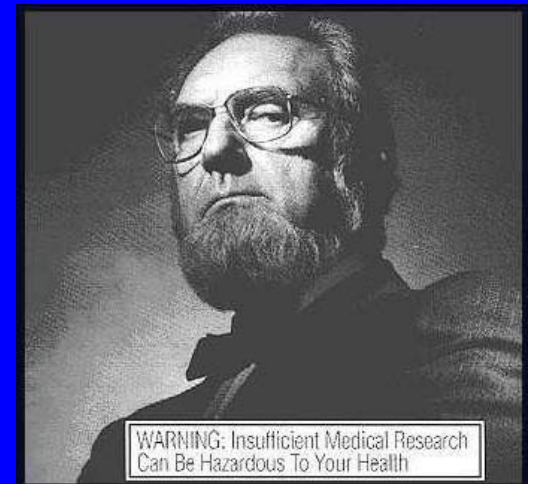


# Biomedical Engineering for Global Health

## 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
- Website:
  - <http://www.owlnet.rice.edu/~bioe301/kortum/class/>
- BIOE 301 Roadmap

## Science of Understanding Disease



## Emerging Health Technologies



## Bioengineering



## Adoption & Diffusion



### Abandoned due to:

- Poor performance
- Safety concerns
- Ethical concerns
- Legal issues
- Social issues
- Economic issues

# 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?

# 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:

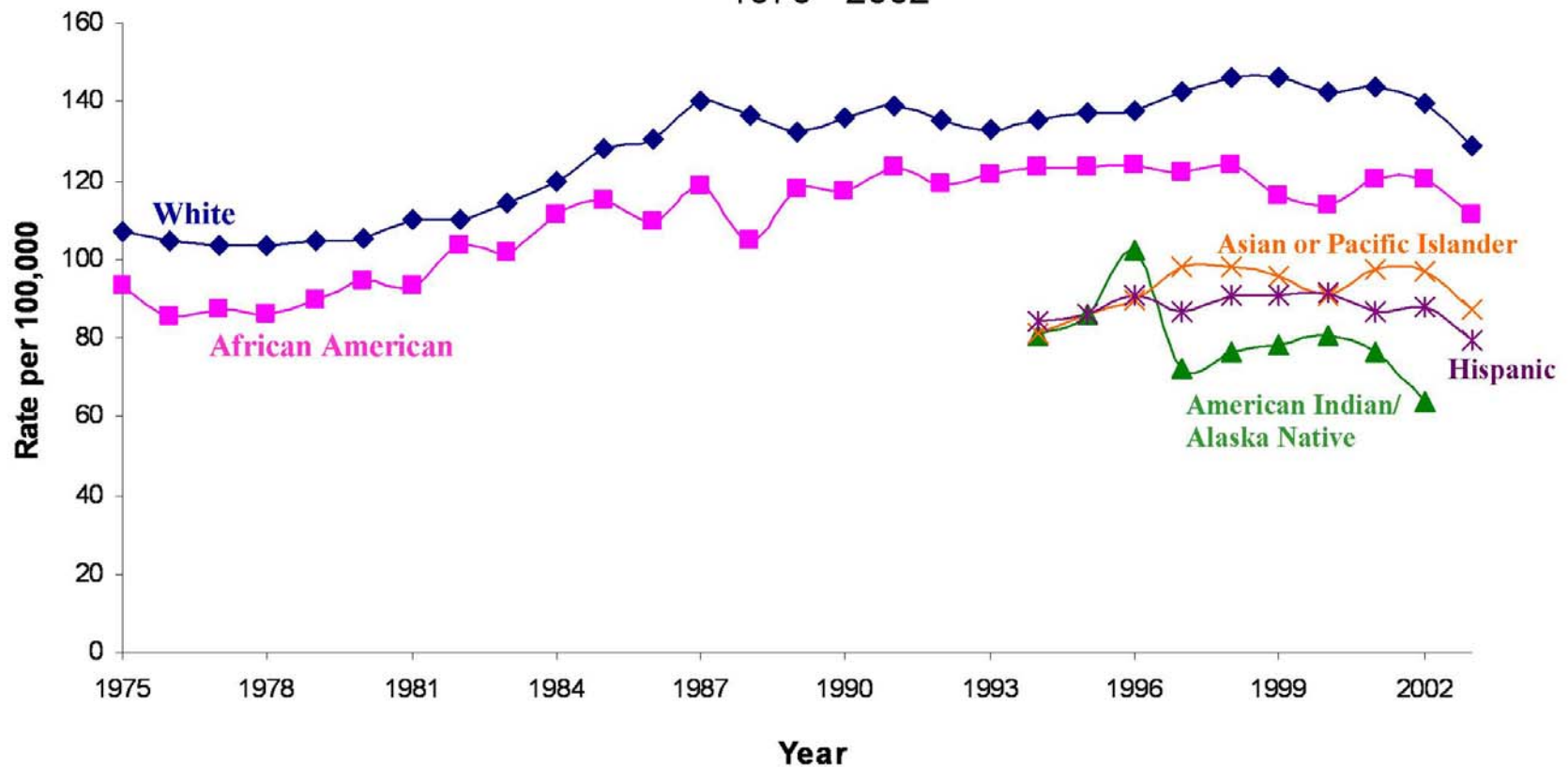
- 1980s: Small clinical trials promising
- Many patients demanded treatment even though there was very little evidence that it worked
- What happened next?

# The Disease

## ■ Breast Cancer

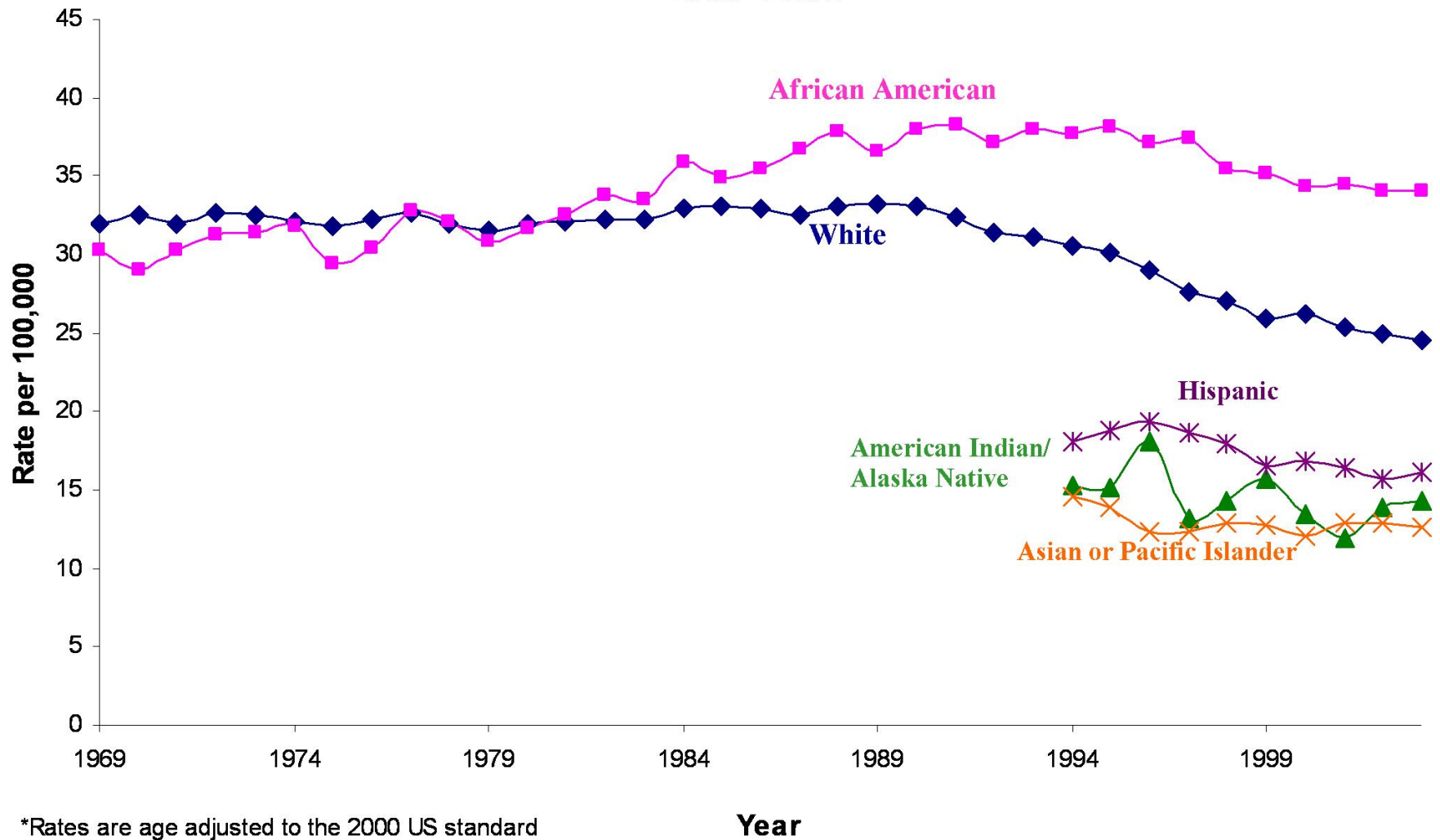
- 211,240 new cases of breast cancer will be diagnosed in the U.S. in 2005
- Over 2.3 million women living in the U.S. who have been diagnosed with & treated for breast cancer
- 2<sup>nd</sup> leading cause of cancer death among women in the U.S.
- Incidence and mortality rates vs. time

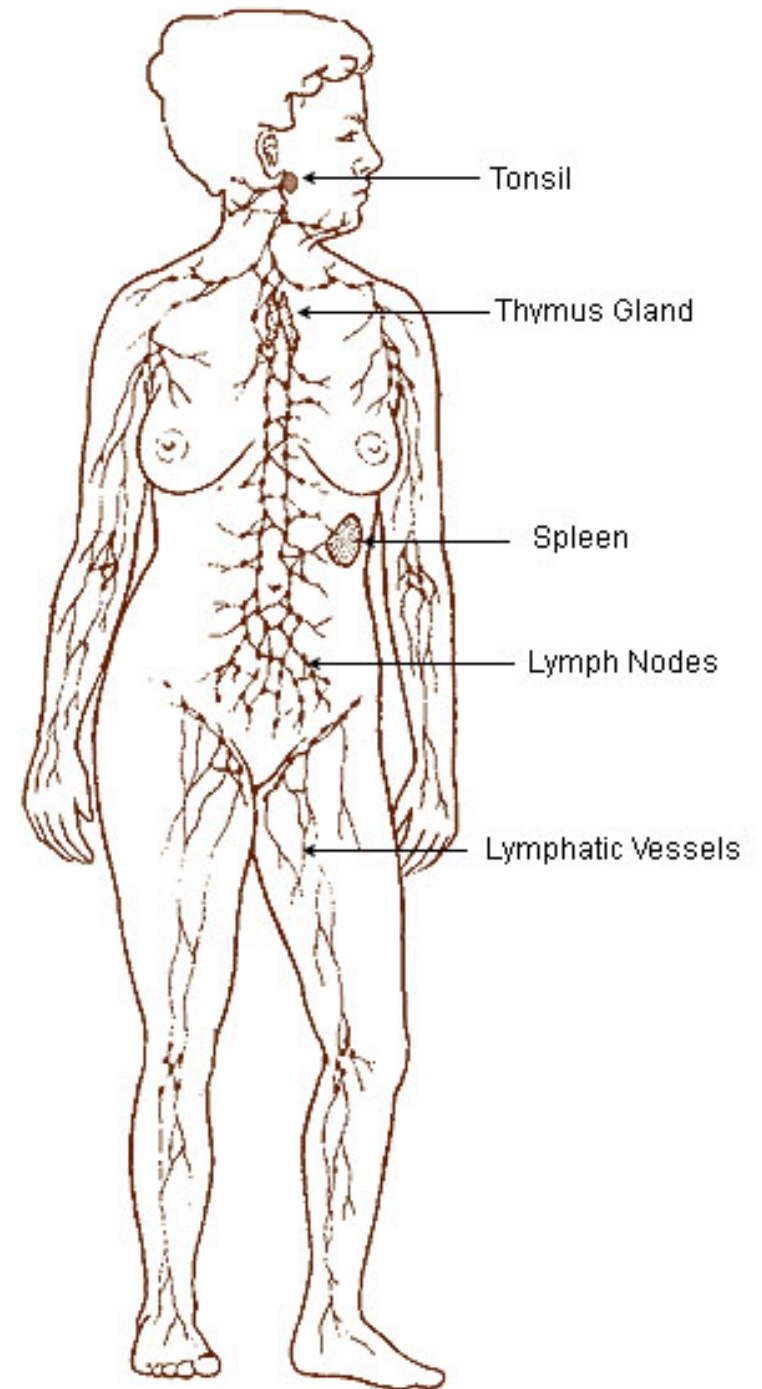
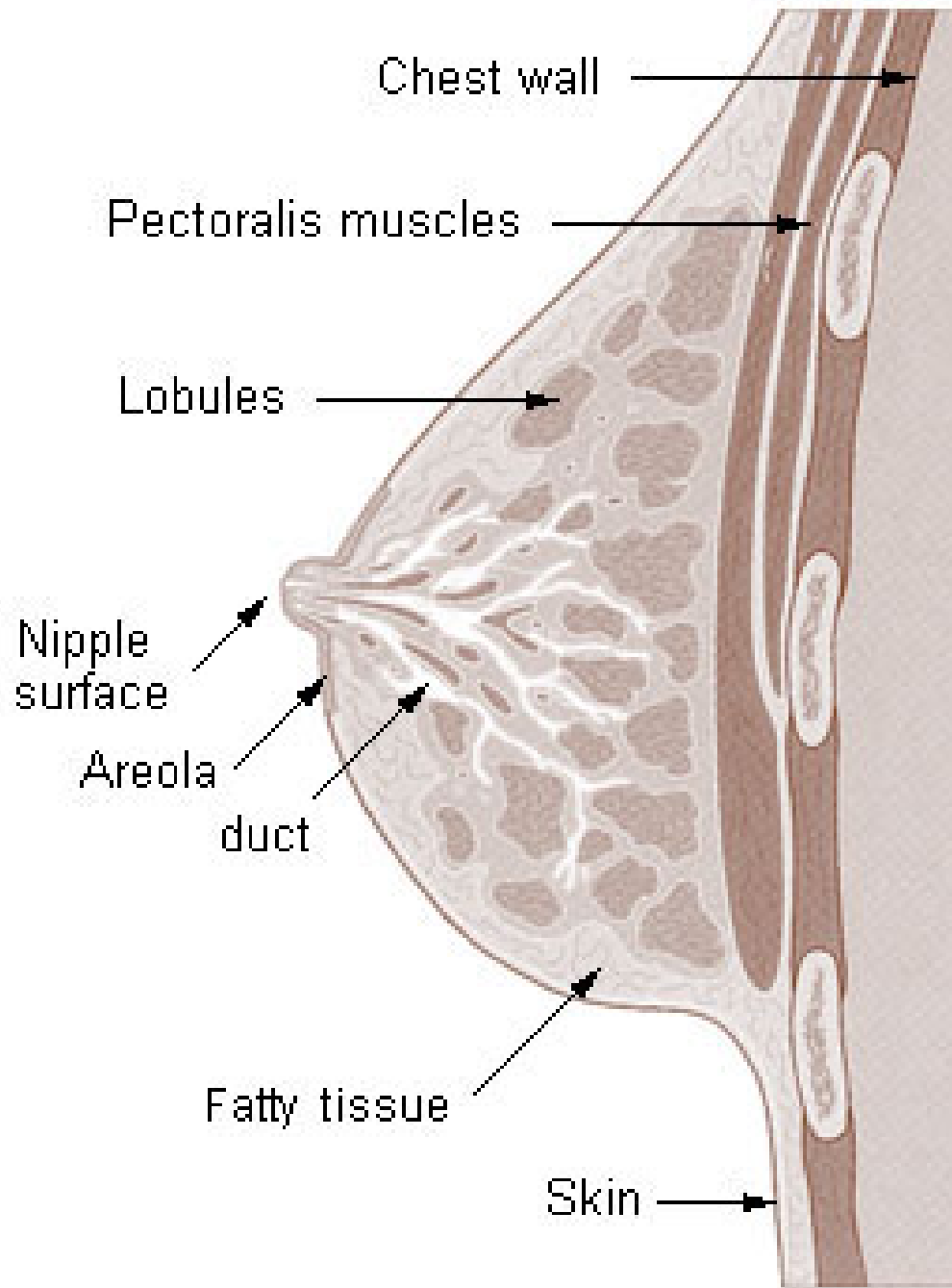
## Trends in Female Breast Cancer Incidence Rates\* by Race and Ethnicity, US (SEER) 1975 - 2002



\* Rates are age adjusted to the 2000 US standard population.

## Trends in Female Breast Cancer Mortality Rates\* by Race and Ethnicity, US (SEER) 1969- 2003





# 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

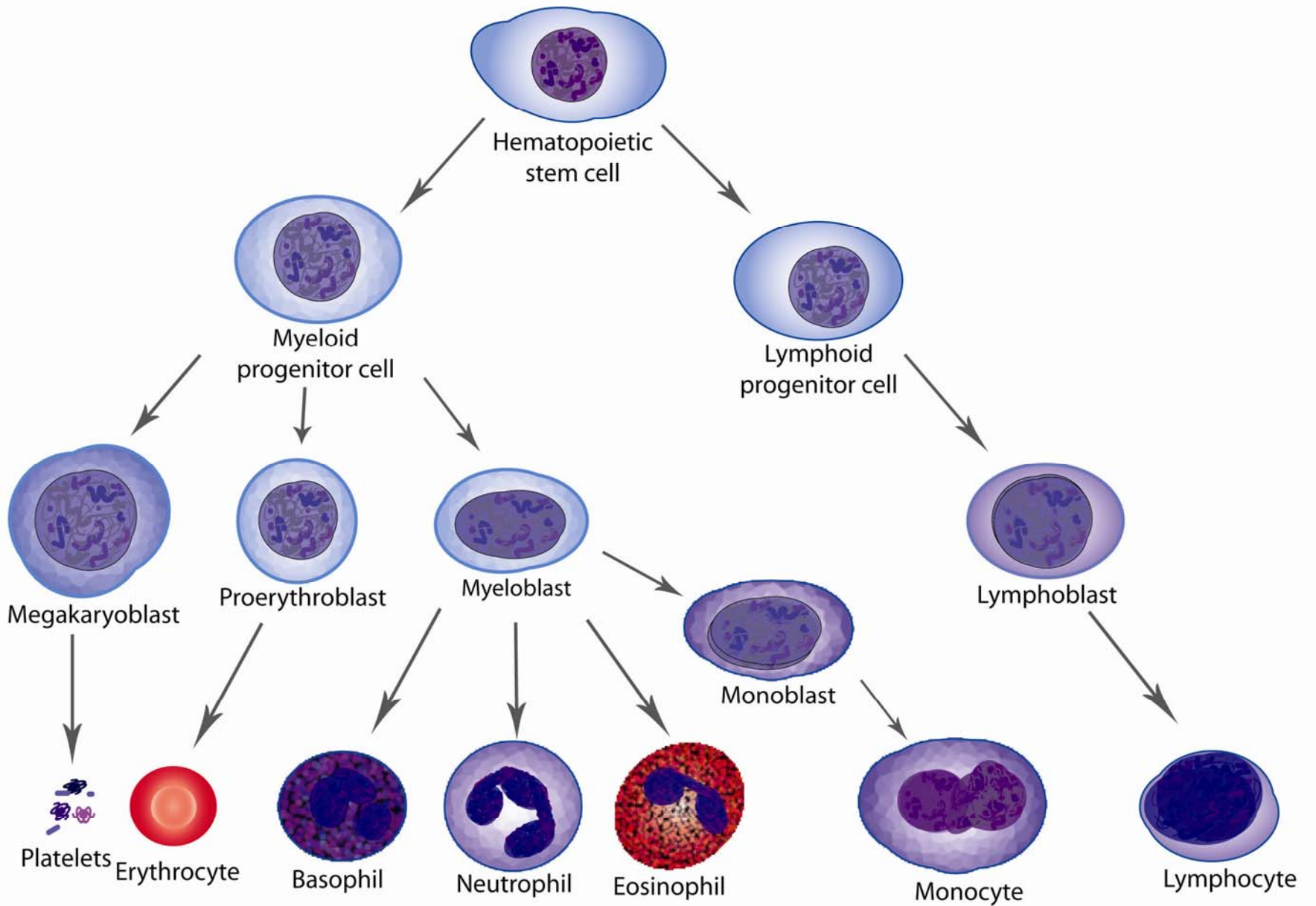
- Balance between goal of completely destroying all cancer cells & causing too much damage to normal cells
- Dose comparison studies of chemo in metastatic breast cancer show high dose is associated with high response rate

## ■ 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. Donnall 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 or 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



# 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

# 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

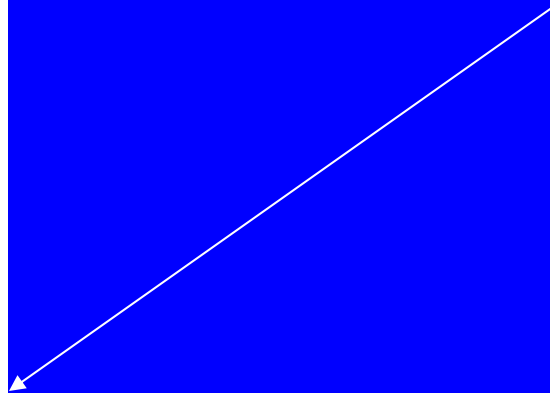
## ■ Apheresis:

- 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

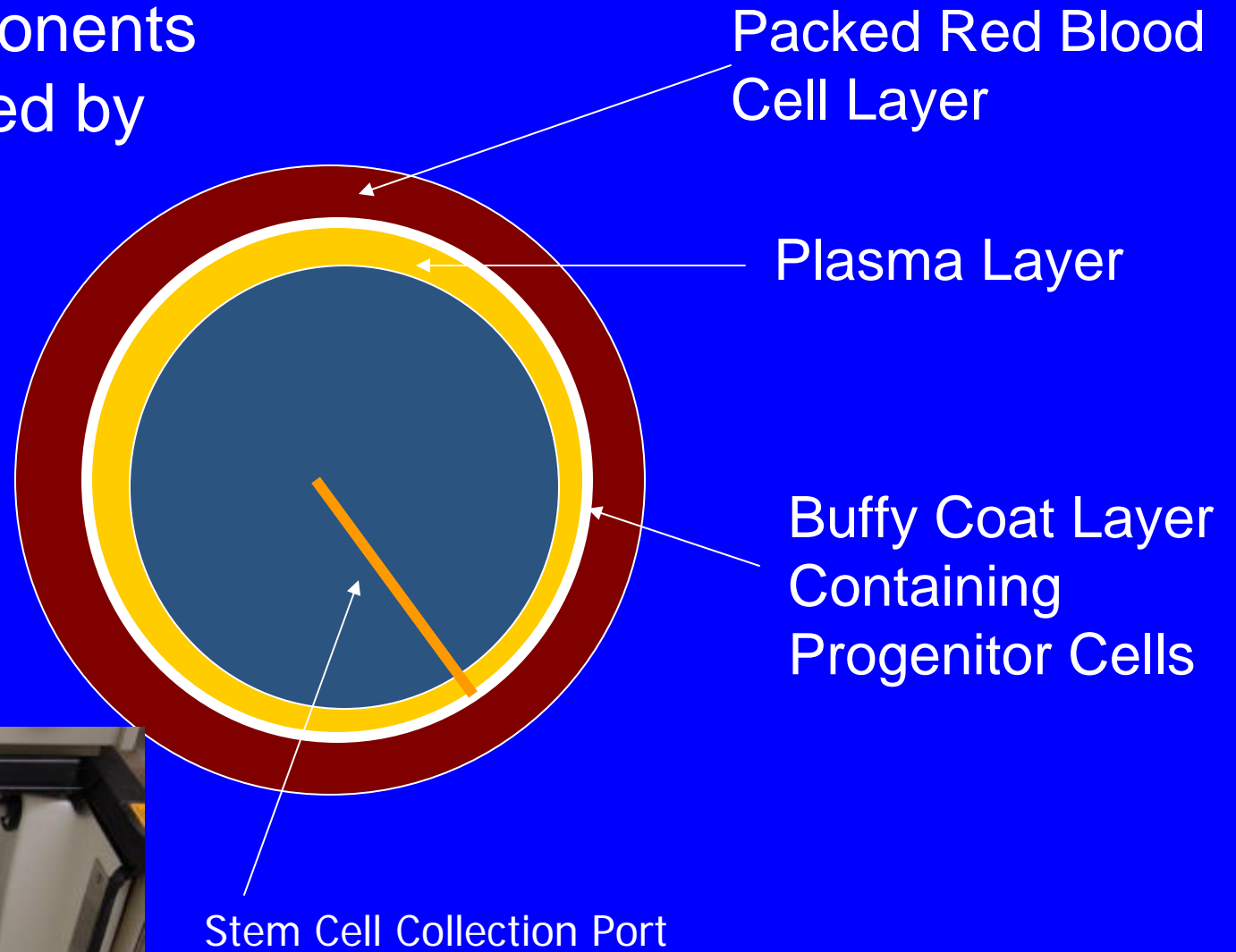
# “The Equipment”



“The Centrifuge”



Blood components are separated by centrifugal force.



# 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

# 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 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

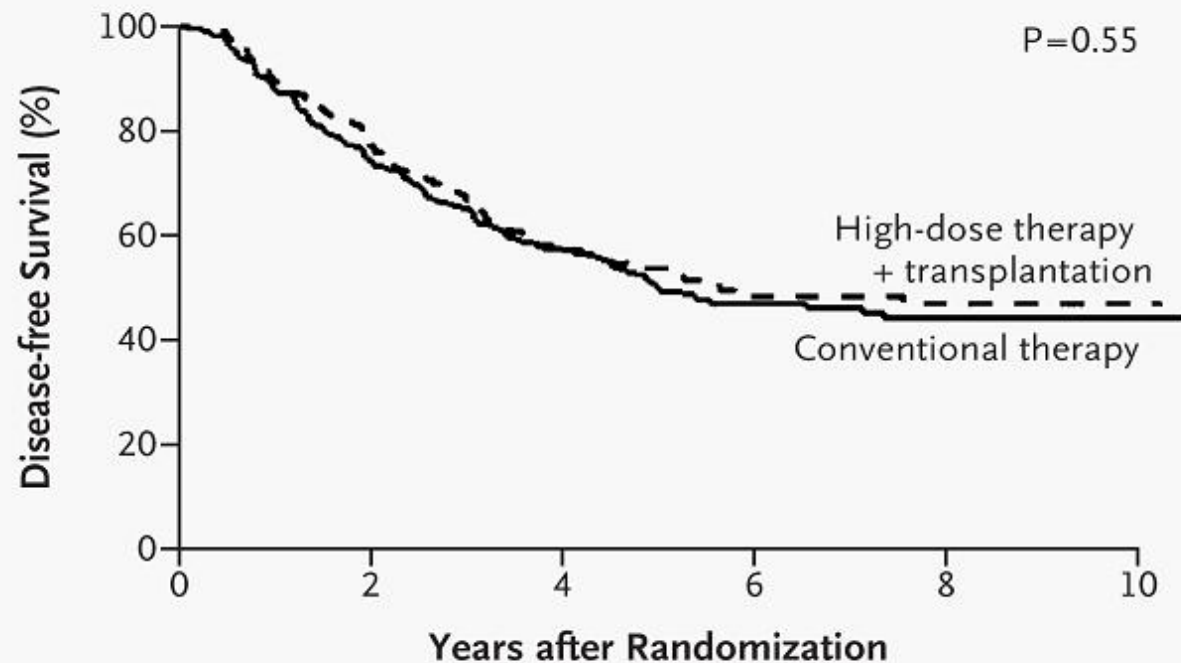
- <http://www.npr.org/templates/story/story.php?storyId=1049404>

# 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

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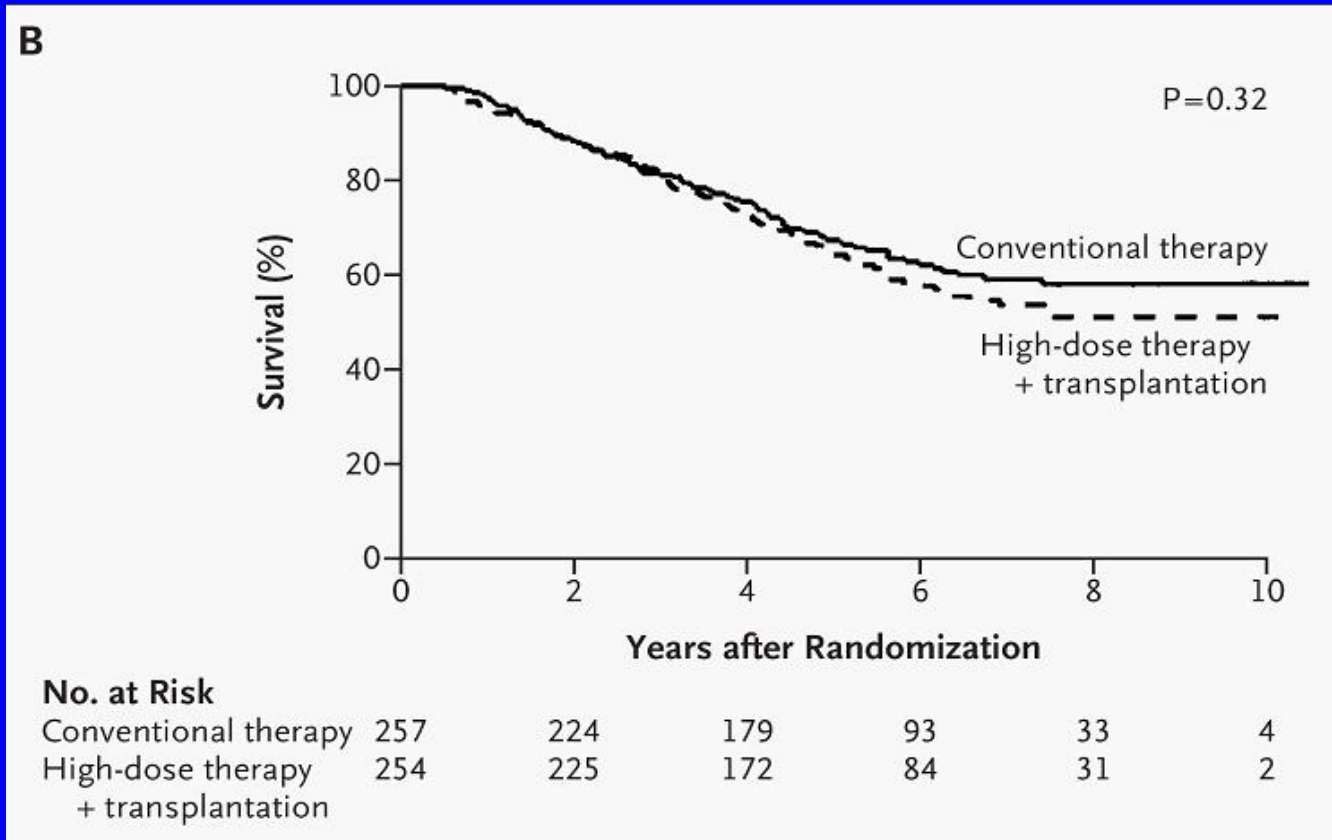


**No. at Risk**

Conventional therapy	257	190	134	69	27	4
High-dose therapy + transplantation	254	196	134	68	28	2

Tallman et al. Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. *The New England Journal of Medicine*. 2003 Jul 3; 349(1):17-26

# RCT Results



Tallman et al. Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. *The New England Journal of Medicine*. 2003 Jul 3; 349(1):17-26

# 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?

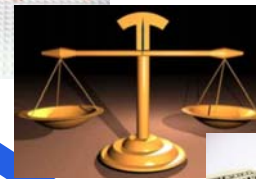
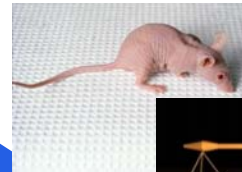
## Science of Understanding Disease



## Emerging Health Technologies



## Bioengineering



## Adoption & Diffusion



### Abandoned due to:

- Poor performance
- Safety concerns
- Ethical concerns
- Legal issues
- Social issues
- Economic issues

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

What is the proper forum to resolve controversies?

# Read More About It:

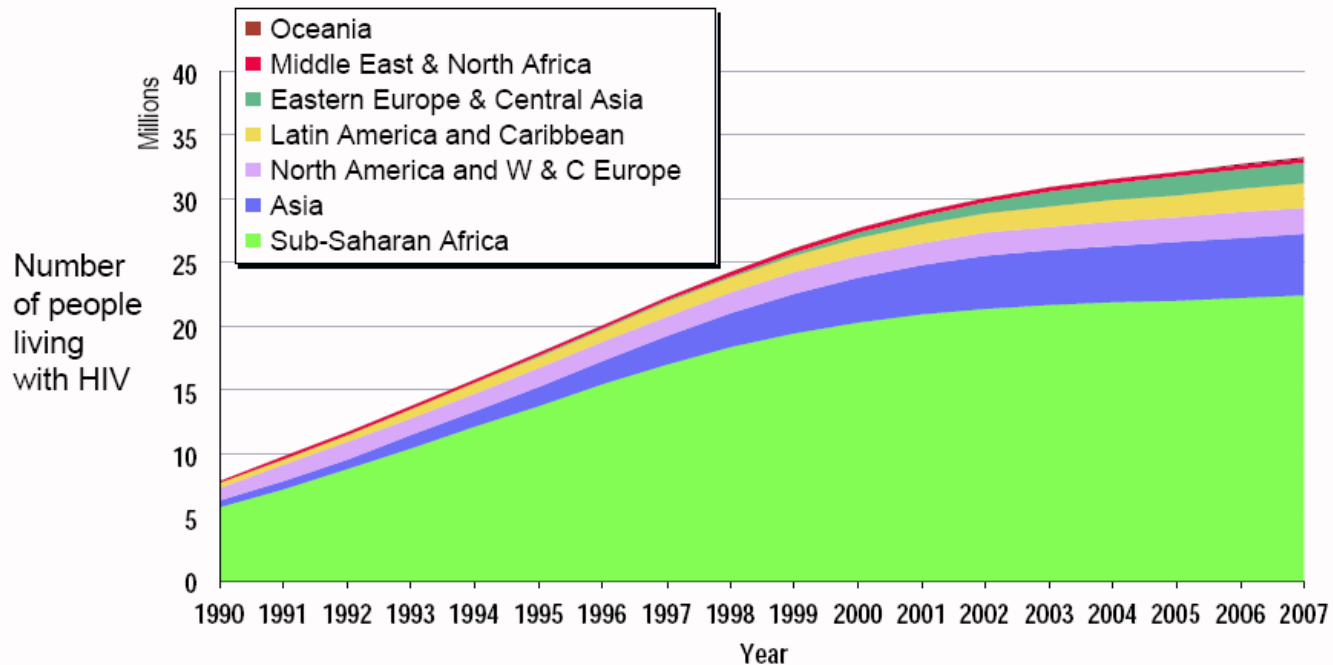
- Breast Cancer Facts and Figures:
  - <http://www.cancer.org/downloads/STT/CAFF2005BrF.pdf>
- Dr. Groopman's article on BMT:
  - <http://www.jeromegroopman.com/bmt.html>
- Aetna announcement on coverage of BMT for breast cancer:
  - <http://www.aetna.com/cpb/data/CPBA0507.html>

# 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

Estimated number of adults and children living with HIV, by region, 1990–2007



# 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

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

# Quantitative measures of health

- Prevalence

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

- Point prevalence

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

# 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**

## Leading causes of mortality among adults worldwide 2002

Age: 15-59			Age: 60+		
Rank	Cause	Deaths (000)	Rank	Cause	Deaths (000)
1	HIV/AIDS	2279	1	Ischemic heart disease	5825
2	Ischemic 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

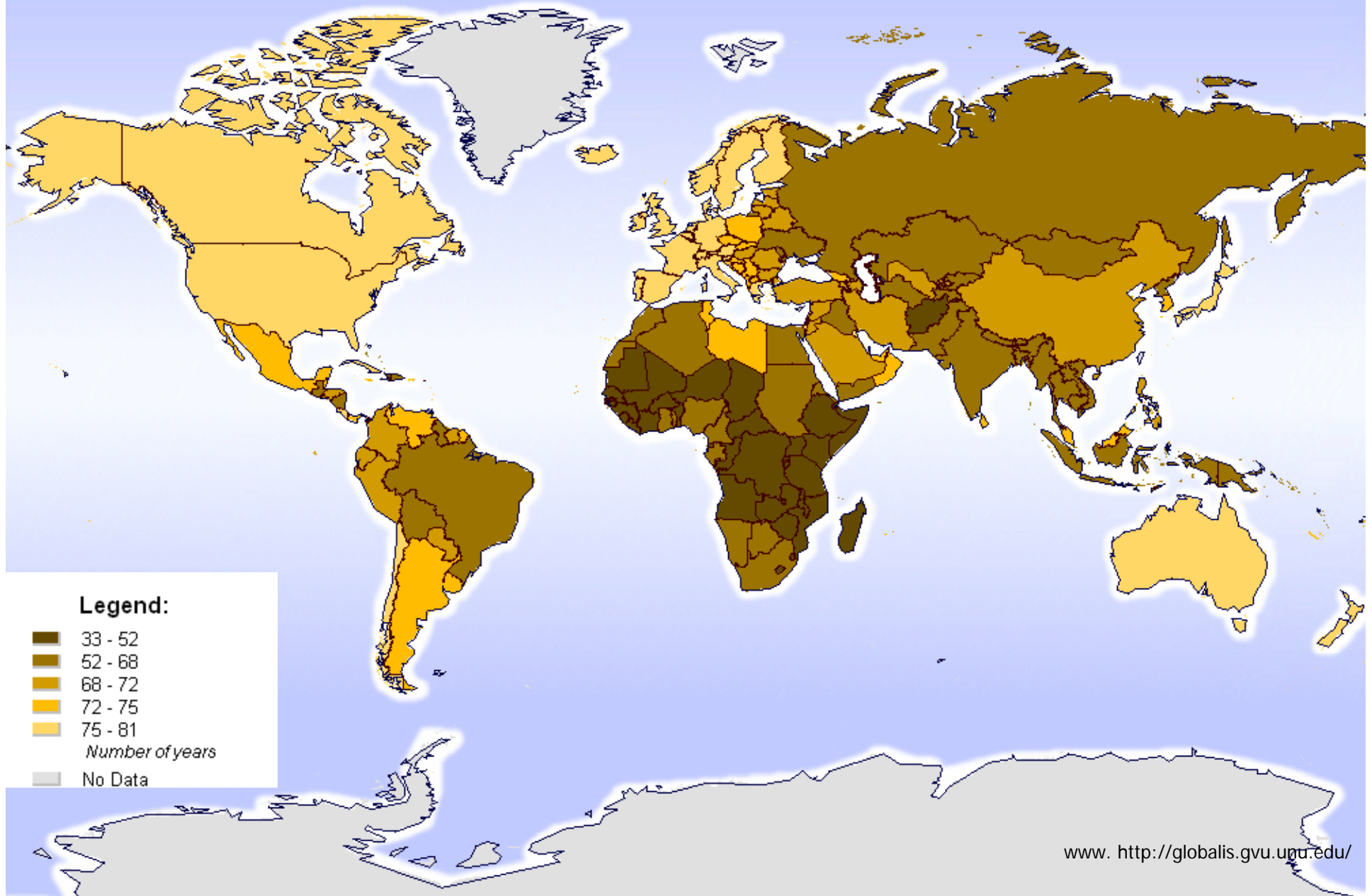
# Leading Causes of Infant Mortality in Developing Countries WHO Annual Report 2003

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

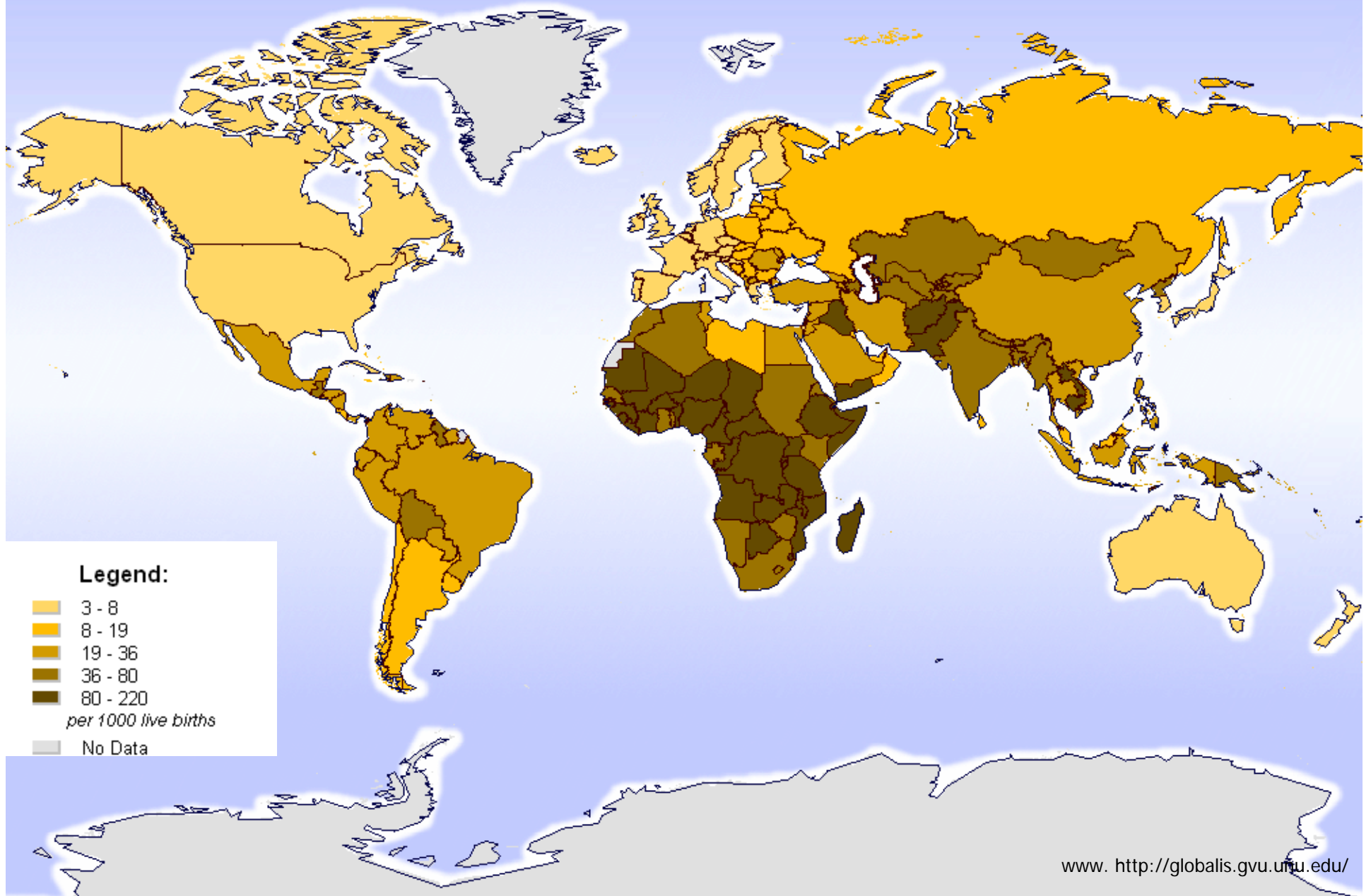
# Your Risk of Major Diseases

- <http://www.yourdiseaserisk.wustl.edu/index.htm>

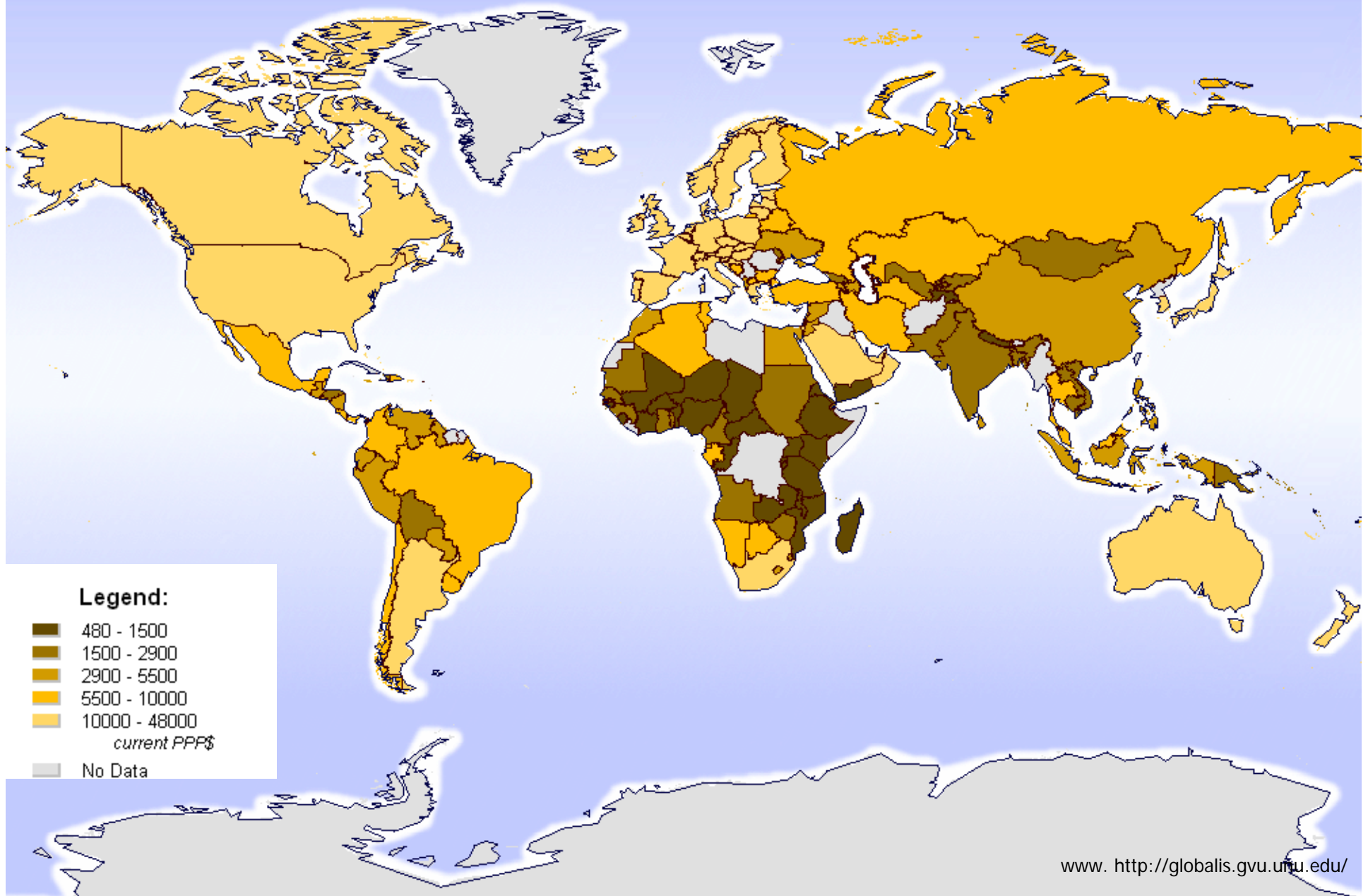
# Life Expectancy at Birth (2000)



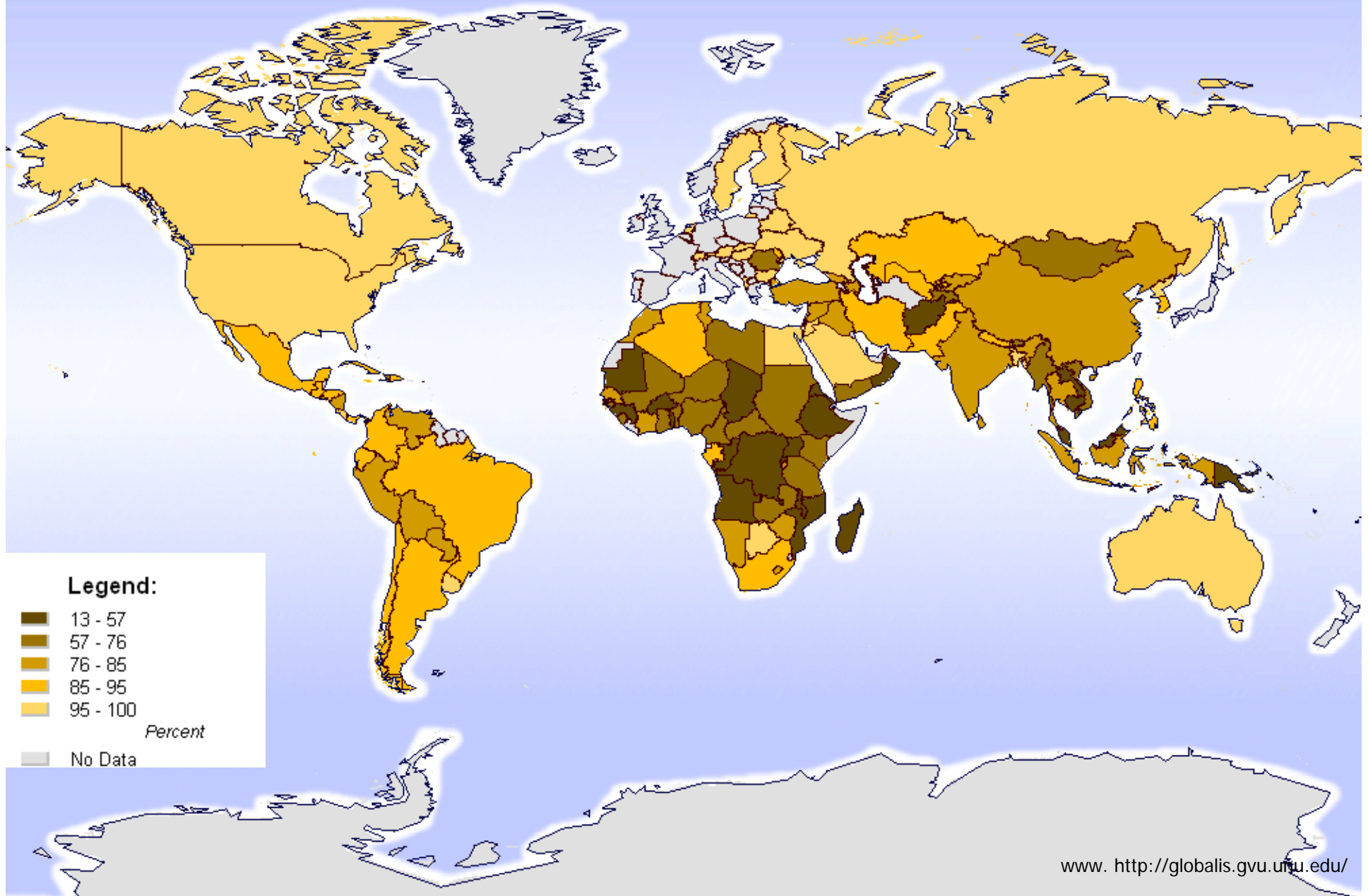
# Infant Mortality Rate (2002)



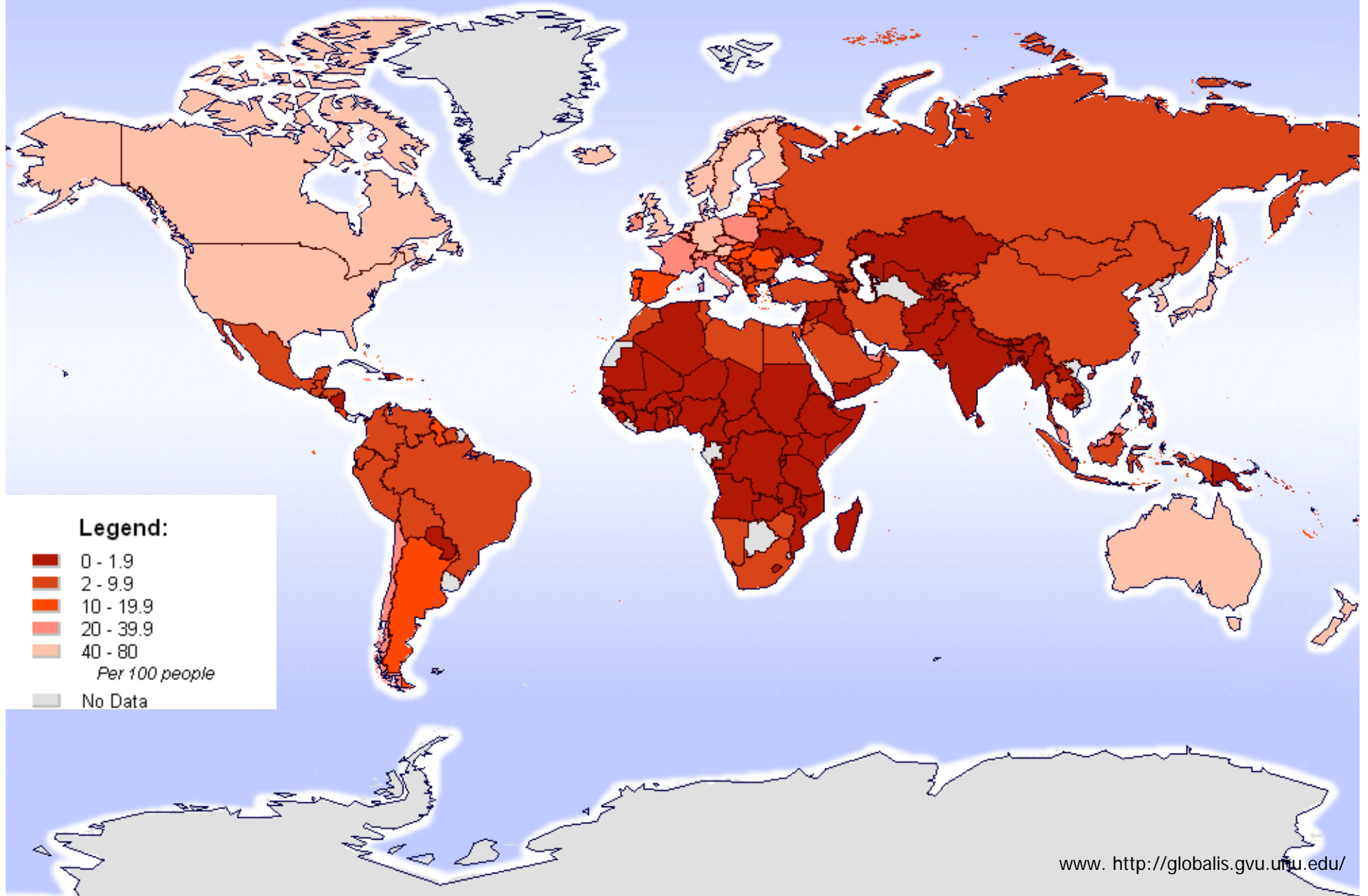
# Gross National Income per Capita at PPP (2001)



# Access to Safe Water (2000)



# Internet Users (2002)



# 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?