BIOE 301

Lecture One

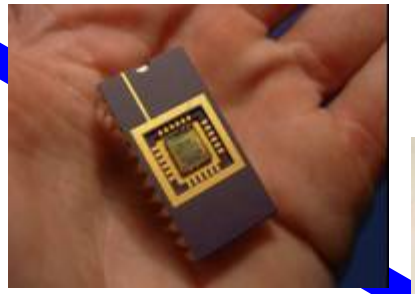
Course Organization

- People
- Syllabus
- Website:
  - http://www.owlnet.rice.edu/~bioe301/kortum/class/
- BIOE 301 Roadmap

Science of Understanding Disease

Bioengineering

Emerging Health Technologies



Preclinical Testing

Ethics of research

Clinical Trials

Cost-Effectiveness

Adoption & Diffusion

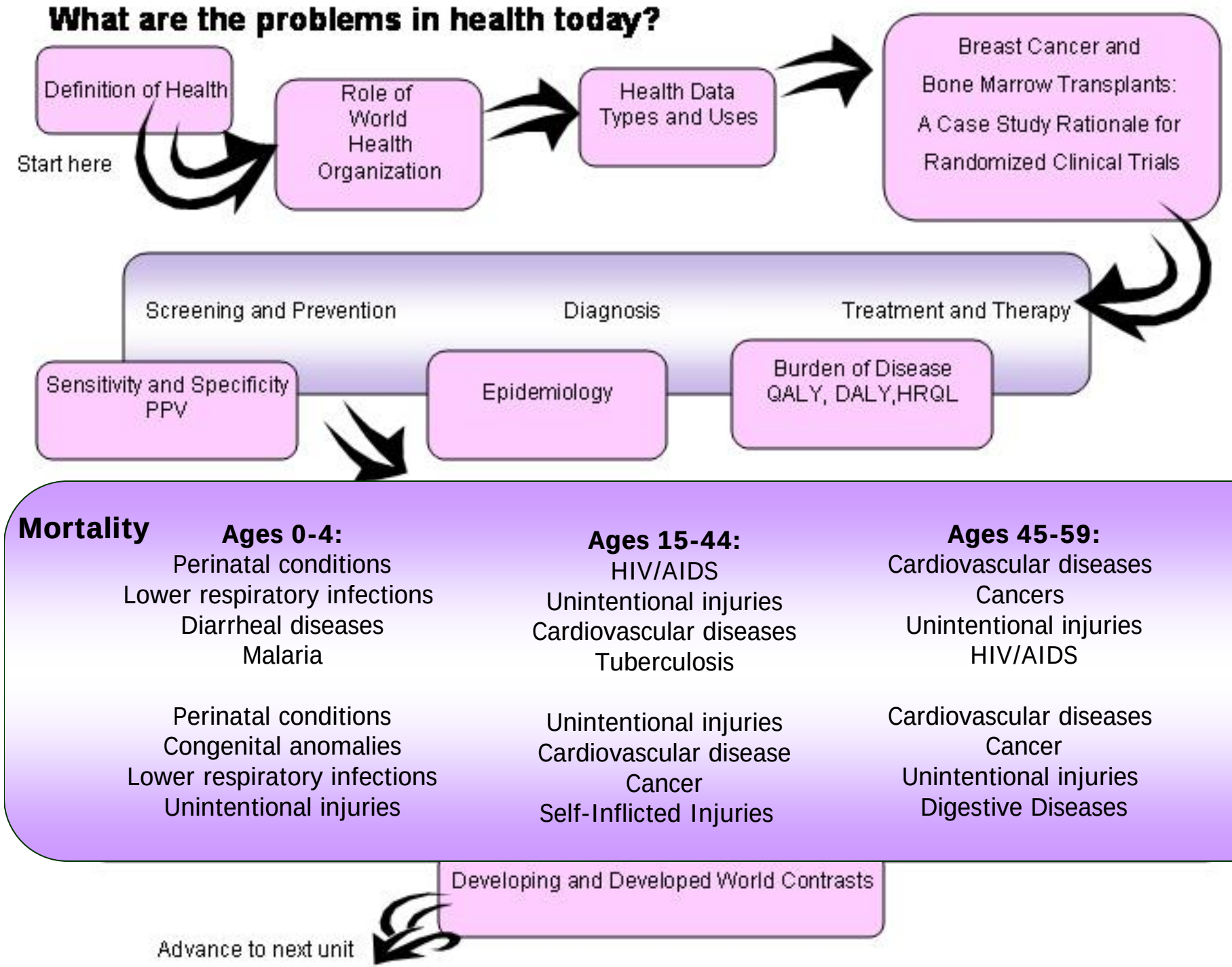
Abandoned due to:

- 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 the lab to the bedside?

- BIOE 301 Concept map


What are the problems in health today?
Definition of Health
Start here
Role of World Health Organization
Health Data Types and Uses
Breast Cancer and Bone Marrow Transplants: A Case Study Rationale for Randomized Clinical Trials
Screening and Prevention
Diagnosis
Treatment and Therapy
Sensitivity and Specificity PPV
Epidemiology
Burden of Disease QALY, DALY,HRQL
Mortality
Ages 0-4:
Perinatal conditions
Lower respiratory infections
Diarrheal diseases
Malaria
Perinatal conditions
Congenital anomalies
Lower respiratory infections
Unintentional injuries
Ages 15-44:
HIV/AIDS
Unintentional injuries
Cardiovascular diseases
Tuberculosis
Unintentional injuries
Cardiovascular disease
Cancer
Self-Inflicted Injuries
Ages 45-59:
Cardiovascular diseases
Cancers
Unintentional injuries
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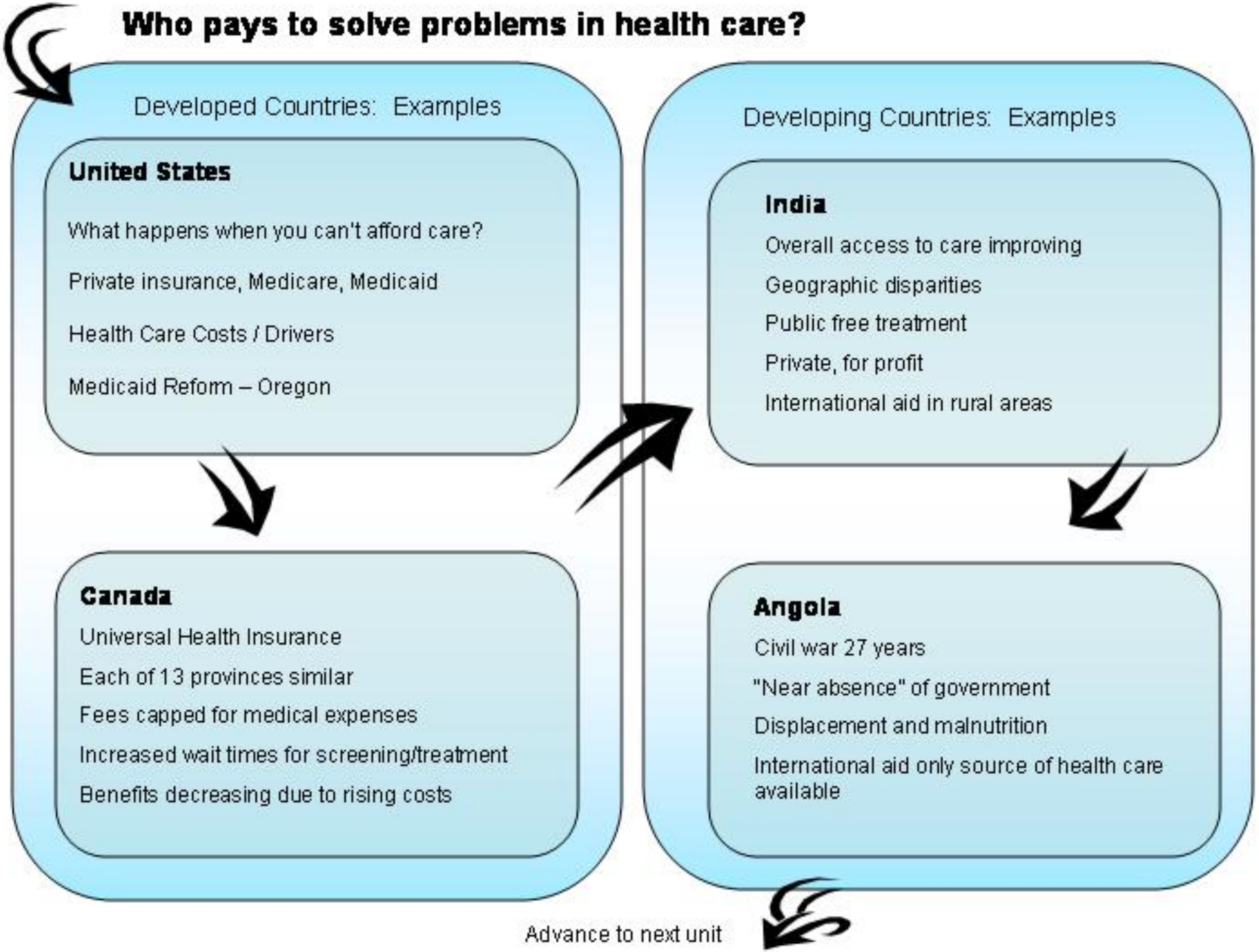
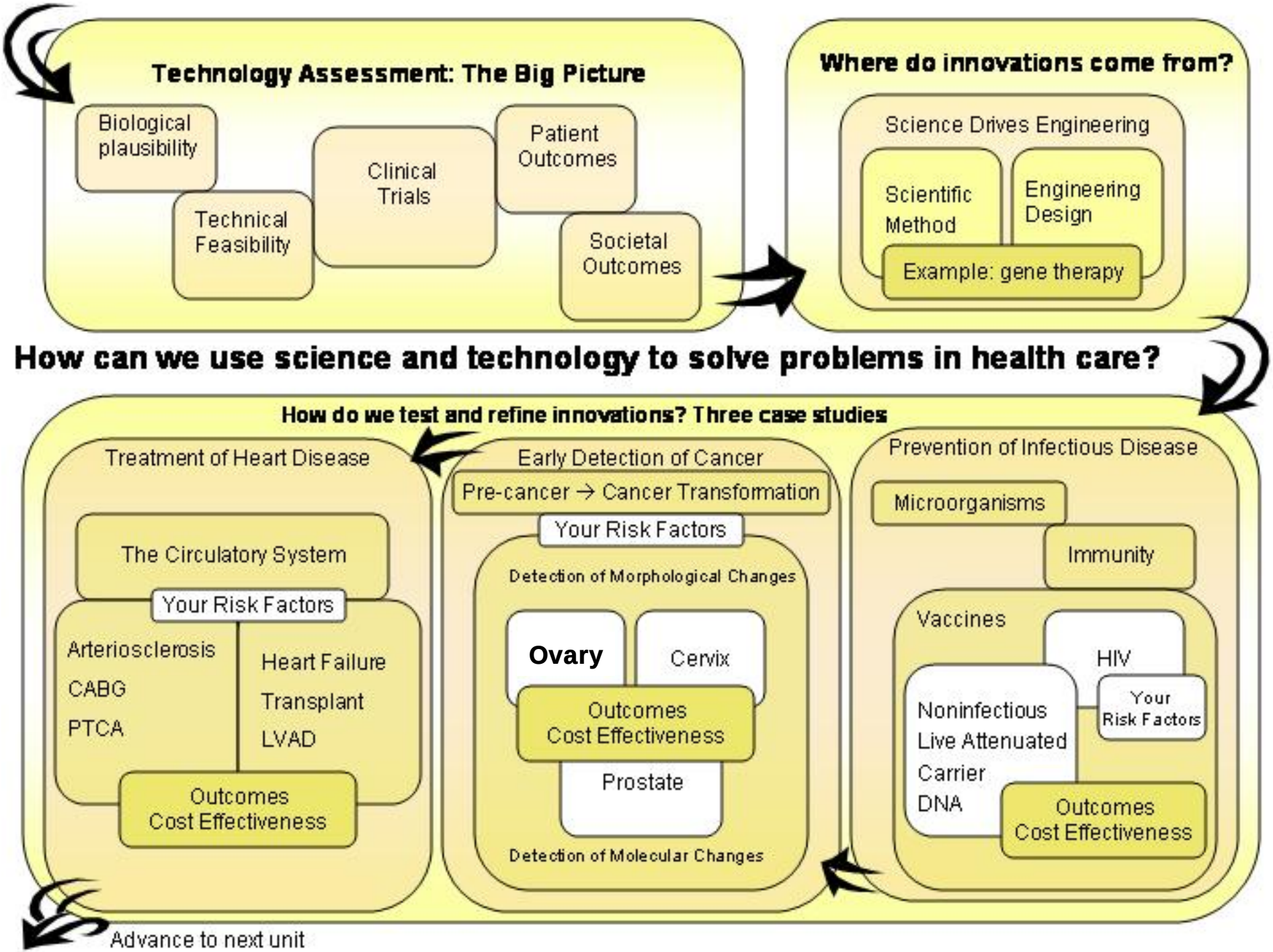
Cardiovascular diseases
Cancer
Unintentional injuries
Digestive Diseases
Developing and Developed World Contrasts
Advance to next unit


Who pays to solve problems in health care?
Developed Countries: Examples
United States
What happens when you can't afford care?
Private insurance, Medicare, Medicaid
Health Care Costs / Drivers
Medicaid Reform – Oregon
Canada
Universal Health Insurance
Each of 13 provinces similar
Fees capped for medical expenses
Increased wait times for screening/treatment
Benefits decreasing due to rising costs
Developing Countries: Examples
India
Overall access to care improving
Geographic disparities
Public free treatment
Private, for profit
International aid in rural areas
Angola
Civil war 27 years
"Near absence" of government
Displacement and malnutrition
International aid only source of health care available
Advance to next unit


Technology Assessment: The Big Picture
Biological plausibility
Technical Feasibility
Clinical Trials
Patient Outcomes
Societal Outcomes
Where do innovations come from?
Science Drives Engineering
Scientific Method
Engineering Design
Example: gene therapy
How can we use science and technology to solve problems in health care?
How do we test and refine innovations? Three case studies
Treatment of Heart Disease
The Circulatory System
Your Risk Factors
Arteriosclerosis
CABG
PTCA
Heart Failure
Transplant
LVAD
Outcomes
Cost Effectiveness
Early Detection of Cancer
Pre-cancer → Cancer Transformation
Your Risk Factors
Detection of Morphological Changes
Ovary
Cervix
Outcomes
Cost Effectiveness
Prostate
Detection of Molecular Changes
Prevention of Infectious Disease
Microorganisms
Immunity
Vaccines
HIV
Noninfectious
Live Attenuated
Carrier
DNA
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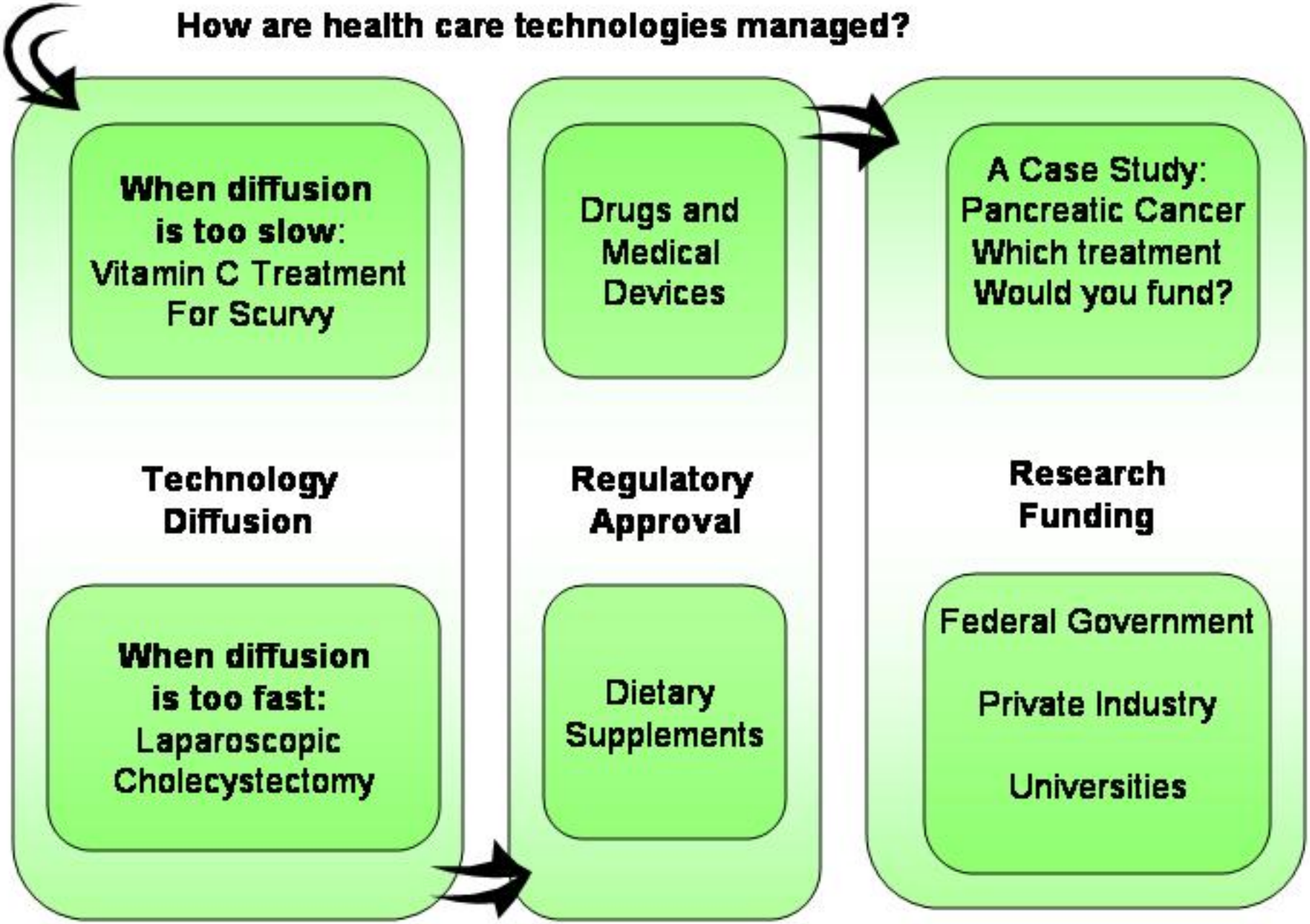

How are health care technologies managed?
When diffusion is too slow: Vitamin C Treatment For Scurvy
Technology Diffusion
When diffusion is too fast: Laparoscopic Cholecystectomy
Drugs and Medical Devices
Regulatory Approval
Dietary Supplements
A Case Study: Pancreatic Cancer Which treatment Would you fund?
Research Funding
Federal Government
Private Industry
Universities

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?

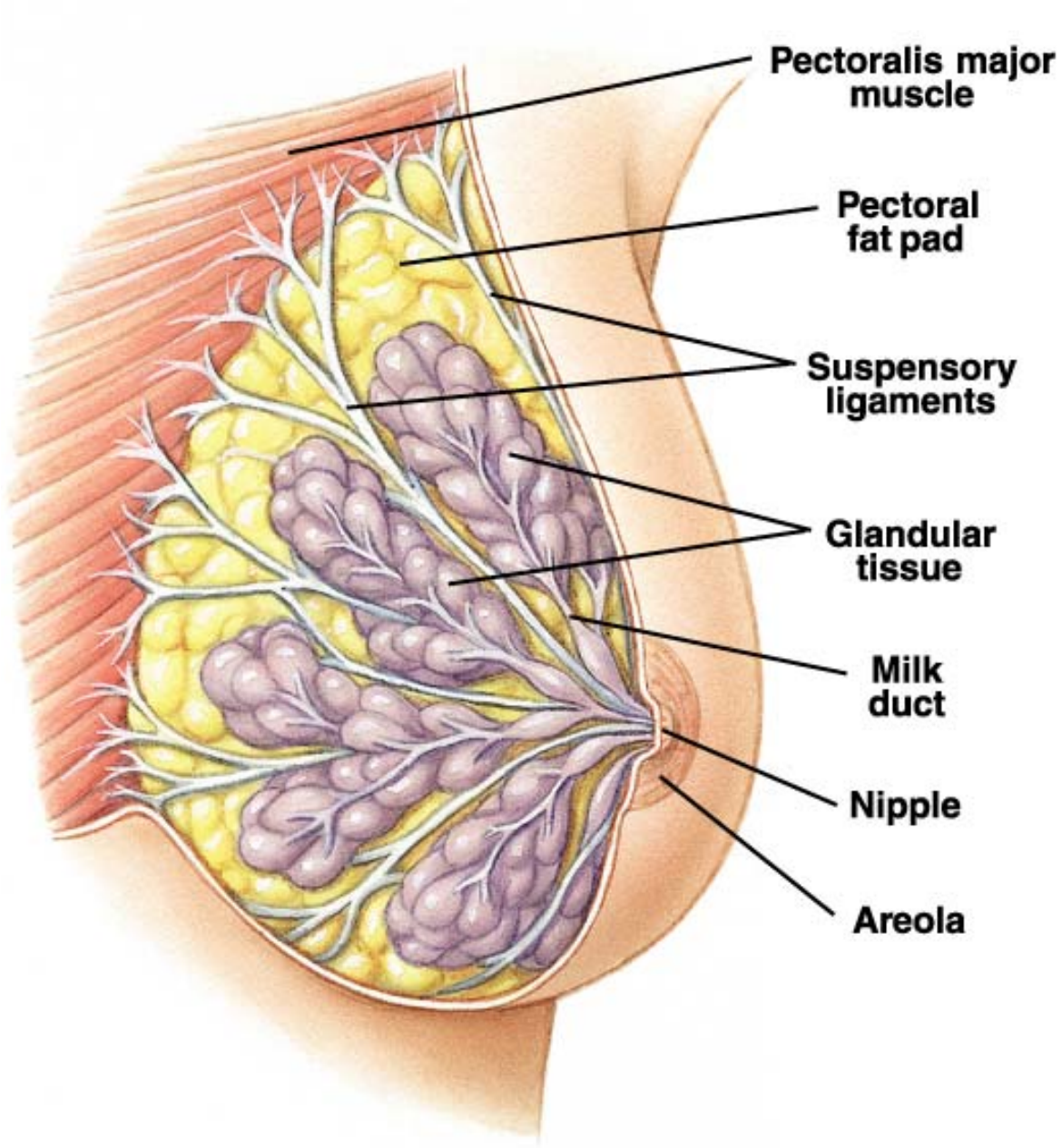
Technology Assessment: Overview

- 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

http://cwx.prenhall.com/bookbind/pubbooks/silverthorn2/medialib/Image_Bank/CH24/FG24_22a.jpg



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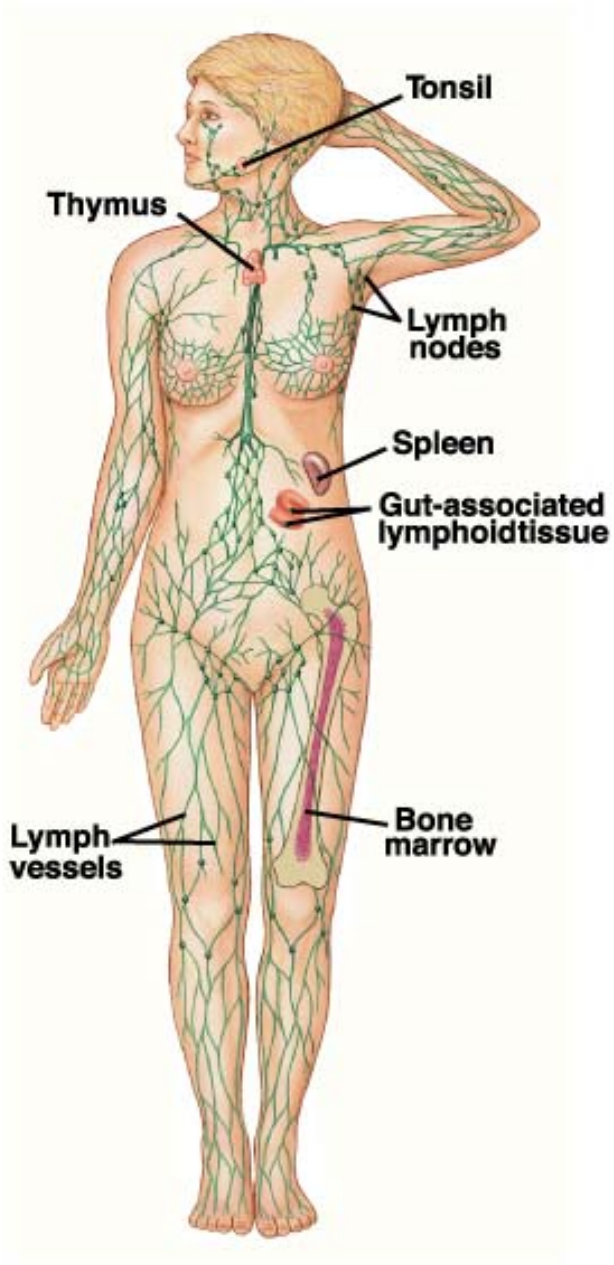


Breast Cancer Staging

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

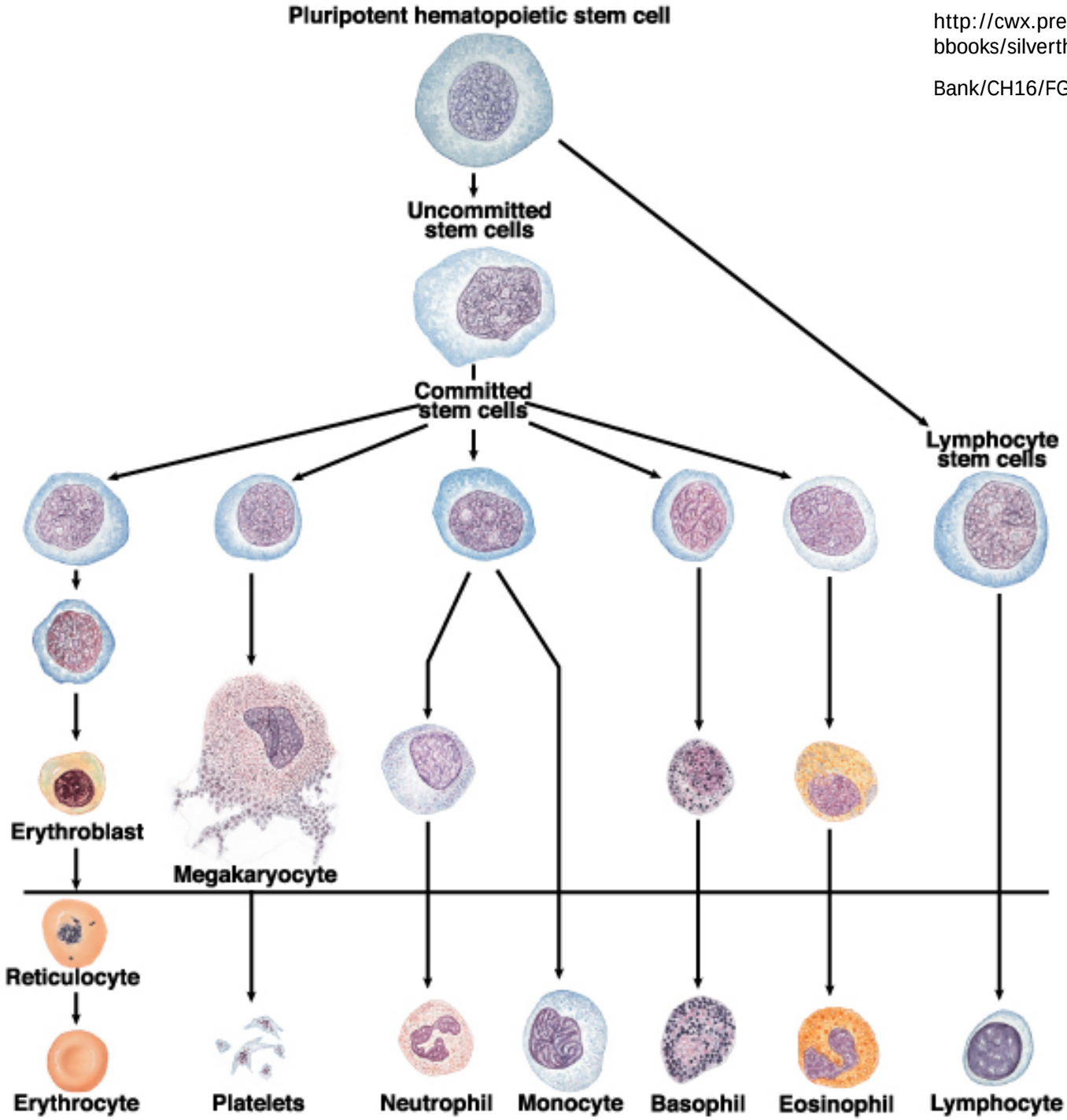
- How does it work?
  - Chemotherapy drugs given IV or by mouth
  - They travel through the bloodstream to reach cancer cells in most parts of the body
  - Interfere with ability of cell to divide
  - Cancer cells cannot repair damage caused by chemotherapy drugs so they die
  - Rapidly dividing normal 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

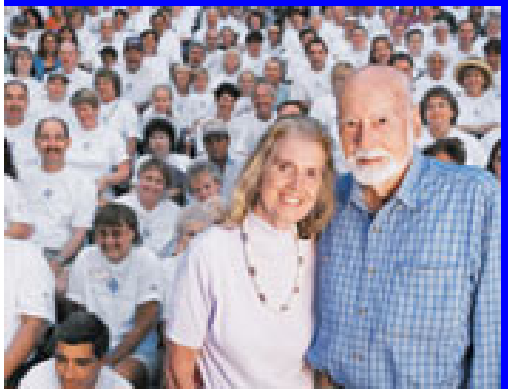
- Conceived in a dog kennel in Cooperstown, NY during the 1950s
  - RBCs could be successfully transfused from compatible donor to needy recipient
  - Marrow cells could not: Body identified them as foreign invaders and destroyed them
  - Hiroshima – one reason that radiation was so deadly because it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

PBSC Transplantation with Apheresis

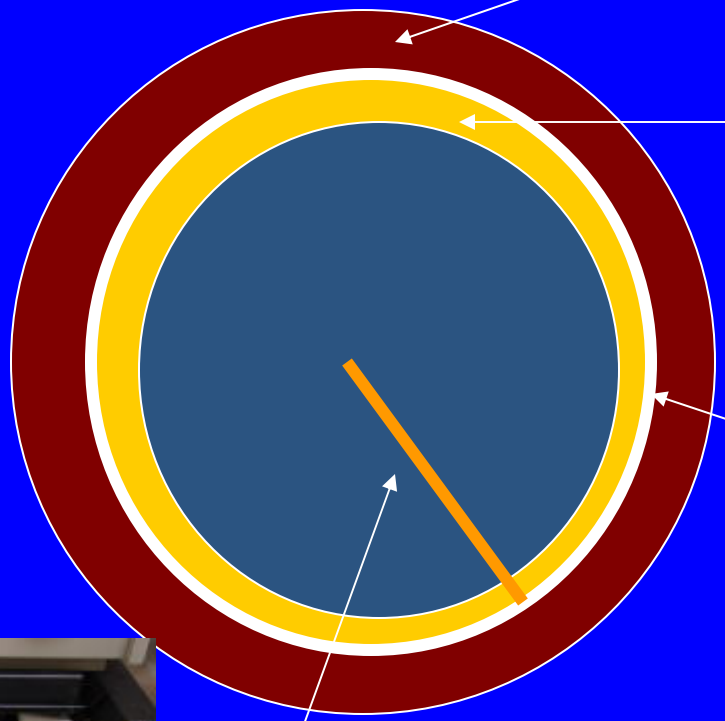
- Where are stem cells?
  - Most stem cells are found in the bone marrow,
  - Some, called peripheral blood stem cells (PBSCs), can be found in blood
- Apheresis:
  - Patient given medication to increase the # of stem cells released into the bloodstream
  - Blood is removed through a central venous catheter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

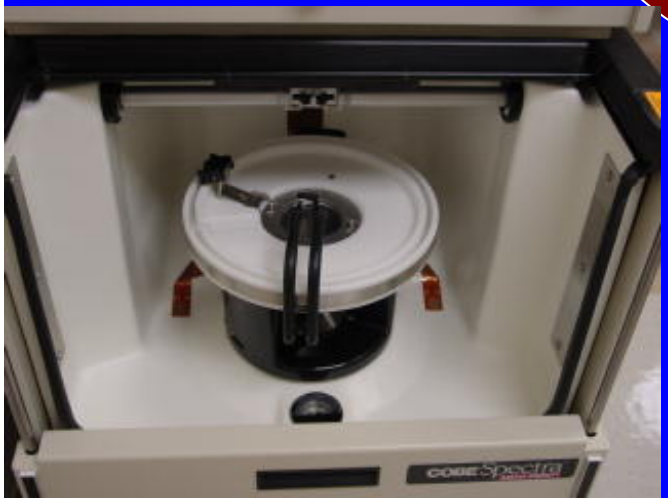
“The Equipment”

“The Centrifuge”

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

Blood components are separated by centrifugal force.



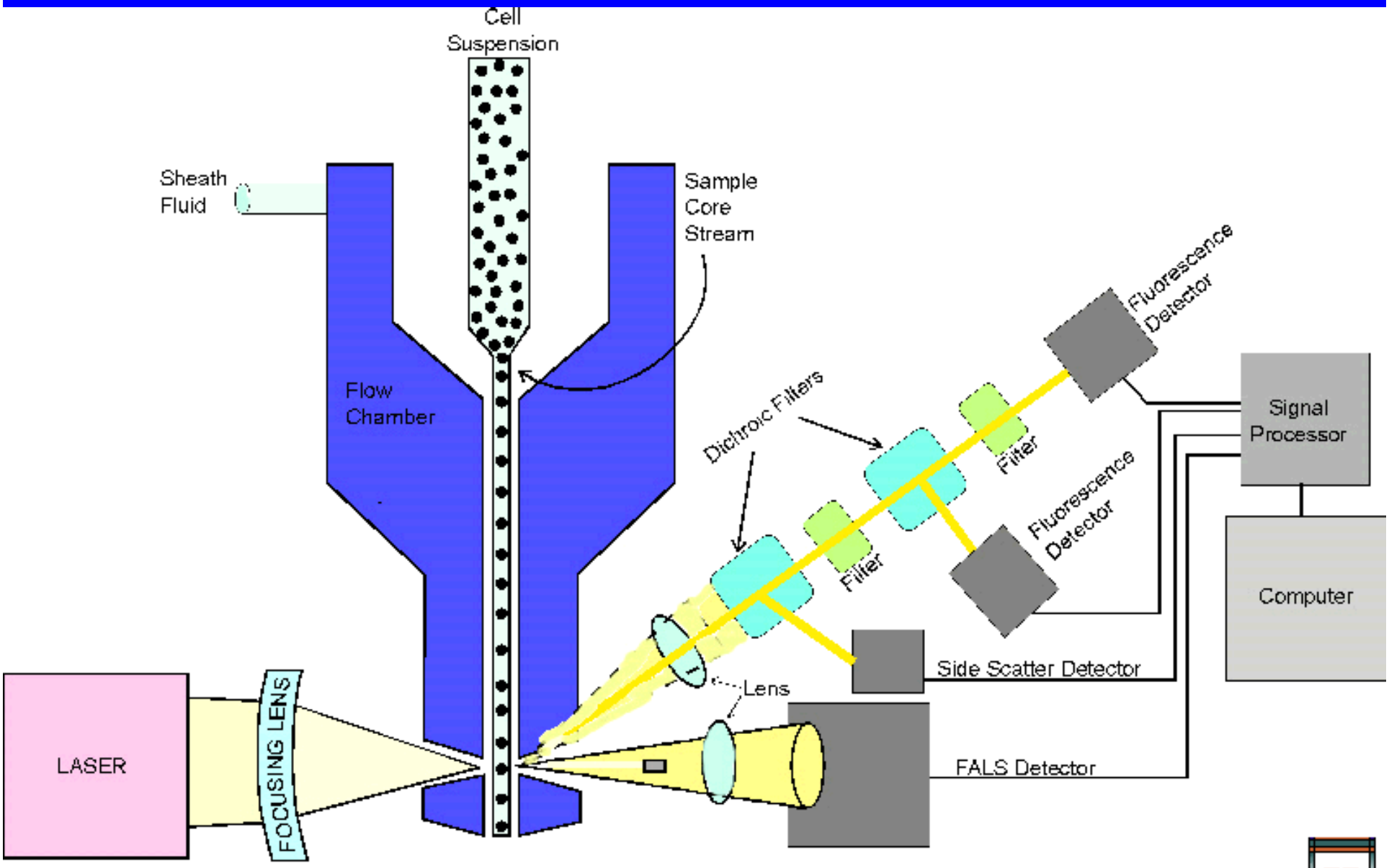


Identification of Stem Cells

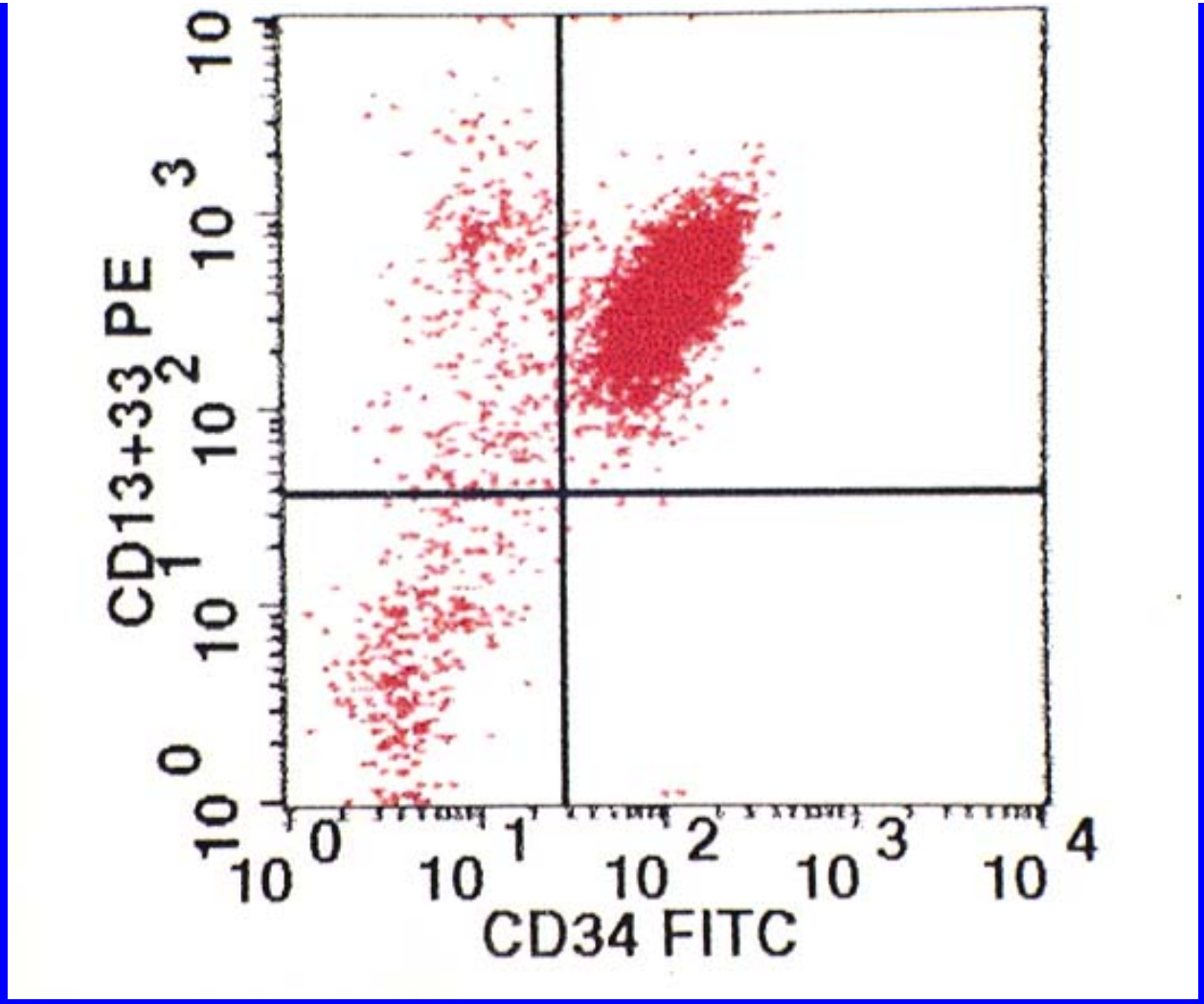
- Stem cells cannot be distinguished from other cells in the bone marrow using a simple microscope.

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



Schematic of flow cytometer instrument



Need 5 million stem cells/kg body weight.
0.1—1.0% of collected cells are peripheral blood stem cells.

Over 20L of blood must be processed.
The entire blood volume must be treated four times.

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 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

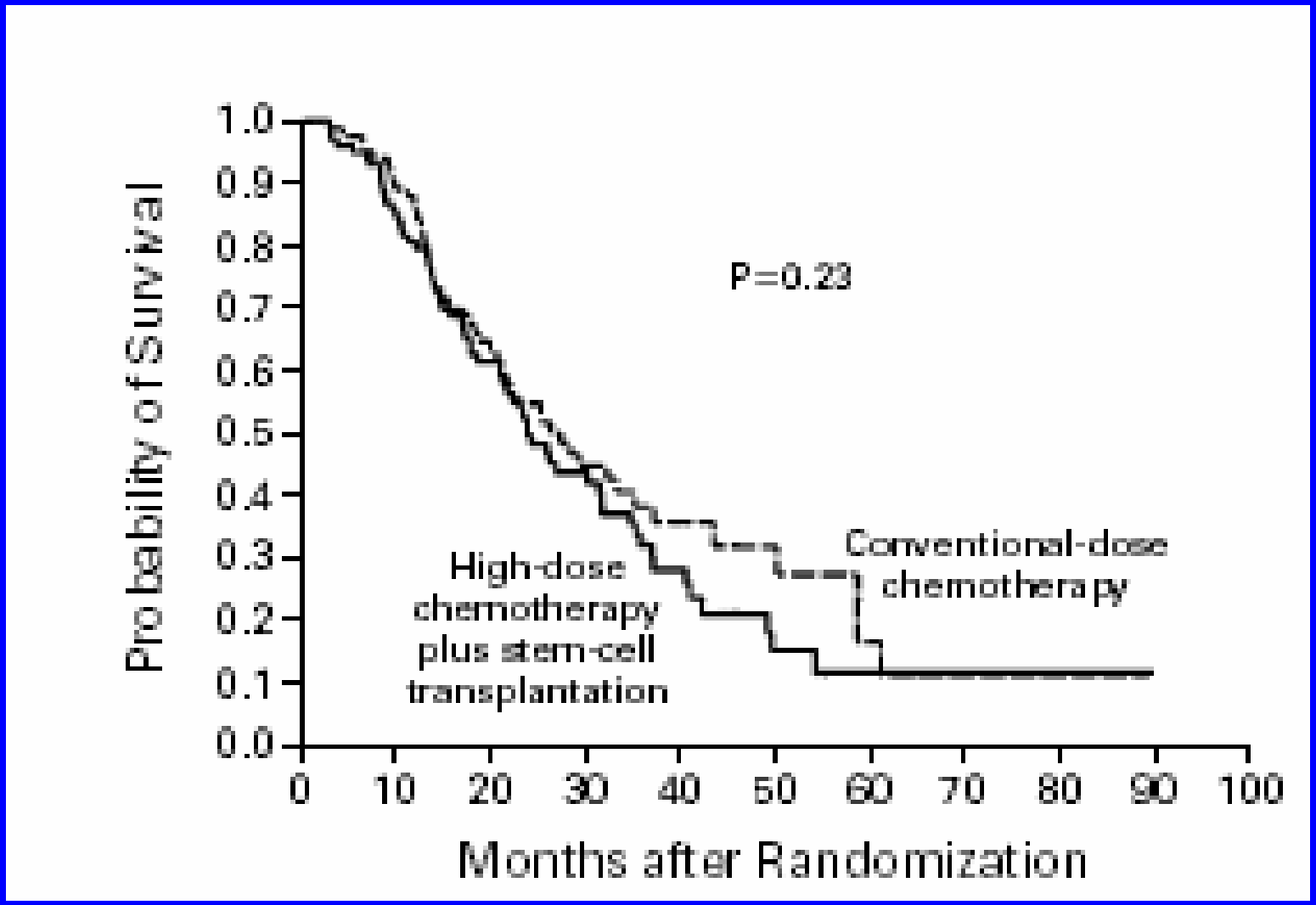
Insurance Coverage

- 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

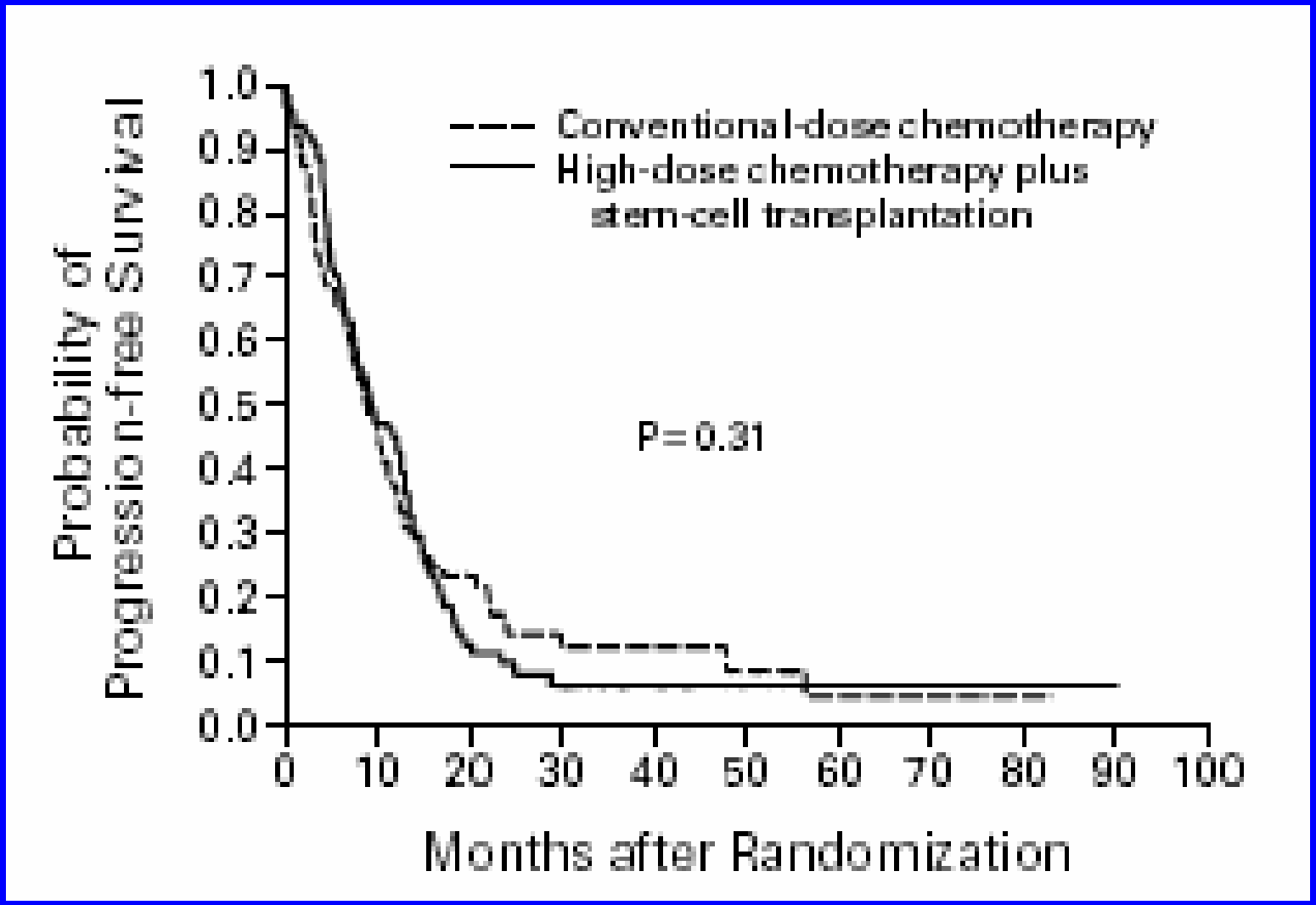
RCT Results

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


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
Conventional-dose chemotherapy
High-dose chemotherapy plus stem-cell transplantation
P=0.31
0
10
20
30
40
50
60
70
80
90
100
Months after Randomization

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

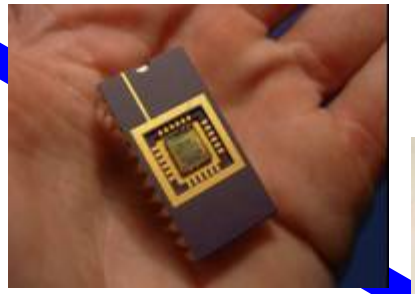
- Biological Plausibility
  - Does the biology support the technology?
- Technical Feasibility
  - Safely and reliably deliver technology to patients?
- Clinical Trials
  - Sensitivity & specificity in a relevant population?
  - Disease-free survival & 5-year survival in a relevant population?
- Patient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



Preclinical 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

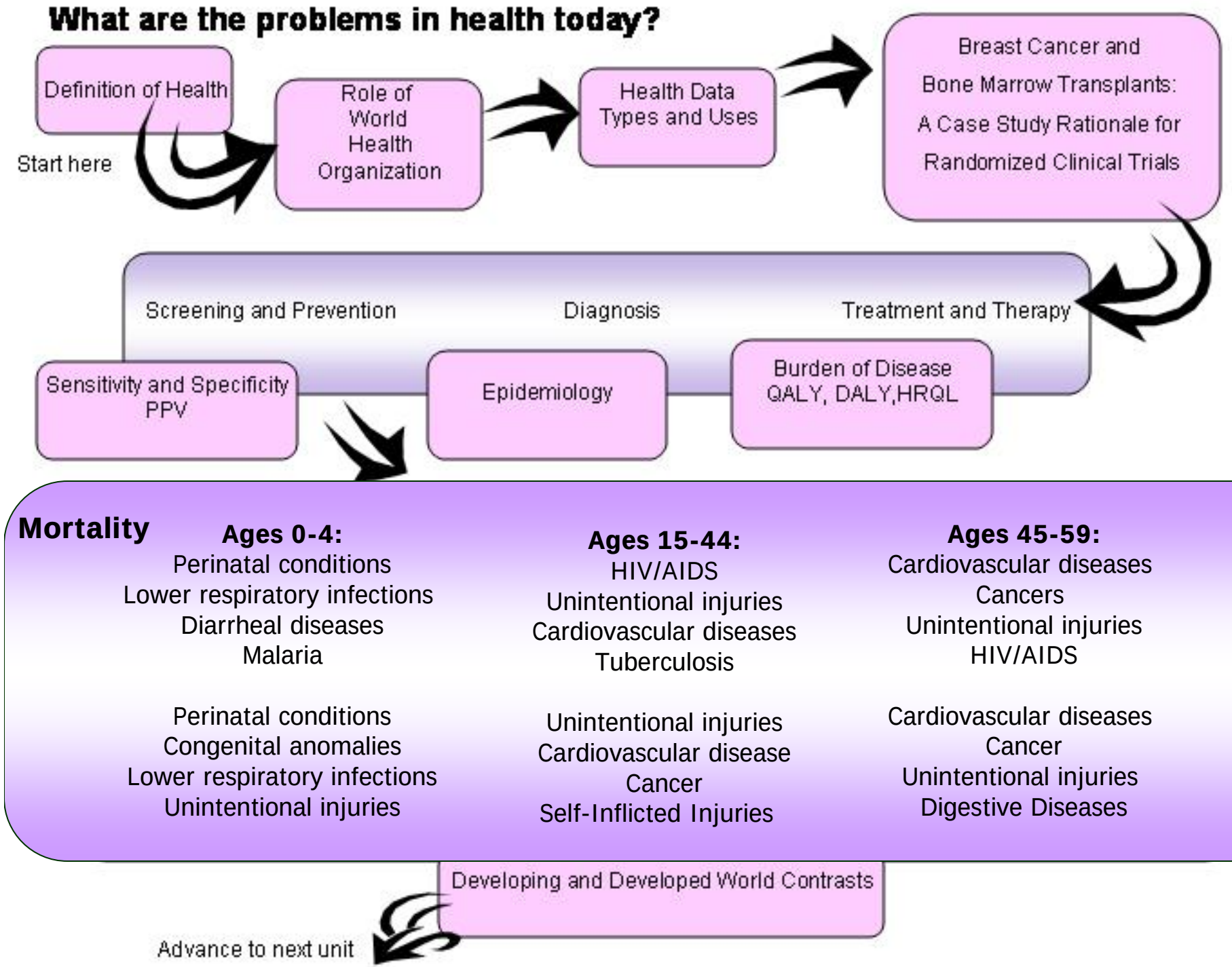
What are the dangers of allowing political pressures to overwhelm science?

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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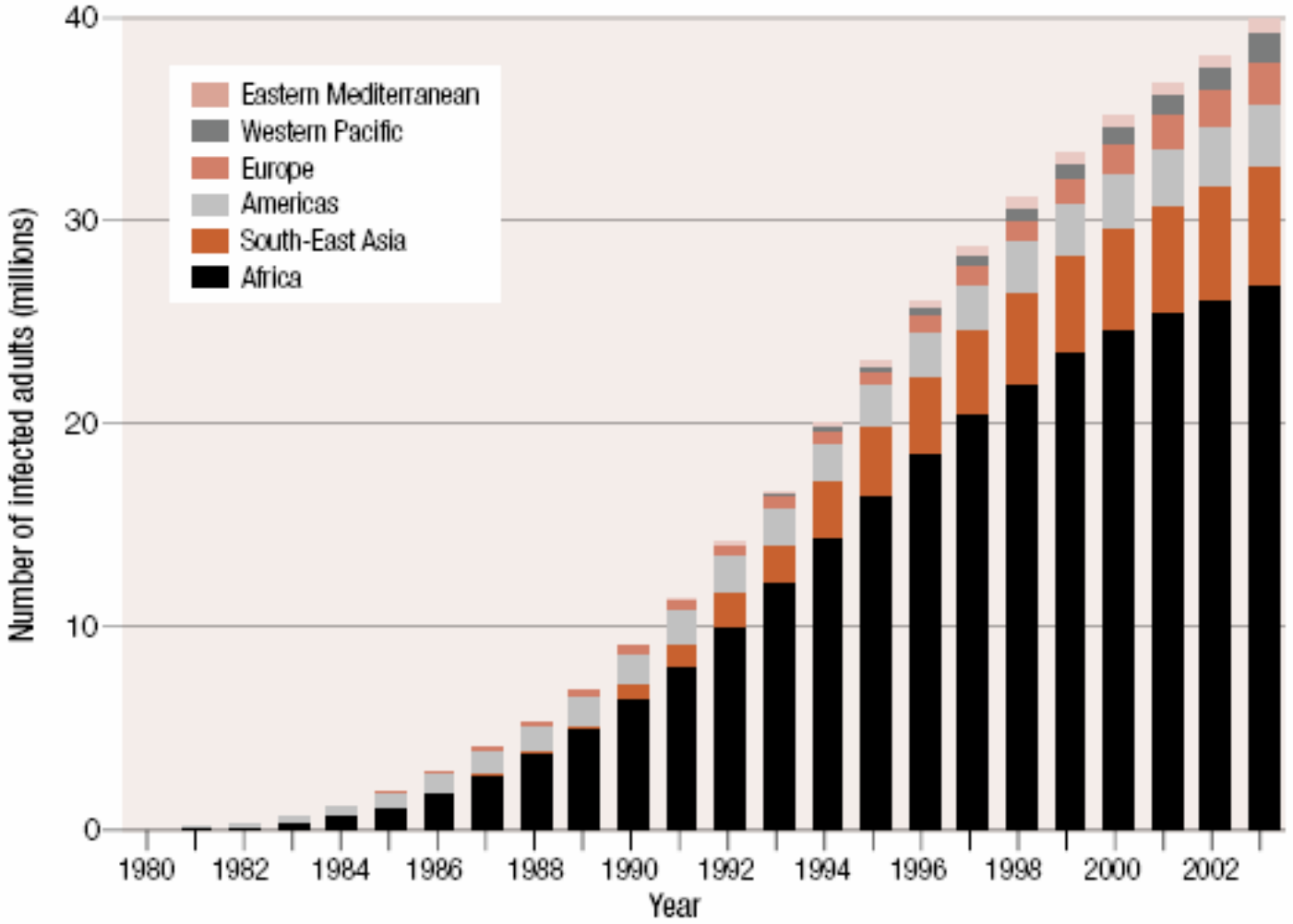
Advance to next unit

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

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

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

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

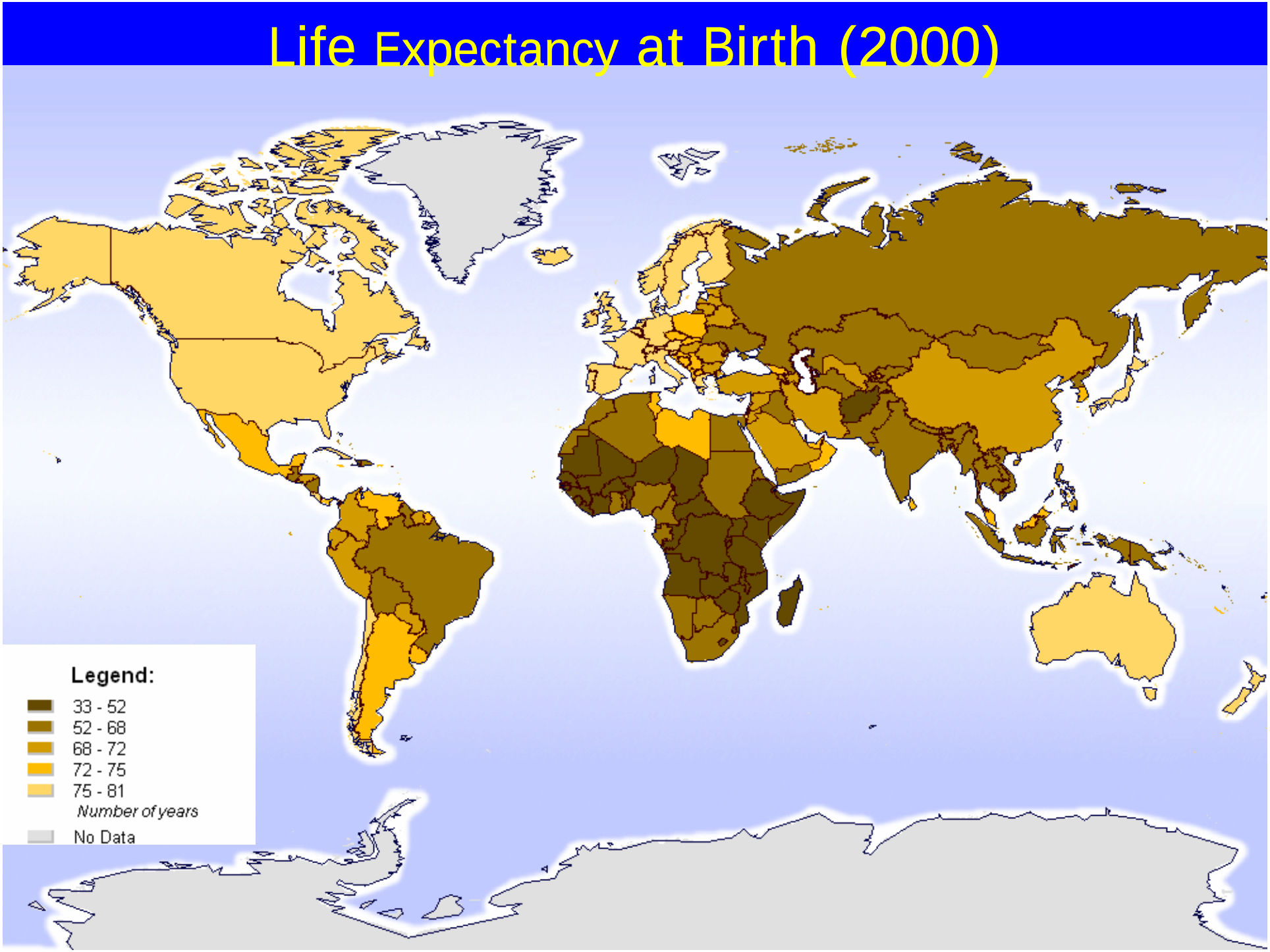
Burden of disease

- 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

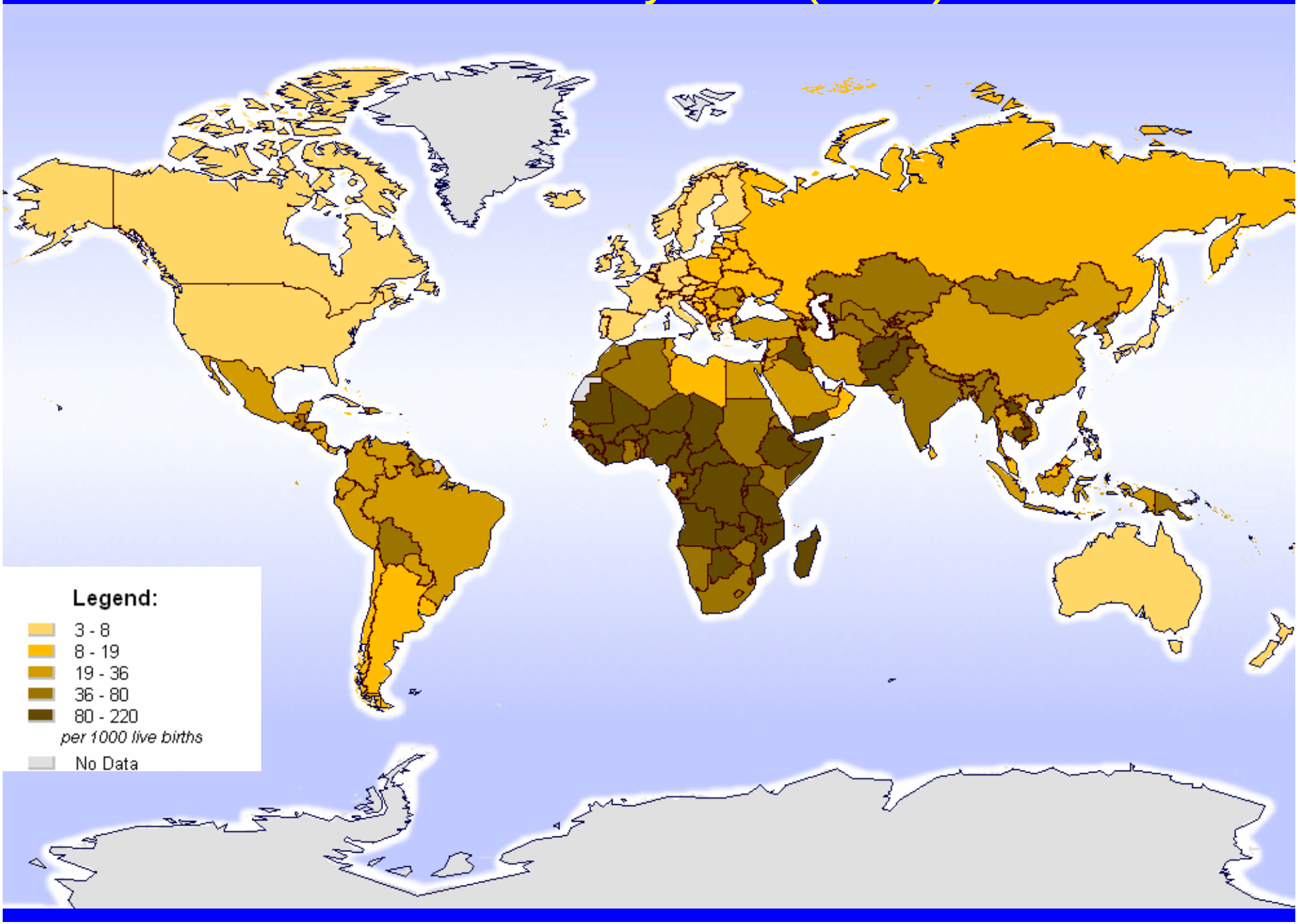
The study of global health

- 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

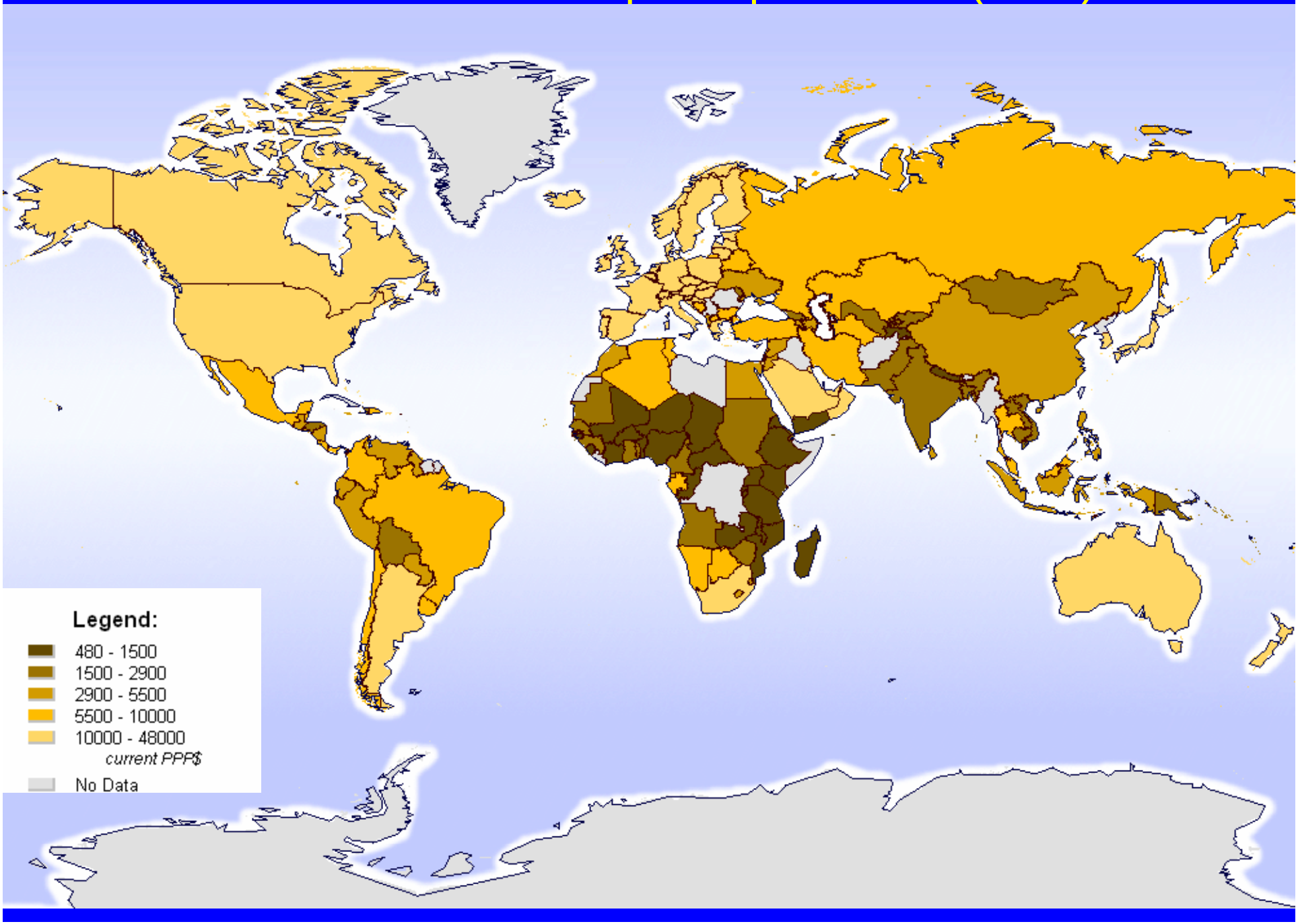
Life Expectancy at Birth (2000)



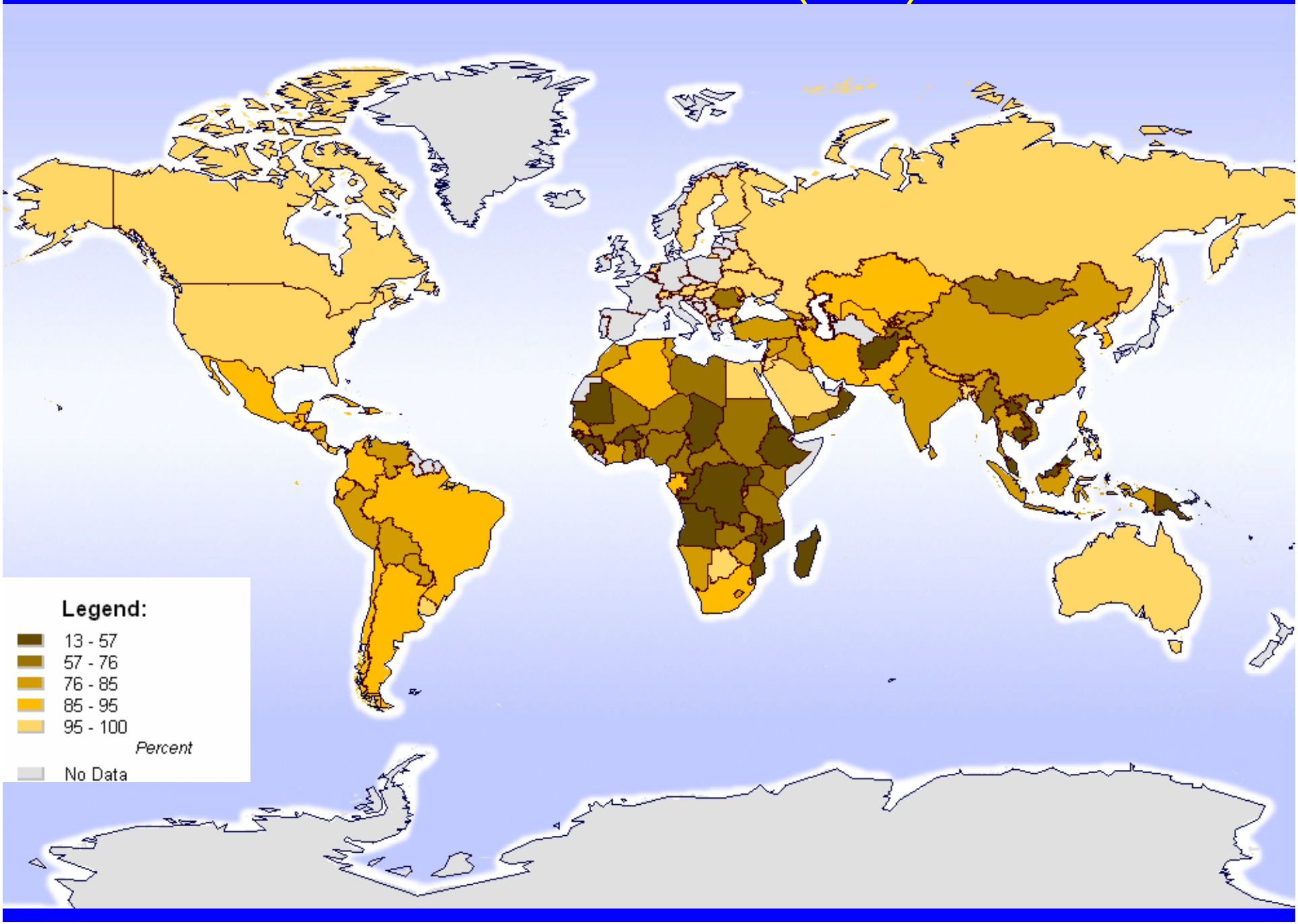
Infant Mortality Rate (2002)



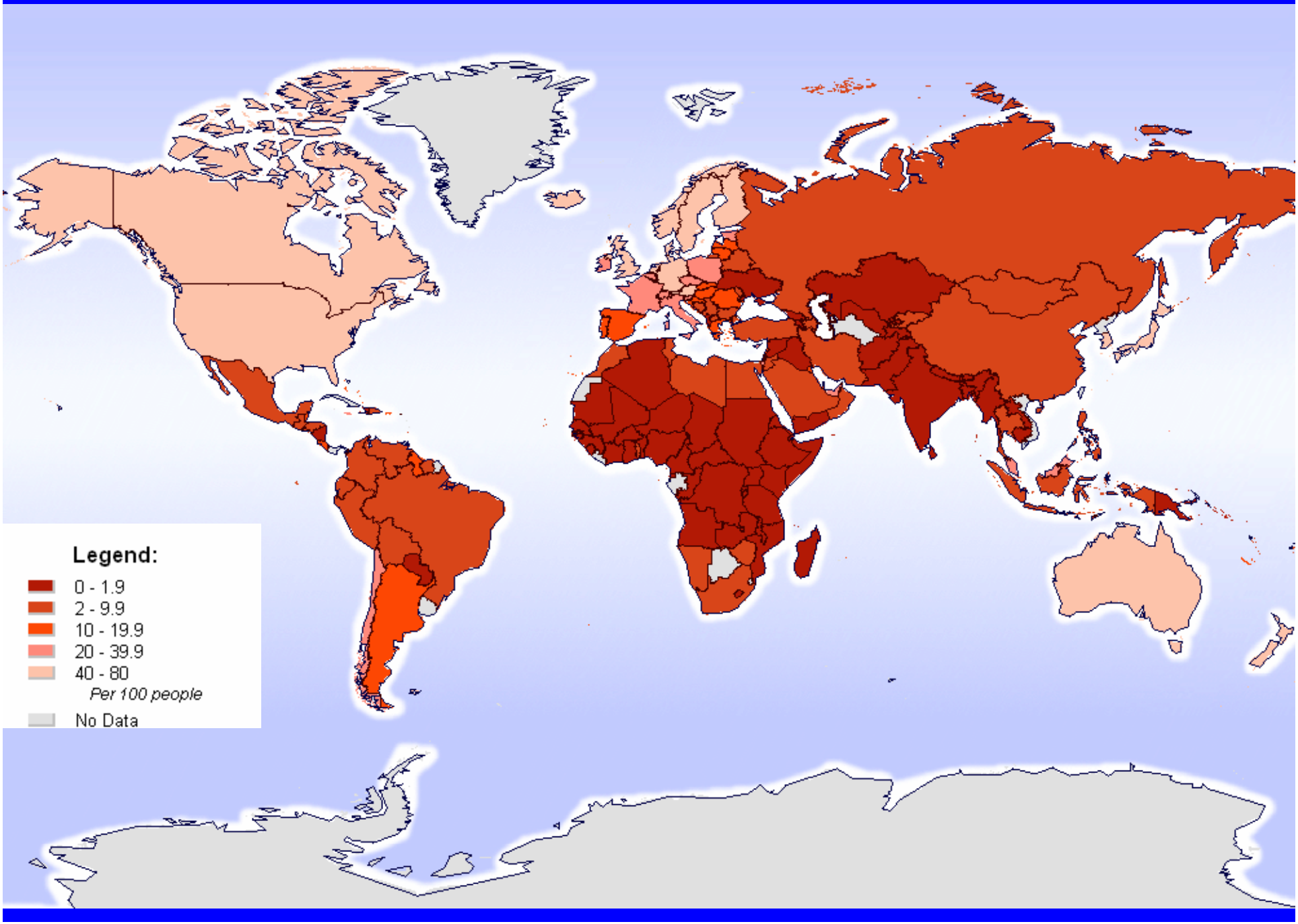
Gross National Income per Capita at PPP (2001)



Access to Safe Water (2000)



Internet Users (2002)



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?