

Chapter 1

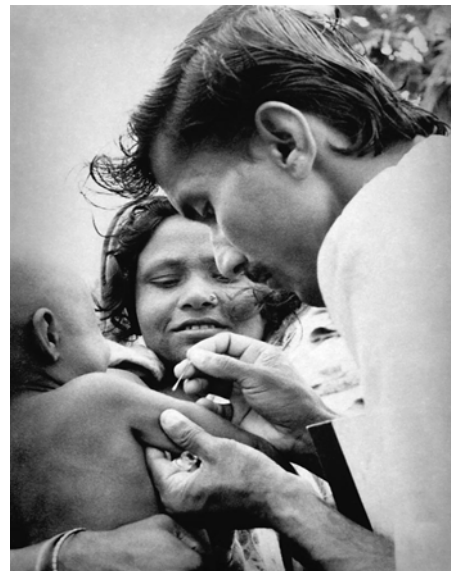
Emerging Medical Technologies: High Stakes Science and The Need for Technology Assessment



In the past century, advances in medical technology have yielded enormous improvements in human health. For example, our scientific understanding of the immune response and the resulting development of vaccines has vastly reduced the incidence of many infectious diseases. Smallpox has killed more people throughout history than perhaps any other infectious disease. Yet, in 1980, the World Health Organization announced that smallpox had been eradicated worldwide through a program of vaccination (Figure 1.1). Despite these advances, many medical technologies are available to only a small segment of the world's population that can afford them.

Today, emerging technologies have the potential to transform the future of health care, offering the potential to diagnose and prevent disease before it strikes, to treat disease in a targeted manner, and to utilize cells and genes for patient-specific therapies. For example, gene therapy offers the promise to cure fatal genetic diseases such as cystic fibrosis and to reprogram a patient's immune system to more effectively fight HIV/AIDS, the leading cause of death in sub-Saharan Africa. Sequencing the genome of *M. tuberculosis* has pointed to new molecular targets for more effective drugs to treat tuberculosis. Small silicon chips containing every gene in the human genome may soon be used to detect cancer at the earliest and most curable stages and to individually tailor therapeutic agents for each patient. Tissue engineering holds the promise to create artificial organs, overcoming problems with the limited supply of donor organs. Novel, biologically active materials may be used to coat blood vessels within the heart to prevent heart attacks, one of the leading causes of death in the United States.

What is needed to bring these new technologies from the research laboratory to your physician's office in a safe and



CDC/ World Health Organization; Stanley O. Foster

Figure 1.1: The development of the smallpox vaccine and the subsequent eradication of the disease is an example of a powerful medical technology.

Medical Technology:

The use of novel technologies to develop new drugs, biologics, or medical devices designed to diagnose, treat or prevent disease.

Bioengineering:

The application of engineering design to develop new medical technologies.

Biotechnology:

The use of living systems to make or improve new products, frequently targeted toward improving human health.

Four central questions addressed:

- (1) What are the major human health problems worldwide and how do these differ throughout the world?
- (2) Who pays to solve problems in healthcare and how does this vary throughout the world?
- (3) How can we use technology to solve world health problems?
- (4) How do new technologies move from the lab to the bedside?

UN Millenium Development Goals:

80% of the world's population live in **developing countries**. In 2000, 189 countries committed to a broad set of goals to meet the needs of the world's poorest citizens. The goals include:

Eradicate extreme poverty & hunger

- Halve the proportion of people whose income is less than one dollar a day by 2015
- Halve the proportion of people who suffer from hunger by 2015

Achieve universal primary education:

- Eliminate gender disparity in primary and secondary education in all levels of education by 2015

Reduce child mortality

- Reduce the under-five mortality rate by two thirds by 2015

Improve maternal health

- Reduce the maternal mortality ratio by 75% by 2015

Combat HIV/AIDS, malaria and other diseases

- Halt and begin to reverse the spread of HIV/AIDS by 2015
- Halt and begin to reverse the incidence of malaria and other major diseases by 2015

Ensure environmental sustainability

- Halve the proportion of people without sustainable access to safe drinking water and sanitation by 2015

Develop a global partnership for development

The Millenium Country Profiles (<http://unstats.un.org/unsd/mi/mi.asp>) provide a source of data to compare economic and health status of countries and to monitor progress toward these goals.

[1]

affordable way? As a society, how should we invest our limited financial and human resources to develop new medical technologies? Can new technologies reduce global disparities in health or will they simply widen the gap in health status between developing and developed countries? In this textbook, we examine how bioengineers integrate advances in the physical, information and life sciences to develop new medical technologies. To be effective, new health care technologies must provide a better means of preventing, detecting or treating disease. At the same time, technologies must also be affordable to those who need them. The goal of bioengineering is to harness science to solve health problems in the face of such constraints. Our study of bioengineering for world health is organized to first understand both global health needs and resource limitations—as we will see, the healthcare problems and economic constraints vary dramatically throughout the world. With this beginning, we profile new technologies emerging from biotechnology and bioengineering which can significantly impact world health. Throughout the book, we present and apply tools to systematically evaluate these new medical technologies. The book is organized to address **four central questions**:

(1) What are the major health problems worldwide?

Global mortality data show a significant gap in health status between developed and developing countries. Leading causes of death in the developed world include cancer, ischemic heart disease, and stroke. In the developing world, infectious diseases like tuberculosis and malaria are far more prevalent due to widespread poverty, poor infrastructure, and a lack of health care resources. A child born today in one of the least developed countries is more than 1,000 times more likely to die of measles, an easily preventable and curable disease, than one born in an industrialized country. Worldwide, more than 38 million adults and 2.3 million children are living with HIV/AIDS, most in developing countries. Over the next decade, noncommunicable diseases such as depression and heart disease are expected to overtake infectious diseases and malnutrition as leading causes of death in developing countries. The fraction of the global burden of disease linked to lifestyle and behavior choices, currently 20-25%, is expected to increase throughout the world—for example, by 2020 tobacco is expected to kill more people than any single disease, even HIV/AIDS.[2] Understanding how health needs differ throughout the world and how these needs are projected to change in the coming years is the first step to enable the development of new

technologies to address these needs.

(2) *Who pays to solve problems in healthcare?*

Despite recent advances, many medical technologies are available only to a small segment of the world's population. As a result, standards of medical care differ radically between the developed and developing world. Average annual health care expenditures in high income countries are more than \$1,800 per person, compared to only \$16 per person in the world's least developed countries (**Table 1.1**). Even in high income countries, the cost of new medical technologies is of great concern. Over the past two decades, healthcare spending has risen dramatically in the United States and throughout the industrialized world, and this rise is expected to continue through the next decade. In the US, healthcare costs now account for one seventh of the nation's expenditures. The increasing use of new, expensive technologies, an aging population, and increased administrative costs all contribute to the overall rise in healthcare spending. As we will see later, increasing health expenditures does not always improve health status. As health spending grows beyond a minimum value, there is a decreasing rate of return on investment, with fewer years of life gained per dollar invested.[4] In order to achieve the promise of new technologies worldwide, our society must develop and evaluate technologies in a cost-conscious manner.

(3) *How can bioengineering solve global health problems?*

Technology development begins with scientific knowledge; in health issues this often means an understanding of a disease and its effects on the body. Bioengineers build on this scientific knowledge to create new technologies that solve healthcare problems. Magnetic resonance imaging, radiation therapy, and vaccines are all examples of health-related technologies that have become widespread within the past century. The heart-lung bypass machine, pacemakers and other technologies have revolutionized the treatment of heart disease, reducing cardiovascular mortality by half over the last 50 years. In this book, we will consider how new technologies can be used to diagnose, treat, and ultimately prevent the three leading causes of death throughout the world: infectious disease, cancer and heart disease. As we will see later, the development of new healthcare technologies must take into account the societal and economic context in which they will be used and their potential status as a priority or a luxury at a given time. For example, development of a totally implantable artificial heart may provide a

Country	Avg. Health Care Expenditure per capita, 2001 (US\$)
Liberia	\$1
India	\$24
China	\$49
Colombia	\$105
Mexico	\$370
Portugal	\$982
Israel	\$1,641
Switzerland	\$3,779
United States	\$4,887

Table 1.1: Average health care expenditures per capita of selected WHO nations. [3]

Major Areas Of Bioengineering:

Tissue Engineering and Regenerative Medicine: The use of engineering design principles to regenerate natural tissues and create new tissues using biological cells and three dimensional scaffolds of biomaterials.

Molecular and Cellular Engineering: Engineering approaches to modify properties of molecules and cells to solve biotechnological and medical problems.

Computational Bioengineering: Use of computational tools to analyze large biological data sets such as in genomics or proteomics; computational models to predict structure and behavior of large biological molecules and to guide design of new drugs.

Biomedical Imaging: Design of imaging systems (e.g. ultrasound), image analysis tools, and contrast agents to record anatomic structure or physiologic function.

Biomaterials: The engineering design of materials compatible with biological organisms that can be used to make implants, prostheses, and surgical instruments that do not provoke immune rejection.

**Major Areas Of Bioengineering:
(cont.)**

Drug Delivery: Design of materials and systems to achieve controlled release of drugs in physiologic systems.

Biomechanics: The study of mechanical forces in living systems and the use of engineering design to create prosthetic devices and tools for rehabilitation.

Biosensors: Engineering design of systems to identify and quantify biological substances. Advances in microelectronics have aided in developing miniature, implantable biosensors.

Biosystems Engineering: Modeling complex, interacting networks of biological systems within cells and organism to understand physiology and disease and suggest therapeutic strategies to modify behavior.

solution to the problem of end-stage heart failure in developed countries, but due to differences in infrastructure and resources is unlikely to be a practical solution in many developing countries. To help illustrate these challenges, throughout this book, we will profile the experiences of several undergraduate students who carried out internships in sub-Saharan Africa as a part of a course in Bioengineering and World Health. Their experiences highlight both the opportunities and challenges of developing new technologies to improve world health.

(4) How do new technologies move from the laboratory bench to the patient's bedside?

New medical technologies developed in research laboratories must be subjected to a rigorous testing procedure to ensure that they are both safe and effective. In many cases, this involves carrying out experiments with human subjects. How can we ensure that these experiments are carried out in an ethical way? How can we balance the desire to bring promising new treatments to patients who need them as soon as possible against the risk of harming patients by allowing them access to therapies that haven't been sufficiently tested? As health care consumers we are often faced with conflicting media reports of the safety of new medical technologies. In order to make choices about our own health care, it is necessary to understand how medical research is funded and how new drugs and medical devices are regulated.

Answers to these four questions are complex and interrelated. We begin our journey to understand how bioengineering can be used to improve world health by examining a case study of the development of a new technology – the use of high dose chemotherapy and bone marrow transplant to treat advanced breast cancer. This case study illustrates the difficult personal and social issues that can arise as new technologies are developed and tested, and will introduce many of the issues that we will examine in more detail throughout the text. We conclude our case study with a look at how the process of healthcare technology assessment can be systematically used to address these complex and sensitive issues in a scientifically sound manner.

Read More About Breast Cancer:

Breast Cancer Facts & Figures 2005-2006. (Atlanta, GA: American Cancer Society, Inc., 2006). [5]

<http://www.cancer.org/downloads/STT/CAFF2005BrF.pdf>



Bioengineering & World Health: Student Projects in Africa



Kim Bennett accompanied Dr. Ellie Click across Malawi conducting intensive training at hospitals as a part of pilot project for the use of bloodspot PCR for infant HIV diagnosis.



Dave Dallas and Tessa Elliott assisted in the design and implementation of World Food Program food distribution system at a pediatric AIDS clinic in Mbabane.



Lindsay Zwiener and Rachel Solnick pilot-tested software that generates pictorial medication guides, which were developed as their Bioengineering & World Health course projects. They assessed whether these guides help caregivers in Botswana in the proper dosing and timing of anti-retroviral (ARV) medications, promoting adherence to ARV therapy.

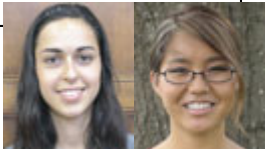


GABORONE, BOTSWANA

MBABANE, SWAZILAND

MASERU, LESOTHO

Christina Lagos and Sophie Kim rolled out their Bioengineering & World Health course project in the SOS Village in Maseru. The project was an after-school activities club to promote interest in science and health education with a focus on HIV/AIDS. They also implemented a Reach Out and Read program at a pediatric AIDS clinic.



The course in Bioengineering & World Health was developed and offered at The University of Texas at Austin and at Rice University. Through a new initiative called Beyond Traditional Borders, made possible by a grant to Rice University from the Howard Hughes Medical Institute through the Undergraduate Science Education Program, students at Rice University can travel to Africa for a summer and implement the projects they developed as part of this course. The inaugural class of interns kept a blog describing their experiences. Throughout the book, we include excerpts from the blog to provide a student's view of how bioengineering can improve world health.

Departure: June 8, 2007

Christina

Coming from a close family, I have been doing a lot of explaining about my goals and purpose for this trip and doing my best to calm the fears of my family. I know that they simply want me to be safe and are concerned about me while I am gone, and I am used to the ways of overprotective Greek relatives. In the end, I think I have convinced them that this will be the experience of a lifetime and that I have been looking forward to something like this since I began college.



Lesotho

I was getting ready to record something in my personal journal last night and found that the last sentence I wrote the last time I made an entry had to do with Africa. From my last weeks in Washington, D.C., working on health policy in Africa, I expressed a desire to go and experience the challenges and situations first hand. "I want to go to Africa...why not me?", that is what I had written as I wondered why it always seemed so far-fetched or impossible that I would one day be able to visit. And now it's quickly approaching, and I feel so fortunate and excited for this opportunity.

I am prepared for some of the best and worst emotions I have ever experienced and am ready to fully immerse myself in the work I am about to do in Lesotho. I feel almost guilty for having somehow cheated during this pre-departure period... I have been looking at tons of Google images of Maseru, Lesotho, and the surrounding area, and I feel like I have some sort of unfair advantage as I travel. When I was younger and did not use or have access to the Internet as much, traveling to a new place was always so much more of a mystery and I always envisioned my destination so differently than it turned out to be. I know that a bunch of Google images and travel sites will not do Lesotho justice, but I still feel like I have done away with at least a bit of the mystery of travel. Maybe I won't do that next time.

I am looking forward to spending the next few days in Johannesburg with a family-friend who grew up there. I will be there until the 12th when I will be meeting up with Sophie at the airport to head to Maseru.

It will be nice to leave the hot and humid start of summer here in Florida and find the cold beginnings of winter in southern Africa!

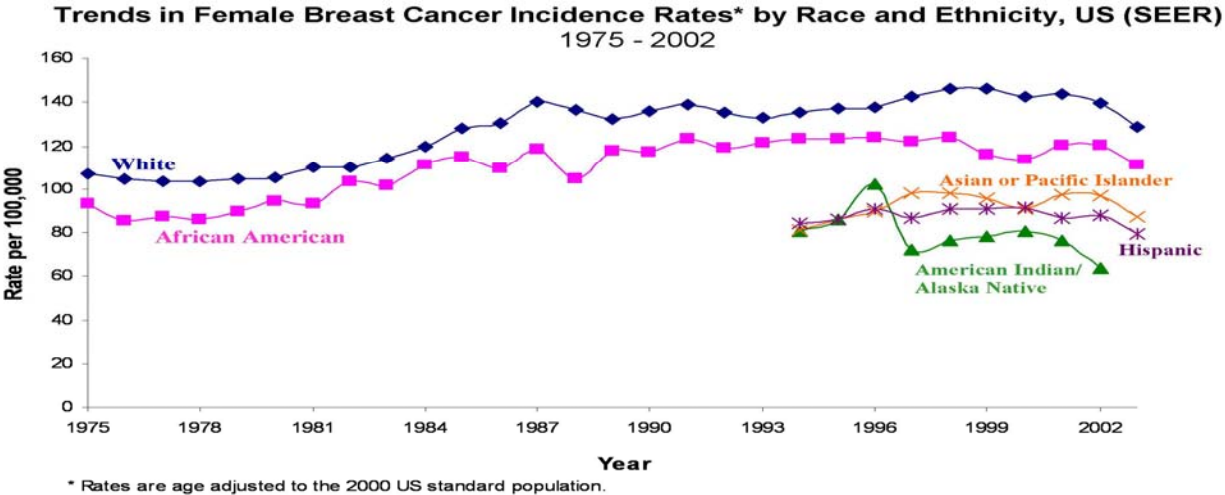


Case Study: Breast Cancer & Bone Marrow Transplant

Breast cancer is both a devastating and a common disease. If you are female and live in the United States, you have a one-in-eight (12.5%) chance of developing breast cancer sometime in your life.[5] When detected early, there are many effective treatments for breast cancer. However, few effective treatments exist for the disease in its later stages. Less than 20% of women are alive 5 years after the detection of stage IV metastatic breast cancer, the most advanced form of the disease. In the 1980s a promising new therapy was developed for women with metastatic breast cancer: high dose chemotherapy followed by bone marrow transplant (HDCT+BMT).

Small, early clinical trials of this technique were very promising. The effectiveness of a new cancer treatment is initially measured by the fraction of patients who experience a complete or total response following treatment. In the 1980s, a number of small studies showed a substantial increase in the number of patients with metastatic breast cancer who responded to this new therapy compared to historical experience for patients treated with standard chemotherapy. Although these results were exciting, they were viewed with caution until the patients could be followed for a longer period of time. Many patients who initially respond to therapy may relapse; thus long term survival rates are often used as a better metric to determine the effectiveness of a new cancer therapy. The three year survival rate measures the number of patients still alive three years after beginning cancer therapy. In the early 1990s, a small study indicated that women with high risk breast cancer treated with HDCT+BMT had a 72% three year survival rate, dramati-

Figure 1. 2: Female breast cancer incidence rates by race and ethnicity in the United States as reported by SEER.[9]



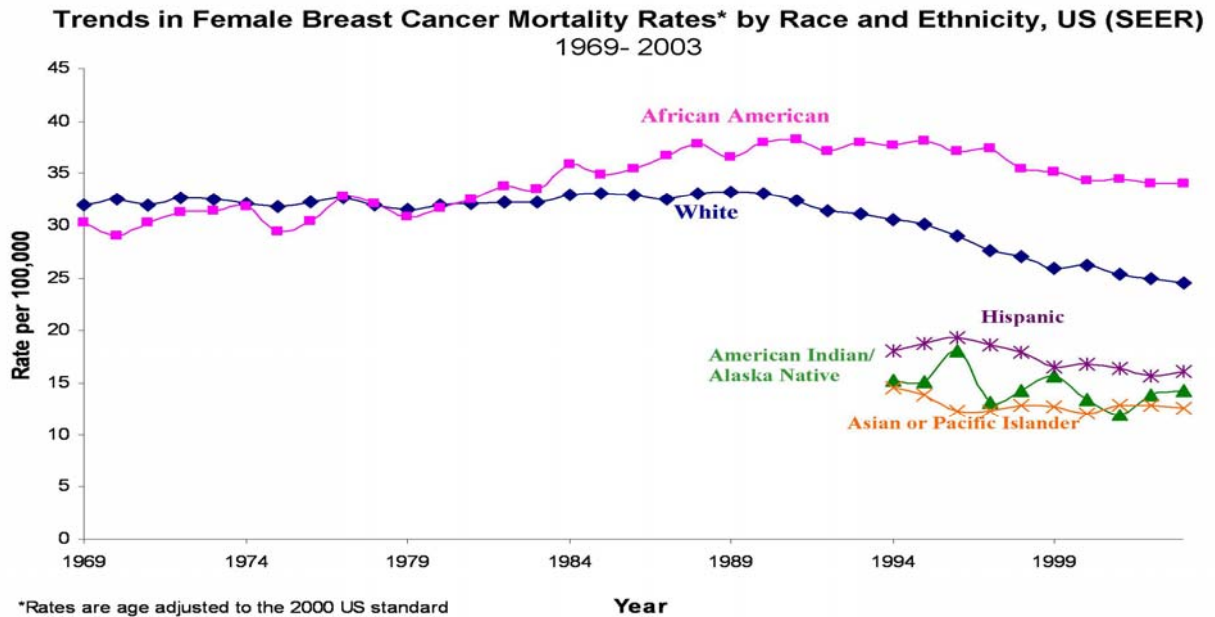


Figure 1.3: Female breast cancer death rates by race and ethnicity in the United States as reported by SEER [10].

cally higher than the historical experience for women treated with standard dose chemotherapy, which was only 38-52%. [6]

These studies offered new hope to women who faced high risk or metastatic breast cancer. HDCT+BMT is a grueling treatment that has been described by Dr. Jerome Groopman as “an experience beyond our ordinary imaginings – the ordeal of chemotherapy taken to a near-lethal extreme”. [7] In desperation, more than 41,000 American women with advanced breast cancer endured HDCT+BMT in the 1990s, even though there was little clinical evidence to show that it was superior to standard therapy. [8] The story of what happened as this technology was developed and tested illustrates how political pressures can overwhelm science, leading to substantially increased medical costs and dramatically reduced quality of life for patients.

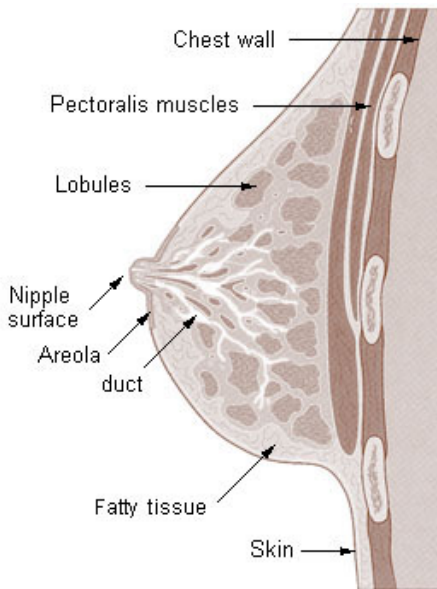


Figure 1.4: The human female breast.

Breast Cancer in the US: After skin cancer, breast cancer is the most common cancer among women, and accounts for almost one of every three cancers diagnosed in women in the United States. [5] In 2005, more than 40,000 American women are expected to die of breast cancer; only lung cancer causes more cancer deaths in women. An estimated 211,240 new cases of breast cancer will occur in the U.S. in 2005, and there are over 2.3 million women living in the U.S. who have been diagnosed with breast cancer.

Female breast cancer incidence rates have risen in the US from 1973 to 1998, as reported by the NCI Surveillance, Epidemiology and End Results (SEER) Program (Figure

Stage	Definition	5 yr survival
Stage 0	Cancer cells are located within a duct and have not invaded the surrounding fatty breast tissue	100%
Stage I	The tumor is 2 cm or less in diameter and has not spread to lymph nodes or distant sites.	100%
Stage II	The cancer has spread to 1-3 lymph nodes close to the breast but not to distant sites	81-92%
Stage III (High risk)	The cancer has spread to 4-9 lymph nodes close to the breast but not to distant sites	54-67%
Stage IV (Metastatic)	Cancer has spread to distant organs such as bone, liver or lung or to lymph nodes far from the breast.	20%

1.2). Incidence rates have increased due to a combination of changes in reproductive patterns (delayed childbearing, having fewer children) and better early detection with mammography. Female breast cancer death rates in the US during the same period have decreased (Figure 1.3), primarily due to better early detection of more treatable cancers and to improvements in breast cancer treatments.

Figure 1.4 shows an illustration of the female breast. After childbirth, milk is produced in glandular tissue in the breast, leading to milk ducts. This glandular tissue is where most breast cancers develop. When cancer cells are confined to these ducts, and have not spread to surrounding fatty tissue, the disease is called Stage 0, and is completely curable with surgical excision. Lesions which have spread to the surrounding fatty tissue but are less than 2 cm in diameter are referred to as Stage 1 lesions, and also have excellent prognosis, with a 100% 5-year survival rate.[12] A series of lymphatic vessels, leading to lymph nodes under the armpit (axillary lymph nodes), drain breast tissue (Figure 1.5). Breast cancer cells can migrate from the initial lesion and enter these lymphatic vessels, providing a way for breast cancer cells to spread to other distant organ sites (metastasize). If the cancer has spread to 1-3 lymph nodes close to the breast but not to distant sites, it is referred to as a Stage II lesion, and the 5-year survival rate is between 81-92%. Stage III breast cancers involve more than 4 nodes, and because the 5-year survival rates are so low (54-67%) are referred to as “high-risk breast cancers”. In metastatic breast cancer (Stage IV), the disease has spread from the lymphatics to other organ sites far from the breast, such as

Table 1.2: Breast Cancer Staging [12].

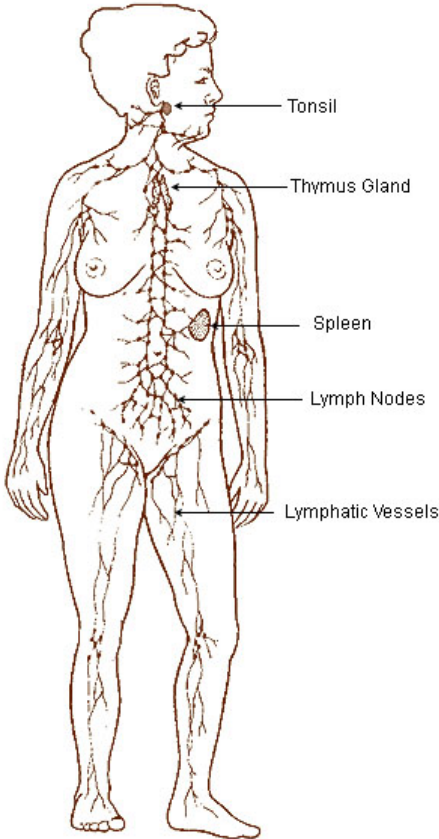


Figure 1.5: Lymphatic vessels.

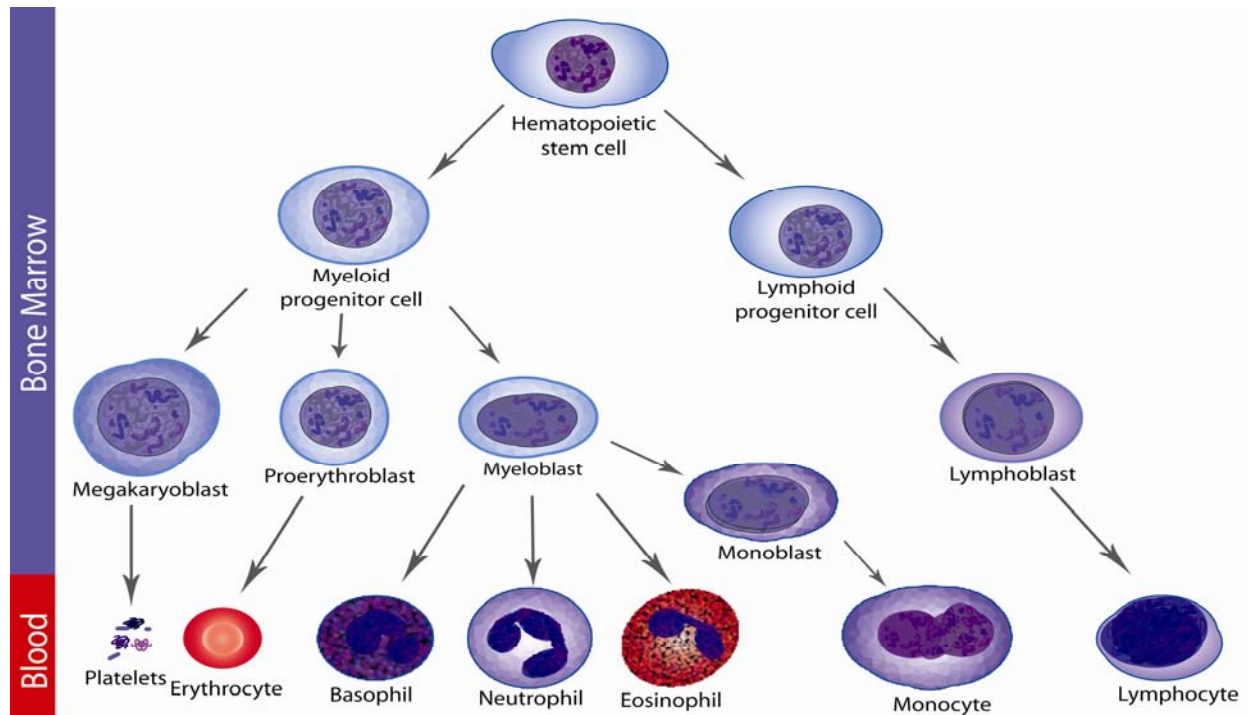


Figure 1.6: Cells of the bone marrow.

the brain. The five year survival rate for metastatic breast cancer is only 20%. The stages of breast cancer and the prognosis for each stage are summarized in [Table 1.2](#). [12]



Figure 1.7: An apheresis machine.

Treatments for breast cancer: There are many treatments for breast cancer. Treatment for most early cancers involves some form of surgery to remove the cancer cells. If the lesion is small, only a portion of tissue may be removed (lumpectomy), or the entire breast may be removed (mastectomy). Larger tumors may be treated using chemotherapy. In some cases, chemotherapy may be used to shrink larger tumors so that they can be removed surgically; in others it may be used following surgery to reduce risk of recurrence. In chemotherapy, drugs which are toxic to cancer cells are given intravenously or by mouth. These drugs travel through the bloodstream to reach cancer cells in most parts of the body. Chemotherapeutic drugs interfere with ability of cell to divide; many cancer cells cannot repair damage caused by chemotherapy drugs so they die.

Rapidly dividing normal cells may also be affected by chemotherapy drugs, but they can repair this damage. Because chemotherapy drugs affect rapidly dividing normal cells, they give rise to many undesirable side effects. The cells which line the gastrointestinal tract divide rapidly; thus chemotherapy can lead to nausea, vomiting, mouth sores and loss of appetite. Cells in the hair follicles divide rapidly and chemotherapy can lead to hair loss. Rapidly dividing cells in

the bone marrow which produce oxygen carrying red blood cells, infection-fighting white blood cells, and platelets important in blood clotting are also affected by chemotherapy drugs. Chemotherapy patients are thus at high risk for infection, bleeding and fatigue. While these side effects are temporary, chemotherapy can also produce permanent side effects such as premature menopause and infertility.

High dose chemotherapy: Because chemotherapy can damage both cancer cells and rapidly dividing, but crucial, normal cells, cancer treatment must strike a balance between completely destroying all cancer cells while causing minimal damage to normal cells. In the 1980s a number of dose comparison studies of chemotherapy to treat metastatic breast cancer showed that a higher dosage of chemotherapy was associated with a higher response rate. Scientists and clinicians hypothesized that metastatic breast cancer could be treated more effectively with higher doses of chemotherapy. Unfortunately, such high doses completely destroy the bone marrow, leaving patients with no way to continue to produce the cells of the blood system and the immune system, which are necessary for life.

Our blood consists of four components: plasma, red blood cells, white blood cells, and platelets. Plasma carries nutrients and hormones throughout the body. Red blood cells deliver oxygen throughout the body, while white blood cells are necessary to fight infections. Platelets are necessary for blood clotting following injury. Throughout our lives, our blood cells are continually renewed within the bone marrow. The source of all these cells is the pluripotent hematopoietic stem cell which can give rise to all the types of blood cells (**Figure 1.6**). Lab experiments in mice show that a single stem cell can yield the half-trillion blood cells of an entire mouse. Clinicians theorized that if the bone marrow was completely destroyed in high dose chemotherapy, a bone marrow transplant could be done to restore these hematopoietic stem cells; in fact such bone marrow transplants had proven very successful in the treatment of cancers of the bone marrow.

Bone marrow transplants: Stem cells are found in high concentration in the bone marrow, and can be harvested for transplantation in a painful procedure. More recently, stem cells transplants have been carried out using peripheral blood stem cells (PBSCs) which are found in the blood. In a transplant, these stem cells are isolated from the blood in a process known as **apheresis**. The patient is given medication to increase the number of stem cells released into the

Read More About Bone Marrow Transplants:

In his article, Bone Marrow Transplant: A Healing Hell, Dr. Jerome Groopman describes the experience of two patients who undergo bone marrow transplants. [7]

J. Groopman. Bone Marrow Transplant: A Healing Hell. *The New Yorker*, (19 October 1998), pp. 34-39. <http://www.jeromegroopman.com/bmt.html>

Apheresis Technology:

Most stem cells are found in the bone marrow, but some, called peripheral blood stem cells, can be found in the blood. It is typically much more difficult to harvest bone marrow than cells in peripheral blood—harvesting bone marrow requires hospitalization and general anesthesia. Typically, the concentration of stem cells in the peripheral blood is very low, so patients are given growth factors to increase the concentration of peripheral blood stem cells for several days prior to harvesting stem cells.

During apheresis, blood is removed from a large vein in the arm and sent to a machine which contains a centrifuge to separate white blood cells. Anticoagulants must be added to the blood to prevent it from clotting. The centrifuge spins the entering blood, and the resulting centrifugal force separates the various components of blood—plasma, red blood cells and white blood cells—based on differences in their density. The red blood cells are pushed to the outside of the centrifuge, while plasma remains near the center of the rotor. A layer of white blood cells called buffy coat separates the plasma and red blood cells. This layer contains the peripheral blood stem cells and is separated. The remaining blood is returned through a tube to the patient's other arm.

A successful transplant requires collection of a large number of peripheral blood stem cells—approximately 5 million stem cells per kg of body weight are required. Thus, we must quantify the number of peripheral blood stem cells harvested during apheresis to determine whether a sufficient number have been collected. When viewed through a standard microscope the stem cells can't be differentiated from other white blood cells. However, stem cells express a protein called CD34 on their membrane. The fraction of CD34 positive cells can be quantified by labeling the cells with a fluorescent dye linked to a molecule that binds to CD34 and using a special machine called a flow cytometer to count the number of CD34 positive cells. In a typical apheresis procedure, between 0.1—1.0% of the collected cells are peripheral blood stem cells. Over 20L of blood must be processed (the entire blood volume must be treated four times) to collect sufficient cells for later transplant, and apheresis is typically performed over several days. These cells are then treated with cryopreservatives and frozen to be injected into the patient following the high dose chemotherapy procedure.[13,14]



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Figure 1.8: Don Thomas and his wife and partner in research, Dottie, with childhood leukemia survivors.

bloodstream. Next, blood is removed from the body through a central venous catheter and passes through a machine that removes the stem cells (**Figure 1.7**). The blood is then returned to patient and the collected stem cells are stored for future transplantation. The entire process takes 10-12 hours, and yields enough stem cells to fill one syringe.

The initial attempts to transplant bone marrow took place in Cooperstown, NY during the 1950s.[7] The effects of the atom bomb used at the end of World War II sparked a tremendous interest in identifying ways to restore bone marrow. One reason that the bomb's radiation was so deadly was because it destroyed the bone-marrow cells of its victims, leading to hemorrhage (uncontrolled bleeding) and the inability to fight off infection. At the time physicians could successfully transfuse oxygen carrying red blood cells from compatible donor to needy recipient. However, bone marrow cells could not be transfused. Invariably, the recipient's body identified them as foreign invaders and destroyed them.

One researcher who was especially interested in the bone marrow transplant problem was Don Thomas. Thomas treated patients with cancer of the bone marrow (leukemia) with chemotherapy. He believed that providing new, healthy bone marrow cells was essential to curing leukemia. He tested various transplant techniques in dogs initially, and then in patients with late stage leukemia. In early trials, every patient who underwent transplantation died. "Things were pretty grim," Thomas later remarked.[7] After 4 years of unsuccessful transplantations attempts, he stopped human trials.

Eight years later, Thomas identified protein markers on the surface of white blood cells.[7] These histocompatibility markers are unique to each individual and are found on the surface of nearly every cell in the body, but are particularly numerous on the surface of white blood cells. Histocompatibility markers enable a patient's immune system to differentiate between foreign invaders and the patient's own cells. The histocompatibility markers explained the failure of previous transplant attempts and held the key to future success. When not properly matched, the patient's immune system would reject transplanted cells. Proper matching of histocompatibility markers between donor and recipient led to successful results in dogs. With this advance, Thomas resumed human trials, which led to successful treatment for leukemia. Thomas (**Figure 1.8**) received the Nobel Prize in 1990 for his important work in this area.

Today bone marrow transplantation is a successful treat-

ment for leukemia. In the past 40 years the 5-year survival rate for leukemia has more than tripled, from 14% in 1960-63 to 49% in 1995-2002.[15] However, it is still a gruelingly difficult treatment. Dr. Jerome Groopman describes the experiences of two patients who received bone marrow transplants in his article, "Bone Marrow Transplant: A Healing Hell".[7] Courtney Stevens was a high school sophomore when she was diagnosed with leukemia. She received a bone marrow transplant, and recounts her experience in Groopman's article. "It was a complete nightmare. For days, I'd be on all fours and just retch and retch. I looked like a lobster, and thought I had bugs crawling on me. I'd hit myself and scream. I was in that sterile bubble, and forgot what skin against skin felt like. That was lost. I just wanted to hold on to my mom or dad, like a two-year-old, and I couldn't. I had terrible diarrhea, a blistering rash all over my body, and jaundice. I was the color of an egg yolk." [7]

A New Technology for Advanced Breast Cancer, HDCT + BMT: With the success of bone marrow transplant for leukemia, clinicians hypothesized that extremely high dose chemotherapy could be used to treat metastatic breast cancer if followed by a bone marrow transplant. In this case, the patient's own stem cells could be harvested prior to the chemotherapy and then reinfused following treatment, thus insuring a perfect histocompatibility match. Compared to standard chemotherapy, this procedure was initially very expensive (>\$140,000) and initial trials had very high treatment associated mortality (death) rates, ranging from 7-22%.[16-17] Despite the extreme expense and side effects, the combination of HDCT+BMT offered some of the only promise for the treatment of metastatic breast cancer. An early study showed that the three year survival rates of women with high risk breast cancer treated with HDCT+BMT were 40% higher than those of women who had not participated in the trial and had received standard chemotherapy.[8] While this study offered hope for the new treatment, it was criticized for several reasons. It was a small study, involving only 85 patients, and did not randomly assign women to receive either the new therapy or the standard therapy. It also only included women whose disease initially responded to standard chemotherapy and who therefore might be expected to do better than those whose disease was not responsive to standard treatment.

In order to gain more evidence, several larger clinical trials were initiated in which women with advanced breast cancer were to be randomly selected to receive either standard chemotherapy or HDCT+BMT. Clinicians planned to com-

Breast Cancer in Developing Countries:

More than 1.2 million people worldwide will be diagnosed with breast cancer in 2005. Women in developed countries have access to imaging technologies such as mammography and ultrasound to aid in early detection and to advances in hormonal treatments and chemotherapy. However, women in developing countries frequently do not have access to these lifesaving technologies.

Maria Saloniki is a 60 year old mother



of ten living in the United Republic of Tanzania. When she was 57 she experienced fever, a swollen armpit and pain. Over three years, she visited local healers, various clinic doctors, and even traveled to Nairobi, Kenya to seek treatment. She was prescribed herbal ointments, antibiotics, and told that nothing could be done for her condition. Finally, three years after her initial symptoms she traveled to Dar es Salaam, where a biopsy showed that she had breast cancer and she began chemotherapy.

Her husband has had to borrow a large sum to finance her care, and can't afford both the cost of the treatment and bus fare to come and visit her.[17]

Photo: WHO/Chris de Bode

Read More About HDCT+BMT:

Drs. Michelle Mello and Troyen Brennan provide a more complete account of the early controversy surrounding the use of HDCT+BMT to treat breast cancer. [8]

M.M. Mello and T.A. Brennan. The controversy over high-dose chemotherapy with autologous bone marrow transplant for breast cancer. *Health Affairs*, 20:5, (2001), 101-117.

Read More About Insurance Coverage for HDCT+BMT:

The Aetna insurance company will only pay for HDCT+BMT as part of a controlled clinical trial sponsored by the Food and Drug Administration or the National Cancer Institute. This article explains their rationale. [19]

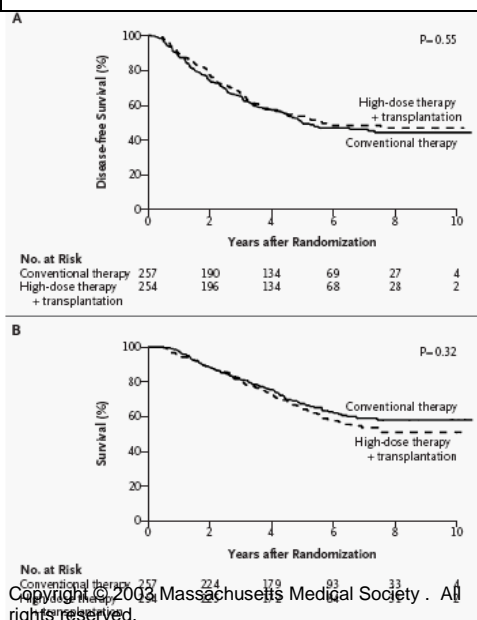
Breast Cancer: High Dose Chemotherapy with Autologous Stem Cell Support. *Clinical Policy Bulletins*, (Aetna Inc, 7 October 2005). <http://www.aetna.com/cpb/data/CPBA0507.html>.

pare the percentage of patients who were still alive (survival rates) 3 and 5 years following therapy in both arms of the trial as well as the percentage of patients whose cancer had not recurred (disease-free survival rates).

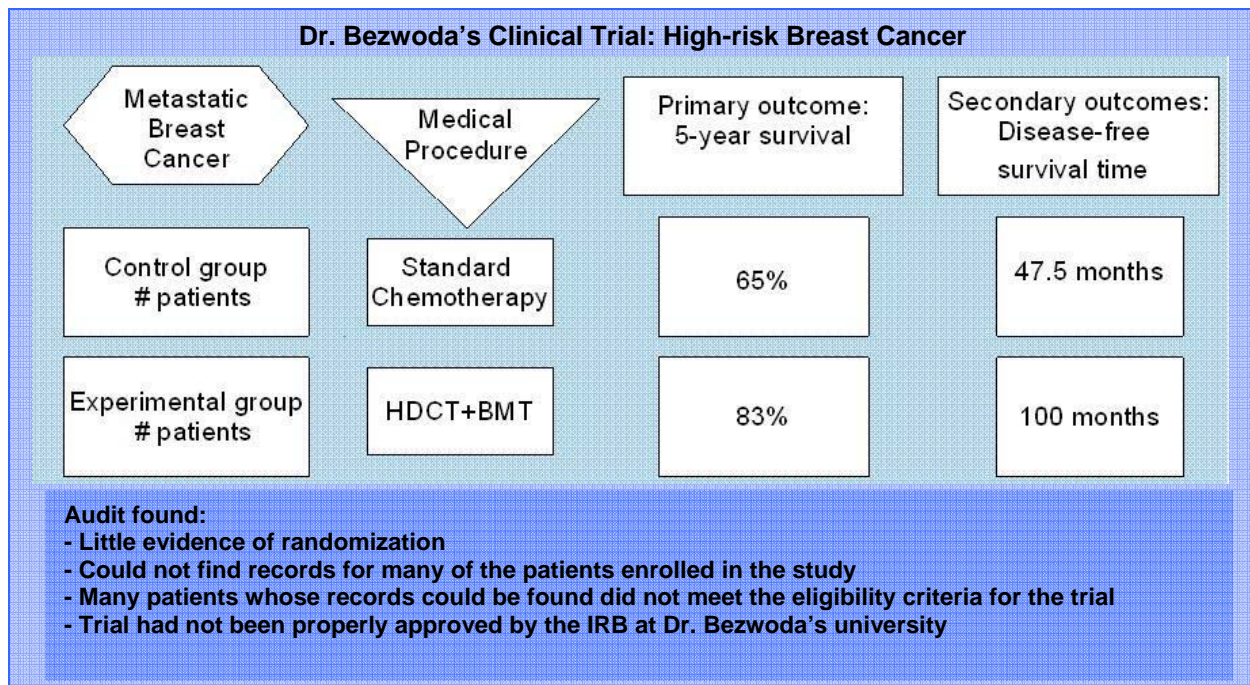
Such randomized clinical trials are considered to be the most important kind of clinical evidence to indicate whether a new therapy is better, the same, or worse than a standard therapy. Typically, in the absence of such evidence, a therapy is considered to be experimental and most insurance companies in the US will not pay for it. Because there are so few effective treatments available for advanced breast cancer however, there was a strong public demand for HDCT+BMT, even in the absence of good clinical evidence to indicate that it worked.

Public reaction to new hope: In 1991, the television show 60 Minutes aired a piece decrying the company Aetna's decision to deny **insurance coverage for HDCT+BMT** to treat breast cancer.[8] At the same time, Nelene Fox, a 38 year old mother of 3 who was diagnosed with advanced breast cancer, sued her insurance company.[8] The company, HealthNet, refused to pay for HDCT+BMT for Fox, even though it had recently paid for a relative of its CEO to receive the same treatment. Mrs. Fox and her family sued HealthNet for failure to provide coverage. In the meantime the family raised more than \$210,000 so she could receive HDCT+BMT. Mrs. Fox died of breast cancer before a verdict was reached; her family argued that the delay in receiving the treatment contributed to her death. The family was awarded \$89M, then the largest jury verdict ever against an HMO. The case received widespread publicity, and in 1993 the Massachusetts legislature mandated that insurers provide coverage for HDCT+BMT for advanced breast cancer. In 1994, insurers approved coverage for 77% of breast cancer patient requests for HDCT+BMT as part of clinical trial participation.[8] However, approval was highly arbitrary, even for similar patients covered by the same insurer. 9 of 12 large insurers surveyed indicated that the threat of litigation was a major factor in their decision to provide coverage.

In 1995, the results of a small, short randomized trial of 90 patients in South Africa was reported by the lead physician, Dr. Werner Bezwoda.[20] Dr. Bezwoda's study showed that, on average, women who received HDCT+BMT for metastatic breast cancer survived twice as long without a relapse than women who received standard chemotherapy. By this time, more than 80% of American physicians believed that women with metastatic breast cancer should be treated with



Figures 1.9a,b: Disease-free survival (a) and survival (b) rates over time in women receiving either HDCT+BMT or standard therapy from a randomized clinical trial.[21]



HDCT+BMT, and these results seemingly supported that conclusion.[8] During the 1990s, more than 41,000 patients underwent HDCT+BMT for breast cancer despite a paucity of clinical evidence regarding effectiveness. In fact, it was so difficult to recruit patients to randomized phase III clinical trials (because women were afraid they would be randomly selected to receive the standard therapy) that the trials took more than twice as long to complete than planned.

In 1999, at the meeting of the American Society of Clinical Oncology, the results of five randomized clinical trials were reported. Sadly and surprisingly, four of the studies showed no survival benefit with HDCT + BMT; some showed it took a little longer for cancer to return. **Figures 1.9a** and **1.9b** compare the survival and disease free survival rates over time in women receiving either HDCT+BMT or standard therapy in one of the trials; no meaningful differences were noted in either case. Only one South African study, again from Dr. Bezwoda, showed a survival benefit.[22] In his study, women with high-risk breast cancer had an 83% chance of five year survival if they received HDCT + BMT, compared to only a 65% chance of five year survival with standard chemotherapy. The average disease free survival time was 100 months for women receiving HDCT + BMT, versus only 47.5 months average disease free survival for those receiving standard chemotherapy. The poor results of the four negative HDCT+BMT trials were widely reported in the media.

Figure 1.10: The results of Dr. Bezwoda's controversial trial [26].

Read More About Public Reaction:

Denise Grady covered the announcement of these results for the New York Times.

D. Grady. Doubts Raised on a Breast Cancer Procedure. *New York Times*, (16 April 1999).

Hear More About Public Reaction:

Joanne Silberner covered the announcement of these results for National Public Radio. [23, 24]

J. Silberner. Breast Cancer. radio program, *National Public Radio*, (16 April 1999), <http://www.npr.org/templates/story/story.php?storyId=1049404>.

Study	# Randomized Patients	% survival	Disease-free survival
Stadtmauer Metastatic	184	32% 3 year BMT 38% 3 year control	9.6 months BMT 9.0 months control
Lotz Metastatic	61	29.8% 5 year BMT 18.5% 5 year control	9% disease free at 5 yrs BMT 9% disease free at 5 yrs control
Peters High Risk	783	79% 3 year BMT 79% 3 year control	71% disease free at 3 yrs BMT 64% disease free at 3 yrs control
Rodenhuis High Risk	885	75% 5 year BMT 73% 5 year control	65% disease free at 5 yrs BMT 59% disease free at 5 yrs control
Tallman High Risk	511	58% 6 year BMT 62% 6 year control	49% disease free at 6 yrs BMT 47% disease free at 6 yrs control

Table 1.3: Results of Five Randomized Clinical Trials of HDCT+BMT for Breast Cancer.[21, 28-30]

Public reaction was again strong. Prior to the negative trial results, in 1996-1998, Anthem Insurance saw the number of women requesting HDCT+BMT for breast cancer increase. [25] In 1999, prior to the trial results, the company expanded indications for which they would approve HDCT-BMT. After the trial results were reported in 1999, they received only 4 requests for such coverage, despite the expanded coverage. Most insurance companies now cover HDCT+BMT for breast cancer only as part of an FDA or NCI sponsored clinical trial.

Scientific misconduct. Scientists could not understand why one trial showed improved survival with HDCT+BMT, while four other trials showed no benefit. A team of scientists was sent to audit the results of the South African trial (**Figure 1.10**). Unfortunately, the audit team could not find records for many of the patients supposedly enrolled in the study. They found that the study showed little evidence of randomization, and that many patients whose records could be found did not meet the eligibility criteria for the trial.[26] They also found that the trial had not been properly approved by the Institutional Review Board at Dr. Bezwoda’s university, which is required to approve all research involving human subjects in advance. The university conducted a formal ethics inquiry, and Dr. Bezwoda admitted to a “serious breach of scientific honesty and integrity”. [27] The university fired Dr. Bezwoda, and many of his publications were formally retracted from the journal in which they had

been published.

Where are we now? Scientists continued to follow the patients enrolled in the four randomized clinical trials originally reported in 1999 (Table 1.3). Even with longer follow up, it appears that there is no survival benefit to HDCT+BMT at either 3 years or 5 years following treatment as compared to standard chemotherapy. There is a small but significant increase in disease free survival at 3 years with HDCT+BMT, but this advantage disappears at 5 years. Serious side effects are more common with HDCT+BMT compared to standard therapy, but most are reversible. Patients report that quality of life is lower at 6 months following treatment with HDCT+BMT, but similar to that of standard chemotherapy one year following treatment. The costs of HDCT+BMT have been reduced to about \$60,000, which is still nearly two times that of standard chemotherapy.

Most physicians and insurance companies now agree that HDCT+BMT should not be used to treat high risk breast cancer outside of a randomized clinical trial. Research in this area continues, to identify if longer follow up (7-10 years) will show advantages of high dose therapy, or to determine if there are sub-groups of women who benefit from high dose therapy (for example those whose tumors are negative for certain genetic markers or who have 10 or more axillary lymph nodes which show cancer cells). New technologies to completely rid the transplanted stem cells of any rogue cancer cells may also reduce recurrence rates in women treated with HDCT+BMT. However, all of these theories must be subject to rigorous testing if they ever are to become methods of standard treatment.

Lessons learned: The example of HDCT+BMT to treat breast cancer illustrates the dangers of allowing political pressures to overwhelm scientific evidence. What is the proper forum to resolve such controversies? Should it be the media, the courtroom or the laboratory? In an age where high-technology treatments are one of the most powerful drivers of health care costs, these are crucial questions.

Healthcare Technology Assessment: Professors Frazier and Mosteller, experts in health policy and management, have stated, "If we are to have good medical care, we need to know what works, and this cannot be known without systematic technology assessment. The intuitions of physicians and the guesses of biologists are not adequate guides to the best treatments".[31] How then do we assess new technologies objectively, avoiding political pressures that can lead us to waste precious health care resources and subject

Healthcare Technology Assessment:

The systematic process of evaluating the safety, short term and long term efficacy, acceptability and cost-effectiveness of a new medical technology.

thousands of patients to punishing, but ineffective, treatments?

Answering these questions is increasingly important in a world where early studies of new medical advances can receive substantial publicity in the popular press before randomized clinical trials are completed. A recent study published in the *Journal of the American Medical Association* compared conclusions presented in highly cited articles in major general clinical journals to those of subsequent studies with larger sample size or better controlled design. Results showed that nearly 1/3 of highly cited studies were later contradicted and that this was most likely for nonrandomized studies.[32] As we examine these important issues in this book, we will build a toolkit to help us answer politically sensitive questions about how to use limited resources in a deliberate and unbiased manner. Technology assessment will be an important part of our toolkit, and it is the subject of Chapter 2.

Bioengineering and Global Health Project

Project Overview: Design a new technology to solve a health problem, present a mock prototype of the new technology to a design review committee, and design a clinical trial to test the new technology.

Throughout this text, you will use the engineering design method to design a new solution to an important health problem. You will identify an important health problem, and carry out research to understand the scope of the problem and limitations of current health technologies. You will follow the engineering method to design a new solution which meets the constraints you identify. You will create a physical prototype of your design and will present it to the class as part of a design review exercise.

Chapter 1 Homework

1. Advanced breast cancer has a high mortality. Initial clinical trials indicated that high dose chemotherapy followed by a bone marrow transplant could reduce the mortality rate by as much as 40%.

- a. Why did physicians and scientists believe that higher doses of chemotherapy would be more effective than standard therapy for advanced breast cancer?
- b. Why is it necessary to give patients a bone marrow transplant following high dose chemotherapy? What will happen if they do not receive a bone marrow transplant?
- c. In the context of this example, discuss how political pressures overwhelmed scientific evidence. How could this be avoided in the future?
- d. Find a news report describing a new health technology published in the last year. In your opinion, does this news report provide balanced discussion of the potential promise and the potential limitations of this technology?

2. The Pew Global Attitudes Project is a worldwide survey of public opinion. In 2002, more than 38,000 people in 44 countries were asked to assess the quality of their own lives, their level of optimism about their lives in the next 5 years, and to rank problems faced by themselves and their countries. In this exercise, you are asked to review the results of this survey and to prepare several graphs summarizing the results.

Pew World Attitudes Website: <http://people-press.org/reports/display.php3?ReportID=165>
 Pew World Attitudes Report: <http://people-press.org/reports/pdf/165.pdf>

You will examine results in countries profiled in Unit 2: the United States, Canada, China, India and Angola. For parts a-e, please construct graphs, for part f provide a discussion which supports your findings.

- a. What fraction of people surveyed in each country expressed satisfaction with their own lives?
- b. What fraction of people surveyed in each country report that they are unable to afford food?
- c. What fraction of people in each country cite the following as a very big problem in their country:

Poor drinking water
 Crime
 AIDS and disease

d. What fraction of people in each country believe that the following is the greatest danger facing the world today:

Nuclear weapons
 AIDS an infectious disease

- e. What fraction of people surveyed in each country are optimistic that their lives will improve in the next 5 years?
- f. Compare general agreement on questions 4 and 5 throughout countries in Africa and Europe.

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