

BREAST CANCER 101


The Evolution of the Science of Breast Cancer
California Breast Cancer Research Program Symposium
Los Angeles 2007
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We Are in a time of transition...

- From an understanding of breast cancer based on size, appearance and sampling to an understanding based on the biochemical "tools" available to the cancer cell.


The Big Bang




- 20 billion years ago, an explosion filled all of space at temperature of 100,000,000,000 degrees Celsius.
- Not even atoms could hold together.
- As the universe cooled, matter condensed into protons and neutrons, which attracted electrons.
- Atoms were born.
- We are all stardust.

Early Medicine & Breast Cancer

- Hippocrates described breast cancer in about 5000 B.C.
- Breast cancer described in ancient Egypt (3000 B.C.).
- Galen (200 A.D.) first suggested mastectomy even while theorizing that breast cancer is a localized manifestation of a systemic disease.




The Dark Ages Really Were



- From the fall of the Roman Empire to the Renaissance, there was virtually no medical progress because anatomic dissection was banned. Surgery was stalled as a discipline and breast cancer viewed as basically untreatable.

Vesalius



- Andreas Vesalius (1514-1564) was a surgeon who began the study of scientific anatomy based on dissection and observation. He operated on breast cancer, using suture ligation of vessels and other careful techniques. The first node dissection was done by Severino in about 1600.

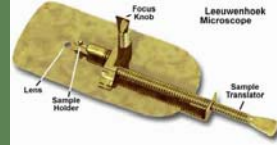
Breast Cancer in Art

- Rembrandt's painting of his mistress, Hendrickje Stoffels, in "Bathsheba at Her Bath," showing locally advanced left breast cancer. Painted in 1654 AD; she died in 1663.



The First Microscope

- Anton van Leeuwenhoek was a lens maker and shopkeeper. His 2mm round glass lens gave 50X to 200X resolution. The stage was set in the 1670s for pathology and for genetic study to begin in earnest.



Theoretical Basis for Local Therapy



- Francois Le Dran wrote in 1757 that since palpable nodes indicated a worse prognosis, the disease must spread to the regional lymphatics first.
- At its earliest stage then, it could be cured by surgery, which was in an early stage of development, and careful technique was not widely available to the public. No anesthesia yet.

Key Parallel Progress

- Rudolf Virchow (1821-1902) established the field of surgical pathology. He also showed that malignant cells evolved from normal cells. Shortly thereafter the special role of epithelial cells in cancer was established.
- General anesthesia was introduced in 1846.
- Antisepsis first described in 1867. Halsted brought it to America 20 years later.
- There was finally at least one pathologist in every US state by the 1950s.

Early Surgery for Breast Cancer



- Halsted was influenced by the theory that cancer remained an orderly regional process until late.
- Began to perform the radical mastectomy in 1882, reporting results in 1898.

Aggressive Local Therapy

- Cure became possible, and even probable, if surgery performed early.
- Women were presenting earlier for care.
- Low intraoperative complication rate.
- BUT, progress in long term mortality stalled.
- 23% of women with negative nodes on microscopy eventually died of metastatic disease.
- There had to be more to the cure than more and more aggressive surgery.

Some Principles of Applied Medical Science

- It is not necessary to notice how something works to see that it works. The explanation of the mechanisms will come later.
- The explanation will come from the basic sciences, and it will lead to more progress.
- With every step of progress, more chaos will result, at least temporarily, as the new knowledge is absorbed and translated into patient care.

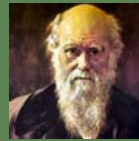
The Cell is a complex and beautiful biological machine

- Tumor cells use the same materials and principles as normal cells.
- They are not alien invaders, but part of us.
- But they care more about themselves and their proliferative advantage, rather than about signals from their community.

How did we begin to understand the cell?

Where is the cell controlled?
Primarily within itself, building, dividing and aggregating based on signals from outside the cell.

Genetics, Mutations & Natural Selection

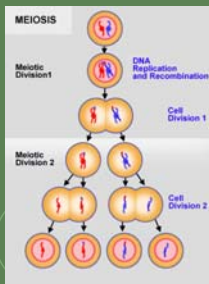


- Charles Darwin published "Origin of the Species" in 1859.
- At about the same time, Gregor Mendel was counting pea seeds, and postulating the abstract concept of genes.



- DNA was isolated as a chemical, but the significance was not known. It was "nucleic acid." 50 years later it was noted that it was in all cells, associated with the chromosomes.

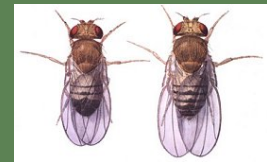
Microscopy Meets Genetics



- In the early 1900s Sutton observed cell division in grasshopper sperm, and made the link between the behavior of the chromosomes and the sorting of traits noted by Mendel. He proposed that genes are carried on chromosomes, but genes were still an abstract concept.

Fruit Flies

- Shortly thereafter, Thomas Hunt Morgan began his work with fruit flies. He described linkage of genes, recombination of genetic material, and began to map the chromosome. Abnormalities in chromosome structure corresponded to different genetic outcomes.



Radiation Arrives

- X-rays were discovered in 1896 and the first breast cancer treatment by radiation was attempted the next year!
- In 1906, it was already recognized that rapidly dividing cells were more susceptible to radiation.
- Dose fractionation first tried in 1919. Local recurrences were the target. The scientific rationale behind it wasn't explained until the 1960s.
- Brachytherapy was first attempted in 1922.
- Radiation was proposed as an alternative to the radical mastectomy in the late 1930s, but radical mastectomy remained the norm instead.

The application of genetics to everyday medicine was still unclear.



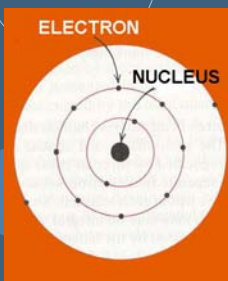
The Beginnings of Systemic Therapy

- In the late 1800s oophorectomy was introduced as an experimental therapy for premenopausal breast cancer patients, in an attempt to make them "a little bit older" since it was observed that postmenopausal women did better overall.
- Staging was introduced in the 1940s in order to identify those patients for whom radical surgery was not indicated. It was not widely used until the 1950s in the USA. Good outcome data not kept until the 1970s and 1980s.
- Treatment for prostate cancer revived interest in endocrine surgery for breast cancer.
- The estrogen and progesterone receptors were not described until the 1970s.

Applied Medical Science

- It worked, but no one really knew how or why.
- There were no controlled trials to try to look at risk and benefit.
- Physics held the key, and was progressing at about the same time.

Atomic Model



- Atoms can be viewed most simply as differing only in the number of positive and negative charges.
- (Handout Page 2)
- Atoms associate to share electrons to fill their outer shells, and thereby form molecules.

Bonds

- In a covalent bond, atoms share electrons with other atoms. This is a strong bond.
- Each electron in the bond shares its time between the atoms involved in the bond.
- Depending on how many protons are in the respective atoms, the sharing is not equal. The atoms that have greater pull have a slightly negative charge, while the other atom in the bond is slightly positive. These can attract each other in a weak bond.
- In living organisms, carbon is crucial. It can share the 4 electrons in its outer shell with as many as 4 other atoms. Usually H, O, N or C.

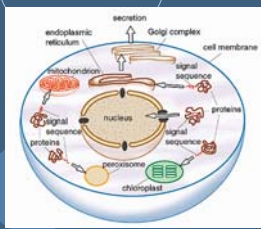
Chemical Reactions

- Are just exchanges of electrons among atoms.
- The exchange can result in combinations or dissociations of associated atoms (molecules).
- 6 elements make up 99+% of all living matter. H,C,N,O,P,S are small and can form stable bonds.
- Living things and non-living things are made of the same components and obey the same laws.

Free Radicals

- "Oxidation" is a process by which an atom or molecule loses one or more electrons.
- It then has powerful potential to steal an electron from another stable more important molecule, disrupting it.
- In large numbers, these "free radicals" threaten essential molecules like DNA. "Antioxidants" can afford to give up one or more electrons to a free radical to stabilize it before it can do damage to other molecules.

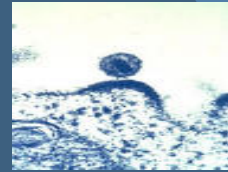
Cell Structure



- Started with light microscopy and refined with biochemical techniques and electron microscope.
- Handout Page 3

Medicine Stalls; Basic Science Accelerates

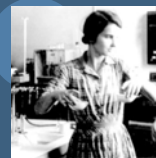
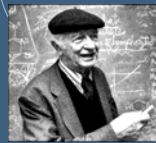
- Fundamental rules of "classical genetics" for all organisms known by 1950s. Still no one knew what a gene really is, beyond the concept.
- Malignant transformation of cells in culture by viruses observed.



Chromosomes

- Equal amounts of DNA and protein found in nucleus. Initially felt the genes had to be proteins. DNA, with only 4 types of nucleotides found on chemical analysis, was thought to be too simple. (Handout page 4)
- Interest in DNA limited to a single biochemist's lab (P.A. Levene) in 1920s.
- The transformation of cells by viruses called attention to the probability that DNA was actually the source of genes (1952).

The Double Helix is Found

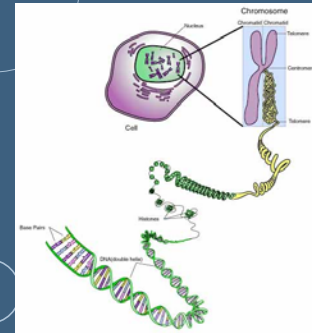


- The DNA molecule known to be long and thin and composed of 4 nucleotides that repeated.
- Linus Pauling had shown that long molecules became curly because of attraction and bonding inside the molecule.
- X-ray diffraction experiments by Rosalind Franklin showed that the structure was a helix.
- The stage was set for Watson and Crick to triumph in 1953, along with Wilkens.

To prove DNA contains genes:

- Must carry genetic information from parent cell to daughter cell, generation to generation, and must carry a lot of information
- Must contain information to copy itself with every cell division, and with great precision
- It must be chemically stable so offspring resemble parents
- It must be capable of mutation, and of copying mutations, or there would be no genetic variation, and no natural selection

Transcription



By early 1950s, we knew

- DNA molecule is very long and very thin
- Only 4 bases
- Only 2 combinations of the 4 bases (but in different order)
- Amount of A (adenine) equals amount of T (thymine), and amount of G (guanine) equals the amount of C (cytosine)
- Molecules curled up. Each is 3-4 cm long. Each cell has 46 chromosomes (so about 2 meters of DNA). Human body has about 25 billion kilometers of DNA double helix

All Cells Initially Contain the Same Blueprint

- We all start as a single cell, and eventually have about ten thousand billion.
- Early embryonic cells are all the same, but then begin to differentiate, consulting different parts of their genome.

Genes in DNA are a blend from both parents

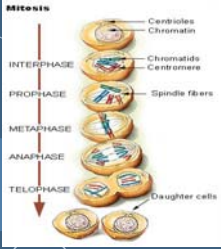
- There are "punctuation marks" in the DNA to show where a gene starts and ends.
- Normal cells have genes to program normal growth and tumor cells have lost this control.

DNA Replication

- Copies made in preparation for cell division.
- Handout page 4

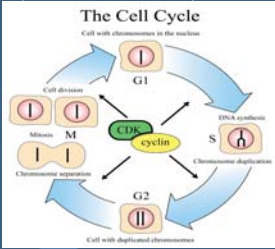


Cell Division



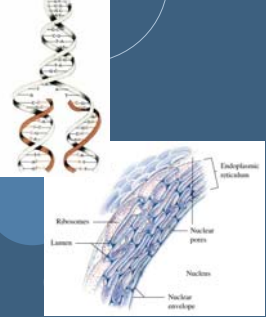
- Equal copies of DNA distributed to both cells.

The Cell Cycle



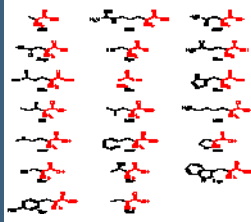
- The mature cell rests, grows, and maintains itself until signaled to divide (G zero and G1).
- When signaled, the DNA copies itself.
- DNA is also used to make other cell components.
- The cells split.
- Proof-reading occurs when the DNA is replicated, and other enzymes monitor DNA integrity throughout the cell's life.
- The DNA is most vulnerable in S and G2.

Protein Synthesis



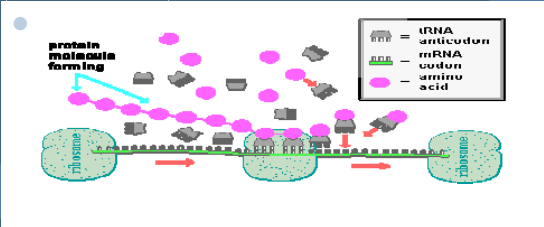
- The segment of DNA is opened, and a pattern made.
- The pattern, called a "messenger" goes out of the nucleus to the endoplasmic reticulum and attaches to a ribosome. Handout page 6A.
- Base pairs read 3 at a time.

Amino Acids



- There are only 20. (Biochemistry is easy).
- They are strung together in different sequences and in different lengths to make all the structural and signaling proteins of living things.
- Their individual structures lead to folding of the protein due to kinks in their structure, and also attractions and interactions between atoms in a long string.
- This folding can create nooks and crannies to form a receptor site.

Protein Synthesis



Proteins

- Used for structure
- Hormones are proteins used for signaling (see Handout page 7)
- Proteins in the cell membrane or nuclear membrane receive and transmit signals (receptors), and transport other molecules inside and outside the cell
- Nooks and crannies formed by the folding of the protein are the receptor regions, and the protein changes shape when it associates another molecule (Handout page 5 at bottom)
- Association can be strong or weak

The Carcinogen-Mutagen Theory

- While all of this was being discovered, epidemiologists were hard at work finding out how environment, behavior and other factors influence the rates of cancer in a population.
- Incidence of cancer rose with the control of infectious disease and improvement in nutrition.
- Some cancers could be tied to particular experiences, such as sweeping chimneys, mining, exposure to radium, and smoking.
- Maybe external factors played a role, just as they did in infectious diseases where bacteria and viruses caused disease.

Carcinogen-Mutagen (con't)

- Carcinogens killed cells though, and cancer consisted of too many cells. This seemed contradictory.
- X-rays and certain chemicals were found to induce genetic changes in fruit flies.
- The concept of "mutation" was born in the 1950s. Some mutations were clearly lethal, and some allowed the damaged cell to live.
- After the structure of DNA was described, mutations were seen as chemical structural problems. It looked like finding these changes would be simple.

Finding the Cause

- Viruses were already known to change bacterial cells by inserting their DNA. Maybe they also caused damage to human cells.
- Virus could tamper with cell's growth control mechanism, forcing proliferation.
- Chemicals were also known to cause cancer though, and pattern of cancer incidence did not appear to be infectious.



Oncogenes

- Both the chemical hypothesis and the viral hypothesis agreed that a small set of genes could cause a cell and its descendants to grow without limits.
- The concept of "oncogene" was born, even if they could not agree how it happened.

The Wars Before the War on Breast Cancer

- Technology from WWII resulted in cobalt's availability as a substitute for the very expensive radium.
- Chemical warfare resulted in interest in basic biochemical mechanisms and provided potential agents for therapy.
- Surgeons returned from war filled with enthusiasm and bravado. This was both good and bad.

Medical Theories of Cancer

- Breast cancer spreads in a centrifugal manner. Early diagnosis and treatment aimed at local and regional control of the disease is paramount.
- Biological determinism is more important than prompt treatment. The tumor is what it is from the earliest stage. (In retrospect, "biological variability" between tumors and over time would have been a better term).

The Randomized Clinical Trial Comes to Medicine

- The NCI was established in 1937, but primarily for epidemiology.
- As late as the 1960s the ethics of RCT were challenged—by the American Cancer Society! Treatment advances were based on retrospective series of surgical results.
- Mammography came into widespread use in the 1970s as it fit the “orderly progression” scenario.

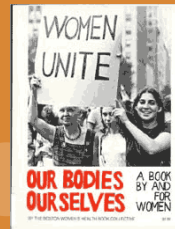
Patterns of Intersections Between Science & Medicine

- Proposed new treatments applied first to patients with advanced disease.
- Subsequent testing to see if the same clinical results obtained with less treatment.
- The concept of “stage” was re-introduced to facilitate recruitment of similar patients to groups being studied.

Intersections (con't)

- There is inherent conservatism on the part of medical practitioners.

Patient Activism & The Women’s Movement



- First version published in 1970.

The Rise of Personal Accounts



Oncogenes

- Some carcinogens found to directly damage DNA but in varying amounts and under varying conditions.
- Tumor viruses were also found.
- Competing theories of causation (infection vs. physical damage).
- The epidemiologists showed that cancers did not behave like infectious diseases in transmission though.
- Both agreed that “oncogenes” were responsible.

The Proto-Oncogene Revolution

- In the 1960s, Varmus and Bishop studied the virus long known to be responsible for sarcoma in chickens, but long abandoned for having no apparent relation to human cancer. They found the gene (src) responsible for endless replications of the cell.
- In the mid-1970s, though, their lab found that src was present in both infected and non-infected chicken cells. It turned out to be universal—including humans and insects. Each cell had it in its normal genome.

The Role of Retroviruses

- Did a virus steal a proto-oncogene from a host and somehow activate it into an activated oncogene?
- Many more were found, including myc, myb, erbB and ras.
- But viruses were not found in most tumors.
- Could chemicals etc. activate the genes?
- DNA from malignant cells could, in the lab, transmit malignant behavior and transform normal cells also. Proto-oncogenes are numerous, ubiquitous and normal. What converted them?

Oncogenes



- Gene sequencing was done in the early 1980s with ras. Both the oncogene and the (normal) proto-oncogene were about 5000 base pairs long.
- The difference turned out to be a single base! GTC instead of GGC.
- Each proto-oncogene had its own mutational mechanism, most less subtle. But the result was always the same.

The “Multiple Hit” Theory

- The excitement over finding a “single-hit” did not fit the epidemiological observations, such as age of developing cancer and the long lag time between exposure and disease (as in tobacco and asbestos).
- Radiation research also showed that cells in culture could recover from sub-lethal damage given enough time between hits.
- Maybe cells in culture for viral experiments were already abnormal, and some already immortalized, when infected? This turned out to be true.
- Need at least 2 hits: immortalization/malignant

Genomic Instability

- It requires a sequence of mutations that progressively change the DNA in a cell to push it closer to uncontrolled growth. Each of the events that cause mutations is in itself rare, but each unrepaired non-lethal hit brings the cell closer to cancer.
- This fit well with Darwin’s theory, with mutations known to happen constantly, but in this case, cancer cells were thought to be “the fittest” (actually they weren’t, though).

Not All “Carcinogens” Cause Mutations

- Some agents, like tobacco, force the cells to replicate more, increasing the total time the DNA is unfurled and exposed.
- Alcohol and tobacco are associated with mouth, throat and esophageal cancers.
- Hepatitis B forces continual replacement of damaged liver cells.
- The estrogen story is still incomplete.

DNA Damage

- Random mistakes
- Inherited mutations
- Environmental exposures
- Faulty repair
- Multiple events in multiple genes
 - Are there specific patterns?
 - Is it all a defect in DNA repair, leading eventually to genomic instability?

Now we know...

- By the time cancer is discovered, there are billions of cells involved, and the process can take decades.
- By fusion of normal and cancer cells, we know that cancer causing genes are recessive.
- This gives us hope for strategies which are based on re-imposing control on tumor cell growth.

What Makes Us Human?

- 98% of our genes are identical to the chimp.
- Large areas of DNA appear to be "junk"—why?
- Now we know that DNA can replicate in non-linear ways (Handout page 8C)

Tumor Suppressor Genes

- An oncogene was not found in some tumors though, and few had more than one. Where were the multiple hits?
- It was assumed that cancer cell genes would be stronger and more dominant compared to normal cells, but instead they turned out to be recessive when cell lines were fused. Normal cells could re-impose control on malignant cells.
- These growth-normalizing genes were called tumor suppressor genes. Defects in these genes could explain heritability of cancer in some cases.

Familial Cancers

- We have 23 pairs of chromosomes. One of each pair is from our father, and one from our mother. If one suppressor gene is damaged, the other copy takes over as backup. We have at least several tumor suppressor genes.
- The damaged copy can also be transferred to the normal copy during cell division. "Loss of heterozygosity."

Familial Cancers (con't)

- Inheritance of a damaged copy in each cell at birth increases the chances that the suppressor function will be lost someday.
- Some are more important in particular organs (Rb) and others are more general (p53). Some are intermediate like the BRCA's.

Accelerators and Brakes

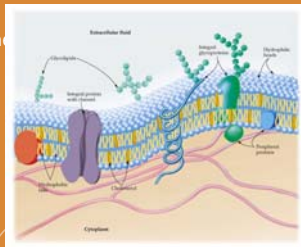
- Cancer cells have lost their brakes. Normal cells can restore them.
- Oncogenes are accelerators.
- Discovery of suppressor genes offered an explanation for familial cancer--loss of the services of the suppressor.
- "Loss of heterozygosity"--intact gene copy is discarded and replaced by the mutated gene.

DNA Repair

- Repair damage to DNA due to chemicals from environment, diet, free radicals.
- Constantly on duty, taking the number of errors in replication down from about one base in a thousand to one in a million.
- DNA damage can also be prevented by intercepting and neutralizing danger via enzymes (like antioxidants).
- This sets the stage for defining particular individuals at particular risk, depending on natural level of these enzymes.

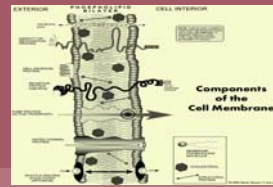
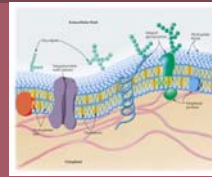
The Cell Membranes

- Same general structure for the outside shell of the cell, and for the nuclear envelope.
- (Handout page 5)
- Transport nutrients and essential elements for construction, communication and adherence.
- Change shape and affinity when approached by other molecules



What Does Signaling Mean?

- Proteins embedded in the cell membrane or nuclear membrane can be used for transport, or used to signal the interior to act, usually to replicate DNA to make a product or to divide.



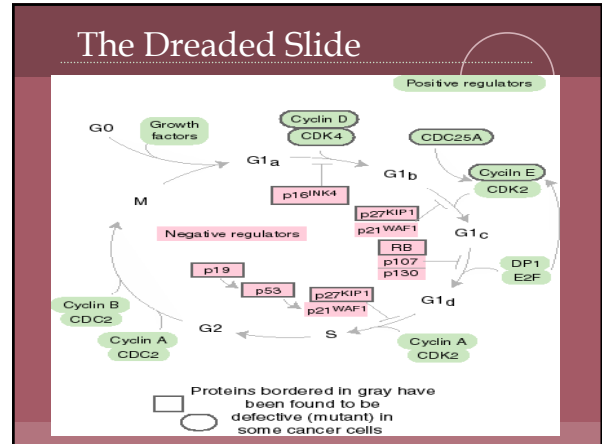
Signals

- Signaling happens when the protein changes shape in response to a stimulus on the outside, like a hormone.
- The molecule carrying the signal bumps up against the protein embedded in the membrane (the receptor), and electrons are transferred. This changes other relationships between molecules in the embedded protein as the change is propagated.
- The change in the shape of the makes the end of it that is inside the cell more likely to bind other proteins. These proteins in turn change their shape, setting in motion a cascade effect. The net result is that a signal is sent to the machinery of the cell, instigating or blocking particular activities in the repertoire of the cell.

The Cell Cycle

- Oncogenes make oncoproteins. The normal version of the gene makes a protein too, and it has a normal function, probably in recognizing the need to grow and divide.
- Genes don't know which type of cell they are in, and when they should become active.
- Signaling is required to tell a cell what to do, and when.
- Cancer cells operate independently from this communication system.

• See also Handout (page 8A)
The Dreaded Slide That You Have Been Expecting (highly simplified)



Signaling

- Id-1 is a gene that has a role in the normal growth and development of breast cells and in milk production. If it is turned on inappropriately, the cell has abnormal growth, spread and loss of apoptosis.
- Transforming growth factor beta 1 (TGF-beta1) is found in a small proportion of breast cells. It is stimulated by hormones to cause the growth of new cells and then to undergo apoptosis. It may have a role in breast cancer when produced inappropriately.

Tamoxifen & the Estrogen Receptor

- A growth factor is released by one cell, moves through intercellular space, and impinges on a target (receptor protein).
- The target responds by initiating growth and division or a product (e.g. insulin).
- Some tissues also make estrogen and some tumors make their own intracellular estrogen, hence the usefulness of aromatase inhibitors which block all synthesis of the hormone when that is desired.

Growth Factors

- Synthesis and release of growth factors is normally tightly controlled.
- Platelets release growth factors as they clot blood, to begin tissue repair process.
- VEGF (vascular endothelial growth factor) stimulates blood vessel formation to heal tissue. It is also involved in angiogenesis in tumors (Handout Page 8D).

Motility, Adhesion & Digestion

- Cancer arises in the sheets of cells that line the ducts and lobules. These cells are surrounded by other types of cells.
- Digestion of these cells happens with normal changes, like milk production. Enzymes are responsible for this action. Cancer cells need to use enzymes too in order to move out of the duct, through the surrounding tissue, and into nearby vessels.

Motility (con't)

- Cells produce proteases, proteins that are exported from the cell to break down nearby proteins. Matrix metalloproteinases are important in clearing out tissue to aid invasion. Some drugs are designed to give these enzymes a deflecting target to tie them up.
- The tumor cells can stimulate neighboring normal cells to produce these enzymes which also cause loss of cell adhesion in the epithelial layer by breaking up the adhesion proteins at the interface between cells.

Cancer Cells & Growth Factors

- Malignant cells are much less dependent on growth factors.
- They give us insight into the operation of a cell.
- Each growth factor has its own receptor.
- A normal resting cell probably needs several growth factors to initiate action. It is also influenced by nearby release of growth-inhibitory factors. The sum of the messages leads to action or inaction.
- Proteins receive the signals, filter them, sometimes amplify them, and pass them on via changes induced in their structure which can turn receptors on and off. "Signal cascades."

Signal Cascades

- Ultimately, the signal reaches the nucleus, stimulating the DNA response.
- Most of this progress in knowledge in the way cells work has come from researchers not directly involved in breast cancer research.
- Cancer results when the signal-processing is disrupted. One method of disruption is to free the cell from its dependence on external growth-stimulating factors. The oncoproteins bypass this step inside the cell.
- The cell grows and divides autonomously.

Signal Disruption Tactics

- Cell can be tricked into making and exporting its own growth factors which double back and stimulate the receptor.
- Abnormally-constructed receptor proteins can fire as if they have a growth factor like EGF in the receptor.
- A cell can be stimulated to make a lot of receptors which fire spontaneously—like HER2/neu (erb2). "Increased receptor density."
- A downstream protein like ras which is supposed to signal and then rest, stays activated.
- Inhibitory proteins malfunction, so signal is unbalanced.

Tumor Suppressor Malfunction

- TGF-beta signals inhibition of growth. Tumor cells can ignore it, even if there is lots of it around the cell.
- Tumor cells also reduce the number of TGF-beta receptors.
- Normal cells have a limited number of doublings before they die. This is a good way of clearing out accumulated mistakes and starting over fresh. The count is kept by the telomeres, structures at the ends of each of the DNA strands.

Apoptosis

- The telomeres are shortened each time the DNA strand is copied. They are composed of TTAGGC repeated over and over.
- Protozoans can repair their telomeres, but higher animals can't (except for our reproductive cells, like the ones that produce sperm).
- When the telomere is depleted, the DNA strands fuse to each other and the cell dies ("apoptosis").
- Tumor cells can also reactivate the repair mechanism so that the cell becomes immortal, or at least has a longer life span.

Apoptosis (con't)

- Anti-telomerase drugs are under development.
- Infected or damaged cells will normally destroy themselves.
- Tumor cells have growth promoters, so they need to devise a strategy to circumvent apoptosis. Otherwise they would die off rapidly as they use up their allotted number of cell divisions.
- Sometimes this is done by a second mutation, such as activating the bcl-2 oncogene.

Apoptosis (con't)

- p53, usually a brake on growth, will stimulate cell death if DNA damage is massive. If inactivated, excess copies of certain genes appear (are "amplified") like HER2/neu. If p53 is inactivated, the cell can replicate beyond the usual number of replications, and can tolerate lack of oxygen without dying.
- Many cancer therapies probably work by stimulating p53 response rather than via direct DNA damage.

Meanwhile, Back in Medicine, the Limitations of Surgery Are Finally Acknowledged.



Time for a 15 minute break

- Correlation with the state of medical practice is coming....

Checking In On Medical Progress

- Size of tumors at diagnosis was smaller, and survival was better.
- By the late 1970s the radical mastectomy was finally slowly losing to the modified radical mastectomy—still done into the late '80s.
- Reconstruction emerged as survival improved.
- Informed consent and participation in decision-making became the norm by the 1990s.



Adjuvant Therapy



- If Dr. Fisher was correct that breast cancer is systemic early, then chemo would be paramount.
- CMF became widely used in the '70s, first for metastatic disease, and then for node-positive disease.
- There was concern that it was over-recommended and over-used.

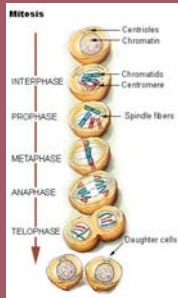
CMF

- Cyclophosphamide is modified mustard gas. Binds irreversibly to the two DNA strands so that they cannot open to replicate. Adriamycin has similar mechanism but is antibiotic-derived.
- Methotrexate inhibits folic acid metabolism, depriving DNA of components it needs to form new strands.
- 5FU is converted to a fraudulent nucleotide which disrupts the mechanisms used to form the new DNA strand.
- The use of 3 is comparable to the use of multiple antibiotics for serious infections.

Changes in Surgical Practice

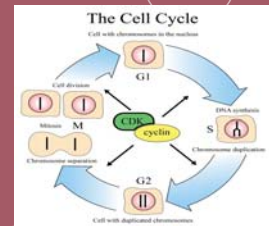
- In 1987, Nancy Reagan had a 1-step procedure, a modified radical mastectomy for DCIS. This choice challenged both the medical and the activist communities.
- In 1990, an NIH Consensus Panel stated that breast conservation was the surgical treatment of choice for Stage 1 and 2 breast cancers.
- BCT caught on slowly, due to geography, unavailability or fear of radiation, personal preference, and surgical training. The field appeared to be in chaos.
- The times and the uncertainties/controversies in treatment choices helped the rapid growth of the activist community by the early 1990s.

Taxanes



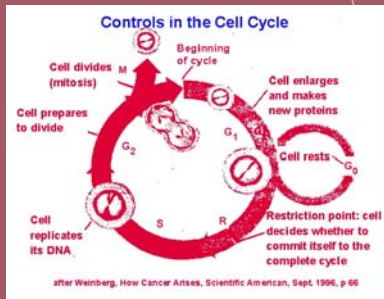
- Approved in 1992.
- Inhibit the assembly of microtubules needed for cell division and motility.
- Derived from the Pacific yew tree; a cautionary tale on the safety of botanicals.

Cell Cycle Control



- Different tissues have different rates of replication.
- Cyclins direct CDK (cyclin-dependent kinase) to attach a phosphate group to certain proteins and instigate progression of the cycle. (All kinases do this.)
- The primary decision is made in the G1 phase
- p53 and other suppressors can direct the cell to make inhibitory proteins to shut down the cycle.

Controls in the Cell Cycle



Putting It All Together: What We Know Now About How the Cell Works

- The Cell Cycle
- Signaling
- Transcription
- Cytoskeleton
- Protein Transport
- Protein Modification
- Adhesion (Handout 8B)
- Angiogenesis
- Apoptosis

Resistance

- Mutant proteins with altered permeability pump drugs out of the cells.
- Metabolic blockades side-stepped.
- Regulation of target genes is changed (e.g. cells stop expressing hormone receptors).
- DNA repair is blocked, or modified to serve the tumor cell.
- Drugs inactivated.
- Apoptosis deregulated.

Status Report: The Statistics

In California:

- About 23,000 diagnoses per year (1995-99)
- 200,000 living with the disease.
- A death every two hours

Nationwide:

- Almost 180,000 diagnoses a year.
- Sharp increase expected as the baby boomers pass 50 years of age, but we have actually seen a recent so-far-unexplained decrease.
- Drop in death rate, especially for white women, and the more affluent

Breast Cancer Risk

- Lifetime risk of an American woman is 1:7
- Chances of incidence related to age:
 - 1 in 2200 by age 30 (0.3% of cases)
 - 1 in 235 by age 40
 - 1 in 50 by 50
 - 1 in 25 by 60
 - 1 in 14 by 70
 - 1 in 10 by 80
 - 1 in 7 ever
- 77% are over age 50

Breast Cancer Risk (con't)

- 58,500 cases of in-situ breast cancer
- 1700 cases/year in men
- Death rate dropped in mid-'90s – earlier detection and better treatments

Breast Cancer & Race

- White, Hawaiian and African-American women have highest incidence of invasive breast cancer (4x that of lowest group, which is Korean, Vietnamese and American Indian, although access to care heavily influences this). Survival heavily influenced by stage at diagnosis.
- African-American women have highest death rate in the under-70 ages, when white women overtake them (SEER).

Other risk factors

- Geography (diet or hereditary?)
- Socioeconomic status and lifestyle choices
- Known genetic factors (about 5-7% of cases): BRCA, Li-Fraumeni, Cowden's syndrome
- Family history: age at onset, bilaterality
- ADH, LCIS
- Personal history of cancer
- Reproductive factors
- Radiation exposure
- Alcohol, fat ingestion, obesity
- Hormone use

Lifestyles Changes to Reduce Risk?

- More physical activity
- Less than 2 beers, 3 glasses of wine, or 2 shots of liquor per day
- Low fat (suggested for women who have had BC)
- Lactation (no proof)
- Tamoxifen

Beware of using most risk factors in clinical practice!

They are good for asking research questions though...

Status Report: Earlier Diagnosis

- Still no blood test for the detection of tiny amounts of disease in the body. We really need this.
- Mammography is more accurate at lower radiation doses in dedicated hands.
- Biopsy techniques, properly applied, can be less invasive.
- Dedicated breast MRI and ultrasound improved markedly.
- PET available, but we really need to know about microscopic disease for diagnosis and to make treatment decisions.

Standards of Care for Diagnosis

- Value of breast self-exam still in question

Breast Self-Exam – Step 1



- Begin by looking at your breasts in the mirror with your shoulders straight and your arms on your hips.
- Here's what you should look for:
 - Breasts that are their usual size, shape, and color.
 - Breasts that are evenly shaped without visible distortion or swelling.
- If you see any of the following changes, bring them to your doctor's attention:
 - Dimpling, puckering, or bulging of the skin.
 - A nipple that has changed position or become inverted (pushed inward instead of sticking out).
 - Redness, soreness, rash, or swelling.

Breast Self-Exam – Step 2

- Raise your arms and look for the same changes.
- Don't squeeze nipple.



Breast Self-Exam – Step 3

- Feel your breasts while lying down, using your right hand to feel your left breast and then your left hand to feel your right breast. Use a firm, smooth touch with the first few fingers of your hand, keeping the fingers flat and together.
- Cover the entire breast from top to bottom, side to side—from your collarbone to the top of your abdomen, and from your armpit to your cleavage.



Breast Self-Exam – Step 4

- Finally, feel your breasts while you are standing or sitting. Many women find that the easiest way to feel their breasts is when their skin is wet and slippery, so they like to do this step in the shower. Cover your entire breast, using the same hand movements described in Step 3.



Mammogram Rates

Percent of American Women Who Have Had a Mammogram Within Past 2 Years

All Women Over 40	66.9%
White, Non-Hispanic Women Over 40	68%
Black, Non-Hispanic Women Over 40	66%
Hispanic Women Over 40	60.2%
Women Over 40 Below Poverty Level	50.5%
Women Over 40 Above Poverty Level	69.3%

National Center for Health Statistics, 1998

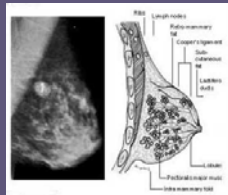
Mammography

- Mammography depends on care taken by technician and radiologists/ facility. This is even more important than equipment.

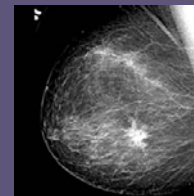


Mammography (con't)

- Standard mammography depends on density of the tissue and its ability to stop x-ray beam from exposing film placed on the other side of the breast.
- Digital mammography works on the same principle, but there is also some ability to manipulate the image by computer. Main advantage is storage of the films.



Mammograms: Cancer

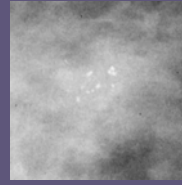


Obvious cancer

Mammography (con't)

- Picks out metal very well, and calcium is a metal. Therefore, able to find patterns of calcification, which may mean earliest stage detectible.
- Computer-aided diagnosis or double-reading of the film can aid diagnosis.

Microcalcifications



Microcalcifications (everyone has some)

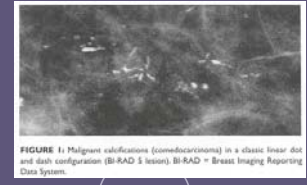
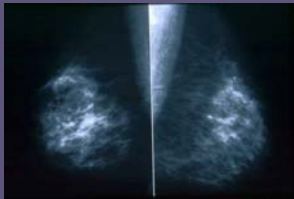


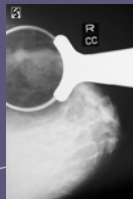
FIGURE 1: Malignant calcifications (comedocarcinoma) in a classic linear dot and dash configuration (BI-RAD 5 lesion). BI-RAD = Breast Imaging Reporting Class System.

Suspicious microcalcifications

Mammograms: 2 Standard Views



Side-to-side comparison



Compression view

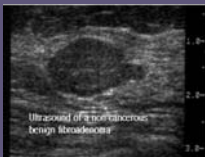
Ultrasound

- Since solid tissue and collections of fluid look the same on mammography, ultrasound is very useful in telling whether a mass is solid or fluid, and, if solid, if characteristics are suspicious.

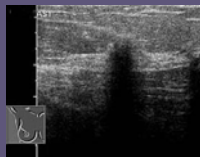


Cyst

Ultrasound (con't)

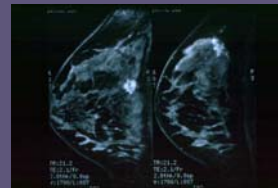


Solid benign mass



Suspicious mass

MRI



- MRI relies on completely different type of wave energy: a strong magnet that affects the charge in the nuclei. As magnetic force is applied and then released, different types of tissue send back different types of radio waves.
- MRI can be extremely useful in very dense breasts, hereditary cases.

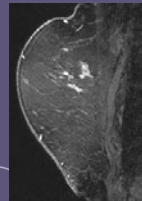
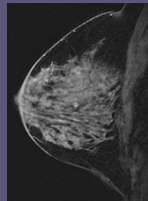
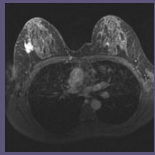
How MRI works

- 75% of human body is water
- H₂O
- Nucleus of hydrogen is a single proton, always spinning, with tiny magnetic field.
- Magnetic field usually random, but they line up when magnetic force is applied.
- Pulses of radiowaves knock protons off balance, causing them to flip.
- If the tissue has more water in it, the darker it looks. Dense and damaged tissue looks brighter.

MRI (con't)

- No radiation and no known risk
- Great detail
- Specificity problems being resolved
- Calcium doesn't show up (based on water)

MRI (con't)



Normal MRI

Suspicious MRI

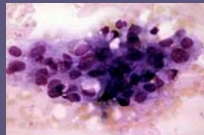
Other Diagnostic Tests

- Thermography depends on increased blood flow, so not for early diagnosis. Tends to be non-specific, and is not well-standardized.
- None of the alternatives substitutes for mammography so far.

Fine Needle Aspiration



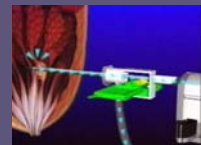
Fine needle aspiration of a palpable mass



- Fine needle aspiration takes individual cells out of mass. Can be done for palpable or non-palpable masses. Does not show architecture, especially wall of duct, so best used to confirm strong suspicions.

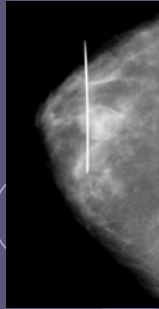
Core Biopsy

- Core biopsy can also be done on palpable and non-palpable abnormalities, and on microcalcifications. If the area is not palpable, this is known as a stereotactic biopsy.



Wire Localization

- Surgical excision, with wire localization, can be used for diagnosis or to guide surgeon if stereotactic biopsy has been done first.



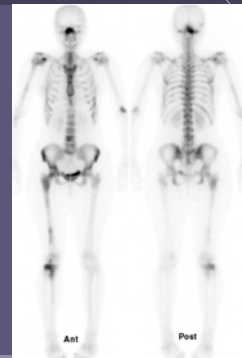
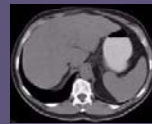
Access to Care

- A problem now, and will get worse.
- Uninsured and underinsured have a tenuous safety net, both for preventative care and treatment.
- Reimbursement for procedures in many cases does not cover out-of-pocket costs of delivering care, and cost-shifting possibilities disappearing as financial pressures on the medical system tighten.

Access to Care (con't)

- CMA surveys indicate physician shortages looming. Academic medical centers under tremendous pressure, and researchers are being diverted from their labs.
- Hospitals challenged to find money for capital improvements.
- Access to exciting new technologies may be limited by the methods of funding for our system.

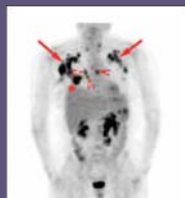
Staging



Staging (con't)



Normal PET scan

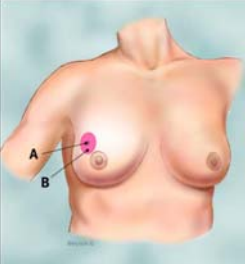


PET scan showing abnormal lymph nodes

Status Report: Surgery

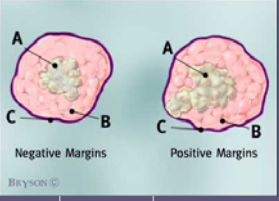
- Breast-conserving therapy is the norm whenever possible.
- Sentinel node biopsy is being used in an attempt to both improve the accuracy of node dissection for staging, while reducing complications.
- More surgeons preserving sensory nerves in axilla.
- Patients recover more promptly from anesthesia and go home sooner.
- Pain relief is improved.
- Drains can be avoided in more cases.
- Reconstruction: still not ideal.

Lumpectomy



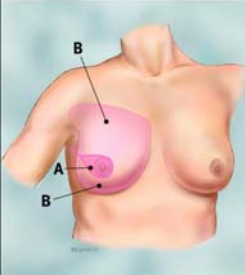
- Woman with lumpectomy.
 - A dark area indicates tumor
 - B pink highlighted area indicates tissue removed at lumpectomy

Biopsy: Margins of Resection



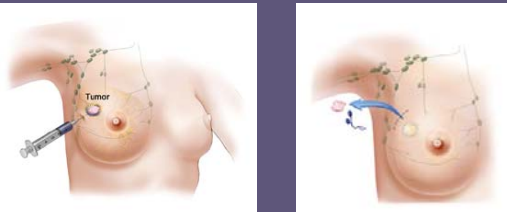
- Negative and positive "margins" or "margins of resection" (the distance between the tumor and the edge of the tissue).
 - A cancer cells
 - B normal tissue
 - C ink marking the edge

Skin-Sparing Mastectomy



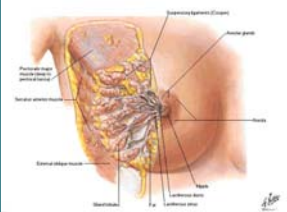
- Woman with skin-sparing mastectomy.
 - A pink line indicates "keyhole"-like incision
 - B pink highlighted area indicates tissue removed at mastectomy

Sentinel Node Biopsy

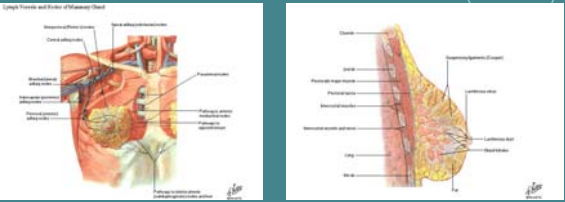


Status Report: Anatomy

- The detailed anatomy of the breast is still not known! (Ductal lavage may help).
- We need to understand normal development
 - Embryology
 - Puberty
 - Pregnancy
 - Involution
- Hormonal regulation
- Genetic control



Anatomy (con't)



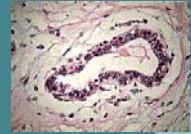
- Until we know how the normal breast develops and functions, it is hard to know what is abnormal, and which abnormalities have implications for the development of cancer.

Stages of Breast Development

- **Fetal development:** breast tissue begins to develop around the 6th week in utero with buds forming along the “milk line.” Buds may form supernumerary nipples in later life.
- **Newborn:** breasts sometimes secrete milk for several days after birth in response to maternal hormones still circulating.
- **Prepuberty:** ducts present but nonfunctional.
- **Puberty:** ducts elongate due to estrogen; breast buds appear. If these are mistaken for a mass and removed, breasts never develop.

Breast Development (con’t)

- **Young adult:** effects of progesterone are influenced by initiation of ovulation; ducts elongate; side branches of ducts and lobular elements form.
- **Maturity:** breasts become pendulous after many ovulatory cycles; lobular elements are well formed and in a resting state.



Maturity

Breast Development (con’t)

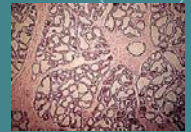
- **Menstrual changes:** rising levels of estrogen and progesterone increase vascularity and ductal and alveolar growth, and cause water retention. Different lobes may respond differently, remaining more or less prominent, eventually leading to increased nodularity.
- Hormonal peaks influence breast sensitivity and perception of breast pain. The breast is most sensitive about 7 to 14 days following ovulation. The best times for any type of breast exam are the days immediately following menses (days 5-10).



Menstrual changes

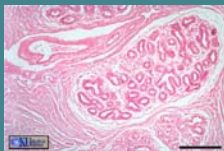
Breast Development (con’t)

- **Pregnancy:** proximal ducts grow and branch; breast enlarges to twice normal weight; increase in blood flow leads to vascular engorgement and areolar pigmentation; sometimes bloody nipple discharge occurs (such discharge during 2nd and 3rd trimester is usually normal).
- **Lactation:** lobules are dilated and engorged with colostrum and milk.

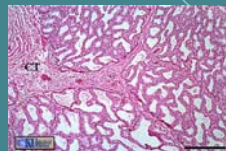


Pregnancy

Anatomy (con’t)



Lactation

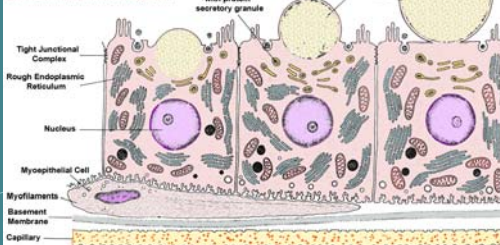


Normal histology

Anatomy (con’t)

Milk Production by Alveolar Secretory Epithelial Cells

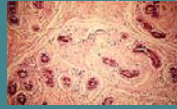
Milk contains: Water, lactose, fat globules, proteins (lactoferrin, non-specific lipase, immunoglobulins, alpha lactalbumin, casein), calcium, phosphate, other minerals, & vitamins. PRL stimulates milk production by the secretory epithelial cells. Milk let-down occurs when suckling produces an afferent neural signal for oxytocin release. Oxytocin stimulates the myoepithelial cells to contract and force alveolar contents into the collecting ducts.



(Modified from Austin & Short (ed) Reproduction in Mammals, Book III: Hormonal Control of Reproduction, Cambridge University Press: Cambridge, UK, 1984.)

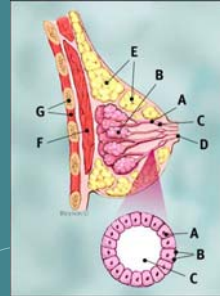
Breast Development (con't)

- **Menopause:** lobules begin to recede leaving mostly ducts, adipose tissue and fibrous tissue; histologically, postmenopausal and prepubertal breasts are very similar.



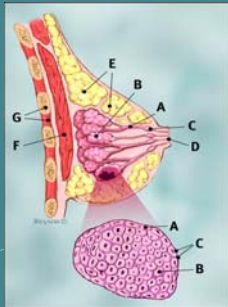
Menopause

Breast Anatomy



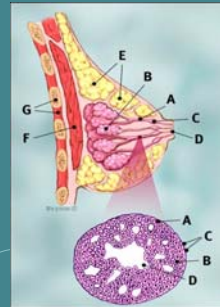
- **Breast profile:**
 - A ducts
 - B lobules
 - C dilated section of duct to hold milk
 - D nipple
 - E fat
 - F pectoralis major muscle
 - G chest wall/rib cage
- **Enlargement:**
 - A normal duct cells
 - B basement membrane
 - C lumen (center of duct)

Lobular Carcinoma In Situ (LCIS)



- Normal breast with lobular carcinoma in situ (LCIS) in an enlarged cross-section of the lobule.
- **Breast profile:**
 - A ducts
 - B lobules
 - C dilated section of duct to hold milk
 - D nipple
 - E fat
 - F pectoralis major muscle
 - G chest wall/rib cage
- **Enlargement:**
 - A normal lobular cells
 - B lobular cancer cells
 - C basement membrane

Ductal Carcinoma In Situ (DCIS)



- Normal breast with non-invasive ductal carcinoma in situ (DCIS) in an enlarged cross-section of the duct.
- **Breast profile:**
 - A ducts
 - B lobules
 - C dilated section of duct to hold milk
 - D nipple
 - E fat
 - F pectoralis major muscle
 - G chest wall/rib cage
- **Enlargement:**
 - A normal duct cells
 - B ductal cancer cells
 - C basement membrane
 - D lumen (center of duct)

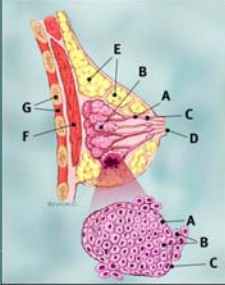
Tumor cells have to subvert apoptosis, antioxidants

- Premalignant cells (like DCIS) may be able to counteract increased proliferation by increasing apoptosis.
- Ongoing battle probably accounts for the confusing biochemical findings in DCIS, e.g. increased incidence of Her2/neu positivity.

DCIS

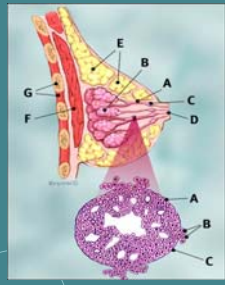
- Still struggling to avoid overtreatment and undertreatment.
- Work of Lagios and Silverstein gaining acceptance while challenging the medical team to do meticulous work.
- NSABP, with less faith in the ability of physicians to change practice, opt for treatment based on the least common denominator. Result is overtreatment for some groups of patients with DCIS.

Invasive Lobular Carcinoma (ILC)



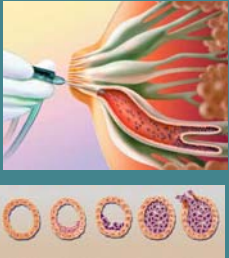
- Normal breast with invasive lobular carcinoma (ILC) in an enlarged cross-section of the lobule.
- **Breast profile:**
 - A ducts
 - B lobules
 - C dilated section of duct to hold milk
 - D nipple
 - E fat
 - F pectoralis major muscle
 - G chest wall/rib cage
- **Enlargement:**
 - A normal cells
 - B lobular cancer cells breaking through the basement membrane
 - C basement membrane

Invasive Ductal Carcinoma (IDC)



- Normal breast with invasive ductal carcinoma (IDC) in an enlarged cross-section of the duct.
- **Breast profile:**
 - A ducts
 - B lobules
 - C dilated section of duct to hold milk
 - D nipple
 - E fat
 - F pectoralis major muscle
 - G chest wall/rib cage
- **Enlargement:**
 - A normal duct cells
 - B ductal cancer cells breaking through the basement membrane
 - C basement membrane

Status of Ductal Lavage & Ductoscopy




- **Ductal Lavage**
 - The Pap Smear of the breast. Potential to obtain epithelial cells before changes can be detected by mammography.

Chemical Mastectomy


- The “chemical mastectomy”
 - More complete than prophylactic mastectomy, while leaving the breast as we see it in place.

Status Report: Radiation



- Most important mechanism for radiation is double strand break in DNA, affecting the cell's ability to replicate itself.
- Linear accelerators produce xrays and electron beams, producing direct and indirect damage to cell.

Radiation (con't)



- Brachytherapy in clinical trials. Convenient, but equivalence studies pending.
- CT planning helping to avoid complications of therapy.
- IMRT coming into use, but not clear how important it is for routine use in breast XRT.

Status Report: Chemotherapy

- Protocols are still being developed, and therapy rarely individualized.
- Some better guidance on proper indications for cytotoxic therapy and for drug choice.
- Push to reduce unwanted side-effects like fertility loss in young women. (Study funded by BCRP in a patient-driven effort).
- Some beginnings in specific therapy, as in Herceptin.
- We are poised to develop drug choice based on the genes in the tumor rather than on group treatment data where differences between groups can be very small. But we aren't there yet. (Gleevec)

Chemotherapy

- BMT and related strategies as we did them did not work better than less toxic treatments. We need to be able to clean and sort the cells better before re-infusion.
- We do better in controlling previously dose-limiting complications and nausea.
- We are still designing trials on group basis, and this may wash out important differences in results.
- There is hope for greater precision in hormone-blocking strategies.

Chemotherapeutic Regimens

- Use based on best estimate of whether disease has spread outside the breast
- Choice of initial regimens not entirely rational
- Main regimens now are CAF, AC, AT, TAC
- "E" (epirubicin) can be substituted for "A"
- CMF rarely used these days
- Principle is damage to DNA or to tubules, with malignant cells less able to repair damage.
- Primary effect on cells that are dividing (DNA exposed)
- This also accounts for the side effects

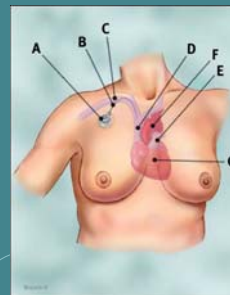
Chemotherapy for Metastatic Disease

- Aim is palliation and prolongation of life, not cure
- Depends on features of the cancer and history of prior treatment, not sensitivity, but gene profiling being researched
- Anthracyclines, if not used before, can have improved response, but generally without improvement in survival time
- Capecitabine, gemcitabine and vinorelbine have tolerable toxicity, with better quality of life

Metastatic Disease (con't)


- Outcome less certain with certain characteristics of the tumor, older age of patient, visceral disease, shorter disease-free interval
- Single agents often used. Taxanes can be useful as single agent or in combination. Herceptin can have long term survivors.
- Remember, recurrence is not necessarily the same as metastasis. Local recurrence can be treated and result in cure.

Venous Access for Chemotherapy



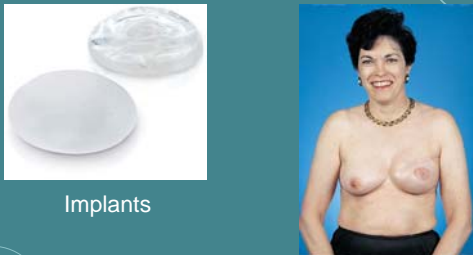
- Port inserted in vein for chemotherapy.
 - A port
 - B catheter [tubing]
 - C subclavian vein
 - D superior Vena cava
 - E pulmonary vein
 - F aorta
 - G heart

Reconstruction



Healed mastectomy without reconstruction

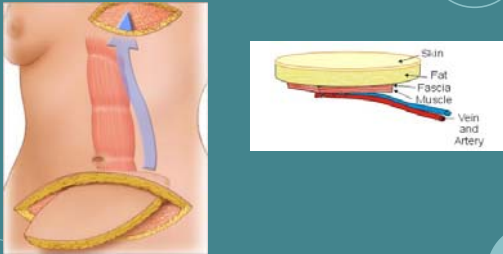
Implants



Implants


After implant

TRAM Flap



TRAM Flap


TRAM (con't)



TRAM after standard mastectomy

Bilateral TRAM after skin-sparing mastectomy

TRAM (con't)



"Free" TRAM

"Free" TRAMS

- Expertise of surgeon and support staff available more critical than for "pedicled" flaps
- Microsurgery needed to sew vessels
- Less muscle used, and cosmetic effect better
- DIEP (deep inferior epigastric vessels) and SIEP (superficial inferior epigastric vessels) use no muscle or fascia, but not everyone is a candidate
- Latissimus dorsi flap useful, but not often used
- All reconstruction requires at least 2 operations

General Trends in Surgery

- Use oncoplastic techniques to allow better lumpectomies, better outcomes, and to avoid reconstruction altogether.
- Consider marginal benefit of entering the axilla, and be more conservative if you do.
- Sentinel node technology has helped here, but to improve accuracy and to decrease potential damage.

Status Report: Clinical Trials

- 3% of women with breast cancer in clinical trials.
- Participation especially important in California, with diverse population.
- Need to account for variability in tumors more exactly than we have.
- Polygenic analysis will lead to more individualization of therapy based on specific characteristics of tumor and specific intracellular targets.

Trial Design Drives Future Treatment

- Since we have evidence only for schedules and doses used in clinical trials, they become the accepted treatment.
- Does “one size fit all”? It doesn’t make sense, but it is the best we can do given the evidence we have.
- When circumstances demand individualization we have to hope and guess.

Interpreting Reports of Medical Progress

- Power of a study is not in the number of participants so much as the number of “events” in each group.
- More enrollees might help to get more events, but this does not necessarily happen.
- We need to demand that results be reported by number of events per unit time, and not % increase or decrease, or relative risk alone.
- The “%” is derived from comparing the events between 2 groups and may be misleading to clinicians and patients trying to make rational decisions.

Reports of Results (con’t)

- For instance, if there are 1000 patients each in Groups A & B, and at 10 years there are 12 events in Group A, and 36 events in Group B, this is reported as a 67% improvement with the treatment given to Group A. But 988 patients in Group A, and 964 patients in Group B did not recur at all. Should everyone get Treatment A? At the very least, the data need to be reported in a clear fashion to aid patients and clinicians in decision-making.

Reports of Results (con’t)

- Remember that statistical significance does not always equal clinical significance. For instance, tumor size in one group could be 1.5 cm and 1.7 cm in the other group. This could be statistically significant, but the difference between 1.5 cm and 1.7 cm is not useful in the clinical setting.

Comparing Risks & Benefits

- Risks and benefits should be honestly reported, and in parallel formats.
- Many clinicians and patients could benefit from skills which allow them to analyze the whole paper to assess methodology and conclusions.
- Important articles should all be available in complete form on line with commentary and discussion from all parties attached.

The Disconnect

- We are still making most treatment decisions based on old criteria.
- Exceptions: the estrogen receptor, tamoxifen and aromatase inhibitors
- HER2/neu codes for a receptor for which we now have a drug (Herceptin).
- Molecular profiling is in its clinical infancy.

Molecular Profiling

- Tumors divided into groups: Luminal A, Luminal B, Basal-Like, HER2+/ER-, and unclassified.
- Basal-like and HER2+ more sensitive to paclitaxel and anthracyclines than luminal types in neoadjuvant regimens.
- Basal-Like more common in premenopausal African-Americans than others.
- Oncotype Dx and recurrence risk in development

Hopes and Challenges for the Future

- Prevention
- Biologic-based therapy that is individualized, or at least better prognostic information to guide treatment choices. Eliminate axillary surgery altogether.
- Improvements in concepts of gene repair
- Improve quality and effectiveness of imaging
- Improve screening rates, especially in older women
- Improve efficacy and reduce toxicity of systemic treatment
- Health care reform

Prevention, Risk Reduction & Lifestyle Factors

- Most US women, even those diagnosed with breast cancer, will die of cardiovascular disease.
- Exercise and a low fat diet with lots of fresh clean food are good for you.
- The age at which risk can be modified may be limited (e.g. late childhood and adolescence may be critical).
- All of life is a balancing of risks and benefits (e.g. alcohol).

Risk Reduction (con't)

- There are important risk factors (heredity, previous disease) that we cannot control, but which give clues to epidemiologists and basic scientists.
- There is great regional variation in tamoxifen use for prevention, and continued controversy over clinical application of the results of the P-1 trial.
- Early diagnosis is still important for "mortality prevention" even though it is not "disease prevention".
- Death rate is falling.

Status Report: Epidemiology

- Need more long term studies, carefully planned. Money is short.
- Need tissue banks and DNA banks expanded, maintained and used to correlate with clinical outcomes.
- Need to continue to maintain and mine the registries. Centralized records would help.
- Need a better model for calculating individual risk.
- Consider voting against Prop 54.

Environment & Breast Cancer

- Panel tomorrow at 8:30 will discuss what is known, what can be done now and in the future, how studies should be designed, and how action should be directed.

Genetics & Breast Cancer

- It is a triumph that we have the information that we do have, but what we have now is only a bare beginning.
- It is still a challenge to plan an individual clinical plan in response to a positive result.

Do We Need *More* Group Data?

- The short-term answer is "yes".
- Despite the limitations, it is the best we have at the present time, and it will provide guidance for current treatment as well as for clues for basic scientists.
- We must demand excellence in study design, and clear reporting with a clinical emphasis.
- These studies are expensive, and we need to emphasize methods that will exploit the genomics of individual tumors instead.

What is "Translation"?

- The movement of basic science research into the clinical setting.
- The pace is picking up, and even though there have been almost unbearable delays in the past, the stage is set for a time of rapid progress for many reasons. Money will be a problem for a while, but much good work is already underway.
- We need to continue to attract the best and brightest to science and medicine, and to keep up the pressure for progress.

BCRP: The \$190 million difference

- Role of Activists
- The Possibility for Innovation in Ideas and in Partnerships
 - Collaboration Awards
 - Targeted Awards
 - Training Awards
 - Innovative Research Awards
- Amazing Program Staff
- Future Funding
 - Tax Check-Off
 - Tobacco Tax
 - Private Donations

Hippocrates 460-400 BC

Life is short, the Art is long,
opportunity fleeting,
experience elusive, and
judgment difficult.

Edwin Krebs

- Now 89 years old.
- Described the mechanism by which the cell generates energy for itself. Note how recent our knowledge re cell basics is! Nobel laureate.
- "I still think there is a fairly general cause of all cancer. And as both a scientist and as someone whose family has been touched by this disease, I would like to see a cure applicable to all cancers. It's not going to come all at once. It will be an incremental process. But the rate of medical discovery is accelerating, and we are in a very strong growth period...."

Krebs 2003 (con't)

- "I think that once the basic causes are really understood, the treatment will rapidly follow. The next ten years will be dramatic."

THANK YOU!

*Breast Cancer 101:
From Research to Action...Seeking Solutions*

M.Ellen Mahoney MD