

2012

Our Chemical Heritage: Its Impact on Our Daily Lives

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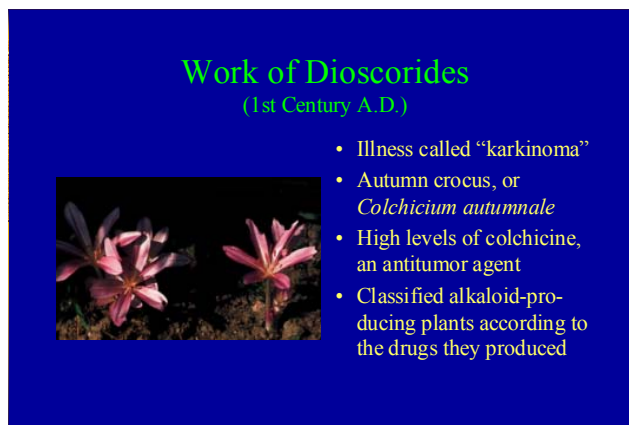
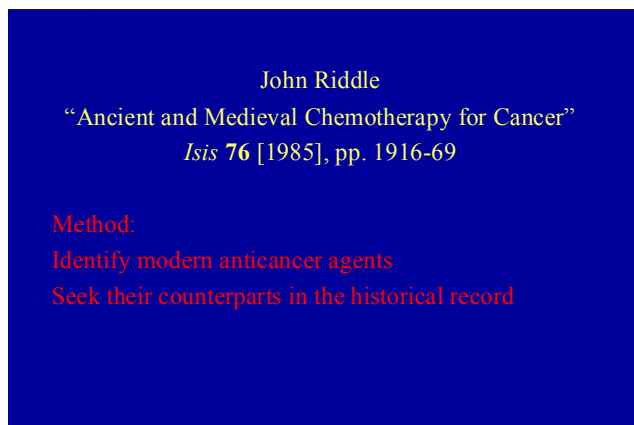
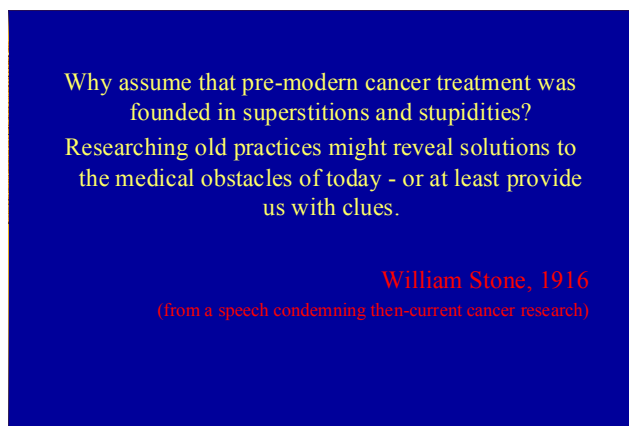
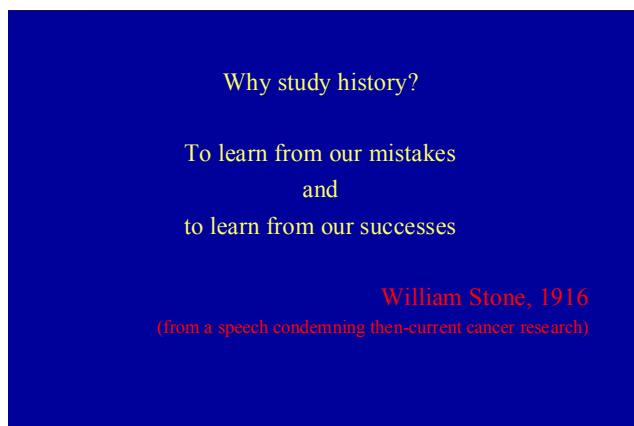
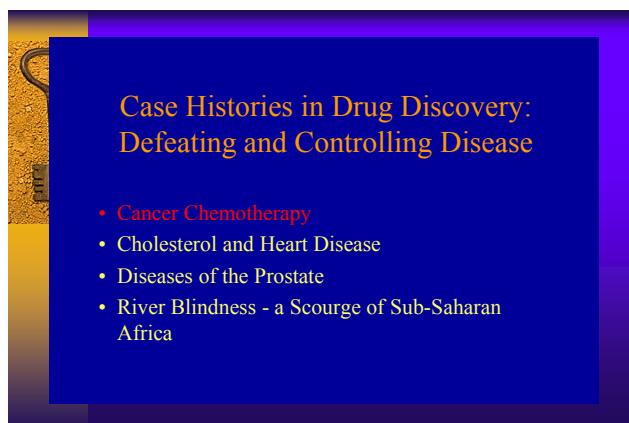
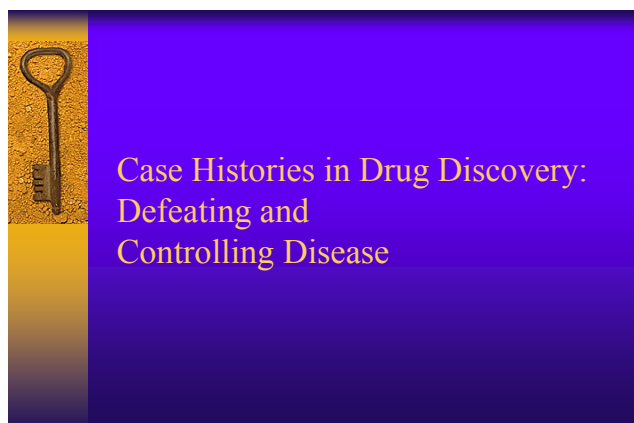
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Orna, M.V. *Our Chemical Heritage: Its Impact on Our Daily Lives*. Presented at University of Puerto Rico Rio Pedras, San Juan, PR 2012. Available at <http://digitalcommons.cnr.edu/facpres/9/>

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Galen (A.D. 129 - post 210) Avicenna (A.D. 980 - 1037)

- Distinguished between benign and neoplastic tumors
- Cautious in using toxic plant substances
- Recognized that side effects such as hair and weight loss were involved in their use

“Modern” Cancer Chemotherapy



- Robert Bentley, Kings College, London, 1861
- Referred to antitumor effect of root extract from the common mayapple, *Podophyllum peltatum*
- Active principle identified by V. Podwyssotzki as picropodophyllin

The Story of Taxol

- 60 B.C. – Caesar in “Gallic Wars” cites yew as poison
- 600 A.D. Native Americans used Pacific yew bark as a disinfectant and topical cure for skin cancer
- 1960 – Bark extract killed leukemia cells
- 1978 – Shown to be effective against advanced ovarian tumors by immobilizing the cell’s microtubules, thus halting mitosis

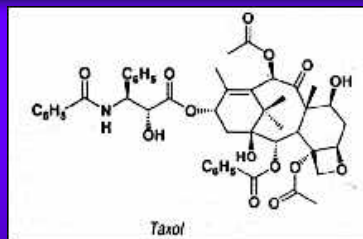
From Natural to Synthetic



- Mansukh C. Wani and Monroe E. Wall
- First isolated **camptothecin** from the Chinese tree *Camptotheca acuminata*
- Determined its structure
- Made synthetic analogs

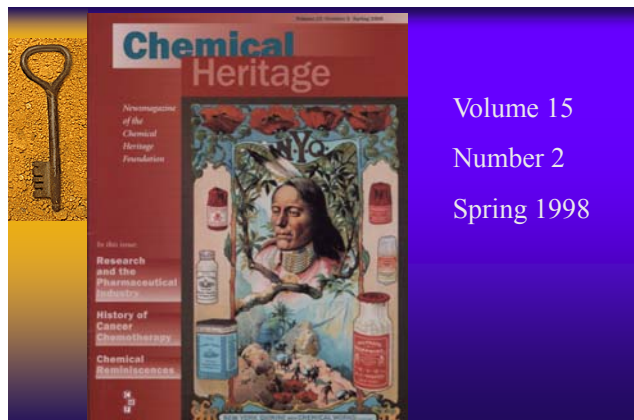
Semisynthetic Approach

- Wall and Wani first isolated **Taxol** from bark of Pacific yew, *Taxus brevifolia*
- 3-6 100-year old trees needed for single 2 g dose
- Main body of structure available from needles of English yew, *T. baccata*



Total Synthesis of Taxol: K.C. Nicolaou and Group (Scripps) and Robert Holton (FSU)

Both methods consist of over 30 synthetic steps since taxol has 11 stereocenters – total synthesis is not commercially viable at this point



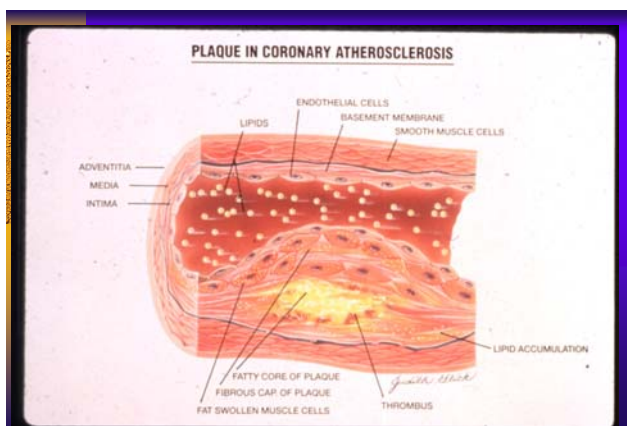
Volume 15
Number 2
Spring 1998

Case Histories in Drug Discovery: Defeating and Controlling Disease

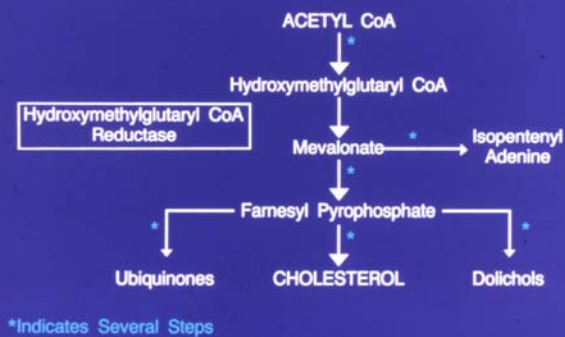
- Cancer Chemotherapy
- **Cholesterol and Heart Disease**
- Diseases of the Prostate
- River Blindness - a Scourge of Sub-Saharan Africa

Cholesterol and Heart Disease

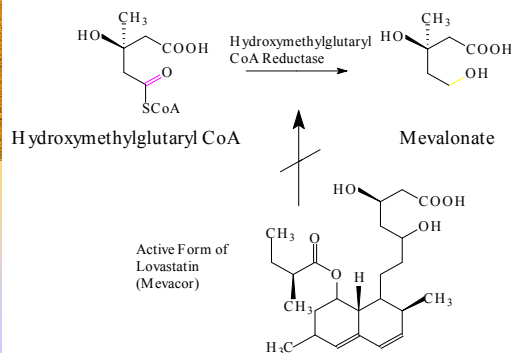
- Each year in the United States:
 - 1.5 million people suffer heart attacks
 - More than 500,000 die of heart disease
 - 330,000 bypass operations
 - 190,000 angioplasty procedures
- Cholesterol a major contributing factor
- "Japanese Phenomenon"

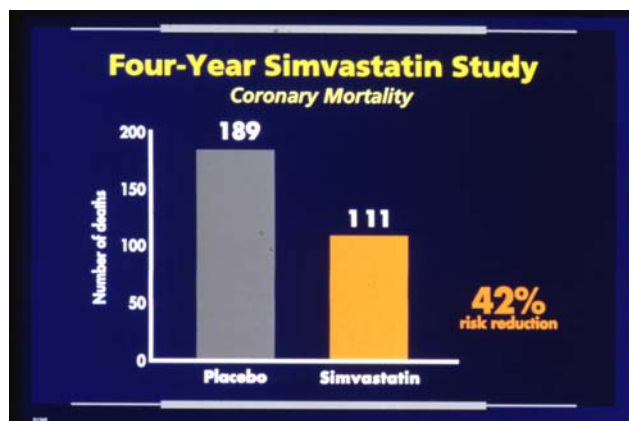
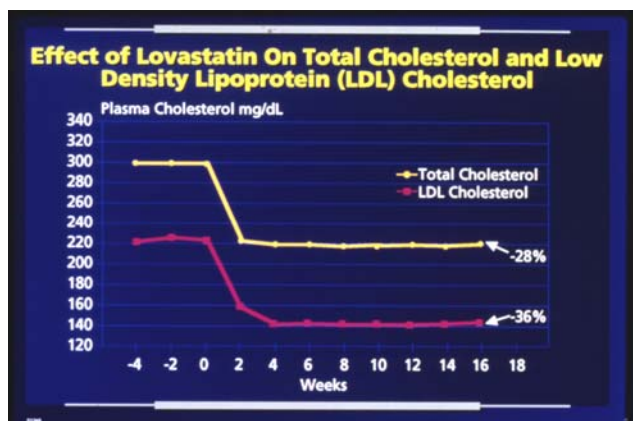


Cholesterol Biosynthetic Pathway



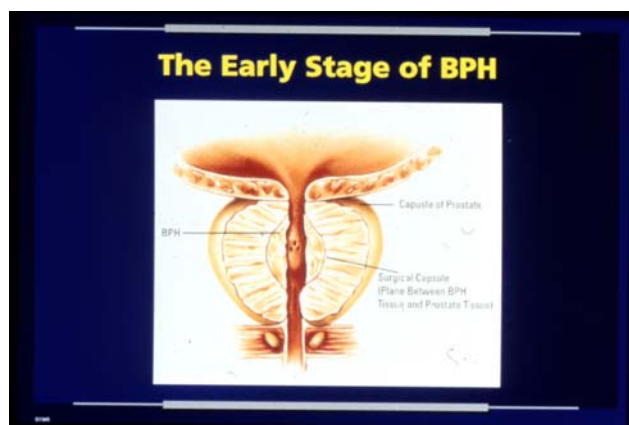
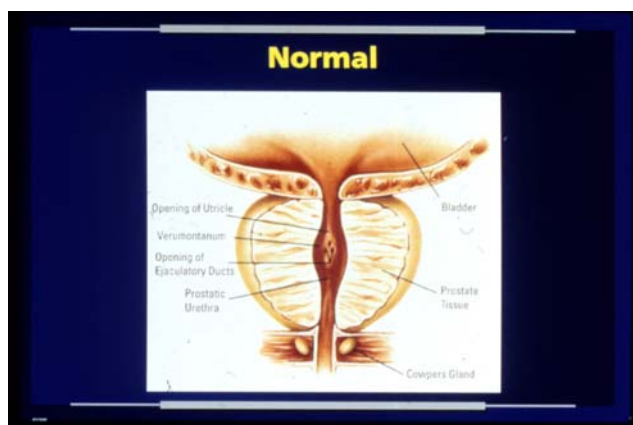
Lovastatin Blockade of Key Enzyr

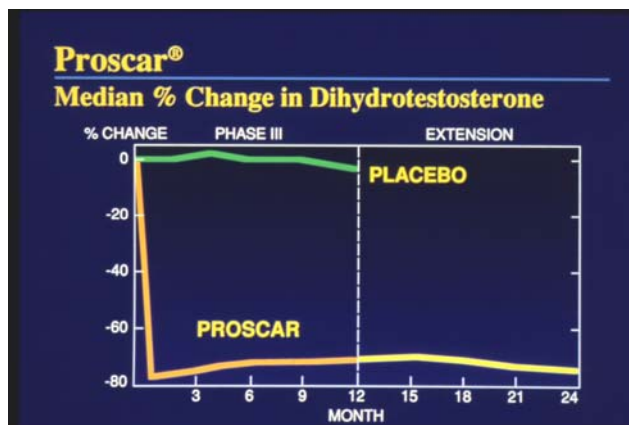
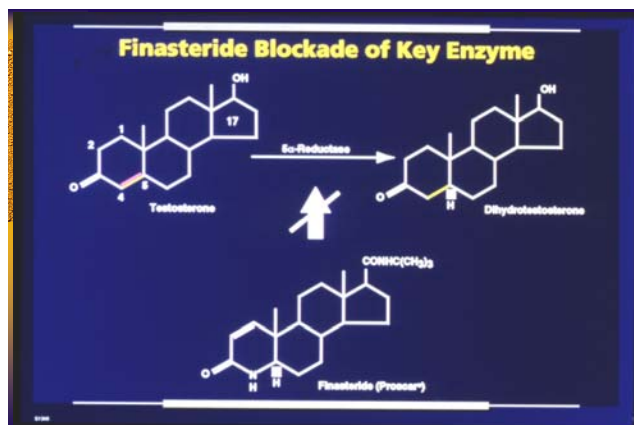
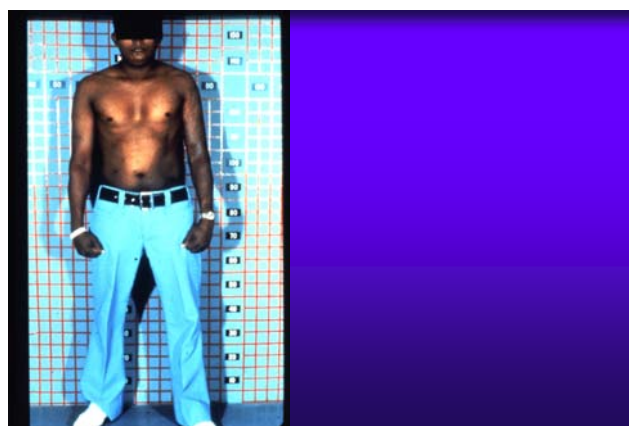
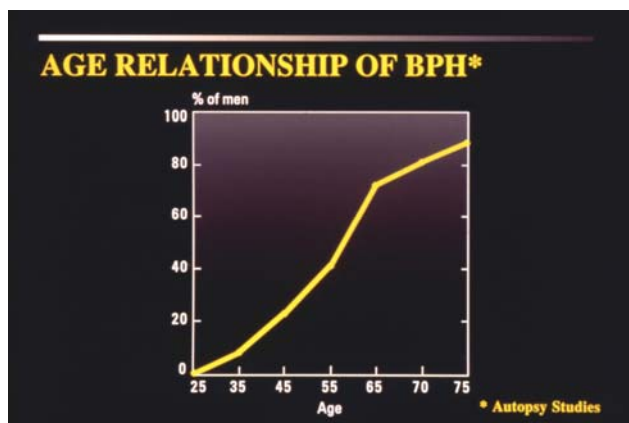
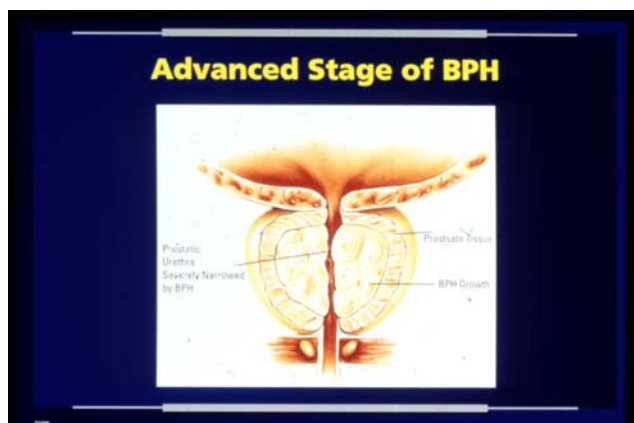


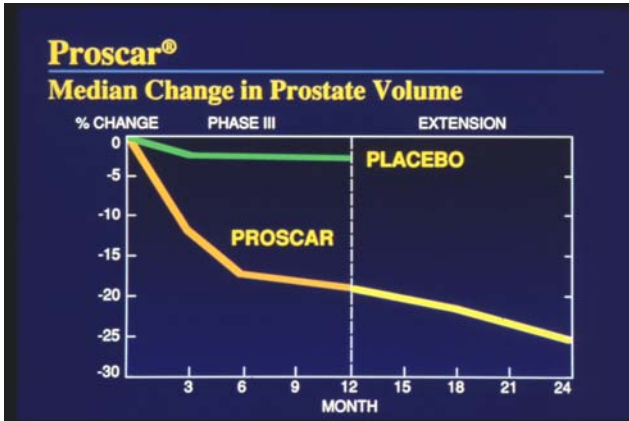


- ### Case Histories in Drug Discovery: Defeating and Controlling Disease
- Cancer Chemotherapy
 - Cholesterol and Heart Disease
 - **Diseases of the Prostate**
 - River Blindness - a Scourge of Sub-Saharan Africa

- ### Diseases of the Prostate
- Benign prostatic enlargement
 - Hyperplasia: an increase in the number of cells
 - Hypertrophy: enlargement of individual cells
 - Prostatic carcinoma: primarily adenocarcinomas that develop in the prostatic acini in the peripheral region of the gland
 - Prostatitis: term used to describe various inflammatory conditions







PROSCAR Benefits Confirmed*

- ♦ Acute urinary retention
 - Reduced 57%
- ♦ Prostate surgery
 - Down 33%

*from 3 clinical studies; over 2 years; 4477 men with BPH

PROSCAR

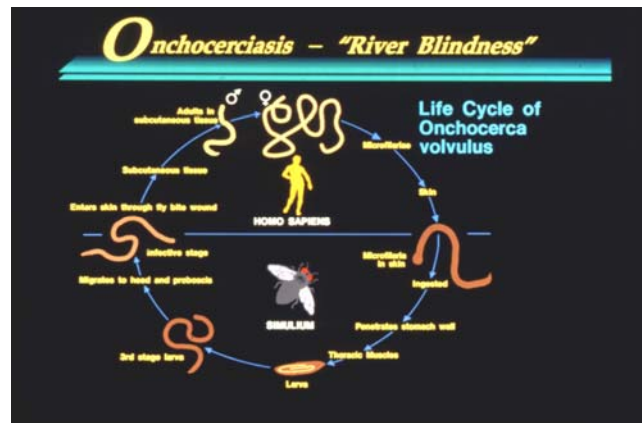
- ♦ Blocks formation of hormone involved in prostate enlargement
- ♦ Does not reduce level of testosterone
- ♦ Shrinks enlarged prostate, improves symptoms of impeded urine flow without significant side effects
- ♦ Expected to stop further enlargements and progression of symptoms

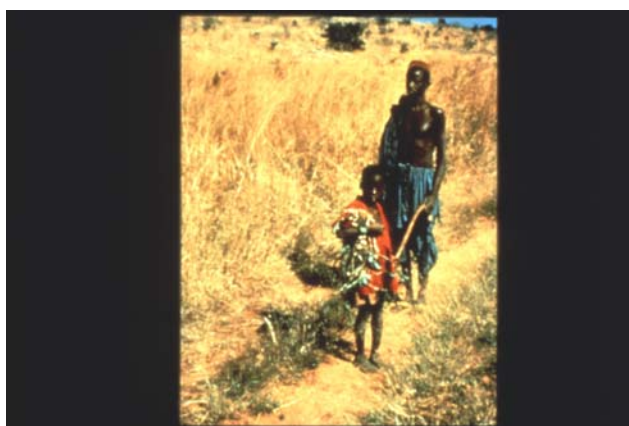
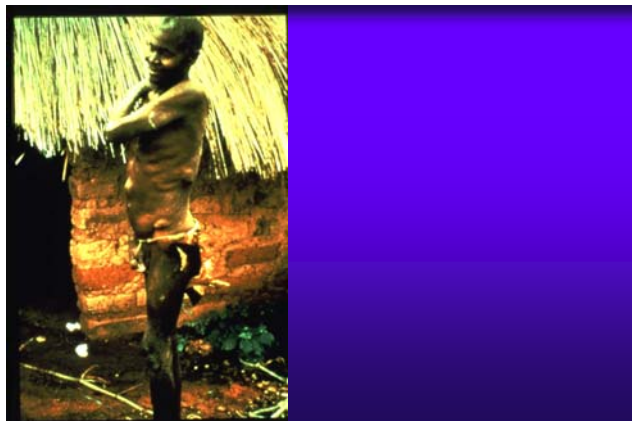
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River Blindness

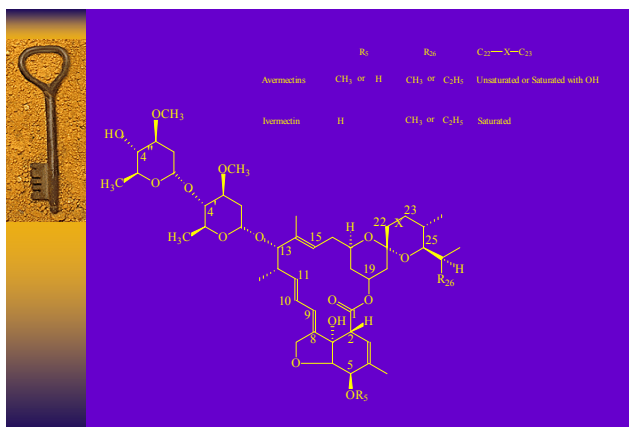
- ♦ 18 million infected
- ♦ 126 million at risk
- ♦ 1 to 2 million blinded

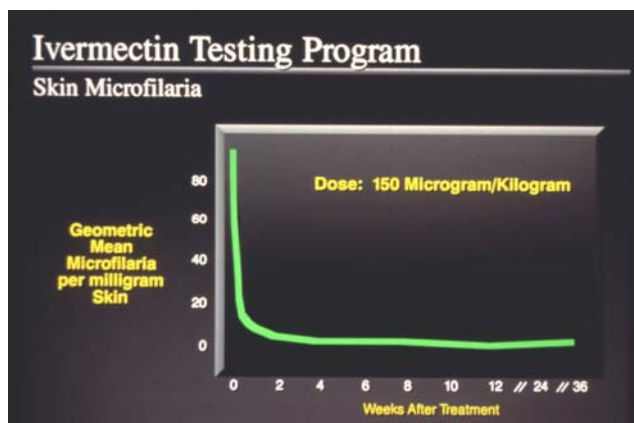





Ivermectin Development Chronology

- 1975** – Japanese Soil Samples Reveal Effective Antiparasitic Ivermectin Discovered – Aimed at Animal Health Market
- 1978** – Ivermectin Shown to be Effective Against Onchocerca Species in Horses and Cattle
- 1979** – Met with World Health Organization on Possible Human Use of Ivermectin
- 1981** – Clinical Testing of Ivermectin Begun





Mectizan Treatment



- ◆ Product donated 1987
- ◆ 13 million people treated in 34 countries
- ◆ Merck commitment to donate as long as needed

