

# BIOE 301/362

## Lecture One

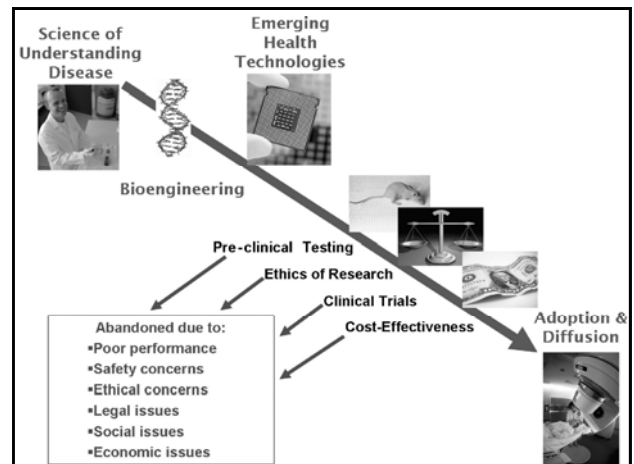


## Overview of Lecture 1

- Course Overview:
  - Course organization
  - Four questions we will answer
  - Course project
- Technology assessment – The big picture
- World health: an introduction

## Course Organization

- Syllabus
- Project
- OwlSpace
- 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 lab to bedside?

## Course Project

- BIOE 301:
  - Design and implement a solution to a health challenge in a developing country
- BIOE 362:
  - Design and implement a solution to a health challenge in a developing country
  - Evaluate and prioritize health challenges suggested for future design projects
- Summer internship opportunities!

## 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

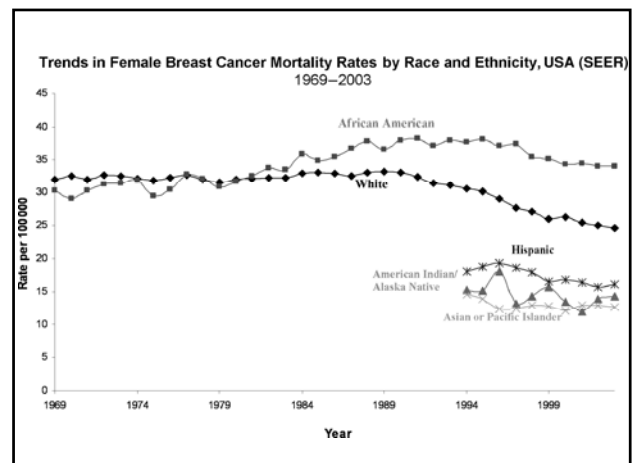
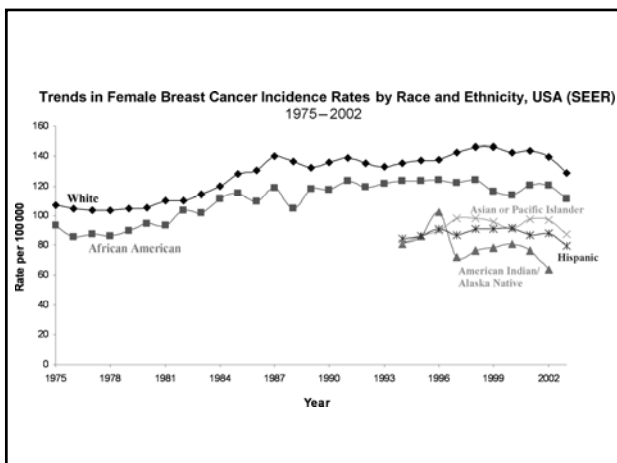
- What is it?
- Why do we need it?
- Example
  - Bone marrow transplants for breast cancer

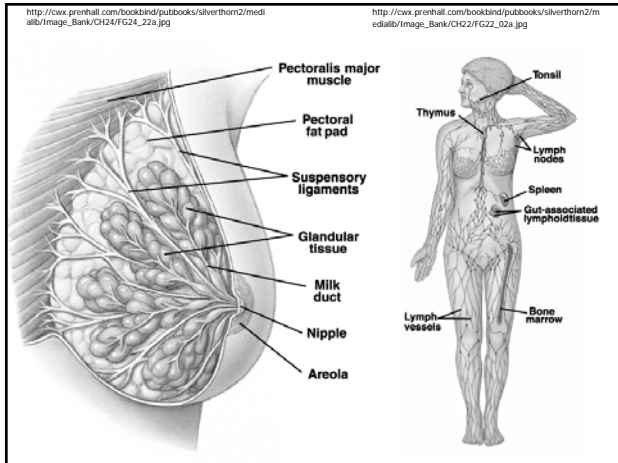
## Technology Assessment: Overview

- 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
  - 2<sup>nd</sup> 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

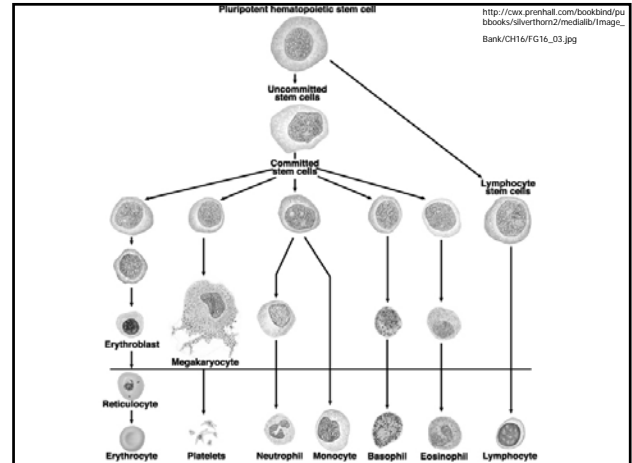
- How does it work?
  - Chemotherapy drugs given IV or by mouth
  - They travel through the bloodstream to reach cancer cells in most parts of the body
  - Interfere with ability of cell to divide
  - Cancer cells cannot repair damage caused by chemotherapy drugs so they die
  - Rapidly dividing normal 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.mede.tucla.edu/images/nobel\\_med.gif](http://research.mede.tucla.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/bmt.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/bmt.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

## An Apheresis Machine



## Clinical Trials of HDCT + BMT

- 1980-1990:
  - Phase II Trials with historical controls
  - Pts with metastatic breast cancer treated with HDCT+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

## 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 HDCT+BMT
  - HealthNet paid for a relative of its CEO to receive HDCT+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 Bezwoda 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)

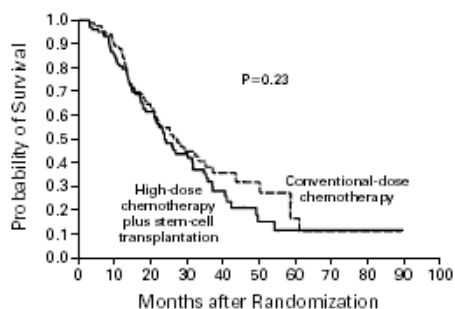
## Timeline

- 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>

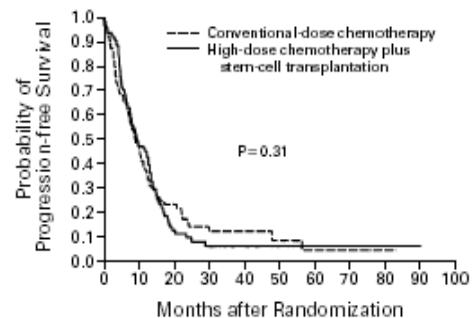
## RCT Results

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

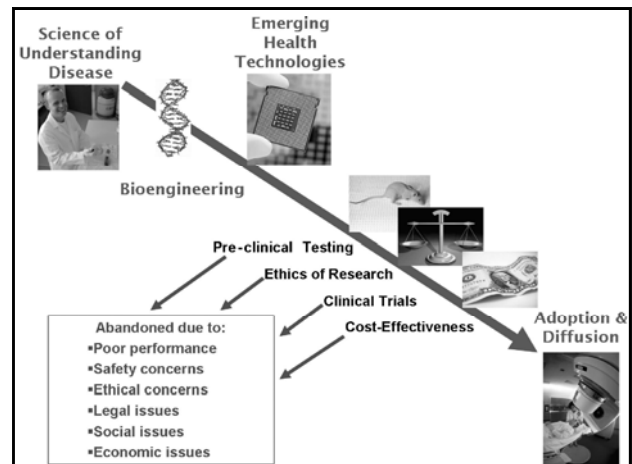
## Current Thinking

- 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

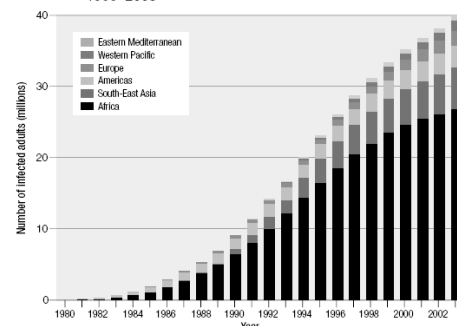


## Assessing Health

- 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



## Questions about health data

- Why do we need it?
- What data do we need?
- Where do we get it?
- How do we use it?

## World Health Organization

- Established by charter of the UN after World War II
- Headquartered in Geneva
- Mission:
  - "Attainment by all peoples of the highest possible level of health"
- Website:
  - <http://www.who.int/en/>

## Functions of the WHO

- Services to governments:
  - Epidemiologic intelligence
  - International standardization of vaccines
  - Reports of expert committees
  - Data on world health problems
- Member countries must provide certain info in regular reports
  - Disease outbreaks
  - Health of population
  - Steps to improve health

## 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

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



## 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

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

- Infant mortality rate

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

## 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

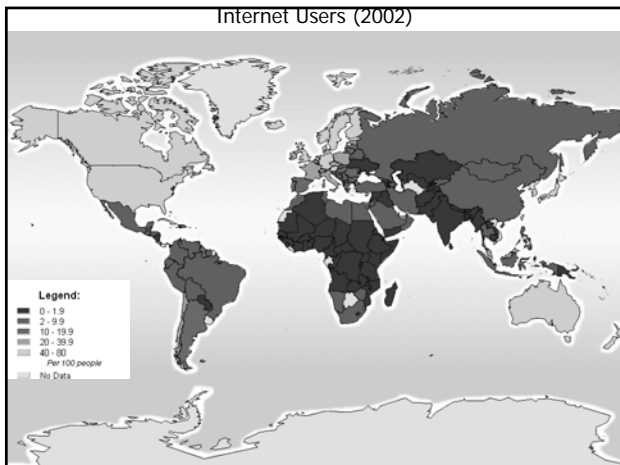
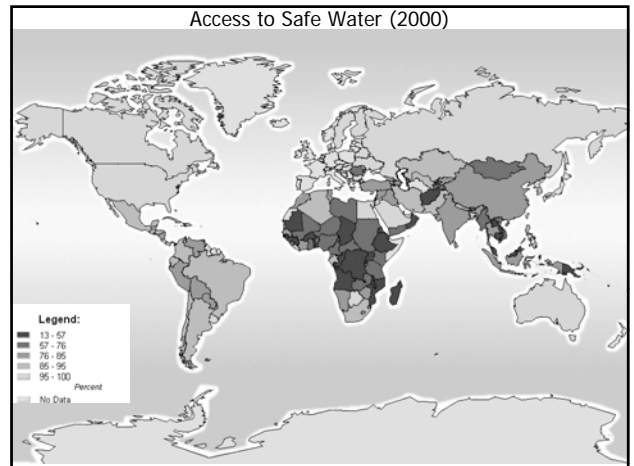
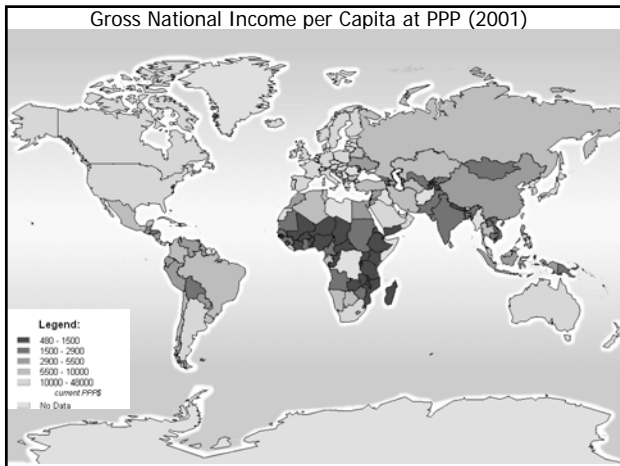
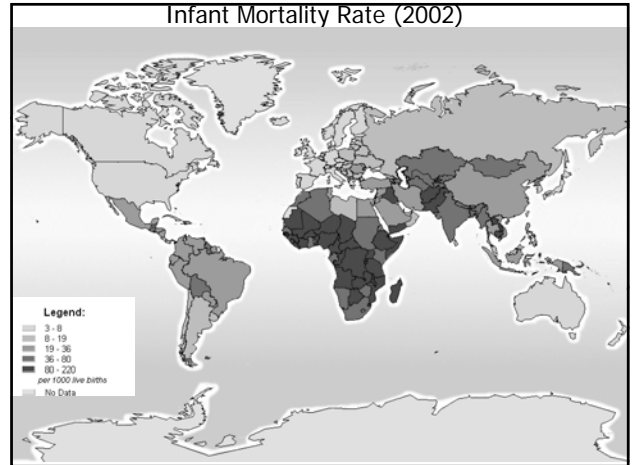
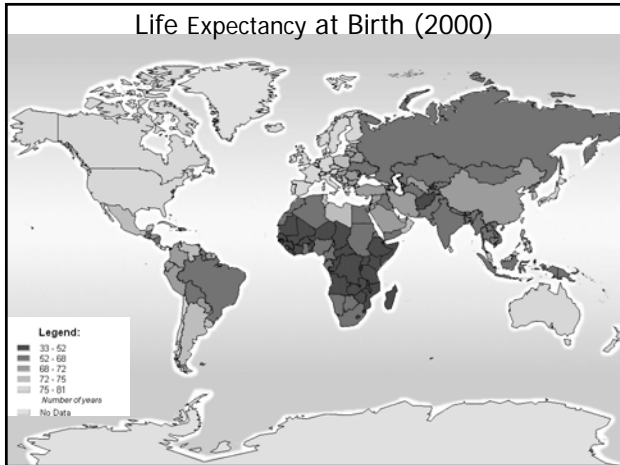
- Epidemiology
  - The study of the prevalence and spread of disease in a community
- Measures of health
  - Vary throughout the world
- Burden of disease
  - Varies throughout the world
- How can technology impact health and disease?
  - Varies throughout the world
- We will examine in detail in BIOE 301/362

Leading causes of mortality among adults, worldwide, 2002

Mortality – adults aged 15–59			Mortality – adults aged 60 and over		
Rank	Cause	Deaths (000)	Rank	Cause	Deaths (000)
1	HIV/AIDS	2279	1	Ischaemic heart disease	5825
2	Ischaemic heart disease	1332	2	Cerebrovascular disease	4689
3	Tuberculosis	1036	3	Chronic obstructive pulmonary disease	2399
4	Road traffic injuries	814	4	Lower respiratory infections	1396
5	Cerebrovascular disease	783	5	Trachea, bronchus, lung cancers	928
6	Self-inflicted injuries	672	6	Diabetes mellitus	754
7	Violence	473	7	Hypertensive heart disease	735
8	Cirrhosis of the liver	382	8	Stomach cancer	605
9	Lower respiratory infections	352	9	Tuberculosis	495
10	Chronic obstructive pulmonary disease	343	10	Colon and rectum cancers	477

## Leading Causes of Infant Mortality in Developing Countries WHO Annual Report 2003

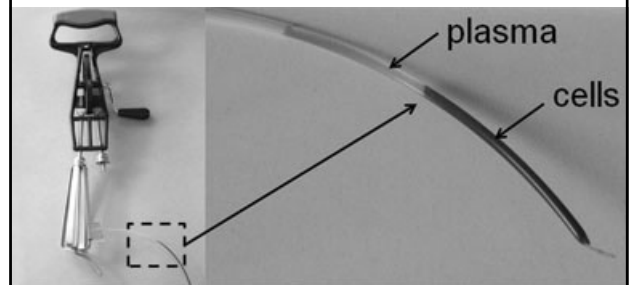
Cause	Numbers (000)
Lower respiratory infections	1856
Diarrhoeal diseases	1566
Malaria	1098
Measles	551
HIV/AIDS	370
Pertussis	301
Tetanus	185



- ### 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?

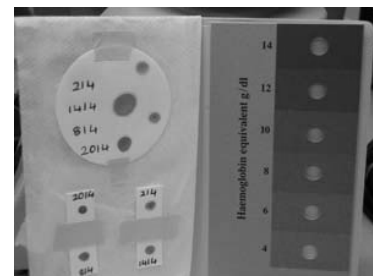
## Projects

- BIOE 301:
  - Project 1:
    - CENTRIFUGE TO ASSESS HEMATOCRIT
  - Project 2:
    - SYSTEM TO LIMIT FLOW VOLUME FOR IV BAG
  - Project 3:
    - SYSTEM TO DISPENSE LIQUID MEDICATIONS



## Projects

- BIOE 362
  - Project 1:
    - AUTOMATED ASSESSMENT OF HEMATOCRIT
  - Project 2:
    - PRIORITIZATION OF POINT OF CARE (POC) TESTS



## Evaluate Clinical Impact, Technical Feasibility

- Urine Test for ARV Adherence:
  - Simple, accurate method to measure adherence
- Electrolytes:
  - Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, and bicarb
- Arterial Blood Gases:
  - pH, partial pressure of CO<sub>2</sub> and oxygen, and bicarb
- Lactate Test:
  - Some ARVs (D4T) associated with elevated lactate
- Anemia Sensor:
  - Noninvasive method to assess for anemia

## Assignments Due Next Time

- Project Selection Sheets