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Original Article

Ethics of Innovation in Surgery for Congenital Cardiac Diseases

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In medicine, innovation generally involves the introduction of a new method, idea, treatment, medication, or device to benefit the individual patient. An example of innovation in surgery for congenital cardiac disease would be the early attempts by Jatene,[1] Yacoub,[2] and others to achieve anatomic rather than physiologic repair of transposition of the great arteries. These innovators were motivated by the belief that their patients would derive a unique benefit from the arterial switch operation because of the theoretical advantages of placing the left ventricle in the systemic circulation. Research, on the other hand, generally involves a hypothesis-driven study, often prospective, aimed at the discovery of new knowledge for mankind, and not necessarily to benefit the individual patient. An example of this strategy would be the conduct of a study in which infants undergo either an anatomic arterial switch operation or a physiologic atrial baffle operation based on random assignment. Analysis of the results would determine the relative merits of each treatment strategy, potentially producing new knowledge, but not necessarily benefitting an individual patient enrolled in the study. Innovation and research, however, are intertwined, and one cannot proceed effectively without the other.[3]

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Innovation in thoracic and cardiovascular surgery has resulted in the development of the heart-lung machine, open heart surgery, the intensive care unit, and strategies of myocardial protection, as well as countless new operations, modified procedures, and new devices. Historical annotations and careful review of these innovations show that most of these advances were not considered casually and were not spur-of-the-moment ideas applied haphazardly by surgeons who were seeking acclaim, promotion, or monetary gain. For instance, C Walton Lillehei performed dozens if not hundreds of studies in animals and carefully considered the accomplishments and advice of many colleagues before embarking on his history-making open-heart procedures using cross-circulation.[4] Norman Shumway and Richard Lower, pioneers in the field of transplantation, perfected the technical aspects of cardiac transplantation in the laboratory, in animals, but patiently awaited the validation of protocols to prevent rejection before ever undertaking the procedure in humans.[5] Although Christiaan Barnard, after visiting Shumway, used the heart of a brain-dead donor in South Africa to perform the first orthotopic cardiac transplant in a human,[6] Shumway continued to conduct research in his careful, thoughtful, and conscientious manner. A life-long inquiry and multiple contributions attended the work of Shumway. These noteworthy contributions, as well as many others, demonstrated the inherent integrity that was deeply ingrained in the training of academic surgeons, even before the

advent of Institutional Review Boards, governmental oversight, and international regulation.

Regulation of surgical innovations

Although over the years, the US Food and Drug Administration has gradually engaged in more monitoring of new drugs and devices, surgical procedures have not been so scrutinized. New procedures, however, have been indirectly regulated by way of "hospital accreditation committees", Institutional Review Boards, professional standards, potential litigation related to malpractice, ethical standards of beneficence and respect for the dignity of humans, requirements of special skills and above all, the standard for informed consent. This is not to say that operations were never formally monitored. New implantable devices such as mechanical valves, bioprosthetic valves, and valves from homografts, are monitored by the US Food and Drug Administration. Likewise, so are pacemakers, defibrillators, and vascular prostheses.

It seems incredible today that some of the first innovations in congenital cardiac surgery were not monitored by a committee, agency, or administrative body. As noted previously, the first procedure using cross-circulation in a human for open heart surgery was tacitly monitored by the Chairman of the Department of Surgery after a number of studies in animals.[4] Institutional Review Boards have since been established to oversee research involving human subjects by insuring that research is ethical, not unduly harmful, and carried out in the presence of informed consent.[7] The mandate for the creation of these Boards and the processes in which they engage is, in fact, a formal and institutional process that earlier in history was the purview of the Chiefs of Service: the respected leaders of the faculty at the leading academic medical centres of our nation. Owen Wangensteen, Chairman of the University of Minnesota Surgery Department, was one of the great surgical educators of the twentieth century.[8–11] It was under him that F. John Lewis, C. Walton Lillehei, Norman Shumway, Richard L. Varco, and others contributed to the development of open heart surgery. In his department, every surgical resident was required to spend time in the laboratory of surgical physiology. To the extent possible, ideas for surgical therapeutic innovations were modelled and tested in the laboratory with animals, often leading to peer-reviewed publications, before being applied in the clinical realm. In 1940, Wangensteen founded the Surgical Forum of the American College of Surgeons, where young surgeons would present ideas to their peers.[8] The environment was fertile for innovations in surgery, but as important, advances were made in the setting of an established and respected hierarchy of responsibility. Wangensteen ultimately exercised control over the approval and timing of the innovations introduced by members of his department. In a way, his personal code of ethics set the tone and established *de facto* requirements and criteria for application of innovations that are fundamentally similar, yet less formalized and cumbersome than those utilized by Institutional Review Boards today. Today, the members of Institutional Review Boards must of course have enough experience, expertise, and diversity to make an informed decision on whether the research is ethical, informed consent is sufficient, and appropriate safeguards have been put in place. One fundamental difference between the contemporary review process and that in the "era of Wangensteen" is the contemporary requirement that Institutional Review Boards include members who are not scientists. When asked about the advisability of some form of "oversight by the public" during a Congressional hearing in the United States of America in 1968 about the social implications of advances in medicine and biosciences, Wangensteen commented, "If you are thinking of theologians, lawyers, philosophers and others to give some direction … . I cannot see how they could help … . the fellow who holds the apple can peel it best."[12]

The first iterations of cardiopulmonary bypass machines, prosthetic valves, and the first attempts at repair of tetralogy of Fallot, ventricular septal defect, atrial septal defect, and coarctation of the aorta, all took place in the setting of internal departmental oversight as noted. The historical considerations were telling, however. Very few of these patients would have survived without surgery. Even the slightest chance of success would have been a major step forward. Once cardiopulmonary bypass became standard, there were more innovations resulting in complex operations such as the Mustard, Senning, Rastelli, and Fontan operations. The chance of success, no matter how slim, was welcomed in those early days. These early successes were followed by the arterial switch operation, the Norwood operation, the Ross operation, and the Cox-maze III procedure for atrial fibrillation. One wonders how "innovation committees" or "Institutional Review Board type committees" would have impacted these early surgical innovations.

It has been said that nothing is new under the sun. However, it was clear that the introduction of operations such as transplantation of the heart, transplantation of the lungs, the Ross procedure, the Fontan operation, the arterial switch operation, the

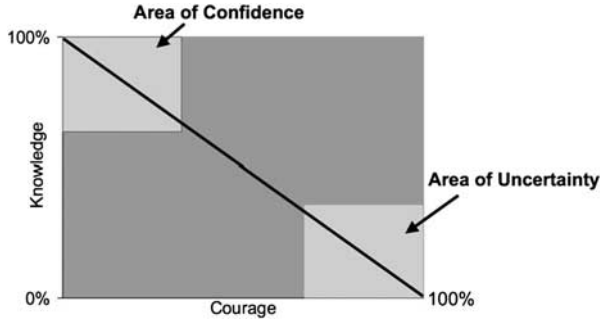

Figure 1.
A graph inversely relating courage and knowledge. Reprinted with permission from Mavroudis C.[13]

Norwood operation and the Maze operation were all new. Other innovations exist, however, that are not entirely new but are variations on a theme that have been previously explored. For instance, lateral tunnel and extracardiac modifications of the Fontan operation are innovative but not entirely new. The same concept is true for the double switch operation for congenitally corrected transposition of the great arteries, the Maze procedure for patients with congenital cardiac disease, banding of the pulmonary artery for left ventricular training, unifocalization, and repair of coarctation through a median sternotomy using deep hypothermia and circulatory arrest.

Many of these pioneering innovations, by the nature of their importance to humanity and paucity of existing solutions, required a rather courageous relationship between the surgeon and the patient.[13] When there is very little knowledge, a significant amount of courage is required for both the surgeon and the patient to persevere. Increased knowledge, however, defines the problem and the solution, which when applied to the care of the patient will require less courage to engage in the plan of treatment (Fig. 1).[13] G. Wayne Miller, in his book titled *King of Hearts*,[11] expressed the dilemma of the early experience of cardiac surgery, "Indeed many doctors dropped out, the human cost was too high, the emotional toll too devastating. But some persevered. Some like C. Walton Lillehei, the father of open heart surgery, pushed ahead through all the bleeding and the dying until they finally got it right."

Other innovations had to take a detour from the original model that was practiced in most surgical laboratories, namely that successful animal models would precede application to the human subject. Francis Fontan had a vision that the right atrium could serve as a pumping chamber in patients with tricuspid atresia. Recently he explained the conundrum he faced four decades ago: "Experimental research on dogs … there were no survivals for more than a few hours" (Personal communication, 2008). This fact was to prove prophetic. Even today after thousands of successful Fontan operations in humans; there is still no long-term model in animals for the Fontan circulation. Clearly, the introduction of the concept of Fontan for managing the functionally univentricular circulation could not await validation in a model in animals. Perhaps an even more delicate balance of therapeutic options became manifest when the arterial switch operation was introduced for the repair of transposition of the great arteries. It was clear that if the arterial switch operation could be performed with low risk, it would likely result in improved long-term results because of the creation of left ventricle to aortic continuity. The difficulty was that excellent short-term results were being widely achieved with the atrial baffle operations. The long-term complications of the atrial baffle procedures were for many a secondary consideration, operative survival being the primary measure of success. To their credit, Drs John Kirklin and Eugene Blackstone, in conjunction with the Congenital Heart Surgeons' Society, undertook a multi-institutional prospective study, which enrolled all patients with transposition of the great arteries and followed their clinical course.[14] In the initial phases of the survey, survival after arterial switch operations in some institutions did not match the excellent results that were being achieved in some institutions with high volume. A candid objective analysis, which included the impact of the institution among potential risk factors, served to emphasize that excellent results could be achieved by committed institutions. This analysis resulted in shared protocols, mutual interinstitutional visits, and ultimately refinements of operative methods. It was not long before the majority of institutions were achieving excellent results for most patients with this rather complex operation. The dilemma of whether to perform the atrial switch operation or the arterial switch operation became moot, with the demonstration of excellent short- and long-term survival with the arterial switch operation.

Is innovation a moral duty?

Of course, innovation is a moral duty. But what moral tenets are we considering? It is no secret to anyone that there are multiple sides to most ethical questions. W. French Anderson, Editor-in-Chief, *Human Gene Therapy,* said, "We as caring human beings have a moral mandate to cure disease and prevent suffering."[15] Lord Sainsbury, Science Minister in Great Britain, speaking in 2000 about research on stem cells, "The important benefits,

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which can come from this research outweigh any other considerations."[16] Joshua Lederberg, Nobel Laureate in 2003 declared, "The blood of those who will die if biomedical research is not pursed will be upon the hands of those who don't do it."[16] These statements are examples of enthusiastic support of biomedical research, which connote a mentality of careful but deliberate progress towards curing disease as quickly as we can. On the other side of this passionate posture is the cautionary note expressed by Hans Jonas, a noted philosopher, "Let us not forget that progress is an optional goal, not an unconditional commitment … . Let us also remember that a slower progress in the conquest of disease would not threaten society … . but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having."[17] If one believes that these words are perhaps too cautionary, consider the news-breaking story and dazzling operation that was performed in Loma Linda, California in 1984 when Leonard Bailey and his team performed a cardiac xenotransplant of the heart of a baboon into a newborn human infant with hypoplastic left heart syndrome.[18,19] The condition was clear: this child would die without an operation. At that time, surgical palliation as described by Norwood was fraught with high mortality and unknown outcomes. So was neonatal cardiac transplantation, to say nothing about xenotransplantation. It was also the time that our society was threatened and challenged by the AIDS virus, which was believed to have had its origins from the primate population. Did anyone consider the possibility, no matter how remote, that a dangerous and contagious "baboon virus" could be contracted by the recipient? Was there danger to the planet? How much danger was there for the patient and the family from overzealous groups advocating the rights of animals? What about the ethical considerations, voiced by many advocacy groups, of using primates as one to one donors for transplantation? There is no doubt that Dr Bailey and his group were and are highly motivated, moral, and well-meaning clinicians and scientists. And no doubt, many of these theoretical and possible outcomes were considered. Xenotransplantation as research, involving mostly porcine models, was continued for its overall utility, especially in relation to the reality of a limited pool of hearts from human donors for patients with cardiac failure. The possibility of transmission of porcine retrovirus to humans, however, limited the application to human subjects until the potential infectious problem could be further studied and remedied. At the present time, the National Institutes of Health of the United States of America are not funding xenotransplantation protocols because of this problem.

The integrity of the individual as it pertains to the advancement of medical and surgical therapeutics is well established. Jacob J. Katz, in *Experimentation With Human Beings* wrote, "When may a society, actively or by acquiescence, expose some of its members to harm in order to seek benefits for them, for other, or for society as a whole?"[20] Clearly, this question is difficult to answer. However, the Declaration of Helsinki in 1964 was written on the premise, "The interest of science and society should never take precedence over considerations related to the well being of the subject." While this view on human research is generally accepted, some have argued that too enthusiastic an endorsement of these tenets may result in a static state of medical therapeutics. Francis D. Moore, wrote, "By establishing arbitrary ethical standards, one might be surprised to find that while he [the researcher] is protecting the individual patient, he is exposing society to the hazard of a static rather than a dynamic medicine."[21] The road to ethical behaviour was considered by Aristotle. In the Nichomachean Ethics, he defined moral virtue or excellence as "The habit of choosing the golden mean, between extremes as it relates to an action or emotion."[22] One's reaction to a moral issue is not always the same. It is based on a lifetime of achieving moral excellence to do what is right in all conditions. Aristotle notes that humans should look into Society and find exemplars of moral excellence and emulate them in their life-long quest of this ideal.

Our institutions have helped us in this quest by establishing guidelines that will allow the participant to understand the basic elements of moral duty and establish a process of thought which will guide the researcher, clinician, and human being to act in a moral manner when there are no written rules. To quote Kant on the categorical imperative, "Act only according to that maxim whereby you can at the same time will that it should become a universal law."[23] In other words, every action can stand on its own as a moral tenet that will be appropriate for that moment and for all time. Now that's something to consider! So what are some of the guidelines that are in place that govern surgical innovation? Presently, surgical innovation is considered as research when it has to meet a variety of formal regulatory requirements, such as approval from an Institutional Review Board for patients involved in evaluations of devices or drugs monitored by the US Food and Drug Administration. If surgical innovation is considered as the

advance in medical practice, it is governed by professional standards and standards of malpractice; surgeons do not have to be reaccredited when they alter practice or when they introduce new procedures.

How do we introduce innovation into practice?

Clearly, the best way to introduce innovation into clinical practice is by "evidence-based decision making". As Douglas Altman states, "Well-designed and properly executed randomized, controlled trials provide the best evidence on the efficacy of health care interventions."[24] However randomized controlled trials in surgery are difficult to perform. It is hard to blind the participants of the study as to the therapeutic options. Surgery is confounded by human factors such as skill and learning curves. Rapidly evolving technologies make it difficult to enroll a large number of patients. Human factors such as surgical skill may influence outcomes more than the actual type of procedure. Randomized controlled trials that do not incorporate blinding are more likely to show advantages of the new intervention over the standard treatment. Moreover, the problem of which surgeons to choose for the trial enters the planning. Questions like, "are all surgeons to be included in the trial or only the better surgeons?" The dilemma of choosing the "better surgeons" is an interesting task, to be sure.

Alternatives to evidence-based medicine can be informative and helpful, especially when a randomized controlled study is not possible. These studies include the following types:

- nonrandomized contemporaneous controlled studies, also known as observational studies;
- nonrandomized non contemporaneous controlled studies, also known as studies with historical controls;
- anecdotal evidence, also known as single-case studies, such as the reports of the first open heart operation, first heart transplant, etc.; and
- uncontrolled case series, which have been the bedrock of surgical research of the past, such as publications about radical mastectomy, tonsillectomy, etc.

Observational studies can establish associations rather than causation between treatment and outcome. They can be a valuable alternative when ethical considerations, costs, resources, or time, prohibit one from designing a randomized controlled trial.

So, what is the answer?

Clinical surgery can continue with what is in place now. There has been enormous success with this model. The system allows frequent adjustments and there are less administrative hassles. Sade and associates argue that "innovation review committees" can be formed within each Institution which, would result in formal collegial review, collective opinions before implementation, and follow-up reports.[25] This system puts into formal structure what is now being performed by responsible institutions that require peer review of new operations and careful follow up of complications and outcomes.

The ethics of innovation in surgery have evolved from the actions and tenets of serious and high-minded individuals who have considered their proposed surgical advances in a sea of patient need, limited knowledge, and moral duty. These principles have served our profession and our patients well. Whether more or less oversight is necessary will be determined by the profession as the road to obtaining "the habit of choosing the golden mean between extremes as it relates to an action or emotion"[22] becomes more manifest.

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References

1. Jatene AD, Fontes VF, Paulista PP, Souza LC, Neger F, Galantier M, Sousa JE. Anatomic correction of transposition of the great vessels. J Thorac Cardiovasc Surg 1976; 72 (3): 364–370.
2. Yacoub MH, Radley-Smith R, Maclaurin R. Two-stage operation for anatomical correction of transposition of the great arteries with intact interventricular septum. Lancet 1977; 1 (8025): 1275–1278.
3. Riskin DJ, Longaker MT, Krummel TM. The ethics of innovation in pediatric surgery. Semin Pediatr Surg 2006; 15 (4): 319–323.
4. Lillehei CW, Cohen M, Warden HE, Ziegler NR, Varco RL. The results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. Surg Gynecol Obstet 1955; 101 (4): 446–466.
5. Lower RR, Shumway NE. Studies on orthotopic homotransplantation of the canine heart. Surg Forum 1960; 11: 18–19.
6. Barnard CN. The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. S Afr Med J 1967; 41 (48): 1271–1274.
7. US Department of Health and Human Services. Food and Drug Administration. FDA Backgrounder: Milestones in US Food and Drug Law History. Available at: http://www.fda.gov/oc/history/default.htm.
8. University of Minnesota Department of Surgery. Owen H. Wangensteen, MD, PhD, Biography. Available at: http://www.surg.umn.edu/surgery/Education/OWSS/wangensteen_bio.html.

9. Gott VL. Lillehei, Lewis, and Wangensteen: the right mix for giant achievements in cardiac surgery. Ann Thorac Surg 2005; 79 (6): S2210–S2213.
10. Shumway NE. C. Walton and F. John. Ann Thorac Surg 1999; 68 (3 Suppl): S34–S36.
11. Miller GW. KING of Hearts: The True Story of the Maverick Who Pioneered Open Heart Surgery: Random House/Times Books; 2002.
12. Ramsey PG. The Patient as Person: Explorations in Medical Ethics. New Haven, CONN: Yale University Press; 2002.
13. Mavroudis C. Presidential address. A partnership in courage. Ann Thorac Surg 2003; 75 (5): 1366–1371.
14. Norwood WI, Dobell AR, Freed MD, Kirklin JW, Blackstone EH. Intermediate results of the arterial switch repair. A 20-institution study. J Thorac Cardiovasc Surg 1988; 96 (6): 854–863.
15. Anderson WF. Uses and abuses of human gene transfer. Hum Gene Ther 1992; 3 (1): 1–2.
16. Callahan D. What Price Health? Hazards of the Research Imperative. Berkeley, CA: University of California Press; 2003.
17. Jonas H. Philosophical reflection on experimenting with human subjects. Daedalus 1969; 98 (2): 219–247.
18. Bailey LL, Nehlsen-Cannarella SL, Concepcion W, Jolley WB. Baboon-to-human cardiac xenotransplantation in a neonate. JAMA 1985; 254 (23): 3321–3329.
19. Jonasson O, Hardy MA. The case of Baby Fae. JAMA 1985; 254 (23): 3358–3359.
20. Katz JJ. Experimentation With Human Beings: The Authority of the Investigator, Subject, Professions, and State in the Human Experimentation Process. New York: Russell Sage Foundation; 1972.
21. Moore FD. Therapeutic innovation: ethical boundaries in the initial clinical trials of new drugs and surgical procedures. CA Cancer J Clin 1970; 20 (4): 212–227.
22. Aristotle. The Nichomachean Ethics Book III. [Translated by Sir David Ross]. London: Oxford University Press; 1954.
23. Kant I . Grundlegung zur Metaphysik der Sitten [Foundations of the Metaphysics of Morals]. 1785.
24. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001; 134 (8): 663–694.
25. Morreim H, Mack MJ, Sade RM. Surgical innovation: too risky to remain unregulated? Ann Thorac Surg 2006; 82 (6): 1957–1965.