really inexpensive items like fecal occult blood test cards.

WHAT IS A YEAR OF LIFE WORTH?

If our own child were sick, we would say that a year's life is worth an infinite amount of money; we would do anything we could to save our child's life. But the job of the cost-effectiveness community is to address this question from a societal perspective, and they have a different answer. The most commonly cited view among experts in cost-effectiveness analysis is about $50,000 per quality-adjusted life-year, although it typically ranges up to $100,000.[13]

This figure has not risen with inflation, and it probably should not. If enough new technologies were developed at the threshold of $50,000 per quality-adjusted life-year, the entire budget of the country would quickly be used up.[14] Making payment decisions based on a certain cost-effectiveness threshold sets no real limit on health care spending. The threshold is not meant to be a realistic number but should illustrate the kind of thinking required about how much we want to spend on health care relative to other things. The aim is to help us decide how much "bang for the buck" we should expect from our dollars spent on health care.

WHAT DO PEOPLE VALUE WHEN SETTING LIMITS?

In light of the above, how do we set limits when trying to decide what the price of life is? Might our limit-setting be changed if we are facing a desperately ill patient? Examination of questions like these reveals that people value other factors beyond just economic efficiency, as can be illustrated with a couple of theoretical policy dilemmas.

Dilemma 1: Cost-effectiveness vs fairness

Imagine that the Medicaid program decides to screen for colon cancer. They have enough money either to offer an inexpensive test ("Test 1") to everyone and save 1,000 lives or to offer a more expensive test ("Test 2") to half the population (selected randomly) and save 1,100 lives.

If the decision were made according to rational cost-effectiveness principles, the choice would be to go with Test 2 in half the population, as it saves 10% more lives and thus maximizes the average health of the population. However, a survey found that the option of offering Test 1 to everyone was favored by 55% of the general US public, as well as by 55% of medical ethicists and even by 45% of cost-effectiveness experts, all of whom were willing to give up some cost-effectiveness for fairness.[15]

Resistance to limiting treatments that are not cost-effective is psychological and political, but it is not ethical.

—Dr. Peter Ubel

This tendency to favor fairness suggests that moral considerations affect health policy decisions in important ways. Yet further analysis raises questions about the extent to which these considerations are based truly on moral values as opposed to psychological quirks.

For instance, my colleagues and I presented this same choice of colon cancer testing scenarios to a separate survey sample, and again a highly similar rate of respondents—56%—favored offering Test 1 to the full population as opposed to offering Test 2 to half the population. However, to test whether this preference for equity over efficiency persists when neither test can be offered to the entire population, we changed the scenarios for a separate group of randomly selected participants. In one version of the scenario, we told participants that only 90% of the population could receive Test 1 and only 40% could receive Test 2. (As in the original scenario, we indicated that Test 1 saves 1,000 lives, whereas Test 2 saves 1,100 lives.) With just this small variation in test availability, the proportion of respondents favoring Test 1 plummeted to 27%. Similarly, we randomly selected another group of participants to receive a third version of the scenario, in which 50% of the population could receive Test 1 and 25% could receive Test 2, saving 1,000 and 1,100 lives, respectively. Once again, the proportion of the respondents favoring Test 1 remained low (28%).[16]

These results suggest that people's preference for equity versus efficiency depends, in large part, on whether the more equitable option can be offered to everyone in a population. But people's preferences are actually not nearly that coherent. Consider a follow-up study in which we repeated the scenario again for each respondent, but with a twist.

In one group, we began with our original scenario: 100% of the population can receive Test 1, saving 1,000 lives, or 50% can receive Test 2, saving 1,100 lives. As expected, 60% of participants chose Test 1. But then we told this same group of participants that the number of people qualifying for Medicaid had doubled, so that the tests could be offered to only 50% and 25% of the population, respectively (still saving 1,000 and 1,100 lives, of course, since the population was now twice as large). Remember that when people were *initially* presented with this 50% versus 25% option (without any other scenario being presented first), the preference for Test 1 plummeted. In this case, however, almost no one changed their mind: the majority (60%) still favored Test 1.[17]

People's preferences for how to allocate scarce health care resources—the moral values that they believe should guide our health system choices—are often disturbingly arbitrary.[18]

Dilemma 2: Targeting severe vs moderate illness

Now imagine a new scenario. A treatment is available that will help patients with an illness that causes severe health problems, but it provides only modest benefit. Another treatment helps patients with an illness that causes moderate health problems, and it provides considerable benefit. The cost of the two treatments is the same. How should funding be allocated?

Although a majority (60%) of survey respondents say that most funding should go toward treating the moderate illness where considerable benefit is expected, a sizeable share of people (40%) favor devoting most funding to the severe illness despite the more modest benefit.[19] This is another instance where moral values seem to come into play, as a large minority will favor helping the severely ill even at the expense of efficiency.

A variation of this dilemma illustrates another salient point—that people like "easy outs." When we present people with an additional option—"How about spending money equally between the two treatments?"—the vast majority (75%) choose that "compromise" option over the option of devoting most funds to either of the individual illnesses.[19] The lesson is that we hate making difficult decisions, both as individuals and as a society.

COST-EFFECTIVENESS IS THE MOST RATIONAL AND ETHICAL WAY TO SET LIMITS

These surveys make clear that many of the moral values that people express are fragile at best or even psychological quirks. I have heard no compelling moral arguments to support treatments that cost more than $500,000 per quality-adjusted life-year, which leads me to conclude that many new medical interventions are unaffordable. The resistance to limiting such treatments is psychological and political, but it is not ethical.

The appropriate response is for third-party payors, such as Medicare and insurance companies, to let industry know that cost-effectiveness matters. If a treatment is not cost-effective, it should be limited to people who pay out of pocket or for experimental purposes. To make this happen, we need cost-effectiveness analyses of new technologies. Because such studies are expensive and time-consuming, we should develop new incentives to motivate companies to conduct such studies of their products, perhaps by extending patent protection for products that are shown to be cost-effective. We need to work with industry on how to implement such a plan. But continuing to ignore the cost-effectiveness of interventions when they come to market is harming patients who can no longer afford insurance, which has real consequences on people's health and well-being.

An industry perspective: Proactive self-regulation through an industry code of ethics

By Christopher L. White, Esq

I serve as general counsel of the Advanced Medical Technology Association (AdvaMed), a Washington (DC)-based trade association that advocates on behalf of the medical device innovation community. Most of the approximately 1,600 companies we represent are small, having fewer than 100 employees. All of our member companies have a great interest in creating an environment that will sustain innovation to fuel additional benefits in patient care.

PHYSICIANS AND THE DEVICE INDUSTRY: INTERACTIONS ARE MANY, VARIED, ESSENTIAL

As noted earlier in this session by Mike Mussallem, who serves as chairman of AdvaMed's board of directors, the medical device industry is very different from the pharmaceutical industry. Device innovation requires a great deal of collaboration with physicians in the field. Moreover, devices are not simply prescribed—they are *used*. That is, many of the inventions are an extension of the surgeon's hand, such that technique influences how devices are deployed and used. As a result, with each incremental innovation, there is often a need for retraining.

Physicians wear many hats in their relationships with the medical device industry. Not only are they purchasers of products but they are collaborators, inventors, trainers, and trainees. They are also recipients of charitable contributions and of research grants. We recognize that these multiple relationships can become intertwined and, from a distance, can arouse confusion or suspicion. But simply because these relationships exist does not mean that there is a conflict of interest—there may be dualities of interest. In most cases we have a common interest and are working toward a common objective: to provide care in the best interest of the patient.

THE ADVAMED CODE OF ETHICS

The key question from industry's perspective is how best to manage these relationships with physicians and any potential conflicts of interest. To that end, AdvaMed has developed a code of ethics to provide guidance relevant to the most common interactions between device manufacturers and health care professionals.[20] The AdvaMed code has been adopted by international device trade associations and embraced or cross-referenced by physician specialty societies.

Although the AdvaMed code has become a "gold standard," it is a living document, and we are in the process of reviewing and revising it in an effort to address challenging new issues such as royalty payments, among others, which have become the focus of public questions and scrutiny.

MOVING FORWARD AFTER THE JUSTICE DEPARTMENT DEFERRED PROSECUTION AGREEMENTS

Recently, five orthopedic hip and knee implant manufacturers entered into novel deferred prosecu-

tion and non-prosecution agreements with the US Department of Justice following a Justice Department investigation into financial relationships and consulting agreements between these companies and orthopedic surgeons. The agreements include the appointment of federal monitors to review virtually every transaction that these companies have with physicians. These agreements impose a level of governmental review over the device industry that has never been seen before.

The agreements also require the five companies to disclose on their public Web sites all payments made to physicians. The disclosures must follow a specified format listing each physician's name and location, the amount of the payments, and limited information regarding the purpose of the payments (eg, for consulting, royalties, charitable contributions, research grants). This requirement has created much interest as well as a good deal of confusion.

If passed, the Physician Payments Sunshine Act would require that virtually all payments from industry to physicians be reported to a federal database.
—Christopher White

These developments have also spurred AdvaMed to work aggressively on federal and state legislative efforts. We are taking a proactive position on the disclosure of financial arrangements between industry and physicians in the context of the proposed Physician Payments Sunshine Act mentioned earlier by Mike Mussallem. If passed, this legislation would change the landscape by requiring that all pharmaceutical and device companies report to a single federal database all transfers of value or other payments, subject to certain exceptions, from industry to physicians. Similar to the federal agreements with the orthopedic implant manufacturers, the bill would require that the name and location of the physicians receiving payments be disclosed, along with the payment amount, but with greater context regarding the purpose of the payment. AdvaMed has been advocating for providing detailed explanations of this context so that everyone, including the public, can understand why such payments are made and how they can be beneficial.

Panel discussion

Moderated by Lawrence K. Altman, MD

Dr. Lawrence Altman: Let us start by opening the discussion to the audience.

Comment from audience: Considerable discussion has focused on the conflict between regulation and innovation, but I find very little evidence that such a conflict actually exists. It was pointed out that the United States is by far the biggest producer and user of medical devices and has been since World War II. Economists estimate that 50% of the growth of the US economy since then has resulted directly from innovations in science and technology. During that same period, the regulatory apparatus—including the FDA—has vastly expanded. Apparently, innovation has not been stifled by regulation but actually seems to thrive in a regulated environment.

I speak often with venture capitalists who finance science technology. They know this history, and they know that regulation is inevitable. Rather than opposing it, they want clarity about regulation. For instance, many of them avoid financing human embryonic stem cell research because the rules around it are not clear, owing to the stigma and political controversy surrounding it.

Michael Mussallem: You make great points. People who invest in medical innovation would like an idea of the rules before they make investment decisions. And good, solid regulation—such as when the FDA pushes companies for the kind of science and evidence needed to clear a hurdle—is absolutely appropriate. But as regulation increases, the time and costs to bring an innovation to market increase. At the moment, the innovation equation is fragile. When too many obstacles are put in the way, the risk of failure becomes too high.

Keep in mind that the success rate in innovation is low. Although I have been in this field my entire career, it would be much easier for me to hit a major league fastball than it is to successfully innovate in medical technology. We are wrong many more times than we are right. For every success, there may be 9 failures, or 19 failures, or even 99 failures.

Rebecca Dresser: I agree that regulation sometimes does not effectively advance its goal. When that is the case, I think we need to be willing to negotiate rather than condemn; we need to show where regulation is not meeting agreed-upon goals (such as pro-

tecting patients) and figure out how to reach those goals more efficiently.

We also should keep in mind the cliché, "If professions do not adequately self-regulate, external regulation will come in." Perhaps that is what has happened. Professionals need to self-examine and organizations need to develop voluntary standards to help avoid stupid regulation.

Christopher White: We need to be mindful of the unique relationships that we have within this niche sector of the health care industry. Issues that might not appear to threaten us directly may have unanticipated implications. Some of the barriers that regulation can impose may not be immediately perceptible and can be masked by otherwise beneficial public policies. For example, we now have a patent reform debate on Capitol Hill promoted by the information technology industry as pro-innovation, but in the context of the life sciences industry, many of the proposed patent reforms threaten innovation by devaluing device improvements.

Also, much of the regulation the device industry confronts is responsive to dynamics in the pharmaceutical industry. For example, one house of the Massachusetts legislature recently passed a bill that would ban gifts to health care professionals and require licensure of pharmaceutical and device sales representatives who work in the state. The term "gift" is defined very broadly and could include not only meals and the other things that we read about regularly but also rebates, educational grants, and training. *[Editor's note: A modified version of this legislation was signed by Massachusetts' governor in August 2008 and will take effect January 1, 2009.]*

The success rate in innovation is low. Though I have been in this field my entire career, it would be much easier for me to hit a major league fastball than to successfully innovate in medical technology.
—Michael Mussallem

Question from audience: As a practicing surgeon, I think the major problem lies in the area of off-label use. If one accepts that the device manufacturer is well-intentioned and living up to the AdvaMed code of ethics, the system falls apart once the device has cleared the hurdle of FDA approval for a labeled indication. The product then reaches the broad market, where it is subject to commission-based sales. Whether or not to use the device in innovative ways is generally at the discretion of the physician, until it reaches the threshold of research and institutional review board approval. We have virtually no postmarket surveillance by the manufacturer. At what point is the manufacturer culpable for the off-label use of its product when patients are harmed and no surveillance exists until enough casualties occur that the problem becomes obvious?

Mr. Mussallem: Put yourself in the shoes of a physician who is facing a difficult situation that has not been studied and is outside the realm of any approved, "on-label" therapies. A classic case is for children with congenital heart defects. Since no one advances a medical device for such small patient populations, physicians treating such cases are forced to be creative. They take devices that were intended and tested for adults and apply them to a child. Do you punish those physicians? Do you punish the company that created the devices?

When you look at the question down at this level, where it becomes quite practical and quite personal, the issue of off-label use takes on a different color. In many ways, it comes down to how much we trust physicians and to what extent we think they should be regulated. I would want to give physicians the freedom to try to do what is best for their patients and to use their judgment to apply a device in a different way—one that they understand has not been tested or approved for that use. But I would also want transparency: I would want them to explain to the patient (or the parents) what is known and unknown about the situation. It is in the absence of that transparency that you enter dangerous ground.

Paul Lombardo: When a new law is passed or a new regulation comes down, it is usually in response to a scandal: something bad enough happened to scare everyone to death. If I were advising industry, I would tell them to go to any length to avoid the kind of scandals that we have seen that challenge the trust of the public. So I agree that transparency is critical. It is one thing to say, "I am trying to do what is best for my patients and trying new things because I do not have access to tools especially designed for children." But when we find out that a doctor or a manufacturer has hidden data about a method of using equipment that has never been approved, and is covertly pushing that use, the predictable result is that somebody will want to regulate it.

Ms. Dresser: Of course, malpractice suits are an option, but they will cover only a few cases, generally the most extreme ones. I think the greatest need

is for information gathering. The medical profession should think about how to encourage data collection for off-label use so that problems can be detected earlier than they are now. This type of data collection is also in device manufacturers' best interest, as it helps to avoid scandal.

Another approach is to extend the patent exclusivity of products whose manufacturers conduct trials in underserved patient populations, thus providing a financial incentive to do such studies. This approach has in fact been adopted in the case of pediatric trials and for orphan diseases. Interestingly, some pediatric trials prompted by this patent extension incentive have shown that certain medications or dosages previously accepted as standard medical practice turned out to be harmful in children once they were formally studied.

Dr. Altman: What about proposals to use published literature—which also is subject to abuse—as a criterion for off-label use?

Ms. Dresser: Peer-reviewed journals do not have access to raw data, which can be manipulated in a lot of ways, so they cannot completely substitute for FDA review. Recent articles in *JAMA* addressed these concerns.[21,22]

Comment from audience: There seems to be a misguided desire to look to our regulatory agencies to tell us how we should manage a patient. As a practicing surgeon who does minimally invasive procedures, I never look to regulatory agencies to tell me what the optimal therapy is for a patient; rather, I look to them to tell me whether a product is a therapeutic option for a patient, and then I use my judgment to decide whether it is the best option for this particular patient.

Consider how Britain's National Institute for Clinical Excellence (NICE) has approached drug-eluting stents. They looked specifically at off-label uses of these stents and determined that the stents confer a benefit in these off-label areas, based on subgroup analysis. But then they did a cost-effectiveness analysis and determined that the benefit was not great enough to offset the cost to society based on the quality-adjusted life-years gained. Well, that may be a fine theoretical discussion, but when I am sitting in front of a 75-year-old who I think will do better with a particular device, it is hard to be concerned about whether it is on label or off label, or does or does not meet cost-effectiveness criteria.

Some of the barriers to innovation that regulation can impose may not be immediately perceptible and can be masked by otherwise beneficial public policies.

—Christopher White

Mr. Mussallem: This comes back to the trust that we have in our physicians. Should product manufacturers be allowed to hand out peer-reviewed journal articles? If physicians are provided with those articles, does that provide too much information for them and steer them inappropriately? Well, if physicians single-mindedly made such articles the sole basis for a treatment pattern, then it absolutely would be inappropriate, but we should give physicians a little bit of credit. Their job is to take a tremendous amount of data—everything that they have learned through their own experiences, plus journal articles and other sources—and apply it to design the best course of treatment they can for a specific patient.

If we try to overprescribe how a physician behaves, we will find it is too complex to regulate or legislate from the top. We should have a lighter hand and design incentives appropriately so that physicians are first and foremost motivated to take care of the patient. We should not try to tell them too much about exactly how to practice; after all, a large study that finds that one treatment has a 62% chance of being superior does not prove that it is the best treatment for a specific patient. You always want to preserve physician judgment.

Dr. Peter Ubel: I agree, but if we are to avoid overmanaging the day-to-day decisions that doctors make, we doctors also have to think more broadly about our responsibilities. If our duty is only to the patient in front of us, we can ignore being told that a treatment offers only a very small benefit for the cost. If we doctors say that it is not our job to be mindful of costs, then somebody is eventually going to have the job of telling us when we can and cannot use those stents, as a way to rein in costs because no one can afford insurance anymore.

For physicians to maintain more room for our judgment in influencing clinical practice, we have to remember that we are stewards not just of individual patients but of the general health care system. The cost of technology plays a huge role in driving up the cost of medical care.

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New surgical devices and ethical challenges:

A collection of perspectives and panel discussion

An FDA perspective on device regulation

By Daniel Schultz, MD

As a surgeon, I know that not making a decision actually amounts to a decision in itself. In my current work with the Center for Devices and Radiological Health (CDRH) at the US Food and Drug Administration (FDA), there are times when we may not have all the information that we feel we need to make a decision but we are obligated to make one anyway. We try to apply a risk-based approach that makes the most sense for patients and for public health. Surgeons probably appreciate this method better than most people do, as they do risk-benefit analyses many times a day and do so almost subconsciously. In the government we have to do so in a more transparent and explainable way.

FDA MISSION ADDRESSES THE FULL PRODUCT LIFE CYCLE

The CDRH mission encompasses the entire life cycle of a device, from encouraging product development, to ensuring postmarket safety, to enabling access to innovation. Our mission is threefold, as outlined below:

- **To get safe and effective devices to market as quickly as possible.** This is a balancing act. On one hand, some people feel that "as quickly as possible" is not fast enough, yet safety and efficacy obviously need to be established. On the other hand, if we wait to be absolutely certain that a new device is safe and effective, large numbers of patients may miss out on potentially benefiting from it in the interim. We try to analyze risks and benefits, and also to bring some common sense to the analysis. Our review process draws on whatever mix of expertise is necessary for evaluating a given product, so we consult with statisticians, engineers, physicians, and other experts as needed. In addition, the CDRH has a medical device fellowship program that brings in experts from academic settings—including physicians, biomedical engineers, computer scientists, statisticians, and law and policy experts—to contribute expertise in the evaluation of cutting-edge technologies.[1]

The CDRH attempts to work with companies prior to submission to understand their technology, what they intend to do, and the population for which they intend their product. We aim for clarification rather than overregulation: our goal is to make the pathway as clear as possible to increase the likelihood that we will get the information we need to make a decision, to give companies a good sense of what to expect, and to promote mutual understanding.

- **To ensure that devices currently on the market remain safe and effective.** We are all well aware of cases in which questions are raised about safety or efficacy after a product has gone to market. From the FDA's perspective, interpreting and dealing with postmarket data can be very complex.

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Dr. Greenberg reported relationships with Cook Inc (consultant, intellectual property rights, grant/research support), W.L. Gore (grant/research support), Boston Scientific (consultant), and TeraRecon (grant/research support). All other authors reported that they have no financial interests or relationships that pose a potential conflict of interest with this article.

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• **To provide the public with accurate, science-based information about devices.** Communicating postmarket data to the public adds another level of complexity. For example, not long ago questions arose about serious adverse events related to implantable cardioverter-defibrillators (ICDs). Because of publicity about these questions, many people who needed an ICD did not get one and many others had their ICDs replaced with a different model. Subsequently, a study in Canada showed that the risk of ICD replacement far outweighed any risk that was inherent in the product.

We can all agree that transparency and timely sharing of information are important, but exactly how to carry these things out is a challenge. When the FDA, as a government agency, makes a statement, it carries additional weight, so we try to be very careful about sending the right message to physicians and to patients.

Finally, we use the information that we gain in the postmarketing period to guide our regulation of the next generation of products, which contributes to all three broad aspects of our mission.

AS DEVICES GET MORE COMPLEX, NEW REGULATORY QUESTIONS ABOUND

It used to be that when people thought of medical devices, they pictured mechanical tools. Now, however, we deal with a huge variety of different types of technology, including computer-related technology, molecular medicine, robotics, minimally invasive techniques, microelectromechanical systems, nanotechnology, organ replacement, and wireless systems.

If the FDA waits to be absolutely certain that a device is safe and effective before approving it, many patients may miss out on its potential benefits in the interim.
—Dr. Daniel Schultz

Not only is the technology new, but the way in which it is used is increasingly novel: devices are being used more and more in nontraditional settings, such as home care, and by nonclinicians who do not normally use medical devices. Can decisions about regulating a medical device that is safe and effective when used by a physician in the hospital be applied to its use by a relative caring for a 90-year-old patient in the home?

In addition, we now see combination products that increasingly blur the distinctions between medical devices and drugs. Genetic biomarkers have implications for the development of new drugs and for the refined use of existing drugs. One example is a test—already in existence—to assess individual patients' sensitivity to the anticoagulant warfarin. There are also drug–diagnostic combinations in which a drug is developed along with a companion diagnostic test.

We are probably seeing just the beginning of these combined diagnostic and therapeutic systems as we move toward the concept of personalized medicine. When we consider the current challenges in designing appropriate clinical trials for specific populations and for off-label uses, it begs the question of how much more difficult trial design will be as technology moves closer and closer to individualized therapies for each patient.

FDA'S APPROACH TO MEDICAL DEVICE REGULATION

Our approach to medical device regulation is based on a number of objectives and principles:

- Basing the degree of control or oversight on the amount of risk with a given device
- Weighing risks and benefits to determine safety and effectiveness
- Using valid scientific evidence, which involves looking at clinical outcomes while recognizing that our mandate is not to regulate the practice of medicine
- Considering the "least burdensome means"—ie, being open to any of several acceptable approaches that answer the pertinent regulatory questions (not, however, giving license to cut corners in submissions)
- Providing "reasonable assurance," recognizing that "reasonable" is in the eye of the beholder and that the agency and applicants may not always agree on its meaning.

Other key elements: Intended use, adequate labeling

Beyond these principles, the FDA's approach to regulating device safety and effectiveness gives priority to at least two other key elements: specifying a well-defined intended use and ensuring adequate labeling. Sometimes applicants who are proposing a new device are very excited about their new technology but are not very specific about exactly how it will be applied to patients, so we need to focus them on clearly defining the intended population and the expected impact on patients. Similarly, device labeling must be developed to contain as much information as possible to help physicians make good choices without overpromoting the product or going beyond the submitted data.

Classifying devices

To ensure that appropriate oversight is applied to different types of medical devices, the CDRH uses a product classification system that differs from that used for drugs and biologics. It breaks down as follows:

- Class I devices, which are very simple (eg, gloves) and most of which are exempt from premarket submission
- Class II devices, which are subject to some special controls and require premarket notification (510[k] submissions)
- Class III devices, which are the highest risk and tend to be the most cutting edge. They require premarket application and approval.

There are two additional classifications:

- **De novo devices,** which have never been marketed in the United States but have a safety profile and technology that are reasonably well understood. Prior to the creation of this classification, a cutting-edge technology would have automatically been deemed Class III and required to go through the premarket approval process. Now a novel product may be recognized as lower risk and can be placed into its appropriate classification immediately.
- **Humanitarian device exemption,** for devices that address orphan diseases (conditions that affect fewer than 4,000 patients per year in the United States and thus may not offer an economic incentive for technology development). The motivation here is to help facilitate getting products to market for underserved niche patient populations with the understanding that some regulatory controls may be added.

We are probably seeing just the beginning of these combined diagnostic and therapeutic systems as we move toward personalized medicine.
—Dr. Daniel Schultz

Postmarket surveillance

The CDRH is working to make postmarket surveillance a stronger part of our program. In the past, people questioned whether the required postapproval studies for devices were actually getting done. Over the last few years, epidemiology staff from our premarket approval area helped design better postmarket studies, and we then transferred tracking and follow-up to the postmarket staff. In 2006, we issued a final guidance to manufacturers about how to submit follow-up reports and we developed a public Web site containing the postmarket studies that are required, including start dates, when reports are due, and whether studies are on schedule.[2] This helps us to have a transparent process and also prompts companies to follow through with agreements.

RISK/BENEFIT ASSESSMENT: REAL-WORLD EXAMPLES

The risk/benefit assessments undertaken by the FDA range from straightforward to highly complex. Devices that are life-sustaining have much potential for significant benefit, which makes most people willing to accept more risk. On the other hand, it can be difficult to quantify the benefit of cosmetic procedures (many of which we regulate), and people are less willing to tolerate risk for these procedures. Consider the handful of examples below.

Drug-eluting stents

When the CDRH first evaluated drug-eluting coronary stents, the data showed a greater than 50% reduction in the need for repeat interventions compared with bare metal stents, as well as low rates of complications. People asked us, "Why is it taking the FDA so long to approve them?" Soon after their approval, drug-eluting stents became the standard of care for about 60% of patients undergoing percutaneous coronary intervention.

Five years later, studies started showing some long-term complications, although the absolute risks and benefits are still not known with certainty. If we had spent another 5 to 10 years studying these devices, a lot of these questions might have been answered, but at what cost to those patients who actually benefited from this technology in the interim?

Cardiac occluder

Although studies showed that the muscular ventricular septal defect occluder had a high procedural success rate (81%), the adverse event rate was also very high: 44%. But because this device is for patients who have no treatment alternatives other than open-heart surgery but are considered to be at high risk from surgery, the risk/benefit assessment favored approval in this case.

Total artificial heart

The total artificial heart went through the humanitarian device exemption process. It is intended for patients with severe biventricular end-stage heart disease who are not candidates for transplant or a left ventricular assist device and are thus essentially at the end of life with no other treatment options.

Although studies showed that the device helped extend life, whether quality of life improved enough to support approval was in question. The device is

clearly not benign: out of 12 patients studied, support was withdrawn secondary to cerebrovascular accident in 6 of the patients. Four patients died of multiorgan failure or sepsis, and all patients had bleeding complications. However, 10 of the patients were able to interact with family members and 4 patients were able to have out-of-hospital activities.

How does one balance this ability to extend life for perhaps a few months—allowing patients to have additional time with their family, maybe to see a grandchild's birthday or attend a wedding—against all of these attendant adverse events?

Breast implants

Saline-filled and silicone gel-filled breast implants are designed for breast augmentation and breast reconstruction. Two saline-filled implants were approved in 2000 and two silicone-filled implants were approved in 2006, but only after complicated regulatory histories. Breast implants were first marketed in the early 1960s and were later "grandfathered" into the FDA's regulatory scheme upon passage of the Medical Device Amendment of 1976. They were classified as Class III devices in 1988, and the FDA called for submission of a premarket approval application in 1991 after the emergence of many reports (but scant solid clinical data) of adverse events related to these devices.

Over this period, breast implants became a considerable regulatory, scientific, and political controversy, for good reason: they are not life-saving devices, yet they involve a lifetime commitment. How much clinical data and how much follow-up should be required? What should be the end points for studies? The FDA cannot determine the value that a woman puts on breast reconstruction or augmentation. What is clear is that adequate informed consent is critical, including a thorough explanation to patients of the benefits, the risks, and the nature of their commitment.

DILEMMAS MOVING FORWARD

Several dilemmas arise out of the FDA's mandates. Although our mission is to ensure product safety and effectiveness, what about patient autonomy? What about the rights of patients to be able to choose the therapies they want? While we are required to protect the public health, what if that conflicts with making products available?

Advertisements are another big challenge. We recently held a panel meeting on the LASIK eye procedure that included some very heart-wrenching stories told by patients who have had bad experiences. Part of the problem is how such procedures are advertised, without a balanced message about potential risks and benefits. People end up with the impression that the procedure is almost like getting their hair cut. Advertisements in newspapers and on Web sites tout a special price "for this month only," exhorting patients to get the procedure done immediately. The surgeons who place such ads are at least as responsible for the problem as industry is, if not more so.

Responsibilities of the media, FDA, and professional societies

By Mary H. McGrath, MD, MPH

My experience with the FDA during the regulatory controversies over breast implants, mentioned above by Dr. Schultz, was the crucible in which my views about devices and the ethics of surgical innovation were forged. My comments here will focus on observations from that experience and then on the function of journalism in these issues, the role of the FDA, and the positive part that professional societies can play as we grapple with emerging technologies.

BREAST IMPLANTS: A CASE STUDY IN REGULATORY COMPLEXITY

A long and winding path to approval

Although breast implants had been on the market in the United States since the early 1960s, they did not fully come onto the FDA's radar screen until 1991. The FDA had not been authorized by Congress to regulate medical devices until 1976, and at that point, other devices had higher priority. By the time of the first FDA panel hearings on breast implants, in November 1991, an estimated 1 million women in the United States had breast implants.

The 1991 hearings were driven largely by anecdotal reports in the literature suggesting a possible association between breast implants and rheumatoid and autoimmune disorders. As a plastic surgeon who specialized in breast reconstruction, I was a member of the panel for the hearings. The wave of public concern and the paucity of evidence in support of safety led then-FDA commissioner David Kessler to call for a moratorium on the use of breast implants in January 1992. Three

months later, the FDA ruled that implants would be limited to use only in clinical trials.

These actions produced a panicked response from the public, with silicone gel-filled breast implants being removed from more than 100,000 US women in the ensuing 2 to 3 years. People do not often consider the risk created by patients going back for surgery based on the fear resulting from a ban.

A huge class action lawsuit was brought against implant manufacturers, which culminated in Dow Corning—the largest manufacturer of implants at the time—abandoning the implant business and settling the suit for millions of dollars. Only two of five manufacturers continued to make breast implants, both of which manufacture them outside the United States.

Meanwhile, subsequent studies required by the FDA were gradually completed, leading the agency to approve saline-filled implants for marketing in 2000. In 2006, the agency approved silicone gel-filled implants after reviewing 553 studies that collectively demonstrated no association between these implants and systemic disorders. Both types of implants are marketed today, yet FDA approval carried some special conditions. Core study patients were to continue to be followed with magnetic resonance imaging screening through at least 9 years. Implant manufacturers were required to submit annual reports to the FDA, and a device retrieval program was set up. An implant registry also was established for postmarket surveillance. The registry was developed in collaboration with the FDA and professional societies, which also have developed content for formal patient education and professional training programs mandated as conditions of marketing approval.

Medical professionals have a responsibility to educate the public about emerging technology.

—Dr. Mary McGrath

Interest groups and the media: Fully in the mix

A multitude of interest groups were present and vocal throughout this entire episode, from the hearings in 1991-92 through the hearings leading up to the most recent approvals in recent years. In addition to obvious stakeholders, such as manufacturers, surgeons, and patients, the media packed the large hearing rooms and interviewed a wide range of interested parties, including investment fund managers, patients, and implant opponents. Groups such as "Fathers Against Breast Implants" typified the frustration that people felt about the sexualization of the culture. Every day, the panel hearings became front-page news.

FDA approval had an immediate market effect, and implant sales surged. At the same time, the media raised questions about whether the FDA's regulatory approach of requiring reasonable assurance of safety was sufficient and whether a higher level of evidence for safety and efficacy should be required for this type of device. News stories also examined societal ethics about quality of life and how much medical risk people should be allowed to accept for the sake of cosmetic procedures.[3–5]

THE ROLE OF THE PUBLIC—AND JOURNALISM

The case of breast implants illustrates the important role that the media can play in how emerging medical technologies are greeted, but this role should be viewed in the broader context of the key relationships involved in the development and use of surgical devices. Central to device development and use, of course, is collaboration between the medical profession and industry, as discussed at length earlier in this conference. I would like to focus now on two other major players that influence device development and use—the public and regulatory bodies (ie, the FDA).

Medical journalism falls short on two core principles

A key determinant of public views of new devices and other medical technologies is the discussion of those technologies in the media. Medical science has become increasingly publicized in both print and electronic media in recent years in response to high levels of public interest in medical news. In 1998, the *New England Journal of Medicine* published a lecture by medical journalist Dr. Timothy Johnson on the relationship between medicine, the media, and the public with regard to emerging devices and other products.[6] Johnson argued that in the rush to satisfy the public hunger for medical news—and also to promote themselves—journalists and medical scientists have failed to adhere to some core principles: that science examines collective data over anecdotal data, and that getting a story right is better than getting it first. Moreover, weakened adherence to these principles has been exacerbated by the proliferation of business-related medical communications (press releases, press conferences, advertising infomercials, and the like) from biomedical product manufacturers, medical centers, and even individual practitioners as they try to increase their market share in today's competitive environment.

Johnson pointed out that whereas journalists used to

present opposing viewpoints based on multiple sources, they now too often strive to be the first to report a medical story and to make it as forceful and dramatic as they can. Medical stories get more attention from the public, he noted, if they are unambiguous and use an anecdotal account to add "human interest."[6] These developments have been aided by the explosion in the number and type of news sources and the eclipse of journalists by public relations firms and—I would add from our 2008 perspective—bloggers.

Despite the challenge, potential solutions are at hand

Johnson argued that such excesses in the media are not in the public interest. Just as general news is based on facts, sources, and opinions, medical news should be based on data, probabilities, and conclusions. He proposed that medical reporters be required to undergo credentialing to demonstrate a background in biostatistics and epidemiology. Although this idea may seem radical, it has a precedent: meteorologists must be scientifically trained before reporting the weather forecast, a topic that is certainly no more important than medicine.

My view is that medical professionals have a responsibility to educate the public about emerging technology. Although we still do not require credentialing of medical reporters, we see more physicians contributing to the better broadcast and print media outlets. Some medical schools now offer training in medical journalism. In addition, the FDA has robustly implemented a directive to make public education a priority on its Web site.

The American Society of Plastic Surgeons now bans its members from exaggerating their skills or claiming to have been the first to use a new procedure when they give media interviews.

—Dr. Mary McGrath

Another hopeful sign is that some medical professional societies have begun to respond to issues like these through their codes of ethics. For instance, the society for my specialty—the American Society of Plastic Surgeons—has long had injunctions against false and deceptive advertising but now also bans exaggeration of one's skills or claims to have been the first to use a new procedure or device, whether in an advertisement or, notably, in a media interview. Members who commit such transgressions can be brought before our ethics committee and asked to account for them.

THE ROLE OF THE FDA—AND AN OPPORTUNITY FOR PROFESSIONAL SOCIETIES

Let me turn to the other major player in device development beyond manufacturers and the medical profession—the FDA.

The FDA's relationship is with the manufacturer; it has never been empowered to regulate the practice of medicine or the conduct of surgery. The FDA cannot dictate how a device is used (except via the manufacturer's product labeling) or which physician specialties may use it. Physicians may use a device off label, but a manufacturer that deliberately markets a device for an off-label use (outside of the conditions outlined by Rebecca Dresser in the previous session in this conference; see pages S63–S64) is subject to regulatory penalties.

Increasing need for training requirements in device approvals

In the last few years, however, barriers preventing the FDA from regulating surgical practice have begun to break down as it has become increasingly obvious that a surgeon's use of a device affects the performance of that device. For this reason, training in the use of a device must be integral not only to early development and clinical investigation but also to eventual use.

Until about 8 years ago, neither device manufacturers nor the FDA required end-user training. When such a requirement was first discussed, it was seen as an invalid effort to regulate medical practice. But a couple of gaps in this thinking eventually became obvious:

- Premarket clinical trials of a device are conducted at only a few institutions and by surgeons who tend to be very familiar with the product. This raises real questions about how transferable the resulting data are to broader clinical practice.
- Mishandling of modern devices, which are increasingly complex and delicate, can easily result in product failure, a problem that can be very costly and damaging to the manufacturer.

Recognition of such problems has prompted the requirement for physician training in the labeling of an increasing number of devices. For instance, tracking done by the American College of Surgeons showed that 2 years ago, 8 of 13 FDA-approved devices for use in general surgery were approved with training requirements. The details of these prescribed training processes have not been very specific, however, and even the general requirement for training raises a host of resulting questions:

- Who should do the training—the device manufacturer, hospitals, or professional societies?

- What should training consist of—a course? Should there be a certificate upon completion?
- Who can take the training? Should it be confined to specific surgical specialties?
- Who designs the curriculum? Who evaluates the quality of the training? Who determines if the trainees are adequately prepared at the end?

Lessons from the American College of Surgeons

I would like to address some of these issues by drawing from the recent experience of the American College of Surgeons, which formed its Committee on Emerging Surgical Technology and Education (CESTE) about 8 years ago. The charge of CESTE was to formulate a comprehensive approach to questions like these and develop guidelines and mechanisms for a threefold mission: assessing new technologies, educating surgeons on new procedures and technology in their postresidency years, and verifying that this training results in actual acquisition of new skills.

Technology assessment. Technology assessment has proved to be the Achilles' heel of the CESTE efforts, because it is a difficult and costly long-term proposition. This is particularly true of device assessment, as devices are frequently modified to introduce incremental improvements over time.

The American College of Surgeons has sponsored only one randomized clinical trial—a collaboration 12 years ago with the Veterans Administration to evaluate open versus closed hernia repair. The study was very successful, eventually producing 42 published papers. However, by the time the follow-up was finished, the research question was moot, as everybody knew that closed hernia repair was a fine and acceptable approach. Firsthand experience with the complexity, the expense, and the 10 years needed to complete this surgical technology trial convinced CESTE that undertaking primary assessment was beyond its scope. It has instead focused on becoming a clearinghouse for identifying new devices and procedures that are on the horizon and preparing surgeons for their arrival via its education mission.

Education. Education has been CESTE's greatest success. The committee has articulated goals for its courses with content and syllabi and has developed formats, instructors, and testing. Partnering with industry, CESTE has set up a number of skill centers around the country that involve cost-sharing, identifying learning needs, approving curricula and content, and assessing and verifying trainees.

Verification. Verification of education and training is necessary—documentation may be important for surgeons when requesting privileges—but is not always easy to do. Some components of training are easily verifiable: one can document that a physician attended a course, or one can ensure that didactic information was learned by using a written test. But demonstrating that someone actually acquired new skills is more difficult, and CESTE is just beginning to apply this level of verification to some of its courses. Ideally, CESTE will one day have a proctoring measure at trainees' home institutions to observe trainees actually applying their new skills in supervised clinical cases.

The first 8 years of the CESTE initiatives have been a learning process with more than a few challenges, but I believe the American College of Surgeons should be applauded for vigorously taking on the responsibility for training postgraduate surgeons in new and innovative technologies. I share its belief that professional organizations should serve this role, and this type of leadership from other medical and surgical societies will help address many of the challenges discussed earlier in this conference.

Promoting swift, safe, and smart innovation

By Thomas H. Murray, PhD

After listening to previous speakers at this conference, I am coming away with the message that we want a system for surgical innovation that is swift, safe, and smart.

In his keynote address, Dr. Thomas Fogarty, who will join us in this session's panel discussion, mentioned that people who want to develop a new technology need to actually talk with those who are working in and familiar with the field. That observation is a fundamental insight behind the interdisciplinary methodology at the Hastings Center, where we identify issues in bioethics, develop relevant questions, and seek out people with various kinds of knowledge and insight to provide as comprehensive an understanding of those issues as possible.

The Hastings Center draws from people who make public policy, from people who interpret policy (such as those at the FDA), and from innovators. Two mem-

bers of our board are biotech entrepreneurs who have created companies that make products that they hope will help many people. I have never found a shortage of people willing to talk to you. The real shortage is of people who are actually willing to listen. So we try to encourage that as well.

In his keynote, Dr. Fogarty also brought up some controversial issues surrounding conflict of interest. The Association of American Medical Colleges (AAMC) report[7] that he criticized was written by a committee that included me as well as leaders from the pharmaceutical and device industries, researchers who were developing new drugs and surgical devices, medical school deans, legal scholars, and ethicists. I stand behind that report and believe that it made a fundamental distinction between drug development and device development. This distinction—which has been pointed out earlier in this conference—is that drug development involves a lot of preclinical and clinical work but results in a product that can simply be given to a patient with simple instructions, whereas device development involves continuous innovation and improvement even after preclinical and clinical testing, and typically requires special expertise and training for proper clinical use.

WHAT DOES INNOVATION REALLY COME DOWN TO?

I see the challenge of innovation as a challenge to balance a number of things that we value: innovation itself, access to that innovation, respect for the human subjects who are part of the testing process, and regard for the patients who will ultimately benefit.

The challenge is to balance a number of things we value: innovation itself, access to innovation, and respect for both the human subjects who are part of the testing process and the patients who will ultimately benefit.

—Dr. Thomas Murray

We also need to acknowledge the realities of how innovative surgical devices and procedures are created and to foster a culture of innovation that incorporates every bit of wisdom we can gather. This includes insight into what motivates inventors, such as royalties, with which there is nothing wrong in principle. It also includes insight into how to bring helpful innovations to patients. For instance, what do investors look for before they put money into a company or a particular development? We also need insights into how institutions and bureaucracies work—including the dreaded committees, to allude again to Dr. Fogarty's keynote. I think we can all agree with the widely held insight, "Among democracy's many virtues, efficiency is not high."

A PERSONAL TAKE ON SUCCESSFUL INNOVATION

Last month marked the 25th anniversary of my Starr-Edwards valve, which replaced a Hancock porcine valve that calcified about 8 years after it was sewn into my heart. I would like to thank prior panelist Michael Mussallem of Edwards Lifesciences for his company's product, which has extended my life and the lives of many others. I am grateful to innovators and determined to ensure a healthy and vigorous culture of innovation in this country.

And I want that innovation to be swift, safe, and smart, though there are always tensions between these three values. The first two—swiftness and safety—are fairly straightforward: we should encourage creativity and innovation as much as possible, and we must respect the human subjects in whom we test new devices and the patients in whom we ultimately use them. But how can we ensure that innovation is smart? We must insist on a base of evidence that is as solid as possible while still being flexible. We also must learn which devices are the best matches for each patient.

Newborn screening is an example of one area that I have recently examined where innovation is fast proceeding in a way that might not be very smart. Recently we have seen a sudden and rapid expansion of the conditions for which newborns are screened. In many cases we do not know what action to take if test results are positive, and in some cases we have no known effective therapies. I have criticisms of the process by which this expansion was decided upon, but most experts—even those supportive of the expansion—agree that we need to become much smarter about systematically studying the new conditions being screened for. Similarly, we need to make our system of surgical innovation as smart as we can in terms of how we gather evidence.

Dr. Joseph Fins opened this conference by declaring, "Let the conversation begin." I will conclude it by saying, "Let the conversation continue, and let it be vigorous, candid, and respectful, with unfailing regard for evidence."

Panel discussion

Moderated by Roy K. Greenberg, MD

SHOULD INNOVATORS BE BARRED FROM USE OF THEIR INVENTIONS?

Dr. Roy Greenberg: Let us begin this roundtable portion of the session with any comments that our one additional panelist, earlier keynote speaker Dr. Thomas Fogarty, may have. Dr. Fogarty?

Dr. Thomas Fogarty: I agree with most of what was said, but one problem I have with the AAMC report that Dr. Murray refers to[7] is the implication that those who develop a technology cannot treat patients with it. If a physician knows more than anybody else about a device, and a patient is referred to that physician, he or she is obliged to take care of that patient. The patient cannot be referred to somebody else who doesn't know anything about the technology—they haven't done the bench testing or the animal testing or the cadaver testing. Sending a patient to someone with no experience in the technology needed for treatment is a gross violation of the Hippocratic oath.

Sending a patient to someone with no experience in the technology needed for treatment is a gross violation of the Hippocratic oath.
—Dr. Thomas Fogarty

Dr. Thomas Murray: As I understand the AAMC report, what you just described would not be prohibited at all. In fact, under the proper circumstances, the innovator could be involved in testing and further development of the device. I am not familiar with the details of any policies related to this at Stanford, where you are affiliated.

Dr. Fogarty: Perhaps the restriction that I described is particular to Stanford, where it is still imposed. In any case, I think that type of restriction is improper.

INNOVATION VS REGULATION: HOW DOES AMERICA STACK UP GLOBALLY?

Dr. Greenberg: I would like to explore innovation in the United States compared with the rest of the world. On one hand, the United States has the reputation among scientists and companies abroad of having the most robust and respected studies, with the best follow-up and the most trusted results. On the other hand, we have an almost paralyzing regulatory system in which to get a study done. So devices become available in Europe, Australia, and elsewhere long before they come to the United States, and American patients complain that they should not have to go to Europe to obtain a device. At the same time, some devices that are available elsewhere should probably never be used in patients. What are the panelists' thoughts on innovation and regulation in the United States in relation to the rest of the world?

Dr. Daniel Schultz: We probably are somewhere in the middle. The European system is much more laissez-faire than ours, especially with regard to devices. They primarily have third-party inspecting facilities, and if they show that the facility is safe and that the company has a manufacturing plan, most devices can go to market without any significant requirement for clinical efficacy. They may require some safety data, but in my mind it is difficult to establish safety if you do not know something about effectiveness. In contrast, many consider the Japanese system far more rigorous and in some ways more inefficient than ours.

The FDA and its counterparts in other countries are trying to harmonize regulatory approaches around the world, recognizing that diseases—and companies—do not have borders. But value systems and public expectations differ a lot between different countries, so I doubt we will ever have a perfectly harmonized system.

Dr. Mary McGrath: As a longtime member of the FDA's General and Plastic Surgery Devices Panel, I have seen a lot of FDA applications that are not ready for prime time. Studies may be incomplete, the data may not reach statistical significance, or the manufacturers may have overlooked important consequences of the data. Some of the critics of the slowness of the FDA review process seem to assume that the minute an application reaches the agency, it is ready for analysis and a determination. In reality, applications often must be sent back for further work, which slows the process considerably.

With regard to other countries, I think it is decreasingly the case that our standards are much more stringent than those of the European Union, which has made great strides in trying to catch up with the US regulatory environment. I know of several devices in plastic surgery, including breast implants, on which the European Union would not rule until they had learned how the FDA ruled, and then they based

their decision on what they heard from our country because they had confidence in our process.

Dr. Murray: Although I do not have a comprehensive viewpoint on this question, I served on an FDA panel—the Cellular, Tissue, and Gene Therapies Advisory Committee—and found the FDA professionals and the members of the panel to be incredibly serious about the work they were undertaking to provide good feedback to the applicants. Although most of the applications in this cutting-edge area were not ready for prime time, the applicants needed good scientific advice about how to proceed, and I think they got some valuable feedback.

We need to recognize, however, that we can never achieve a perfect system. We will always have a tension between the values of swiftness, safety, and smartness. All three cannot be maximized at the same time. We have to keep adjusting and looking for the appropriate balance. A forum such as this one—where innovators, companies, ethicists, legal experts, and clinicians are present—is the right way to examine these issues, and we need to encourage more forums like this.

The United States has the reputation of having both the most respected regulatory studies and an almost paralyzing regulatory system in which to get a study done.
—Dr. Roy Greenberg

Dr. Fogarty: My experience with the FDA goes back to the initial device legislation; I was at the National Institutes of Health when we were asked by the FDA to help categorize devices in terms of risk. I have found that people in the upper levels of the FDA, especially those who have been practicing physicians, understand issues of safety and efficacy very well.

One challenging issue, however, is the goal of the "least burdensome means" in negotiating the regulatory process. Who determines the least burdensome means? It should not be an individual FDA reviewer. Input from patients and doctors is essential, since a reviewer may have a very different perception of burden than a patient or a treating physician does.

I agree that slowdowns often occur at the FDA because of inadequate preparation on the part of physicians or institutions. Applicants should not be going to the agency with inadequate data. But sometimes reviewers change, and one reviewer may emphasize different end points than his predecessor did, which makes the process less predictable. There should be a guarantee that nobody is going to change a study requirement midstream; often that leads to starting over, which can be very expensive, especially if randomized, double-blind, prospective trials are involved. If a midstream study change is required for a product that serves only a small population, the developers will not pursue it further.

I think all of the issues I have mentioned can be resolved with frank, open conversations between the FDA and the physicians, institutions, and companies that it deals with. Beyond those issues, the FDA also can be subject to political influence, which is a different matter and which should not be the case.

WHERE DOES THE IRB FIT IN?

Question from audience: Could you clarify what the role of institutional review boards (IRBs) is in relation to the role of the FDA in approving and implementing studies of new devices in human subjects?

Dr. Schultz: For medical devices, the FDA has a process called an investigational device exemption that allows a clinical study to be performed for the collection of safety and effectiveness data, provided that certain requirements are met. These requirements include appropriate premarket or preclinical testing, evidence that the product is biocompatible and is manufactured appropriately, and other evidence that the product generally reaches a level where we think testing in patients is appropriate. At that point there are essentially two pathways: "significant risk studies" and "nonsignificant risk studies." For products requiring significant risk studies, the study protocol must be reviewed and approved by both the FDA and the relevant IRB before a trial can be initiated in humans, amounting to a sort of dual oversight. For nonsignificant risk studies, the protocol is approved solely by the IRB, which the FDA essentially uses as a surrogate for oversight in these less risky settings. Regardless of the type of study, the review of data resulting from the clinical study is done by the FDA, not the IRB.

WHO SHOULD MAKE CALLS ABOUT COST-EFFECTIVENESS?

Comment from audience: I found it interesting that when Dr. Schultz discussed the total artificial heart, no information was presented on cost. In the previous session, Dr. Peter Ubel asserted that we should be considering cost as an important feature of product assessment and that the FDA does not do so and in fact is not is not legally allowed to. I would like Dr. Murray to comment on the ethics of that.

Dr. Murray: If you want to see what I think about how to take costs into consideration in a general sense, take a look at an article I just published in the *Hastings Center Report*.[8]

To address your specific request, I agree with Dr. Ubel: to have a health care system that delivers the optimum care to people, you have to be mindful of the costs of care, the trade-offs, and the opportunity costs being incurred. But that does not preclude innovation; innovation can actually lower costs. Innovation can lead to delivering more care to more people at a lower price—look at what has happened in the semiconductor industry. You always have to be mindful of the policy choices, and cost is an inescapable factor.

Being mindful of the costs of care does not preclude innovation; innovation can actually lower costs.
—Dr. Thomas Murray

Dr. Greenberg: I think Dr. Ubel used the term "psychological quirks" when he described the values that people bring to bear when they look at health care costs. Really, the most cost-effective way to deal with someone who needs an artificial heart is to let him die. For a lot of diseases, that is actually the most cost-effective way, but we have to somehow ascribe some value to what we are doing.

Dr. Murray: That may be the cheapest way, but it might not be the most cost-effective way. As an ethicist—not an economist, mind you—I think we must recognize that with the health care system we have in the United States, which is the most expensive in the world and gets middling results at best, we need to encourage innovation but we also need to think about effectiveness.

Prior commenter from audience: I do not dispute that we need to think about cost-effectiveness. But individual physicians at the bedside should not be the ones who do that. We need a more sophisticated approach.

Dr. Murray: I absolutely agree; after all, doctors are not economists. We want them to focus on providing for patients the best they can. Decisions about cost-effectiveness need to be reached at a policy level and incorporated into medical training.

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