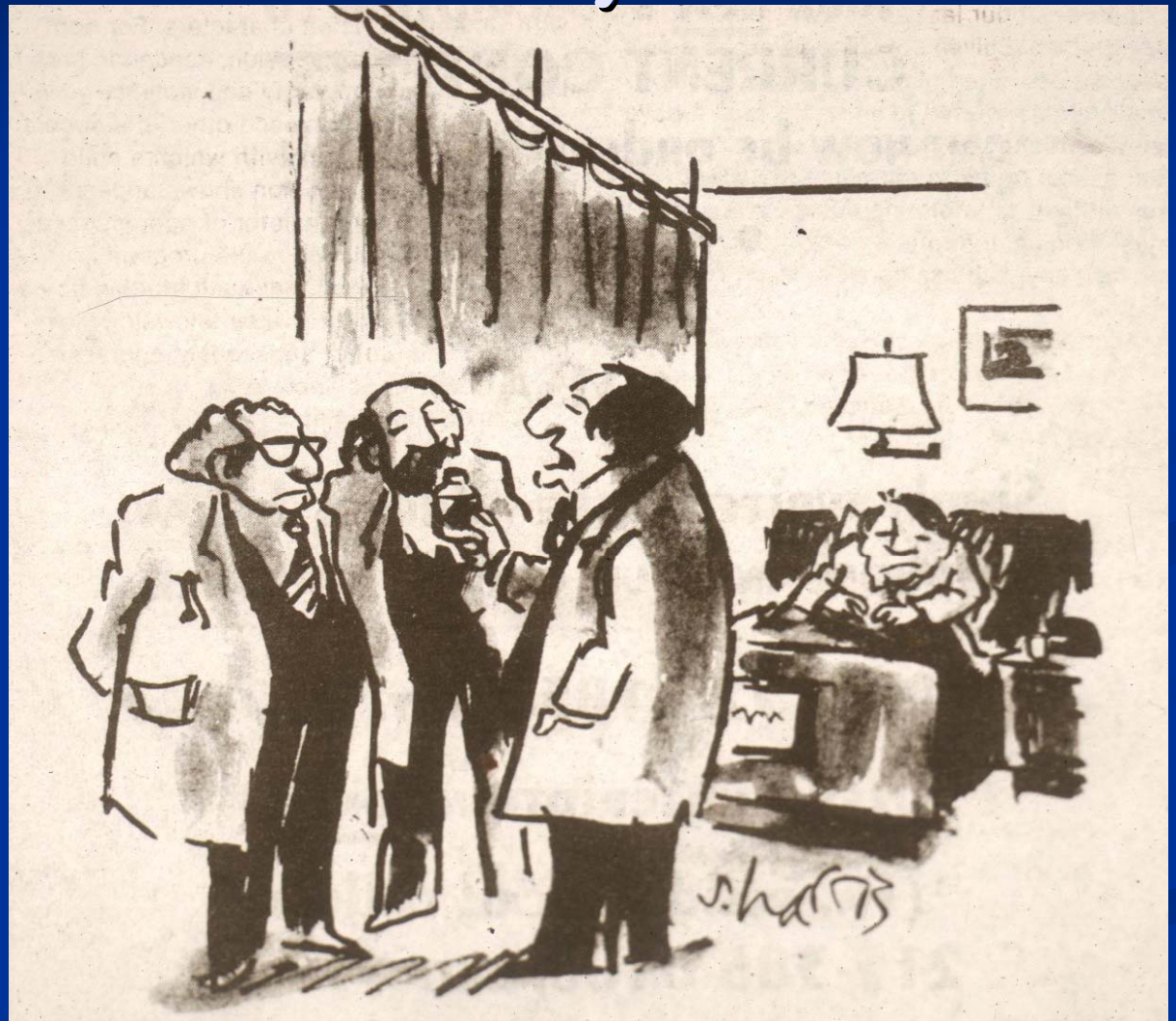
Respiratory Pathology of Laboratory Animals



"Don't forget, this medicine worked better on the rat than it did on the guinea pig, and I think he's more like a guinea pig."

Introduction

- The mouse is now the preferred species for most biomedical research, so the mouse lung has become the focus of basic research, toxicology and drug development.
- While the mouse is genetically closely related to man, it differs in lung anatomy, physiology, and immunology.

Introduction (cont.)

- Reasons for use of mice for pulmonary research
  - Technology for over expression or ablation of target genes.
  - Mouse gene defect leading to disease phenotype may translate to human genotype responsible for disease.
  - Increased understanding of mouse immune system.

Creation of GEM Pulmonary Models

- Lung directed – e.g. Clara cell 10kDa (CC10) protein promoter
- Externally regulated – e.g. tetracyline-inducible (use of two transgenic constructs) – for timing of expression. Allows adult, rather than developing lung to be targeted.
- Often used together with exogenous agent such as cigarette smoke, infection

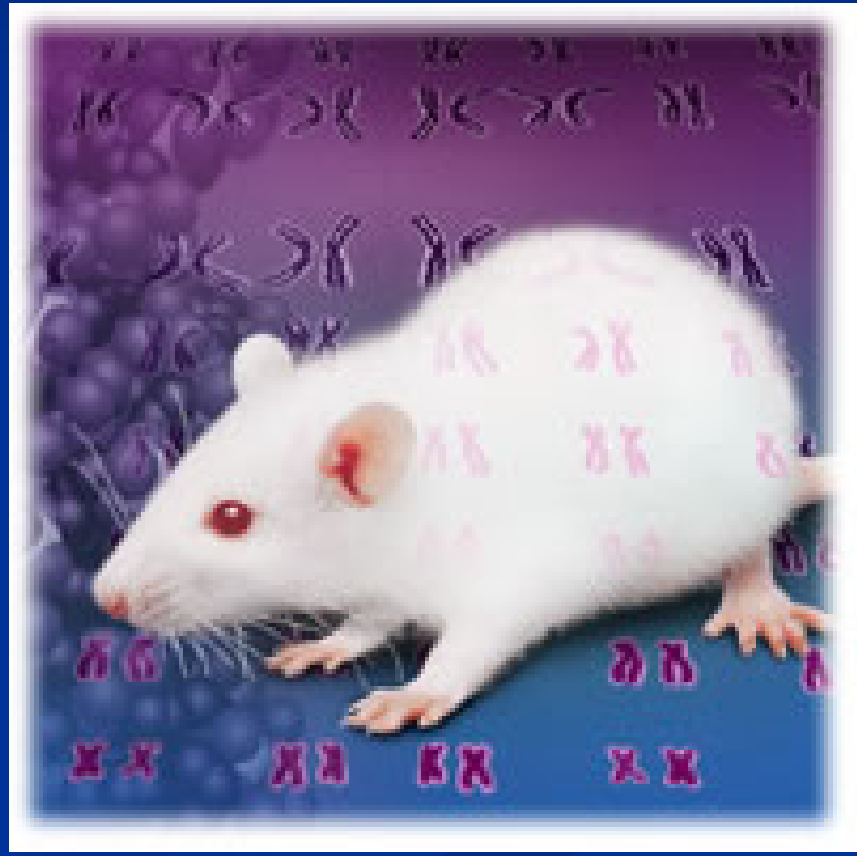
Advent of Genetically Engineered Mice (GEM)

- Increased prevalence of mouse pathogens
  - Increased trafficking of mice among laboratories
  - Increased susceptibility of GEM to infections

Rats !!!

- Recent advances in development of genetically engineered rats

- Likely to see a similar increase in pathogen prevalence



What pathogens are being found in genetically engineered rodents?

- Reemergence of previously recognized pathogens
- Emergence of new pathogens

Postnatal Lung Development

Completed Stage	Mouse/Rat	Human
Alveolar Development	4-7 days	Birth
Capillary Fusion and Septal Thinning	3 weeks	3 years
Alveolar Multiplication	5 weeks	8 years
Lung Growth	6-10 months	20 years

Comparative Respiratory Anatomy/Physiology

	Mouse	Rat	Human
Vomeronasal Organ	Present	Present	Absent
Nasal Turbinates	Double scroll	Double scroll	Simple Scroll
Lung Anatomy	Right: 4 lobes Left: 1 lobe	Right: 4 lobes Left: 1 lobe	Right: 3 lobes Left: 2 lobes
Pleura	Thin	Thin	Thick
Secondary Lobulation	Absent	Absent	Incomplete
Total Lung Capacity (TLC)	~1ml	10 ml	6000 ml
Total Lung (Parenchyma)	18%	24%	12%
Blood-Gas Barrier Thickness	0.32μm	0.38 μm	0.62 μm
Pulmonary Veins	Cardiac muscle	Cardiac muscle	Thin, mainly fibrous wall

Human Pulmonary Disease Models

- Chronic Obstructive Pulmonary Disease (COPD)
  - Emphysema
  - Asthma
- Lung Cancer
- Pulmonary Alveolar Proteinosis (PAP)
- Cystic Fibrosis
- Pulmonary Hypertension
- Pulmonary Fibrogenesis
- Pulmonary Toxicity