TOXICOLOY AND PHARMACOLOGY IN LABORATORY ANIMAL PATHOLOGY AND MEDICINE

PATHOLOGY OF LABORATORY ANIMALS

DAVIS-THOMPSON FOUNDATION
for veterinary and comparative pathology

University of Pennsylvania
School of Veterinary Medicine
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* Toxicology: the science and study of poisons, especially their effects

* Pharmacology: the science and study of drugs (and other therapeutic agents), especially their effects

* The specialty of the laboratory animal veterinarians and pathologists is in the field of biology of health/care and pathogenetic processes of disease of laboratory animals .

* Study of health/care—of what affects the organism's functions that are congruent with aliveness and well being

* Study of disease—of the mechanisms associated with- and the course of injury and functional impairment (including recovery form thereof)

* The veterinarian provides knowledge predominantly for animal health/care

*The pathologist provides knowledge predominantly for recognizing/identifying disease, and pathogenesis

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FROM "IDEA" TO MARKETED PRODUCT
("reduction to practice")

1. Biological lead/potential agent/unexpected-incidental observation

2. Pharmacologic effects

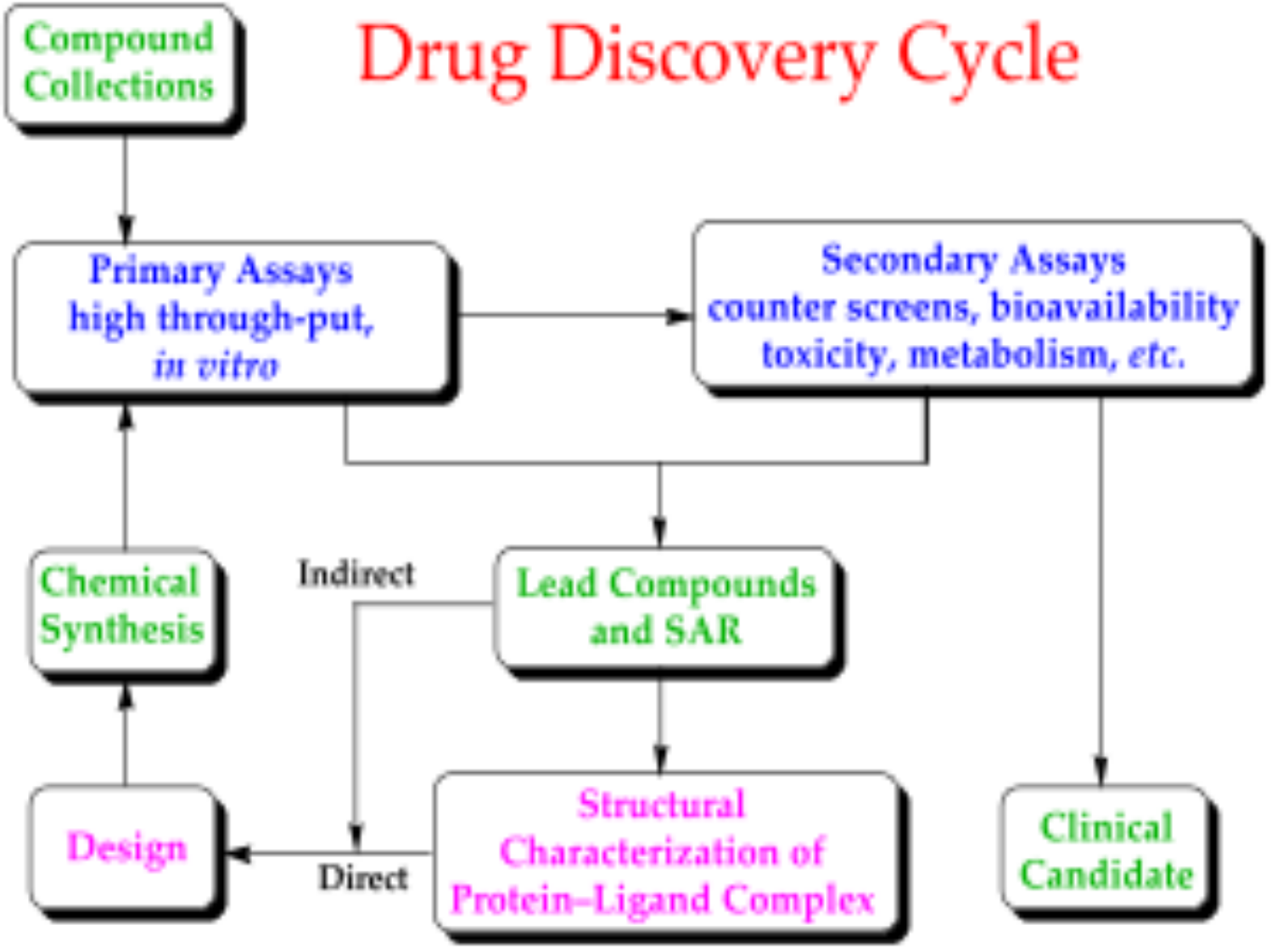
3. Non-clinical pre-Investigational New Drug (**IND**) toxicological assessment

4. Clinical trials—a Phases I, II, III along with further non-clinical evaluation, leading to a New Drug Application (**NDA**) and approval for marketing

5. Marketed product and further (post-marketing) monitoring

* In R&D 1 and 2 are the **"R"**, 3 and 4 are **"D"**; 3 and 4 are **regulatory-driven**

Bottom line:
provide evidence for **efficacy/potency**, **safety** and **manufacturing fidelity**



Wikipedia: drug discovery

PHARMACOLOGIC PATHOLOGY

* Pathologic evaluation of the effect on the intended therapeutic target

* Animal models of disease [target lesion(s)]

* Clinical observations, clinical chemistry/hematology, necropsy, etc.

* Histopathology

* Immunohistochemistery and other investigational methods

* Electron microscopy

* Provide “interpretation” and further directions based on the findings

* “Non-standard” (compared to regulatory-driven safety assessment)

* **Strategic Pathology (Candidate Optimization; Exploratory Toxicology)**

DIABETIC NEPHROPATHY/FIBROSIS

Histopathologic severity scoring for:

* Fibrous tissue

* Tubules

* Interstitium (other than fibrous tissue; e.g., inflammatory cell infiltrate)

* Vasculature

* Glomeruli

* Overall nephropathy

Interpretation/suggestion in addition to severity scoring analysis:
Fibrous tissue decrease occurred but not the desired collagen fiber type
Effect on overall nephropathy did not match the effect on fibrous tissue

NONALCOHOLIC STEATOHEPATITIS (NASH)

Severity scoring for:

* Steatosis

* Inflammation

* Hepatocellular ballooning

* Fibrosis stage

* Published NASH scoring is based on steatosis, inflammation and ballooning

Interpretation/suggestion in addition to scoring analysis:
NASH scoring did not always reflect the severity of liver pathology. Consider comments on mitosis, necrosis, degeneration, bile duct proliferation, etc. to reflect pathologic state of the liver.

NON-CLINICAL TOXICITY (SAFETY) ASSESSMENT

* Safety: product's toxicology profile, nature of toxicity, margin of safety, and **relevance to man**

* Studies in animals and *in-vitro*

* Oral and intravenous routes of administrations are basic; others as needed

* Rodent (rat/mouse) and non-rodent(dog) are basic, usually also rabbit, g. pig, hamster, NHP, others

* Clinical observations, food consumption, clinical chemistry, hematology, urinalysis, ophthalmic/cardiac evaluations, body weights, necropsy, organ weights, histopathology, etc.

* Carcinogenicity, reproductive and genetic toxicity, and "special" as needed

* Safety pharmacology: cardiac, respiratory and renal, and more as needed

INVESTIGATIVE TOXICOLOGIC PATHOLOGY

* Investigative pathology of the nature of findings during the course of the regulatory non-clinical toxicology studies

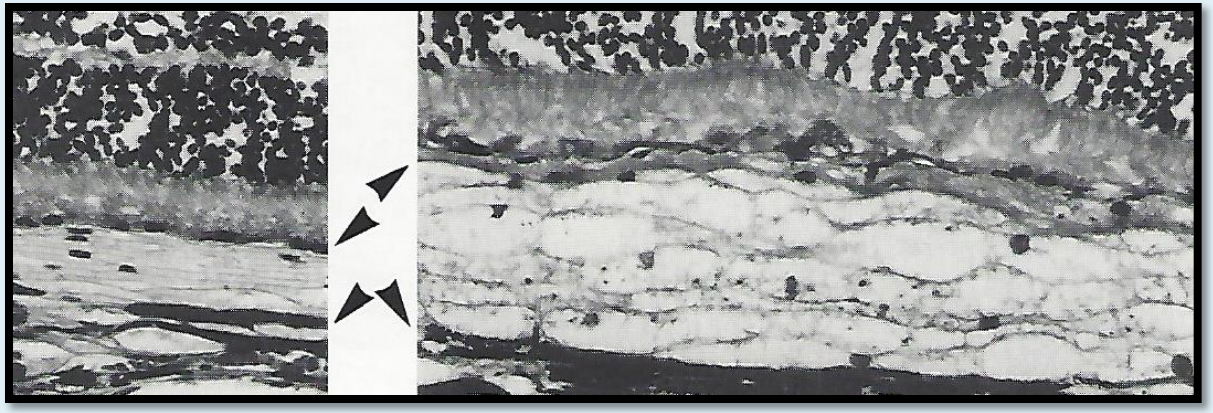
* In depth clarification to assist in the determination of safety, particularly relevance to man

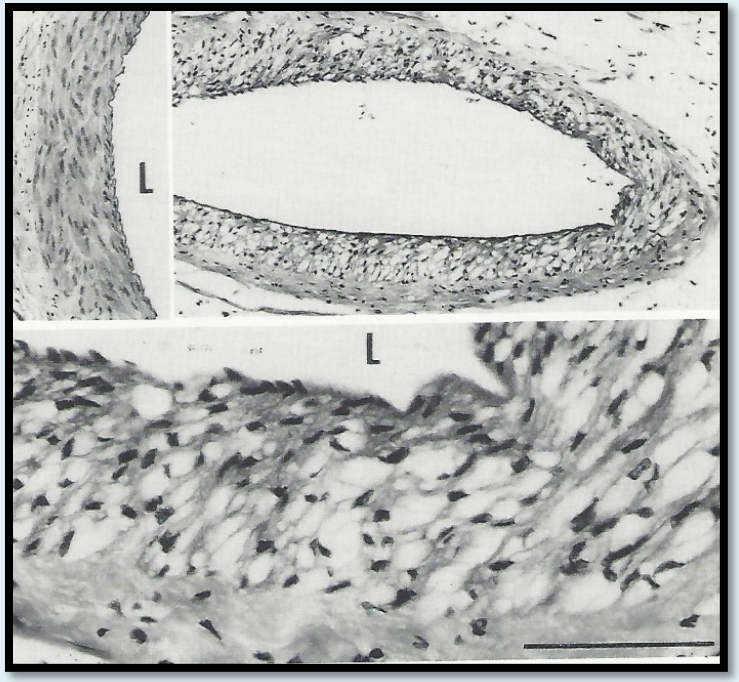
* Comparative anatomy, physiology and pathology

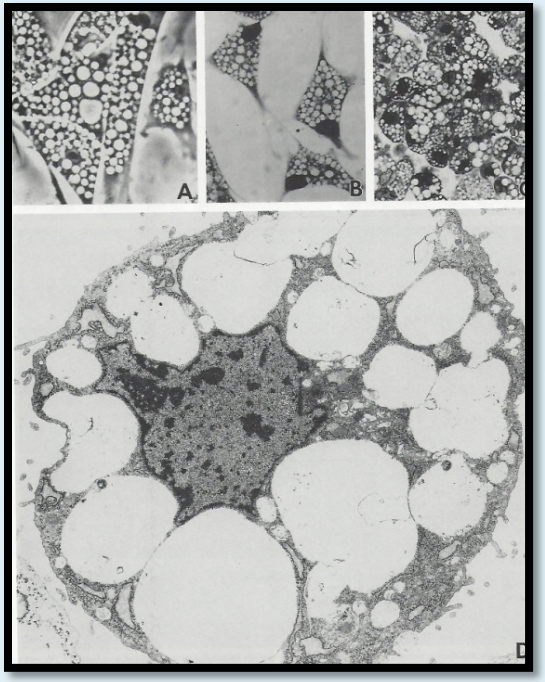
* A good deal of similarities between animals and man, yet considerable dissimilarities (in animals but not in man, and in man that cannot be predicted in animals)

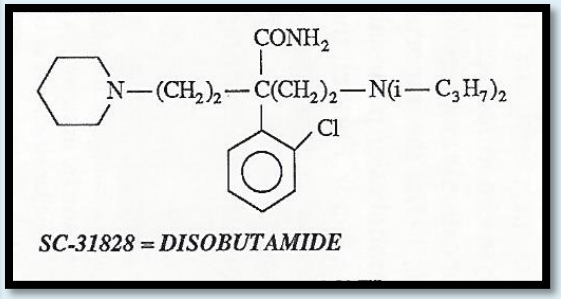
* Is every change induced by the test article a sign of toxicity?

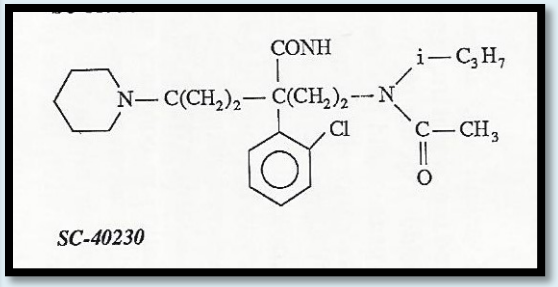
THE CASE OF DISOBUTAMIDE











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THE TERRAIN

* “In jargon” (NCE, SAR, MTD, NOEL, NOAEL, etc.)

* Potential for a highly inter-disciplinary professional growth

* Investigation of a wide variety of **novel** agents intended for a wide variety of diseases

*The vast repertoire of physiologic and biochemical processes is manifested via a comparatively limited types of clinical and morphological changes (the limitation of “if do not see it, it is not there”)

* Species and genetic (spontaneous and engineered) strain differences: applications to non-clinical toxicological evaluation and relevance to man

THE TERRAIN (continued)

* The Animal Welfare Act [AWA (USDA)] and Good Laboratory Procedures [GPLs (FDA)]

* Collaboration with non-medical scientists:
  communication with the “specialist”
  inter-disciplinary opportunities *vs*. “leave me behind the microscope”
  GLPs’ Study Director and the American Board of Toxicology

* Collaboration with non-scientific managers:
  “independence” and “team playing”

* The for profit business environment:
  unavoidable changes and ethical considerations

CAREER DEVELOPMENT

* When research, regulatory (development) and for profit business are “driving” the work environment

* Academia

*Government (NIH-NIEHS/NTP; FDA-NCTR)

* CIIT/The Hamner Institute for Health Sciences

* Industry (pharmaceutical (ethical) vs. chemical)

* Toxicology contract laboratories

* American Board of Toxicology (ABT)

* Toxicologic Pathology societies (STP, BSTP, ESTP, JSTP)

* Toxicology Societies (SOT, ACT)

SUMMARY

The fields of pharmacology and toxicology offer an exciting and rewarding interdisciplinary specialty for laboratory animal veterinarians and pathologists.

Veterinarians are trained as interdisciplinary comparative medical professionals. In the context of what was presented, their contribution is unmatched by other scientific-medical professionals.

The potential for personal career satisfaction and advancing pathology, medicine and health is great.