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Case Histories of Significant Medical Advances: Coronary Artery Bypass Grafting

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Working Paper 20-010

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Abstract: We describe how Coronary Artery Bypass Grafting (CABG, or more popularly, "bypass") operations revolutionized the treatment of coronary disease (that can produce fatal heart attacks and debilitating angina). Specifically we chronicle the: 1) development of the foundational procedures and technologies that provided a base for CABG; 2) early CABG operations performed in the 1960s; 3) rapid – and controversial growth – that occurred in the US in the 1970s and, 4) emergence and rapid diffusion of the less invasive angioplasty alternative that slowed the growth of CABG in the last two decades of the 20th century.

Note: This case history, like the others in this series, is included in a list compiled by Victor Fuchs and Harold Sox (2001) of technologies produced (or significantly advanced) between 1975 and 2000 that internists in the United States said had had a major impact on patient care. The case histories focus on advances in the 20th century (i.e. before this millennium) in the United States, Europe, and Japan -- to the degree information was available to the researchers. Limitations of space and information severely limit coverage of developments in emerging economies.

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Case Histories of Significant Medical Advances

Coronary Artery Bypass Grafting

Coronary heart disease affects about half of all men and nearly a third of all women over 40. By coating the insides of coronary arteries with plaque and thus constricting the flow of oxygenated blood to the heart muscle, the disease can produce recurring and debilitating chest pain – a condition called "angina" -- and shortness of breath. Worse, plaque deposits can lead to complete – and often fatal – blockages of the blood flow (popularly called "heart attacks"). Such heart attacks are now the leading cause of adult death, accounting for nearly a third of all adult fatalities. And while drugs and diets can reduce the risks of blockages, they cannot restore the blood flowing through coronary arteries already narrowed by coatings of plaque. Rather, physicians rely on surgical procedures.

Two "revascularization" procedures to restore blood flow to the heart muscle have emerged as the standard of care: Coronary Artery Bypass Grafting (CABG) which became popular in the 1970s and Percutaneous Transluminal Coronary Angioplasty (or "angioplasty") which took off in the following decade. Although CABG is more invasive – requiring surgeons to cut open the thoracic cavity (chest) -- and requires more extended hospitalization, it is considered more suitable for difficult cases (e.g. patients with obesity or diabetes) or in cases where angioplasty hasn't worked. Therefore, even though operations are now below their peak, CABG continues to extend the lives of hundreds of thousands of patients around the world.

1. Disease and Treatment Alternatives

Coronary Disease. Coronary arteries provide all the oxygenated blood needed by the heart's muscular tissues -- the heart cannot absorb oxygen from blood that passes through its chambers. Constrictions of the arteries due to plaque deposits therefore reduce the oxygen provided to heart muscles and by extension to all the other tissues and organs that receive oxygenated blood pumped by the heart.

Coronary arteries get their name from how they "crown" and surround the heart (*corona* being the Latin word for crown).[1] Two main coronary arteries come out of the left and right side of aorta (that carries all the oxygenated blood pumped out of the heart) close to where the aorta leaves the heart. The two arteries – the "left main" and the "right main" -- then branch out to carry blood to different parts of the heart. One branch of the left main artery, for instance, supplies blood to the front and bottom of the left pumping chamber while another branch supplies blood to the side and back of this chamber. Even the main branches are extremely narrow – 4 millimeters at their widest – so it does not take much plaque to significantly narrow them. Narrowness also makes operations difficult and requires physicians to use a magnifying apparatus. Surgeons once even used microscopes to operate on the fine sub-branches of coronary arteries.

Unlike other parts of the body which receive oxygenated blood from more than one artery there is no redundancy of supply to the heart muscle, although a "collateral" network of tiny blood vessels -- do provide a degree of backup by allowing blood to flow around constrictions or to another nearby artery. This "collateral" circulation typically forms only when blockages develop and cannot carry as much blood as an open, un-constricted artery.

"Multi-vessel" disease which constricts two or more coronary arteries poses greater risks of heart attacks and angina. The risks also depend on the nature of the constrictions, such as the extent of the narrowing they produce, their length, and their location (upstream or "proximal" constrictions pose more risks). Other

diseases such as diabetes, hypertension and obesity also increase – and often accompany -- the problems caused by constricted arteries.

Many of the factors (such as multiple blockages and diabetes) that increase the risks of heart attacks and angina also increase the risks of bypass operations that can include death, strokes and brain damage. But generally, bypasses on high risk patients are thought to produce greater increases in life expectancy, because the alternative of not restoring blood flow is worse.

Bypass Surgery. CABG reroutes much more blood surgically, instead of naturally through activated collaterals. Operations to treat a constricted left main artery for instance can create an alternative supply of blood (to parts of the heart served by the artery) using the Internal Thoracic Artery (ITA). As its name suggests[*], the ITA is located inside the chest and close to the heart but it normally supplies blood to tissues and organs inside the chest, not to the heart muscle. A surgeon performing a bypass procedure first cuts away the ITA from the chest wall (which can be safely done because other blood vessels can also service the tissues and organs inside the chest). The detached end of the ITA is then grafted into the left main artery, at a "downstream" point on the artery, past the constriction. The grafting, which involves cutting into the coronary artery to sew in ("suture") the detached end of the ITA, causes blood to flow into the heart muscle instead of flowing into the pectoral muscles.

Or, surgeons may extract ("harvest") a segment of a blood vessel from outside the thorax, say from an artery in the arm. (The remaining portion is sealed while other blood vessels take over its circulatory function). One end of the extracted segment can then be grafted into the patient's aorta to draw in oxygenated blood while the other end, through which the blood is let out, is grafted past the constriction in a diseased coronary artery.

Extracting segments from outside the thorax (instead of diverting the ITA) reduces the time the patient's chest has to remain cut open, and thus the risks of the bypass operation. Moreover, surgeons can now use endoscopic, "minimally invasive" techniques for extracting segments from outside the thorax. Yet, ITAs remain the preferred conduit for CABG because segments of blood vessels extracted from outside the thorax have a greater tendency to clog up over the years.

Surgeons can perform double, triple or even quadruple bypass operations on patients whose "multi-vessel" disease has constricted more than one coronary artery. Such operations require multiple grafts and thus preclude relying just on redirecting the ITA. Multiple bypasses also take considerably longer. Yet, one long operation can be less arduous and more effective than several somewhat shorter operations to bypass individual constrictions.

CABG is performed under general anesthesia – typically administered intravenously – that can be supplemented with epidural anesthesia injected into the spinal cord. And as is routine with general anesthesia, patients are also given neuromuscular blockers (to immobilize them for the course of the operation). The immobilization induced by the blockers (and cutting open the chest) also prevents natural breathing, so patients' lungs are infused with oxygen-rich air through a tube inserted into the patients' windpipes.

Physicians monitor patients' hearts during bypass operations through electrocardiograms to monitor electrical signals and, towards the end of operations, through images (transoesophageal echocardiographs) generated by ultrasound probes passed into the patient's esophagus.[2] Physicians may also insert computer-controlled "balloon pumps" into patients' aortas before, during or after operations. These devices increase the flow of oxygenated blood to heart muscles, without requiring the heart to pump harder. They can help speed recovery, especially of high-risk patients. Beta-blockers and ACE-Inhibitors are also now commonly

[*] Physicians typically refer to the ITA as the IMA – internal mammary artery. Since the audience for this case includes readers who are not physicians, we use ITA since it more naturally indicates its location (namely inside the rib cage.)

prescribed before and after CABG operations. The drugs (like balloon pumps) can speed recovery by reducing the load on heart muscles.

Using Cardiopulmonary Bypass (CPB) is common but no longer routine. CPB involves connecting patients to "heart-lung" machines that perform the circulatory function of the heart, allowing surgeons to operate on a still, bloodless organ. But CPB involves a complex procedure (see box "How CPB works") and the administration of drugs that can produce dangerous side effects such as uncontrolled bleeding. Where feasible, many CABG operations are now done "off-pump" i.e. without CPB.

How CPB Works

Blood is removed from the body through a tube inserted into the right chamber of the heart or the vein that carries blood to the chamber. The removed blood is then cooled, diluted with a chemical solution,[3] its carbon dioxide replaced with oxygen (to mimic what normally occurs when blood passes through the lungs) in an 'oxygenator', and is then pumped back into the body through a tube inserted into the aorta (which would normally receive its blood from the heart's left chamber).

Patients on CPB are administered a drug (such as heparin) to offset the clotting of blood that occurs when it is outside veins and arteries. Other drugs, administered during the operation, reduce blood loss and transfusions needed to compensate for the blood loss. Then, as patients are being taken off CPB, they are given another drug (such as protamine sulfate) that reverses the effects of the anti-clotting drug.

The heart is iced down and stopped for the duration of the operation by the topical application of "cardioplegic" drugs.

This complex procedure can introduce debris (such as bits of tubing and blood cells chopped by the pumping machinery) or air bubbles into the blood stream (when patients are attached and detached from the CPB apparatus). The debris and bubbles increase the risks of strokes and impaired cognitive functions. Similarly, anti-clotting drugs increase the risks of excessive post-operative bleeding.

"Off-pump" CABG eliminates tube debris and chopped blood cells and the risks of clotting posed by blood leaving the body and the side-effects of the anti-clotting drugs. Bleeding is also naturally lower and the heart, which continues to receive and pump out oxygenated blood, doesn't need to be stopped with cardioplegic drugs. However off-pump CABG can require more surgical skill and healthier patients and overall, off-pump operations have not demonstrated significantly better outcomes.

Teams comprising several kinds of medical professionals, not just cardiac surgeons, perform CABG operations and provide post-operative care (see Exhibit 1). A typical operation will take at least four hours from the time a patient is wheeled into the operating theatre.

Alternatives to CABG. Angioplasty offers simpler and, as mentioned, much less invasive treatment. The procedure attempts to restore blood flow to heart muscles by expanding a constricted artery rather than by bypassing the constriction.

Angioplasty is performed by a cardiologist rather than a cardiac surgeon. The procedure does not require opening the chest, CPB and cutting or suturing of blood vessels. Instead a long, narrow tube called a catheter, with a small balloon at its tip, is inserted into a blood vessel in a patient's arm or leg. The catheter is then guided to the diseased coronary artery (with the aid of a special x-ray machine) and the balloon tip is positioned near where plaque has narrowed the artery. Inflating the balloon presses the plaque against the walls of the artery, widening the artery.

When the balloon is deflated and withdrawn, along with the catheter, the plaque may however immediately or gradually re-expand again obstructing blood flow. Typically, therefore angioplasty now includes stenting. In this variant, the balloon is sheathed in a stent, a tiny metal tubular mesh. Inflating the

balloon expands the mesh of the stent. When the balloon and catheter are withdrawn, the expanded mesh remains in the artery, keeping the plaque pressed against the walls of the patient's artery.

Hospitals stays after angioplasty procedures are short. According to a 2011 estimate between 6-18% of angioplasties were performed on outpatients in so-called "23-hour stays."[4]

The simplicity, speed of procedure and quicker patient recovery and relative non-invasiveness has made angioplasty (with stenting) the more frequently used procedure. But CABG is often considered more suitable for patients with multi-vessel coronary disease and (as mentioned) patients with other diseases such as diabetes. CABG may also be favored in patients whose arteries have previously re-narrowed after angioplasty.

Choosing and planning treatment. Angiography helps cardiologists decide whether to perform an angioplasty or refer a patient to a cardiac surgeon for a CABG operation. This diagnostic procedure is very like its near namesake treatment technique (angioplasty). In fact, angioplasty grew out of angiography, which also entails threading a catheter into the coronary arteries. However, in angiography the catheter is used to inject contrast material (a kind of dye which shows up in X-rays) rather than to inflate a balloon. X-ray photographs and movies produced as the contrast material moves through the heart's chambers and blood vessels show constrictions in the coronary artery.

Angiographies may also be supplemented with Computed Tomography (CT) or Magnetic Resonance angiographs, ultrasound scans, blood-tests, electro-cardiograms and blood tests to decide what kind of treatment is warranted and to formulate treatment and surgical plans.

2. Foundational Procedures and Technologies

Getting to the treatments and procedures just described took more than 100 years. The French surgeon Alexis Carrel (who would win a Nobel Prize in 1912 for developing techniques for sewing together severed blood vessels) had proposed bypass surgery to treat constricted coronary arteries in 1905. Autopsies had by then suggested a link between constricted coronary arteries and heart attacks (and chest pains and breathlessness) and the field of surgery had made great advances in the previous half century.[5] But as we will see, daunting obstacles to any kind of heart operation made Carrel's proposal more visionary than practical, and it took another 45 years for a surgeon to perform the first bypass on a patient.

Barriers to heart surgery. Reforms of medical education that followed the French Revolution had elevated the status of surgery in the West. Previously, learned physicians had significantly higher standing than surgeons who did not have university educations. General anesthesia (thought to have been first used to remove a neck tumor in 1842) and antiseptic wound dressing (starting with the treatment of a boy with a compound fracture in 1865) then significantly expanded the scope of surgery. Anesthesia enabled long, difficult operations without inflicting intolerable pain while antiseptic dressing slashed infections which had previously killed about half of surgery patients.

But, about fifty years after anesthesia and antiseptic dressing, prospects for heart surgery seemed remote. A British surgeon, Stephen Paget had predicted in 1896 that "Surgery of the heart has probably reached the limits set by Nature to all surgery: no new method, and no new discovery, can overcome the natural difficulties that attend a wound of the heart."[6] And, in the first two decades of the 20th century, only a few surgeons attempted to operate on hearts (see box Hazards of Heart Surgery).

Hazards of Heart Surgery
Several problems, many discovered from experiments on dogs, discouraged surgeons from operating on human hearts in the early 20th century.

• Access to the heart required incisions to open the patient's normally air-tight thorax which could cause the patient's lungs to collapse. If both lungs collapsed the patient would suffocate. This problem did not arise in operations on other vital organs such as the kidneys and liver (located in the abdominal cavity) or the brain (located inside the skull)

• Constant pumping made it more difficult to operate on hearts than on other nearly motionless organs. If the pumping could somehow be suspended that would also stop blood flowing to the rest of the body. And cessation of blood circulation – in the case of the brain for even a few minutes -- could be fatal.

• Heart surgery could be expected to produce profuse bleeding. But drugs to limit bleeding and knowhow and facilities for blood transfusions, did not exist. 'A' and 'B' blood types had just been discovered (in 1901). The life-saving potential of transfusions wasn't realized till the 1940s after more precise categorization of blood types had been made, anticoagulants developed, and blood banks established.

• Surgical treatment of most heart problems (such as diseased arteries and leaky heart valves) required repair or reconstruction and not, as with typical operations on other internal organs, cutting out of tumors or diseased tissue. But techniques for surgical repairs inside the body had not been developed (except in orthopedic surgery). As mentioned, even sewing together blood vessels was in its infancy,

• Diagnosis was unreliable. Several kinds of heart diseases, as well as some lung diseases, could produce the same symptoms and could not be distinguished through physical examination. X-rays offered definitive identification of tuberculosis and bone fractures but could only helped diagnose some heart diseases. In particular, the most common, namely coronary disease, did not clearly show up in X-rays. Even when observable symptoms strongly suggested that coronary disease had constricted a patient's arteries, physicians could not ascertain the location of the constrictions. And problems of collapsing lungs, operating on a pumping organ, and excessive bleeding discouraged exploratory or diagnostic surgeries.

A few physicians did nonetheless attempt heart surgery, typically on patients who were expected to soon otherwise die. In 1895, the year before Paget had offered his pessimistic forecast, Norwegian surgeon Axel Cappelen tied up a bleeding coronary artery of a 24-year-a stabbing victim, who seemed to recover but died a few days later. The following year, a German surgeon Ludwig Rehn, sewed close a hole in the heart of a stabbing victim, saving the patient' life. By 1902, 39 similar emergency heart operations – 38 in Europe and one in the US -- had been reported. Fifteen of the patients had survived. But, most surgeons did not attempt to operate even on shooting and stabbing victims. They tended as one US surgeon put it in 1914 "to leave such situations in the hands of God, lawyers and police officers."[7]

Chest (thoracic) surgeries. Efforts to treat tuberculosis and other lung diseases produced advances that surgeons would eventually use in heart operations. Lung surgery already had a long history, going back to Hippocrates and entailed less difficulty and risk: Many conditions could be precisely diagnosed from clinical symptoms, and (as mentioned) from X-rays. Patients could be treated by removing diseased tissue (rather than repair). Bleeding was less profuse and lung movements were less vigorous.

Chest incisions made to operate on lungs could however cause lungs to collapse. This risk spurred efforts to prevent such collapses. In the early 1900s a German surgeon, Ferdinand Sauerbruch, developed an apparatus that kept the patient's chest inside a pressure chamber while the head remained outside.[8] Sauerbruch popularized his innovation through demonstrations in Europe and the US. Sauerbruch, and other pioneering surgeons, also widened the range of operations performed inside the chest and helped make thoracic surgery a recognized sub-specialty by the 1920s.

The 1930s posed challenges for the new specialty. Many tuberculosis and other patients with lung diseases had limited means – or during the Depression employment even – and no health insurance. Specializing in chest operations was not economically attractive for physicians. Besides, even though antiseptic practices had reduced mortality rates, the risks of major operations remained high. Edward

Graham, a pioneering chest surgeon would later recall, it was "remarkable" that any patients survived when there were no antibiotics and blood transfusions. And high mortality created a "vicious circle," wrote Graham: "The only patients referred to us were those who were in bad condition" while "our lack of conspicuous success with many of those about to die led in turn to our failure to obtain patients in good enough condition for the operations to justify any reasonable optimism in the surgical treatment of the given diseases." Nonetheless, the pace of thoracic surgery accelerated in the 1930s, to the point that, according to Graham, "the difficulty of keeping abreast with the newer developments" seemed at times to be "insurmountable."[9]

Repairing and bypassing constricted heart valves. Some thoracic surgeons – and their methods -- would later move into heart surgery but not in the 1920s and 1930s. Progress in heart surgery remained slow as new procedures, usually developed through animal experiments, failed to produce acceptable results in humans. Notably, surgeons successfully operated on two patients with thickened ("stenotic") mitral heart valves – a debilitating and usually deadly consequence of rheumatic fever that reduces the flow of blood through the heart's left chambers. But, patients in eight of the ten stenosis operations, performed at six institutions by 1929, had died within a week. Stenosis surgery was then abandoned till after World War II.

Operations, which started in the 1940s, to treat "blue babies" born with tight heart valves had more success. The congenital condition that limited the blood that hearts could pump into lungs made simple physical activities impossible and virtually ensured death before adulthood. The Blalock-Taubssig operation developed at John's Hopkins (See box Blue Baby Operations) could -- in infants and children who survived it -- immediately turn skins from blue to pink, improve the capacity for physical activity and extend life spans.

Blue Baby Operations

In the early 1940s, Helen Taussig, a pediatrician at Johns Hopkins (and director of its Children's Cardiac Clinic) envisioned rerouting blood that would normally flow through the heart's right chamber and into the pulmonary artery (and thence to the lungs for re-oxygenation). A conduit that rerouted de-oxygenated blood directly into the pulmonary artery, Taussig imagined, might improve or prolong the lives of babies born with excessively tight pulmonary valves that restricted flow of blood to their lungs and thus the re-oxygenation of their blood (turning their skin 'blue'). Taussig teamed up with her Hopkins colleague, and chief of surgery Anthony Blalock to implement the concept in a procedure that came to be known as the Blalock-Taussig (or blue baby operation).

The first such operation was performed on a 16-month-old girlwho was critically ill in November 1944. The case was written up (along with two others) in the May 1945 issue of the *Journal of the American Medical Association* (JAMA).

Although at the outset mortality rates were high – 23% for Blalock's first 110 cases -- and blue baby births were very rare, the operation was regarded as a breakthrough. Blalock attracted patients from all over the country and abroad to John's Hopkins. *Life*, a popular weekly magazine with millions of readers, published a photo-essay featuring patients like the seven-year old Michael Shirmer whose "lips and fingernails were always blue", "had to be carried up and down stairs," and "seemed destined to be crippled until a premature death." Blalock's operation, *Life* reported, made Shirmer the healthy child he had never previously been.[10]

Developments in World War II helped broaden the ambitions of cardiac surgeons. High survival rates from operations performed in military hospitals to remove fragments of artillery shells from the hearts of soldiers "disproved the notion that it was too risky to cut a small hole in the heart's wall in order to operate inside it."[11] The war also improved prospects for heart surgery by catalyzing the widespread collection, storage, and transfusion of blood. And, when the war ended, a few surgeons revived efforts to repair

stenotic valves that had been abandoned in the 1920s, this time with more success (See Box Revival of Stenotic Valve Surgery).

Revival of Stenotic Valve Surgery

Charles Bailey, a Philadelphia surgeon who at the age of 12 had lost his father to mitral stenosis was one of the pioneers of post-War efforts to operate on stenotic mitral valves. Bailey tried to use a tiny knife attached to his finger to widen the valves. His first attempt on a human in 1945 – after several animal experiments -- failed when the patient died on the operating table before Bailey could use his knife. By the spring of 1948, Bailey had attempted two more operations. Both patients died within a week of their surgery. A fourth patient then died on the operating table. Finally, in June 1948, Bailey successfully operated on a 24-year old woman. A week after her operation the woman accompanied Bailey on a 1,000 mile train trip to the annual American College of Chest Physicians meeting in Chicago. There Bailey presented her in a lecture he gave on the operation he had just performed.

As it turned out, Bailey was not alone. After Bailey's lecture, Horace Smithy, a South Carolina surgeon told the audience that he had already operated on seven patients with mitral stenosis. Five had survived. And just as Bailey was delivering his lecture in Chicago Dwight Harken was preparing to operate on a 27-year old patient in Boston. Harken, "a very aggressive and supremely confident surgeon," who had successfully operated on the hearts of more than 100 soldiers in the Second World War also failed to keep his first human patient alive. Harken's second operation, performed 10 days after Bailey's first success, resulted in dramatic improvements in the patient's health, however.[12]

The *New England Journal of Medicine* (NEJM) published Bailey's detailed descriptions of his two operations that very November. The same month, the mass-circulation (but now defunct) *Saturday Evening Post* ran an article subtitled "For the Millions Whose Hearts Have Been Crippled by Disease, There Is New Hope." It reported that Dr. Smithy, a South Carolina surgeon, had "slipped a valve knife of his own design into the heart of frail 24-year-old Betty Lee Woolridge….and snipped away part of her thickened mitral valve." Woolridge, who had been incapacitated by severe breathlessness, had pleaded with Dr. Smithy: "Couldn't you find some way to even help me? You won't be losing anything. It will be me. I am taking and asking for the chance… Experiment on me, and I will do my part or even more." Woolridge had survived her operation the article reported, and her symptoms had improved dramatically. A photograph showed her shaking her surgeon's hand as she climbed the steps of her airplane home."[13]

Heart Lung Machines Efforts to treat other congenital heart diseases and valve defects prompted the development of large incision ("open heart") techniques through which surgeons could actually see and operate inside the heart – while suspending its pumping without damaging other vital organs, particularly the brain.*

The first successful open-heart operation was performed on a five-year-old girl with a congenital heart defect at the University of Minnesota. In September 1952, Drs. F. John Lewis and Mansur Taufic clamped the blood vessels that carry blood out of the heart with silk string after lowering the girl's body temperature to 79 degrees Fahrenheit: other surgeons had previously established that inducing hypothermia to cool the brain would protect the organ from the damage that suspending the flow of oxygenated blood would normally cause. But cooling gave surgeons only five or six minutes to operate before brain damage would occur, so this approach could only be used for simple defects.

Walt Lillehei -- another University of Minnesota surgeon – invented and implemented "cross-circulation" operations on children whose circulation was physically connected to a parent's circulation.

* The Blalock-Taussig blue baby procedure avoided this problem because it did not require surgeons to operate inside the heart. Widening mitral valves did require cutting into the heart but with incisions so small that surgeons relied on touch to manipulate the tiny knives attached to their fingers.

Thus, the parent's circulatory system would supply oxygenated blood to the child, giving the surgeon more time to operate on the child's stopped heart. But, although Lillehei used cross circulation to successfully operate on many children, no other surgeon ever did. (See Box 'Using Cross-Circulation in Open Heart Surgery').

Using Cross-Circulation for Open Heart Surgery

In March 1954 Lillehei first used cross-circulation – in spite of the opposition of some University of Minnesota colleagues – to sew closed a hole between the lower chambers of a sickly eleven-month boy's heart. Although the boy died of pneumonia 11 days after the operation Lillehei was encouraged by an autopsy showing the hole was 90 percent closed. By November 1954, eight months after his first operation, Lillehei announced the results of 30 operations he had performed using cross circulation: 19 patients and all parents had survived.

The same month *Life* magazine provided a picture-filled account of Lillehei's operations to "a public that had a big appetite for medical breakthroughs" and the National Heart Institute director James Watt applauded Lillehei's "remarkable achievement." Nonetheless all other cardiac surgeons avoided cross-circulation "mainly because operating on one patient's heart could result in two deaths," according to Fye.[14]

Rather, surgeons began using heart lung machines (as described earlier in the section on "Disease and Treatment Alternatives") to stop hearts for operations. John Gibbon, a Philadelphia surgeon had built experimental machines in the 1930s and in 1939 reported using one to take over the heart and lung functions of cats (who had survived the experience). After a break for military service in World War II, Gibbon resumed development at Philadelphia's Jefferson Medical School. A 1950 article in *Life* highlighting Gibbon's work noted that surgeons had "excised lungs, spliced nerves and even probed the brain"; but because the risks were so great "only rarely is the inner heart exposed. In the near future, however surgeons may be able to do this routinely, with the world's first mechanical heart and lungs" which would allow surgeons "to expose and repair damage inside a virtually quiet, bloodless heart."[15]

But again, it was a University of Minnesota surgeon who first used a heart lung machine on a human: In April 1951, surgeon Clarence Dennis operated on a "rapidly failing" six-year old girl using a machine Dennis's group had been developing for the previous four years. A record 16 participants helped perform the operation including four surgeons, two anesthetists, four people operating the heart lung machine, one managing the transfusion apparatus and one drawing blood samples. The machine supported the girl's circulation for forty minutes while the surgeons tried to close a hole in her heart. Unfortunately, massive blood loss lead to her death on the operating table. Dennis nonetheless declared that the heart lung apparatus had proved "adequate" and provided "much valuable information."[16]

Gibbon's turn came the following year, in February 1952, when he used a heart lung machine (that IBM had helped build) to operate on a fifteen-month-old girl. Again, the machine seemed to work but the girl died after surgery. Moreover, the operation had apparently been guided by a faulty diagnosis: When Gibbon opened the girl's heart, he discovered a different defect than the one diagnosed before the operation. In July of that year, Forest Dodrill, a surgeon at Wayne State University's medical school in Detroit successfully repaired the mitral valve of a 41-year old man, rerouting blood around the patient's heart and into a mechanical pump. Volunteer engineers from General Motors had constructed the pump, which looked like a Cadillac V-12 car engine, according to Dodrill's conceptual designs.[17] Dodrill's "Michigan Heart" did not however include an artificial oxygenator; rather the apparatus relied on oxygenation in the patient's own lungs (and thus Dodrill's 1952 operation is not considered the first successful operation using a heart-lung machine).

In May 1953 Gibbon performed the first successful operation using a machine that included a mechanical oxygenator but patients in two subsequent operations – both five-year old girls – did not

survive. Gibbon attributed the deaths to "human error and not failure of the apparatus" -- but stopped doing open-heart operations.[18]

Before stopping, Gibbon – and through his intervention, IBM -- helped the Mayo Clinic build its own heart lung machine. The Clinic, based in Rochester, Minneapolis, less than 100 miles from the university whose surgeons had pioneered open-heart surgery, was more focused on treating patients than academic medical centers. But it was owned by a charitable foundation and regarded research as important to its mission (see Exhibit 'The Mayo Clinic'). In April 1953, Mayo's Board of Governors approved a heart-lung machine project. They expected the machine to cost $27,000 and to be used once a month. A Mayo team comprising a cardiologist, biomedical engineer, cardiac pathologist and two physiologists and a surgeon designed a machine, which came to be known as the Mayo-Gibbon machine. They used engineering specifications from IBM and advice from Dennis and Dodrill.

In March 1955, surgeon John Kirklin's team first used the Mayo-Gibbon machine to close a hole in the heart of a five-year old girl who survived the procedure. Word spread quickly. The Mayo Board had already approved an eighteen-point publicity plan and Mayo's Section of Publications had prepared for media coverage. In about a month Kirklin operated on seven more children, selected from an "otherwise doomed to die" list. Three had survived.

Kirklin and his colleagues wrote up their operations for the May 18th issue of the *Proceedings of the Staff Meeting of the Mayo Clinic* in which they concluded that despite the high mortality rate, their heart-lung machine had established it could provide "excellent conditions for precise, unhurried" surgery. In September, a television program with six million viewers – TV was then rapidly eroding the dominance of mass circulation magazines and newspapers -- devoted an entire show to open heart surgery at Mayo.[19]

News of Mayo's open-heart surgery and the absence of alternatives – the University of Minneapolis was the only other place regularly performing the operations – produced a surge in referrals of children with congenital disease to Mayo (from six in January 1954, to forty-one in January 1956). Yet, in February 1956, a cardiac pediatrician at Mayo doubted that the operations would ever be performed "in appreciable numbers at very many institutions."[20] One reason for the pediatrician's skepticism was the cost and complexity of the heart-lung machines; another was that open-heart surgery was only used to treat relatively rare congenital defects. Both would change.

A dozen groups were already "racing to construct heart-lung machines that would be less expensive and easier to use than the Mayo-Gibbon apparatus"; and in January 1956 physicians at the University of Minnesota announced a machine with a "simple, disposable" oxygenator[21] which they had by then used in seven operations in which five patients had survived. The next month the Cleveland Clinic (founded in 1921 and modeled after the Mayo Clinic) announced its first operation using a heart-lung machine which was also less complex than the Mayo-Gibbon machine.[22] Other surgery centers also designed and built their own machines. A British surgeon observed in 1957 that there were "nearly as many varieties of machines as there are motor cars" with designs "partly dictated by sound mechanical and physiological principles; partly by whim."* [23] And, improvements in heart-lung machines increased the scope of open heart surgeries. After University of Minnesota surgeons performed the first repair of the aortic valve (which controls blood leaving the heart's left chamber) using a heart-lung machine in 1956, open-heart surgery was soon performed on a variety of diseased valves.[24]

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* Acquiring the skills, experience and organizational capabilities needed to perform open-heart surgery was apparently more difficult. The Cleveland Clinic's initial mortality rate was, as elsewhere, high. Alarmingly it rose – thirty nine of the first hundred patients died – – to the point that the clinic suspended the operations. Johns Hopkins which had pioneered operations to treat congenital heart disease did not of even attempt to start an open-heart surgery program. Meanwhile, Mayo topped the number of surgeries performed in 1956 with two or three operations each week (Fye p. 232).

Diagnostic Advances. More operations stimulated improvements in and increased the use of diagnostic techniques. Gibbon's first experience with operating on a misdiagnosed patient was not uncommon: physical exams and x-rays could not reliably locate diseased valves or establish the nature of congenital heart defects. And, although important diagnostic foundations had already been established, researchers had little incentive to refine them or physicians to develop the skills needed to use them until heart-lung machines made cardiac surgery less experimental.

Cardiac catheterization was one important diagnostic technique spurred by open-heart operations. Researchers had previously used catheters to draw blood samples from the right chambers of patients' hearts (see Box, Evolution of Cardiac Catheterization). But they had not risked inserting catheters into the heart's left chambers. More surgical repairs of aortic valves (and other operations on the heart's left side) accelerated the development of safe catheterization of the heart's left chambers.

Evolution of Cardiac Catheterization

In 1844 a French researcher, Claude Bernard, (who coined the term "cardiac catheterization") had inserted catheters into the hearts of animals to draw blood samples. In 1929 a strong-willed surgical resident in Germany, Werner Forssmann, performed the first documented catheterization of a human heart. He inserted a catheter into a vein in his elbow (that he had anesthetized), used a fluoroscope (an x-ray device that projected images on a screen) to thread the catheter into the right chamber of his heart, and took chest x-rays to record the insertion. All this required tricking a nurse and defying the chief of his department who had warned him against the self-experimentation. Forssmann then successfully used a catheter to deliver medication directly into the right heart chamber of a terminally ill-woman. Continued self-experimentation – – Forssmann would perform eight more self-catheterizations – – and "failure to meet the scientific expectations of his chief" forced the would-be surgeon to switch to urology.[25]Eventually his pioneering contributions were recognized: Forssmann shared the Nobel Prize in medicine in 1956 (though he was never able to secure a professorship because he had not finished his PhD).

In the early 1940s, André Cournand and Dickinson Richards (who received the Nobel Prize with Forssmann) of Bellevue Hospital in NYC significantly advanced the diagnostic use of catheterization. They used catheters to draw blood samples rather than to deliver drugs as Forssmann had done. And they developed techniques (based on the blood samples) to estimate cardiac output -- the rate at which the heart pumped out oxygenated blood and intra-cardiac pressures -- blood pressure within the heart's chambers. Estimates of cardiac output and intra-cardiac pressures in turn helped make diagnosis of heart disease more accurate.[26]

Angiographic diagnostic techniques developed along with catheterization. As mentioned, angiography entails taking X-rays (or observing x-rays projected on a fluoroscope) that track contrast material injected into a patient's blood stream. A Portuguese neurologist had first used contrast materials to diagnose brain tumors in 1927. Physicians then performed a variety of angiographs – for instance on the blood vessels in the lungs, arms, and legs. Unprecedented blood vessel injuries in the Second World War stimulated the use of angiographs to guide vascular surgeries. Similarly, as the number of heart operations expanded in the 1940s and 1950s, cardio-angiographs (which had been invented the 1930s) entered clinical use.

Cardio-angiography also benefitted from advances in cardio-catheterization: physicians could use catheters to precisely deliver contrast agents at desired locations in the heart's chambers (to for instance assess the functioning of heart valves). Then in 1958, a catheter that accidentally flooded a patient's coronary artery with a contrast agent opened the door to coronary angiography. Previously, physicians believed (on the basis of animal experiments) that high concentrations of contrast agents in coronary arteries would trigger heart attacks. But to the relief and surprise of Dr. Mason Sones – a well-known cardiologist at the Cleveland Clinic whose catheter tip had strayed close to the opening of a patient's coronary artery – the patient tolerated the accidentally inserted contrast agent quite well, although his heart did stop beating briefly.

Sones then ordered catheters with tips designed to inject contrast agents into coronary arteries and proceeded to become a leading authority and advocate of coronary angiography. This technique could potentially help physicians determine whether patients with symptoms of coronary diseases actually had constrictions in their coronary arteries – and if they did – where these constrictions were located. Most other cardiologists did not however quickly start performing coronary angiographies, possibly because no treatments were available to take advantage of the diagnostic advance. But, Sones's enthusiasm and expertise encouraged Sones's surgical colleagues at the Cleveland Clinic, most notably Donald Effler, to operate on patients with constricted coronary arteries.

Indirect revascularization – the Vineberg implants. Effler's team attempted two kinds of surgeries to treat patients with constricted arteries. Although both had significant limitations, the attempts helped establish a base at the Cleveland Clinic which would make it a leading center for CABG operations.

Effler performed his first operation for coronary disease on a 45-year old man in 1962. The operation (an "endarterectomy" which had been first attempted by another surgeon in 1957) sought simply to restore the normal flow of blood through the coronary artery by surgically extracting the plaque that was blocking it. But mortality rates were extremely high: Effler operated on 147 patients between 1962 and 1967, with a hospital mortality of 11 percent for endarterectomies on right coronary arteries and 65 percent when applied to the left coronary arteries. Moreover, the operation could not be easily performed if plaque had constricted an artery at several places.

Cleveland Clinic surgeons also did "Vineberg" implant operations, which the Montreal surgeon, Arthur Vineberg, had first performed in 1950. Here, as in later CABG operations, surgeons would cut away the ITA (internal thoracic artery) from the patient's chest wall. But, instead of grafting the detached end into a coronary artery, surgeons would implant it on the surface of the patient's heart (as, roughly speaking, hair follicles can be implanted on scalps). Experiments on dogs had shown that new blood vessels naturally formed after such implants carried oxygenated blood from the implanted ITAs to tissues of the heart muscle.

The procedure did relieve the symptoms of many patients and some angiographs showed that blood continued to flow through implanted arteries suggesting that (as in the dog experiments) the surgically "redirected" artery was somehow carrying oxygenated blood to heart muscles. And, the Cleveland Clinic's low mortality rates (of about 4%) in Vineberg implants made Effler a great enthusiast of the technique, declaring the arrival, in a 1968 editorial, of "A New Era of Surgery for [Coronary]Heart Disease." By then Cleveland Clinic surgeons had performed more than 2,000 Vineberg implants supported by more than 12,000 coronary angiographs. They also attempted to improve the technique by for instance doing "double" implants using both the right and left ITAs and by combining implants and endarterectomies.

Physicians outside the Cleveland clinic were not enthusiastic. Previous and similarly "indirect" ways of stimulating new channels to supply blood to heart muscles (without "directly" operating on coronary arteries) had not worked. And, the evidence that the new blood vessels formed after Vineberg implants provided an adequate supply of blood to human hearts (as they did in dogs) seemed inclusive. Moreover, few medical facilities outside Cleveland had the equipment or the expertise to perform and read coronary angiographs and therefore no reliable way to select patients who were good candidates for implants and to monitor their progress. Even at the Cleveland clinic, reliable criteria for selecting patients had not yet been established. The consensus therefore favored continued use of drugs rather than surgical treatment of coronary disease. Overall, from 1950 to 1970 physicians performed only about 5,000 Vineberg implants[27] (including more than 2,000 at the Cleveland Clinic.)

3. Finally, CABG

Although the expertise and tools that Cleveland Clinic physicians had accumulated in treating heart disease would later make them leaders in CABG, they did not pioneer the procedure. Rather, Robert Goetz

the head of cardiovascular surgery at the Albert Einstein College of Medicine in New York led the first successful bypass operation in 1960 (two years before Effler's first endarterectomy in Cleveland). The first patient was a 38-year old taxi driver who had been taking 70-90 tablets of nitroglycerine a day to relieve the symptoms of his severe angina. Goetz, assisted by two other physicians, cut away a thoracic artery from the patient's chest wall and connected the detached end of the artery to a right coronary artery using a titanium ring that Goetz had designed. The physicians operated without a heart-lung machine and managed to connect the thoracic to the coronary artery in just 17 seconds.

The patient's angina disappeared and an angiography showed an unobstructed flow of blood flowing through the redirected artery into the patient's coronary artery. Nonetheless this was the last CABG that Goetz's department head allowed him to perform (See Box "The World's First -- and Dr. Goetz's Last -- CABG"). Goetz did not even publish an article about his pioneering operation: he merely summarized his experience in an addendum to an article he published about the animal experiments he had undertaken to develop this procedure.

The World's First -- and Dr. Goetz's Last -- CABG.

According to the letters Robert Goetz sent to a Mayo surgeon (whose article[28] this box summarizes) a "bumpy" path led the German-born Goetz to Albert Einstein in New York. Goetz had left Frankfurt for Switzerland in 1934 after completing his final examination (but before starting his internship) because the Minister of the Interior had declared him "politically unreliable" and had blocked the grant of his diploma. Fortunately, a University of Frankfurt professor of anatomy who had preceded him to Switzerland found Goetz a job which enabled him to get an MD degree. In 1936, Goetz gave up his relatively safe job in Switzerland to do research at the University of Edinburgh; but, the Home Office in the UK didn't consider him a bona fide refugee because the wasn't Jewish and denied him permission to work. Fortunately, he saw an advertisement for a research position at a department of surgery in South Africa so he set sail for Cape Town in 1937. His European medical credentials were not accepted and his German passport required him to report regularly to the police. In 1944, after passing the necessary exams, Goetz finally became a licensed physician, secured an appointment as an Associate Professor of Surgical Research in Cape Town, and proceeded to build an international reputation in the field of blood circulation.

In 1954, when Goetz was lecturing at Georgetown, he met the recently appointed Chairman of the Department of Surgery at Einstein College in New York. The Department had just begun recruiting its first faculty and its chairman offered Goetz the position of head of its cardiovascular unit. Again, after crossing the hurdle faced by foreign medical graduates of securing US credentials, Goetz tried to get cardiac surgery going at Einstein, focusing attention on operations to treat blocked coronary arteries. Presumably because Einstein didn't have a heart lung machine, Goetz adapted a titanium ("Payne") ring to connect detached thoracic arteries to coronary arteries without any time-consuming suturing, and refined his ring-based technique on dogs.

Most of Goetz's medical (i.e. cardiology) colleagues were "violently against" using his technique on a human. Goetz's team therefore "literally had to snatch" their first patient from the medical department (with the help of a solitary sympathetic cardiologist). After the operation succeeded, "medical colleagues were not impressed" with an operation they "considered not only highly experimental but also unwarranted." Goetz even received "severe criticism" from his fellow surgeons. And the head of the surgery department unilaterally appointed a cardiac surgeon and told Goetz to concentrate on vascular surgery.

A few sporadic and unplanned CABG operations followed: in 1962, David Sabiston operated on a patient who unfortunately died of a stroke three days later. Sabiston did not publish an account of his case until 1974. Garrett, Dennis, and DeBakey performed a successful and unplanned operation in November 1964 and did not publish the results until 1973. Both CABGs had been performed in the course of attempting endarterectomies (in which, plaque is surgically extracted from arteries, as described above).

Vasilii I. Kolesov, chairman of the Department of Surgery at the First Leningrad Medical Institute is widely credited with performing the first successful, planned, "modern" CABG in February 1964. Kolesov operated without using a heart-lung machine or titanium ring (that Goetz had used). Kolesov then performed 12 more operations over the next three years – – as chairman of his department he could not be stopped. But again, the operations were not enthusiastically received by other surgeons. In 1965, after Kolesov reported his first results to the Cardiology Society in Russia, the society passed a resolution that "the surgical treatment of coronary artery disease is impossible and has no prospects for the future." Similarly, when Kolesov reported his first 12 cases in a US journal in 1967, an accompanying editorial noted that "the opinion concerning the management and surgical treatment of angina pectoris as expressed in the paper by Professor V. I. Kolesov are at variance with the concepts of many surgeons in the United States." And indeed, very few surgeons had attempted bypass operations in the United States by then.

One of the few was René Favaloro, an Argentinian surgeon at the Cleveland Clinic (see box Favaloro's Star-crossed Journeys) who would come to be known as the "father" of CABG. In addition to having exceptional surgical skills and diligence in documenting results, Favaloro benefited from the support of a deep Cleveland Clinic "bench" (as he would later call it). This included surgeons, cardiologists, nurses, technicians and top-class facilities including a heart-lung machine, diagnostic equipment, library of angiographic films and images (with "every conceivable manifestation of coronary artery anatomy and pathology"[29]), and an Intensive Care Unit.

Favaloro's Star-crossed Journeys.

Favaloro and his wife arrived – uninvited – at the Cleveland Clinic in 1962 hoping for a Fellowship in cardiac surgery under Effler. He had been forced since 1950 to practice surgery in a small village in the southwest of Argentina after refusing to sign a political declaration supporting the "national doctrine" of president Juan Peron. In 1960 he began to "cherish the idea of traveling to the United States to train in thoracic and cardiovascular surgery"[30] and was advised by one of his old professors to go to the Cleveland Clinic who also sent a letter of introduction to a physician there.

But, no one was actually expecting Favaloro in Cleveland. When the Argentinian explained in his "broken English" the reason for his trip to Effler, Effler made it clear that because Favaloro wasn't licensed to practice in the United States, he could only be an unpaid observer. Favaloro agreed, saying he was not asking for money, only an opportunity to learn.

The 38-year-old observer who had performed "hundreds and hundreds" of operations in Argentina, made himself useful placing catheters, pushing beds back and forth to the Intensive Care Unit, helping the anesthetists, and cleaning the Clinic's heart-lung machine. Favaloro also befriended Mason Sones (who had pioneered coronary angiography). Every evening, and often late into the night, Favaloro reviewed Sones's library of angiographic films and learned about the anatomy of diseased and healthy coronary arteries under Sones's tutelage.

A year later, after passing the necessary Council of Foreign Medical Graduates examination Favaloro became a fully credentialed Fellow at the Cleveland Clinic and, in 1964, a senior resident. Favaloro returned to Argentina after completing his residency but found the political climate there "disappointing." In December 1966, he came back to start a position on the Cleveland Clinic staff. And in just four years, Favaloro built an international reputation for his contributions to CABG.

In June 1971 Favaloro again returned to Argentina to "the great disappointment of all" – especially Sones -- in Cleveland and established the Institute of Cardiology and Cardiovascular Surgery in Buenos Aires. In the late 1990s, defaulted payments by the Argentinian government and other payers inflicted large losses on Favaloro's Institute. Favaloro pleaded with the country's president to resume payments but with no success. "Broken and destitute, he took his own life on June 29, 2000 at age 77."[31]

Favaloro performed his first CABG in May 1967. By then Cleveland surgeons had accumulated considerable experience in using saphenous vein grafts (extracted from patients' legs) to reconstruct renal arteries. Favaloro, Mason Sones and some other Cleveland Clinic colleagues agreed to try using such grafts to replace constricted segments of right coronary arteries — but only in cases where collateral circulation was already compensating for the constricted blood flow (so that if the operation failed, the patient would not be worse off).

The first operation, on a 51-year-old woman was a success: an angiograph after the operation showed blood flowing freely through the grafted vein. By the end of 1967 Favaloro had performed similar operations on fourteen more patients as well as one operation in which he used a vein graft to divert some blood from the patient's aorta into a constricted coronary artery (at a point "downstream" from the constriction). This fifteenth aorta-to-coronary graft, rather than the grafts which replaced segments of constricted arteries, would become the standard bypass procedure. [32]

Favaloro described his 15 operations in an article submitted to *The Annals of Thoracic Surgery* in December 1967. The article, published in April 1968 and now considered a "landmark",[33] included an addendum noting that Favaloro had by then performed 55 operations with only two hospital deaths.

In 1968, Favaloro pioneered emergency CABG on patients who were having or about to have heart attacks. His results, later reported in the *American Journal of Cardiology* in 1971 (and in a 1970 monograph), suggested that emergency CABG performed within six hours of an acute heart attack could preserve most of the patient's heart muscle.

Favaloro also began to perform (although did not pioneer) CABGs on left coronary arteries in 1968* as well as double bypasses (on both left and right coronaries), CABGs combined with heart valve repairs or replacement and with surgeries on the heart's left chambers. By the end of 1968, Favaloro had operated on 171 patients and summarized the results in an article accepted for publication by the *Journal of Thoracic and Cardiovascular Surgery* in December 1968.

By December 1969 Favaloro and his colleagues had performed CABG operations on 570 patients with an overall mortality rate of 5.4%. About half of the 570 patients also received Vineberg implants: their previous experience with the implants made it difficult for the Cleveland surgeons to stop using them, so they often combined implants and CABG. In the next six months, the Cleveland Clinic's cumulative tally of CABG nearly doubled while mortality rates fell: By June 1970 1086 operations had been performed with a mortality rate of 4.2%.

Favaloro himself did not pioneer many CABG procedures. Milwaukee's Dudley Johnson operated on left coronary arteries before Favaloro. And, Favaloro favored saphenous vein grafts for to bypass constrictions; other pioneering surgeons (like Kolesov) started using thoracic artery grafts — which would turn out to be the more reliable choice — in 1968.[34] Rather, Favaloro often simplified and improved what others had pioneered. And, besides performing more operations than other surgeons, Favaloro was exceptionally diligent in disseminating his techniques and results in journal articles, textbooks and at conferences.

The Cleveland Clinic also did not dominate CABG operations the way it had Vineberg implants. By 1967 (when Favaloro did his first CABG) operations to repair diseased heart valves and congenital heart defects using heart-lung machines had surged, tuning open-heart surgery from "an experimental procedure in 1955 to a standard technique."[35] In 1969 nearly 40 hospitals were performing more than 200

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* Milwaukee's Dudley Johnson was the first to operate on left coronary arteries. And in some accounts Johnson, rather than Favaloro is called the "father" of CABG.

operations a year[36] and apparently, several open-heart surgeons started performing CABG.*As of 1971, CABGs had been performed in at least 16 centers, completely relieving 60 to 70% of patients of their angina and other symptoms. Mortality rates however were often higher outside Cleveland -- in some places exceeding 10% -- possibly because they lacked the Clinic's exceptional multi-faceted capabilities.[37]

Favaloro's participation in a symposium at the Sixth World Congress of Cardiology in London in 1970 was especially noteworthy. The symposium according to Favaloro "opened the doors for the worldwide use of CABG. Thousands of doctors from all over the world were exposed to a critical analysis that showed the benefit of this new approach." Some surgeons who had been skeptical of the low mortality rates claimed by Favoloro, accepted his invitation to visit the Cleveland Clinic and "check our files." And, during that visit to London, a leading British surgeon invited Favaloro to operate at the National Heart Hospital. There, Favaloro performed the first coronary artery bypasses in England, with most of the prominent cardiovascular surgeons from Europe watching the surgery from behind, almost on top of Favoloro's shoulders.

4. Controversial Growth

CABG took off in the 1970s; US surgeons were performing more than 100,000 operations annually by the end of the decade.[38] However, as we will see, the growth prompted concerns about effectiveness, risks and costs. Although these concerns do not seem to have had much practical effect in the US, they likely restrained CABG operations in many other countries.

Press reports in the early 1970s gave broad exposure to the enthusiasm of cardiologists and heart surgeons. A 1971 *Life* magazine article entitled "Lifeline for a Man with a Dying Heart: New Surgery Saves Doomed Coronary Victims" told stories of how bypass grafting, had saved some two thousand lives and totally freed nearly 90% of those undergoing it from debilitating pain. And "although the article noted that the operation was less than three years old, it implied that the benefits lasted indefinitely."[39]

In October 1971, United Press International (that provided news stories to several thousand media outlets) reported that a Harvard Medical School professor had told a meeting of heart specialists, that developing CABG and beta-blocker drugs† was "more important than putting a man on the moon." Previously, "we used to just watch" heart patients die; "nothing really could be done." And, "vast numbers of people were really crippled by [chest] pain. Now they can live nearly normal lives." Another specialist, speaking at the same meeting had said bypass surgery was now a "proven technique and was becoming routine in the nation's hospitals."

But not all physicians were convinced. Henry Zimmerman, a catheterization pioneer and cardiologist, published an editorial in the American Heart Journal (in 1970) noting that numerous surgical procedures to "to provide 'so-called' revascularization" of the heart muscle had previously been introduced with much "blowing of bugles and beating of drums" but no evidence of efficacy. Bypass surgery – "the latest rage" was also no "cure-all." And without a "critical objective evaluation carried out on a well-planned study" cardiac surgeons would "have another field day doing procedures by the hundreds, basing their proof on the premise that the 'patient who has been revascularized feels better.' "[40]

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* For instance, surgeons at the Mayo Clinic who had had not performed a Vineberg implant until 1966 performed their first CABG in 1968.

† As mentioned earlier beta blockers drugs are given to patients undergoing bypass surgery. They can also be used to treat hypertension; and in fact this use of beta-blockers preceded their use in bypass surgery.

In December 1972 the *Boston Globe* published a front-page story on "bypass vein grafts" which it called "one of the most exciting and controversial operations ever developed." More than 70,000 procedures had been performed: "20,000 in 1971 - 10 times the number in 1969."

"Enormous" public demand for the operation, despite its $6000 to $10,000 cost, reflected the "devastating fact" of 600,000 annual deaths in the US from heart attacks and the unquestionable value of the surgery to relieve the intense and often disabling pain of advanced stages of angina pectoris."

Although the operations weren't always successful, the story suggested the risks were worthwhile: patients undergoing the surgery at the Cleveland Clinic had died at the rate of four percent a year (five years after their operation), compared to eight percent of similar patients not treated surgically. Similarly, after performing hundreds of operations, major Boston teaching hospitals had "reduced the mortality rate considerably." Mortality one year after bypass operations at the Massachusetts General Hospital ("Mass General") typically ran from about two percent when surgeons bypassed a single arterial blockage to about four percent for two or more blockages.

Some physicians favored surgery only after medication to treat patient's angina had failed. Others, most notably, Favaloro favored operating on patients with mild or no angina pain if they had relatives who had died at an early age of coronary disease. Surgeries on high risk patients before their heart muscles were damaged by an inadequate blood supply, Favaloro believed, could prevent heart attacks.

Charles Sanders, Mass General's general director however said that preventative surgery or operating on everyone with angina would require "turn[ing] the whole hospital over to open heart surgery" and overwhelm the nation's surgeons. Furthermore, doctors couldn't be sure that bypass operations actually prolonged lives and could treat angina with medication, exercise, diet and changes in lifestyles "without resorting immediately to surgery."

The *Globe* article cited other concerns about the rapid expansion of bypass operations: Small hospitals might enter the field "without the necessary supporting resources" and patient base -- it was estimated that hospitals needed to perform at least 200 bypasses a year to "keep the[ir] operating teams sharp." Hospitals with empty beds and surgeons ("one of the few specialties not in short supply" in 1972) might be "tempted to take patients not appropriate for bypass surgery."

Alternatives under development also suggested "going a little slow in plumping for the vein graft operation." The article cited:

- Work on using thoracic arteries instead of vein grafts: with arteries, according to NYU's Dr. Green, there were fewer problems due to graft length, twisting or tension; only one connecting suture was needed; and because thoracic arteries were of similar diameter to coronary arteries, grafts produced "a better flow pattern" with less mechanical stress.

- "External counterpulsation" for treating angina without surgery. This experimental technique, which had received "considerable claim" at a recent Heart Association meeting, enclosed the patient's legs in a hydraulically actuated boot which applied pressure between heart beats. A Tufts Medical Center physician had "reported benefits to 17 out of the first 21 patients tested, with some helped dramatically..."

The stakes for the US Federal government were also high. Medicare legislation signed into law in 1965 required the government to provide "usual and customary" reimbursement for surgeries performed on patients above 65. And typical costs of $6-10,000 per procedure "meant that the government faced enormous expenditures if bypass surgery grew unchecked."[41]

A 1973 editorial in the British journal *Lancet* observed that "pioneer work at the Cleveland Clinic" had produced a "snowball" that was "still increasing;" with major cardiac centers "organizing a production

line" for the operations. But without scientifically reputable appraisal of the results…we are at risk of making many serious errors of judgment."[42]

Yet by then "the Cleveland Clinic's production line was already running at top speed" performing fifty open-heart operations a week, most of them coronary bypass procedures. *Cleveland Magazine* featured these operations (and the physicians doing them) in a cover story entitled ""Effler and Sones and the Boys at Cleveland Clinic Have Taken the You-Bet-Your-Life Out of Heart Surgery, So Don't Wait Around to Get Zapped by a Heart Attack, Head It Off at the Coronary Artery." The story also speculated that the procedure provided significant income for the Clinic – it paid surgeons who performed the operations salaries of about $100,000 while billing out their services for over $1 million. The non-profit Clinic did not pay taxes on the difference, allowing it to add more than 300 beds, a new catheterization laboratory, and a surgical suite.

And the "scientifically reputable" appraisals urged in the Lancet editorial hadn't been done to the satisfaction of many physicians. Cleveland cardiologist William Sheldon had compared outcomes for the first 1000 patients operated upon between 1967 and 1970 against outcomes for patients with coronary disease who had not been operated upon. Sheldon's study suggested that surgical treatment improved the survival of patients with more severe disease — constrictions of the left main artery or, constrictions in three arteries — and was least beneficial for patients with single constrictions.[43] But, Sheldon hadn't done a randomized clinical trial; and, starting in the early 1960s, many medical researchers had started trusting randomized trials more than after-the-fact evaluations of treatments.[44] (After 1962, the US Food and Drug Administration had required randomized trials before it approved new pharmaceutical treatments. The requirement did not cover new surgical procedures, however).

In 1968, the US Veterans Administration (VA) had started a randomized trial to evaluate the Vineberg implant technique: The government-funded VA, that provides medical care to millions of military retirees, could conduct randomized trials of many treatments entirely within its own hospitals. The Vineberg trial ended with fewer than a hundred patients enrolled when attention shifted to CABG. Therefore, in 1970, VA surgeons modified their trial design to compare the results of bypass operations to drug treatments.

In 1971 the National Heart and Lung Institute (operated by an agency of the US government and renamed the National Heart, Lung and Blood Institute in 1976) decided it had to take a position on the "highly controversial and emotional" subject of bypass efficacy. Otherwise, some other "less-knowledgeable" governmental body could "perhaps improperly, label surgical procedures for coronary artery disease as "experimental" (and thus non-fundable by private or government insurance programs) or "therapeutic" (and thus fundable, albeit at great cost, as presently done."[45] And two years later, in 1973, the Institute sponsored the Coronary Artery Surgery Study (CASS), a randomized trial to compare medical and surgical treatments.

The CASS study enrolled fewer than 800 patients in fifteen hospitals, "reflecting a reluctance to enter patients into randomized trials, even when the value of the procedure was not yet clear."[46] Another Heart, Lung and Blood Institute-sponsored trial, to compare bypass and drug treatment for unpredictably triggered ("unstable") angina, included less than 300 patients. The VA study similarly enrolled only about 700 patients in 13 VA hospitals. One VA hospital, whose chief of surgery believed the study would be "an expensive and time-consuming effort without valid conclusions," did not participate.

Cleveland Clinic physicians were "outspoken" in their opposition to the randomized trials. Its angiography pioneer Sones compared them to the notorious Tuskegee Syphilis trial in which minority prisoners with syphilis were randomized to either placebo, or to antibiotic treatment.[47] When the Heart and Lung Institute was considering its trial, Sones wrote "I hope we do not let the Federal government, through the insistence of the National Heart and Lung Institute, con us into a prospective randomized study in institutions which now 'enjoy' a 2-3% surgical mortality rate in an attempt to tell us whether we can do a good job prospectively."

A University of California heart surgeon, Jack Love, offered other objections to trials of CABG and other new surgical procedures:

• Operations, unlike drug treatments, required manual skills which were not uniformly distributed across surgeons: poor results could simply indicate poorly performed rather than bad procedures.

• Procedures were "rarely introduced as fully defined, easily reproducible techniques." Rather, they came as "principles for solving particular problems" that could be implemented in a wide variety of ways. For instance, more than 200 specific procedural combinations could be used for the same general principle of heart valve replacement.[48]

• Procedures -- and surgeons' abilities to perform them also improved with experience: "The history of cardiovascular surgery" in the past quarter century wrote Love "has been a story of decreasing mortality and increasingly better results." If every new development "had been decreed acceptable or unacceptable on the basis of initial clinical results" observed Love "one wonders how many cardiovascular procedures would be available today."[49]

On the other side, a Wisconsin heart surgeon (at a hospital participating in the CASS trial) noted that bypass operations had "been the salvation of many cardiologists and cardiac surgeons and preserved many heart surgery programs." But all physicians should support randomized trials, putting their "vast economic considerations" aside, "to provide more rational and, therefore, better care for our patients."[50]

Regardless, bypass operations continued to expand before the multi-year VA and Heart and Lung Institute trials could produce any results. By the mid-1970s about 70,000 operations were being performed annually[51] -- including at many community hospitals.[52] And research performed outside the randomized trials suggested that the benefits exceeded the risks. For instance, in January 1976 Dr. Nicholas T. Kouchoukos, reported that 1,341 bypass operations had been performed at the University of Alabama's hospital with an overall mortality rate of 2.3 percent; of the 732 operations performed in 1974 and 1975 the mortality rate had been reduced to 1.4 percent. The chief of surgical services at the Mass General reported similar results and disputed the suggestion that too many bypass operations were being performed. "When this operation can allow a completely disabled man of 40 an 80 percent chance of returning to work it is a humanitarian and economic procedure of great importance."[53]

In April 1977 the Heart, Lung and Blood Institute released the results of its trial of 288 patients suffering from unpredictable angina. The results seemed to suggest that unpredictable angina did not justify CABG: patients responded well to drug treatments and experienced fewer heart attacks than patients who underwent bypass surgery. But, this trial, covering just 288 patients, did not attract much attention.

The first results of the VA trial in September 1977, covering 600 patients who suffered from chronic or stable angina, however stirred vigorous controversy. The results published in in the *New England Journal of Medicine* also suggested that a large proportion of CABG operations were unwarranted.

A front-page article in the *Boston Globe* that followed the *New England Journal of Medicine* article noted the apparent consensus among specialists that CABG increase the longevity of patients with diseased left main arteries. But, this group accounted for only 12% of operations. Bypass procedures on many of the other 88% were thus often being performed (according to the *Boston Globe*'s interpretation of the VA study) on a "false premise of improved longevity" when "more conservative management with drugs would be more appropriate." One of the VA researchers contacted by the Boston Globe agreed that some patients did get "dramatic relief of their chest pain initially" but how long this improvement would last was uncertain.

Moreover, Dr. Eugene Braunwald (writing an editorial accompanying the *New England Journal of Medicine* article on the VA results) estimated that only about half of CABG operations were being done to relieve severe pain that could not be reduced by drugs. The other half were done at the insistence of patients

who had mild or no pain but who believed the operation would extend their lives. And physicians often did not resist: according to Dr. Braunwald the surgery had developed into a mammoth industry "with a momentum and constituency of its own."

Two Cleveland Clinic heart specialists immediately sent a letter to the *New England Journal of Medicine* rebutting the VA results, which the *Journal* declined to publish. The rebuttal (published by another journal)[54] offered several criticisms of the VA results such as:[55]

• The low quality of surgery performed at many of the VA hospitals (evidenced by operative mortality rates of 5.6 percent compared to the 1-2% rates at places like the Cleveland Clinic).

• Enrolling low risk patients in the study as evidenced by unusually low mortality for patients treated with drugs (where competently performed CABG was less likely to improve outcomes).

• "Crossovers": Performing bypass surgeries on patients who had initially been chosen for drug treatments (but recording outcomes in the drug treatment category).

The VA researchers – and other physicians favoring RCTs defended the study, producing a "contentious and intractable debate."[56] In 1981, Braunwald, who had written the *NEJM* editorial commending the VA trial, would recall that the "conflicts among cardiologists and cardiovascular surgeons spilled into the lay press, confusing patients and physicians alike."[57]

The VA study results initially had, according to the Cleveland Clinic's Sheldon, a "profound effect" with the waiting list for CABG surgeries at the Clinic dropping from 300 in 1976 to 71 in 1977.[58] But, the total number of bypasses performed in the US did not fall and by 1980, the number of bypass operations had nearly doubled from the time the 1975 VA report had been published.[59] Even the Cleveland Clinic saw growth in bypass procedures resume in 1979.

One reason, according to cardiologist Sheldon was that later reports from the VA "somewhat tempered the conclusions of the initial study." Additional results coming out of the Heart and Lung Institute's trial and a randomized study conducted in Oregon state also showed that the surgery benefitted subgroups of patients.[60]

But continuing trials could not definitively establish which conditions warranted surgery:

A European trial (the "European Coronary Bypass Study") conducted at 11 centers that had been started in 1973 published its results in 1979. The European results suggested that surgery benefitted patients who had three constricted arteries bypassed: the survival rate after triple bypass operations was 96 percent after five years compared to 90 percent for those only treated with drugs.[61] The trial which had randomized 768 patients but with several exclusions including women, men over 65, patients with single vessel disease, patients with severe angina that could not be treated with drugs, patients whose left main chamber was functioning poorly, and patients with severe hypertension. And, as in the VA study, patients initially assigned to medical treatment had CABGs in under five years because their angina had become intolerable. Yet the survival of these "crossover" patients (accounting for about a quarter of the medical group) was credited to medical treatment, not CABG.

In 1980, the National Heart, Lung and Blood Institute organized a Consensus Development Conference on CABG. The conference, concluded on the basis of the then available evidence, that CABG was "a major advance." Bypasses relieved "chronic, stable angina", reduced "cardiac related events, the amount of medication required and the frequency of hospitalization."[62] The consensus also cautioned however, that the operation was risky and patients with mild angina could be effectively treated with drugs.[63]

In November 1983, publication of the first results of National Heart, Lung and Blood Institute's randomized CASS trial renewed controversy. The study -- which had taken ten years, cost $24 million, and covered 780 patients treated between August 1975 and May 1979 -- had found that:

• The six-year survival rate of patients with mild to moderate chest pain who had had surgery was statistically indistinguishable from the survival rate of patients who had been treated with drugs.

• Early surgery (on patients whose angina had not become severe) did not reduce the risks of subsequent heart attacks or stop the progression of the underlying coronary disease.

• Plaque deposits progressively narrowed implanted blood vessels (in about 40 percent of bypassed patients) and produced blockages in other coronary arteries that had not been bypassed (in about half of the remaining 60% of patients).

• The severity of blockages (and anginas) did not increase the risk of bypass operations but second-time bypasses were less successful and riskier. The Institute's researchers therefore recommended postponing surgery on patients with tolerable chest pains.[64]

Braunwald, who had praised the VA trial -- and then regretted the controversy it had caused – quickly published an editorial in the *New England Journal of Medicine* calling CASS an "excellent clinical trial." And, Braunwald argued, because the trial had found no improvement in the survival of bypass patients, CABGs should be restricted to cases where "intensive medical therapy ha[d] failed" or when trials had shown "unambiguously demonstrated" improved survival after surgery.[65]

Critics again criticized the CASS study for the "crossover" problem – about a quarter of the patients who had initially been chosen for drug treatments had had surgery during the trial period but their survival was credited to drug treatments.[66] In fact CABG pioneer, Favaloro and other critics argued, the survival of "switched over" patients (many of whom were "difficult" cases with multiple coronary blockages) should have been counted as a success of surgery – and the switch as a failure of drug treatments.

Critics also suggested that CASS had systematically enrolled unusually low-risk patients whose life-expectancy was naturally high regardless of what treatment they received. The study had identified about 3,000 eligible cases from a registry of nearly 25,000 patients. 1,315 of the eligible patients had refused randomization; with 69% of these refusals decided by the patients' physicians. And, according to critics, the 780 patients who were randomly assigned surgery or medical treatment were unrepresentative low-risk cases. Nearly two-thirds (620 patients) had mild angina and about a fifth (160 patients) had no angina, whereas in the "starting" registry less than 5% of cases had low or no angina. Similarly, nearly 75% of randomized patients did not have significantly impaired heart-pumping capacities and a tiny proportion of patients with 3-vesssel disease had risky, "proximally" located blockages. And, the good prospects of randomized patients masked the potential benefits of CABG in riskier, more representative patient populations.

Moreover, as Jack Love, had previously suggested, CABG techniques had changed materially between 1979 (when the last patients in the CASS trial had been treated) and 1983 when the trial results had been published. Notably, in the early 1980s, cardioplegic drugs that temporarily suspend the operation of the heart during surgery had reduced mortality rates. Similarly, physicians were also changing the blood vessels they used to bypass constricted arteries. In the 1970s they had mainly used leg vein grafts. For instance, veins were used in 87 percent of bypass operations performed in the US in 1979.[67] But, after researchers found that implanted vein grafts had a high tendency to clog, surgeons had starting ITAs which remained unclogged for much longer. This potentially reduced a major benefit of waiting for intolerable angina that the CASS researchers had suggested. Therefore, more generally, even if the CASS trial had "correctly" identified conditions justifying bypass surgery using early 1970s practices, there was no assurance that the conditions would be the same for practices being used when the study ended in 1983.

In any event, although (like the earlier VA study) the CASS study did produce controversy and may have temporarily reduced CABG operations in parts of the US, it did not reduce the total number of bypasses performed in the US. In fact, robust growth continued from an already high base.

Adoption outside the US. The US Office of Technology Adoption (OTA) had sponsored studies to compare the diffusion of several new medical technologies, including CABG, in ten industrialized countries. [68] A compilation of the studies published in 1980 showed bypass surgery rates were considerably lower outside the United States in the 1970s. Overall, the OTA compilation noted "general agreement" that coronary bypass rates in most European countries were too low, U.S. rates were probably too high" but that no knew the appropriate rate of use. [69]

An expert cited in the OTA volume speculated that European patients were "less aggressive than Americans in seeking out the new treatment." [70] The OTA studies also reported a "high degree of skepticism among physicians about the efficacy and cost effectiveness of the bypass procedure" outside the US and public policies that directly or indirectly limited the facilities available. At the same time, attitudes and policies outside the US were not uniform:

UK general practitioners reportedly had "conservative" attitudes in referring patients with angina to cardiac surgeons. Bypass operations were also limited by a backlog of heart valve operations at centers which could perform open heart surgeries – and by constraints on the budgets of the National Health Service that funded and operated these centers. The launch of the European Coronary Bypass Study in 1972 had also provided a reason "for saying that increased facilities would not be made available until more was known about the effectiveness of the procedure." (As mentioned, the results of the study weren't published until 1980). [71]

French physicians who wanted more evidence of the effectiveness of CABGs also had "ethical objections" to randomized trials – and refused to participate in such trials. But they also wanted to wait for the results of studies being conducted elsewhere. Additionally, French cardiologists "channeled access" to CABG and generally only referred relatively young (35 to 45 year-old) patients who had had certain kinds of heart attacks or whose chest pains they could not reduce with drugs. The French government's sickness funds (which paid for much of the country's health care) did not however seek to restrict bypass procedures or facilities for performing such operations.[72]

In West Germany (the two Germanys did not reunite till 1989) state governments exercised indirect control over open-heart facilities – and thus CABG capacity) through the per-diem rates they paid hospitals. Only large hospitals were paid enough to afford the necessary equipment and bypass operations were performed at just seven centers affiliated with medical schools – at a time when community hospitals in the US were doing them. Limited capacity had produced a waiting list of patients who "constitute[d] an enormous political pressure group." [73]

In the Netherlands too facilities that could not satisfy "ever growing demand" had made bypass surgery "a very hot political issue." CABG had been performed at two university hospitals since the late 1960s when coronary disease had become the leading cause of death in the country. In 1971, the country's Health Council had recommended increasing capacity but the Ministry of Health "ignored this recommendation." Another committee again recommended expansion in 1972, but this was rejected as unaffordable by the Ministry of Finance. Two years later the Dutch Heart Patient Association staged a massive demonstration and occupied the Parliament building. The Minister of Health then announced an increase in the capacity for CABG in university hospitals but would not support new centers. [74]

In 1976, patients on a waiting list were flown out for CABGs to the United States, Britain, and Switzerland. The Health Council again recommended increasing capacity and this time the government agreed to add two new centers in general hospitals with a target of performing 1,000 more bypasses each year.[75]

Sweden had been at the forefront of (pre-bypass) experimental operations to treat angina but their failure to increase life expectancies created skepticism about "miracle" heart operations. Swedish authorities therefore rejected heart transplants (after they were performed in South Africa in 1967) but did decide to start bypass operations on a "small and experimental scale" in 1973 in four hospitals that already

had facilities for open-heart surgery. Many candidates for coronary bypass surgery were not given treatment or put on waiting lists during this "trial" period but Swedish patients were willing to "wait their turn" because of a "collectivist orientation" and faith that experts exercising "good judgment" would only restrict "questionable" treatments (like heart transplants) and not "life-saving ones" like kidney dialysis.[76]

Australian surgeons had started performing CABGs in nine public teaching hospitals (under "rationalization policies" which sought to control overcapacity). The nine hospitals had expanded operations from 158 in 1971 to 1,978 in 1977. No other hospitals, public or private, had started performing the procedures and the OTA compilation did not report any controversy about this. [77]

In Canada too CABG procedures, nearly all performed in teaching hospitals, had grown without apparent controversy about costs or waiting lists. Provincial governments in Canada had been concerned however about the quality of operations in hospitals which performed less than 100 procedures a year. Two such hospitals in the province of Quebec had been sent letters requesting them to stop performing heart surgery. One had complied, while the other had increased its surgical staff to get above the 100-procedure threshold. [78]

The OTA study of Japan made no mention at all of CABG – and provided no reason why not. (It did discuss the other new medical technologies surveyed in the OTA report.)

5. Angioplasty Slows CABG Growth

Origins of Angioplasty. Dr. Charles Dotter, a radiologist at Oregon Health & Science University in Portland, Oregon had coined the term angioplasty in the early 1960s to describe a procedure he had developed to treat blocked leg arteries by snaking in a catheter to clear the blockage. Dotter's procedure was strongly opposed by vascular surgeons in the US (who dubbed him "Crazy Charlie") but it did get the attention of a few European physicians.

In 1964, Cleveland Clinic's Sones had unsuccessfully tried to clear a blocked right coronary artery with a catheter. Sones then tried to develop a "rotorooter" catheter with a rotating tip to clear blocked coronary arteries (in collaboration with an engineer, Lowell Edwards, who had previously co-invented a prosthetic heart valve). Sones's second effort was also unsuccessful.[79]

In 1971, Eberhard Zeitler, a West German radiologist who had traveled to Portland to learn Dotter's technique to treat narrowed leg arteries, taught it to Andreas Grüntzig, an East German-born cardiologist at the Medical Policlinic of the University of Zürich. Grüntzig, who had attended medical school in Heidelberg, studied epidemiology in London, and worked as a doctor in Darmstadt in south-western Germany, tried extending Dotter's technique to treat angina. Dotter had previously tried – but failed – to add balloons to the ends of catheters to clear arterial blockages. Grüntzig developed a functional balloon-tipped catheter through animal experiments and in 1974 successfully used the device clear a blockage in a femoral artery (which passes through the thigh). After more experiments and development on animals and cadavers (which included making catheters thin enough to penetrate narrow coronary arteries) Grüntzig successfully performed a balloon angioplasty on a conscious, awake 38-year old with severe angina in September 1977 at the University of Zürich's Medical Policlinic.

Grüntzig reported his experience to large audience at the annual meeting of the American Heart Association in November 1977. His post-operative angiogram showing that the patient's arterial blockage had been removed produced an eruption of applause. The Cleveland Clinic's Sones had tears streaming down his cheeks as he rushed to the stage to embrace the startled speaker.

Grüntzig's superiors in Zurich did not encourage angioplasties however. Grüntzig therefore performed two of his first five procedures at the University of Frankfurt in collaboration with a German physician and 65 out of the first 169 patients who underwent angioplasty in Zürich were referred from outside

Switzerland. The reluctance of Grüntzig's colleagues was understandable: a third of the first 12 angioplasties attempted were not successfully completed, whereas CABG was by then a well-proven procedure.

In March 1978 Richard Myler in San Francisco and Simon Stertzer in New York performed the first angioplasty procedures outside Zurich and Frankfurt. That July, *Time* magazine described how Stertzer had successfully performed this "new and highly experimental operation" in less than an hour on a forty-seven year old New York chauffeur "stricken with suffocating spasmodic chest pains of severe angina." Two days after his operation the patient had returned to work, his angina gone. The article reported that up to 15% of bypass surgery patients could be treated with angioplasty "at about one-tenth the $15,000 average cost of a bypass."[80]

In March 1979 the US National Heart, Lung and Blood Institute published a position paper cautiously predicting (on the basis of about 30 procedures performed by then) that angioplasty had "limited promise.., for a small number of categories of patients" and urged a "rational, scientific evaluation of the technique."[81] A month earlier, two Philadelphia cardiologists had complained that promotion of angioplasty in the news media, including *Time* magazine, the *New York Times*, and the *CBS Evening News* had extended to encouraging patients to ask their physicians about this "less risky, less costly" alternative "free of the discomforts of coronary surgery." They too, called for controlled studies and long-term follow-up to compare angioplasty, CABG and drug treatments for angina. Nonetheless, by June 1979 about 275 angioplasties had been attempted in 19 centers in Europe and North America, mainly by younger cardiologists. A year later the number had risen to about a thousand.

Grüntzig actively promoted his technique through live demonstration courses in Zurich. Twenty-eight attendees at his first course watched him perform seven angioplasties in August 1978. In later courses, hundreds would see Grüntzig's operations projected on a large video screen (which was then itself a new teaching method in medicine) in an auditorium. Then in 1980, Grüntzig relocated to the US hoping to find more enthusiasm than his Zurich colleagues were providing. After nearly accepting a position at the Cleveland Clinic, he joined Emory University's medical faculty. Emory offered Grüntzig "virtually unlimited resources" for a new research laboratory. The Atlanta, Georgia based university also secured the German cardiologist exemption from the examination immigrant physicians were normally required to pass – and a professorial title (which apparently appealed to Grüntzig's European sensibilities and which the Cleveland Clinic could not match.)

Grüntzig attracted patients from all over the world to Atlanta allowing the cardiologist to perform two angioplasties a day, whereas in Zurich he could only do two a week.[82] Thousands of physicians also attended the four-day training courses Grüntzig offered twice a year until his death in a plane crash in 1985.[83] By then angioplasty was "spreading like wildfire," chiefly according to Mayo cardiologist Fye, because "the lack of formal training guidelines" made it easy for cardiologists who had performed "diagnostic" angiograms of patients' coronary arteries to transform themselves into "interventional" cardiologists who used catheters as therapeutic tools. Most started by attending Grüntzig's course at Emory or learned the technique from colleagues, following the 'see one, do one, teach one' model. Grüntzig recommended first practicing on dogs. But many cardiologists were private practitioners in community hospitals with no access to animal laboratories. Hospitals, "eager to add the new therapeutic procedure," readily gave cardiologists who were already doing diagnostic angiograms permission to perform angioplasty. By 1988, cardiologists were performing angioplasties in 1,000 hospitals (including some which did not have facilities for CABG).

Angioplasty was usually performed under local anesthesia (which was less costly and risky than administering general anesthesia) and did not require operating rooms (although many physicians preferred having back-up operating facilities if something went wrong). The less-invasive procedure also reduced hospital stays: a 1981 study found that patients stayed 4 (+/- 2) days in hospitals for angioplasty compared to 12+/- 2 days for CABG. Therefore, although angioplasty wasn't priced at one-tenth the price

of CABG as *Time* magazine had reported in 1978 patient charges were considerably lower. The 1981 study found that the average hospital and professional fees charged for angioplasty ($5,315 +/- $2159) was about a third of the average ($15,580 +/- $7,2181) charge for comparable CABG procedures.

Higher risks of "restenosis" – reconstrictions of cleared blockages -- reduced the advantages of angioplasty, however. Restenosis occurred in about a third of cases, usually within six months of the procedure. Patients had to then undergo another angioplasty or a CABG. A 1991 RAND Corporation study that included these costs estimated a five-year cost of $33,000 for angioplasty and $40,000 for CABG. Later studies would question whether angioplasty provided any long-term economic advantages at all.

Angioplasty also created potential conflicts of interest: because the physician who evaluated patients could also provide the treatment, "the checks-and-balances of the internist – to – surgeon referral" were lost. According to one critic, cardiologists who in the 1970s had favored treating patients with single blockages with drugs (rather than recommending CABG operations) now called such patients 'ideal' candidates for angioplasty (which cardiologists could themselves perform).

At some institutions, such as the Mayo Clinic, which paid physicians fixed salaries, angioplasty did not threaten the incomes of heart surgeons. Surgeons' roles were nonetheless diminished. Previously, surgeons "were used to being in charge;" cardiologists merely "treated patients with pills and referred some of them for surgery." Angioplasty required surgeons to "sit on the sidelines" according to Mayo cardiologist Fye "ready to rush into action (to perform emergency surgery) if an accident occurred."

Moreover, increased use of angioplasty to treat patients with multiple blockages of their arteries increased competition. Initially, the procedure was used only on patients with single blockages, at least some of whom in the 1970s would have been treated just with drugs. But, as early as 1983, Mayo Clinic cardiologists reported successfully using angioplasty to treat patients with multiple blockages (although some cardiologists, including Grüntzig remained skeptical about such use).

As it happened surgeons' fears that angioplasty would replace CABG proved unfounded. Angioplasties in the US had soared, from under 1,000 in 1980, to 26,000 in 1983 to 360,000 in 1992. But although angioplasties exceeded CABG operations by 1991, the expectation that angioplasties would "supplant" CABGs had not been realized (as the OTA's 1994 update of its 1980 study reported)*. CABGs performed in the US had more than tripled, from about 100,000 in 1979 to 309,000 in 1992. And CABGs would continue to grow, until the number of operations finally peaked at 519,000 in 2000.[84]

One reason was that complementary advances continued to improve CABG. In 1983, coating on the insides of tubes carrying blood to-and-from heart-lung machines with the anti-clotting drug, heparin, was introduced. This reduced the risks of complications such as strokes and excessive bleeding. The use of the drug aprotinin during heart surgery (first reported in 1987) significantly reduced blood loss and the need for blood transfusions. And, as surgeons and surgical units performed more operations their skills improved. Improved technologies and skills in turn encouraged surgeons to operate on older and sicker patients who previously would have been considered unsuitable candidates for the CABG (because of the high risk of dying from the procedure.)

The unintended consequence of reimbursement rules introduced by the US government may also have sustained the continued growth of CABGs, according to a Brown University economist's analysis. As mentioned, the government's Medicare program paid for about half the CABGs performed in the United States. And, as with other procedures, the program paid whatever physicians and hospitals billed –unless the amounts were obviously excessive. In 1984, Medicare set fixed payments for procedures at rates intended to reflect the average cost of the procedure. This reform was intended to both control excessive

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* The OTA's 1994 update of its 1980 review of the diffusion medical technologies in industrialized countries combined angioplasty and CABG in a broadened category of coronary disease treatments. Studies in the 1980 volume had covered just bypass surgery.

billing and discourage hospitals from offering procedures they could not efficiently perform (because a high-cost provider would only receive "average" reimbursement).

But, hospitals performing CABGs at higher than average costs (because for instance they operated in sparsely populated areas without suitable patients) had already made large investments (e.g. in heart lung machines) and incurred high fixed costs in sustaining their operating capabilities. Therefore, economist Daeho Kim suggested, they had an incentive to perform procedures as long as reimbursements exceeded just their variable costs (in order to amortize their investments and cover fixed costs.) In fact, according to Kim's analysis, the need to cover high fixed costs encouraged "inefficient" hospitals to nudge patients from angioplasty to CABG even in cases where angioplasty would have been more suitable.

Patient suitability remained controversial, however. According to the OTA's 1994 report angioplasty was "particularly indicated" for short blockages and blockages of more than 50% -- but not total blockages. These indications had not been verified in randomized controlled trials, however; as of 1994, trials comparing angioplasty and CABG had been started but not completed in the US and Europe. A VA trial had compared angioplasty with drug treatment but by the time the results were published in 1992, the use of stents was transforming angioplasty procedures. Stent-based angioplasty had been developed in Europe and first used there in human patients in 1986. Angiographic images taken before and after stent-based procedures "provided dramatic visual proof of success" and stents seemed to be an ideal way to reduce the risks of restenosis. By 1995, according to the chief of cardiology at the Cleveland Clinic, US cardiologists had caught "stent fever" with manufacturers unable to keep up with demand.[85] The VA's trial had however evaluated angioplasty done without stents; therefore one critic cited by Favaloro, "tens of thousands of patients [we]re receiving a prosthetic metal device in their coronary arteries without adequate long-term follow-up, and most of these patients [we]re receiving it for indications that ha[d] not been systematically or rigorously evaluated".[86]

The cost-effectiveness of angioplasty had been analyzed (by RAND corporation and other researchers as mentioned above) but not in randomized trials and according to the OTA the results were "not entirely convincing because of the lack of definitive information on the effectiveness of the procedures."

In 1985 an agency of the US Department of Health and Human Services had, after reviewing data from patient registries had recommended that in the absence of trials comparing drugs, angioplasty, and CABG physicians "base their therapeutic decisions on current reported results and sound clinical judgment." But, as the OTA noted, despite "inadequate evidence" and guidance from trials the government had approved Medicare reimbursement ensuring "rapid dissemination" of the treatments. Similarly, the American College of Cardiology in collaboration with the American Heart Association had issued guidelines for the use of CABG and angioplasty, again without any trial data. And, the 1991 RAND Corporation report comparing the costs of CABG and angioplasty had also produced criteria for the "appropriateness and necessity" of the two treatments. For this, RAND researchers had extensively reviewed research publications and synthesized "expert opinion" using a form of the so-called "Delphi technique."

The 1994 OTA report also observed that US government regulation had not significantly affected the adoption of either angioplasty or CABG. The government had not for instance established credentialing requirements for physicians performing these procedures (although professional associations had developed guidelines that hospitals could voluntarily apply.) And, the FDA did not require clinical trials for the devices used in angioplasty or CABG.*

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* The 1976 Medical Device Regulation Act had given the FDA authority to require clinical trials for new devices; previously the FDA only had such authority over new drug introductions. The Act also gave the FDA the discretion to exempt devices from trial requirements if the agency decided the devices were "substantially equivalent" to existing devices. And even though angioplasty was introduced after 1976 the FDA decided that the balloon catheters used were substantially equivalent to the diagnostic catheters that cardiologists had used before 1976.

Adoption outside the US. According to the OTA's 1994 report, the diffusion of angioplasty and CABG was lower outside the US (in every country covered in the report). As in the US, the diffusion of angioplasty had not reduced CABG operations even though governments that had tried to control or restrict high-cost CABG facilities and operations (to a greater degree than in the US) had been relatively "lenient" with angioplasty. Other factors also favored angioplasty: centers, many in the private sector, that could not afford to establish CABG facilities performed angioplasties.

In France for instance 49 public hospitals and 24 private clinics (or a total of 73 units) were authorized to perform CABGs in 1990. In contrast a total of 145 centers performed angioplasty. 55 of these centers were private and these carried out half the 20,000 angioplasties performed in France in 1990. Similarly, in Canada 37 centers performed CABG and other open-heart surgeries compared to 78 centers that could perform angioplasties and other heart catheterizations. (Performing angioplasties in facilities that lacked the capacity to switch to open heart surgery in case of emergencies was considered risky; nonetheless this was in fact done in many countries, including the United States).

As in the US, media coverage of the convenience and faster recovery times had spurred patient demand for angioplasty (which in turn had encouraged opening more facilities). By the mid-1990s angioplasty had become the preferred treatment for single vessel blockages. And stent use was growing quickly: stents were used in about 30% of angioplasties performed in Europe in 1995, compared to just 10% in 1994.

Yet, the 15 to 20 percent decline in CABG that many health authorities had anticipated would result from angioplasty growth had not materialized. In fact, waiting lists developed in several countries because demand increased faster than capacity. In Germany, where demand for CABG was believed to be twice the available supply, the press carried stories of patients forced to go outside, especially to the United States for bypass operations. The press in Canada, the Netherlands and Sweden also reported long waiting lists. Waiting lists in Stockholm, Upsala and some other Swedish locations grew to more than a year by 1985. Deaths of patients on waiting lists were estimated to be as high as 10 percent per waiting year. Complaints from patients, who until then had not protested, prompted Sweden's Ministry of Health to start a scheme to limit patient waits to three months.

The main reason for the concurrent growth of angioplasty and CABG cited in the OTA report, was that indications for CABG everywhere (and not just in the US) had expanded to include older and sicker patients. In Holland, according the OTA report, surgeons were operating on 85-year-olds. Additionally, countries that had resisted adding CABG capacity in the 1970s had started catching up. Moreover, although angioplasty had started being used to clear multi-vessel blockages about 85% of angioplasties performed in Europe in 1995 had been used to treat patients with single-vessel disease.[87]

Just as some centers only offered angioplasty, some only offered CABG. Therefore, where a patient first went to for treatment could (regardless of the patient's indications) determine the revascularization procedure performed. For instance, in Germany patients diagnosed in centers without angioplasty were more likely to have a CABG revascularization whereas patients diagnosed in centers with both facilities were equally likely to receive CABG or angioplasty treatments.

As in the US, many physicians and health authorities urged randomized trials to evaluate the efficacy of angioplasty but no results had been published by the mid-1990s. The OTA study reported for example that "consideration" was "being given to setting up a comprehensive, randomized study" in the UK while in the Netherlands heart surgeons had "refused to cooperate with cardiologists to join in a prospective study."

Inconclusive Comparisons, Ambiguous Indications. Results of several trials comparing angioplasty and CABG revascularization were published after the second OTA report. The five largest, namely Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI), Randomized Intervention Treatment of Angina Trial (RITA), Emory Angioplasty versus Surgery Trial (EAST), German Angioplasty Bypass Surgery Investigation (GABI) and Bypass Angioplasty Revascularization Investigation (BARI), evaluated

patients treated between 1986 to 1992. Altogether, the five trials covered 4,645 patients – 2,346 who received angioplasty and 2,299 who had CABG operations. The largest trial, BARI, had -- starting with an initial pool of 12,530 "clinically eligible" patients --randomly assigned 915 to angioplasty and 914 to CABG.

The trials used different criteria for selection. RITA, which excluded patients with three narrowed coronary arteries, was the only trial with a sizeable number of patients with single vessel disease. GABI had a very high proportion of patients (82%) with two vessel disease whereas BARI, CABRI and EAST all had about 40% of patients with three narrowed arteries. CABRI also excluded patients with "severe" three vessel disease, and patients were included RITA, GABI and BARI only when surgeons and cardiologists agreed that both angioplasty and CABG could be used.

All but CABRI reported more in-hospital deaths and non-fatal heart attacks for CABG patients than for angioplasty patients (7.6% vs. 4.6%). One-year deaths and heart-attacks remained higher for CABG (12.8% vs. 11.3% for angioplasty). But after three and five-year periods, angioplasty had slightly higher rates of deaths and heart attacks. CABG expectedly also required longer initial hospitalization but in the longer-term patients were more likely to be angina free, require fewer anti-anginal drugs and additional procedures.

Robert Frye, who presented the early results of the BARI trial to the American Heart Association in November 1995 stated they addressed the question of patients with multi-vessel blockages who wanted to avoid the trauma of CABG operations: could less invasive angioplasty "delay or prevent the need for CABG without adverse consequences?" The answer, according to Frye was "clearly yes" – for "selected" patients.

But "selected" how? By the mid-1990s physicians routinely favored angioplasty to clear many single vessel blockages – even though randomized trials had not convincingly validated this practice. Conversely, physicians had long favored CABG to treat single vessel blockages of the left main coronary artery – again without convincing trials – going back to the 1970s. And, BARI and other smaller trials apparently did not conclusively settle the question of how to treat patients with multi-vessel disease: according to Favoloro and other critics, the published trial results produced an exaggerated impression of the advantages of angioplasty for such patients.

Critics again complained about miscounted "crossover" patients. As mentioned, arteries cleared by angioplasty did not always remain unclogged. But although CABG was often used to treat the reclogged arteries, trial results credited the survival of the patients to their initial angioplasty. And again, Favoloro questioned how patients were selected for randomization: the prognoses for patients with three vessel blockages, varied significantly, depending for example on the length of the blockages, where in the artery the blockages were located and other diseases, such as diabetes, that patients might also have. But, because in practice the trials gave cardiologists more influence than surgeons in patient selection, the trials had only compared low-risk patients. These comprised a "small proportion of patients with multi-vessel disease" rather than the population that surgeons faced every day in operating rooms," wrote Favoloro .[88]

A task force -- without many surgeons -- formed in 1999 by the American College of Cardiologists and the American Heart Association to recommend practice guidelines for CABG also expressed concerns. It noted that the results of several randomized trials comparing angioplasty with bypass surgery had been published but most did not have "long-term follow up, i.e. 5 to 10 years" and "most notably" only about 5 percent of the patients screened at the enrolling institutions had been included in the trials: half the patients had been excluded because they had blockages in their left coronary main arteries or some other reason. Only half the patients with multivessel blockages had actually been randomized: physicians had routinely referred those with three vessel blockages to CABG surgery and those with 2-vessel disease to angioplasty instead of allowing them to be randomized.

The task force also noted that angioplasty reduced initial costs and hospital stays but CABG produced greater improvements in blood flow to the heart muscles. The BARI trial seemed to show a small advantage overall in five-year survival for CABG (with a 5-year rate of 89.3% compared to 86.3% for angioplasty) and

greater survival benefits in high-risk patients including those with diabetes, unstable angina and patients with heart failure. Other trials, with small sample sizes and short periods of follow-up, had not confirmed the BARI findings but they had shown a 4 to 10-fold higher rates of reintervention for patients who had initially received angioplasty treatments.

Differences and changes in techniques added to the difficulty of generalized comparisons. For instance, the CABG task force reported there was no "universally applicable" technique for protecting the heart muscle ("myocardial protection") during the bypass operations performed on patients with normal heart-pumping capacities: "Cardioplegic" drugs and solutions (that provided myocardial protection) were administered in a variety of ways and "no strong argument [could currently be made for warm versus cold and crystalloid versus blood cardioplegia." (The report did note that "certain techniques may offer a wider margin of safety for special patient subsets" but, understandably, did not cite any randomized trials to support this possibility or identify the special subsets.)

The task force similarly reported that administering corticosteroid drugs could reduce the side-effects of using heart-lung machines, but "proper timing and duration" was "incompletely resolved." Likewise, methods for reducing wound infections in patients undergoing CABG included "skin preparation with topical antiseptics, clipping rather than shaving the skin, avoidance of hair removal, reduction of operating room traffic, laminar-flow ventilation, shorter operation, minimization of electrocautery, avoidance of bone wax, use of double- glove barrier techniques for the operating room team, and routine use of a pleural pericardial flap." Here too, as in numerous other potentially useful techniques to improve CABG outcomes, there was no standardized protocol – let alone any clinical trials of utility.

Changes in techniques during and after trials intended to evaluate long-term outcomes also limited the utility of trial results. For instance, the transition from leg-vein grafts used to bypass clogged coronary arteries to ITA grafts (which remained unclogged for longer) was occurring while patients were being enrolled in BARI and other randomized trials. The apparent superiority of ITA grafts had led to a search for other arterial blood vessels that would also remain unclogged for longer. By the mid to late 1990s radial arteries, taken from patient's arms, were often used as substitutes or complements to ITA grafts (after studies had shown that radial grafts were almost as good as ITAs).*

Techniques were also developed in the 1990s to improve "off-pump" CABGs performed without heart-lung machines. Following Goetz and Kolesov's pioneering example in the 1960s, Benetti, Calafiore, and Subramian had performed bypasses off pump in 1973 and Benetti et al and Buffalo et. al had reported excellent off-pump results in the early 1980s. But, as mentioned, off pump operations required considerable dexterity and skill and with the development of safer heart-lung machines and better myocardial protection, most CABGs were performed "on pump."[89] Then, in the 1990s, a variety of drugs and mechanical devices helped make off-pump operations less difficult. For instance, beta-blockers and calcium channel blockers helped reduce (but not stop) the heart's beating motion. Mechanical retractors elevated the heart, making it easier for surgeons to access coronary arteries, and stabilizers helped keep the arteries still when they were operated on.

Innovators were also developing "minimally invasive" CABG techniques. As in minimally invasive laparoscopy that had previously transformed gall-bladder removals, surgeons sought to operate through small "keyhole" incisions. One technique for instance involved using a small, 8 mm incision and a series of small ports instead of the usual 30 mm incision through the patient's sternum. And, because operating on fine coronary arteries through small incisions was more difficult than removing a gall bladder, variants of

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* According to Favaloro (1998 p. 5b) the French surgeon, Carpentier, had first used the radial artery in 1971 but then, after post-operative angiograms showed blockages, had recommended against such use. 18 years later it was accidentally discovered that the blockages seen in the angiograms had been temporarily induced by a spasm and that blood had in fact continued to flow through the implanted radial artery. In 1988 Carpentier's group revived use of the radial artery and by 1995 this conduit had been successfully used in 327 patients. Thereafter, most centers performing CABGs used radial arteries (as a second choice after ITAs).

minimally invasive CABG incorporated robotics: a French surgeon performed the first minimally invasive bypasses using a *Da Vinci* robotic system on four patients in 1998. The *Da Vinci* system, developed by a Sunnyvale, California company, received US regulatory approval the following year.

Angioplasty was concurrently changing during and after BARI and other clinical trials. The first stents were bulky and difficult to place in their intended locations: stents would sometimes fall off the catheters used to insert them and would then be carried off to remote parts of the patient's body. This problem was addressed by making stents thinner and by using high pressure balloons to more precisely place the stents.

New designs and techniques also attempted to control scarring: the early 90s stents had, as expected, provided a scaffolding that nearly eliminated the rapid restenosis sometimes produced by Plain Old Balloon Angioplasty (as it later came to be known). But the metal surfaces of the stents could also produce scar tissue that obstructed blood flow in the arteries that the stents were supposed to keep open. Stent producing companies then tried a variety of materials, coatings and shapes for their stents to limit scarring. Physicians also prescribed orally administered drugs but with limited success. Then in 1999, a Brazilian physician introduced a revolutionary "drug eluting" stent. The inside of this stent was coated with an anti-scarring drug that was slowly released into the patient's blood stream.

About 85 percent of angioplasties performed in 1999 used stents spanning about 20 designs. Sales of stents had grown from nothing in the early 1990s to over $1 billion, spurring companies like Boston Scientific, Johnson & Johnson, Guidant Corp. and Medtronic Inc who produced the stents to invest heavily in research to improve their safety and efficacy.

This profusion of alternatives and diversity of patient symptoms and pathologies apparently discouraged the American Cardiologists and Heart Association task force report from firm recommendations about CABG treatments. Instead it constructed tables estimating different kinds of risks (such as of dying during the procedure, brain damage, and serious wound infections) depending on patients' age, prior bypass surgeries, alcohol use, prior neurological disease and so on. Moreover, because these tables could not be derived from clinical trials the task force relied on a synthesis of a "computerized search of the English literature since 1989, a manual search of final articles and expert opinion." The task force report also summarized the existing evidence (much of it based on observational studies rather than randomized trials and beliefs about practices used in the course of bypass operations (to for instance limit strokes, brain injuries and damage to heart muscles.)

6. Epilogue (after 2000)

Deaths from coronary heart disease in the United States had declined sharply in the last two decades of the 20th century: Age-adjusted deaths fell to 266.8 per hundred thousand men in 2000 from 542.9 deaths in 1980, and to 134.4 deaths per hundred thousand women from 263.3. And, research published in the *New England Journal of Medicine*, attributed about 47 percent of the decrease to a "revolution" in treating patients with coronary disease, notably through CABG, angioplasty, and drugs that dissolved clots, and about 44 percent to preventing or reducing the risks. The second category included declines in smoking (after anti-smoking campaigns had been launched in the 1960s); a small rise in physical activity; medications to lower high blood pressure; and, statins to reduce "bad" cholesterol.[90] (Merck's cholesterol reducing statins, Zocor and Mevacor were widely prescribed -- both made Merck over US$1 billion in 1995 -- after a 1994 Merck-sponsored study suggested they reduced fatal heart attacks by 42 percent.)[91]

CABG operations, which had peaked by the end of the 1990s as coronary disease declined, steadily fell in the first decade of the 21st century. According to an article published in 2011 in the *Journal of the American Medical Association* (JAMA)[92] CABGs performed in the US, dropped from 1,742 operations per million adults in 2001 to 1,081 per million in 2008. Meanwhile, angioplasty procedures had declined more modestly -- from 3,827 per million adults in 2001 to 3,667 per million. Authors of the *JAMA* article inferred that many

patients who would have had bypasses under the 1999 American Cardiologists and Heart Association task force recommendations were having angioplasties.

The number of hospitals performing CABGs, including new specialty cardiac hospitals that did not perform other operations, had increased by 14%, however. As more hospitals performed fewer CABGs, the JAMA article estimated that more than a quarter of the hospitals were preforming fewer than 100 CABGs per year. And, as mentioned, performing fewer than 100 CABGs per year was believed to jeopardize quality – although this was a disputed suggestion. The number of centers performing angioplasties had grown even more rapidly, increasing by 35% between 2001 and 2008.[93]

Efforts to market innovations in CABG that had been incubated in the 1990s were less successful than angioplasty innovations. Adoption of minimally invasive robotic CABG was extremely slow. By 2007 American and European hospitals had purchased about 150 robotic systems at a price of $1.5 million each. But many heart surgeons were uncomfortable using robots which did not provide any tactile feedback to operate on coronary arteries. And cameras in the systems that surgeons used to guide the robots were finicky: a drop of blood could block the view and require surgeons to remove and clean the cameras.[94] By 2016 only about 1,700 robotic heart operations were being performed in the US while in Europe robot assisted CABGs had fallen to just 80 procedures from a peak of 173 in 2001.[95] The robotic systems did however become more popular for urological operations which had not been their initial targets. [96]

In contrast, after the FDA approved the marketing of drug eluting stents in 2003 their adoption was extremely rapid. Although they were called "revolutionary" the drug eluting stents did not require hospitals and cardiologists to make large investments in new equipment or training. And, by the third quarter of 2005 – just two years after FDA approval -- nearly 90% of angioplasties in the US used drug eluting stents. Reports of unexpected side-effects did cause the proportion to fall to about 68% of angioplasties in 2008 but the usage and sales remained significant and newer generations of drug eluting stents were developed to improve safety.[97]

Clinical trials remained inconclusive. Some researchers attributed the more rapid decline of CABG vis a vis less invasive angioplasty in the 2000s to the results of previous clinical trials: for instance, BARI results, had (albeit controversially) not shown "survival benefit" from the more arduous bypass procedure. Moreover, trials in the early 2000s had suggested angioplasty with drug eluting stents produced better outcomes than the older balloon angioplasty used in the BARI trials. But, later trials "contradicted these findings." Results of a trial that had randomized 1800 patients to CABG and angioplasty performed with drug eluting stents, published in 2012 by *The Lancet* had found CABG provided significant benefits for patients with complex multi-vessel disease. Results of an "observational" study published that year by the *New England Journal of Medicine* similarly suggested that CABG increased lifespans of older patients with multi-vessel disease. But although the results, which covered 86,000 CABGs and 103,549 angioplasties, were statistically significant, the differences in magnitudes were relatively small. Four-year mortality after CABG was 16.4% compared to 20.8% after angioplasty. This translated, according to a subsequent analysis of the data, to a 3 to 4 ½ month gain in life years from CABG (at an about $10,000 additional cost).

Moreover, the diversity of specific choices about how CABG was performed continued to make comparisons with angioplasty difficult. The administration of cardioplegia to stop the heart during bypass operations remained unstandardized. The clinical benefit of numerous other measures to protect heart muscles before, during, and after bypass operations remained "debated."[98]

Yet even without standardization – or high-profile breakthroughs -- CABG apparently continues to improve. CABG is used to treat ever older and sicker patients. For instance, in the 1970s and 1980s the average age of patients was between 50-55. By the 2010s, patients were about ten years older. "Less exercise, amplified dietary intake, more stress, and sleep deprivation" made CABG patients "increasingly high risk." The proportion of CABG patients with diabetes had increased from 33 to 40% between 2000 and 2009 and the proportion with high cholesterol had increased from 60 to 84%. The proportion of patients with

hypertension and lung diseases such as emphysema, and patients whose kidney disease required dialysis had also increased. But the proportion of patients surviving CABG had remained the same as when patients were younger and healthier.[99] Therefore, while CABGs don't cure coronary disease (and its companion ailments like diabetes) advances in the procedure provide a valuable if palliative lifeline for millions of patients.

Exhibit 1

Your Care Team During Coronary Bypass Surgery

Dowloaded from:

http://www.scai.org/SecondsCount/Resources/Detail.aspx?cid=dad17232-c7a9-4c4d-9dac-e5a14f77c635#.Wgr7AKJbXZV

Coronary artery bypass graft surgery requires the coordinated efforts of a team of medical professionals who will not only perform the operation and monitor your vital signs, but who will also prepare you before the procedure and look after your comfort and well-being when the surgery is complete.

Cardiac surgeon. The lead person on your team will be your cardiac, or **cardiothoracic**, surgeon, who will perform the actual coronary artery bypass graft surgery. These surgeons specialize in treatment of the heart, lungs, esophagus, and chest. A cardiothoracic surgeon will have completed medical school, followed most often by a five-year residency in general surgery. After the general surgery residency, the physician will have completed a two- or three-year residency specifically in cardiothoracic surgery. Additionally, a board-certified cardiothoracic surgeon will have a valid license, be in good ethical standing in the profession, have passed tests demonstrating knowledge, and will demonstrate lifelong learning.

The cardiac surgeon is responsible for opening the patient's chest, chooses which blood vessel will be [extracted] from elsewhere in the body to use for the graft, and sews that blood vessel to the aorta and then the heart artery after the blockage to allow blood to flow around the blockage to the heart muscle. The surgeon will also wire the breastbone back together and close the incision with stitches.

Before, during, and after your procedure, your cardiac surgeon will be assisted by other care team members, including the following:

An anesthesiologist. An anesthesiologist is a medical doctor trained to administer the drugs that will take you "under" and block any feeling of pain or unpleasant sensations. Your anesthesiologist is involved in your care before, during, and after your surgery. He or she may do a medical evaluation before your surgery to determine an anesthesia plan tailored for you. During surgery, the anesthesiologist oversees life support and pain control. And after the surgery, he or she also provides pain management during your recovery. If time allows before surgery, you should discuss the anesthetic plan, as well as alternatives, risks, and benefits of the chosen anesthetic techniques, with the anesthesiologist.

A perfusionist. During the bypass surgery, the heart is stopped while the surgeon grafts (sews) a blood vessel (a "**graft**") to the clogged artery to create a bypass around a blockage. The perfusionist on the care team operates the heart-lung bypass machine -- the machine that takes over the responsibilities of the heart (to pump blood to the body) and the lungs (to exchange carbon dioxide in the blood for oxygen) during bypass surgery. The perfusionist may be a specially trained nurse or technician who has been certified by the American Board of Cardiovascular Perfusion. Those who are not certified should have at least two years of supervised experience working in an operating room during open heart surgeries. Some bypass surgeries called "off-pump" bypasses will take place with the heart beating and no heart-lung bypass machine.

Operating room nurses and technicians. Operating room nurses and technicians support the cardiac surgeon as he or she performs the procedure. They also monitor your condition and work to make you as

comfortable as possible.

An intensivist. An intensivist (or ICU doctor) is a medical doctor who specializes in the care of critically ill patients, usually in an intensive care unit (ICU). An intensivist may be trained in internal medicine, anesthesiology, or another medical specialty. In addition, the ICU doctor will have completed a fellowship of one or more years' duration in critical care medicine. Depending on your hospital, you may be under the care of an intensivist while in the ICU or the cardiac surgery ICU.

Intensive care nurses. If you are moved into the hospital's intensive care unit following bypass surgery, you will be cared for by intensive care (or critical care) nurses. These nurses have special training in caring for patients facing life-threatening problems, including cardiac and respiratory emergencies.

Cardiac care nurses. Cardiac care nurses are specially trained to work with heart disease patients and their families. They may have an additional specialty –that of critical care nurse – that prepares them to work with patients in the hospital. Otherwise, you may be visited by a cardiac care nurse in your home following bypass surgery.

Physical therapists/occupational therapists/rehab nurses. Both while you are in the hospital and after you are discharged, these medical professionals work with you to help you build up your strength, restore function, and regain your ability to move.

Cardiac rehabilitation team. A team of health care professionals, including nurses, exercise physiologists, physical therapists, occupational therapists, dieticians and nutritionists, counselors and others, will provide education and coaching to speed your rehabilitation. During cardiac rehab, the team will support you as you learn and adopt a heart-healthy lifestyle, such as eating a healthy diet, becoming physically active, and managing stress.

Cardiologist and primary care physician. Your cardiologist and primary care physician will continue to be an integral part of your care. Your cardiologist will be closely involved with your case while you are under the care of the cardiac surgeon. He or she, in turn, should also provide reports and updates to your primary care physician in order to ensure your continued coordinated care.

Exhibit 2: The Mayo Clinic

The Mayo Clinic originated in the solo, country doctor style practice of Dr. William W Mayo in the small town of Rochester, Minnesota. The doctors two sons, William and Charlie had joined the practice after they graduated from medical school in the 1880s. The sons, known as Dr. Will and Dr. Charlie focused on surgery through an unusual collaboration with a local Catholic order, the Sisters of St. Francis. The sisters raise money to build a hospital, St. Mary's, which opened in 1889. They provided nursing services to hospital patients and required all admitted patients to be treated by one of the Mayo brothers, and later members of the Mayo organization. The Mayo's in turn helped design a state-of-the-art hospital equipped for aseptic and antiseptic techniques that were revolutionizing surgery. And they performed all their operations at St. Mary's -- previously physicians outside urban centers had operated in homes and hotel rooms.

Except in emergency surgeries, the Mayos examined and diagnosed all patients before their operations in the Mayo's offices located about a mile from St. Mary's Hospital. Dr. Will believed that thorough preliminary examination to "fit the operation to the patient" was "an absolute necessity" and that patients, not the surgeons, should be at the center around with everything else revolved. Extensive examination-- along with the brother's surgical skills and patient focus, precautions against postoperative infections, and the nursing care provided by the Sisters -- kept mortality rates exceptionally low. Two thirds of the patients admitted at St. Mary's in its first four years had surgery, of whom 98% survived even though many of the cases required difficult operations. Low mortality rates attracted more difficult cases for afar, with many patients making long train journeys to Rochester on the recommendation of their hometown physicians. The brothers themselves traveled extensively attending speaking at medical meetings. They also published nearly 75 articles in medical journals in the 1890s. By 1900 the Mayos had acquired national reputations, attracting visits from other physicians who wanted to see how the Mayos performed so many major operations with so few deaths.

To satisfy growing demand, the Mayos added an experienced physician to their practice in 1892 and in 1895 a recent medical graduate. Neither performed any operations, however. For the first 15 years after St. Mary's opened the Mayo brothers did every surgery themselves. Rather, the physicians specialized in preoperative diagnosis, with the recent medical graduate relying on his more current knowledge of diseases compensating for his inexperience with, tests and treatments. Between 1895 in 1905 added about a dozen more physicians, again mainly to increase the capacity to evaluate patients. Many of the physicians recruited were "internists" drawn from the newly emerging specialty of internal medicine. In 1905 the Mayos hired a physician–bacteriologist to improve the laboratories at St. Mary's Hospital who in turn hired nonmedical technicians as laboratory assistants. The high number of patients enabled by the specialization of evaluation also spurred efforts to develop a "medical production machine" providing "a highly organized set of services."[100]

The machine provided "Better Doctoring for Less." Of about 35,000 patients in 1915, 30% paid nothing and another 20% less than the cost of their evaluations. The other patients paid lump sums for which they got whatever examinations they needed. Most physicians received fixed salaries: the Mayos shared the profits of their practice with just two physicians in 1905 and four physicians (who were also relatives by marriage) in 1915. Other doctors denounced the salary and fee arrangements for unethically undermining the custom of paying individual physicians who provided "peculiarly personal and individual services" to their patients, not to anyone else or to any institution." [101] "

Advances in medical knowledge in the 20th century, appealed to the Mayos who had long been committed to "modernity and technology." They were early purchasers of new diagnostic technology – X-Rays machines in 1900 and electrocardiograms in 1915 – and enthusiastic participants in the "efficiency" movement spearheaded in industry by people like Henry Ford and Taylor. The Mayos also however recognized more medical knowledge required more specialization – and cooperation than an

efficient division of labor between surgical treatment and preoperative diagnosis. "The sum total of medical knowledge" had become so great Dr. Will observed that it was futile for any individual physician to acquire a "good working knowledge of the whole." But responsibility for treating different parts of the body could not be divided as might the manufacture of different parts of a wagon: humans had to be treated "as a whole" with "the clinician, the specialist, and the laboratory workers uniting for the good of the patient, each assisting in the elucidation of the problem at hand and each dependent on the other for support."[102]

Salary-based compensation which limited competition between physicians and a tradition of putting patients at the center helped provide a foundation for cooperation. The Mayos used this foundation – and the considerable profits generated by their high-volume, low-fee practice to "to invent and invest in the multispecialty group practice model of surgical and medical care."[103] The Mayo version would become the largest of the genre, spanning every major medical specialty, including cardiology and cardiac surgery. It would also become a significant provider – and not just a user -- of medical training and producer of medical knowledge.

An early investment in the development of a cohesive multi-specialty practice was the construction of a five-story building that had more than thirty combination office-examination rooms, dozens of rooms for laboratories and diagnostic equipment. The building, completed in 1914, brought together the more than 100 physicians and staff who had previously been scattered across several locations in Rochester. Systems invented or adapted to promote efficiency and encourage collaboration included a unified medical record system.

The Clinic adopted formal rules and policies to promote a professional, patient oriented culture. At the outset, adherence to the organization's norms had been personally monitored enforced by Dr. Will. As the workforce grew rules were written down to discourage for instance, surgeons from "prima-donna" behavior or "cursing, nagging or displaying irritation while operating." Similarly, staff were reminded in writing that "while the patients are here in large numbers, each must be treated as an individual with every courtesy possible. (p. 73)" At the same time Mayo gave its physicians time to renew their medical knowledge – and, continuing the example of Drs. Will and Charlie, to write articles for medical journals, usually after they had been edited by an in-house editor. In 1911 the Clinic started publishing annual compilations of articles published by its staff and later, around 1926, *The Proceedings of the Staff Meetings of the Mayo Clinic,* a free weekly publication sent to hundreds of libraries and thousands (and later tens of thousands) of physicians.[104]

In 1915 Drs. Will and Charlie created – and funded with what was then a very large gift of $1.5 million the Mayo Foundation for Medical Research and Education. The Foundation helped expand significantly a relatively small internship program to train physicians that Mayo had started a decade earlier through an affiliation with the University of Minnesota's medical school. The affiliation sought to combine "the best features of the old apprenticeship system with the best features of graduate education." Trainees were required to work in areas complementing their chosen fields – – surgical trainees had to spend two years in pathology for instance – – and expected to participate in research. (Clinical and laboratory research at Mayo preceded the University of Minnesota affiliation. As mentioned, Mayo physicians had long contributed to medical journals and the Clinic's 1914 building contained laboratories for medical research (including facilities for performing surgical experiments on animals).

In 1919, Drs. Will and Charlie profoundly changed the Mayo Clinic's "ownership, legal status, and organizational structure" by creating The Mayo Properties Association to which they (and their partner relatives) gifted all of the Clinic's buildings and equipment and endowments. The Association, like the Foundation was intended to promote medical research and education, and thus establish a self-perpetuating academic program that would complement… patient care activities."[105] Yet, although Mayo/s research and educational programs would expand significantly in subsequent decades, the

clinic's first priority would remain patient care, and it continue to build its reputation for personalized treatment of difficult cases (such as children with congenital disease using cutting edge techniques (such as heart-lung machines).

Mayo's distinctive patient-centered professionalism and teamwork would similarly endure. For instance, a witness to one of Walt Lillehei's open-heart operation at the University of Minnesota observed that "it was like a circus. People were rushing in and out. They started at seven or eight in the morning and Lillehei came in about eleven. The operating room was chaos with pipes and tubes everywhere." The same observer who then saw John Kirklin perform open-heart surgery at Mayo recorded that "walking into Kirklin's operating room was like walking into a church; there was no sound, no excitement. The door opened, the heart-lung machine was wheeled in and connected to the patient and he then did the operation. I was dumbfounded that you could do this very complex procedure so quietly with no drama."[106]

Endnotes

[1] Morris, *The Matter of the Heart: A History of the Heart in Eleven Operations*. First U.S. edition, Thomas Dunne Books, St. Martin's Press, 2017. p. 187

[2] Transoesophageal echocardiographs are also used before CABGs to confirm diagnoses.

[3] To offset the thickening that follows cooling.

[4] Epstein AJ, Polsky D, Yang F, Yang L, Groeneveld PW. Coronary revascularization trends in the United States, 2001-2008. *JAMA*. 2011;305(17):1769–1776. doi:10.1001/jama.2011.551

[5] This was not universally accepted, however.

[6] Fye, Bruce. *Caring for the Heart: Mayo Clinic and the Rise of Specialization*. Oxford University Press, 2015. p. 181

[7] Fye, Bruce. *Caring for the Heart: Mayo Clinic and the Rise of Specialization*. Oxford University Press, 2015. p. 183.

[8] Earlier, in 1887 a physician from Buffalo, New York used an apparatus based on bellows to keep patient's lungs inflated while a tumor inside her chest was removed.

[9] Fye *ibid* p. 188

[10] Fye *ibid* p. 193

[11] Fye, *idid*. p.196 .

[12] Fye *ibid* p. 96

[13] Similarly, a *Reader's Digest* story described the transformation of a 32-year-old woman who before her surgery "could not climb a flight of stairs; she now does housework, shops, bowls and dances." Fye, *idid*. p. 201.

[14] Fye, *ibid* p. 218

[15] Fye *ibid* p. 205

[16] Fye *ibid* p. 207

[17] Wayne State University | School of Medicine. 10 June 2007, https://web.archive.org/web/20070610010058/http://www.med.wayne.edu/news_media/2002/press14.asp.

[18] Fye *ibid* p. 211

[19] Fye *ibid* p. 225

[20] Fye *ibid* p. 228

[21] Dennis, Minnesota's heart-lung pioneer, had by then moved from Minnesota to Brooklyn while Lillehei (who remained at Minnesota) had turned his attention from cross-circulation to machine supported surgery. Lillehei had encouraged a recent medical graduate in his lab to develop the oxygenator.

[22] A thoracic-turned-cardiac surgeon (Donald Effler), a pediatric cardiologist (Mason Sones) and a physician-engineer (Willem Kolff) had led the Clinic's open-heart initiative. Kolff, who had emigrated from Holland to join the Cleveland Clinic, was responsible for designing and building a heart lung machine: no one was the selling such equipment and even IBM had shown no interest in commercializing its design. Kolff first contacted Gibbon who, as mentioned, had helped the Mayo team, for engineering blueprints. But Gibbon did not respond, so Kolff – who had invented an artificial kidney in the Second World War – designed his own heart-lung machine.

[23] Fye, *ibid*. p 209

[24] As mentioned, surgeons had started widening stenotic mitral valves in the 1950s using touch to manipulate tiny knives in "unopened" hearts. But, surgeons could not safely or effectively widen other valves (notably the aortic valve) and repair or replace leaky valves without deep incisions and seeing what they were operating on. Heart-lung machines use to operate on children with congenital disease with therefore soon used in open heart surgeries to treat the diseased heart valves of adults.

[25] Forsmann then joined the medical corps of the German army. Following brief internment as a POW after the Second World War Forssmann worked as a general practitioner and urologist. Heiss, H. W., "Werner Forssmann: A German Problem with the Nobel Prize." *Clinical Cardiology*, vol. 15, no. 7, July 1992, pp. 547–49. *DOI.org (Crossref)*, doi:10.1002/clc.4960150715

[26] Cardiac catheterization also facilitated the diagnosis and treatment of soldiers suffering from shock in World War II.

[27] Mehta, Nirav J., and Ijaz A. Khan. "Cardiology's 10 Greatest Discoveries of the 20th Century." *Texas Heart Institute Journal*, vol. 29, no. 3, 2002, pp. 164–71.

[28] Konstantinov, Igor E. "Robert H. Goetz: The Surgeon Who Performed the First Successful Clinical Coronary Artery Bypass Operation." *The Annals of Thoracic Surgery*, vol. 69, no. 6, June 2000, pp. 1966–72. *DOI.org (Crossref)*, doi:10.1016/S0003-4975(00)01264-9.

[29] Sheldon, William C. *Pathfinders of the Heart: The History of Cardiology at the Cleveland Clinic*. Xlibris Corporation, 2008. p. 31.

[30] Favaloro, René G. "Landmarks in the Development of Coronary Artery Bypass Surgery." *Circulation*, vol. 98, no. 5, Aug. 1998, pp. 466–78. *DOI.org (Crossref)*, doi:10.1161/01.CIR.98.5.466. p. 466

[31] Sheldon *ibid* p.67

[32] Garrett, Dennis, and DeBakey had also successfully used an aorta-to- coronary graft in their 1964 operation, but as mentioned, did not publish the result till 1973.

[33] Sabik, Joseph F. "50th Anniversary Landmark Commentary on Favaloro RG. Saphenous Vein Autograft Replacement of Severe Segmental Coronary Artery Occlusion. Ann Thorac Surg 1968;5:334–9." *The Annals of Thoracic Surgery*, vol. 99, no. 2, Feb. 2015, pp. 385–86. *DOI.org (Crossref)*, doi:10.1016/j.athoracsur.2014.12.013.

[34] A CABG performed by Bailey and Hirose in 1968 also used ITAs instead of vein grafts.

[35] Fye *ibid.* p. 253

[36] Fye, *ibid*. p. 347-48

[37] "By 1969, the operative mortality for CABG was reported to be about 12 percent" according to the OTA 1995 report (U.S. Congress, Office of Technology Assessment, *Health Care Technology and Its Assessment in Eight Countries*, OTA-BP-H-140 (Washington, DC: U.S. Government Printing Office, February 1995)

[38] According to some estimates about 150,000 procedures were being performed by 1980. Jones, David S. "Visions of a Cure: Visualization, Clinical Trials, and Controversies in Cardiac Therapeutics, 1968-1998." *Isis*, vol. 91, no. 3, 2000, pp. 504–41. JSTOR. p. 516

[39] Fye, *ibid*. p 354

[40] *Ibid* p. 346-7.

[41] *Ibid*. p. 354

[42] Other medical journal also urged going slow, Fye reports, publishing editorials with titles such as "Surgical Treatment of Coronary Artery Disease: Too Fast, Too Soon?" and "Direct Coronary Revascularization: A Plea Not to Let the Genie Escape from the Bottle." (Fye *ibid* p. 353-4)

[43] Sheldon *ibid* p. 57.

[44] Although his conclusions, Sheldon (*ibid* p. 57) writes, were "essentially confirmed by later multicenter randomized studies.

[45] Fye, *ibid*. p 354

[46] U.S. Congress, Office of Technology Assessment, *Health Care Technology and Its Assessment in Eight Countries*, OTA-BP-H-140 (Washington, DC: U.S. Government Printing Office, February 1995)

[47] Sheldon *ibid* p. 42

[48] Love, Jack. W. "Drugs and Operations. Some Important Differences." *JAMA: The Journal of the American Medical Association*, vol. 232, no. 1, Apr. 1975, pp. 37–38. *DOI.org (Crossref)*, doi:10.1001/jama.232.1.37. p. 38

[49] Love, Jack W. "A Reply to Dr Spodick." *JAMA: The Journal of the American Medical Association*, vol. 234, no. 9, Dec. 1975, p. 915. *DOI.org (Crossref)*, doi:10.1001/jama.1975.03260220019008.

[50] Fye, *ibid*. p. 357

[51] This was the most commonly cited number at the time. Other estimates put the number as high as 100,000.

[52] "Hopeful News from Medical Science" *Changing Times*; Sep 1976; 30, 9; ABI/INFORM Collection p. 25

[53] "Doctors see hope for success in battle against heart disease" Black, Herbert *Boston Globe* ; Jan 25, 1976; pg. 3

[54] Sheldon *ibid.* page 95-96

[55] Fye, *ibid*. p. 359

[56] Jones *ibid* p. 525

[57] Jones *ibid* p 525

[58] Sheldon p. 95-96

[59] According to Jones (*Ibid.* p. 516 and Figure 7) about 150,000 procedures were performed in the US in 1980. Other estimates put the number at about 100,00. The lower number also represents a significant increase over the number of procedures performed in 1975

[60] Sheldon *Ibid* p. 95-96

[61] The State of Haig's Health, Lawrence Altman, 8 January 1981 *The New York Times*

[62] Favaloro, René G. "Critical Analysis of Coronary Artery Bypass Graft Surgery: A 30-Year Journey." *Journal of the American College of Cardiology*, vol. 31, no. 4, Mar. 1998, pp. 1B-63B. *DOI.org (Crossref)*, doi:10.1016/S0735-1097(97)00559-7. p. 9B

[63] The *New York Times* (6 December 1980 Pg. 9, Col. 4) emphasized the caution rather than the overall favorable assessment.

[64] Brody, Jane "Study Finds Much Heart Bypass Surgery Can Be Put Off Or Avoided" *New York Times* Oct 26 1983

[65] Braunwald, Eugene. "Effects of Coronary-Artery Bypass Grafting on Survival: Implications of the Randomized Coronary-Artery Surgery Study." *New England Journal of Medicine*, vol. 309, no. 19, Nov. 1983, pp. 1181–84. *DOI.org (Crossref)*, doi:10.1056/NEJM198311103091911

[66] Deborah Yaeger, "Improved Tests Help Doctors Diagnose Disease Earlier, Attempt to Avoid Surgery --- Search for a 'Silent Enemy'" *Wall Street Journal,* July 2 1984

[67] Head, S. J., et al. "Coronary Artery Bypass Grafting: Part 1--the Evolution over the First 50 Years." *European Heart Journal*, vol. 34, no. 37, Oct. 2013, pp. 2862–72. *DOI.org (Crossref)*, doi:10.1093/eurheartj/eht330.

[68] United States. Congress. Office of Technology Assessment. *The Management of Health Care Technology In Ten Countries.* Washington, D.C.: Congress of the United States, Office of Technology Assessment , 1980.

[69] United States. Congress. Office of Technology Assessment. *The Management of Health Care Technology In Ten Countries.* Washington, D.C.: Congress of the United States, Office of Technology Assessment , 1980 *p.*

[70] United States. Congress. Office of Technology Assessment. *The Management of Health Care Technology In Ten Countries.* Washington, D.C.: Congress of the United States, Office of Technology Assessment , 1980 *p.*

[71] United States. Congress. Office of Technology Assessment. *The Management of Health Care Technology In Ten Countries.* Washington, D.C.: Congress of the United States, Office of Technology Assessment , 1980 *p.*

[72] By the end of the 1970s 23 public and six private hospitals had these facilities.

[73] United States. Congress. Office of Technology Assessment. *The Management of Health Care Technology In Ten Countries.* Washington, D.C.: Congress of the United States, Office of Technology Assessment , 1980 *p.*

[74] United States. Congress. Office of Technology Assessment. *The Management of Health Care Technology In Ten Countries.* Washington, D.C.: Congress of the United States, Office of Technology Assessment , 1980 *p.*

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[76] United States. Congress. Office of Technology Assessment. *The Management of Health Care Technology In Ten Countries.* Washington, D.C.: Congress of the United States, Office of Technology Assessment , 1980 *p.*

[77] United States. Congress. Office of Technology Assessment. *The Management of Health Care Technology In Ten Countries.* Washington, D.C.: Congress of the United States, Office of Technology Assessment , 1980 *p.*

[78] United States. Congress. Office of Technology Assessment. *The Management of Health Care Technology In Ten Countries.* Washington, D.C.: Congress of the United States, Office of Technology Assessment , 1980 *p.*

[79] Sheldon *ibid* p. 96-97

[80] Fye, *ibid*. p. 365

[81] Fye, *ibid.* page 366-7

[82] Barton, Matthias, et al. "Balloon Angioplasty – The Legacy of Andreas Grüntzig, M.D. (1939–1985)." *Frontiers in Cardiovascular Medicine*, vol. 1, Dec. 2014. *DOI.org (Crossref)*, doi:10.3389/fcvm.2014.00015.

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[95] Pettinari et. al. 2017 Matteo Pettinari1, Emiliano Navarra, Philippe Noirhomme and Herbert Gutermann "The state of robotic cardiac surgery in Europe" *Annals of Cardiothoracic Surgery* 2017; 6(1): 1-8

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[98] These include "whether CPB flows should be non-pulsatile or pulsatile to mimic the physiological blood flow, whether direct and remote ischaemic preconditioning through a number of brief periods of ischaemia proves to have a clinical benefit by increasing the tolerance of the myocardium to sustain a large period of ischaemia, as well as the use of prophylactic or adjunctive pharmacological agents to minimize ischaemia and/or reperfusion injury." Head et. al. *Ibid* p. 2867

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