

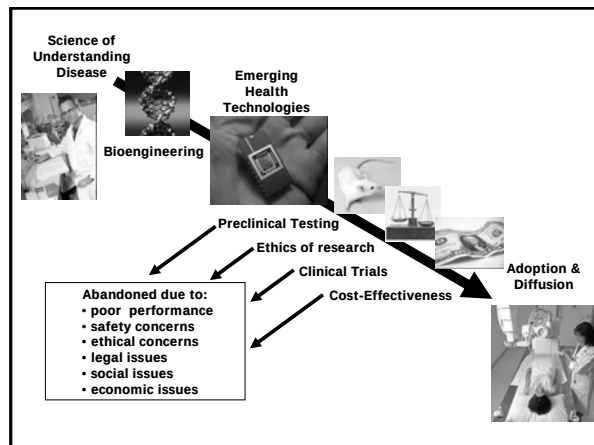
BIOE 301

Lecture One



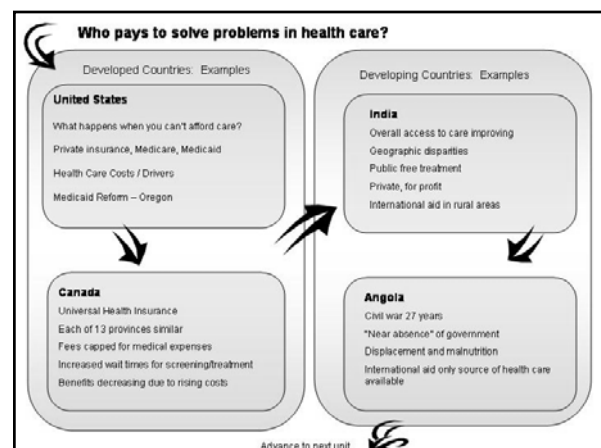
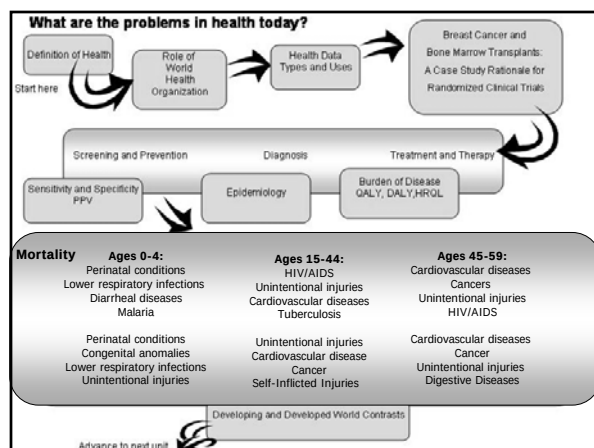
Course Organization

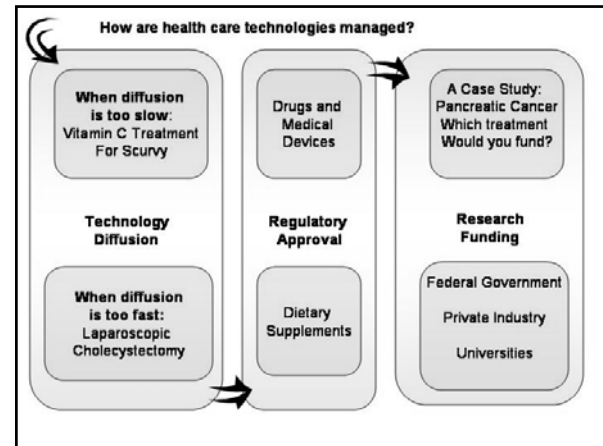
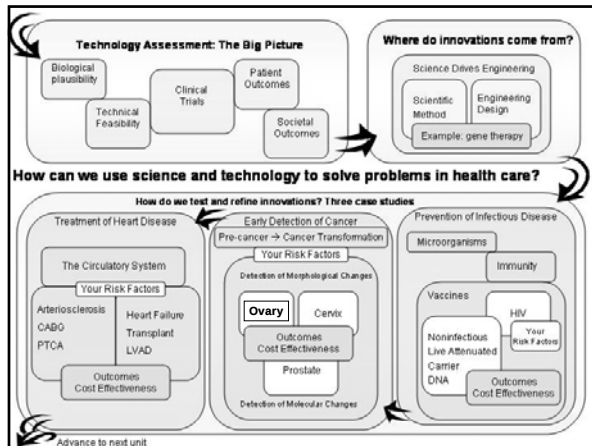
- People
- Syllabus
- Website:
 - <http://www.owl.net.rice.edu/~bioe301/kortum/class/>
- BIOE 301 Roadmap



Four Questions

- What are the problems in healthcare today?
 - Who pays to solve problems in healthcare?
 - How can we use science and technology to solve healthcare problems?
 - Once developed, how do new healthcare technologies move from the lab to the bedside?
- BIOE 301 Concept map





Technology Assessment

- What is it?
- Why do we need it?
- Example
 - Bone marrow transplants for breast cancer

Your Situation

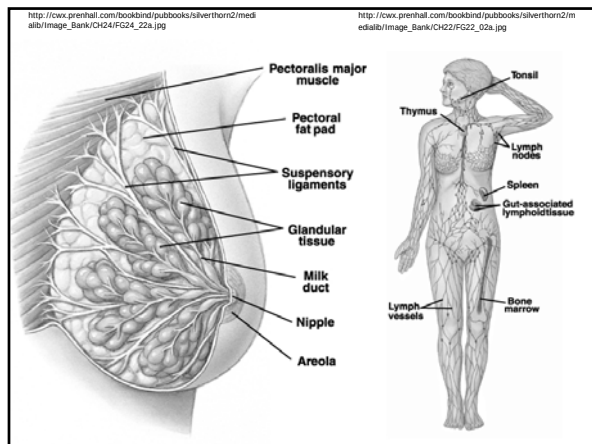
- You have just been diagnosed with advanced cancer
 - Your physician tells you that with standard treatment, there is only a 15% chance that you will survive 5 years.
 - She informs you that she is testing a new therapy which may increase your chance of surviving 5 years by more than 40%.
 - The new therapy has extremely painful side effects and there is limited scientific evidence that it works.
 - The new therapy costs \$150,000 and your insurance company refuses to pay for it.
- What do you do?

Technology Assessment: Overview

- The disease:
 - Breast Cancer
- The technology:
 - High dose chemotherapy (HDCT) with autologous stem cell support (ASCS)
 - \$80,000-\$150,000, high morbidity, initially high mortality
- The assessment:
 - 1980s: Small clinical trials promising
 - Many patients demanded treatment even though there was very little evidence that it worked
 - What happened next?

The Disease

- Breast Cancer
 - 211,240 new cases of breast cancer will be diagnosed in the U.S. in 2005
 - Over 2.3 million women living in the U.S. who have been diagnosed with & treated for breast cancer
 - 2nd leading cause of cancer death among women in the U.S.
 - Incidence and mortality rates vs. time



Breast Cancer Staging

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.	98%
Stage II	The cancer has spread to 1-3 lymph nodes close to the breast but not to distant sites	76-88%
Stage III (High risk)	The cancer has spread to 4-9 lymph nodes close to the breast but not to distant sites	49-56%
Stage IV (Metastatic)	Cancer has spread to distant organs such as bone, liver or lung or to lymph nodes far from the breast.	16%

Treatments for Breast Cancer

- Surgery
 - Lumpectomy
 - Mastectomy
 - Used to remove small tumors
- Chemotherapy
 - May be used to shrink larger tumors so that they can be removed surgically
 - May be used following surgery to reduce risk of recurrence
 - May be used to treat stage IV breast cancer
 - e.g. cyclophosphamide with doxorubicin or epirubicin
- Radiation Therapy
 - May be used following surgery to reduce risk of recurrence
- Hormone Therapy
 - May be used to shrink larger estrogen positive tumors so that they can be removed surgically
 - May be used following surgery to reduce risk of recurrence
 - e.g. Tamoxifen – an anti-estrogen drug

The Technology

- High dose chemotherapy (HDCT) with autologous stem cell support (ASCS)
 - How does chemo work?
 - How does high dose chemo work?
 - Why do we need ASCS?
- Bone marrow transplants
 - What are they?
 - How were they developed?

Chemotherapy

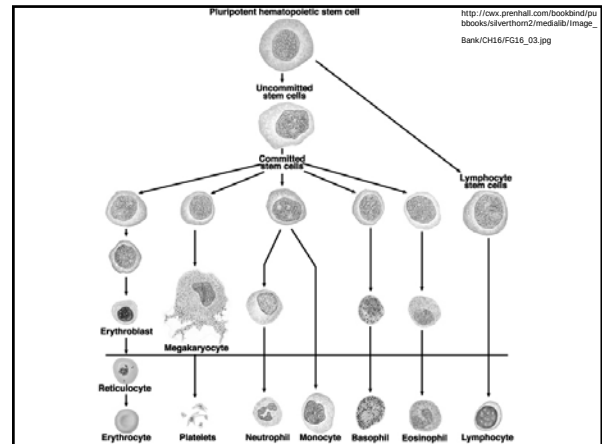
- How does it work?
 - Chemotherapy drugs given IV or by mouth
 - They travel through the bloodstream to reach cancer cells in most parts of the body
 - Interfere with ability of cell to divide
 - Cancer cells cannot repair damage caused by chemotherapy drugs so they die
 - Rapidly dividing normal cells may also be affected by chemo drugs but they can repair this damage
- Possible Side effects
 - Temporary: Nausea and vomiting, loss of appetite, hair loss, mouth sores, low blood cell count (infection, bleeding, fatigue)
 - Permanent: Premature menopause and infertility

High Dose Chemotherapy

- Dose of chemotherapy
 - Balance between goal of completely destroying all cancer cells & causing too much damage to normal cells
 - Dose comparison studies of chemo in metastatic breast cancer show high dose is associated with high response rate
- High dose chemotherapy (HDCT)
 - Wipe out cancer cells with extremely high doses of chemotherapy
 - Such doses also destroy bone marrow, including stem cells that eventually mature into cells of the blood and immune system
 - Patients receiving HDCT must undergo a transplant to restore the bone marrow cells

Bone Marrow Transplants

- Components of blood
 - Plasma
 - Cells
 - Red blood cells
 - White blood cells
 - Platelets
 - Cells are produced in the bone marrow from pluripotent hematopoietic stem cells
- Lab expts: a single stem cell can yield the half-trillion blood cells of an entire mouse



History of Bone Marrow Transplants

- Conceived in a dog kennel in Cooperstown, NY during the 1950s
 - RBCs could be successfully transfused from compatible donor to needy recipient
 - Marrow cells could not: Body identified them as foreign invaders and destroyed them
 - Hiroshima – one reason that radiation was so deadly because it destroyed the bone-marrow cells of its victims – hemorrhage, infection
 - Need: ability to restore bone marrow

History of Bone Marrow Transplants

- E. Donnal Thomas
 - Grew up in Texas, attended Harvard Med School
 - Treated leukemia patients with chemotherapy
 - Believed that providing new, healthy bone marrow cells was essential to curing leukemia
 - Tested various transplant techniques in dogs
 - Tested them in patients with late stage leukemia
 - Every patient who underwent transplantation died during the procedure of shortly thereafter. After 4 years stopped human trials.
 - “Things were pretty grim.”

History of Bone Marrow Transplants

- E. Donnal Thomas
 - 8 years later, identified genetic markers on WBCs of histocompatibility
 - Enabled close matching of donor and recipient
 - Led to successful results in dogs
 - Resumed human trials
 - Led to successful treatment for leukemia
 - Received the Nobel Prize in 1990



http://research.mednet.ucla.edu/images/nobel_med.gif



Bone Marrow Transplants: Leukemia

- Courtney Stevens
 - High school sophomore with leukemia
 - Treated with a bone marrow transplant
- “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.”

<http://www.jeromegroopman.com/articles/bone-marrow-transplant.html>

Bone Marrow Transplants: Breast CA

- Chemotherapy is often ineffective for Stage IV breast cancer
- Would higher doses of chemotherapy be more effective?
- Requires bone marrow transplant
- Can do autologous transplant (use patient's own bone marrow)
- HDCT + BMT:
 - Harvest stem cells from patient
 - Give HDCT
 - Perform autologous stem cell transplant (ASCT)
- Expensive, high morbidity and mortality

Bone Marrow Transplants: Breast CA

- Tamar Lowenstein
 - 39 yo lawyer with widely metastatic breast cancer
 - Treated with HDCT and bone marrow transplant
 - Peripheral blood stem cell transplantation

"It's getting worse every hour."

Lips were so blistered that speaking was painful

Chemical burn throughout her entire GI tract

"I wish I hadn't done it. It was a mistake."

Could not eat for 5 weeks. Weight dropped 46 lbs

Tumor did respond to therapy

<http://www.jeromegroopman.com/articles/bone-marrow-transplant.html>

PBSC Transplantation with Apheresis

- Where are stem cells?
 - Most stem cells are found in the bone marrow,
 - Some, called peripheral blood stem cells (PBSCs), can be found in blood
- Apheresis:
 - Patient given medication to increase the # of stem cells released into the bloodstream
 - Blood is removed through a central venous catheter
 - Blood goes through machine that removes stem cells
 - Blood is returned to patient and collected cells stored

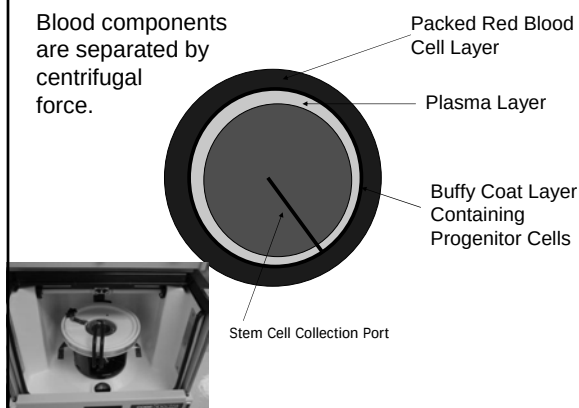
"The Equipment"



"The Centrifuge"

<http://www.rush.edu/bone-marrow/autologous/images/graft3.jpg>

Blood components are separated by centrifugal force.



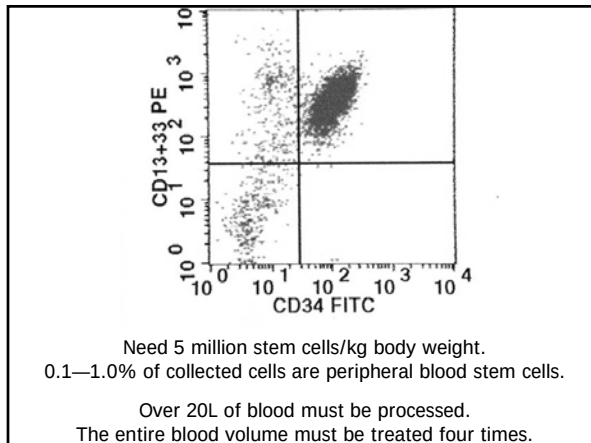
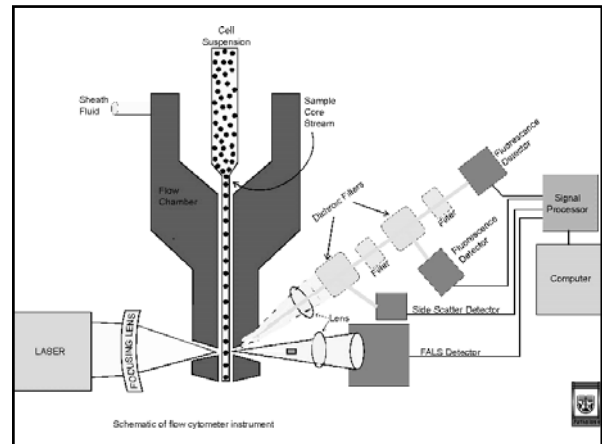
Identification of Stem Cells

- Stem cells cannot be distinguished from other cells in the bone marrow using a simple microscope.



Flow Cytometry:

- Stem cells express a certain protein on the surface of their cells:
 - CD34
- CD34+ cells are measured using a flow cytometer
- Sophisticated test
- Takes several hours



Clinical Trials of HDCT + BMT

- 1980-1990:
 - Phase II Trials with historical controls
 - Pts with metastatic breast cancer treated with HDC+BMT
 - 40% improvement in 3-yr survival compared to historical controls treated with standard chemo
 - Increased adverse effects: high mortality (0-22%) and morbidity
 - Increased cost: \$160,000 (now \$60,000)
 - Selection bias??
 - Only included patients that responded to initial standard-dose chemotherapy
 - Prospects better for treating responsive disease

Science vs. Politics

- Media coverage
- Patients demands
- Legal cases
- Legislation
- Insurance coverage

Timeline

- 1991: 60 Minutes
 - Aired piece decrying Aetna's decision to deny coverage for HDCT+BMT for breast CA
- 1993:
 - Nelene Fox (38 yo mother of 3) sued HealthNet for failure to provide coverage for HDC+BMT
 - HealthNet paid for a relative of its CEO to receive HDC+BMT, but denied coverage to Fox and others
 - Fox's family raised \$210k for the transplant
 - Fox died of breast cancer before the verdict
 - Fox's family was awarded \$89M, largest jury verdict against an HMO at the time
 - Received wide publicity

Timeline

- 1993:
 - Massachusetts legislature mandated benefit law for HDC+BMT
- 1994:
 - Insurers approve 77% of breast cancer patient requests for HDC+BMT clinical trial participation
 - Approval is highly arbitrary, even for similar patients covered by the same insurer
 - 9 of 12 large insurers surveyed say threat of litigation was a major factor in their decision to provide coverage

Timeline

- 1995:
 - Small (90 pts), short randomized trial by Bezvoda showed survival benefit for HDCT+BMT for metastatic breast cancer
 - More than 80% of American physicians believe that women with metastatic breast cancer should be treated with HDCT+BMT
- 1990s:
 - More than 41,000 patients underwent HDCT+BMT for breast cancer despite a paucity of clinical evidence regarding effectiveness
 - Difficult to recruit patients to randomized Phase III clinical trials (took twice as long to complete as planned)

Timeline

- 1999:
 - American Society of Clinical Oncology Meeting
 - Results of 5 randomized clinical trials reported
 - Four studies showed no survival benefit with BMT; some showed it took longer for cancer to return
 - One South African study showed survival benefit
 - 83% five year survival for BMT
 - 65% five year survival for controls
 - 100 months average disease free survival for BMT
 - 47.5 months average disease free survival for controls
- 1999 NY Times articles
 - **Doubts Raised on a Breast Cancer Procedure**
By DENISE GRADY
April 16, 1999, Friday
- NPR Story
 - <http://www.npr.org/templates/story/story.php?storyId=1049404>

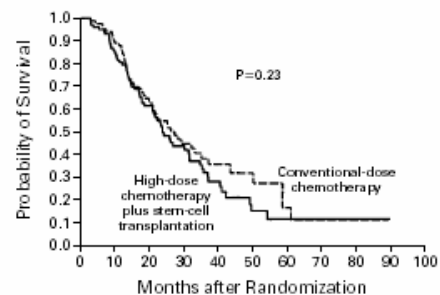
Insurance Coverage

- Anthem Insurance
 - 1996-1998: # requests for BMT increased from 64 to 83 per year
 - 1999: company expanded indications for which they would approve BMT
 - 1999: Results of RCTs released
 - 1999: Only 42 requests for BMT (only 4 requests in last 5 months of 1999)
- Most insurance companies now cover HDCT+BMT for breast cancer as part of FDA or NCI sponsored clinical trial
 - http://www.aetna.com/cpb/medical/data/500_599/0507.html

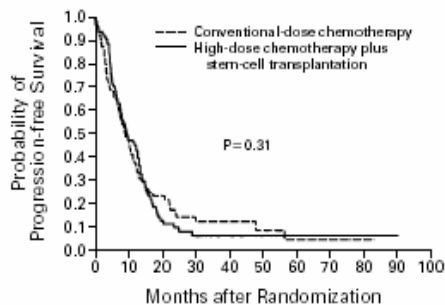
RCT Results

Study	# Pts Randomized	% 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 p=0.09*
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

RCT Results



RCT Results



Why was only one study positive?

- Team of scientists sent to audit trial results
 - Study showed little evidence of randomization
 - Records for many patients could not be found
 - Many patients did not meet eligibility criteria
 - Trial was not approved by the University's IRB
 - No signed informed consents forms
- University conducted formal ethics inquiry
 - Dr. Bezwoda admitted "serious breach of scientific honesty and integrity"
 - University fired Dr. Bezwoda

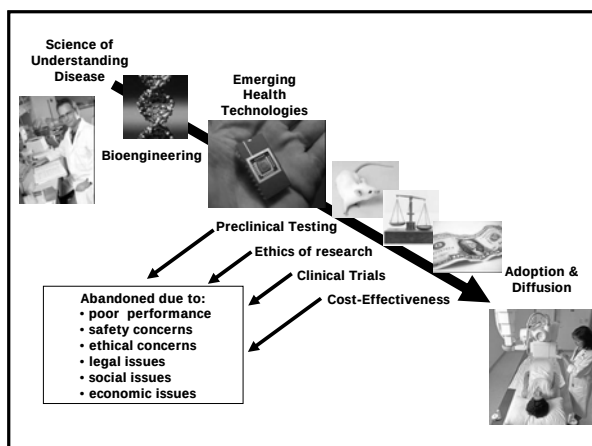
Current Thinking

- Appears to be no survival benefit to HDCT+BMT
 - 3 years
 - 5 years
- There is a significant increase in disease free survival at 3 years with HDCT+ BMT
- This increase disappears at 5 years
- Side effects are more common with HDCT+BMT, most are reversible
- Quality of life is lower at 6 months, but similar at 1 year

Technology Assessment

- Biological Plausibility
 - Does the biology support the technology?
- Technical Feasibility
 - Safely and reliably deliver technology to patients?
- Clinical Trials
 - Sensitivity & specificity in a relevant population?
 - Disease-free survival & 5-year survival in a relevant population?
- Patient Outcomes
 - Does the technology improve the patient's health?
- Societal Outcomes
 - Cost and ethical implications of the technology?

Littenberg B. Technology Assessment in Medicine. Academic Med 67:424, 1992



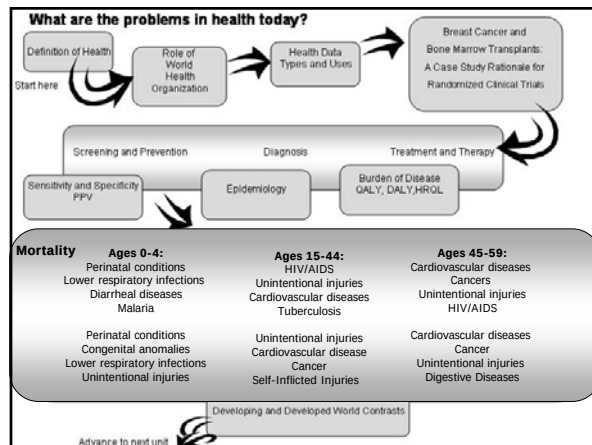
What are the dangers of allowing political pressures to overwhelm science?

What is the proper forum to resolve controversies?

“In an era in which technological imperative is one of the most powerful drivers of health care costs, these are crucial lessons.”

More Research?

- Longer follow up may show advantages of high dose therapy
- There may be sub-groups of women who benefit from high dose therapy
 - HER-2/neu negative tumors
 - 10 or more positive axillary nodes
- Better technology to eliminate cancer cells from stem cell transplants

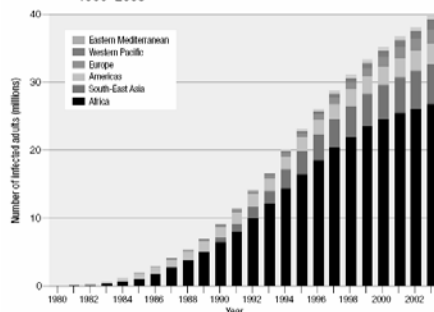


Individual Health vs. Population Health

- Pooled figures such as:
 - Infant mortality rates
 - Numbers of deaths and causes
 - Immunization rates

Example of Health Data

Figure 1.1 Estimated number of adults infected with HIV, by WHO region, 1980–2003



<http://www.npr.org/templates/story/story.php?storyId=16476764>

Uses for health measures

- Identify emerging problems (early warning)
 - Rubella during pregnancy
 - Thalidomide during pregnancy
 - AIDS → Kaposi's sarcoma, PCP
- Help determine public policy
 - Estimate impact of health problems
 - # people affected, ages, locations
 - Set funding priorities– Millenium Development Goals
 - Educate legislators
- Monitor progress toward goals

Types of health data

- Data on the population
 - # of people
 - Age, sex, ethnic origin, urbanization
- Vital statistics
 - Live births
 - Deaths (including infant deaths) by sex, age, cause
- Health statistics
 - Morbidity by type, severity and outcome
 - Data on reportable diseases
 - Tumor registries
- Statistics about health services
 - # and type of facilities
 - # and qualifications of health personnel
 - Services and utilization rates
 - Costs and payment mechanisms

Quantitative measures of health

- Incidence
 - Number of new cases of a disease in a population over a period of time
- Annual incidence rate

$$\text{Annual Incidence Rate} = \frac{\text{\# of new cases of a defined condition in a defined population in one year}}{\text{\# in that population at mid-year of that same year}}$$

Quantitative measures of health

- Prevalence
 - Number of existing cases of a disease in a given population at a specific time
- Point prevalence

$$\text{Point Prevalence} = \frac{\text{\# of cases of a defined condition in a defined population at a point in time}}{\text{\# in that population at same point in time}}$$

Quantitative measures of health

- Mortality rate
 - Mortality = Death
 - Crude death rate, Infant, Neonatal, Post-neonatal, Maternal

- Mortality Rate

$$\text{Mortality Rate} = \frac{\text{\# of deaths in a defined population in a year}}{\text{\# in that population at mid-year of the same year}}$$

- Infant mortality rate

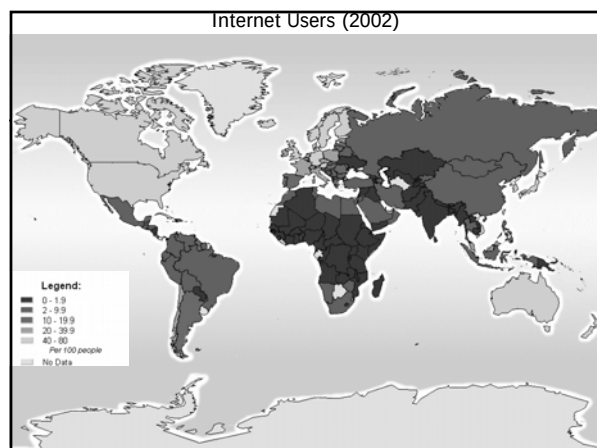
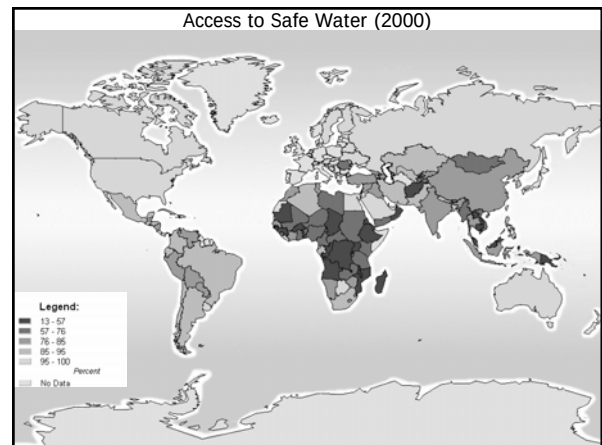
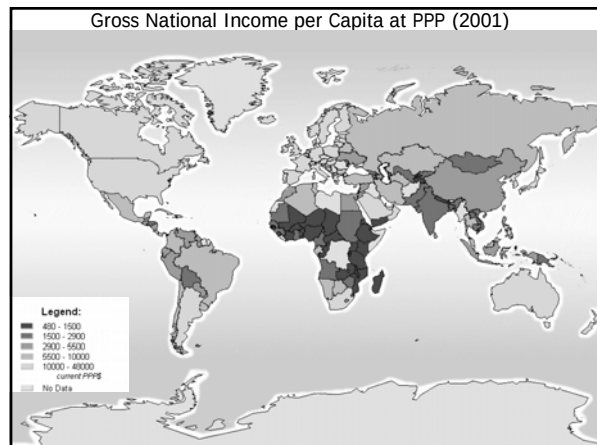
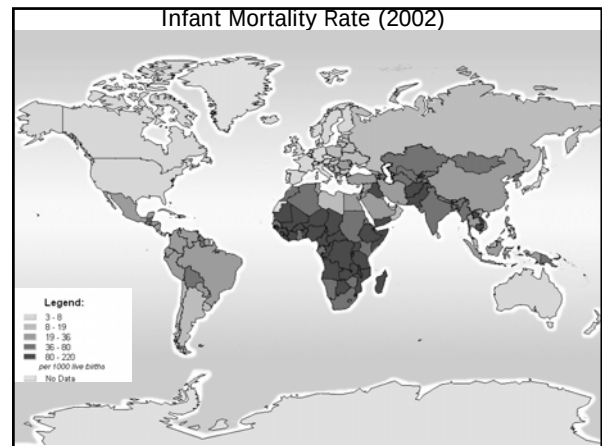
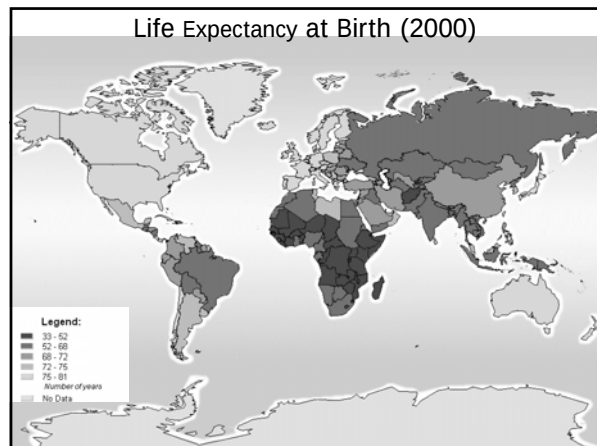
$$\text{Infant Mortality Rate} = \frac{\text{\# of deaths under 1 yr of age in a defined population in a year}}{\text{\# of live births in that population in same year}}$$

Burden of disease

- Quality adjusted life year (QALY)
 - Measure of quality adjusted life years gained by an intervention
- Disability adjusted life year (DALY)
 - Years of disability free life lost
 - Combines several elements
 - Levels of mortality by age
 - Levels of morbidity by age
 - Value of a year of life at specific ages
- Examples:
 - Stroke: 6 DALYs
 - Car accidents: 9 DALYs
 - Self inflicted injuries: 17 DALYs
 - Violence: 9 DALYs
 - Lower respiratory infections: 1 DALY
 - HIV: 28 DALYs

The study of global health

- Epidemiology
 - The study of the prevalence and spread of disease in a community
- Measures of health
 - Varies throughout the world
- Burden of disease
 - Varies throughout the world
- How can technology impact health and disease?
 - Varies throughout the world
- We will examine in detail in BIOE 301



GapMinder

- <http://www.gapminder.org/>

Summary of Lecture One

- Course organization
- Technology assessment
- Health data and uses

Questions We Will Consider

- How do we bring new technologies from lab to bedside in a safe and affordable way?
- How should we invest limited financial and human resources to develop new medical technologies?
- Will new technologies reduce health disparities or widen the gap between developed and developing countries?