

CHAPTER 1

INTRODUCING BIOMEDICAL ENGINEERING

1.1. Advancements in Biomedical Engineering

The past 30 years have seen an explosion of activity in the healthcare field. Medical researchers and entrepreneurs have identified and developed a range of new products and processes that are intended to address an ever expanding range of medical conditions. This growth has been led by the medical device and biotechnology industry and, more recently, the expansion of the molecular diagnostics industry. Although the medical device and biotechnology industry has experienced a number of periods of boom or bust during that time, the overall growth in the number of medical products and product revenues has been dramatic.

We anticipate that the coming years will continue to see tremendous opportunities in the field of biomedical engineering. In particular, those individuals who are able to marry their clinical and engineering capabilities with an entrepreneurial mindset have the potential to become this century's Bill Gates or William Hewlett.

During the first three years of the 21st century, important and exciting developments have taken place in education and research funding in the field of biomedical imaging and bioengineering, including the following:

- The National Institutes of Health (NIH) granted a total of \$500 million for research and development to small businesses in the United States in 2003.
- The National Institute of Biomedical Imaging and Bioengineering was established at the NIH, with a 2003 budget of \$121 million, which will be used primarily to support research in the area of biomedical imaging and bioengineering. Its budget for the 2008 fiscal year is \$300 million.
- The map of human genetic codes was completed by high-speed sequencing machines.

- The Whitaker Foundation awarded more than \$700 million to universities to enhance their education programs and research conducted by their biomedical engineering faculties and students.

On the industrial front, we also can report these exciting developments and projections:

- The Food and Drug Administration (FDA) has taken steps to streamline its approval process in order to shorten the time required for safe and effective medical devices and drugs to reach the market.
- There is a rapid increase in the use of medical devices and prescription drugs.
- The medical and healthcare industry makes up 14 percent of the 2003 gross domestic product, and the bio-based industry is projected to make up to 30 percent of the GDP in this decade.

With such tremendous progress and developments in mind, this book is written for undergraduate and graduate students who want to acquire the basic knowledge necessary for the development of biomedical engineering entrepreneurship. In writing the book, the author had the opportunity to interview many successful biomedical engineering entrepreneurs, as well as visionary educators in the field of biomedical engineering. Their foresight, leadership, accomplishments, satisfaction, and positive impact on human health and our nation's economy are revealed in the text to draw attention to the subtle aspects of becoming successful BME entrepreneurs.

The materials presented in this book will also be useful for working biomedical engineers who wish to build up their own companies or develop new ventures with the participation of their team members.

1.2. Scope of Biomedical Engineering

The Biomedical Engineering Society (BMES) describes on its website www.bmes.org a biomedical engineer as one who uses traditional engineering expertise to analyze and solve problems in biology and medicine with the objective of providing an overall enhancement of healthcare (24). Some of the well-established specialties within the field of biomedical engineering that are mentioned on the website are:

- Bioinstrumentation

- Biomaterials
- Biomechanics
- Cellular, tissue and genetic engineering
- Clinical engineering
- Medical imaging
- Orthopedic surgery
- Rehabilitation engineering
- Systems physiology.

Work done by biomedical engineers may include a wide range of activities in the development of:

- Artificial organs
- Automated patient monitoring
- Blood chemistry sensors
- Advanced therapeutic and surgical devices
- Application of expert systems and artificial intelligence to clinical decision making
- Design of optimal clinical laboratories
- Computer modeling of physiological systems
- Biomaterials design
- Biomechanics of injury and wound healing
- Sports medicine.

As described above, biomedical engineering covers many diversified specialties. In teaching the topic of biomedical engineering entrepreneurship, we first define biomedical engineering companies as those that produce products for the diagnosis, prevention and treatment of diseases and the maintenance and improvement of health. Their products can be medical, diagnostic, or rehabilitation devices; materials for implantation; software for data or image processing; or drugs for the alleviation, treatment or cure of diseases.

1.3. Medical Device and Pharmaceutical Industry

Global medical device sales in 2008 were estimated to be \$336 billion by MX (12). In 2006, the medical device industry employed about 411,000 workers in the United States, accounting for nearly one third of all US jobs in bioscience (18). There are an estimated 20,000 medical device companies around the world. The 2007 revenues of the top 20 companies are given in Table 1.1. As one can see, the device market is

dominated by US companies (14 of the 20 companies are U.S.-based), which received 2/3 of the revenue. The prospects for medical devices look robust as the revenues of these 20 companies grew by 9% from 2007 to 2008. Only one company had no revenue growth, although another experienced a decrease of 1%.

Table 1.1. The world's top 20 medical device companies (18).

Company	Country of Origin	2007 Revenues (\$ billion)
1. Johnson & Johnson	U.S.	\$21.7
2. GE Healthcare	U.S.	\$17.0
3. Siemens Medical Solutions	Germany	\$14.4
4. Medtronic	U.S.	\$12.9
5. Baxter International	U.S.	\$11.3
6. Covidien	U.S.	\$10.0
7. Philips Medical Systems	Netherlands	\$8.9
8. Boston Scientific	U.S.	\$8.4
9. Roche	Switzerland	\$8.0
10. Becton Dickinson	U.S.	\$6.5
11. Abbott Labs	U.S.	\$6.3
12. Stryker	U.S.	\$6.0
13. Cardinal Health	U.S.	\$5.0
14. Olympus	Japan	\$4.2
15. 3M Healthcare	U.S.	\$4.0
16. Zimmer Holdings	U.S.	\$3.9
17. St. Jude Medical	U.S.	\$3.8
18. Smith & Nephew	U.K.	\$3.4
19. Beckman Coulter	U.S.	\$2.8
20. Synthes	Switzerland	\$2.8
Total		\$161.2

The medical device market is about 50% of the world pharmaceutical market, but is growing faster than its drug counterpart. For purposes of comparison, the revenues of the top five pharmaceutical companies and the top three biotechnology companies are listed in Tables 1.2 and 1.3 respectively. Revenues of the top five pharmaceutical companies grew by 24% in 2008. The total revenues of all pharmaceutical companies in 2006 were \$643 billion (22). The US accounted for 45% of world sales.

Table 1.2. Revenues of the top five pharmaceutical companies (22).

Top Five Pharmaceutical Companies	Country of Origin	2008 Revenues (\$ billion)
Pfizer	U.S.	\$70.8
Johnson & Johnson	U.S.	\$61.1
GlaxoSmithKline	U.K.	\$45.5
Hoffmann-LaRoche	Switzerland	\$40.3
Sanofi-Aventis	France	\$40.0
Total		\$257.7

The 2006 revenues for the sector biotech are estimated at \$60 billion. The revenues of the top three biotech companies are shown in Table 1.3. These three companies experienced a growth of 23% from 2007. The American biotech industry surpassed pharmaceutical companies to become the primary source of new medicines for the years 2002 to 2005.

Table 1.3. Revenues of the top three biotech companies (21).

Top Three Biotech companies	Country of Origin	2008 Revenues (\$ billion)
Amgen	U.S.	\$15.0
Genentech	U.S.	\$10.5
Gilead Sciences	U.S.	\$5.3
Total		\$30.6

1.4. Supporting Societies and Professional Activities

The Biomedical Engineering Society (BMES) was founded in 1968 to serve as a professional society that represented both biomedical and engineering interests. Its stated purpose is "To encourage the development, dissemination, integration, and utilization of knowledge in biomedical engineering" (24). Members include leading researchers from major universities, government agencies and BME corporations worldwide, as well as doctors and industry leaders in pharmaceuticals and prosthetic devices. BMES is the approved leading society for ABET accreditation of BME, bioengineering and technology programs. In 2008, the BMES Annual Fall Meeting attracted more than 2,200 practicing engineers, as well as medical specialists, from more than 20 countries. Tracks areas of recent meetings have included: Cardiovascular Engineering, Respiratory Engineering, Orthopedic and

Rehabilitation Engineering, Neural Engineering, Cellular and Molecular Engineering, Tissue Engineering and Biomaterials, Bioinformatics and Systems Biology, Device Technologies—from Nano to Micro, Biomedical Imaging and Optics, BME Education and New Frontiers.

In 1991, the American Institute for Medical and Biological Engineering (AIMBE) was established in Washington D.C. The principal activities of AIMBE include acting as an advocate for public policy and disseminating information about medical and biological engineering (23). Its four components are College of Fellows, Academic Council, Council of Societies and Industry Council. As of 2008, the College of Fellows had some 1000 scientists, clinicians and engineers who had distinguished themselves in the practice of medical and biological engineering. The Academic Council is made up of the programs or departments of biomedical engineering of some 110 universities. The Council of Societies has 14 society members (the society members who practice medical and biological engineering number more than 50,000). The fourth component, the Industry Council, comprises large and small bioengineering companies.

The year 2009 also marked the 40th anniversary of the Association for the Advancement of Medical Instrumentation (AAMI). In its founding year 1969 and under the leadership of Dwight Harken, AAMI organized a National Conference on Medical Device Regulation in Bethesda, MD to address the device safety concerns of the medical community and the government. As John Abele, AAMI founder and Board Member, noted, “This conference was a huge event. It was the first time that the presidents of every American Medical Association — recognized society were present in one room.” The taskforce recommendation on device regulation that came from this conference formed the framework of the “Medical Device Amendments” legislation that was passed by Congress in 1976.

The Advanced Medical Technology Association (AdvaMed) was formed by companies that produce medical devices, diagnostic products and health information systems. It is a trade association to promote policies that foster the highest ethical standards, rapid production approvals, appropriate reimbursement and access to international markets. AdvaMed’s 2009 priorities are to foster continued innovation and ensure the delivery of the best possible healthcare for all Americans.

The Medical Device Manufacturers Association (MDMA) is a national trade association that provides educational and advocacy

assistance to innovative and entrepreneurial medical technology companies. It has been a voice for small companies and plays a proactive role in helping to shape government policies that have an impact on medical device innovators.

In addition to the professional magazines that are published by these societies, a number of prominent magazines serve the medical device industry. The premium magazines for the biomedical engineering community and medical device industry include BMES' Annals of Biomedical Engineering; AAMI's Biomedical Instrumentation & Technology; IEEE's Engineering in Medicine and Biology Magazine; MX: Business Strategies for Medical Technology Executives; MD&DI (Medical Device and Diagnostic Industry) Magazine; Medical Device Link; Pharma Med. Device; and Nature, Biotech.

1.5. Innovations in Biomedical Engineering

"Innovation will be the single most important factor in determining America's success through the 21st century... America's challenge is to unleash its innovation capacity to drive productivity, standard of living and leadership in global markets... For the past 25 years, we have optimized our organizations for efficiency and quality. Over the next quarter century, we must optimize our society for innovation." This is the opening resolution of an Innovate America report that was presented by Samuel J. Palmisano, Chairman and Chief Executive Officer of IBM Corporation and G. Wayne Clough, President of the Georgia Institute of Technology at the 2004 National Innovation Initiative Summit in Washington DC (15).

On the subject of medical innovations, three papers in the journal *Health Affairs* (vol. 20, 2001) conclude that

- Americans believe that opportunities for medical miracles are endless, and thus are willing to pay for progress.
- When costs and benefits are weighed, technological advances have proven to be worth far more than their costs.
- The ten most important medical innovations developed during the last 25 years and ranked by a survey of physicians are:
 1. Magnetic resonance imaging (MRI) and computed tomography (CT) scanning,
 2. Angiotensin converting enzyme (ACE) inhibitors,

3. Balloon angioplasty with stents,
4. Statins,
5. Mammography,
6. Coronary artery bypass graft (CABG),
7. Proton pump inhibitors and H2 blockers,
8. Selective serotonin reuptake inhibitors (SSRIs) and non-SSRI antidepressants,
9. Cataract extraction and lens implant,
10. Hip and knee replacements.

One of AIMBE's goals is to accelerate the growth of the nation's economy and the improvement of healthcare by innovations in medical and biological engineering. Promoting awareness of the contributions made by biomedical engineers and assuring development of a public policy for a healthy environment for medical and biological engineering innovation led to the selection of 24 innovations of medical and biological engineering for induction to the AIMBE Hall of Fame. Grouped according to the decades in which the innovations first gained wide usage, they are:

- 1950s and earlier
 - Artificial kidney
 - X-ray
 - Electrocardiogram
 - Cardiac pacemaker
 - Cardiopulmonary bypass
 - Antibiotic production technology
 - Defibrillator
- 1960s
 - Heart valve replacement
 - Intraocular lens
 - Ultrasound
 - Vascular grafts
 - Blood analysis and processing
- 1970s
 - Computer assisted tomography
 - Artificial hip and knee replacement
 - Balloon catheter
 - Endoscopy
 - Biological plant/food engineering

- 1980s
 - Magnetic resonance imaging
 - Laser surgery
 - Vascular stents
 - Recombinant therapeutics
- 1990s to the present
 - Genomic sequencing and micro-arrays
 - Positron emission tomography
 - Image-guided surgery

The following three criteria were used by the fellows of AIMBE to make their selections from a list of 60 innovations that were nominated for entry to the AIMBE Hall of Fame:

- The innovation must represent a significant engineering achievement
 - It must be in general use
 - Most importantly, the innovation must save lives and improve the quality of life for a large number of people.

As described earlier in this Section, six major medical innovations that were identified by physicians are in the AIMBE's Hall of Fame. (The other four are innovative drugs.) To further contrast the significance of these two lists (one by physicians and one by biomedical engineers), we quote from the article by Fuchs and Sox (2) on the physicians' ranked list that




“The most surprising finding of their study was the extent to which the leading innovations were an outgrowth of physical sciences (physics, engineering, and computer science) rather than disciplines traditionally associated with biomedical sciences.”



2009 was the 30th Anniversary of the magazine MD&DI. To celebrate this occasion, the readers of MD&DI chose 30 innovative medical devices that had a significant impact on healthcare over the previous 30 years (1). They are listed below thanks to the courtesy of MD&DI. The first year that the device was used in the United States appears first.

1. 1979 Blood and Cell Separator. This device draws whole blood, keeps the desired component, and returns the





remaining blood components to the donor to eliminate the risk of contamination. It enables donors to give blood more frequently and patients to receive blood from fewer donors.

2. 1980 Implanted Cardiovascular Defibrillator for patients who are at risk of sudden cardiac death due to ventricular defibrillation.
3. 1980 Angioplasty Balloon Catheter. This percutaneous coronary intervention has both improved and saved the lives of patients. 
4. 1980 Cochlear Implants, which give deaf people the ability to hear.
5. 1980 Intra Articular Arthroscopic Shaver System. Its shaver is used in orthopedic procedures to remove bone or cartilage and other soft tissue from a patient's joint. 
6. 1980 Personal Glucose Meter. This development advances significantly the treatment of diabetes by moving glucose testing from the hospital to the home.
7. 1981 Laryngeal Mask Airway. This assures that a patient who is under anesthesia has an unobstructed airway.
8. 1981 Pulse Oximeter, a non-invasive way to measure continuously the oxygen saturation level of a patient's blood.
9. 1983 EXCEL and PAB IV Containers. These simple "devices" provide users of infusion fluid that is free of Di(2-ethylhexyl)phthalate. Its leaching from the container to the contained fluid may be a critical concern.
10. 1985 Automated External Defibrillator. This has been instrumental in saving lives since its introduction.
11. 1987 Digital Hearing Aid. Its introduction enables manufacturers to enhance features and provide users with more comfort and higher-quality hearing.
12. 1988 Safety Needles and Syringes. These inventions contribute greatly to the reduction of needle-stick, the most frequent cause of blood-borne infections in healthcare settings. 

13. 1991 Demineralized Bone Matrix Gel. This is an off-the-shelf product used by surgeons for bone healing.
14. 1992 Ventricular Assisted Device, a pump to help a weak heart to pump blood through the body and a “bridge implant” to help patients survive until they obtain a new heart.
15. 1992 Smart Infusion System. At the time of introduction, it was the first infusion system to have a dose rate calculator.
16. 1994 Palmaz-Schatz Balloon Expandable Stent. This introduced a new wave of treatment to solve problems that angioplasty alone could not.
17. 1994 Headless Cannulated Bioabsorbable Interference Screw. A replacement of the metal screw with the advantage that the body absorbs the polymer, replacing it with bone and eliminating the need for further surgery to remove the screw.
18. 1995 Medical Lasers for surgery. Their most popular application is LASIK to correct myopia, hyperopia and astigmatism.
19. 1996 Angio-Seal, which uses bioabsorbable components to seal punctures in the femoral artery after arterial catheterization.
20. 1998 LightCycler PCR (Polymerase Chain Reaction). This is one of the best known devices in point-of-care diagnoses for infectious diseases. The quick disease identification enables immediate treatment and protection for those at risk.
21. 1999 da Vinci Surgical System. Its microchip technology and 3-D optics enable surgeons to perform complex procedures by making tiny incisions to treat in minimally invasive fashion a broad range of pathological conditions.
22. 1999 Cyber-Knife Robotic Radiosurgery System. A miniature linear accelerator that delivers non-invasively concentrated beams of radiation to a targeted tumor. A cumulative dose of radiation kills the tumor cells while minimizing radiation exposure to the surrounding healthy tissue.
23. 2001 PillCam, a capsule that houses a miniature video camera, lights, a transmitter, and batteries. As it is swallowed for passage through the intestine, the device takes photos and sends them to a small recorder.

that is affixed to the patient's belt.

24. 2002 OraQuick Advance Rapid HIV-1/2 Antibody Test. The test correctly identified 99.6% of people who were infected with HIV-1 and 100% of people who were not infected.
25. 2003 Drug Eluting Stent. The use of medication with the stent has reduced restenosis rates and provided significantly better clinical outcomes for patients. Its introduction ushered in the era of combination products.
26. 2003 LifePort Organ Transporter. This system pumps a cold solution through the organ to reduce tissue damage while the organ is in transport. 
27. 2003 Sidne (Stryker Integrated Device Network) Voice Activation System, which uses voice recognition to give the surgeon control over endoscopy equipment in the operation room without touching a button.
28. 2005 OxyMask. Its open oxygen design eliminates CO₂ rebreathing and avoids mucosal drying, nose bleeding, facial sores and the claustrophobic feeling that the mask can give. It also enables a patient to communicate more easily and to drink through a straw. 
29. 2007 Pinnacle TPN (Total Parenteral Nutrition) Management System, which provides a safe and easy way to check, compound, and deliver TPN to patients.
30. 2008 Impella 2.5 Circulatory Support System. This is a catheter that can be inserted into the femoral artery and on into the heart. The 12F motor and impeller inside the catheter pump blood at a rate up to 2.5 liter per minute.

The readers of MD&DI also chose the following five “older” technologies:

1. 1800-1970s Hemodialyzers and Dialysis Machines
2. 1960s-1970 Artificial Pacemakers
3. 1972 Computed Tomography Scanner

4. 1973 Vena Cava Filter. This filter has the same basic shape as that used in oil refining to trap sludge and debris, but is used to prevent life-threatening pulmonary embolisms.
5. 1977 Magnetic Resonance Imaging

The following excerpts from the MD&DI article on 30 Years/30 Devices say it the best about the innovations coming out of the medical device industry:

“Some of the devices nominated by our readers are small enough to travel through a blood vessel. Some are so large they fill an entire room. Some cost thousands of dollars but will stay in the body for 10 years, and some cost pennies and are designed to be thrown away after one use. This industry is characterized by innovators looking for the best way to engineer a solution to a problem. And device designers are noted for their ability to borrow ideas from other industries.

In the last 30 years, we have witnessed the industry’s coming of age, with its first blockbuster device and its shift from individual inventors and small start-ups to globally recognized brand names. Here (the above list) is a look back at the devices that have changed the industry and the world.”

1.6. Hemodialysis and its Innovators

Today 400,000 patients with chronic kidney failure, which is known as the end stage renal disease (ESRD), in the US and 3.5 million worldwide are undergoing or requiring chronic dialysis (19). If left untreated, both acute renal failure and end-stage renal disease produce uremia and death. Here are excerpts from a speech that was given at the ceremony of the 2002 Lasker Award for Clinical Research. It celebrates the achievements of the two scientists who made hemodialysis possible: Willem Kolff (who is acknowledged as the “Pioneer of Artificial Organs”) and Belding Scribner (3).

“Our story begins in 1938 at a small medical ward at the University of Groningen Hospital in the Netherlands. The physician in charge was Willem Kolff, who had just graduated from medical school. One of his first patients was a 22-year-old man in uremic coma. The young Dr. Kolff, then only 28 years old, watched helplessly for four days as the young man died in front of his eyes. He had no treatment to offer — if only he could find a way to remove the toxic metabolic

wastes that accumulate in blood when the kidney fails...Despite the difficult circumstances of Nazi-occupied Netherlands, Kolff miraculously cajoled an enamel manufacturing company to help him obtain scarce materials in order to construct the first artificial kidney. This machine, which came to be known as the "rotating-drum hemodialyzer," consisted of 130 feet of cellophane tubing made from sausage casing, wrapped 30 times around a horizontal drum made out of aluminum strips. As the drum rotated through a bath of salt solution contained in an enamel tank, the patient's blood was exposed to the dialysis bath, allowing rapid and efficient removal of the toxic wastes.

When World War II ended, Kolff donated all five of his artificial kidneys to hospitals in London, Poland, The Hague, Montreal, and Mt. Sinai Hospital here in New York City. This extraordinary act of generosity enabled physicians throughout the world to become familiar with the new technique of dialysis. He also provided blueprints of his "rotating-drum hemodialyzer" to George Thorn at the Peter Bent Brigham Hospital in Boston. This led to the manufacture of the Kolff-Brigham kidney, which was an improved stainless steel version of the original...

The Kolff kidney solved the problem of acute renal failure, but what about the hundreds of thousands of patients with chronic end-stage renal disease for whom prolongation of life requires repeated dialysis three times a week forever? In the late 1950s, the conventional wisdom among kidney experts was that chronic intermittent dialysis would never be possible because of two insurmountable problems, one technical and one psychological. The technical problem was one of circulatory access; whenever a patient was hooked up to a dialysis machine, veins and arteries were damaged, and after six or seven treatments, physicians would run out of places to connect the machine. The psychological problem stemmed from the widely held mystical belief that a cellophane dialyzer outside the body could never permanently replace the complex functions of a normal organ. After all, according to the experts, the kidney was a sacred organ. Above and beyond its excretory function, it produces three essential hormones: erythropoietin for forming red blood cells, renin for maintaining blood volume and blood pressure, and hydroxylated vitamin D for preventing breakdown of the bones.

In 1960, the impossible suddenly became possible. The psychological and technical barriers to chronic dialysis came crashing

down through the research of Belding Scribner, a young professor of medicine at the University of Washington in Seattle...His idea was elegant in its simplicity: sew plastic tubes into an artery and a vein in the patient's arm for connection to the artificial kidney. When the dialysis treatment was over, keep the access to the circulation open by hooking the two tubes together outside the patient's body via a small U-shaped device, made of Teflon. This U-shaped Teflon device, which came to be known as the Scribner Shunt, served as a permanently installed extension of the patient's own circulatory system, shunting the blood from the tube in the artery back to the tube in the vein. Whenever the patient needed to be dialyzed again, no new incisions in the blood vessels had to be made. The Shunt was simply disconnected from the tubes in the patient's arm, and the patient was hooked up again to the machine...

The contributions of Willem Kolff and Belding Scribner revolutionized the treatment of kidney disease, saving and prolonging the useful lives of millions of people....”

As the US Renal Data System indicates, the population of patients who have chronic kidney disease increases by 8% a year. The healthcare cost incurred by these US patients came to \$20 billion in 2001 (19). The annual mortality rate of hemodialysis patients is about 18%.

The patients go to dialysis clinics three times a week. In each hemodialysis treatment the patient is hooked up to the dialyzer for three to five hours. 30% of the patients experience symptoms, such as cramps, headaches, nausea or dizziness. Although these symptoms usually develop before a measurable decrease in blood pressure is detected, they are commonly referred as intradialytic hypotension (ID). In severe cases, shock or death can occur. ID is the key reason why these patients suffer such a high mortality rate.

The close association of hemodialysis to the development of ID indicates that ID is caused by the blood flow reduction to the brain resulted from the lowering of cardiac output. Since the patient's heart still functions normally, Starling's principle characterizes the development of low cardiac output as a result of low venous return. The low blood volume (i.e., hypovolemia) and pooling of blood in the microcirculation are two factors that lead to low venous return (9). If hypotension results from hypovolemia, one treatment is to replenish the low blood volume with fluid infusion in the circulation. On the other hand, if blood is pooled in the microcirculation of the liver, fluid

infusion may not increase the venous return. At present, physicians do not have a technique that can determine whether the symptoms and ID result from hypovolemia or vascular pooling. Typically, the counter measure chosen is not effective in alleviating the hypotensive symptoms.

In the US about 0.4% of patients undertake hemodialysis at home while 14% of the patients in New Zealand did in 2003 (19). Because patients can undertake home hemodialysis more often and more readily than travel to a hospital for service, the patient experiences smaller fluctuations in blood pressure and hypotensive symptoms are less likely to develop. An increase in the use of home hemodialysis requires better assurance of patient safety. There still are challenges and opportunities for biomedical engineers to further improve the monitoring techniques that can lead to the selection of countermeasures and/or adjustment of the hemodialysis process for the alleviation of hypotensive symptoms and the assurance of a safe hemodialysis for the patient.

In this book, some work undertaken to develop Global Monitors, Inc. and its anti-pooling vest are used to exemplify the processes that you will use to assess, launch and build your own venture. The mission of the company is to improve the delivery of hemodialysis care to millions of patients. The overview of hemodialysis in this book, the reason why GMI is working on its R&D and the commercialization of anti-pooling vest and blood volume monitor (11), and the impact that the vest and monitor have on the quality of life of hemodialysis patients and operating costs of dialysis clinics are presented as an example for the readers develop the justifications for their own venture products.

1.7. The Impact of Medical Device Innovations on Healthcare

When you review the list of innovations described in Section 1.5, you will probably be impressed by how these innovations save lives and improve the patients' quality of life. On the other hand, you will also read news items that contain these messages:

- The high cost of medical technology: who's to blame? In most industries, technology tends to lower costs. Not healthcare. Why is medical technology out of control and is there any way to curb its cost and spread? Technology and its associated costs account for as much as 50 percent of medical inflation (4).

- Technology could increase healthcare costs without markedly improving quality, according to experts at Wharton (7).
- Propelled by the increasing use of new drugs, imaging technologies and other wildly expensive innovations, (health) insurance premiums are rising fast (20).

The table below was used in Congressional testimony by Peter Orszag, Director of the Congressional Budget Office to illustrate the factors that contribute to the growth of healthcare spending (14). The contributions from technology-related changes in medical practice range from 38% to 65%. A technical review panel that was formed to advise the Center for Medicare and Medicaid Services on future healthcare cost trends used similar information to conclude that about half of health expenditure growth is attributable to technology change. However, the research quoted in Table 1.4 merely suggests that the change in medical practice due to technology advancement contributes to about one half of health expenditures. In no way does it support the three news messages that were given previously.

Table 1.4. The estimated contributions of selected factors to long-term growth of healthcare spending per capita, 1940 to 1990 (Source: Congressional Budget Office, 14)

	Smith, Heffler & Freeland (2002)	Cutler (1995)	Newhouse (1992)
Aging of the Population	2%	2%	2%
Changes in Third-Party Payment	10%	13%	10%
Personal Income Growth	11-18%	5%	<23%
Prices in the Healthcare Sector	11-22%	19%	Not Estimated
Administrative Costs	3-10%	13%	NE
Defensive Medicine and Supplier-Induced Demand	0	NE	0%
Technology-Related Changes in Medical Practice	38-62%	49%	65%

Let us examine the meaning of the large percentage (i.e., 38% to 65% in Table 1.4) by analyzing how an invention is likely to change the medical practice, increase expenditures, save lives and produce higher productivity. The study selected would be the implantation of pacemakers in patients done by Moss and Rivers (13) and with the implantation expenses listed by Rinfret et al (16). For all living patients their productivity would be \$50,000 per year. Table 1.5 lists the total

medical expenditures, total productivity, productivity/expenditures and device cost/total expenditures.

Table 1.5. A comparison of a hypothetical expenditures and productivity for 50 patients with pacemaker implantation and historic heart operation.

	With pacemaker implantation*	With the historic operation**
Total Medical Expenditures	\$1,975,029	\$400,000
Total Productivity	\$19,500,000	\$4,000,000
Productivity/Expenditures	9.9	10
Device Cost/Total Expenditures	20%	NA

* 11 patients died during the 10-year study of Moss and River. For simplicity, we assume that these patients were not productive since day one and that their cost of operation was \$18,000 per patient. There were implantation costs and follow-up costs for living patients at a total expenditure of \$45,452 per patient. 39 patients lived beyond the study period. The pacemaker would be dual-chamber at a unit cost of \$7,720. The age of the patients was 68 ± 8 years. For a younger group, the total productivity would be higher.

** For purposes of comparison, we assume that 80% of 50 patients would receive an open heart surgery to correct the abnormal heart rhythm at a lower cost of \$10,000 (in 2008 dollars) per operation. 50% of the patients with this “historic” surgery were assumed to have a productive life of four years as the surgery might not enable the patient to regain fully his or her normal heart function.

These hypothetical calculations certainly indicate that the total health expenditures increase significantly because of the change in medical practice. However, the continuation of the lives of these patients contributes a productivity that is 10 times the expenditures. This benefit is an add-on to the fact that there are 39 patients living beyond 10 years as shown by the study of Moss and Rivers on pacemaker implantation. Even though the price of the pacemaker is much higher than that of the pacemakers for most current uses, the total cost for pacemakers is estimated to constitute only a small fraction (20%) of the total expenditures.

The introduction of expensive medical technology has led to some increases in healthcare cost while the effectiveness of the technology is still under evaluation. Blaming technology innovations as the reason for run-away healthcare expenditures is not justified and does not satisfy our desire to have quality healthcare at an affordable price. As concluded in Chapter 18, it is the responsibility of all constituents, citizens, engineers, physicians, hospitals, industry, professional societies, trade organizations and educational institutions, to work

together to utilize innovations and improvements for the good of the nation and the people of the world.

1.8. Career Interests of Biomedical Engineering Students

The top career choice of 401 biomedical engineering (BME) undergraduates 10 to 20 years after their university graduation is entrepreneurship (10). It is time to not only recognize this, but also to modify our curriculum so that it can prepare students to meet their career interest and expand the biomedical engineering industry.

Advances in electronics, computers and materials have contributed greatly to the development of the medical devices and diagnostic industry. The growth in this industry leads to not only a better understanding of biology and medicine, but also to better healthcare. This industry differs from a consumer-oriented industry.

First, most of the products of the biomedical industry serve a smaller subset of people, as exemplified by the use of the glucose sensor for people who have diabetes. However, as we acquire a better understanding of health and disease, this industry will be ready to produce many new devices, diagnostic methods and treatments for the prevention and alleviation of a wide array of diseases. Thus, the BME industry is fertile ground for BME graduates who wish to assume a leadership role in the development and growth of BME ventures.

Many of the brightest university students have chosen to study BME. This is certainly an exciting field in which to carry out leading research. They will be well rewarded as their work can save lives and improve the health of patients. The author believes that, for the new discipline of BME to mature into a full-blown engineering discipline, it needs more entrepreneurs and jobs for our graduates. For this reason, I undertook a survey of the career choices of 401 BME undergraduates studying at the University of California San Diego, Johns Hopkins University and the University of Southern California. I wanted to learn whether these undergraduates were interested in becoming BME entrepreneurs immediately after graduation or 10 to 20 years after they had gained more professional experience and education.

As an introduction to the career survey, a brief lecture entitled “Challenges and Opportunities in BME Entrepreneurship” was presented to students who were taking BENG 1 “Introduction to Bioengineering” (UCSD, Instructors: Shu Chien and Peter Chen), BME

202 “BME in the Real World” (JHU, Instructors: Sasha Popel and Art Shoukas), and BME 101 “Introduction to BME” (USC, Instructors: Jean-Michael Maarek and Jesse Yen). 63% of respondents were freshmen. Sophomores, juniors, seniors and others made up 9%, 12%, 11% and 5% respectively.

In the lecture, I highlighted the challenges and opportunities in BME entrepreneurship by quoting from an article that appeared in the January, 2006 issue of MD&DI magazine. It says that *the implantable medical device industry has grown exponentially over the last thirty years*. When a large number of patients are using a medical device, the industry has large revenues and employs many engineers. On the other hand, this quote also implies that a much longer time is required for patients to accept medical devices for example, than for consumers to accept a new type of television. Should the medical device cause even a few patients to experience a serious incident, it may mean the end of that device company.

Several medical devices were discussed to further highlight the challenges and opportunities. For example, total knee replacement has enabled patients to regain motion without pain. However, about 10% of implanted total knee replacements may become defective in 10 years. The annual Medicare cost for defective knee replacements came to \$208 million for the year 2005. One of every 200 patients dies during the day following the replacement. The message to the students is that there is still a great need for them to improve the engineering of total knee replacement and its implant procedure.

In 2005, one million cardiac pacemakers were implanted in patients worldwide. Medtronic and Guidant (now part of Boston Scientific) are major companies that produce many pacemakers. They had 2005 revenues of \$10 billion and \$3.8 billion respectively. Medtronic was founded as a two-person company in 1949. The precursor of Guidant began as a three-person company in 1972. The message is that many large medical device companies had humble beginnings and required many years to succeed.

At the end of the lecture, 3”x5” index cards were handed out to students during the discussion period for their use in recording their names, class years, majors, and minors. The following six career choices for the students to prioritize were listed on PowerPoint:

1. Industry
2. Government

3. Graduate or Professional School
4. University or Research Laboratory
5. Entrepreneurship
6. MD or LLD.

I advised the students that, if they choose Category 5 Entrepreneurship, it would mean that they will work on an entrepreneur team to build, organize and manage a business venture. The selection of Category 6 MD or LLD would mean that they will be clinicians who work with patients or attorneys who work with clients. If they obtain an MD and want to teach at a university or do research in a research institute, then they should choose Category 4.

I also reminded the students that employees in industry can form an entrepreneur team within to work on projects that are an extension of the company's work. Further, the industrial jobs are more stable. Many small ventures will fail during their first three to five years. On the other hand, the entrepreneurs own the companies and employees of a large company may only own a small share.

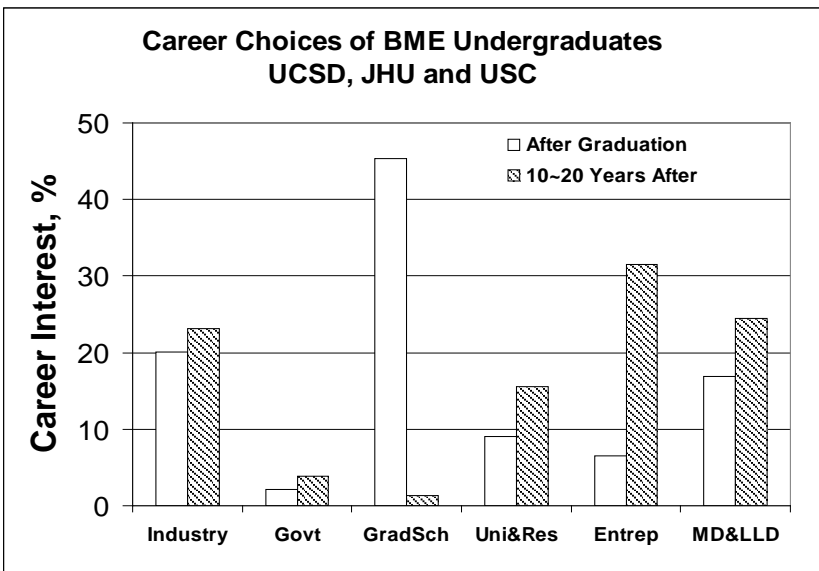


Fig. 1.1. Career choices of BME undergraduates of the University of California San Diego, Johns Hopkins University and the University of Southern California.

The first question asked the students to identify their first and second choices from the six categories of career choices to pursue upon graduation from university. By appropriately ranking the first and second choices, I obtained the distribution of their career choices that are depicted by the open bars in Fig. 1.1 of the previous page. One can see that 45% of these students indicated that they would choose to attend graduate or professional school. Many of them then wanted to go on to teach at a university or to practice as clinicians or attorneys. 20% chose to be employed in industry right after graduation. Only 6.5% thought that they might work as entrepreneurs.

Similar two-choice answers for their career interests 10 to 20 years after graduation were obtained and appear as shaded bars in Fig. 1.1. By that time, few would be thinking of going to university. Instead, the top choice is entrepreneurship at 32%. The second is the MD or LLD category (25%) and the third is the Industry (23%).

These distributions are quite similar for each of the three universities, as the standard errors for the distributions are less than 2%. The response seems to indicate that the students had given considerable thought to their future career well before my lecture presentation and understood the challenges and opportunities in BME entrepreneurship. Based on my informal discussions with the students, I believe the students who chose an entrepreneur career really want to translate their BME knowledge into inventions and then commercialization for the benefit of people.

1.9. Three Development Phases to Success

Most medical device enterprises are started by persons who have a desire to solve medical problems and a good idea that promises to do so. Unfortunately, desire and ideas alone do not guarantee success. A great deal of hard work and critical thinking is required to get any venture off the ground. In this book, the development of a company is addressed in chapters written for the following three development phases:

Phase I. Assessing your invention

Phase II. Launching your venture

Phase III. Building up your enterprise.

Section II of this book will help working and would-be biomedical engineers **assess** how well their ideas will succeed. The three chapters in Section II provide guidelines for potential entrepreneurs to work on the following issues of Phase I development:

- Evaluating what they have and need in order to prepare themselves to become successful entrepreneurs,
- Designing a creditable medical-device invention that will appeal to patients, physicians, hospitals, medical device makers, and drug manufacturers, and
- Carrying out meaningful research on the marketing potential of the invention
- Raising funds to do a feasibility study with the goal of showing that you can use state-of-the-art technology to build your device. A feasibility study may be interpreted as synonymous with proof of the concept.

Section III will guide the entrepreneurs in **launching** their ventures to the point where pre-production models are produced. The seven chapters in the Section are written to help you deal with the following issues:

- Describing the financial preparations needed to start a company, as well as building the entrepreneurial team,
- Patenting the invention and maximizing its profit generation potential,
- Advancing the company with governmental and community support,
- Winning grant money and investment from an angel to carry out the research and development of the medical invention,
- Understanding FDA device regulations,
- Preparing for FDA 510(k) submission of a new medical device,
- Presenting the business plan to attract more capital.

With the tasks of Part II accomplished, we assume that by now your company has demonstrated the efficacy of your product and raised sufficient funds to proceed to the manufacturing and sales phases. To provide guidelines for **building up** your enterprise, the six chapters of Part III address the following issues:

- How to manage the company's finance and to price the product.
- How to negotiate employment and licensing deals, mergers, acquisitions and the sale of a company.
- How to lead the company with effective management of people, time and resources.
- How to get the product manufactured.
- How to establish a market niche for your product.

- How to globalize the company once you have established a strong US market.

The book concludes with two chapters on what to invest in the future and how to succeed in biomedical engineering entrepreneurship with really trying. The former is a collection of bits of wisdoms from prominent academicians, community leaders, government officials, entrepreneurs and philanthropists. The latter is written by Shu Chien of UCSD.

1.10. About the Author

Jen-shih Lee, Ph.D., was professor and former chairman of the Department of Biomedical Engineering at the University of Virginia, as well as Director of the University's Institute for Technology in Medicine. He served as President of the Biomedical Engineering Society in 1994/1995 and as Chair of the Council of Societies of AIMBE from 1995-1997. Lee received the Distinguished Lectureship Award from the Biomedical Engineering Society in 1998 in recognition of his research contribution to the biomechanics of microcirculation and its therapeutic impact on blood volume control, as well as the Distinguished Service Award in 2002. He is also a scientific consultant to CardioResearch Inc., which his wife, Lian-pin Lee, Ph.D., founded to build on their academic research in the field of fluid mechanics and blood flow and to develop state-of-the-art medical devices and therapy for better diagnoses and treatment of cardiovascular disease. Following their move to San Diego in 2004, L. P. and J. S. Lee merged CardioResearch Inc. into a newly founded Global Monitors, Inc. (GMI) to work on the manufacturing and marketing of two products - the Lee Monitor and anti-pooling vest for the improvement of hemodialysis care.

In preparing this book, Jen-shih Lee consulted more than 100 experts on how best to motivate students and biomedical engineering entrepreneurs so that they will build successful enterprises for better healthcare delivery and improvement of the nation's economy. These experts are educators in leading academic biomedical engineering departments, founders of biomedical engineering enterprises, authorities on business and administration, attorneys and certified public accounts, inventors of medical devices, government officials, and visionaries in the field of biomedical engineering. Their ideas, experiences, thoughts, and advice are woven throughout the text and were drawn from personal

interviews, telephone conversations, and lectures given to students of Lee's "Biomedical Engineering Entrepreneurship" class, which was offered at the University of Virginia in the spring semester of 2003 and at the University of California San Diego in the spring of 2007. In addition to the contributions made to the course and book by lecturers and consultants, my students of the class made valuable suggestions that helped improve the book's presentations.

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