The History of Surgical Research

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Imagination is more important than knowledge.
Albert Einstein

Abstract

There are different options available for classifying the history of surgical research by social and cultural eras. A simple classification divides surgical research history into two periods: the first spans the centuries from Antiquity to the Early Modern and the second from the Early Modern to the present. The first "operations" were trepanations. In the ancient world, research activity that can be considered "surgical" rather than just "anatomical" may be attributed to Galen of Pergamon. Throughout the Middle Ages the Church impeded surgical research by opposing any manipulation of a dead body. During the Renaissance research flourished. To date, only nine research surgeons have been awarded the Nobel Prize in Physiology or Medicine. Many eminent research surgeons, despite lives spent pursuing experimentation and making contributions to medicine, have not been honored with such recognition.

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2.1 Surgical Research from Antiquity to Early Modern

The word "surgery" derives from the ancient Greek *cheirourgia*, meaning "to work with the hands." It is a fusion of the terms *cheir* (hand) and *ergon* (work). It evolved into the Medieval Latin *chirurgia*, that evolved into Old French *cirurgerie,* which, over the centuries became anglicized to *surgery* [1, 2]. From what we know, the first "operations" were trepanations. Most evidence dates trepanation to 3000 BC, but other sources date the practice as far back as 10,000 years [3]. It was a surprisingly common practice among the Incas. The hole perimeters in the trepanned skulls of many Incas were rounded off by the ingrowth of new bony tissue, indicating that patients frequently survived the procedure. Trepanation was also a common practice in ancient Greece. Hippocrates (450–355 BC), in his tome *On the Injuries of the Head*, wrote extensively about how and when to perform trepanation [4]. The first real efforts at research were anatomical in nature. Herophilus of Calcedon (280 BC) and Erasistratus of Chios (304–250 BC) were among the first to pursue anatomical research [5]. They carried out hundreds of dissections on animals and human cadavers, and Erasistratus even performed vivisections on criminals. In Egypt in Alexandria, the Pharaohs Ptolemy I Soter and Ptolemy II Philadelphus encouraged anatomical research [5]. Research activity that can be considered "surgical" rather than just "anatomical" may be attributed to Galen of Pergamon (129–200 AD), a prominent physician and philosopher, and well known as the gladiators' surgeon. His theories dominated Western medical science for over a millennium. He merits consideration as a true research surgeon because in Rome he dissected animals with the goal of understanding anatomy, relating it to physiological function, and finding surgical solutions to pathologies. However, Rome imposed legal limitations on the dissection of human bodies, hampering his research. So Galen was obliged to dissect animals rather than human cadavers and extrapolate his findings to man. This methodology inevitably led to errors. In spite of the limitations, Galen performed some audacious operations and it seems he was the first to carry out cataract surgery [5]. Throughout the Middle Ages the Church impeded surgical research by opposing any manipulation of a dead body. Some popes, such as Innocent III, Gregorius IX, Sixtus VI, and Bonifatius VIII, excommunicated anybody who dissected cadavers. Only on rare occasions did the Church tolerate dissections, e.g., in the suspicious circumstances surrounding the deaths of high priests, popes, or nobility. Despite these limitations Mondino de Liuzzi (1270–1326) in Italy was the first to publicly use cadaver dissections as a teaching tool. The dissections were performed in the amphitheater of Bologna University with a horizontal rather than a vertical cadaver [5]. Church restrictions on surgery led to the development of barber–surgeon corporations. At that time, monks were the traditional practitioners of medicine, but were forbidden to spill blood and hence were unable to practice surgery. Barbers replaced the monks as surgeons and in addition to cutting hair, amputated limbs, administered leeches, carried out blood-letting, and extracted teeth. Barber schools were established, but their medical culture was limited. They embodied a medieval paradox, i.e., "physici" (hence the modern term "physician"), who understood anatomy and pharmacology, did not perform surgery, while barber–surgeons, who had a poor grasp of anatomy and pharmacology, did [5]. Henri de Mondeville, an eminent surgeon from Montpellier and Paris, and author of a five-volume textbook on surgery, addressed this paradox head on. Mondeville defended the fusion of artisan surgery and intellectual medicine, and defined the ideal surgeon as *cyrurgicus* and *medicus*, i.e., representing the union of medical culture, science, and manual work. He also sought to circumvent church-based obstacles to surgery by elevating the image of surgeons, despite their work with blood. Frenchman Guy de Chauliac took another step in that direction [5]. His surgical activities emerged from the combination of a strong medical and philosophical background with an anatomical and surgical approach. More progress was made by Flemish-born Andreas Vesalius and Frenchman Ambroise Paré, the latter a leader in the use of surgical techniques and battlefield medicine during the Renaissance. At one time he cared for two soldiers who lay side by side with similar wounds. He treated one wound by the standard method (cauterization with boiling oil) and the second wound with debridement, cleansing, and application of a clean dressing. He spent a restless night pondering the outcome and the next morning discovered that the second patient had no symptoms, while the first suffered from fever and tachycardia [5]. This was among the first medical applications of comparative methodology and helped lay the groundwork for *controlled experiments*.

During the Renaissance the Italian Fabrizi d'Acquapendente dissected animals in order to investigate the progressive development of the fetus [5]. In Padua he discovered membranous folds in the lumina of veins, which he called valves. William Harvey, a father of cardiovascular physiology and one of d'Acquapendente's disciples at the University of Padua, also studied under Galileo Galilei, professor of mathematics at the same university. Harvey applied the Galilean mathematical method to his research on blood circulation, which led to the publication of *Motu Cordis*, a landmark text in Renaissance medicine [6]. Fabrizi d'Acquapendente was one of many researchers who participated in the 16th century enlightenment. Matteo Realdo Colombo, Gabriele Falloppio, Bartolomeo Eustachi, and Gaspare Aselli in Italy; Jean Pecquet and Jean Riolan (the Younger) in France; Thomas Bartholin in Denmark; and Pieter Pauw in Holland all contributed to the flourishing of innovative theories and notions about anatomy, physiology, and surgery in the 16th and 17th centuries [5, 6].

2.2 Surgical Research from Early Modern to the Present

The first figure of note in the Contemporary Era was John Hunter [7]. Born near Glasgow in 1728, Hunter was interested in comparative anatomy and in the natural history of disease. He was a true research surgeon whose inquiries often led to experiments and to operations. Many students attended his London school to study his research methods. To him we owe the understanding that smaller vessels may, through necessity, take on the work of larger vessels. He is famous for an operation performed on a coachman in 1785—later called the Hunterian operation.

Joseph Lister (1827–1912) was the father of surgical antisepsis [7]. Before Lister's discoveries, nearly every wound became infected and suppurated. Following Pasteur's lead he chose phenol (carbolic acid) rather than dry heat to ensure adequate sterilization during surgery. Lister developed his theories on surgical antisepsis by examining infected surgical wounds, performing experiments, and applying the results clinically. At first, the scientific community rejected his ideas and at the third meeting of the American Surgical Association he encountered strong opposition.

The 19th century witnessed the birth of the first surgical and research training program in Europe thanks to Bernard von Langebeck, professor of surgery at the University of Berlin [7]. He was also founder of the first journal dedicated entirely to surgery (*Archiv für klinische Chirurgie*) and taught some renowned research surgeons such as Theodor Billroth, Frederick Trendelembourg, and Theodor Kocher. In North America the first surgical and research training programs were developed at the newly established Johns Hopkins Medical School (1886) by William Halsted [7]. As for John Hunter, he experimentally tested all his surgically related theoretical concepts, which led to the emergence of new types of operations: radical mastectomy, radical hernia cures, goiter operations, etc. At Johns Hopkins, staff members received broad support to pursue surgical research. As new research centers cropped up in the 19th and 20th centuries, ideas about surgery evolved rapidly. In a famous painting by Thomas Eakins, *The Gross Clinic*, one sees people huddled around the surgical team. This was the custom in the 19th century—surgeons operated while observed by students and admirers. At the start of the 20th century there was a shift in the way surgeons worked. They began operating alone or with few assistants. Eugene Doyen, a French surgeon at the beginning of the 19th century, performed surgery with almost no one around—in the modern way. But he still worked with no hat, mask, or sterile gloves—in the old way [8]. Overall, these work habits signaled a transition period in which surgery edged closer to the use of modern techniques.

2.2.1 The Nobel Prizes

To date, only nine research surgeons have been awarded the Nobel Prize in Physiology or Medicine. Alexander Fleming, who received the Nobel Prize in 1945 for the discovery of penicillin, had been trained as a surgeon but never practiced surgery and was primarily regarded as a bacteriologist [9].

The first Nobel laureate surgeon was Emil Theodor Kocher from Switzerland [10]. He intensively studied hypothyroidism-related myxedema, which he called "cachexia stumipriva". He solely performed more than 2,000 thyroidectomies, and a further 7,000 were performed in his clinic. The 1909 Nobel Prize was awarded to him for his work on the physiology, pathology, and surgery of the thyroid.

Allvar Gullstrand, from Denmark, began his career in 1890 at the Royal Caroline Institute with a dissertation on the origins of astigmatism. He applied his knowledge of mathematics and physics to ophthalmology. He performed the first operation for symblepharon and received the Nobel Prize in 1911 for his work on dioptrics and accommodation [10].

Alexis Carrel was a French surgeon who moved first to Canada and then to the United States [11]. He developed the vascular anastomosis technique and in 1910 performed an experimental descending thoracic aorta to left coronary artery bypass using a cold temperature-preserved bovine carotid artery [12]. He was interested in organ storage and preservation and artificial organ perfusion. He was able to perfuse the thyroid gland of a cat for 18 days, after which he achieved perfusion of the heart and other organs for several days [8, 11]. He was awarded the Nobel Prize in Physiology or Medicine in 1912 [13]. Charles Lindbergh, the famous aviator (and neither a Nobel laureate nor a physician), worked with Carrel to discover a treatment for a family member suffering from mitral stenosis for which the corrective procedure required stopping the heart. They aspired to create a machine capable of carrying on heart function while the surgeon accessed the mitral valve. Together, they built a new organ perfusion apparatus capable of doing the job [11].

Robert Barany, from Austria, studied the vestibular canals, vertigo, and nystagmus. During the First World War, he was captured by the Russian army and while interned received news that he had been awarded the Nobel Prize. Upon returning to Vienna, despite the acclaim, he was accused of plagiarism by his colleagues. He was fully exonerated of these defamatory charges, but, tired of the injustice he endured, eventually left Austria and moved to Sweden, where he accepted the rather modest appointment of assistant professor at the University of Uppsala [10].

Frederick Banting was a Canadian surgeon who studied the endocrine function of the pancreas by removing its exocrine function [10]. He approached John James Rickard Macleod, chief of a research laboratory in Toronto, with his research proposal, but was repeatedly rebuffed. But Banting persisted and eventually Macleod relented. He allowed the young surgeon to use his Toronto laboratory in his absence. Charles Best, a medical student, was assigned to work with Banting. They observed that an extract of the atrophic pancreas could reverse diabetic coma in dogs [14]. In 1922 a crude preparation was used to treat a young boy with diabetic ketoacidosis. Banting was awarded the Nobel Prize in 1923 for his discovery of insulin. The Nobel Prize was also conferred upon Macleod, despite his initial resistance to Banting's proposals. The exclusion of Best wounded Banting's sense of fairness. By sharing half the award with Best he ignited a controversy on the "anatomy" of scientific collaboration [10, 15].

Walter Hesse, from Switzerland, studied the biological control of emotions. He observed that electrical stimulation of the hypothalamus elicited a rage response in experimental animals. His research led him to attribute specific physiological functions to specific areas of the brain [16]. In 1949 he received the Nobel Prize for his work on the diencephalon (interbrain) as coordinator of internal organ activities [10].

The German physician Werner Theodor Otto Forssmann was a surgery resident who sought a method by which drugs could be introduced directly into the heart. He performed a cardiac catheterization on himself through the basilic vein! Rather than being lauded he was fired by his department chief, who told him he was a clown and that the department was not a circus. In spite of this reaction, Forssmann continued his experiments elsewhere and stopped only when he had no veins left to access. A historical X-ray of Forssmann's thorax shows the catheter through the arm vein reaching the superior vena cava, the innominate vein, and finally the right atrium [17]. Sometimes life has its compensations—for the very reason Forssmann was humiliated he was awarded the Nobel Prize in 1956. He shared the prize with Andre Cournaud, a French researcher who worked in the USA, and the American, Dickinson Richards [8, 10].

The Canadian Charles Huggins observed that in the canine model, normal prostatic secretion is regulated by androgens and estrogens. He noted that orchiectomy reduced serum levels of acid phosphatase, a marker of metastatic prostatic cancer [18]. He received the Nobel Prize in 1966 for the discovery of hormonal therapy as a treatment for prostate cancer [10].

Finally, in the United States in 1954 Joseph Murray performed the first human kidney transplant in identical twins [19]. He was actually a plastic surgeon with wide experience in skin grafting. He performed many animal experiments in which he induced host tolerance for transplanted organs and he concluded that transplantation is feasible when the host immune response can be suppressed [20]. Murray shared the 1990 award with E. Donnall Thomas for discoveries in the field of organ and cell transplantation [21].

It is worth noting that many eminent research surgeons, despite pursuing lives of experimentation and contributions to medicine, were not honored with the Nobel Prize. There is still hope that those alive will in time receive due recognition. Among those deserving the highest praise are John Heymann Gibbon, for the first clinically functional heart–lung machine [22]; Norman Shumway, for heart transplantation techniques [23]; Thomas Starzl, for liver transplantation [24]; and Alain Carpentier, still active in research and a pioneer in valve reconstructive surgery, valve-prosthesis-preservation methods, radial-artery-arterial revascularization, and current investigations into a new intraventricular assist device [25–27].

Not all who helped revolutionize surgical outcomes were surgeons. Three worth recalling are Jonathan Rhoads, Stanley Dudrick, and Harry Vars [28]. They collaborated in the area of parenteral nutrition to dramatically improve postoperative outcome for millions of chronic intensive care patients.

The history of surgical research is too complex to be covered in these few pages, and many deserving research surgeons had to be excluded from this record. In forthcoming chapters the work of surgeons who specialized in cardiac research will be elaborated.

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