פיתוח תרופות חדשניות – חיזוי פוטנציאל סיכון במהלך הניסויים הפרה- קליניים

The Toxicologic Pathologists - Their Role and Responsibilities During Drug Development – Challenges in Interpretation of Preclinical Safety Studies

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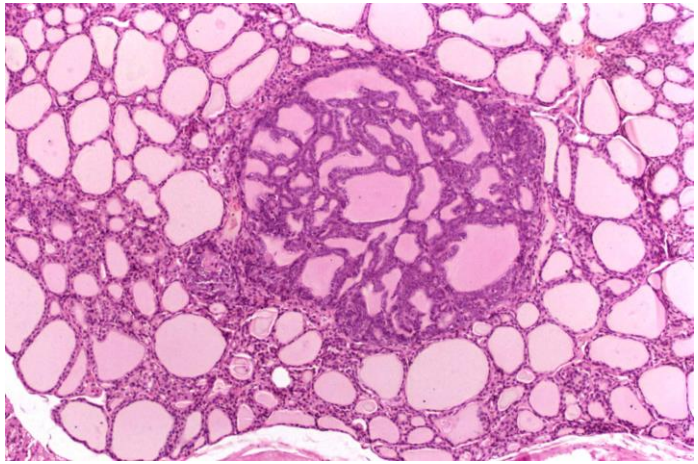
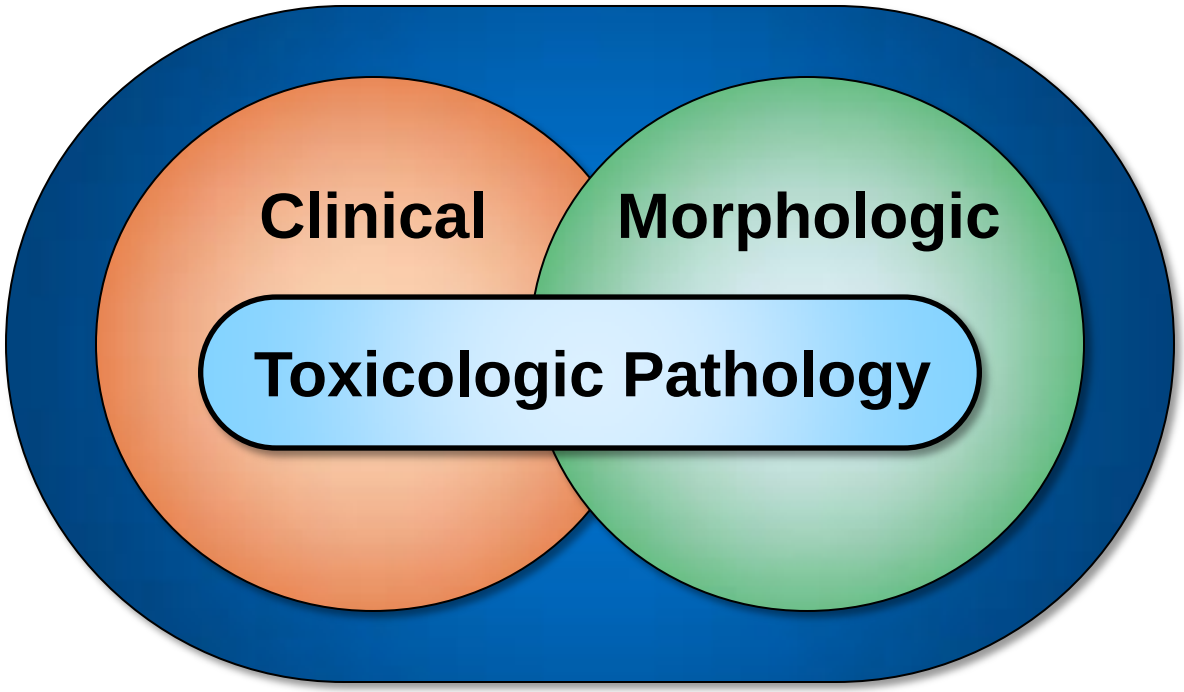


OUTLINE OF THE LECTURE

- 1st half - Role of **Toxicologic Pathologist** in drug development
- 2nd half – Application of imaging technologies in Toxicologic Pathology – **"The Magnetic Resonance Imaging (MRI) Histology = Smart sections"**

The Discipline of Toxicologic Pathology

Definition: Investigation of structural and functional consequences of injurious stimuli (i.e., chemicals, drugs or physical agents)



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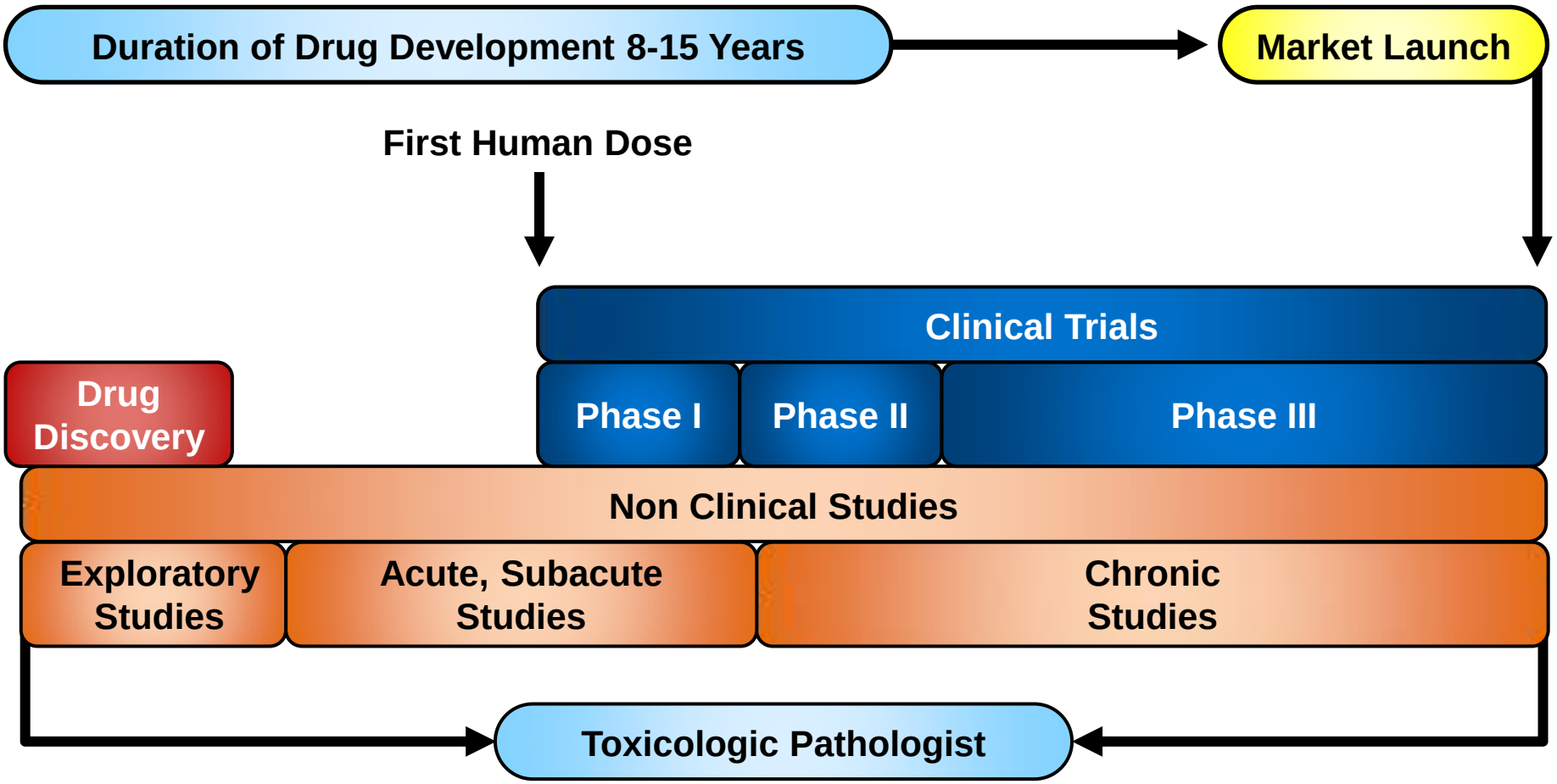
The Role of the Toxicologic Pathologist in the Biopharmaceutical Industry

Susan van Tongeren[1], Jane A. Fagerland[2], Michael W. Conner[3], Kelly Diegel[4], Kevin Donnelly[5], Branka Grubor[6], Alric Lopez-Martinez[7], Anne Provencher Bolliger[8], Alok Sharma[9], Sarah Tannehill-Gregg[10], Patricia V. Turner[11] and Lyn M. Wancket[12]

Abstract

Toxicologic pathologists contribute significantly to the development of new biopharmaceuticals, yet there is often a lack c awareness of this specialized role. As the members of multidisciplinary teams, toxicologic pathologists participate in all aspects c the drug development process. This review is part of an initiative by the Society of Toxicologic Pathology to educate scientist about toxicologic pathology and to attract junior scientists, veterinary students, and veterinarians into the field. We describe th role of toxicologic pathologists in identifying candidate agents, elucidating bioactive pathways, and evaluating efficacy and toxicit in preclinical animal models. Educational and specialized training requirements and the challenges of working in a global environmer are discussed. The biopharmaceutical industry provides diverse, challenging, and rewarding career opportunities in toxicologi pathology. We hope that this review promotes understanding of the important role the toxicologic pathologist plays in dru development and encourages exploration of an important career option.

The Pivotal Role of the Toxicologist Pathologist in All Phases of Drug Development



The preclinical evaluation – What are the goals?

- **Pre-clinical pharm/tox data are used to:**

  - Identify target organs and make correct interpretation about their significance
  - Identify need for specialized clinical safety monitoring
  - Select starting doses/regimens
  - Estimate pharmacokinetics, i.e. investigate the relationship between exposure and toxicity

The purpose of animal (preclinical) safety studies is not to use it for direct extrapolation of animal data to humans. Rather, the goal is to use animal data to characterize potentially adverse changes that might be expected to occur in humans in response to administration of a particular drug and recommend the dose level that should be safe to start with.

Challenges in drug development - The importance of correct evaluation and interpretation of preclinical toxicity findings

- The successful navigation of a new molecule or chemical through the Discovery and Development process to market requires a series of carefully considered "**GO, NO GO**" decisions. Decisions related to toxicity issues that result in the unnecessary termination of a promising molecule are as unfortunate as allowing a potentially harmful molecule to progress.
- It is therefore pivotally important, using extensive investigation, experience and knowledge, to make a careful and integrated assessment of in-life, anatomic and clinical pathology findings derived from toxicity studies

The optimal outcome of preclinical program…

- **The optimal goal - outcome is to predict the preclinical long-term SAFETY OF THE DRUG from the 14 days and 3 months studies**
- **The pharmaceutical companies are eager to predict unsafe drugs as early as possible, without wasting expensive resources, but on the other hand, not to loose good drugs that induce irrelevant pathology in preclinical program**

NEWS & ANALYSIS

FROM THE ANALYST'S COUCH

Does size matter in R&D productivity? If not, what does?

Michael Ringel, Peter Tollman, Greg Hersch and Ulrik Schulze

Freudian couch, Steve Hellerstein/Alamy

NATURE REVIEWS | DRUG DISCOVERY VOLUME 12 | DECEMBER 2013 | 901

- Importance of much experienced director of R&D, known for exercising good judgment.
- Importance of location of the company headquarter, market size and therapeutic area.
- It is estimated that 90% of industry R&D expenditures now go into molecules that never reach the market. In this context, making the right decision on what to progress to late-stage clinical trials is paramount in driving productivity.
- **According the Pfizer: *"about 2/3 of the phase I compounds could have been predicted to be likely failures on the basis of available data"*.**
- There is strong bias in most R&D organization in **"progression seeking"** behavior instead of **"truth seeking"** behavior (for reasons such as **job-security, position in the organization and passion to the compound).**

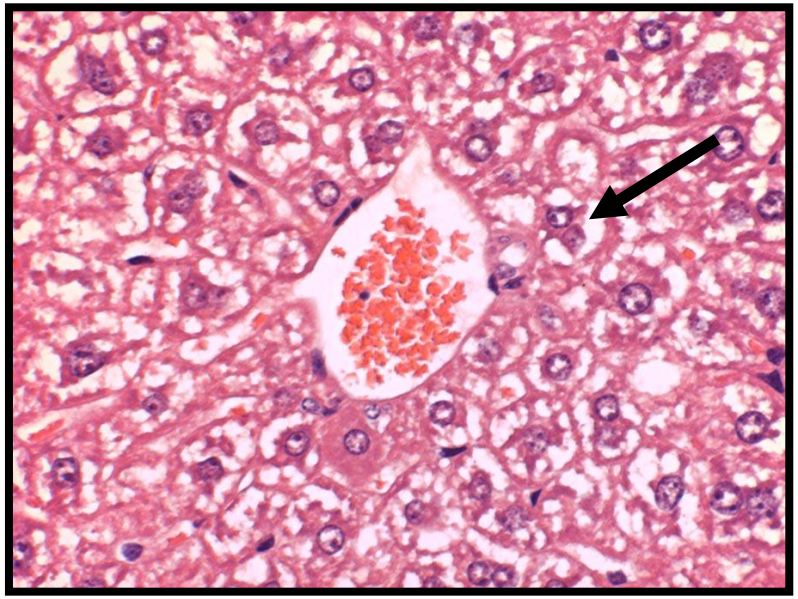
Histopathology –
The Art of Vision and Description…

Microscopy Will Remain a Cornerstone of Surgical Pathology

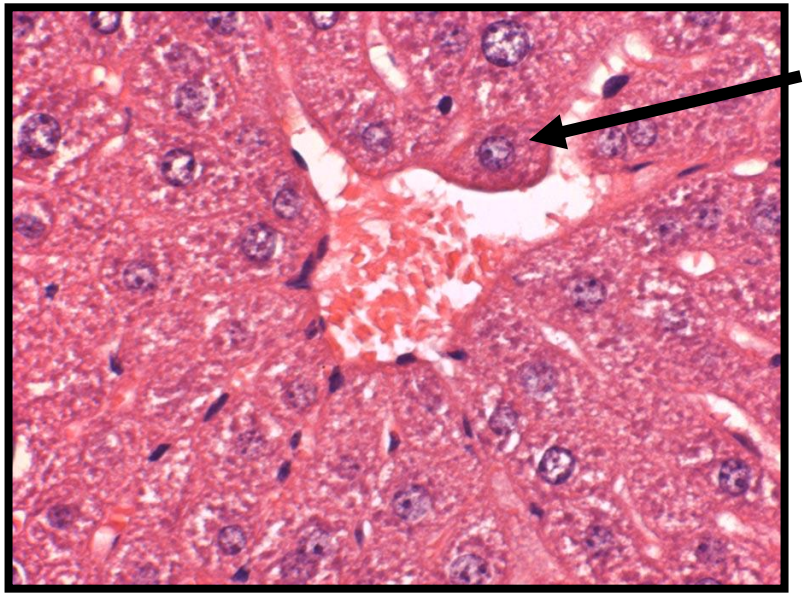
Rosai J, Laboratory Investigation (2007) **87,** 403–408

A “Pharmacological” (Adaptive) Effect in the Liver

Control

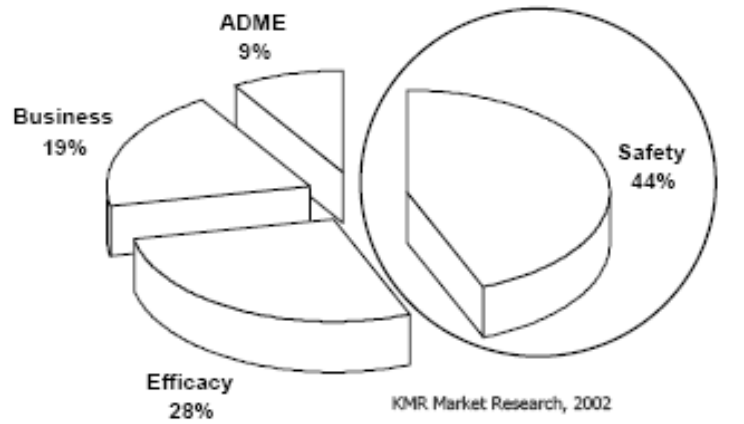


Treated – Hepatocytic Hypertrophy



Drug-induced target organ toxicity

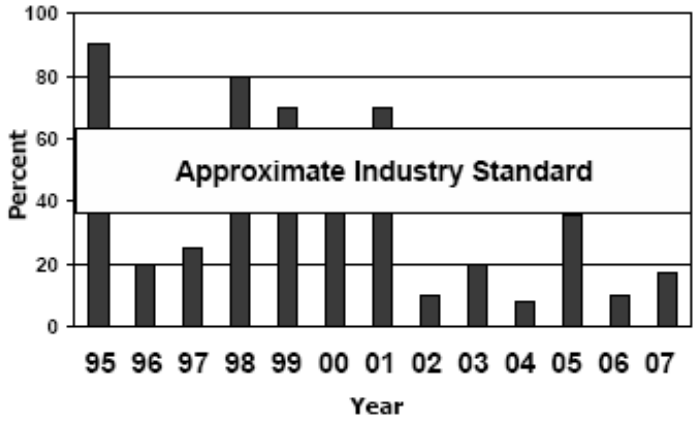
Causes of Attrition of Pharmaceutical Candidates: The Opportunity



KMR Market Research, 2002

Kola I. *Clin Pharm Ther* 83: 227-230, 2008

Candidate Attrition Due to Toxicity: BMS Experience



Historic Causes of Attrition
All Therapeutic Areas

Toxicity mechanism (safety)	%*
Pharmacologic target-based	23.3
Biotransformation-related	21.9
Immune-mediated	11.0
Target toxicity organ or tissue	
Cardiovascular	27.4
Liver	11.0
Fetal tissues (teratogenicity)	9.6
Hematologic	8.2
CNS/PNS	8.2
Retina	6.8
Genotoxicity	5.5
GI, pancreas, testis, muscle, lung, carc, renal, acute toxicity	<4.1

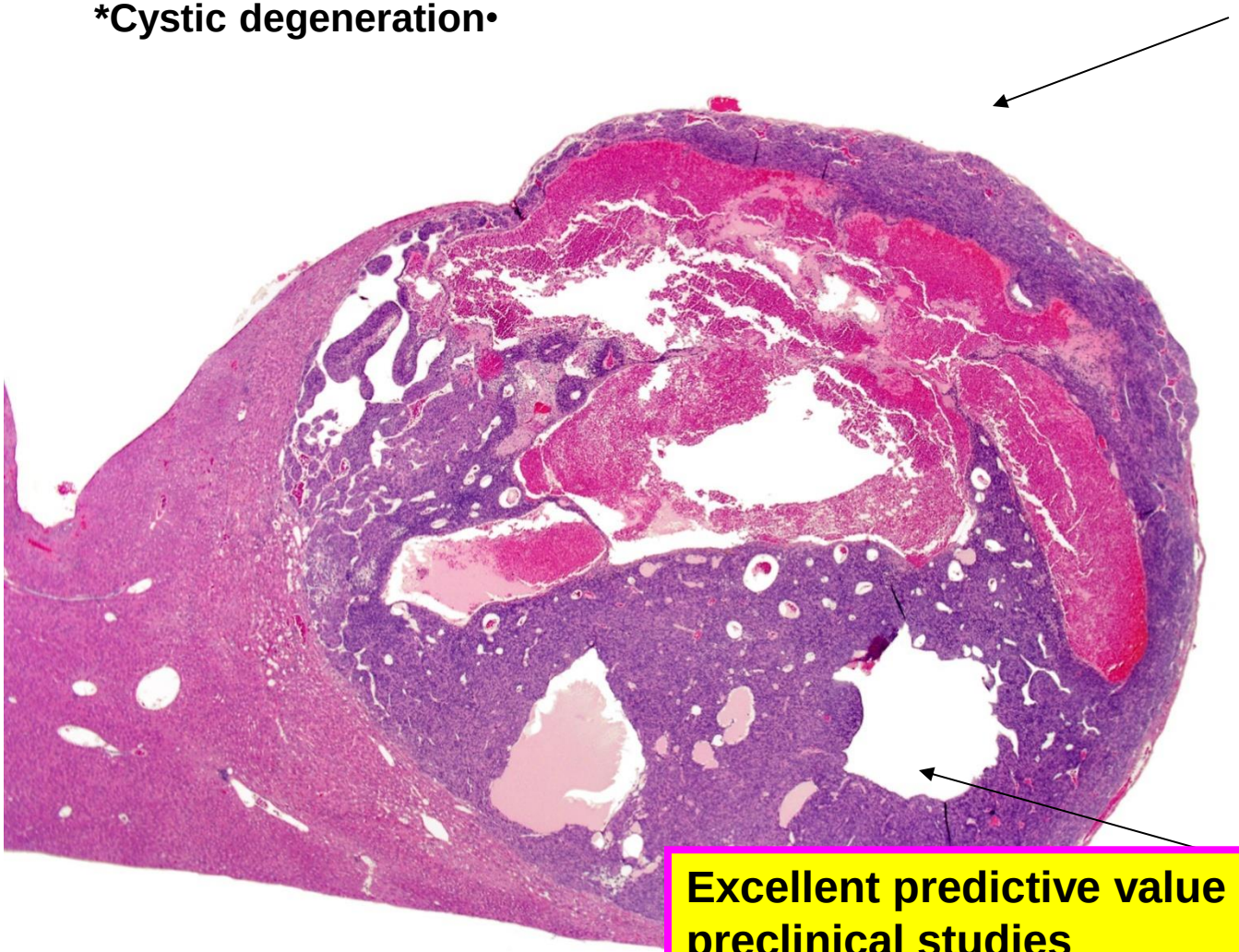
* Total ≥ 100% due to overlapping categories multiple toxicities (Car BD. *American Drug Discov*, 1:53-56, 2006)

Liver section from a male mouse treated with 1 mg/kg Kawa Kawa for 2 years. Note (arrows), hepatoblastoma.

Other toxic lesions observed in the liver of Kawa Kawa treated mice:

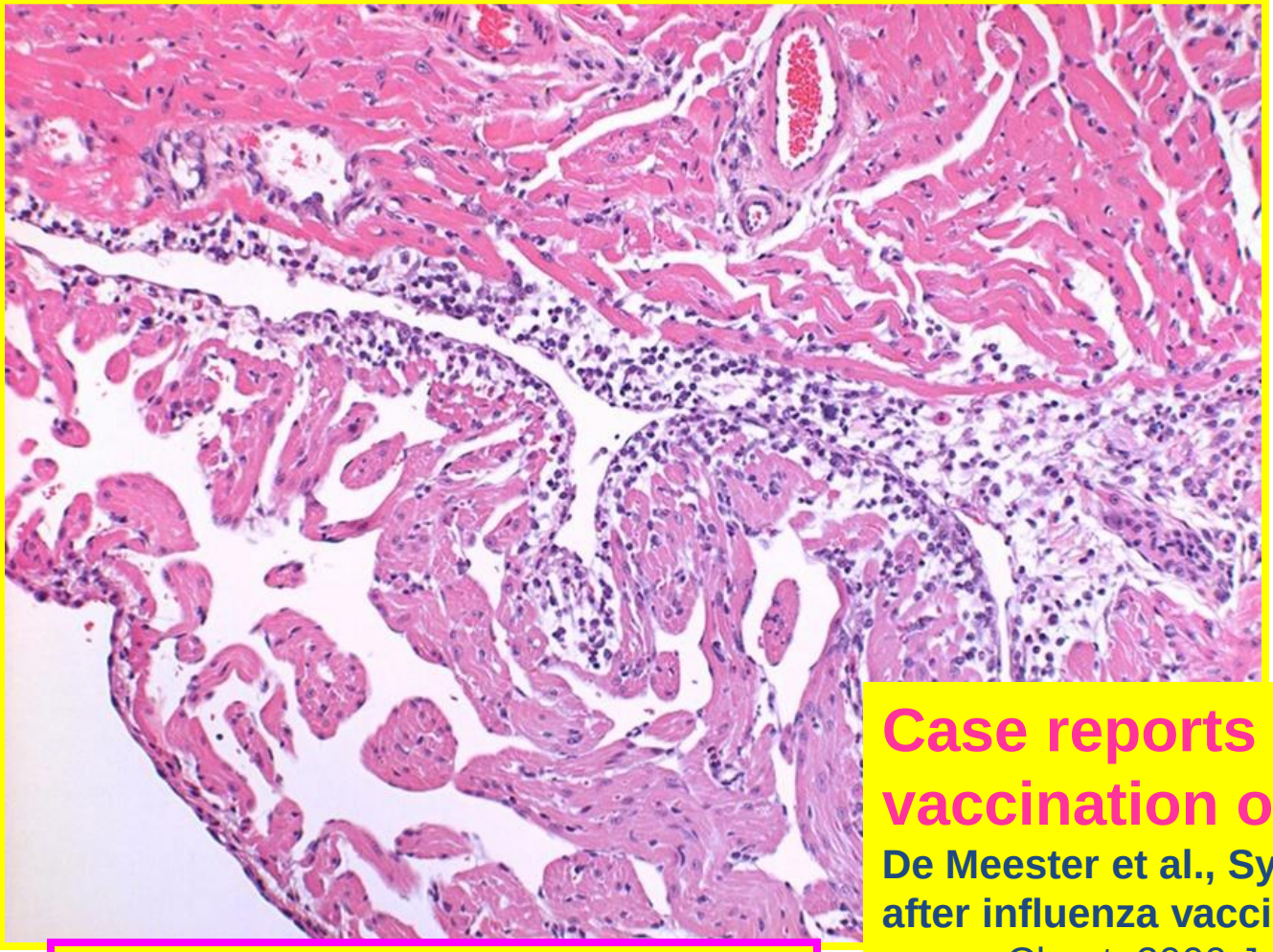
***Hepatpcytic fatty changes•**

***Cystic degeneration•**



Excellent predictive value of preclinical studies

Flu vaccine-induced pericarditis in mice



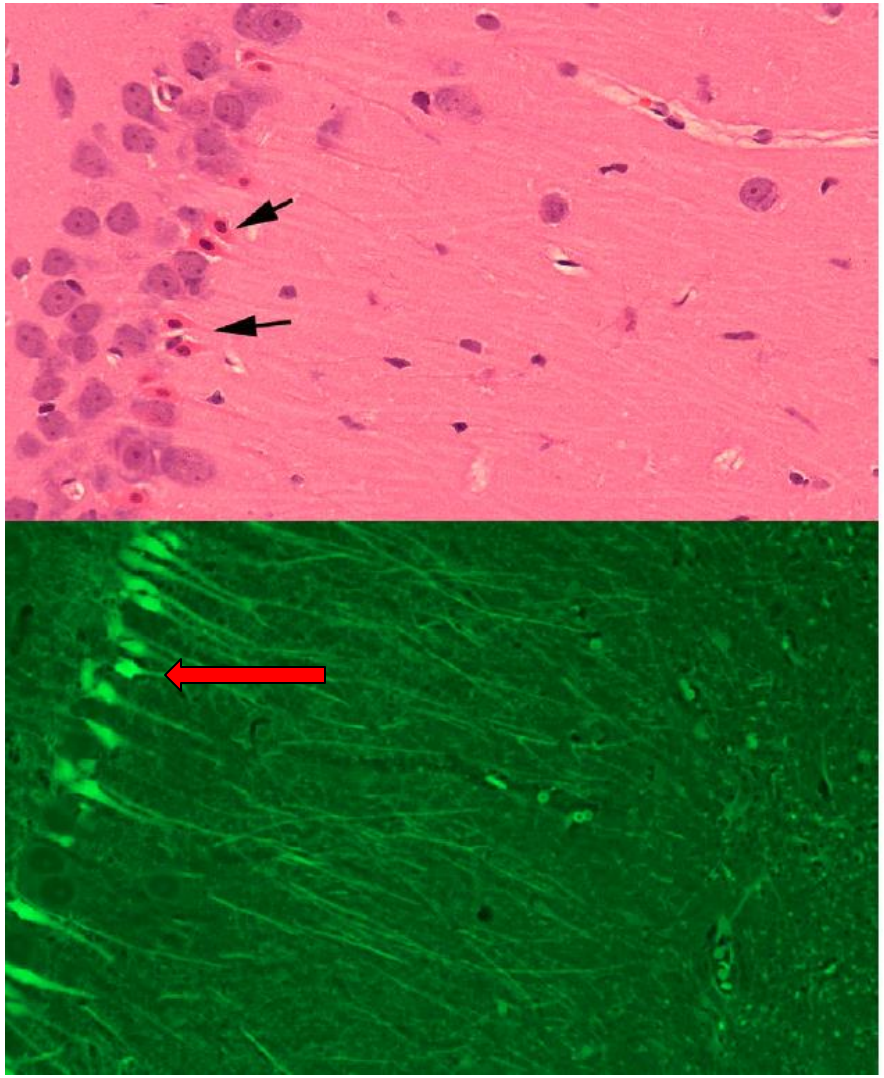
Excellent predictive value of preclinical studies

Case reports of post-flu vaccination of pericarditits

De Meester et al., Symptomatic pericarditis after influenza vaccination: report of two cases Chest. 2000 Jun;117(6):1803-5

Godreuil wt a., Acute haemorrhagic pericarditis following influenza vaccination Presse Med. 2003 Feb 15;32(6):258-9.

Opioid Neurotoxicity: Neuropathologic Effects in Rats of Different Fentanyl Congeners – Acute effect

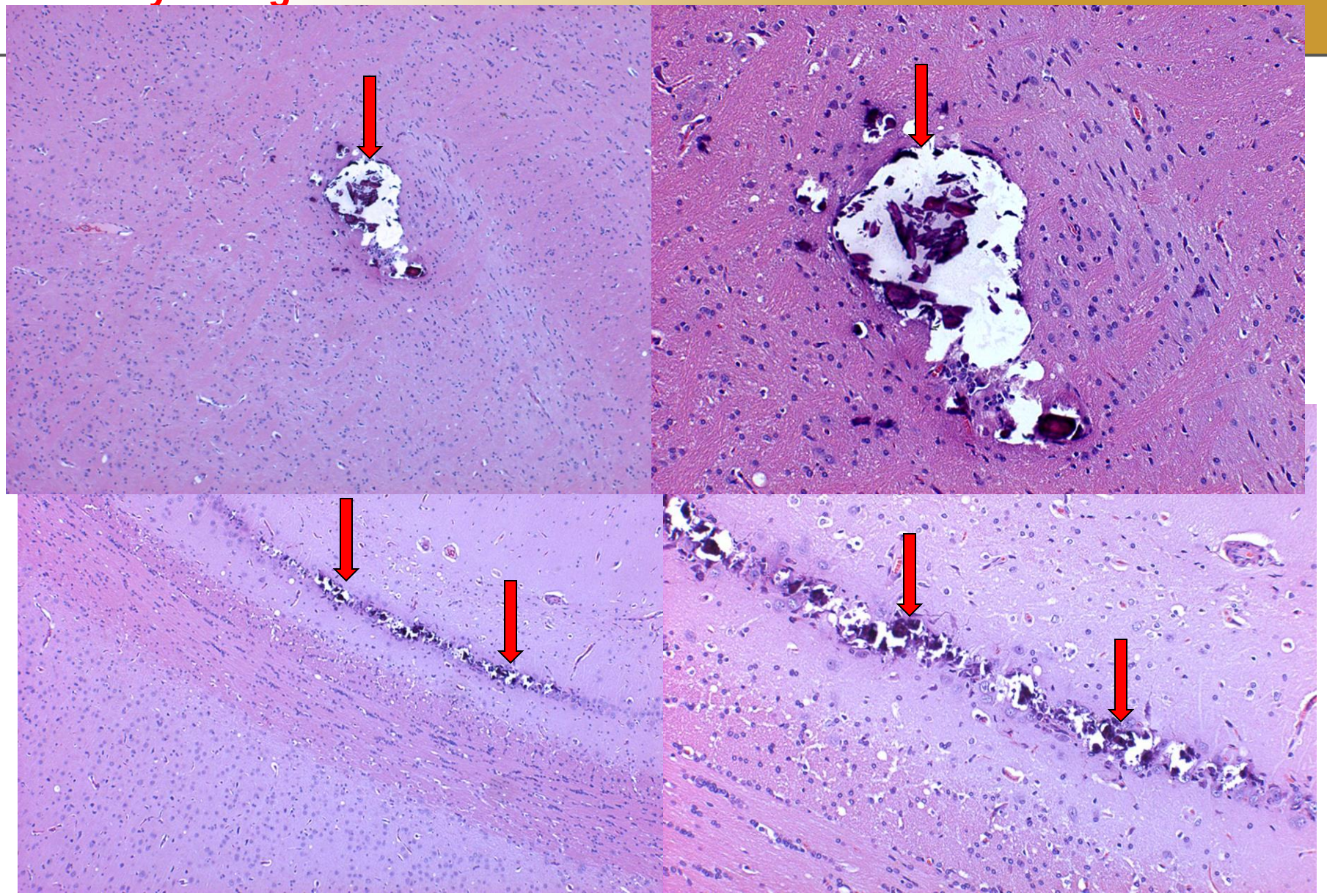
- 

Hippocampal CA_1 sector (rat) 24 hrs. after fentanyl treatment

(H&E- *vs.* Fluoro-Jade B-stained sections)

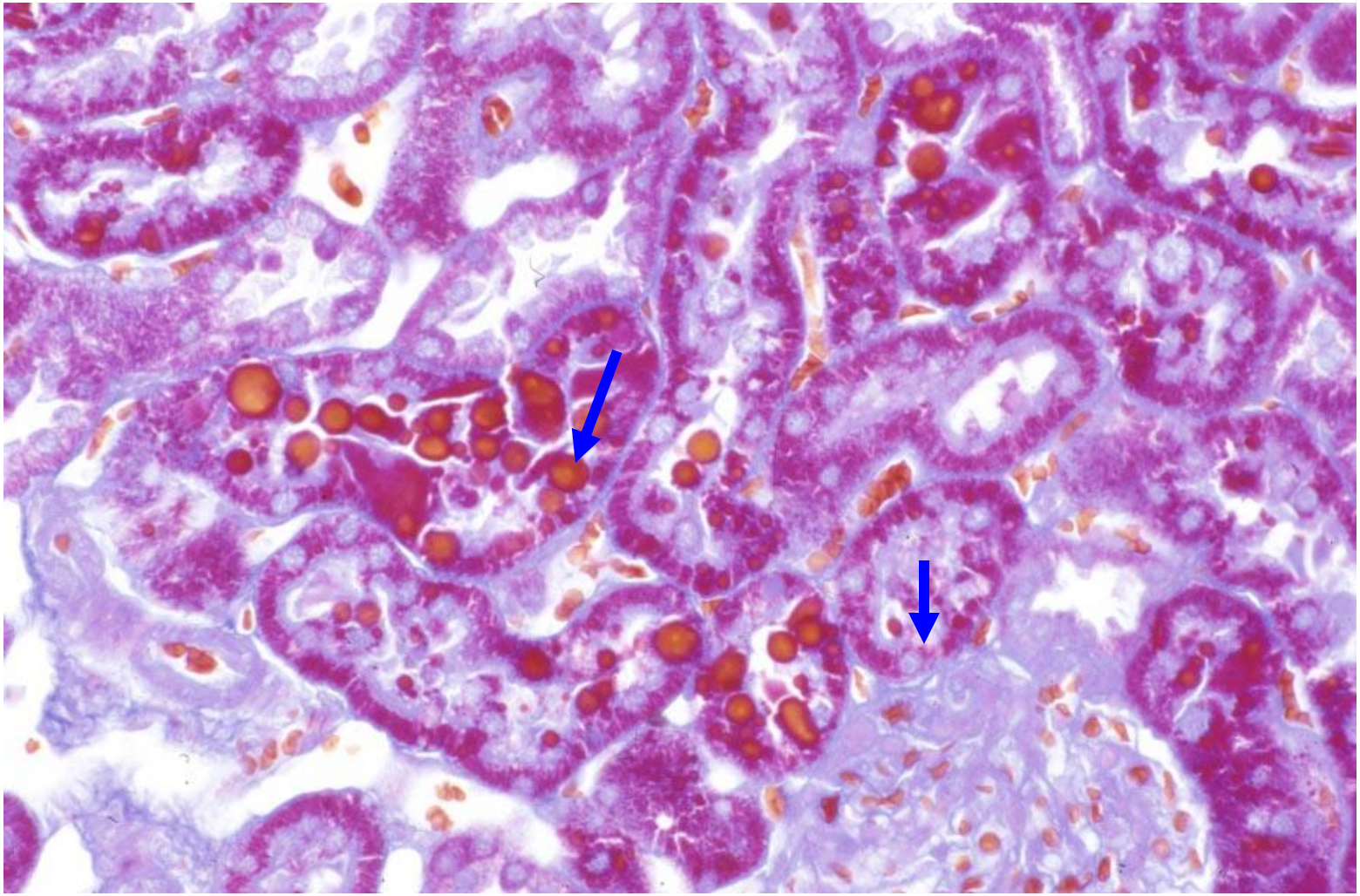
rats

Opioid Neurotoxicity: Neuropathologic Effects in Rats of Different Fentanyl Congeners – Chronic effect



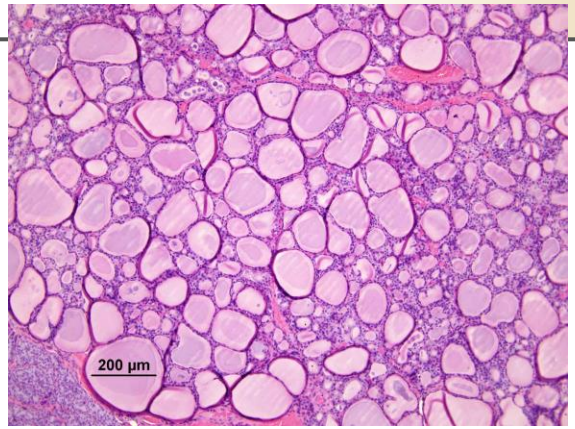
Histopathological finding that may be of no relevance to human

HYALINE DROPLET NEPHROPATHY (MALLORY-HEIDENHAIN STAIN – MALE FISCHER 344 -O-NITROTOLUENE

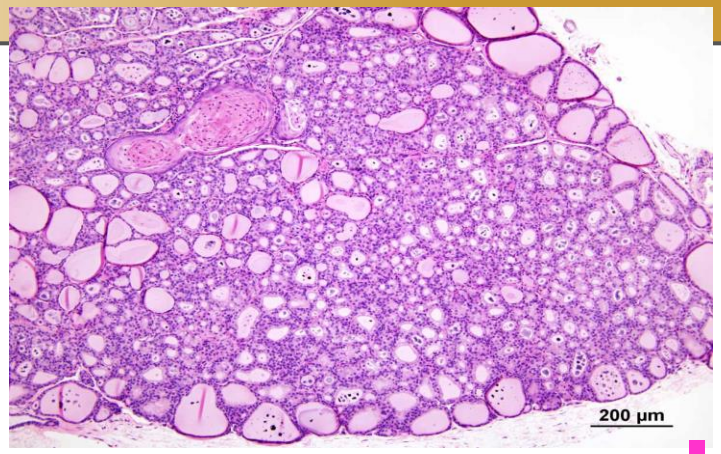


The case of irrelevance of thyroid adenomas noted in rats treated with hepatic liver inducers of P450 enzymes

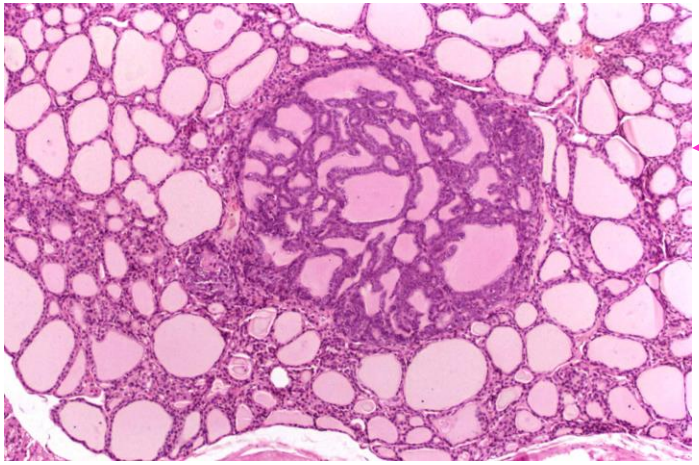
Treatment related thyroid hypertrophy, hyperplasia and adenoma secondary to liver microsomal induction



Control thyroid



Thyroid from a treated rat –
follicular hypertrophic epithelium



Follicular cell adenoma

Quantitative Toxicologic Pathology

TOXICOLOGIC PATHOLOGY, vol 30, no 1, pp 93–96, 2002

Qualitative and Quantitative Analysis of Nonneoplastic Lesions in Toxicology Studies

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[3]*National Institute for Environmental Health Sciences, Research Triangle Park, North Carolina, 27709*

TABLE 1.—Some commonly used severity grading schemes.

Grading scheme I

0 = Not present
1 = Minimal (< 1%)
2 = Slight (1–25%)
3 = Moderate (26–50%)
4 = Moderately Severe/high (51–75%)
5 = Severe/high (76–100%)

Grading scheme II

	A	B
Grade 1 = Minimal	(< 10%)	(0–25%)
Grade 2 = Mild	(10–39%)	(26–50%)
Grade 3 = Moderate	(40–79%)	(51–75%)
Grade 4 = Marked	(80–100%)	(76–100%)

Grading scheme III

Grade 1 = Minimal
Grade 2 = Slight (same as mild)
Grade 3 = Moderate
Grade 4 = Marked (same as severe)
Grade 5 = Massive (same as very severe)

TABLE 2.—Severity grading scheme criteria for various organs.

Grade 1 (+1): *Minimal*. This corresponds to a histologic change that may be barely noticeable to changes considered so minor, small, or infrequent as to warrant no more than the least assignable grade (0–10%). For focal, multifocal or diffusely distributed lesions, this grade is used for processes where < 10% of the tissue is involved. For hyperplastic/hypoplastic/atrophic lesions, this grade is used when the affected structure or tissue has undergone < 10% increase or decrease in volume.
Grade 2 (+2): *Mild*. This corresponds to a histologic change that is a noticeable but not a prominent feature of the tissue. For focal, multifocal or diffusely distributed lesions, this grade is used for processes where between 11–20% of the tissue is involved. For hyperplastic/hypoplastic/atrophic lesions, this grade is used when the affected structure or tissue has undergone between an 11% and 20% increase or decrease in volume.
Grade 3 (+3): *Moderate*. This corresponds to a histologic change that is a prominent feature of the tissue. For focal, multifocal or diffusely distributed lesions, this grade is used for processes where 21–40% of the tissue section is involved. For hyperplastic/hypoplastic/atrophic lesions, this grade is used when the affected structure or tissue has undergone between a 21% and 40% increase or decrease in volume.
Grade 4 (+4): *Marked*. This corresponds to a histologic change that is an overwhelming feature of the tissue. For focal, multifocal or diffusely distributed lesions, this grade is used for processes where 41–100% of the tissue section is involved. For hyperplastic/hypoplastic/atrophic lesions, this grade is used when the affected structure or tissue has undergone between a 41% and 100% increase or decrease in volume.

Histopathology raw data

- The signed final pathology report, representing the consensus of the primary and peer review pathologists
- Slides, tissues, paraffin blocks, and slides

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Revised guides for organ sampling and trimming in rats and mice – Part 2

A joint publication of the RITA*) and NACAD**) groups

Birgit Kittel[1], Christine Ruehl-Fehlert[2], Gerd Morawietz[3], Jan Klapwijk[4], Michael R. Elwell[5], Barbara Lenz[6], M. Gerard O'Sullivan[7], Daniel R. Roth[8], and Peter F. Wadsworth[9]

With 65 figures

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Key words: Trimming; RITA; NACAD; rat; mouse; standardization; guidelines; nasal cavity; nasopharynx; paranasal sinus; larynx; trachea; bronchus; bronchiole; lung; testis; rete testis; epididymis; prostate; coagulating gland; seminal vesicle; ovary; oviduct; uterus; uterine cervix; vagina; pituitary gland; thyroid gland; parathyroid gland; adrenal gland.

*) RITA: Registry of Industrial Toxicology Animal-data. Members: Abbott GmbH & Co KG, Ludwigshafen, Germany; ALTANA Pharma AG, Hamburg, Germany; AstraZeneca, Södertälje, Sweden and Macclesfield, England; Aventis Pharma Deutschland GmbH, Hattersheim, Germany; BASF AG, Ludwigshafen, Germany; Bayer HealthCare AG, Wuppertal, Germany; Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany; Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany; Hoffman-LaRoche AG, Basel, Switzerland; Merck KGaA, Darmstadt, Germany; Novartis Pharma AG, Basel, Switzerland; Pfizer, Amboise, France; Pharmacia, Nerviano, Italy; Syngenta CTL, Macclesfield, England

**) NACAD: North American Control Animal Database. Members: 3M Pharmaceuticals, St. Paul, MN, USA; Adolor Corporation, Malvern, PA, USA, Bayer CropScience, Stillwell, KS, USA; Pfizer, Inc., Groton, CT, USA; Pfizer, Inc., Ann Arbor, MI, USA; Pharmacia, Inc., Kalamazoo, MI, USA; R.W. Johnson Pharmaceutical Research Institute, Spring House, PA, USA; Schering-Plough Research Institute, Lafayette, NJ, USA

Summary

This is the second part of a series of three articles on trimming instructions of rat and mouse protocol organs and tissues in regulatory type toxicity studies, covering the respiratory, male and female genital, and the endocrine systems. The article is based on the experience of the European RITA and American NACAD working groups and is an extended revision of trimming guides published in 1995 (Bahnemann et al.). The optimum localization for tissue preparation, the sample size, the direction of sectioning and the number of sections to be prepared is described organ by organ. These descriptions are illustrated for each organ by a schematic drawing and/or a macro-photograph showing the plane of section as well as a low magnification of the H&E stained slide demonstrating the optimum "end-product".

The objectives of this work, as addressed in detail in the first part (Ruehl-Fehlert et al. 2003), are to stan-

4 Male genital system

4.4 Prostate

Localization:	Dorsolateral and ventral lobe
Number of sections:	1
Direction:	Longitudinal horizontal after special preparation (see below).

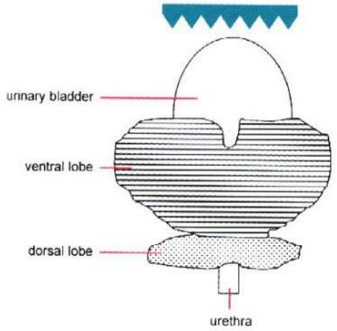

Fig. 4.4a. Prostate, rat, ventral aspect. Lateral lobes not visible, dorsal lobe: only caudal part visible.

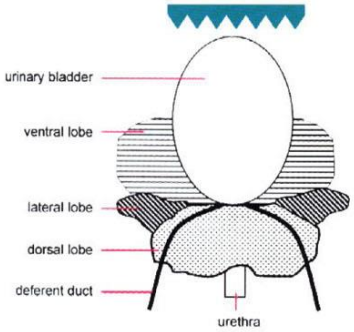

Fig. 4.4b. Prostate, rat, dorsal aspect.

The dorsolateral and ventral lobes that normally lie in a vertical axis above each other (with urinary bladder and seminal vesicle in between) are spread in a horizontal axis and embedded with the "outer" aspect down into the cassette.

Preparation: The group of adjacent organs consisting of prostate, urinary bladder, seminal vesicles and coagulation glands is removed (see figures 4.4.d through 4.4.f) and (if weights are not required) fixed *in toto* to prevent leakage of the glandular secretions.

After fixation, the ventral lobe is detached from the urinary bladder and is flipped back. The urinary bladder and seminal vesicles with coagulation glands are removed. The two ventral lobes are separated from each other, but are left attached to the dorsolateral parts. The dissected prostate is put into a cassette with the "outer" surfaces down; i.e. ventral face of the ventral lobes down and dorsal face of the dorsolateral lobes down (see figures 4.4.g through 4.4.i). After histotechnical processing, a section at the mid level of the ventral lobes is made.

The dorsocranial lobe of the prostate (i.e. coagulating gland) is processed with the seminal vesicle.

Chemically induced or spontaneous proliferative lesions of the rat prostate can be found in all three lobes. The dorsal and lateral lobes exhibit the same spectrum of proliferative lesions. These differ from spontaneous and induced lesions in the ventral lobe. Additionally, some strain specific deviations in the interlobular distribution of benign and malignant neoplasms consequently require the assessment of all compartments. Accordingly, a longitudinal-horizontal section through the prostate complex, including dorsolateral and ventral lobes, urethra and, optionally, ureter and ductus deferens represents a less time consuming method, applicable to routine histological processing and examination.

Related references

Boorman et al. 1990b, Ferm 1987, Lee and Holland 1987, Mitsumori and Elwell 1988, Suwa et al. 2001, Suwa et al. 2002

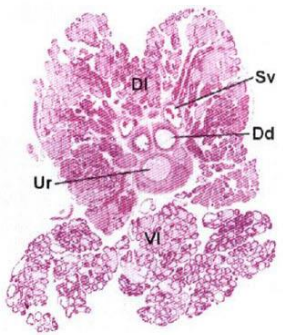

Fig. 4.4c. Prostate.

Abbreviations used in figures 4.4c to 4.4h:

Cg: Coagulation gland
Dd: deferent duct
Dl: dorsolateral lobe of prostate
Dsv: Duct of seminal vesicle
Sv: Seminal vesicle
Ub: Urinary bladder
Ur: Urethra
Vl: ventral lobe of prostate

Trimming of the liver

2 Digestive system

2.7 Liver and Gall bladder (mouse only)

Localization:	1) Left lateral lobe 2a) Rat: right medial lobe 2b) Mouse: left and right medial lobe including gall bladder 3) *Optional:* caudate lobe
Number of sections:	2 (3)
Direction:	1, 2a, 3) Transverse, 2b) longitudinal-vertical
Remarks:	Sample sizes should be as large as possible but can be adapted so that all pieces fit into one cassette. For identification purposes, standardized shaping of one of the larger lobes can be performed.

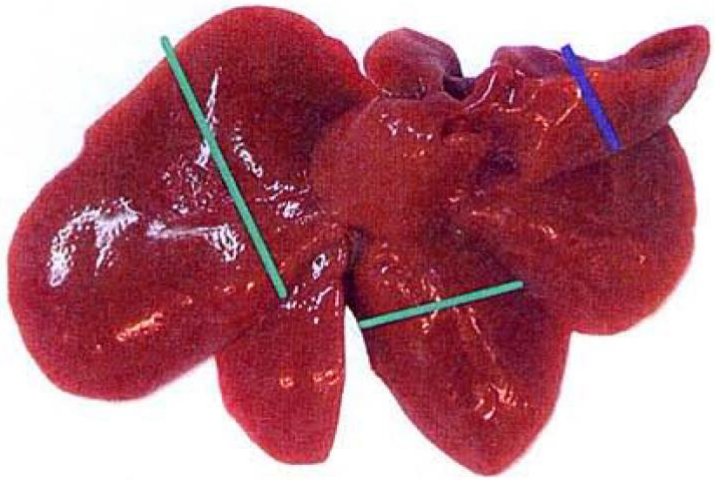

Fig. 2.7b. Rat liver, visceral aspect.

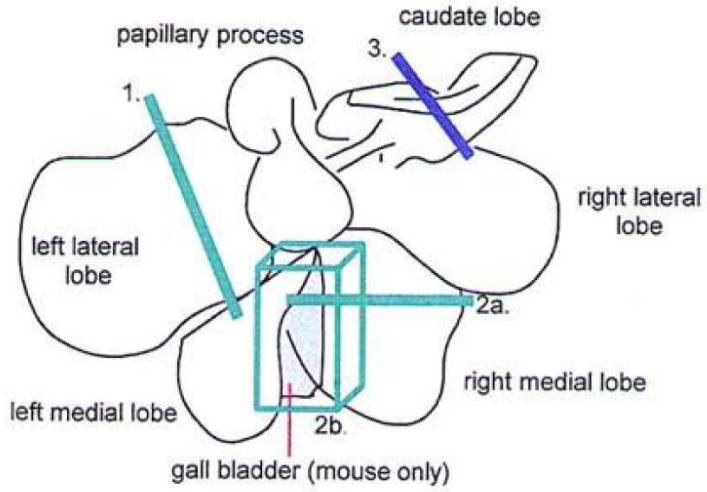

Fig. 2.7a. Liver, visceral aspect, indicating the cut levels for rats and mice.

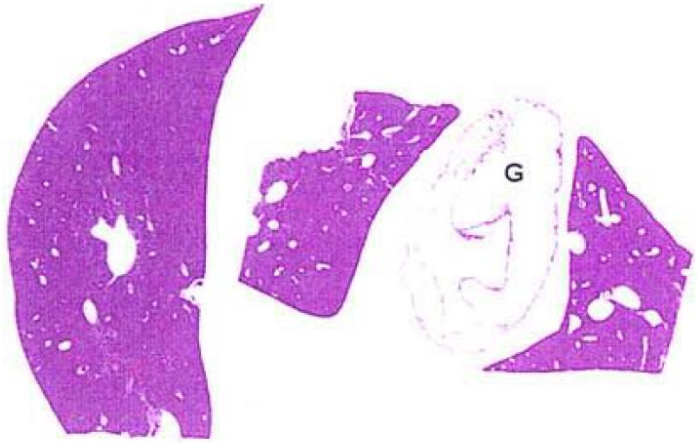

Fig. 2.7d. Mouse: liver and gall bladder (G), sections 1 and 2b.

Society of Toxicologic Pathology Recommendations

Toxicologic Pathology, 32:269–270, 2004

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DOI: 10.1080/01926230490274443

Recommendations to Guide Determining Cause of Death in Toxicity Studies

Determination of cause of death - principles

- The pathologist is responsible for identifying the cause of death (COD) and/or morbidity in animals that die or are euthanized prior to scheduled necropsy in toxicology studies, including carcinogenicity studies.
- The COD may not be the proximate event leading to death, but should be the overall process that leads to the proximate cause.

Determination of cause of death – principles (cont.)

- The pathologist should have and use all available information for each animal to determine the COD. This includes data such as hematology, clinical chemistry, body weights, clinical observations, metabolism, etc.
- The pathologist should determine whether overall mortality and any differences in mortality among groups are the result of compound administration.
- If the COD cannot be determined, this should be stated as COD undetermined or COD not determined from the available information.

Guest Editorial

Toxicologic Pathology, 38: 1009-1010, 2010

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DOI: 10.1177/0192623310385361

Pathology Peer Review

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[3]*U.S. FDA, College Park, Maryland, USA*
[4]*Maronpot Consulting LLC, Raleigh, North Carolina, USA*

- The purpose of the peer review process is to ensure the pathology report is an accurate reflection of the pathology findings for the study….

Regulatory Forum

Toxicologic Pathology, 000: 1-3, 2010

ISSN: 0192-6233 print / 1533-1601 online
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A Commentary on the Process of Peer Review and Pathology Data Locking

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In conclusion, for the reasons outlined above and in accordance with current U.S. and European guideline recommendations on pathology peer review, we support the JSTP in their pursuit of a revised Japanese pathology peer-review guideline (1) allowing sponsor peer review prior to locking of pathology data and (2) acknowledging that interim worksheets are not raw data and therefore do not need to be retained or submitted.

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Recommendations for Pathology Peer Review

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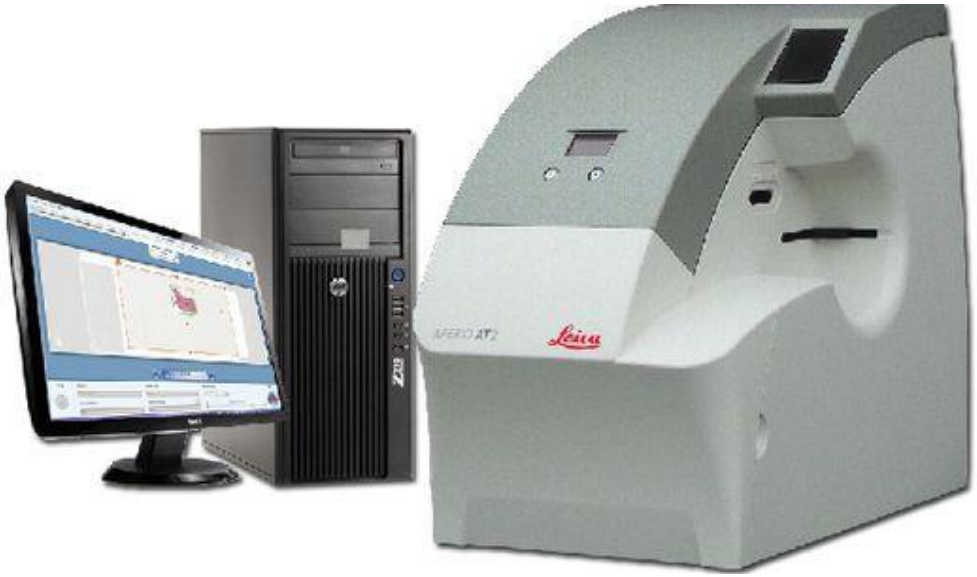
Abstract

Pathology peer review verifies and improves the accuracy and quality of pathology diagnoses and interpretations. Pathology peer review is recommended when important risk assessment or business decisions are based on nonclinical studies. For pathology peer review conducted before study completion, the peer-review pathologist reviews sufficient slides and pathology data to assist the study pathologist in refining pathology diagnoses and interpretations. Materials to be reviewed are selected by the peer-review pathologist. Consultations with additional experts or a formal (documented) pathology working group may be used to resolve discrepancies. The study pathologist is solely responsible for the content of the final pathology data and report, makes changes resulting from peer-review discussions, initiates the audit trail for microscopic observations after all changes resulting from peer-review have been made, and signs the final pathologist's report. The peer-review pathologist creates a signed peer-review memo describing the peer-review process and confirming that the study pathologist's report accurately and appropriately reflects the pathology data. The study pathologist also may sign a statement of consensus. It is not necessary to archive working notes created during the peer-review process.

DRAFT OECD guidance document on pathology peer review

- Records and reporting of the peer review should be sufficiently detailed to allow reconstruction of the process and verification that the correct tissues were examined.
- The GLP compliance status of the peer review should be clearly stated in the final report.

Scanning of the slides on the web –
Aperio – Leica system
The incoming "future" of the peer review



Pathology Working Group

The New Nomenclature Project INHAND

International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice

Objectives of the INHAND

- Established at 2006, as a joint initiatives of the American, Japanese, European Societies of Toxicologic Pathology
- To produce publications for each organ system that provide a standardized nomenclature and differential diagnosis for classifying microscopic lesions observed in laboratory rats and mice in toxicity and carcinogenicity studies.
- To serve in advisory role for the FDA SEND initiative with the goal of mapping INHAND terminology to SEND codelists of preferred terms

Structure of the INHAND Organization

- Management by a Global Executive Steering Committee (**GESC**) with representation from major societies of toxicologic pathology
- Composed of 15 organ system working groups (**OWG**) defined by the GESC (dealing with rodents only)
- 4 non rodent species working groups to be formed

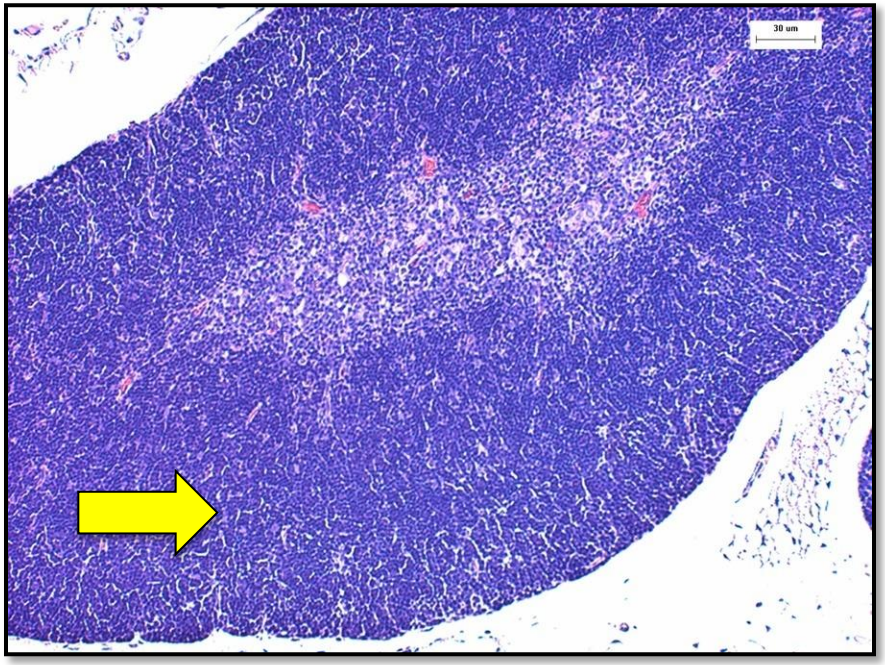
EXAMPLE: Recommended Terminology for Immunopathologic (i.e., Immunotoxic) Treatment-related Findings

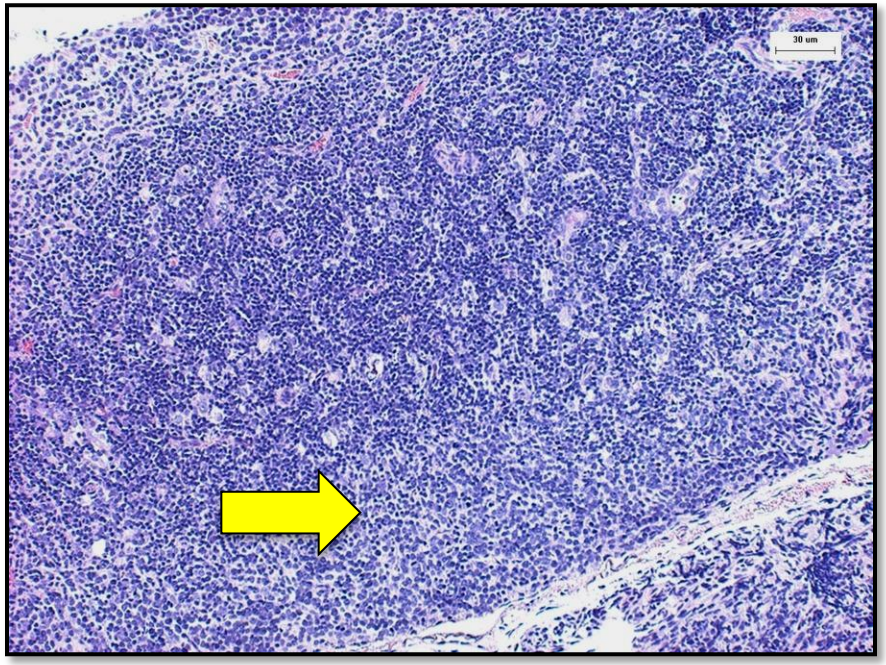
Descriptive vs. Interpretative Terms

Descriptive (preferred)	Interpretative (not recommended)
Decreased cells	Atrophy Lymphoid depletion Involution Hypoplasia
Increased cells	Hypertrophy Hyperplasia Proliferation

Thymus

Drug Induced Decreased Thickness of the Cortex, Due to Decreased Number of Lymphocytes





Control Animal
No abnormality detected

Treated Animal
Cortex – Lymphocytes, decreased
Cellularity, moderate

On-line Free Available Manuscripts
https://www.toxpath.org/inhand.asp

Proliferative and Nonproliferative Lesions of the Rat and Mouse Hepatobiliary System

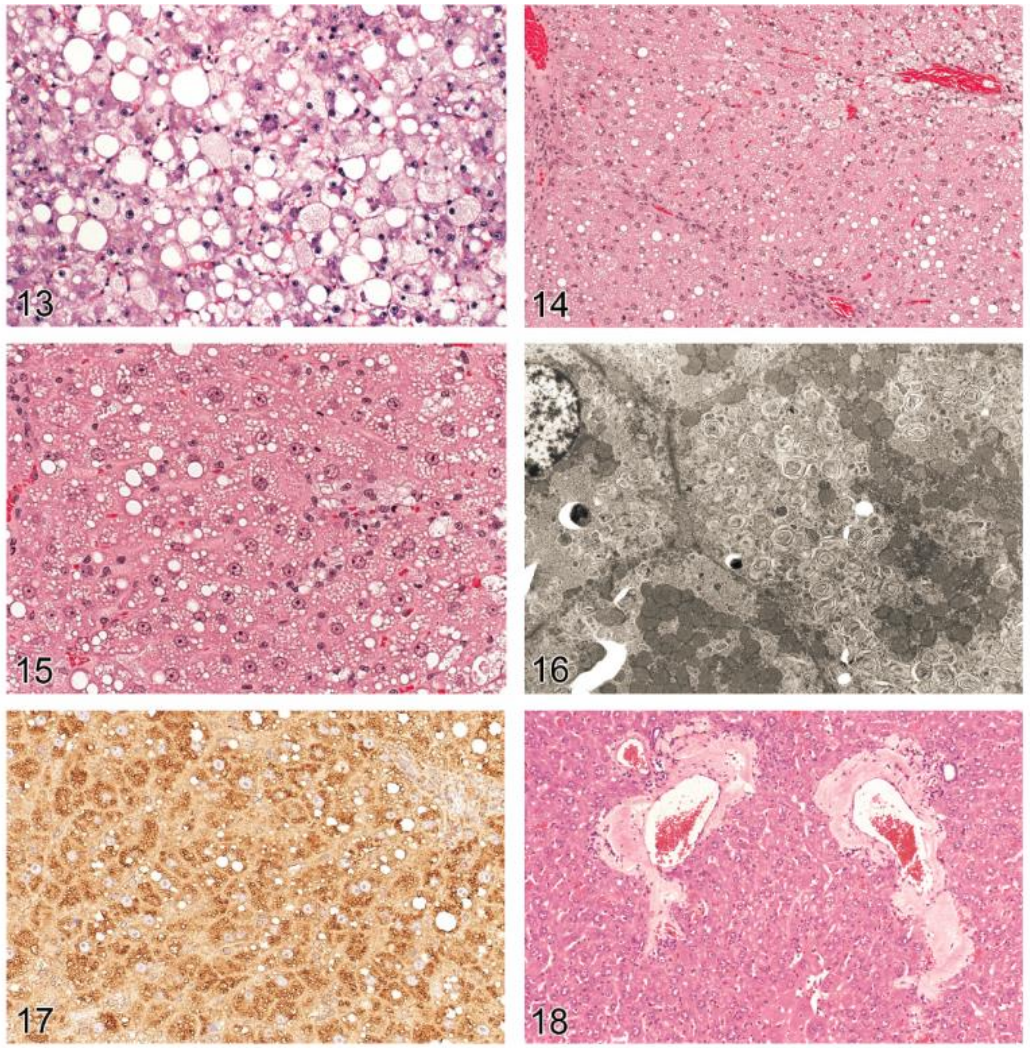


FIGURE 13.—Rat liver. Focal fatty change. Higher magnification of Figure 12. FIGURE 14.—Rat liver. Phospholipidosis. FIGURE 15.—Rat liver. Phospholipidosis. Higher magnification of Figure 14. FIGURE 16.—Rat liver. Phospholipidosis. EM concentric membrane bound lysosomal myeloid bodies/lamellar bodies. FIGURE 17.—Rat liver. Phospholipidosis. Central microvesiculation; positive LAMP-2 staining. FIGURE 18.—Mouse liver. Amyloidosis.

Toxicologic Pathology, 38: 5S-81S, 2010

INHAND Collaboration with the FDA on SEND (Standard for the Exchange of Nonclinical Data)

Background:

- During 2011, the INHAND Global Editorial Steering Committee (GESC) had discussions with representatives of FDA Center for Drug Evaluation and Research (CDER) and members of the Clinical Data Interchange Standards Consortium (CDISC) to examine the potential use of INHAND terminology in the software being developed for Standard for Exchange of Nonclinical Data (SEND) submission to the FDA.
- The decision of the Government and industry toxicologists is that SEND terminology will widely accept the INHAND nomenclature.

Summary – Benefits

- Standardized submitted data will result in submission efficiencies such as providing one standard used by sponsors and vendors, reduce review time, and increase reviewer efficiency.
- Electronically submitted data for drug development program, when submitted in standardized format, can be searched within a study, across studies within a program, or across different programs.
- It will allow reviewers to communicate their questions more precisely to the sponsor.

References and presentation can be submitted upon demand – anyska@bezeqint.net

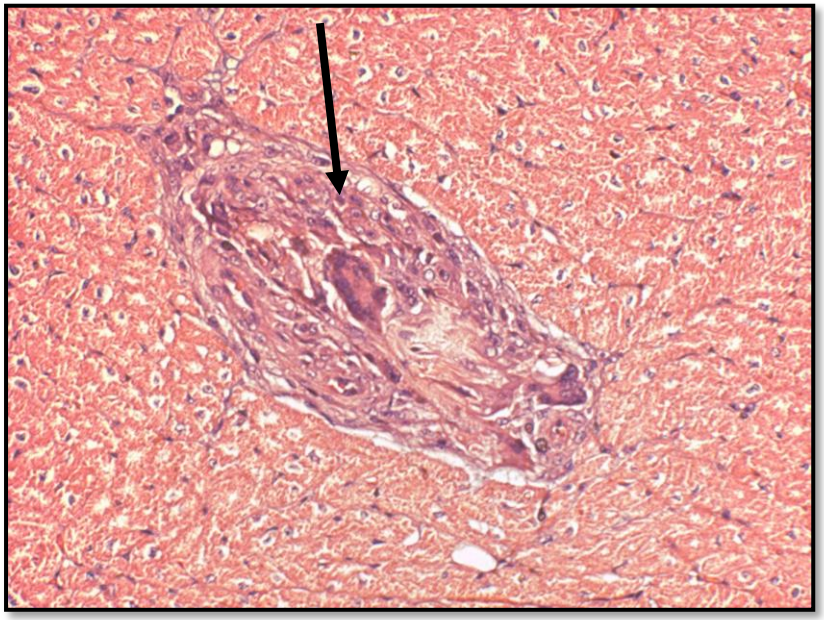
Challenges in Interpretation of Pre-clinical Histopathological Data

It is All a Matter of Right Interpretation…

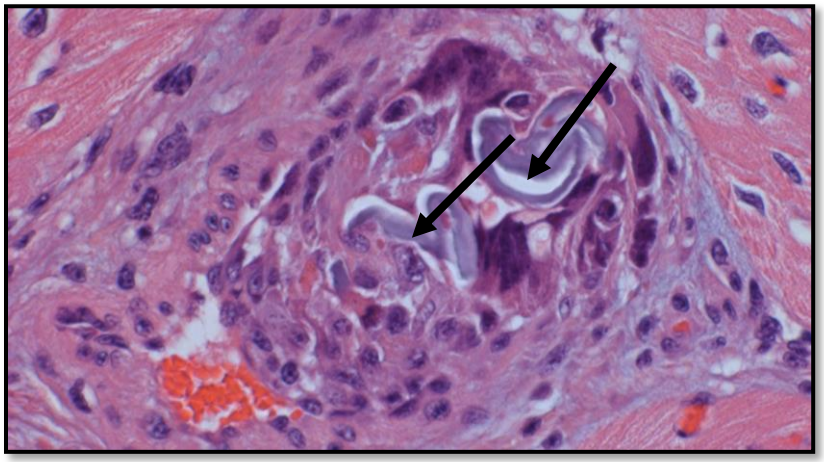
Intramyocardial Injected “Drug” (Considered A Medical Device) Contaminated by Foreign Material, Provoking Granulomatous Reaction

A Drug "Contaminated" with Gauze – Cotton Fiber

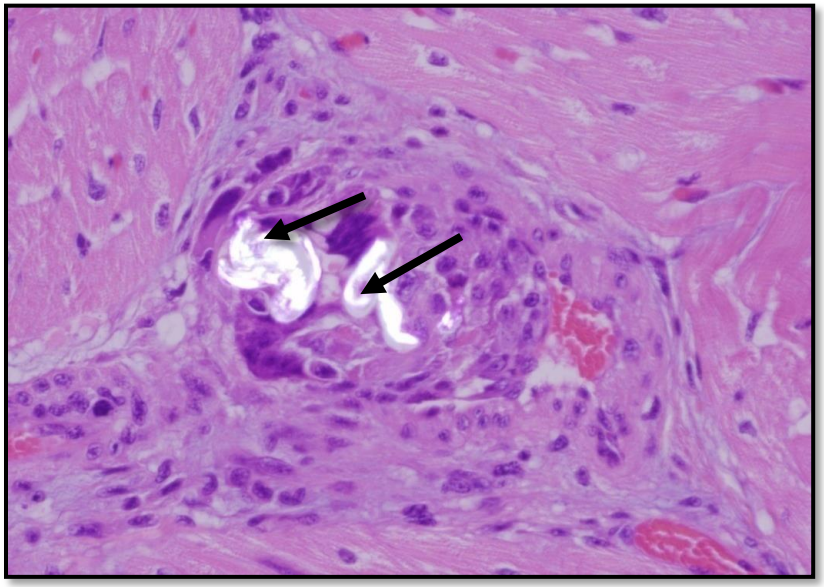
Foreign Body Coronary Arteritis



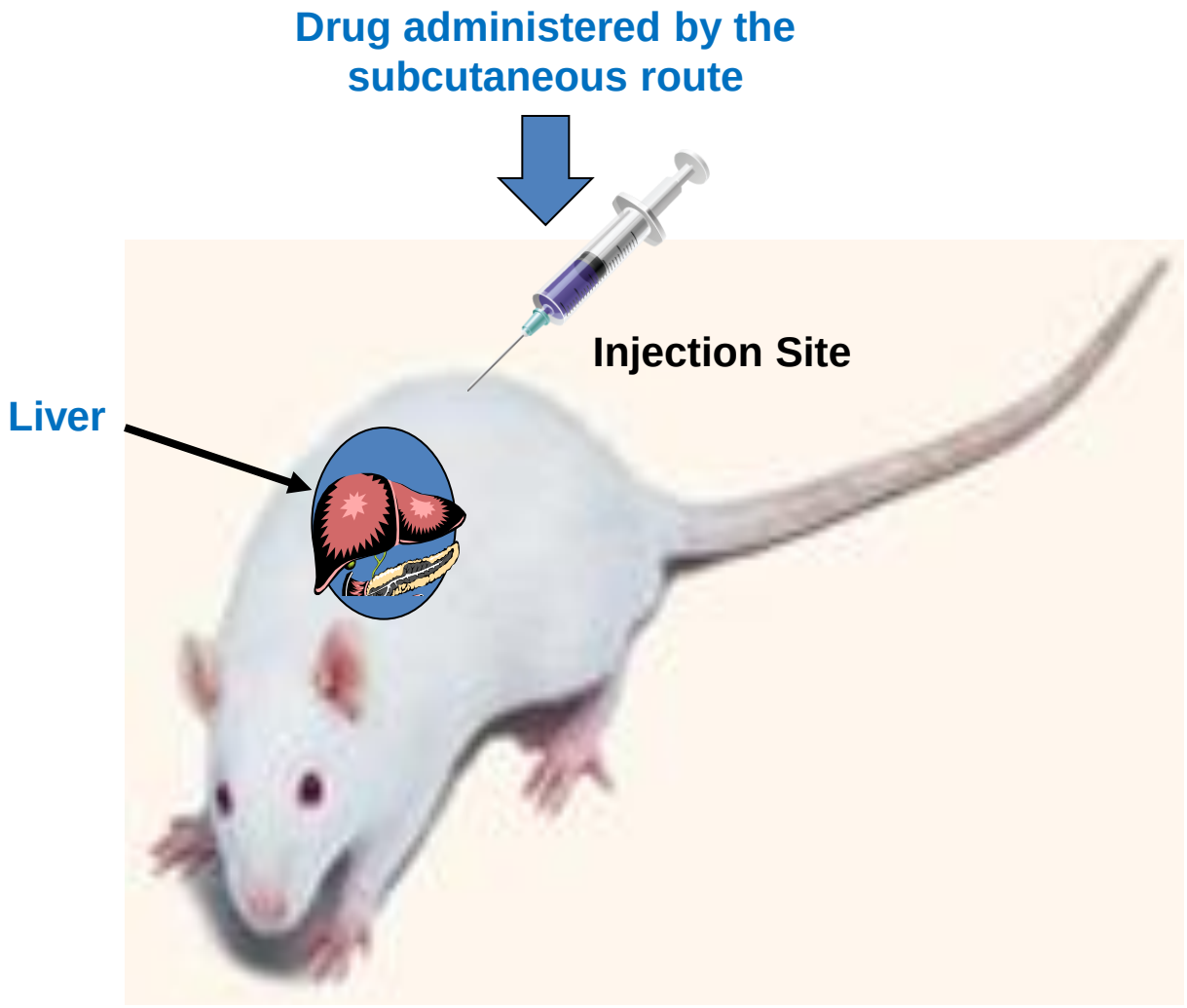
Hematoxylin and Eosin



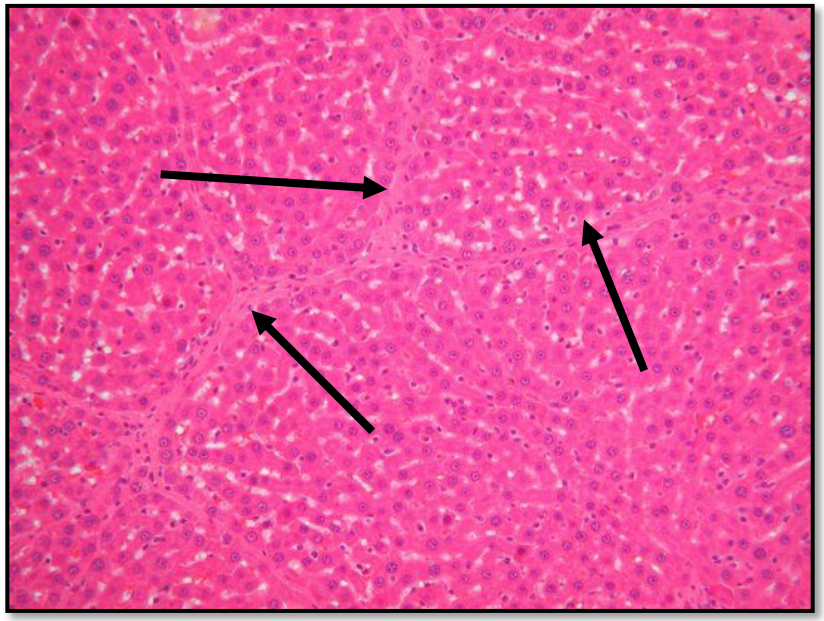
Polarizing Microscope



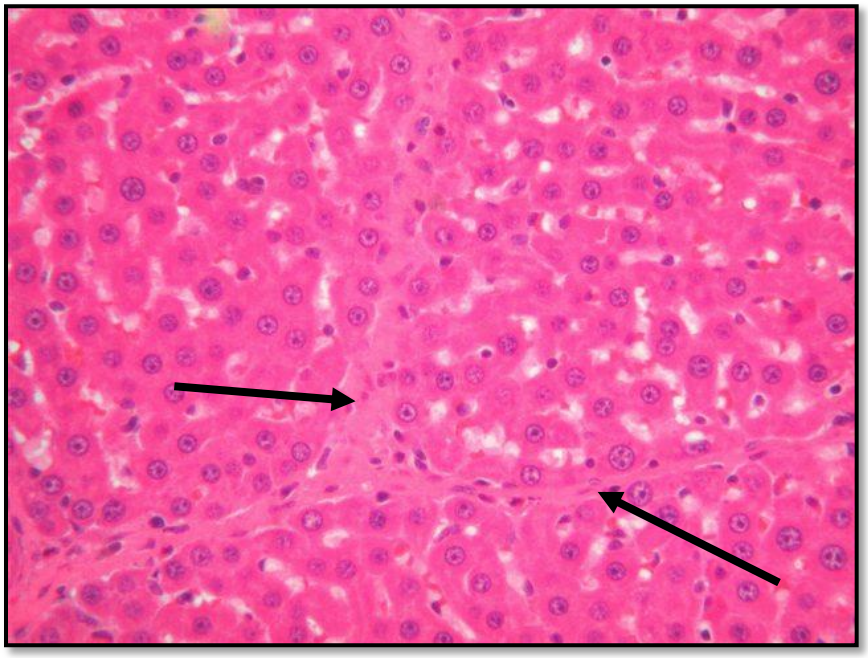
Issue of Hepatic Centrilobular Bridging Fibrosis Observed in Dermal Toxicity Studies



26 Weeks Dermal Toxicity Study in Rat – Centrilobular Hepatic Fibrosis



Arrows – Centrilobular fibrosis



The Liver Acinus

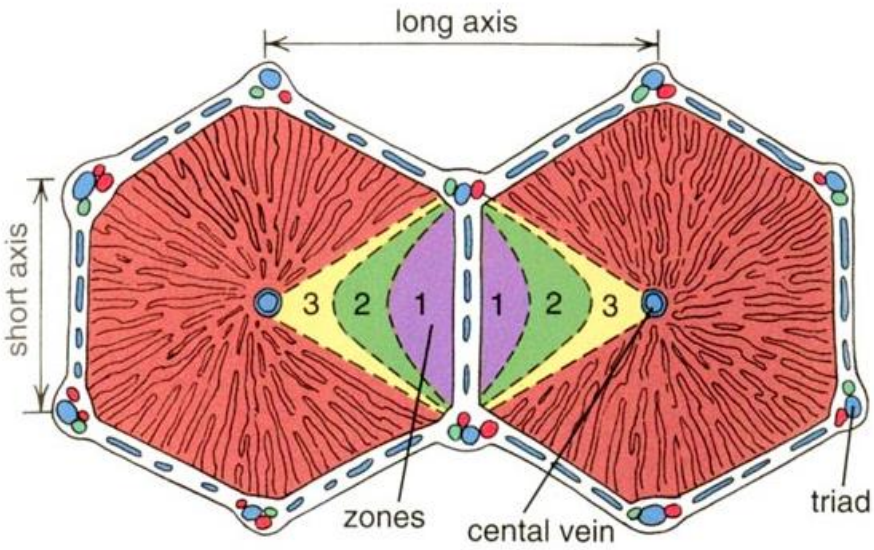
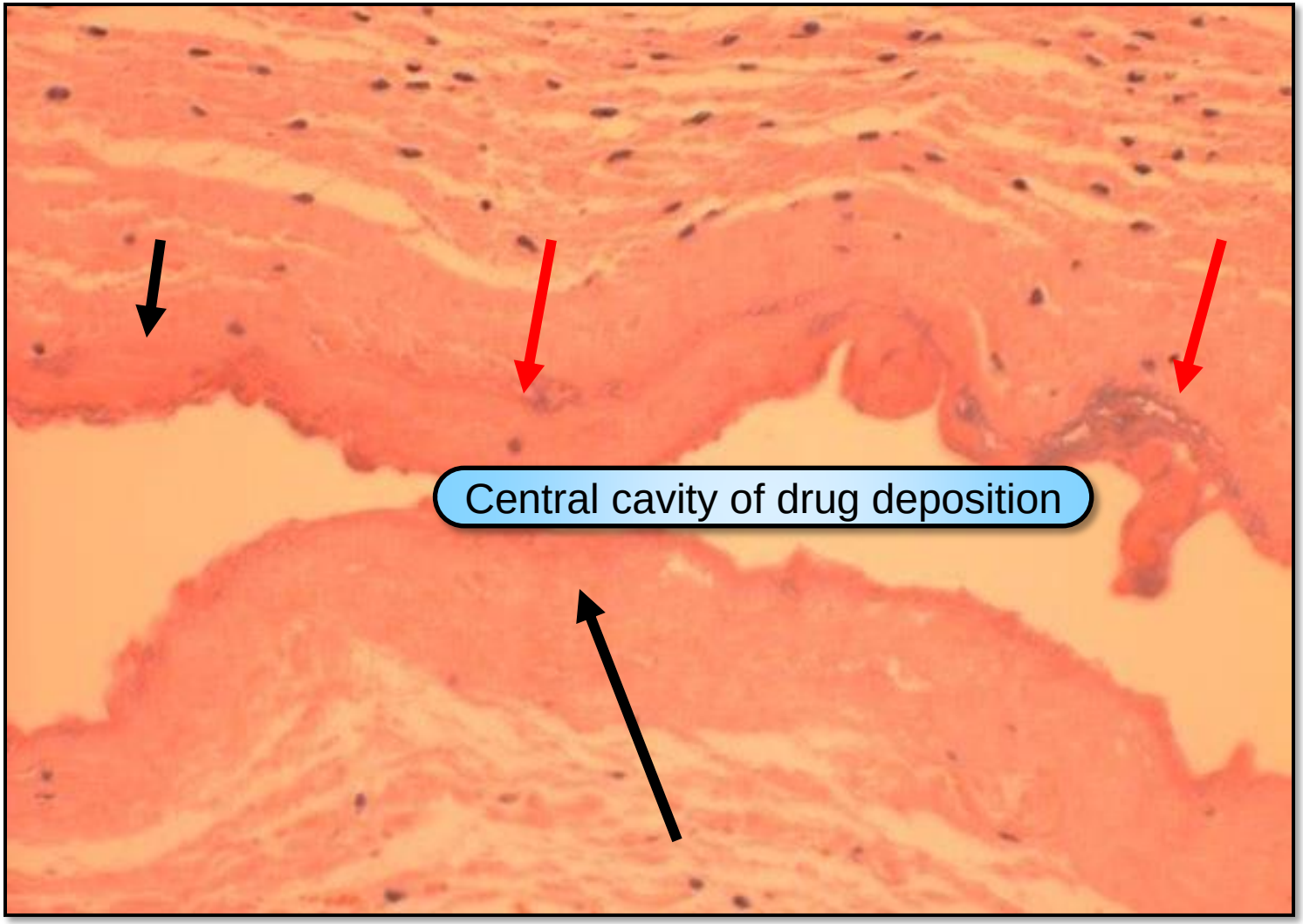


FIGURE 17.6

The liver acinus. The liver acinus is a functional interpretation of liver organization. It consists of adjacent sectors of neighboring hexagonal fields of classic lobules partially separated by distributing blood vessels. The zones, marked 1, 2, and 3, are supplied with blood that is most oxygenated and richest in nutrients in zone 1 and least so in zone 3. The terminal hepatic venules (central veins) in this interpretation are at the edges of the acinus instead of in the center, as in the classic lobule. The vessels of the portal canals, namely, terminal branches of the portal vein and hepatic artery that, along with the smallest bile ducts, make up the portal triad, are shown at the corners of the hexagon that outlines the cross-sectioned profile of the classic lobule.

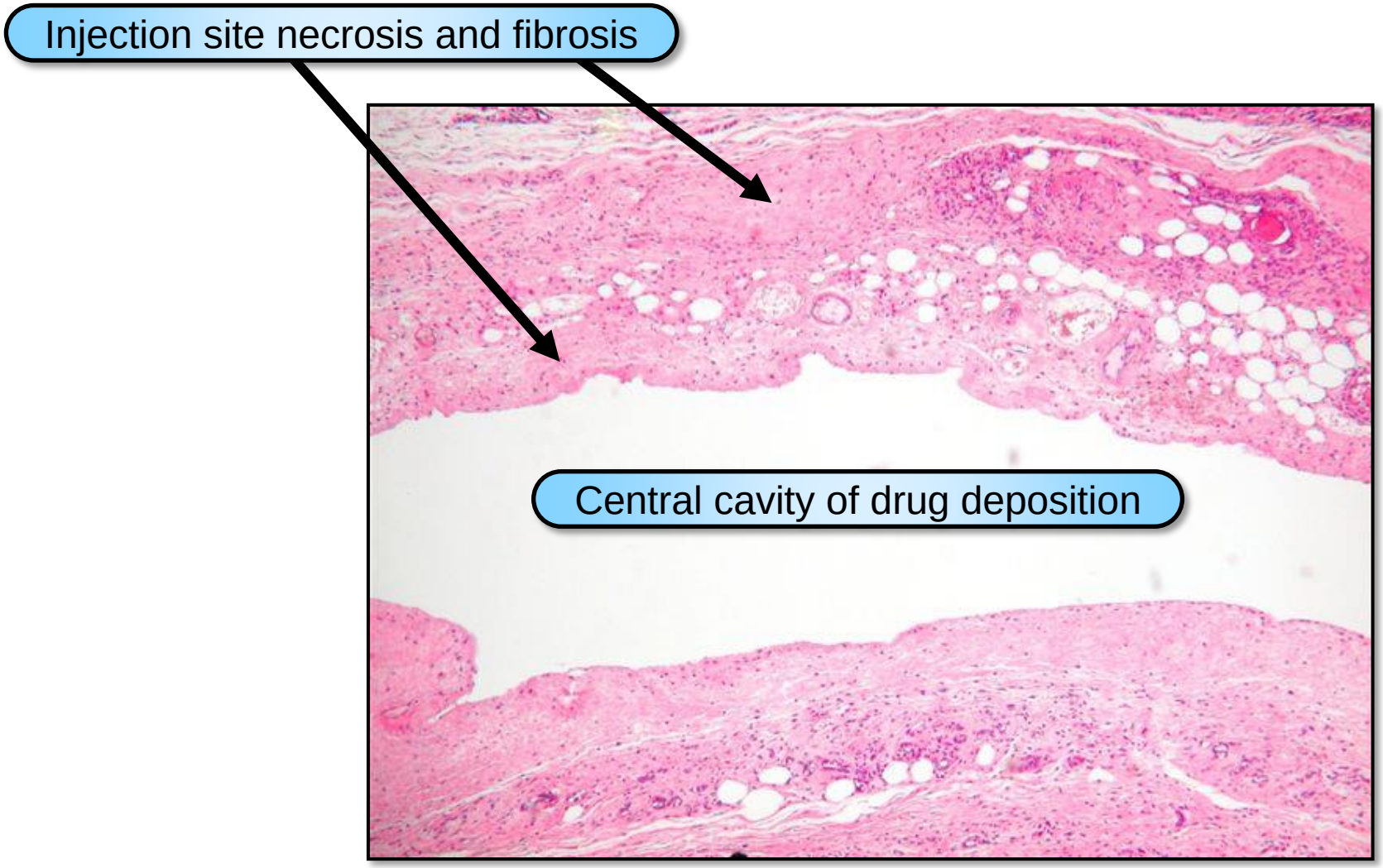
Injection Site – 13 Weeks Dermal Toxicity Study –

Cavity formation Surrounded by Necrosis (black arrows) and Bacterial colonies (red arrows)



Arrows – Necrosis

Injection Site – 13 Weeks Dermal Toxicity Study –
Cavity formation Surrounded by Necrosis and Chronic Inflammation (black arrows



Human Cases of Liver Necrosis and Fibrosis in Comparable Circumstances…

- "Focal or multifocal hepatic necrosis, known as "**corset liver**", was seen in women in times when **severely stringent corsets** were fashionable… The lesion was presumably due to **interference with vascular perfusion in compressed areas** of the liver and may be similar to the hepatic lesions observed in our work"…

Parker GA, Gibson WB. Liver lesions in rats associated with wrapping of the torso. *Toxicol Pathol.* 1995, Jul-Aug; 23(4):507-12

Rodent Cases of Liver Necrosis and Fibrosis in Comparable Circumstances…

- The long-term wrapping of the animal caused constriction and physical compression of the abdomen
- Hepatic centrilobular degeneration and fibrosis were attributed to passive congestion… rats that died during the course of the study had severe hepatic congestion and dilated cardiac ventricles, which were attributed to cardiac or respiratory failure due to pressure exerted by the wrap

Nyska A, Waner T, Wormser U, Gur E, Kuttin E, Dayan D. *Arch Toxicol.* 1992;66(5):339-46.
Possible pitfalls in rat extended dermal toxicity testing: an hepatic-ocular syndrome.

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Dermal Toxicity Studies: Factors Impacting Study Interpretation and Outcome

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Abstract

The field of dermal toxicity continues to evolve in order to accurately predict dermal (and systemic) responses in humans to topically applied chemicals. Although the testing methods have undergone extensive refinements, idiosyncrasies and unexpected issues during the conduct of these studies are not unusual due to the plethora of new vehicles available for formulating test substances, changing regulatory requirements, and introducting new strain and/or species of laboratory animals as no single species or method seems to suffice for evaluating skin toxicity. The objective of this article is to illustrate some pragmatic issues that should be considered during the conduct as well as interpretation of dermal toxicity studies. Routine procedure-related issues such as hair clipping, tape stripping, and wrapping the animal's torso to prevent oral ingestion can influence the interpretation. Excipients used in dermal toxicity studies may be nontoxic when used alone but complex dermal formulations can result in unexpected irritation and toxicity. In conclusion, interpretation and risk assessment of dermal toxicity studies should be done in a comprehensive manner, taking into account procedure-related impact on study results, unique species susceptibility, limitation of gross visual (naked eye) observation for evidence of toxicity, and normal anatomical variation.

Dermal Toxicity Studies: Factors Impacting Study Interpretation and Outcome

WRAPPING PROCEDURE

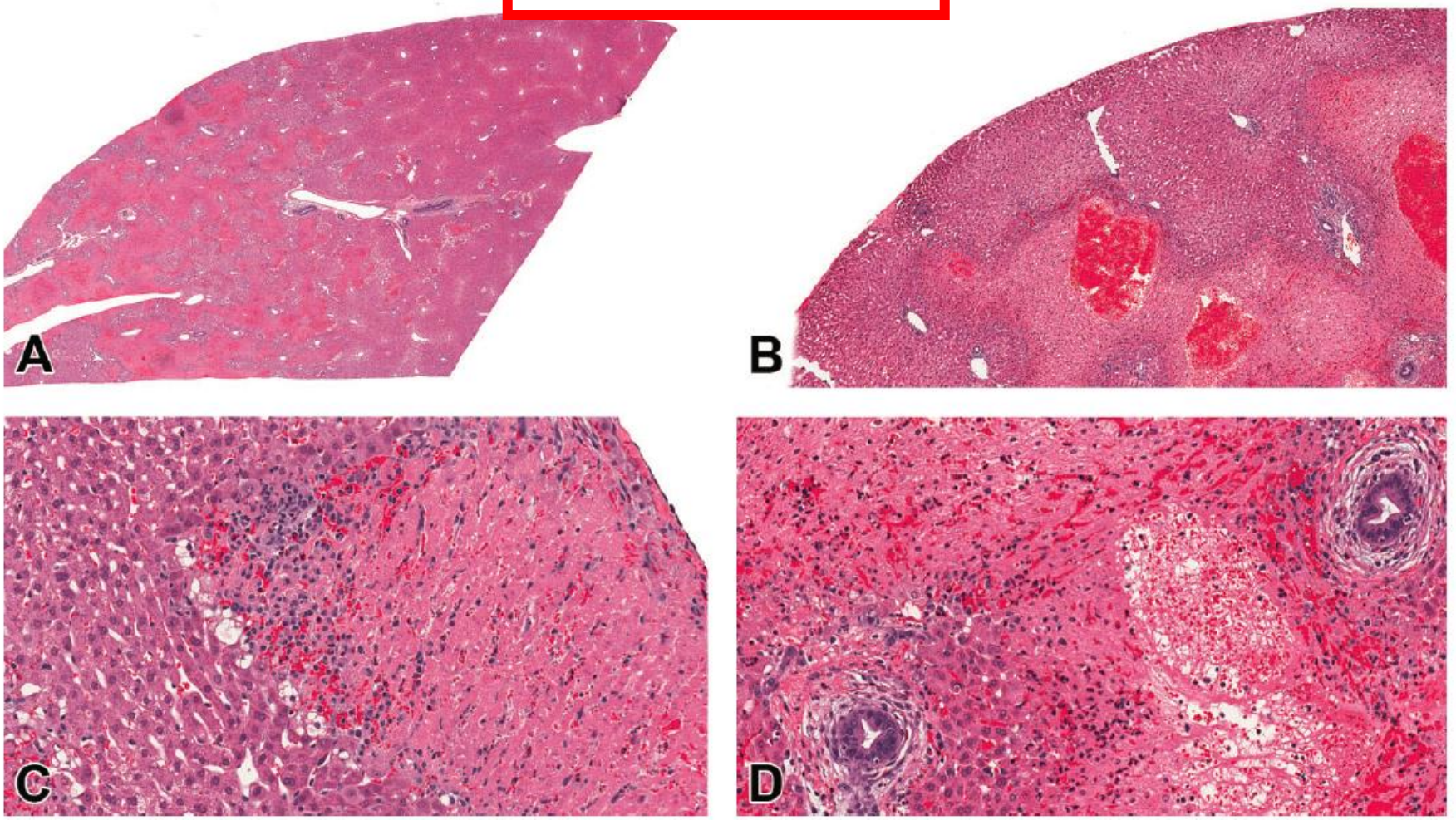
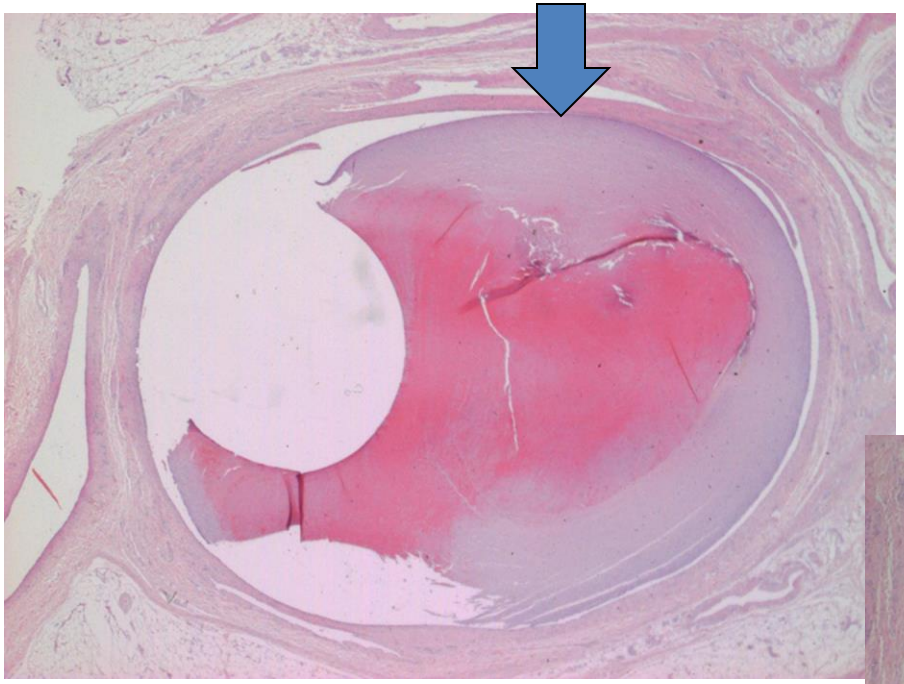


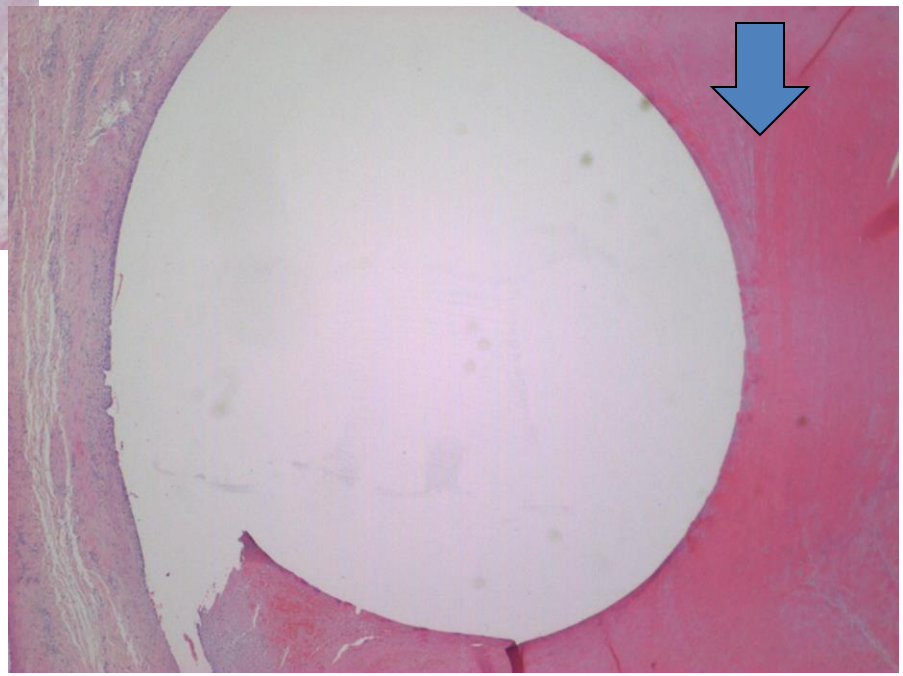
FIGURE 2.—Hepatocellular necrosis in rabbits associated with wrapping the torso. The changes are characterized by bridging coagulative necrosis affecting some portions of a lobe while sparing other regions (A and B). Discrete subcapsular area of necrosis (C) sparing the portal areas (D). HE.

LESIONS RELATED TO IV ROUTE OF ADMINISTRATION - TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD

- A range of lesions were seen at the local implantation and injection site, in the heart, aorta, and lungs, resulted from the **catheter used for the drug administration, introduced through the right jugular vein**.
- Such changes included: capsule formation at the implantation site, inflammation in the jugular vein and subcutis, presence of singular organized thrombi in the lungs and a single case of minimal focal inflammation in the heart and aorta.
- **In particular,** a single male animal from group 4 had minimal centrilobular vacuolation, associated with single cell hepatocytic cell necrosis. This change is considered to reflect systemic circulatory problem, secondary to focal heart inflammation seen in this animal, provoked by the introduction of the catheter.

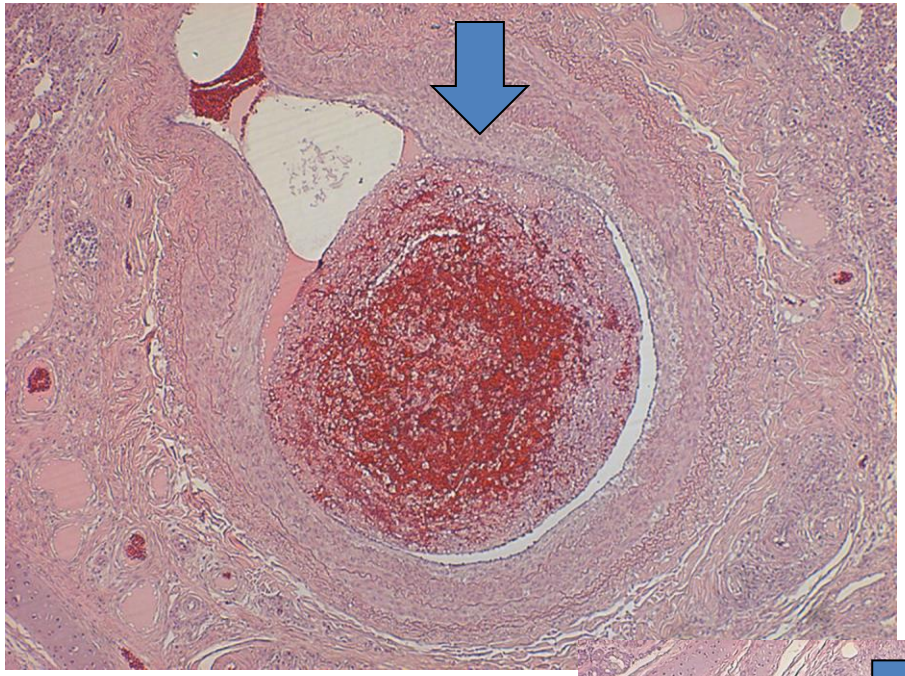
26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LESIONS RELATED TO IV ROUTE OF ADMINISTRATION – JUGULAR VEIN THROMBOSIS

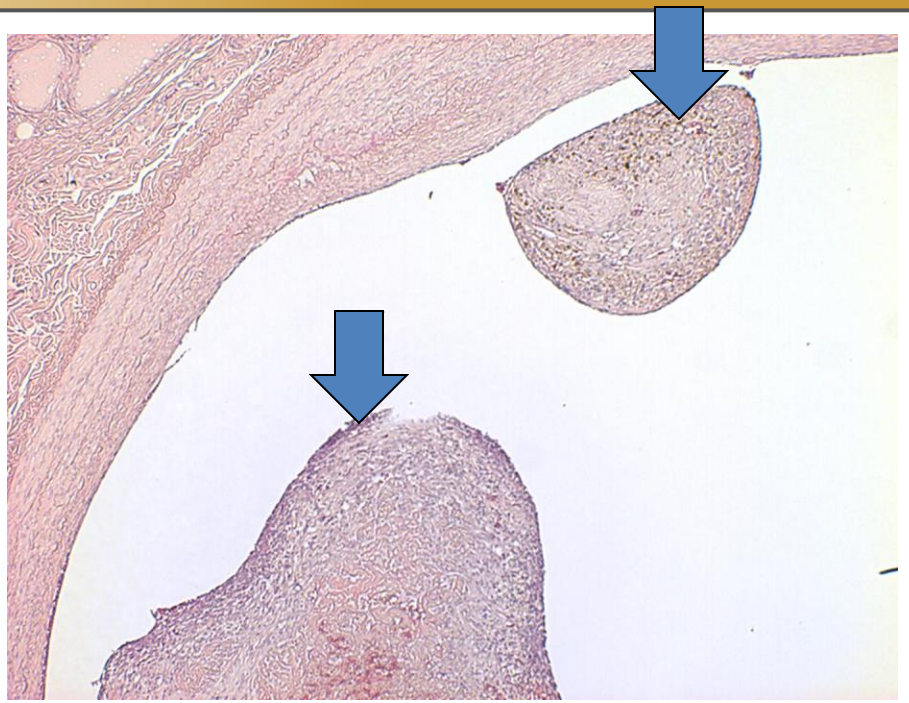


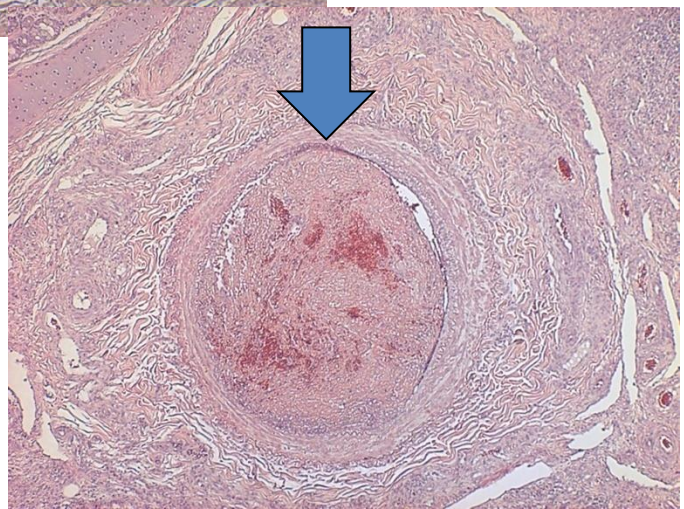


Detachment of fragments from the jugular vein thrombosis, leading to pulmonary thrombosis

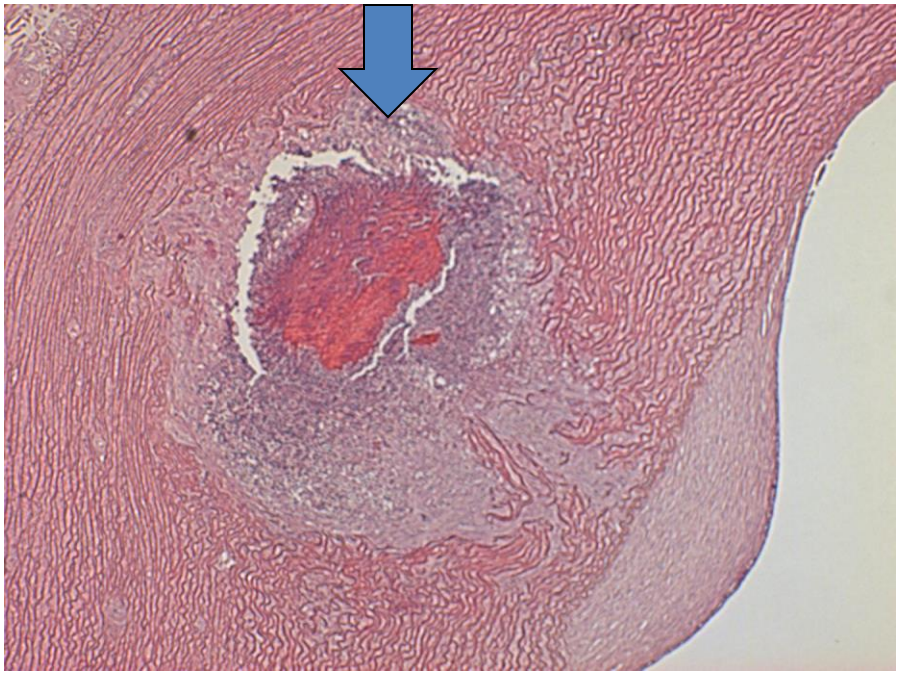
LESIONS RELATED TO IV ROUTE OF ADMINISTRATION– 26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LUNG THROMBOSIS (different grades of vascular obstruction)

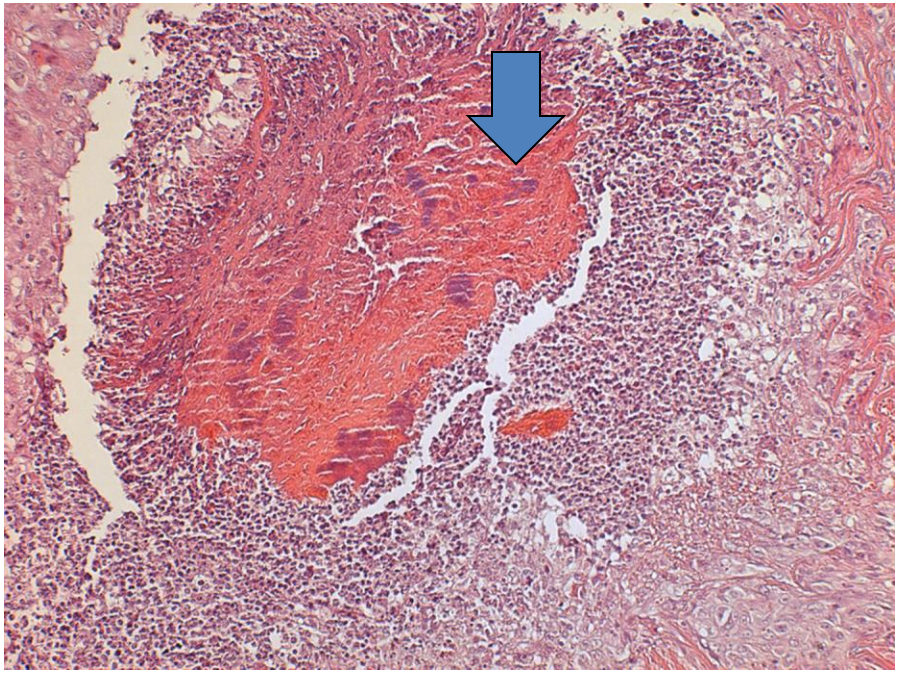




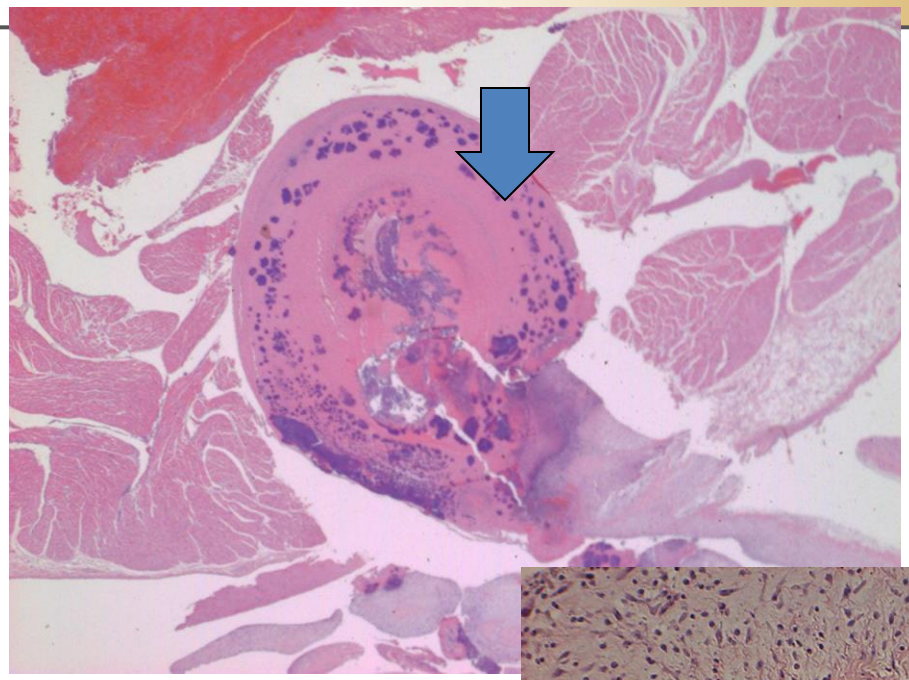


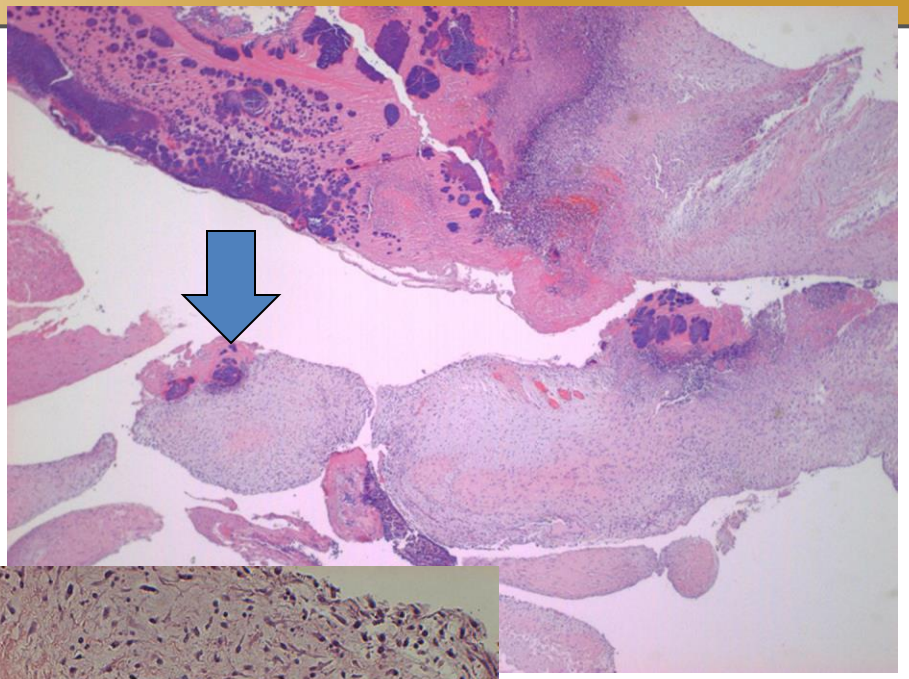
26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LESIONS RELATED TO IV ROUTE OF ADMINISTRATION – AORTA – AN ABCESS (DUE TO TRAUMATIC LESION BY THE CATHETER)

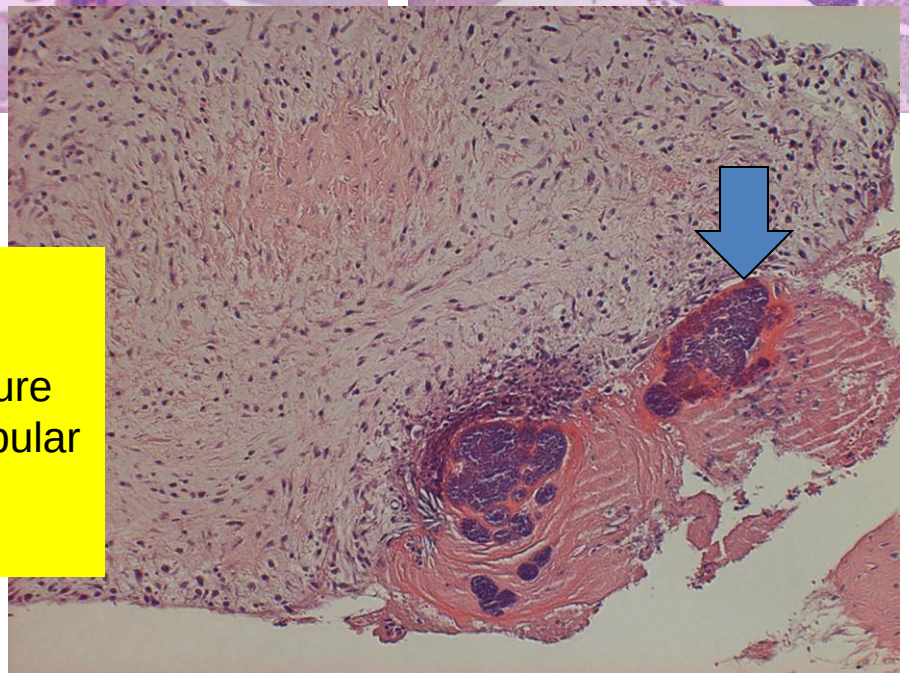




26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LESIONS RELATED TO IV ROUTE OF ADMINISTRATION – HEART – BACTERIAL VALVULAR ENDOCARDITIS (DUE TO TRAUMATIC LESION BY THE CATHETER)

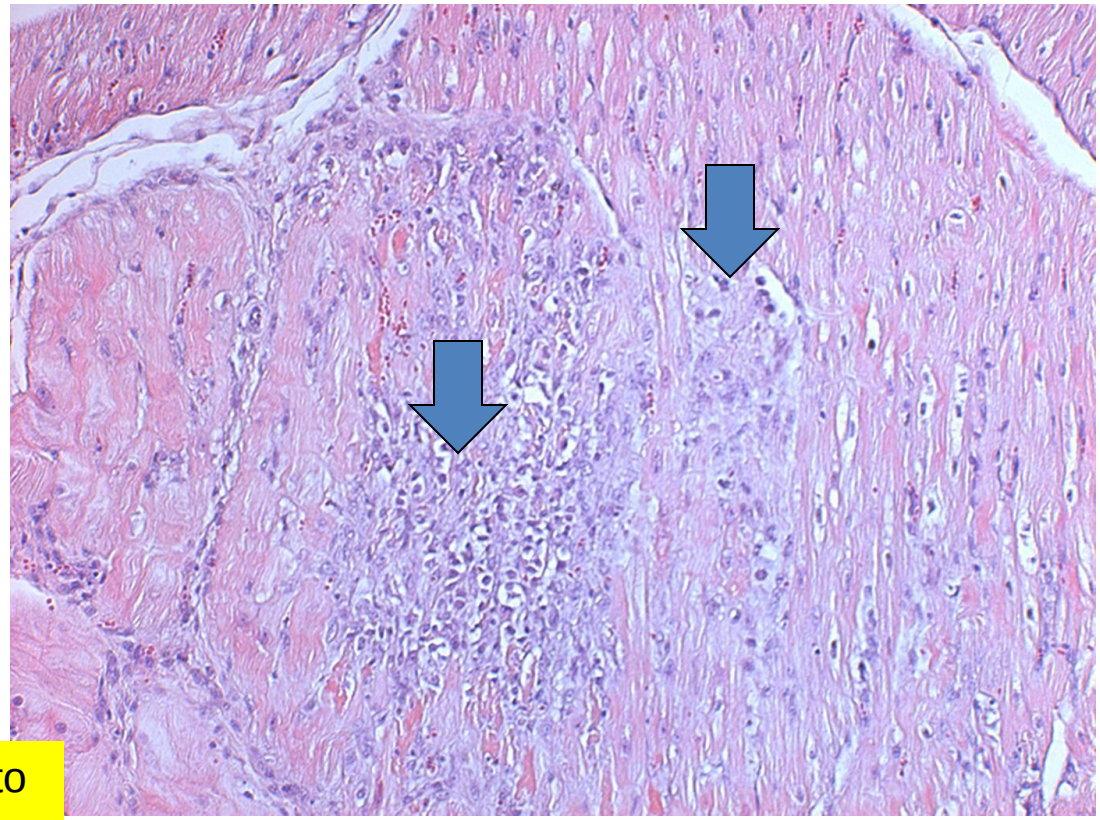






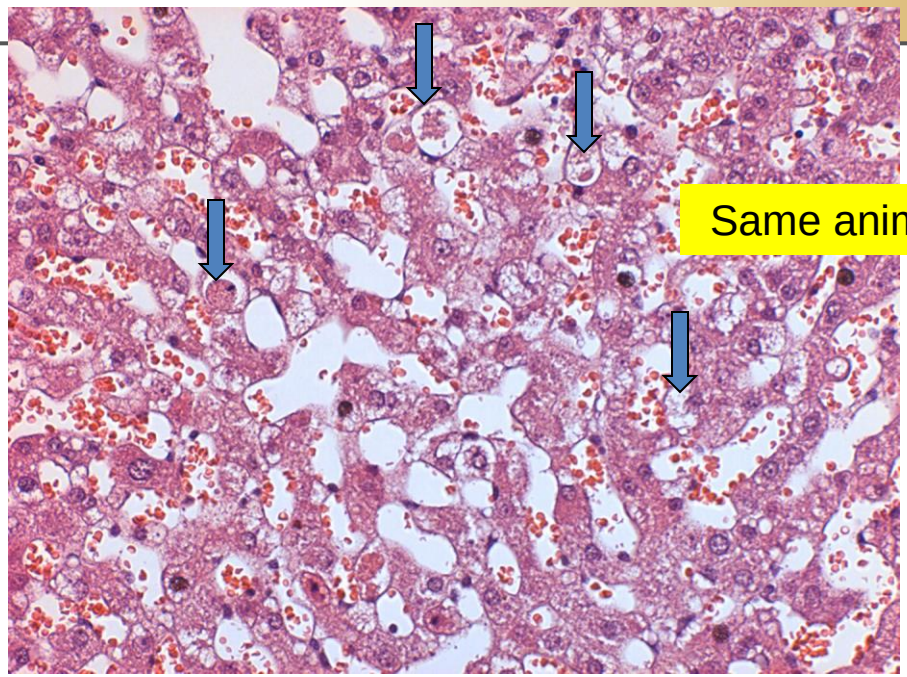
Severe heart pathology leading to congestive heart failure with hepatic centrilobular congestion

26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LESIONS RELATED TO IV ROUTE OF ADMINISTRATION – HEART – FOCAL MYOCARDITIS (DUE TO TRAUMATIC LESION BY THE CATHETER)

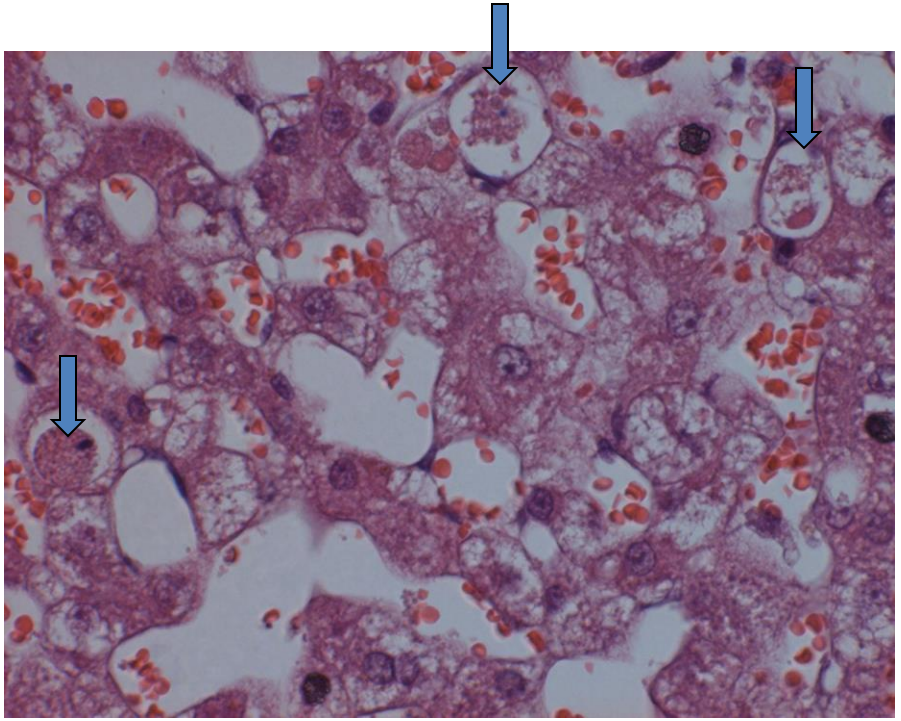


Heart pathology leading to congestive heart failure with hepatic centrilobular degeneration and necrosis

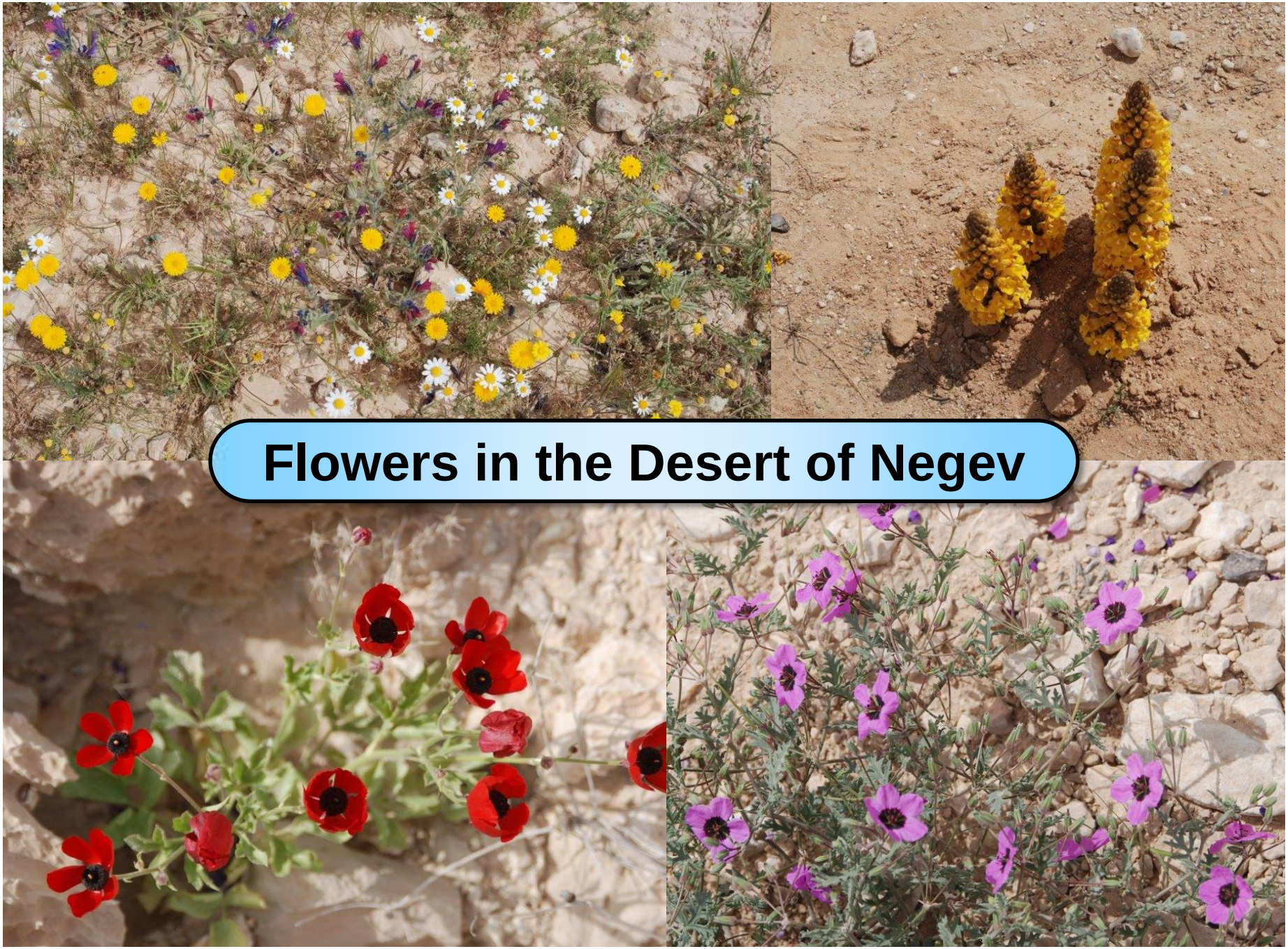
26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LESIONS RELATED TO IV ROUTE OF ADMINISTRATION – CENTRILOBULAR HEPATOCYTIC DEGENERATION AND NECROSIS (APOPTOSIS) - this lesion is reflecting systemic circulatory stasis due to congestive heart failure



Same animal as the previous photo of focal myocarditis



END 1ST PART


Flowers in the Desert of Negev