

Orphan Drugs: An American Success Story

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Accelerating therapies for Rare Diseases
Rockville, MD

Intro to Orphan Drugs --- How to get from here to there

- The Orphan Drug Act: Rationale, Realization and Rewards.
- Medically Relevant subsets
- Examples: the scope of orphan drugs?
- Question time....

Economic Realities: 1982

- Rare diseases = Few potential pill buyers
- 1973-1982: 10 new drugs for rare diseases
- $\approx 7,000$ rare diseases; 25 million people
- Congressmen/Senators regularly besieged by requests for assistance/research

Abbey Myer: Grassroots Political Mover

“They are like orphans
in that they require
special care.” Henry
Waxman



The New Deal of the ODA

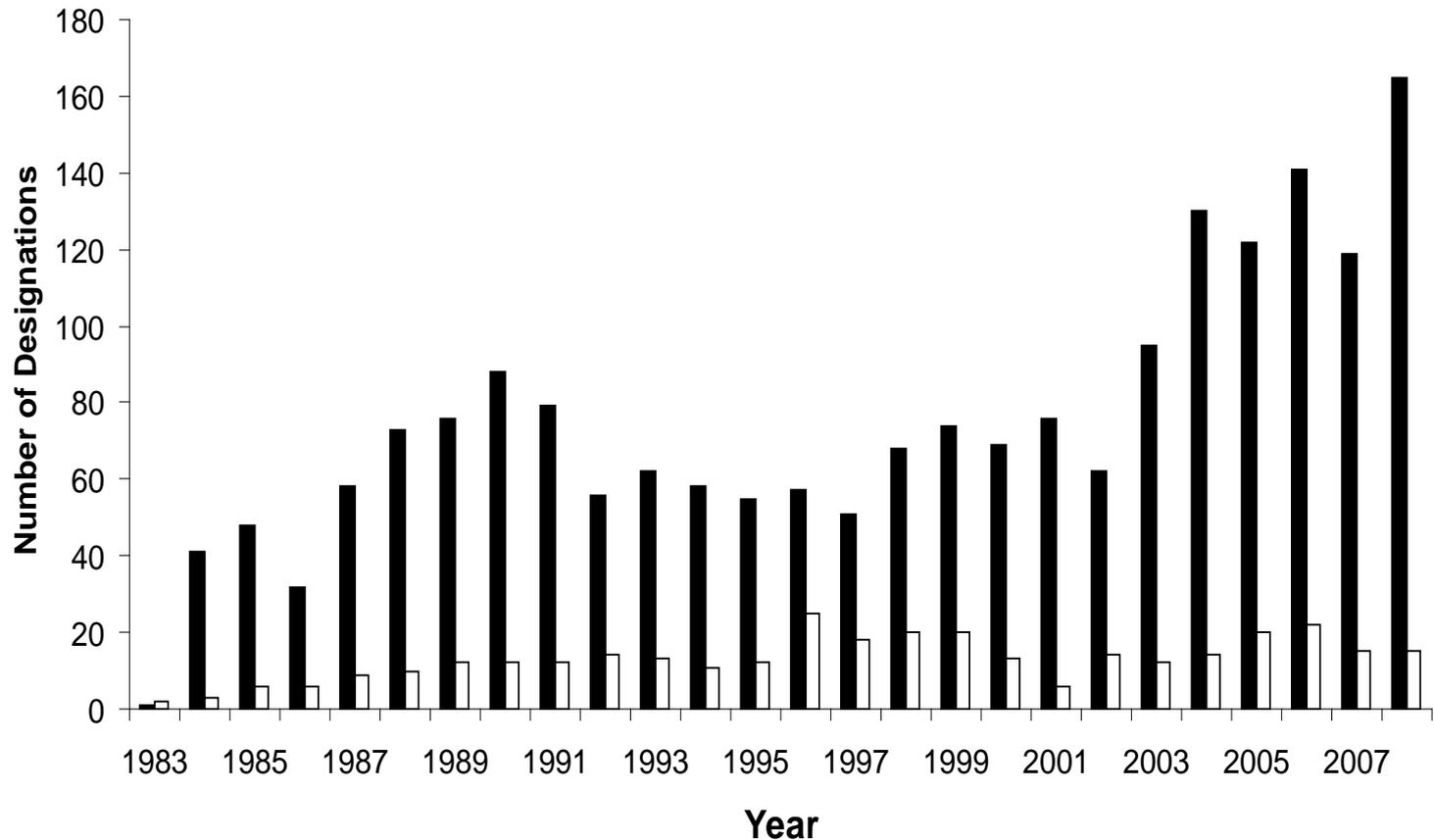
- Get a drug designated as an “orphan drug”
 - Show (with data) that it’s “promising”
 - For treating <200,000 person in the US
- Do the clinical trails/get marketing approval
- Receive incentives:
 - MARKET EXCLUSIVITY
 - Tax credits
 - Fee exemptions

ODA: A MAJOR SUCCESS

- 361 Approved Drugs
- ≈2,250+ Designated Orphan Drugs
- 2008: 38% of all FDA-approved NMEs were Orphans

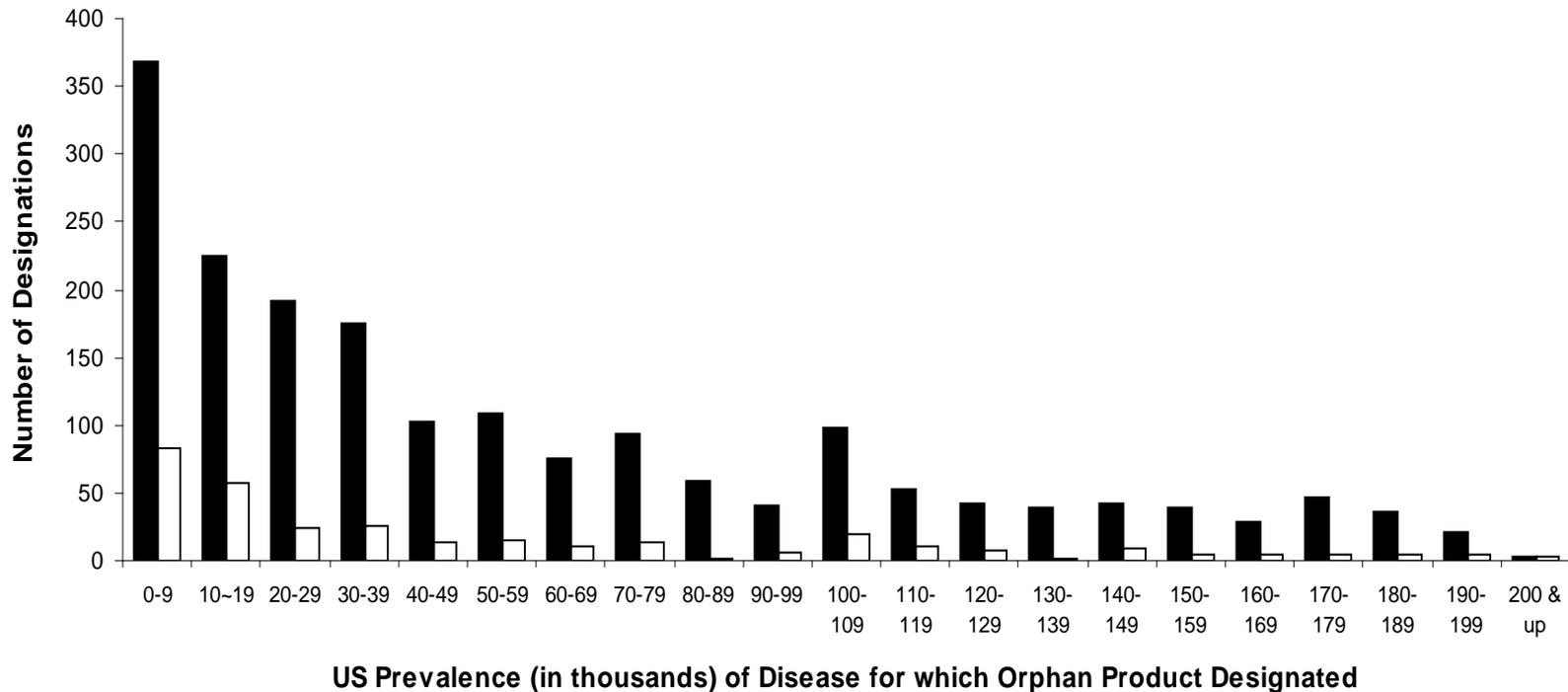
The US Orphan Drug Act has been HUGELY Successful

Number of Orphan Designations and Approvals by Year, 1983-2008



The Diseased Populations Served have been VERY Small

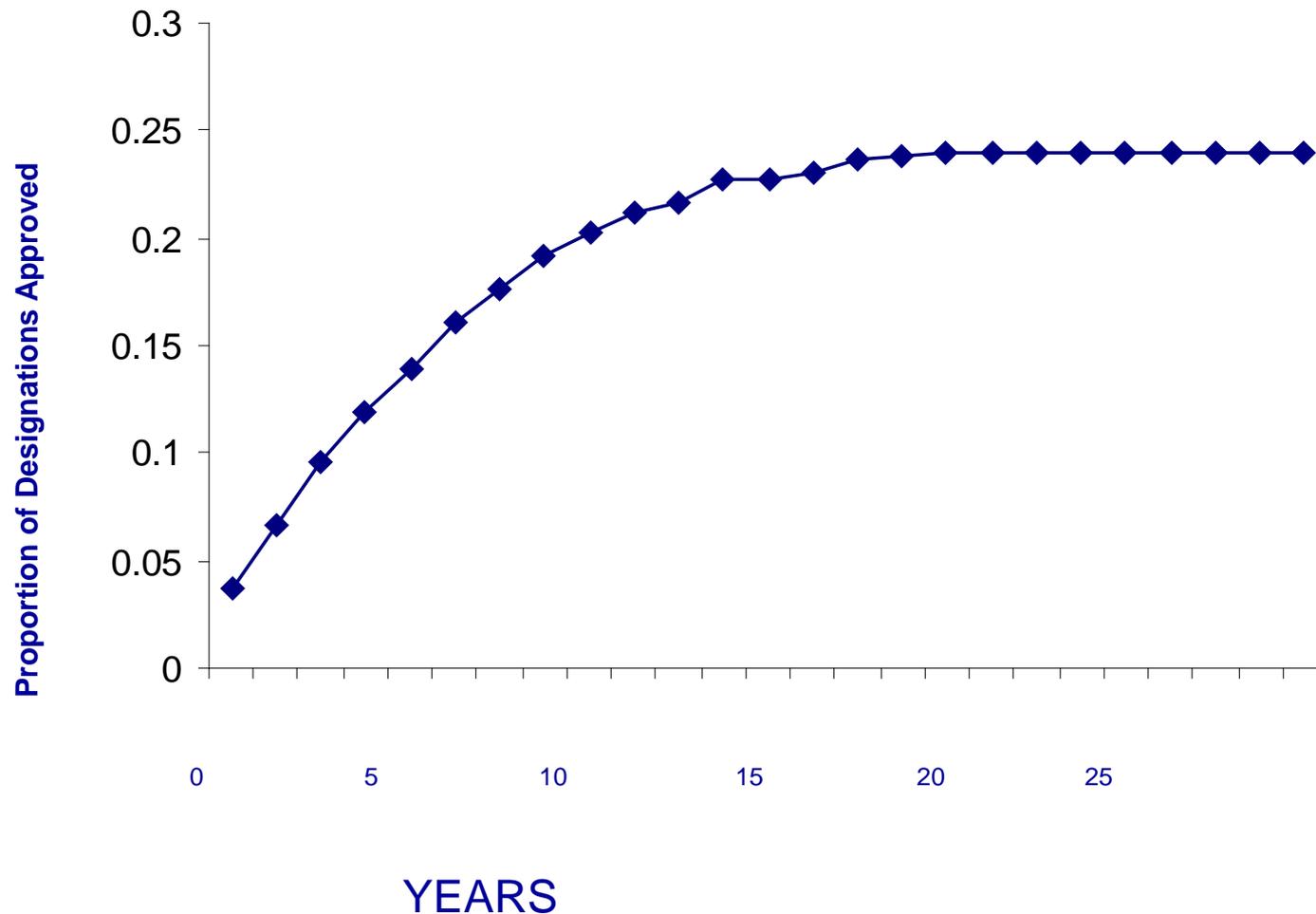
Distribution of Orphan Designations and Approvals by Size of Patient Population



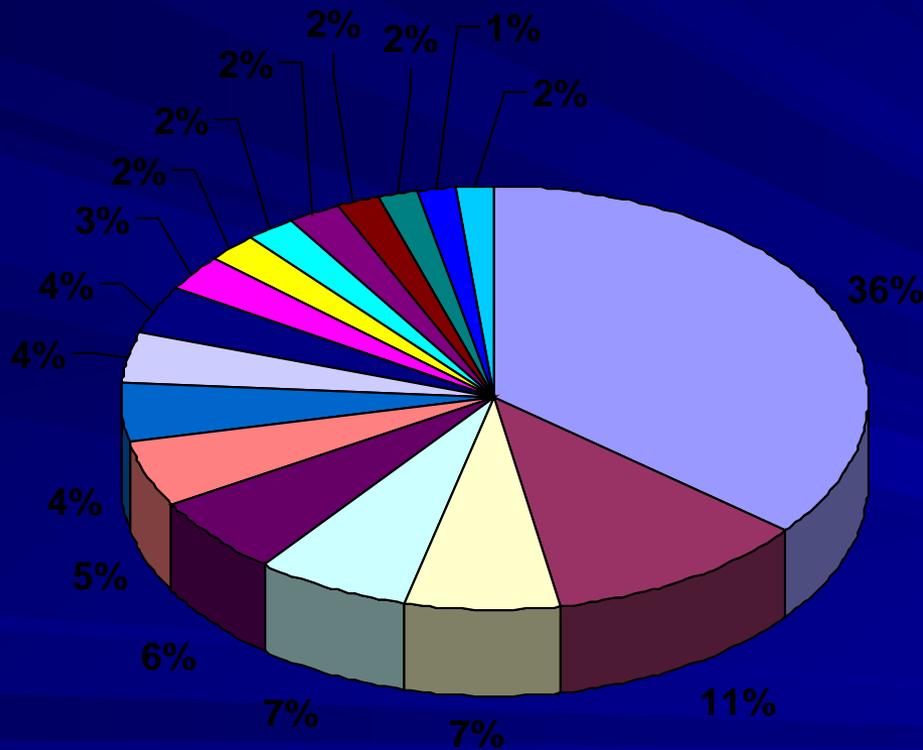
Source: FDA/OOPD, M. Braun et al



Time from Designation to Market Approval



And all human pathology is targeted by designated orphan drugs*



- Oncologic
- Metabolic
- Hematologic-immunologic
- Neurologic
- Infectious/parasitic
- Cardiovascular
- Transplantation
- Gastrointestinal
- Respiratory
- Endocrinologic
- Dermatologic
- Ophthalmic
- Musculoskeletal
- Injury/poisoning
- Perinatal
- Congenital abnormalities
- Others

* 2000-2006 Data

Orphan Designation and IND Status

- Independent processes
- Orphan drugs must proceed through IND and NDA/BLA to become marketed
- Orphans not treated differently in review: safety/efficacy still required but flexibility is common practice.

Personalized Medicine

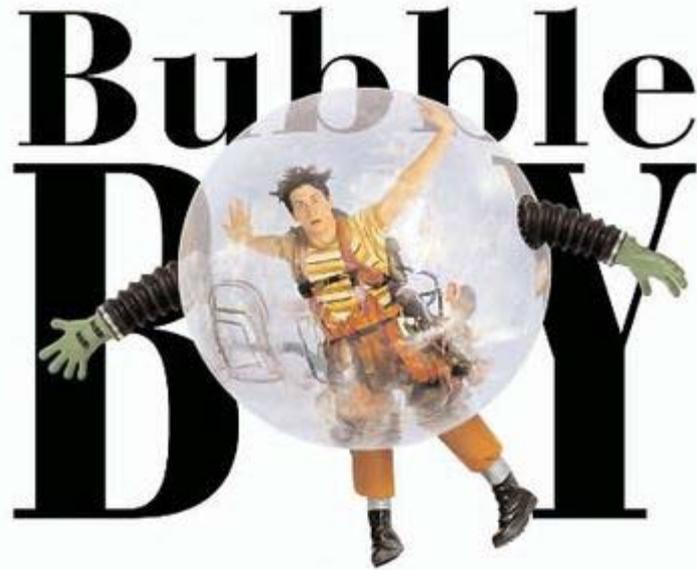
- Orphan drugs are part of medicine's personalization.
- Personalized medicine is better than impersonal medicine

Can diseases be subset?

- “Salami slicing” is frowned upon
- But subsets are permissible.
- Question #1---What is the disease?
- Question #2---Could the drug be useful for treating the disease outside the subset?
- Example: mAb for Breast cancer: YES
- Example: 2nd line therapy for renal cancer. NO
- Example: Stage IIb-VI melanoma

So what is a typical orphan
drug?

A JOURNEY OF 2,755.8 MILES
BEGINS WITH A SINGLE BOUNCE.

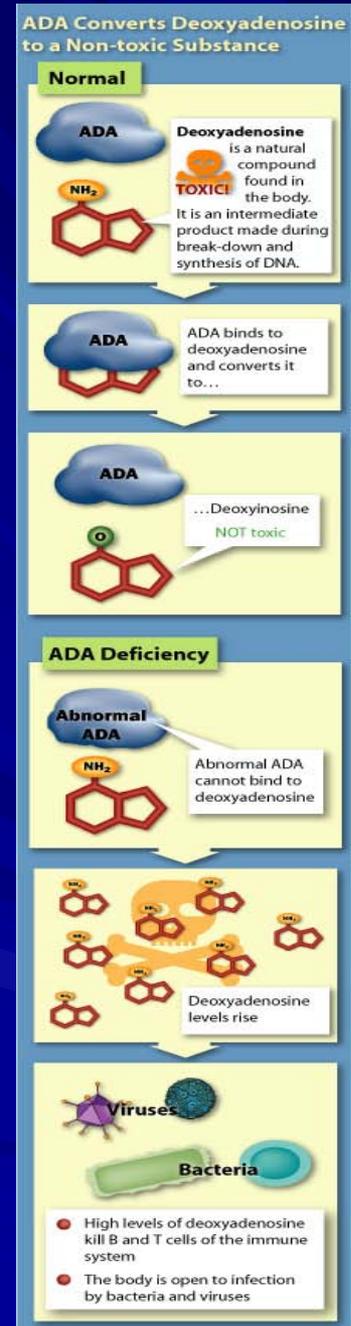


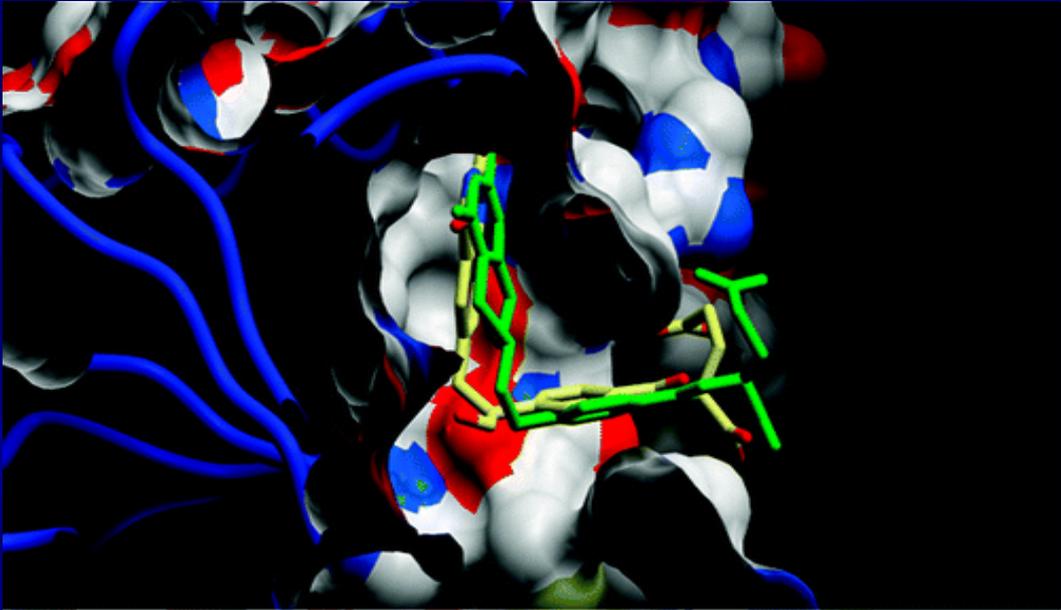
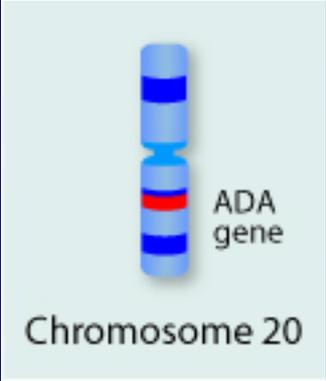
LIFE IS AN ADVENTURE. DON'T BLOW IT.

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Touchstone Pictures

Example: Adagen for ADA

- Population: 1:2x10⁵ to 1:1x10⁶ born with homozygous mutation.
- Causes Severe Combined Immunodeficiency
- Adagen is one of the first orphan drugs (based on n=12!); enzyme replacement therapy. Designated in 1984.







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Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

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ABSTRACT

Background We investigated the long-term outcome of gene therapy for severe combined immunodeficiency (SCID) due to the lack of adenosine deaminase (ADA), a fatal disorder of purine metabolism and immunodeficiency.

Methods We infused autologous CD34+ bone marrow cells transduced with a retroviral vector containing the ADA gene into 10 children with SCID due to ADA deficiency who lacked an HLA-

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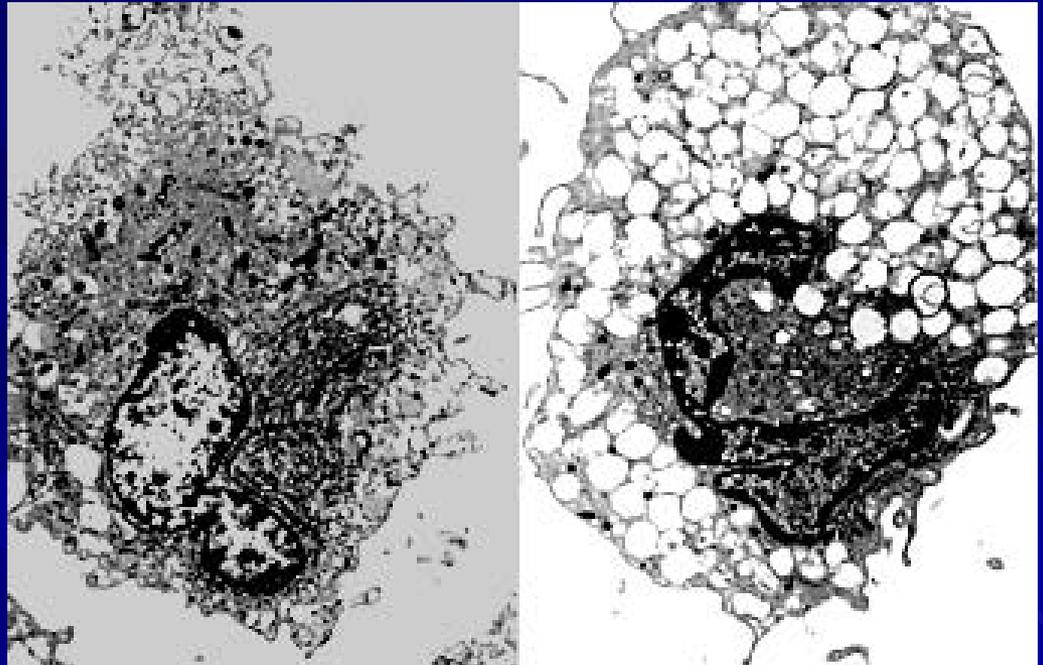
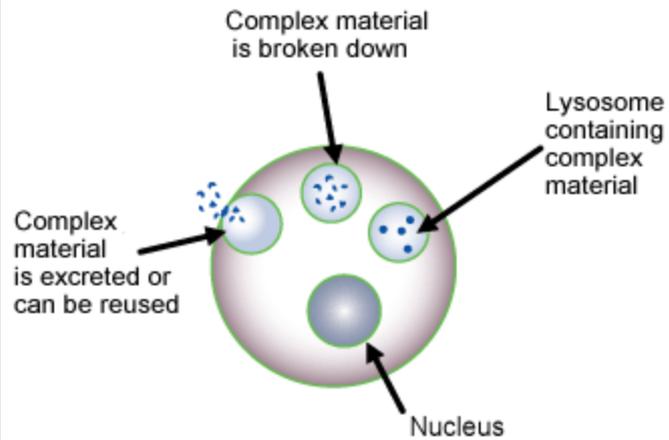
Naglazyme for MS Type VI (Maroteaux-Lamy syndrome)

- Mucopolysacharridosis, liposomal storage disorder.
- Estimated only 1,100 persons world-wide.
- Enzyme replacement can prevent these changes



Lysosomes—Intracellular Organelles

These membrane-bound structures contain numerous hydrolytic enzymes responsible for degrading a variety of cellular components, including polysaccharides, polypeptides, lipid-linked glycosyl groups, and damaged organelles.



Enzyme Replacement Therapies

- Some of the most extraordinarily expensive treatments in the history of mankind (some \approx \$400,000/pt/yr).
- FDA does not regulate price.
- Radically transformative beneficial to patients lives.
- Exclusivity lasts 7 years; knowledge is eternal.

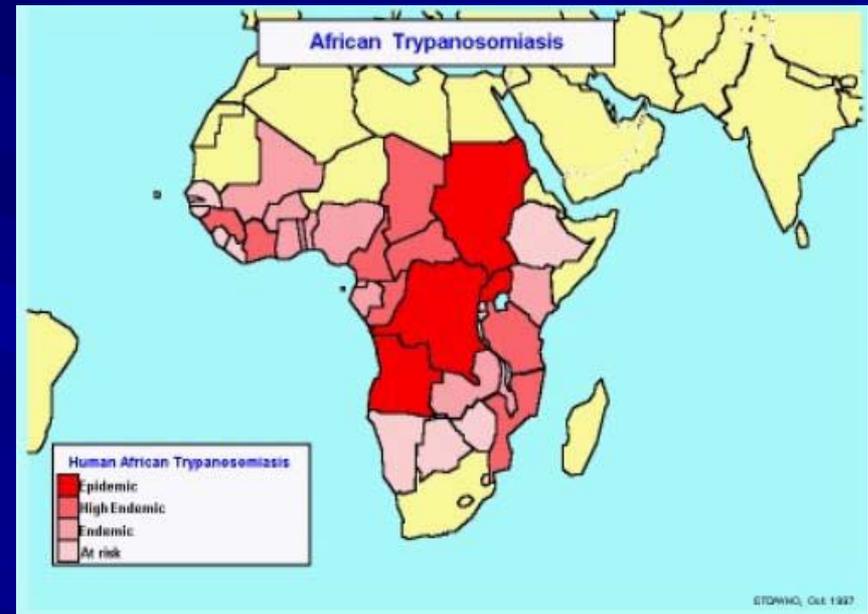
ExPTPA and Radiogardase for Radiologic Poisonings

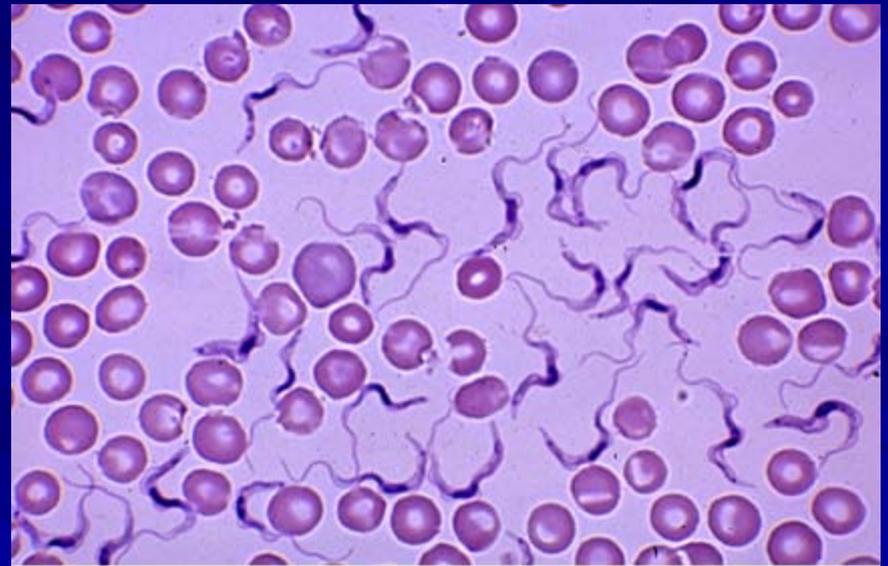
- Two approved therapies for heavy metal poisoning, designated as orphans in 2003, 2004.
- Chelation for highly-specific indications; current zero prevalence.



Example: Eflornithine for African sleeping sickness

- Extremely rare disease in the US and Europe
- Treatment would be highly personalized, based on travel history





Source: Lichtman MA, Shafer MS, Felgar RE, Wang N:
Lichtman's Atlas of Hematology: <http://www.accessmedicine.com>
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OOPD Grants Program

- \$16Million/yr
- Grants are up to \$400,000/yr x 4yrs
- Only for clinical testing of orphan drugs, phase I-III
- Manage about 60 grants, 10-15 new ones awarded annually
- About 30% of submissions are funded
- 47 have gone on to full market approval

Summary

- Basics of the Orphan Drug Act
- A bit about subsetting
- Wide variety of applications
- Much more to come

Questions?