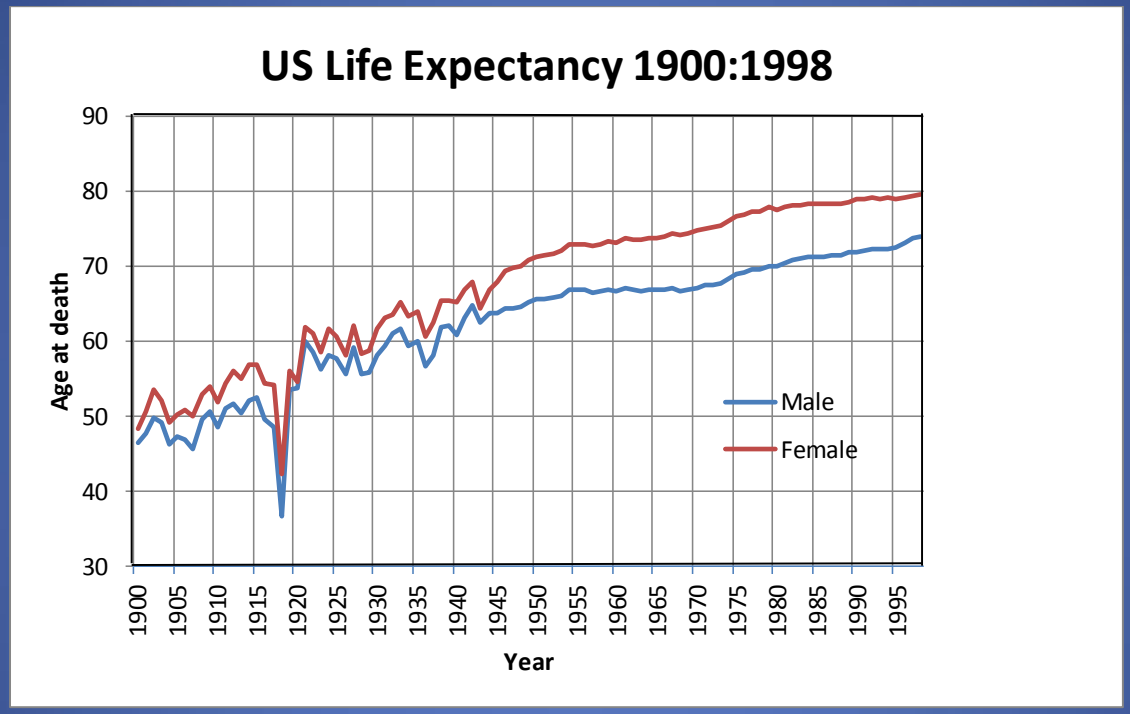
FDA Drug Approval

The process by which drugs are approved for human use in the USA by the Food and Drug Administration

History of the FDA

- The precursor of the Food and Drug Administration was the Division of Chemistry of the US Agriculture Dept. in 1883
- It was active in response to the expose of the Chicago meat markets by Upton Sinclair in his book “The Jungle” in 1906
- Later they took on the “snake oil salesmen” who roamed the West selling cure-alls to gullible citizens
- In 1906 Pres. Theodore Roosevelt signed the “Food and Drug Act” that gave the FDA its legal responsibility for testing and approving all food and drugs in the USA

Life expectancy



There are two conclusions: Scientific medicine has doubled life expectancy in 100 years; Women always live longer than men

Drug discovery

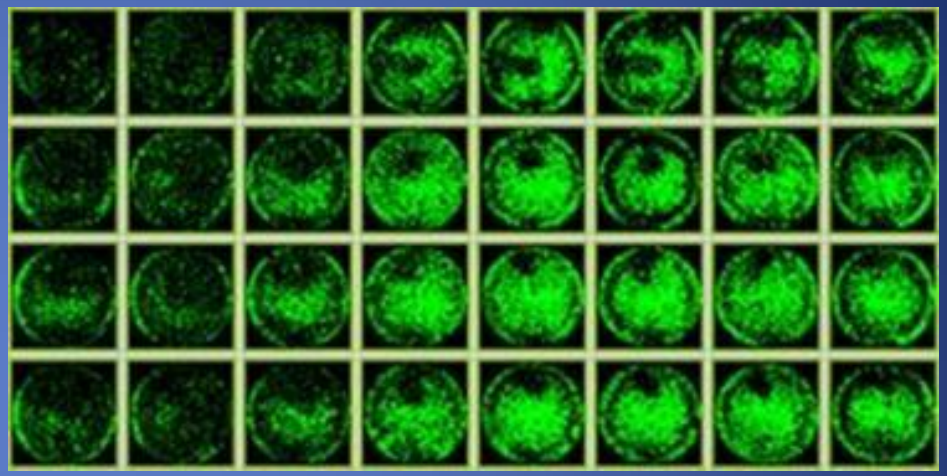
- Drugs are mainly discovered from natural sources, from animals and plants, called natural products
- The first drug discovered in modern times from willow tree bark was aspirin, first isolated in extracts and then synthesized in 1853 by Bayer
- Other sources include Pacific Ocean sponges, African trees, S. American frogs and insects
- Some people are specialists at scouring the world for new sources of drugs

Drug Discovery

- Initially extracts of plant or animal tissues are tested on a standard cell assay that gives a color reaction if the cells are killed, called High throughput screening
- Less than 1% qualify for further testing
- Then the extracts are further purified and tested until the active ingredient is found
- Then the substance is chemically synthesized
- The mechanism of action and the pharmacokinetics and pharmacodynamics are then evaluated in mice
- A new drug is called a “New molecular entity” (NME) and each is given a code number by the FDA

Colorimetric cell assay

A microtiter plate is filled with cells and a dye indicator (MTT) is added. Then increasing amounts of the drug are added. If the cells die the indicator changes color



For high thru-put the process is automated in a machine that adds the solutions and measures the color automatically

The process of drug approval

1. Preclinical - Tests in animals
2. Phase 1 – Toxicology tests in patients (usually terminal) using Fibonacci escalating doses
3. Phase 2 – Efficacy tests in a small sample of patients with the chosen disease
4. Phase 3 – Multi-center clinical trials on a large cohort of selected patients

Clinical trials

- Note the process of drug testing and approval can take up to 6 years (after bench studies)
- As a result of pressure from AIDS victims groups an accelerated process of 1-2.5 yrs was introduced
- Note the testing process is not carried out by the FDA, but the approval for human use is based on the results of Clinical trials carried out independently by hospitals with their own staff
- Each hospital has an Institutional Review Board (IRB) that oversees clinical trials
- The two criteria tested are toxicity and efficacy
- The cost of a complete clinical trial can be m$250
- Less than 1 in 10 candidate drugs pass the test

Clinical trials

- All patients in a clinical trial must sign informed consent forms
- All clinical trials must have suitable controls
- The best controls are "randomized double blind studies"
- Because there is inherent bias in both doctors and patients neither must know the identity of the drug and/or the placebo
- The doctors because they may have a great deal depending on the results of the trial
- The patients because of the "placebo effect"

What is the placebo effect?

- The placebo effect is the feeling of improved health that many patients feel when given a null drug, ie. a placebo (eg. sugar or sugar solution).
- This effect is real and has been documented many times
- This is why it is necessary to use a control cohort of patients given placebo

Examples: Laetrile

- Laetrile is a supposed anti-cancer drug that is an extract of peach or apricot pits
- It contains mainly cyanide and amygdaline
- In the 1960s there were multiple claims for laetrile as an anti-cancer drug, but since it was proscribed in the USA (not approved by the FDA) patients went to Mexico for treatment
- In the 1980s patients accused the NCI of covering up the use of laetrile and so there were congressional hearings and NCI was forced to carry out a full clinical trial of laetrile
- The results were totally negative, there was no substantive benefit either against cancer or extension of life span

Examples: Vitamin c

- In the 1960s Linus Pauling claimed that large doses of vitamin c would cure many human diseases
- Some people took huge doses (1 gram per day) and developed toxicity
- Clinical trials by the NCI found no therapeutic effect against cancer
- Note each clinical trial costs ca. m$200

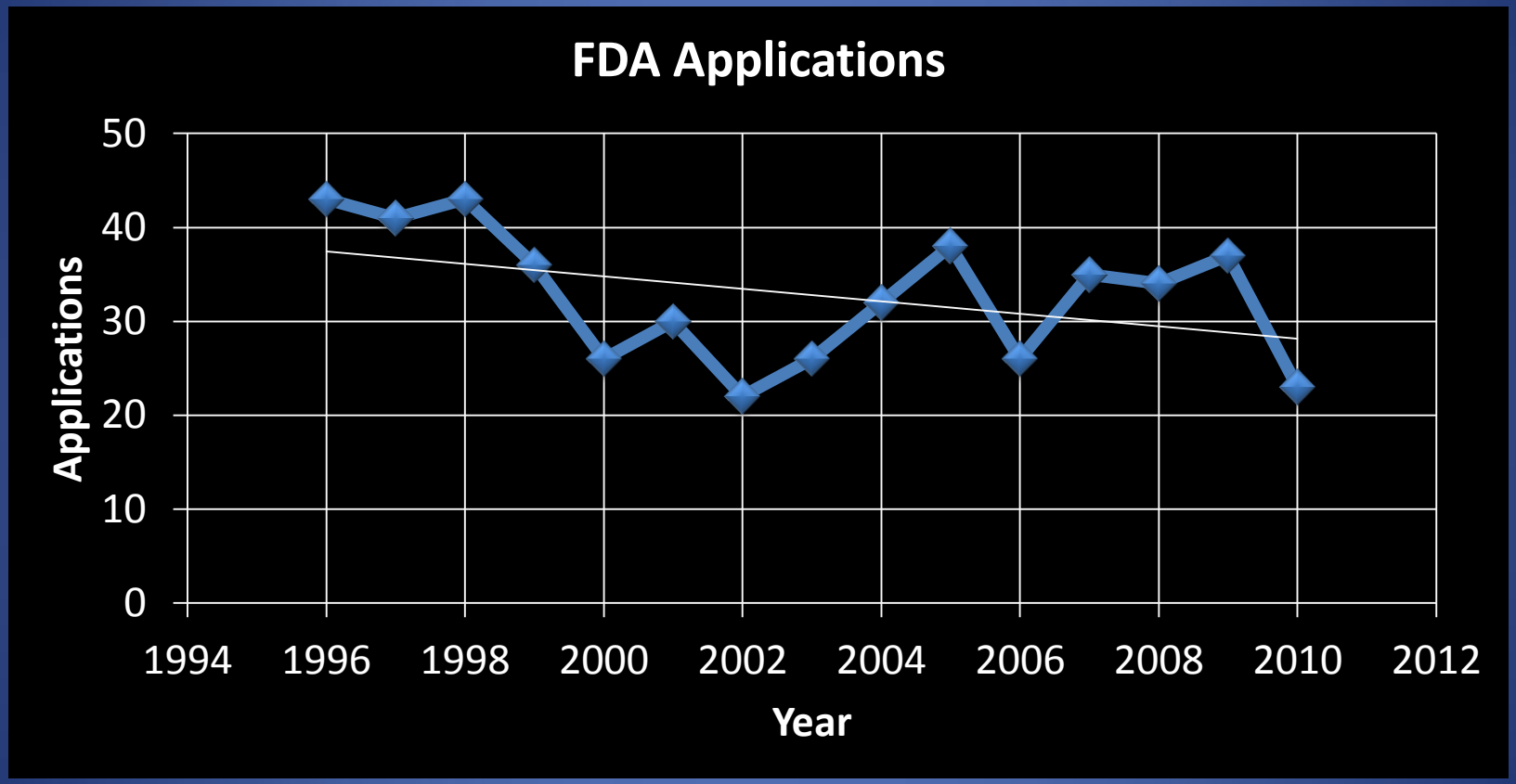
Examples: Adriamycin

- Also named Daunomycin, isolated from soil microbes in Italy in the 1950s
- A red substance, it had activity against mouse tumors
- Widely used in anti-cancer chemotherapy
- It is also toxic to normal cells and its side effects are unpleasant
- Known as “the black death” to its patients

Examples: Taxol

- Taxol was discovered in 1967 from the bark of the Pacific yew (taxus) tree in NCI screening
- First indications of activity of extracts in cell screens were only moderate, but purification gave higher activity against cancer cells
- Taxol is now the most widely used drug against breast cancer
- It is actually a fungal product and has been synthesized

Number of new drug applications



Note the number declines with time

Chemotherapy

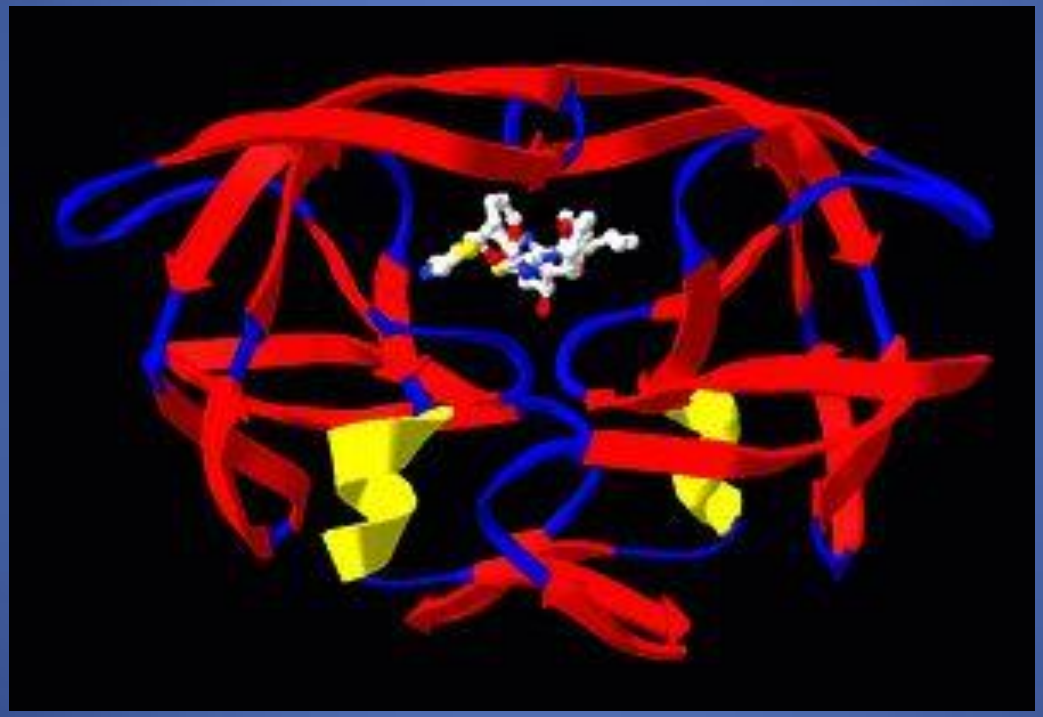
- Chemotherapy is the name given to the treatment of cancer by naturally derived drugs
- Chemotherapeutic agents are mostly toxic to animals and cells
- They work by killing dividing cells such as cancer cells, but they also kill other dividing cells, such as mouth mucosa, skin and hair follicles
- Their efficacy is determined by the ratio of killing of cancer to normal cells

Rational drug design

- Because of the difficulty in finding new drugs from natural sources and the cost, scientists have tried to develop drugs by using rational approaches
- These include designing molecules that fit in protein receptor sites like known drugs
- This uses computer molecular modeling and energy calculations known as CADD
- Another approach is to develop genetic drugs such as Gene therapy and Antisense

Example of Drug Binding

- HIV protease with inhibitor in binding site



- Structure determined by X-ray crystallography and computer-aided design

Summary

- Many drugs are efficacious and scientific medicine has resulted in the extension of the average age of mortality from ca. 50 to ca. 80 over the past 100 years
- Nevertheless many drugs have side effects, and should not be taken unless approved for human use and even then with caution
- It is appropriate to apply *skepticism* to all pharmacological products, especially and including those that have not been subjected to the rigorous testing of the FDA