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

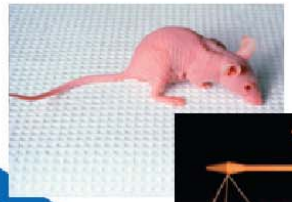
Course Organization

- Syllabus
- Project
- Owlspace
- BIOE 301 Roadmap

Science of Understanding Disease

Bioengineering

Emerging Health Technologies



Pre-clinical Testing

Ethics of Research

Clinical Trials

Cost-Effectiveness

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?

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

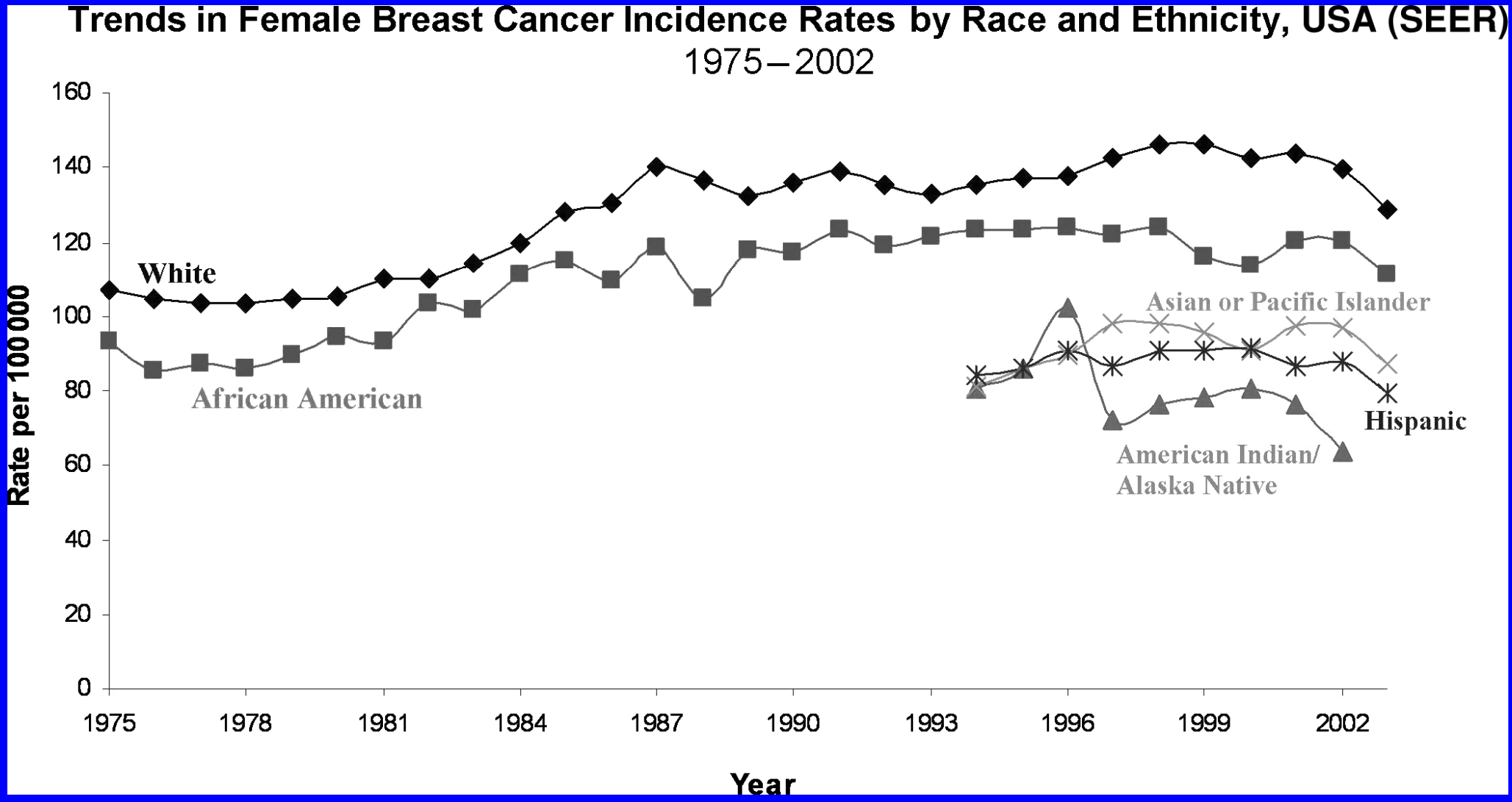
- What is it?
- Why do we need it?
- Example
  - Bone marrow transplants for breast cancer

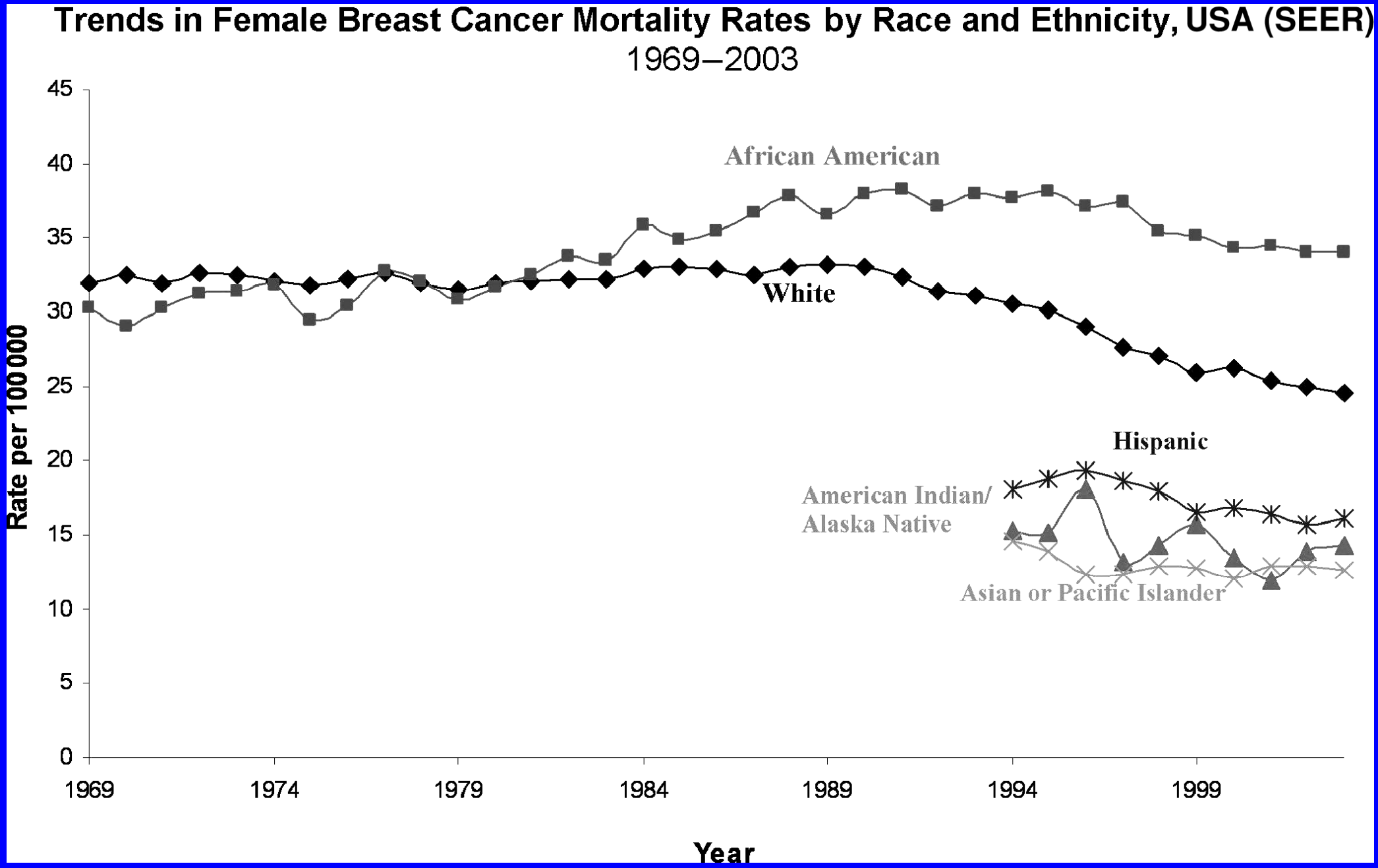
Technology Assessment: Overview

- 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
  - 2nd 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, USA (SEER)
1975–2002
Rate per 100 000
160
140
120
100
80
60
40
20
0
1975
1978
1981
1984
1987
1990
1993
1996
1999
2002
Year
White
African American
Asian or Pacific Islander
Hispanic
American Indian/
Alaska Native


Trends in Female Breast Cancer Mortality Rates by Race and Ethnicity, USA (SEER)
1969–2003
Rate per 100 000
45
40
35
30
25
20
15
10
5
0
1969
1974
1979
1984
1989
1994
1999
Year
African American
White
Hispanic
American Indian/
Alaska Native
Asian or Pacific Islander

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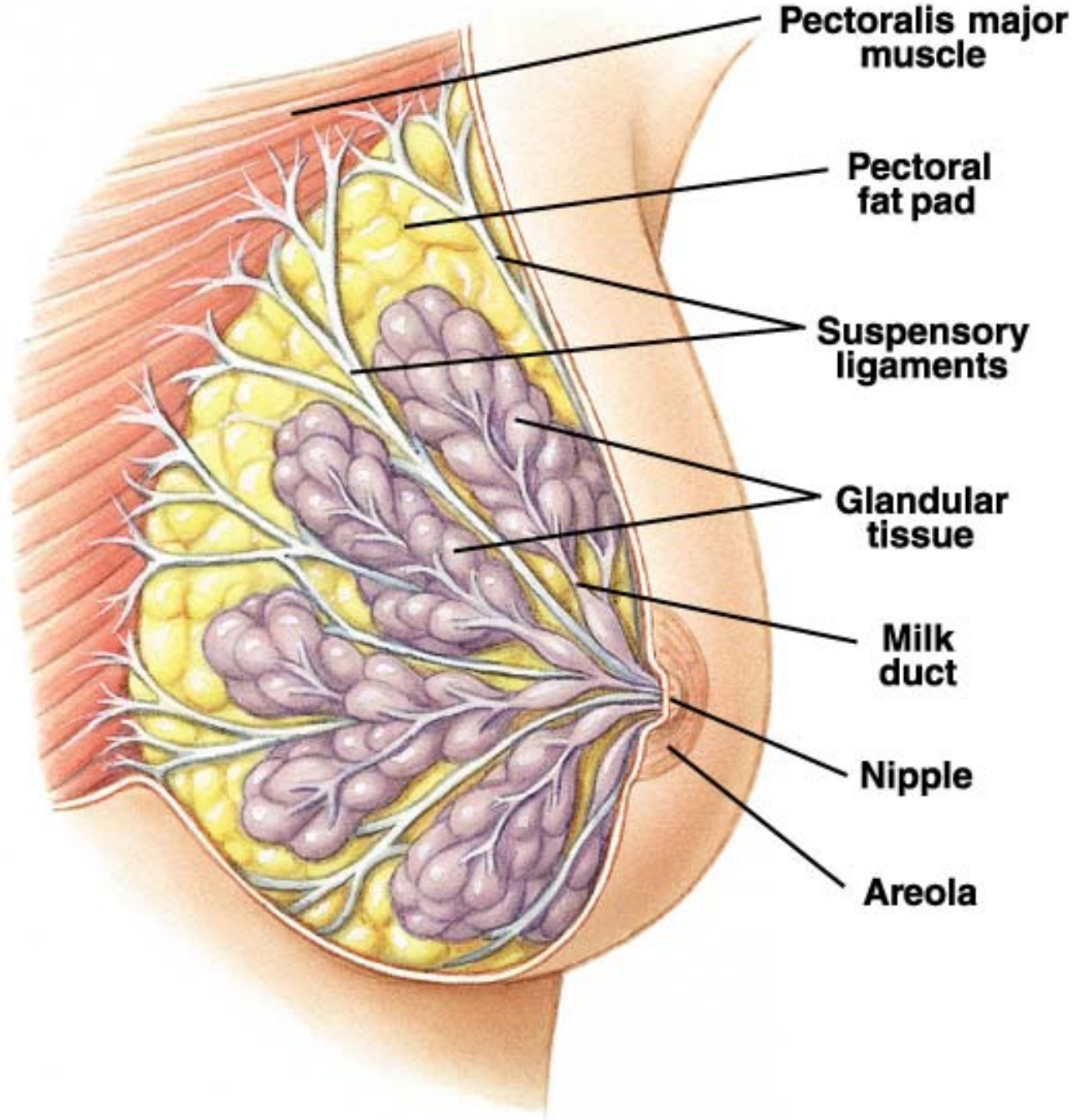

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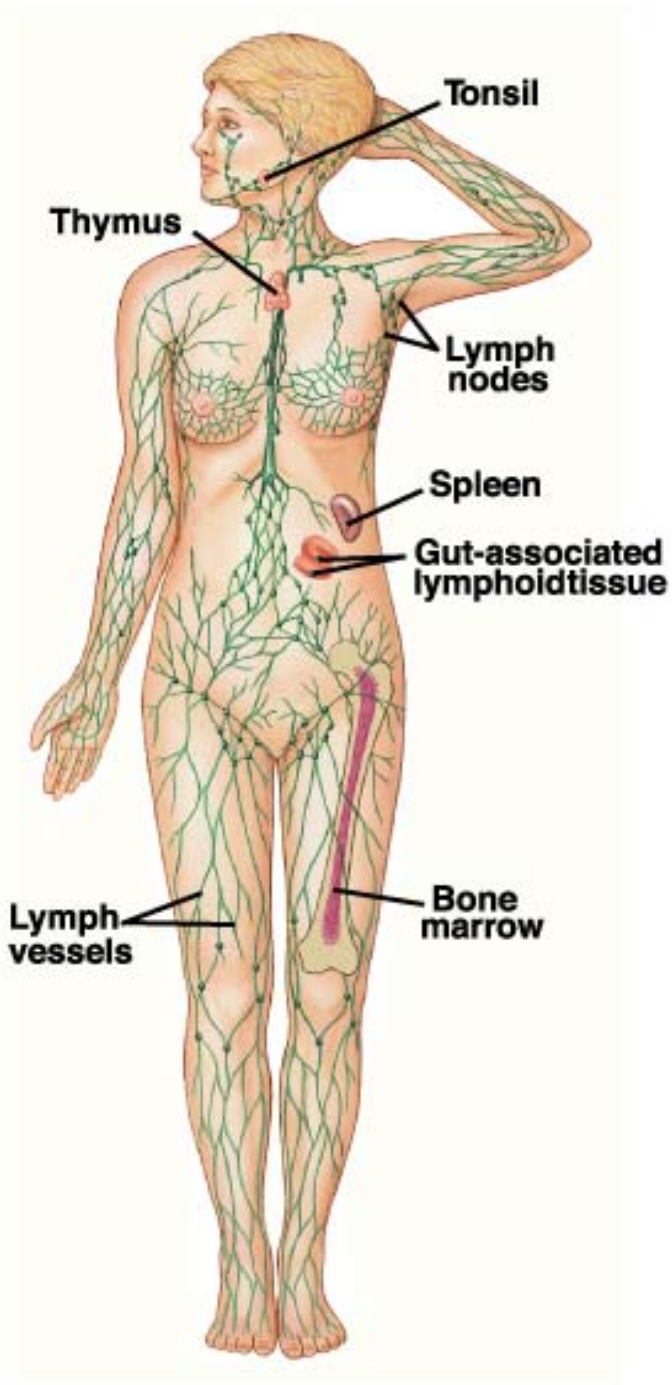


Breast Cancer Staging

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

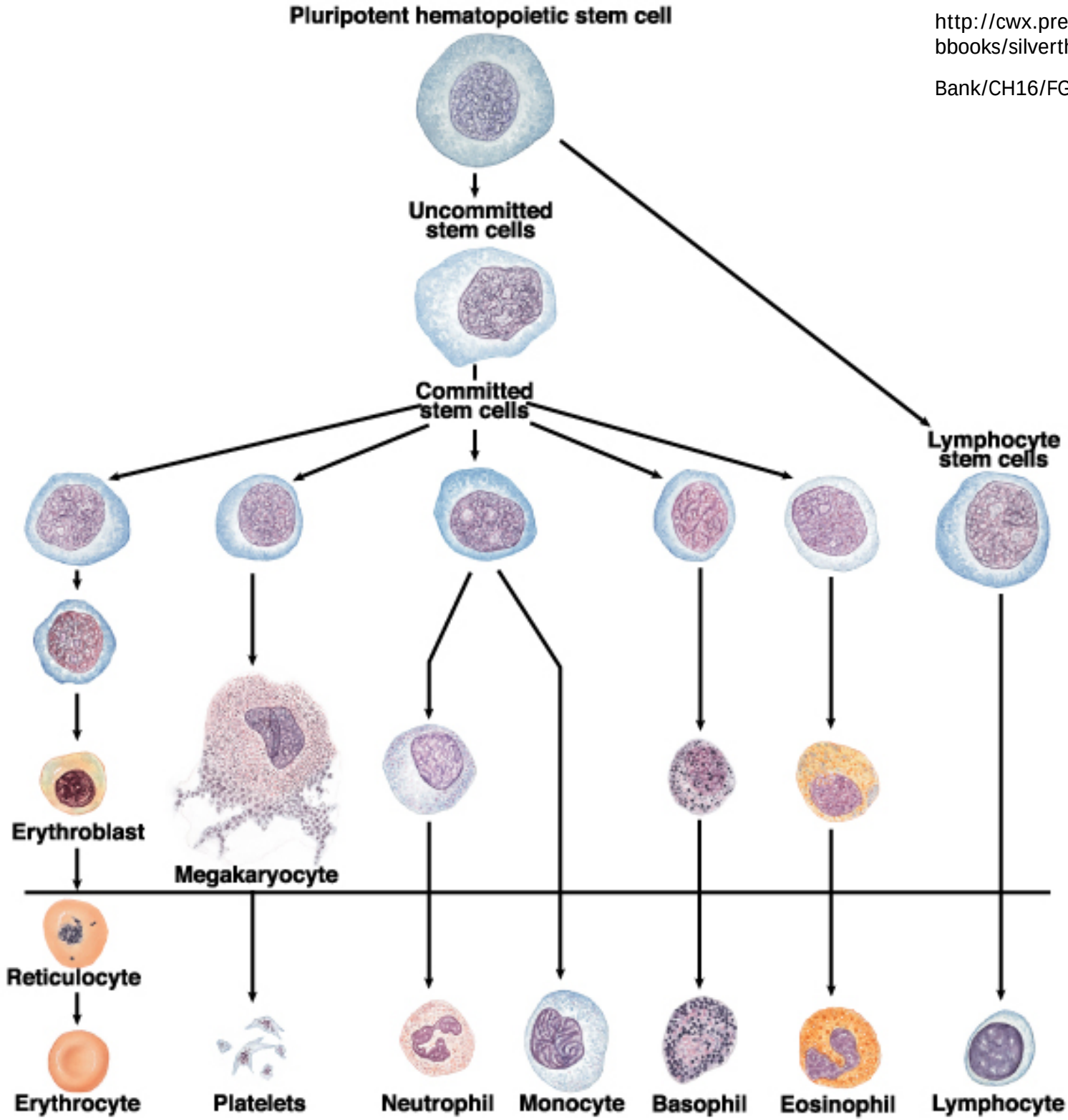
- How does it work?
  - Chemotherapy drugs given IV or by mouth
  - They travel through the bloodstream to reach cancer cells in most parts of the body
  - Interfere with ability of cell to divide
  - Cancer cells cannot repair damage caused by chemotherapy drugs so they die
  - Rapidly dividing normal 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 hematopoeitic stem cells
- Lab expts: a single stem cell can yield the half-trillion blood cells of an entire mouse



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History of Bone Marrow Transplants

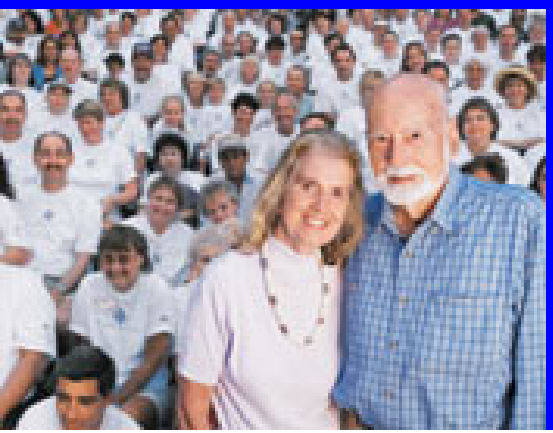
- Conceived in a dog kennel in Cooperstown, NY during the 1950s
  - RBCs could be successfully transfused from compatible donor to needy recipient
  - Marrow cells could not: Body identified them as foreign invaders and destroyed them
  - Hiroshima – one reason that radiation was so deadly because it 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/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 autologus 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

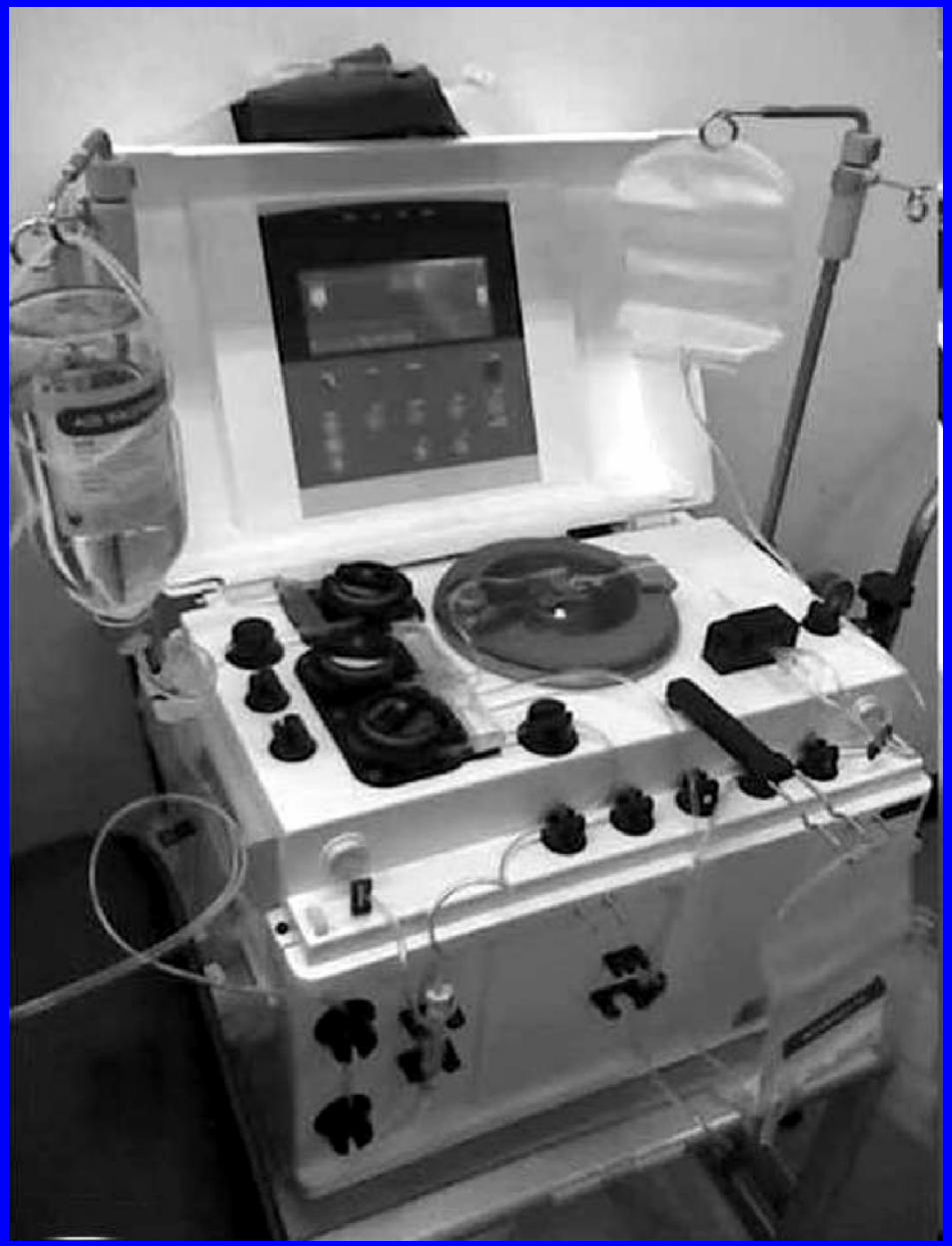
Tumor did respond to therapy

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 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)

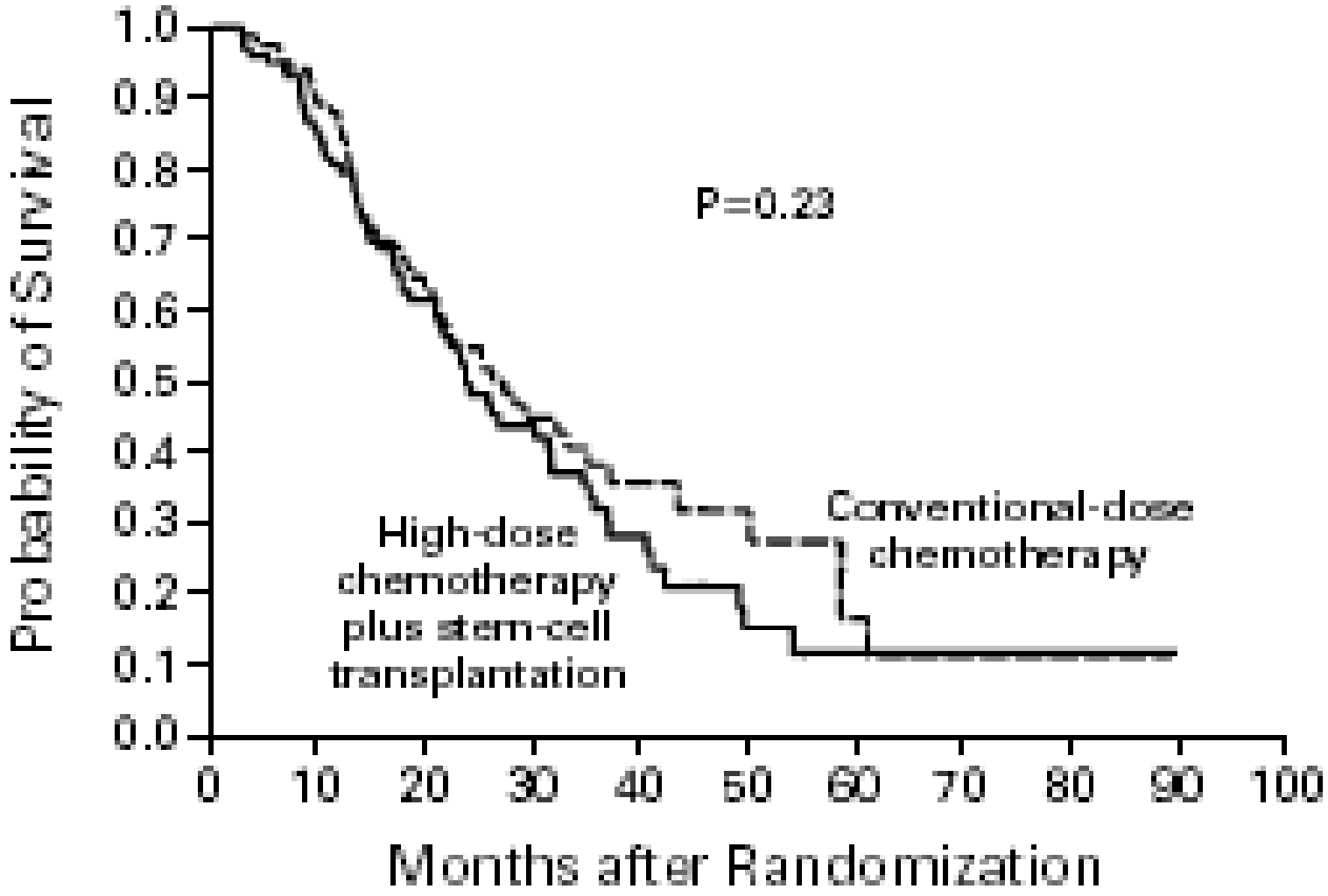
Timeline

- 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

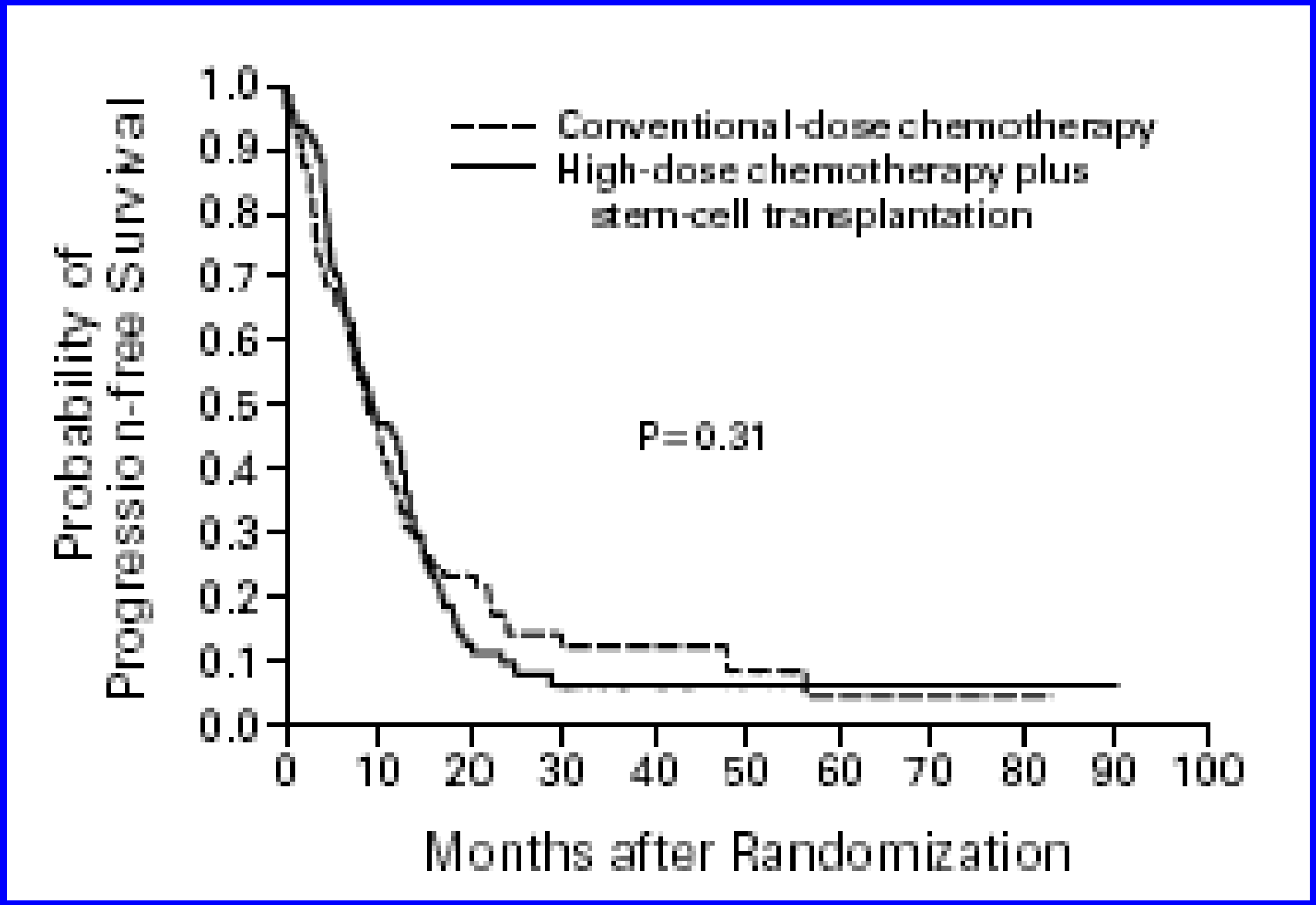
RCT Results

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


Probability of Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
P=0.23
High-dose chemotherapy plus stem-cell transplantation
Conventional-dose chemotherapy
0
10
20
30
40
50
60
70
80
90
100
Months after Randomization

RCT Results


Probability of Progression-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
80
90
100
Months after Randomization
Conventional-dose chemotherapy
High-dose chemotherapy plus stem-cell transplantation
P=0.31

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

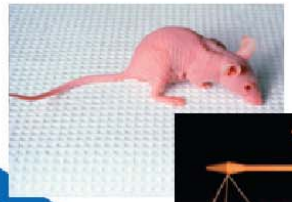
- Biological Plausibility
  - Does the biology support the technology?
- Technical Feasibility
  - Safely and reliably deliver technology to patients?
- Clinical Trials
  - Sensitivity & specificity in a relevant population?
  - Disease-free survival & 5-year survival in a relevant population?
- Patient 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

Science of Understanding Disease

Bioengineering

Emerging Health Technologies



Pre-clinical Testing

Ethics of Research

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Cost-Effectiveness

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Abandoned due to:

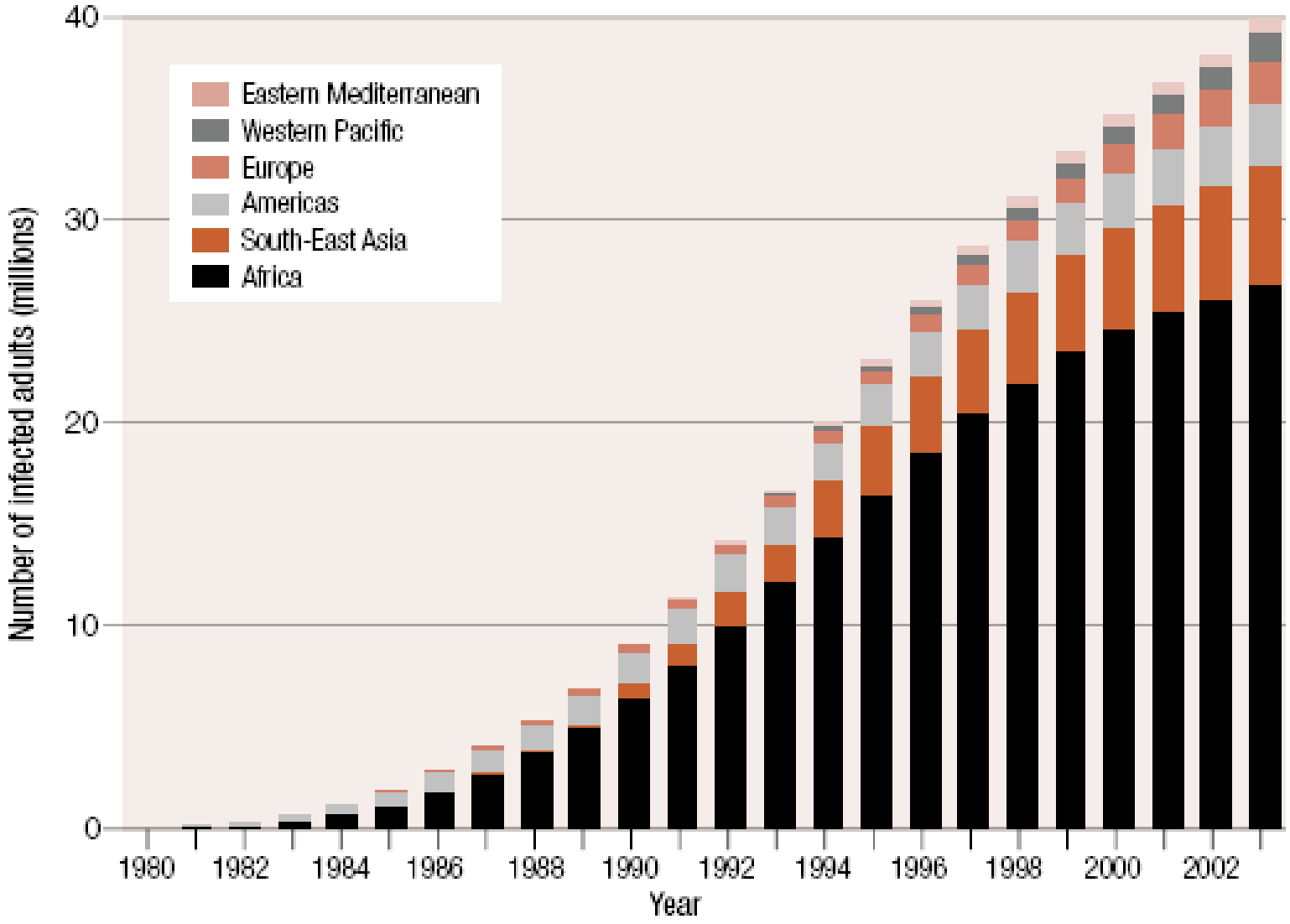
- Poor performance
- Safety concerns
- Ethical concerns
- Legal issues
- Social issues
- Economic issues

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

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

Quantitative measures of health

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

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

Quantitative measures of health

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

- Mortality Rate

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

- Infant mortality rate

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

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

Rank	Cause	Deaths (000)
1	HIV/AIDS	2279
2	Ischaemic heart disease	1332
3	Tuberculosis	1036
4	Road traffic injuries	814
5	Cerebrovascular disease	783
6	Self-inflicted injuries	672
7	Violence	473
8	Cirrhosis of the liver	382
9	Lower respiratory infections	352
10	Chronic obstructive pulmonary disease	343

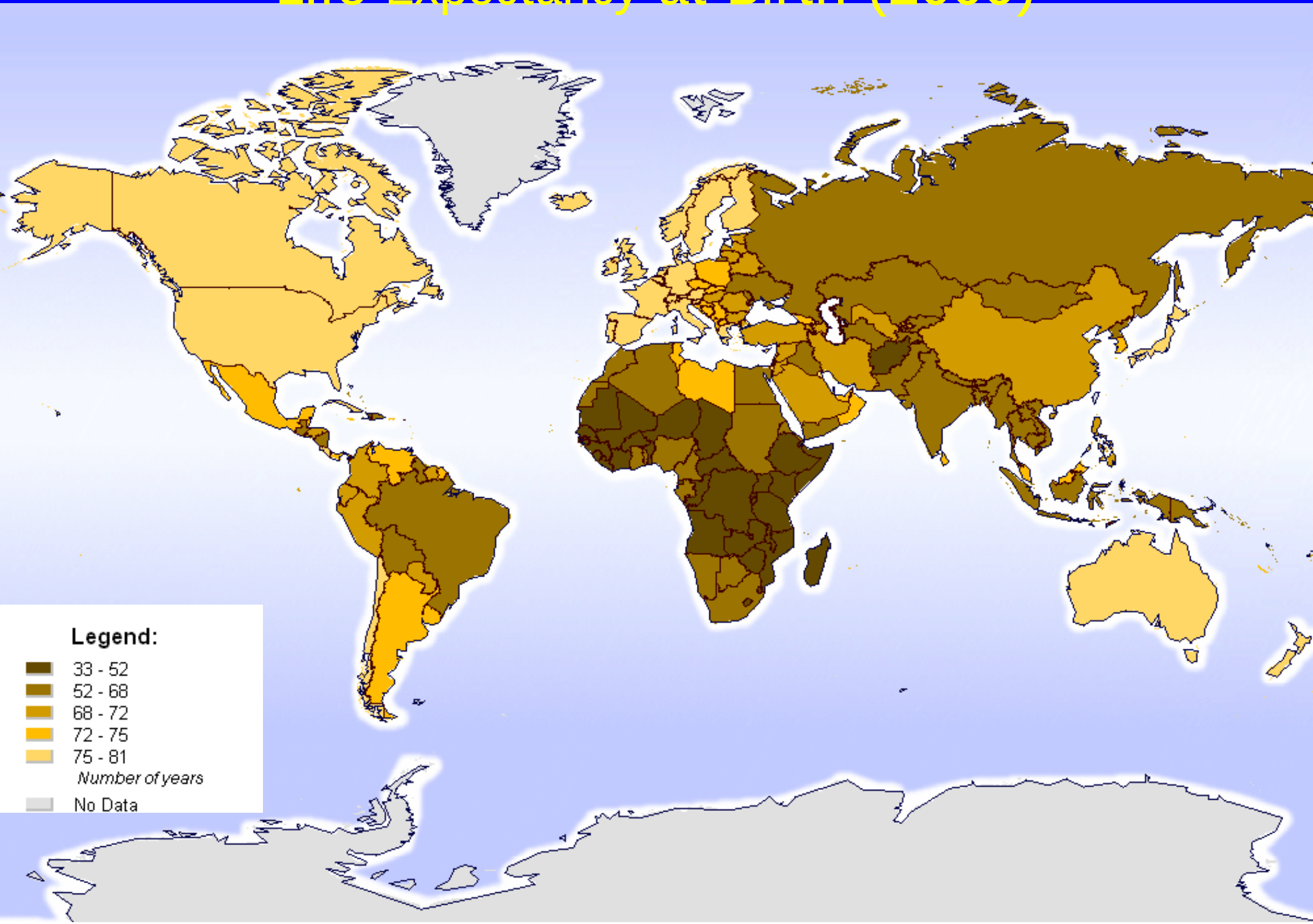
Mortality – adults aged 60 and over

Rank	Cause	Deaths (000)
1	Ischaemic heart disease	5825
2	Cerebrovascular disease	4689
3	Chronic obstructive pulmonary disease	2399
4	Lower respiratory infections	1396
5	Trachea, bronchus, lung cancers	928
6	Diabetes mellitus	754
7	Hypertensive heart disease	735
8	Stomach cancer	605
9	Tuberculosis	495
10	Colon and rectum cancers	477

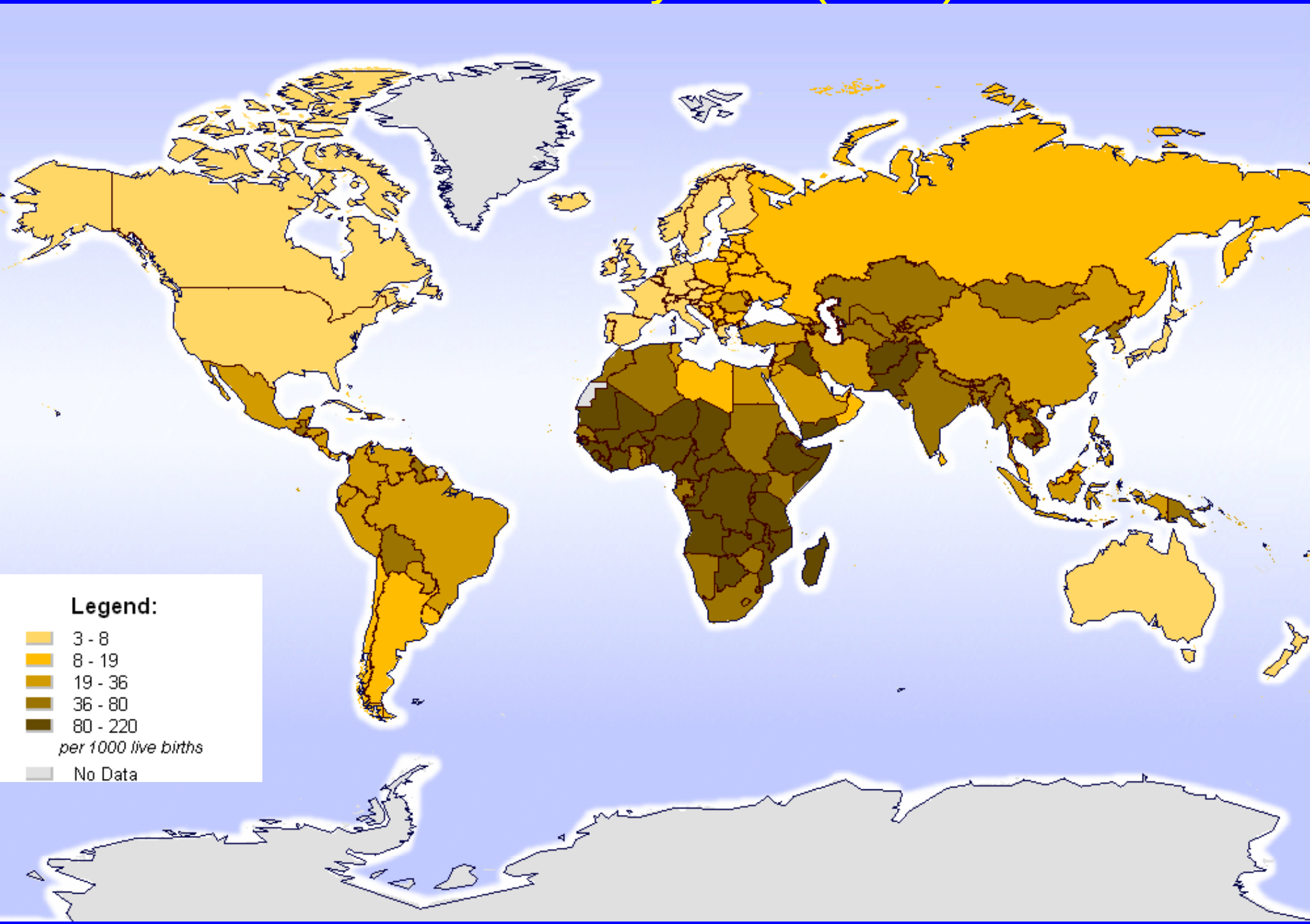
Leading Causes of Infant Mortality in Developing Countries WHO Annual Report 2003

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

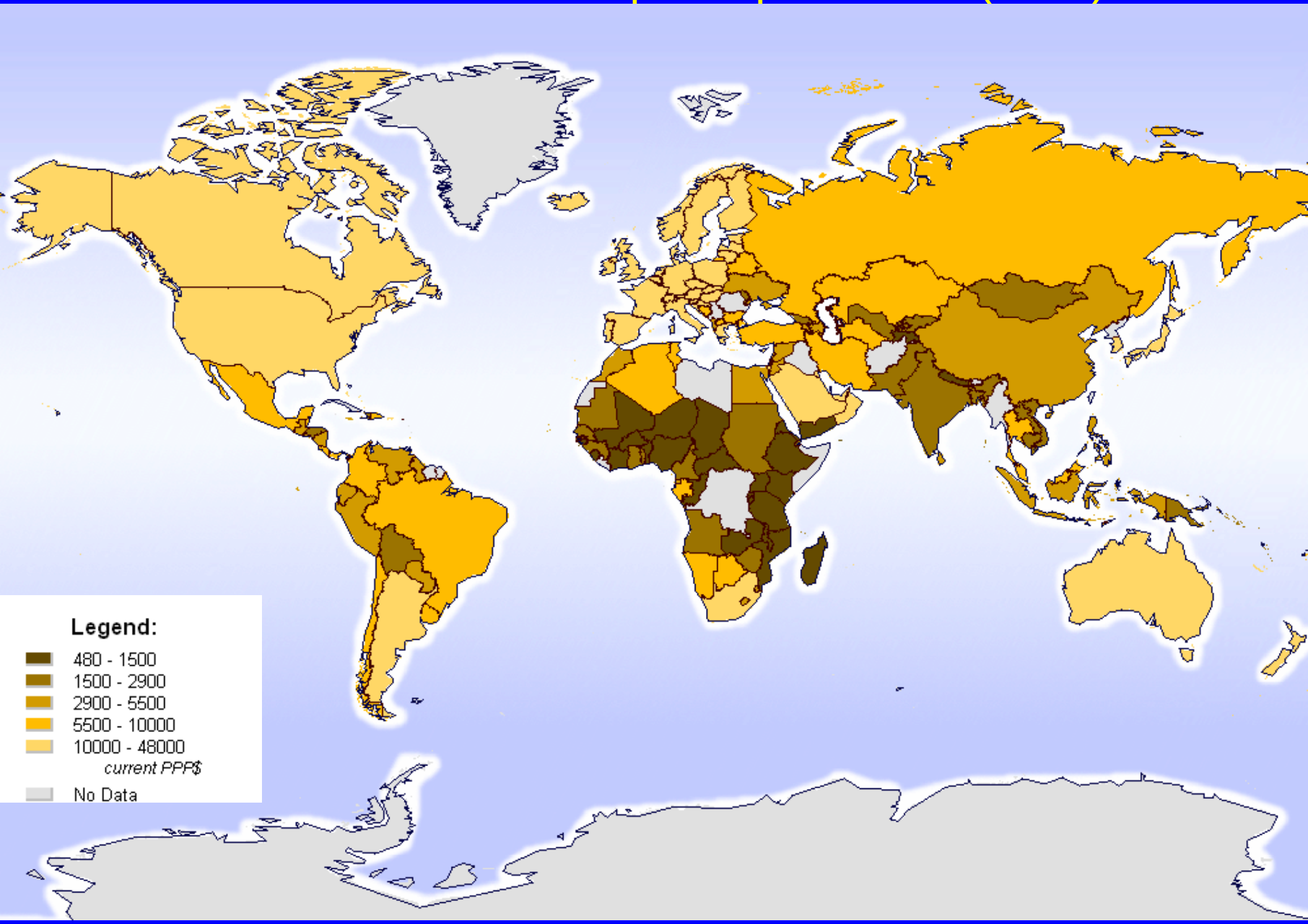
Life Expectancy at Birth (2000)



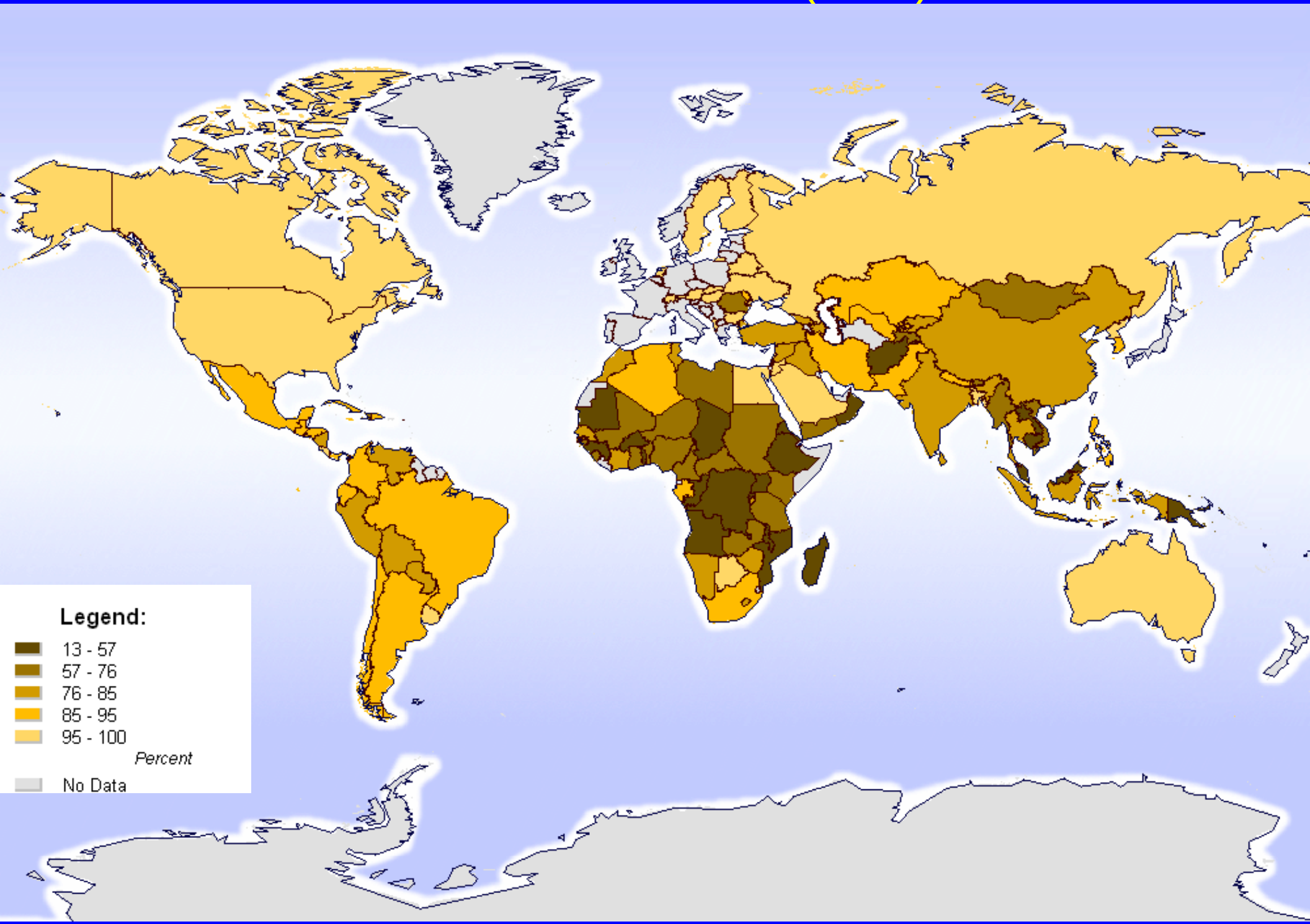
Infant Mortality Rate (2002)



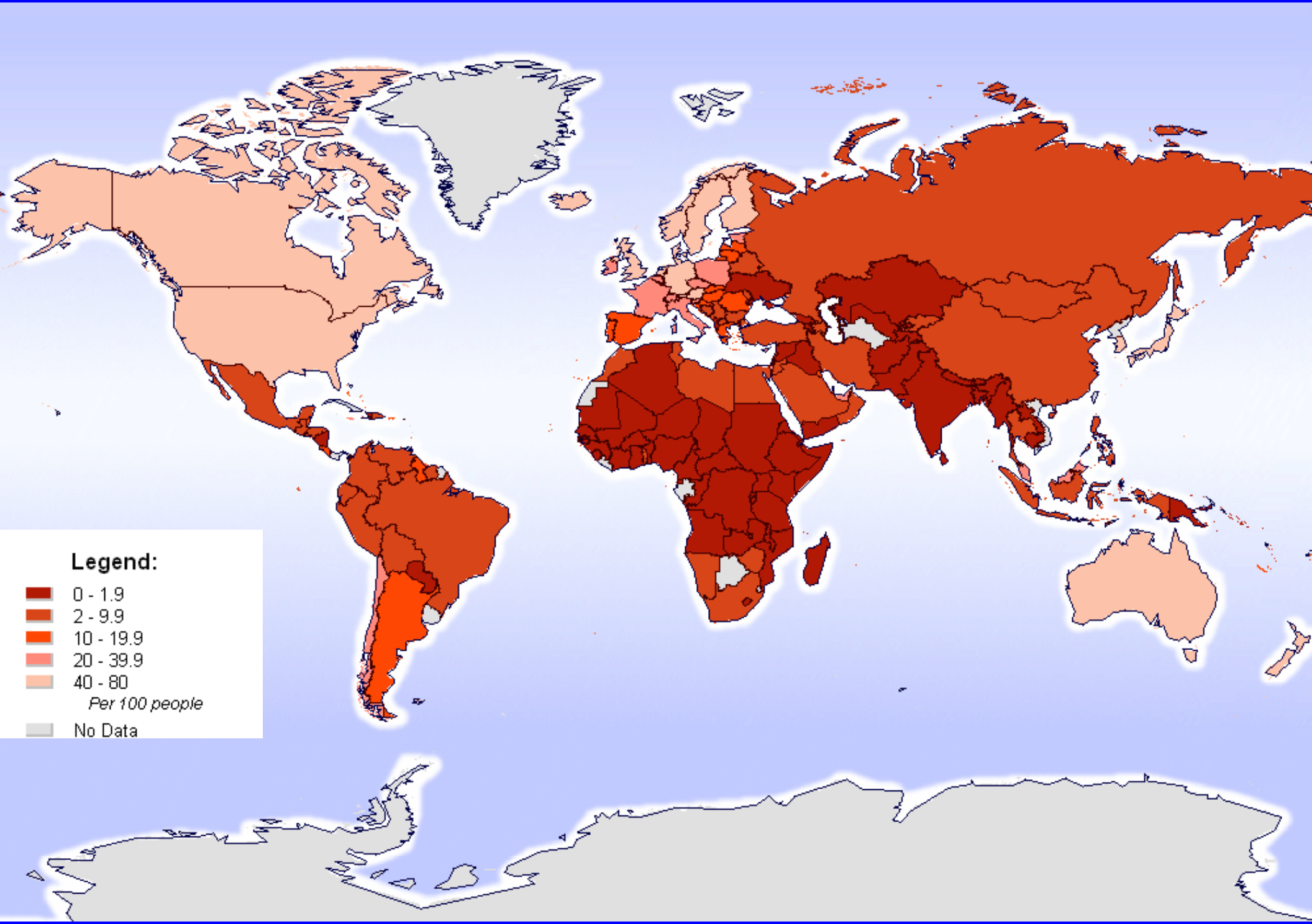
Gross National Income per Capita at PPP (2001)



Access to Safe Water (2000)



Internet Users (2002)

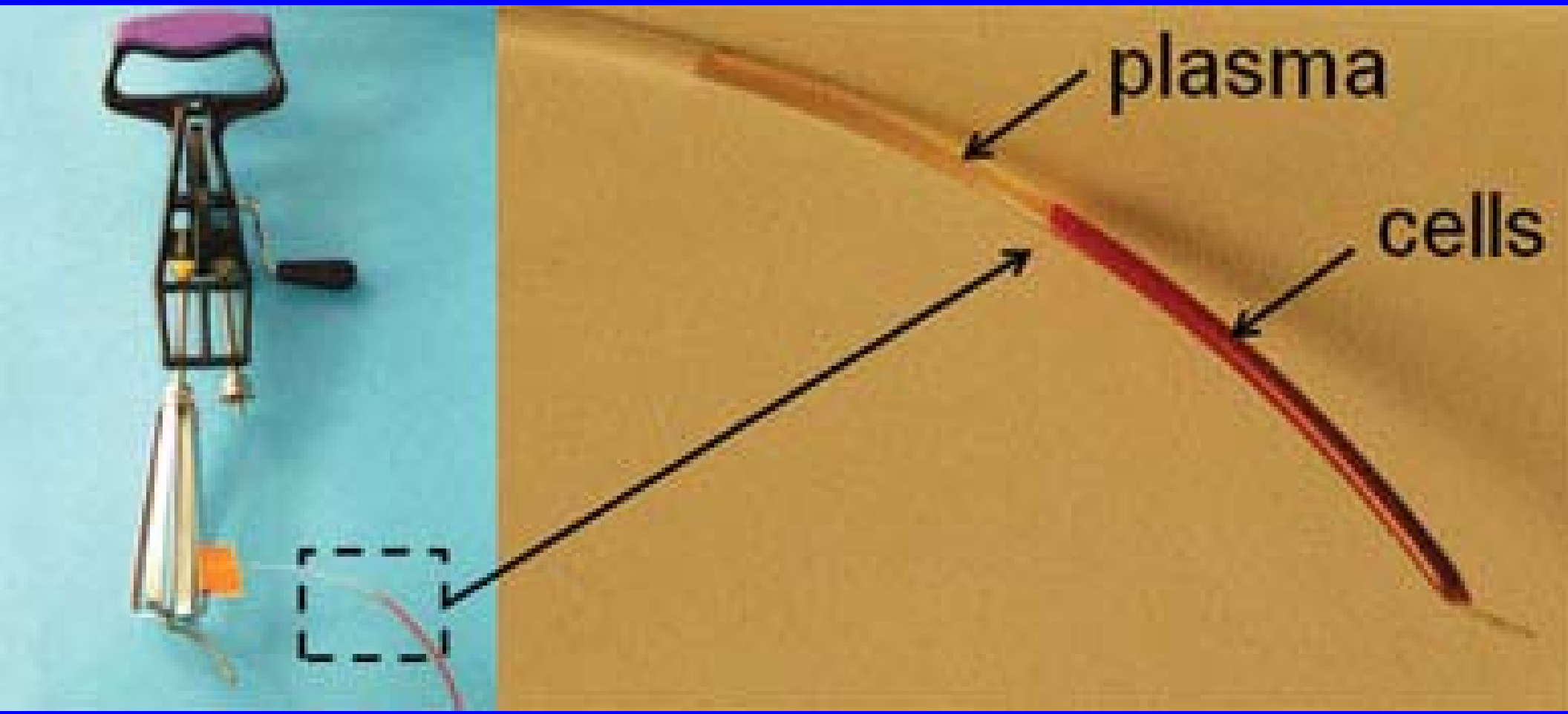


Questions We Will Consider

- 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?

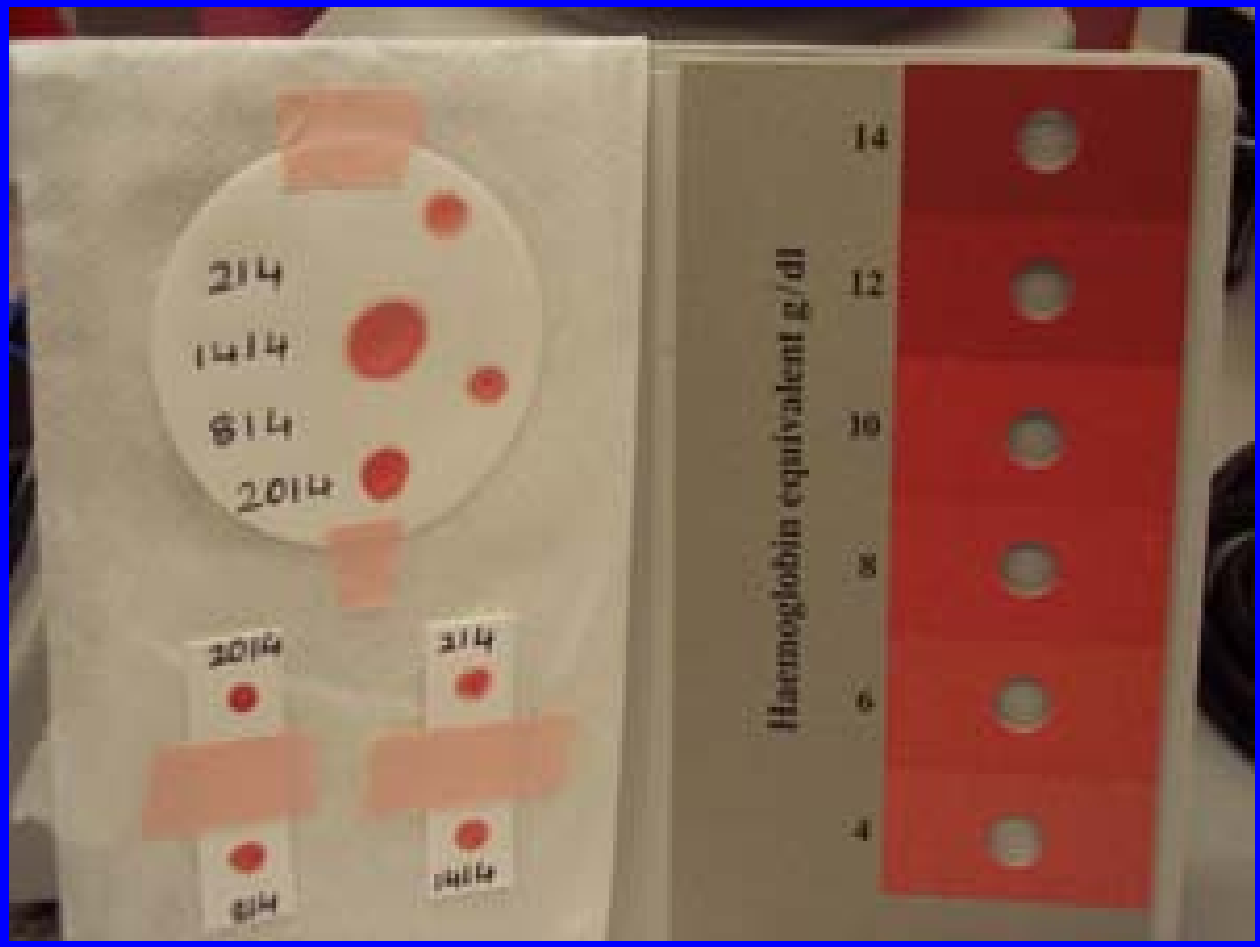
Projects

- 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


plasma
cells

Projects

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


Haemoglobin equivalent g/dl
14
12
10
8
6
4

Evaluate Clinical Impact, Technical Feasibility

- Urine Test for ARV Adherence:
  - Simple, accurate method to measure adherence
- Electrolytes:
  - Na+, K+, Cl-, and bicarb
- Arterial Blood Gases:
  - pH, partial pressure of CO2 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