Rodent models of metabolic disorders

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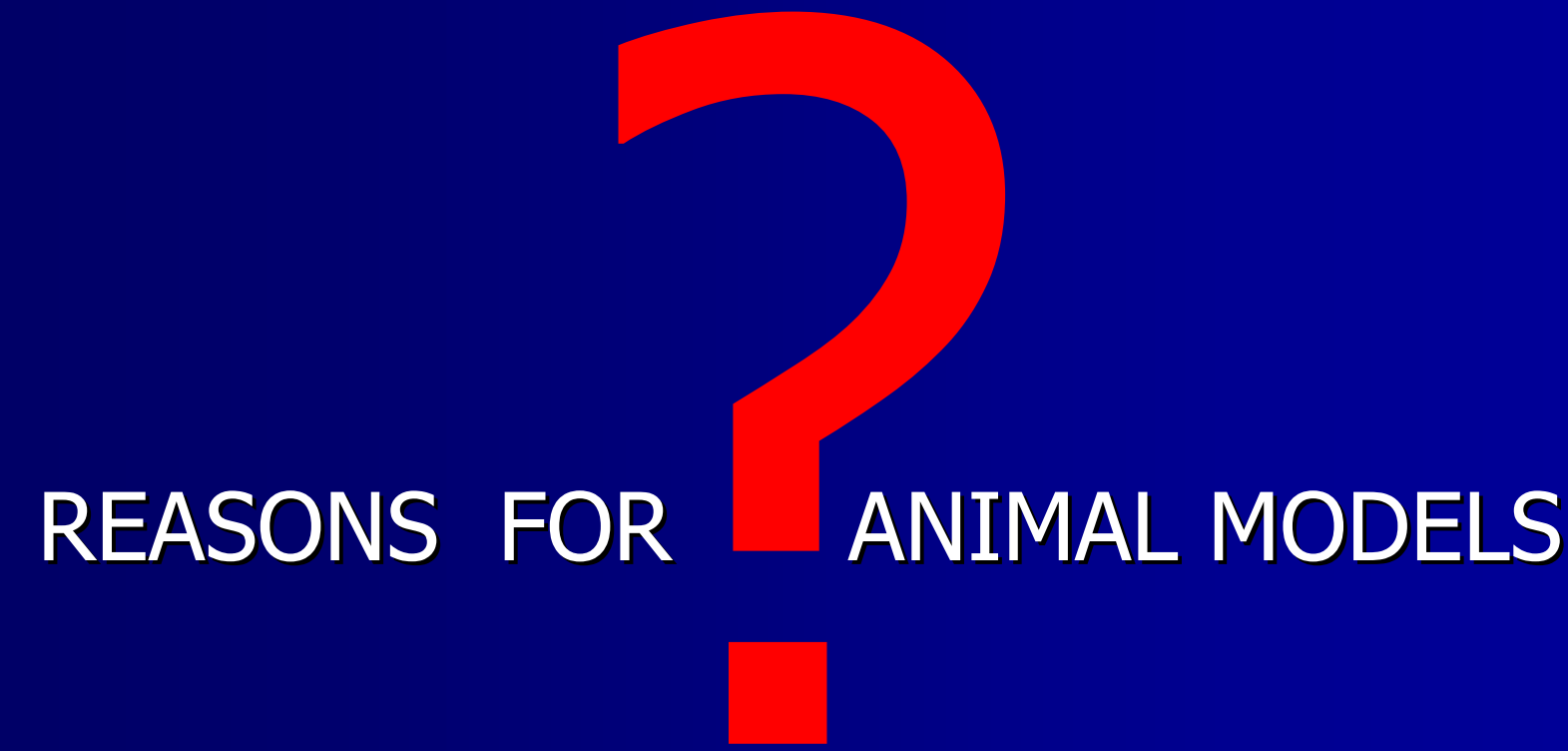
Animal models for metabolic disorders



Metabolic diseases (MD)

- Global increase in metabolic diseases
- Increase has been exponential
- Forecast for 2020-2030 → 2/3 of population would suffer from MD
- New methods and technologies to investigate these conditions take on an ever increasing priority

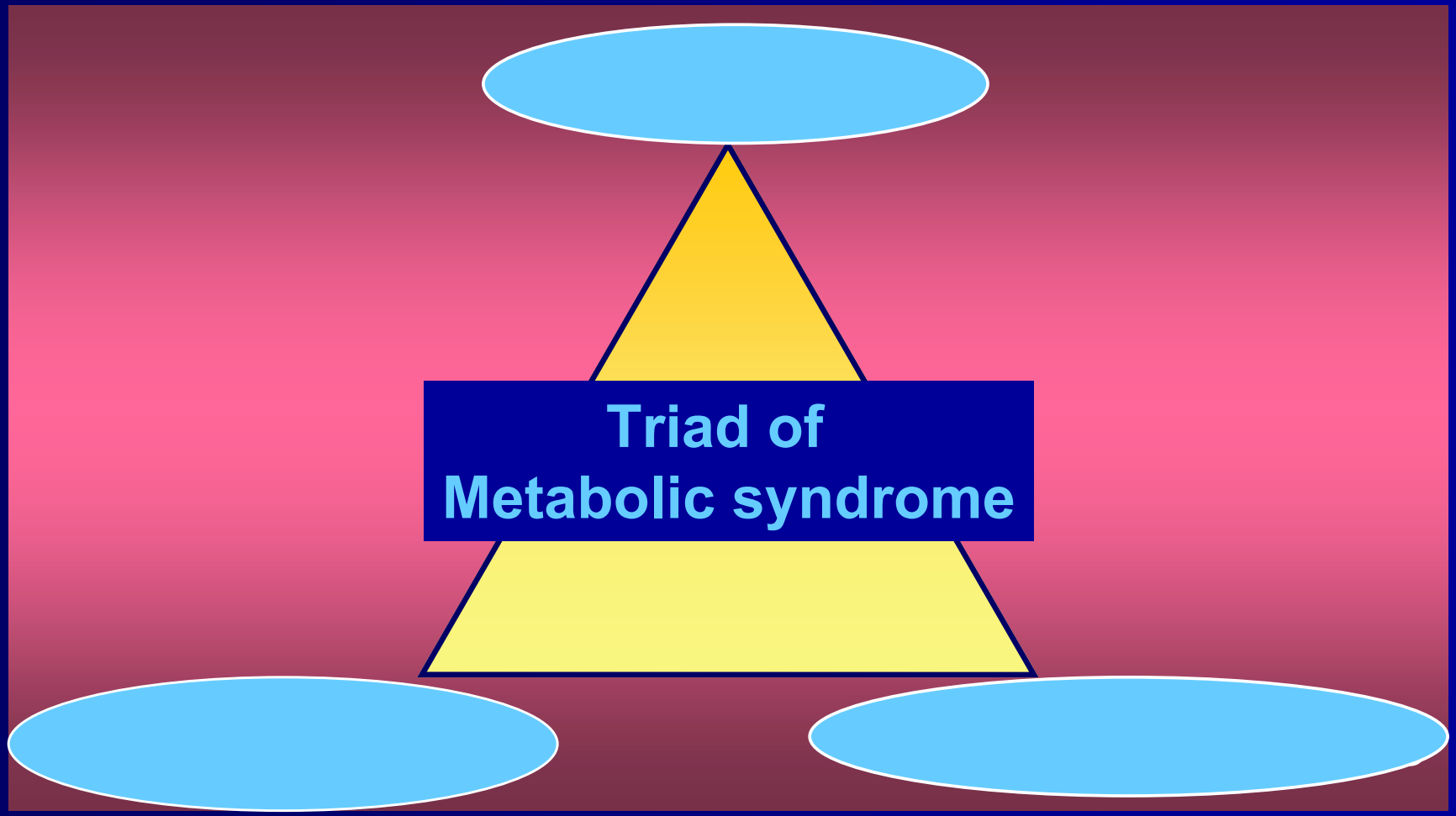
COMMON METABOLIC DISEASES

- Obesity
- Diabetes
- Hyperlipidemia
- Related complications

Importance of metabolic syndrome

- The metabolic syndrome is a prototypical web of causality diseases
- The metabolic syndrome is a leading cause of morbidity and mortality in modern societies
- The metabolic syndrome carries a high risk of renal disease and diabetes

The hall mark of metabolic syndrome



Animal models

- Diet induced
- Chemically induced
- Genetically altered animals

DIET INDUCED

- Salt induced hypertension
- High fat induced obesity

Chemical induced

- STZ induced diabetes
- CCL4 and Paracetamol induced hepatic injury
- Catacholamines (Isoproterenol) induced myocardial necrosis
- NSAIDS induced gastric ulcers

Genetically induced

Two basic types of animal models

- Animals that are genetically modified, typically with respect to a *SINGLE TARGET GENE*, in order to increase the sensitivity for a specific and known pathway of toxicity

- Animal models is not focused on one gene but rather on a complex, often *POLY GENETICALLY CONTROLLED* disease state

- Rat models of metabolic syndrome are now readily available and reasonably well described

Development of rat models of metabolic syndrome

In 1961, Zucker and Zucker - spontaneous mutation in an out bred rats

Homozygous male – Obese Zucker rats

- Obesity
- Mild insulin resistance
- Prediabetic (Normoglycemic)

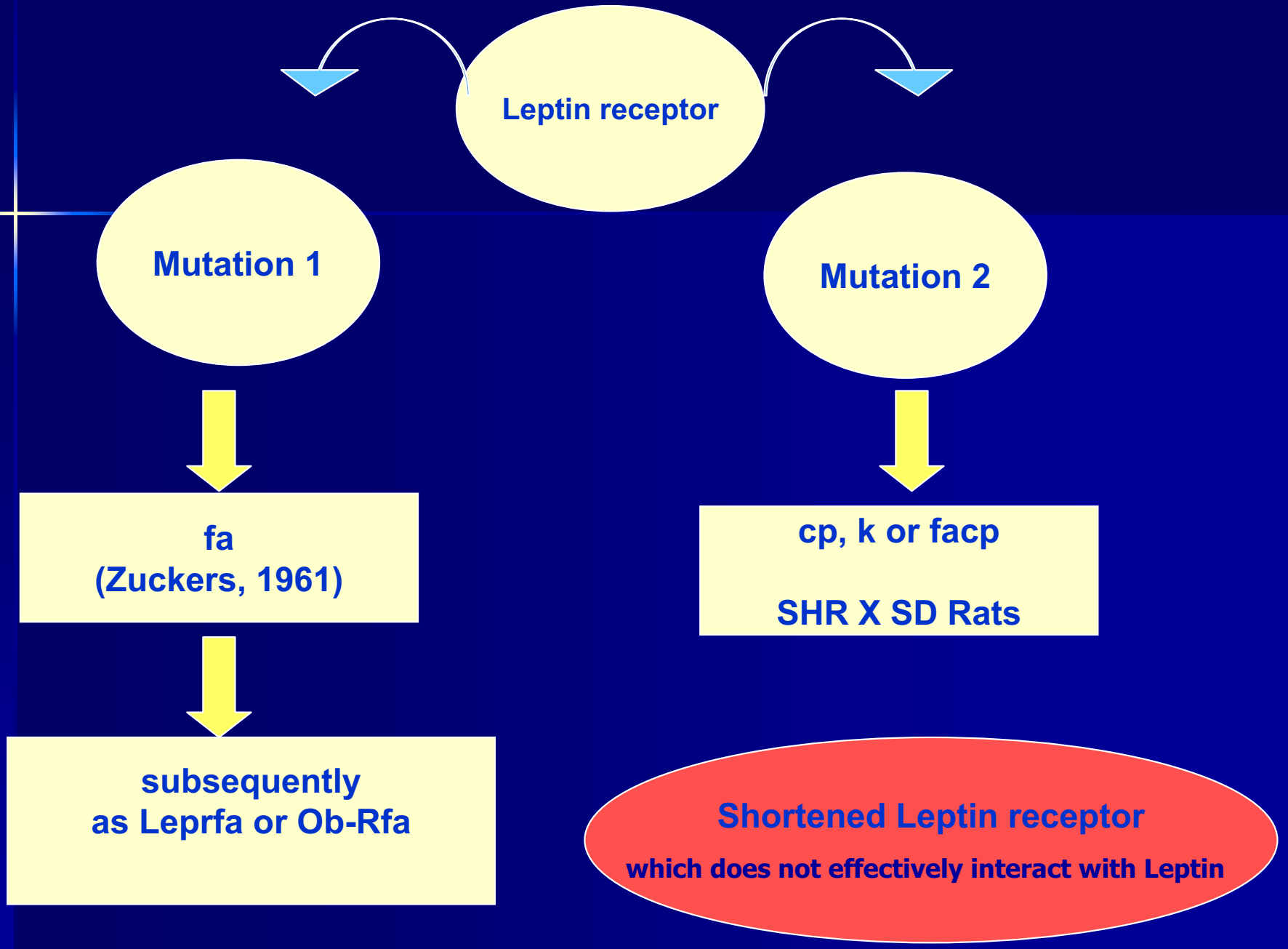
Heterozygotes for the mutation or homozygous normal -- Lean zucker rats.

- Non obese
- Non prediabetic

Different animal models of metabolic syndrome

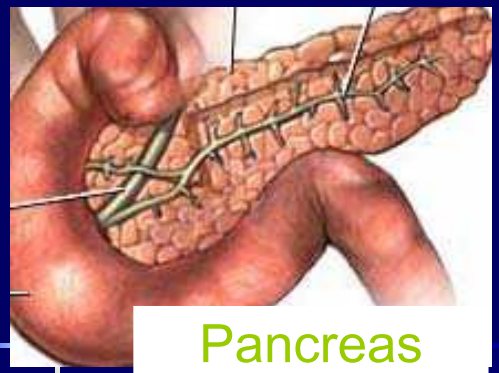
- Zucker fatty Rat
- ZDF Rat
- ZSF1 Rat
- SHR
- Obese Koletsky Rat
- JCR Rat
- SHHF Rat

What defects does ZDF have?



Peterson et al. 2001

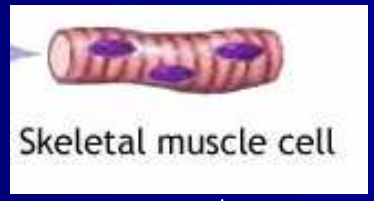
What Leptin does?



Pancreas

Modulation of insulin secretion
↓ TG content of the islet

Insulin



Skeletal muscle cell

Leptin

Fat cell

↑ Glucose uptake
Glycogen synthesis and
fatty acid oxidation

↓ Insulin-stimulated glucose uptake
↑ Lipolysis
↓ Lipogenesis

ZSF1 Rat

Nomenclature **-Crl:ZSF1- Lepr fa lepr cp**

Origin **: A hybrid between a ZDF female and SHHF male developed at genetic models inc.**

Characteristics

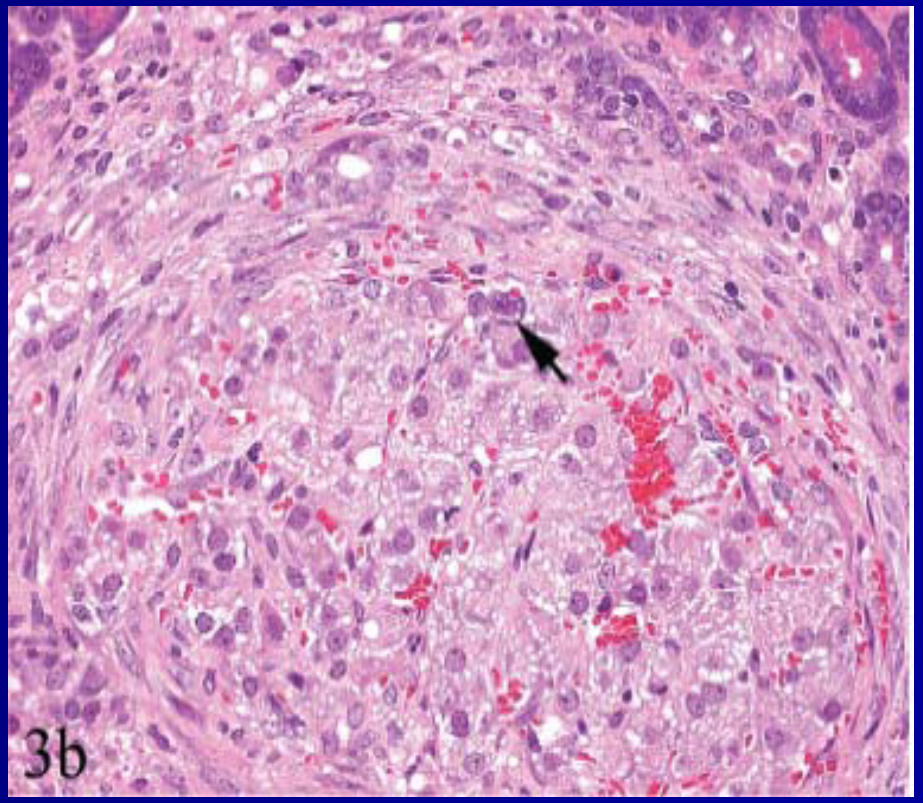
- Obesity - increased feed intake and body weight
- Type 2 diabetes,
- Insulin resistance
- Hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia
- Hypertension
- Nephropathy
- Congestive heart failure.

Phenotypic characteristics

- Insulin resistance and Type 2-diabetes

6 weeks

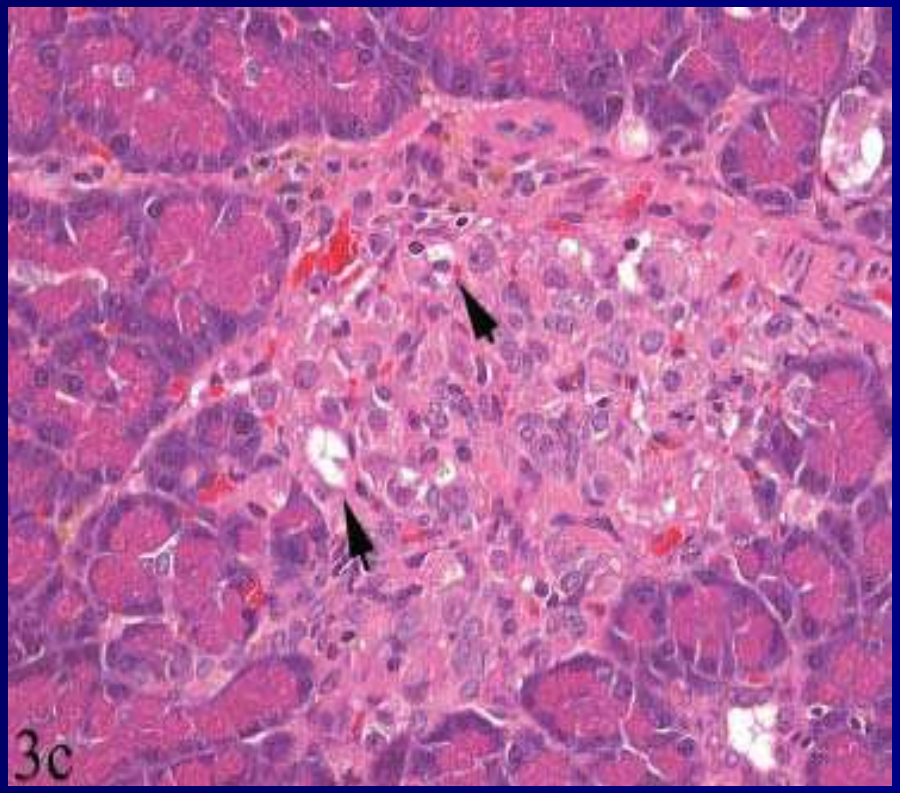
- Islet showing the substantial,diffuse β-cell vacuolation
- β-cell death (arrow) interlacing, thin skeins of fibrous tissue
- Vascular congestion and hemorrhage



Toxicologic Pathology, 36: 529-551, 2008

14 weeks

Pancreas



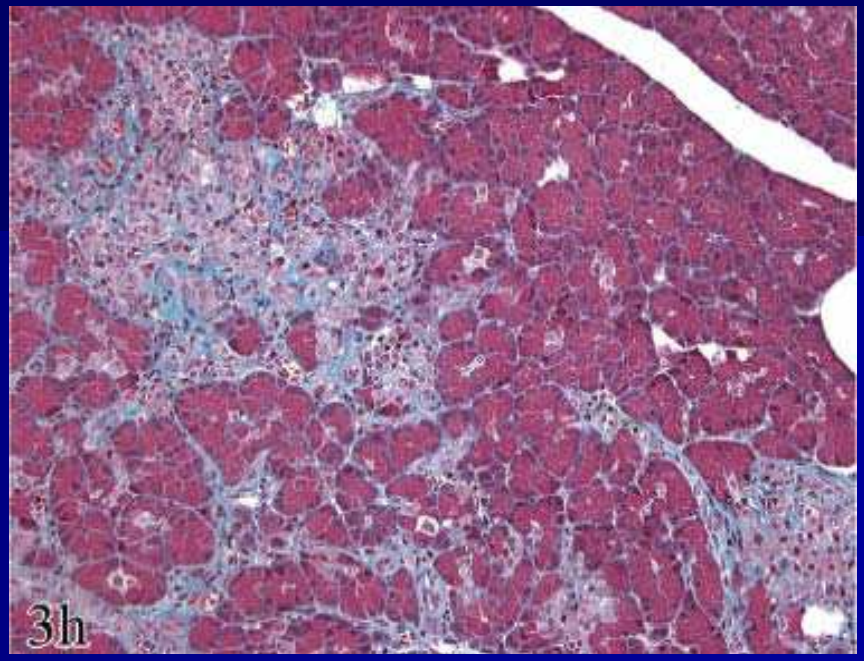
- Islet showing β-cell vacuolation and degeneration (arrows) and numerous fibroblasts

Toxicologic Pathology, 36: 529-551, 2008

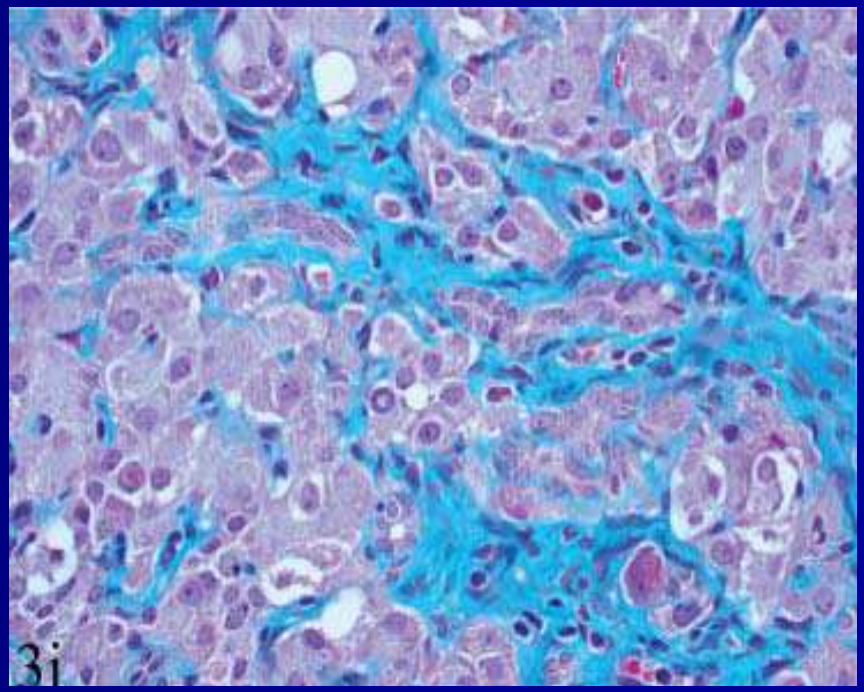
Pancreas

14 weeks

- Abundant collagen distribution in a degenerate islet and interconnecting in adjacent areas



- Higher magnification of degenerate islet tissue showing β-cell vacuolation and degeneration, minimal inflammatory cell infiltration with abundance of collagen in fibrous tissue



Toxicologic Pathology, 36: 529-551, 2008

Phenotypic characteristics

- Hypertension

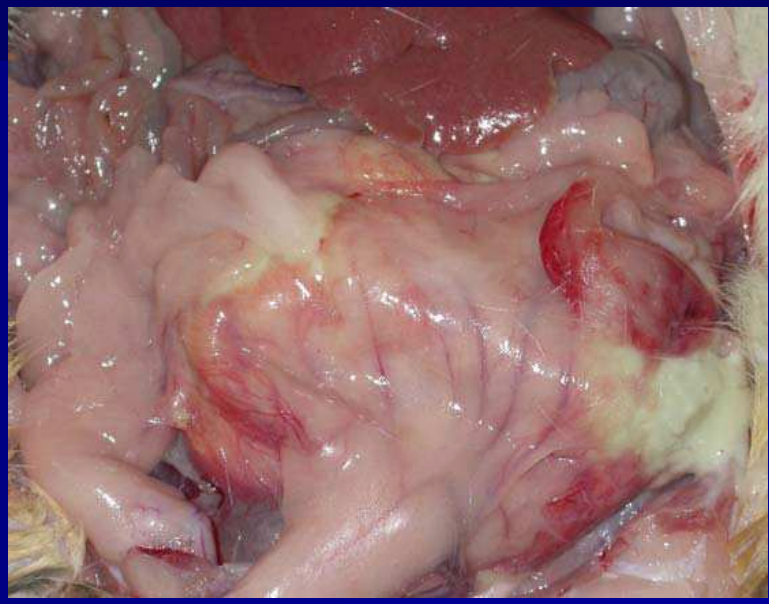
Mean arterial blood pressure (mmHg) → 151.4 ± 2.5

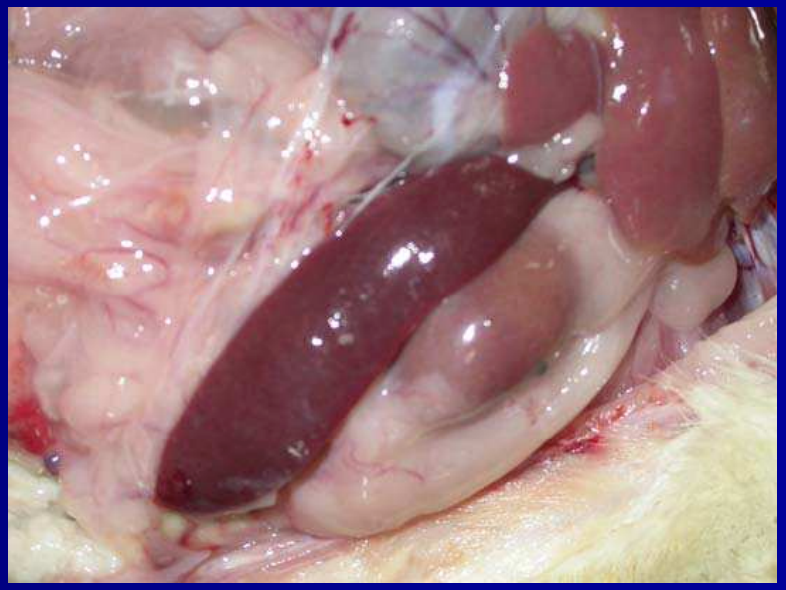
Normal : Average mean pressure = 103 mmHg

Phenotypic characteristics

- Obesity

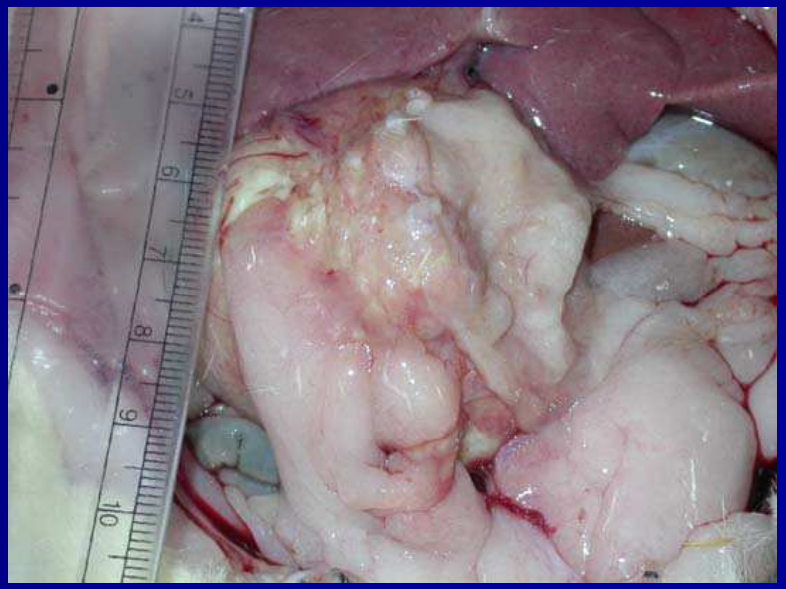
Obesity





Obesity

Abdominal fat



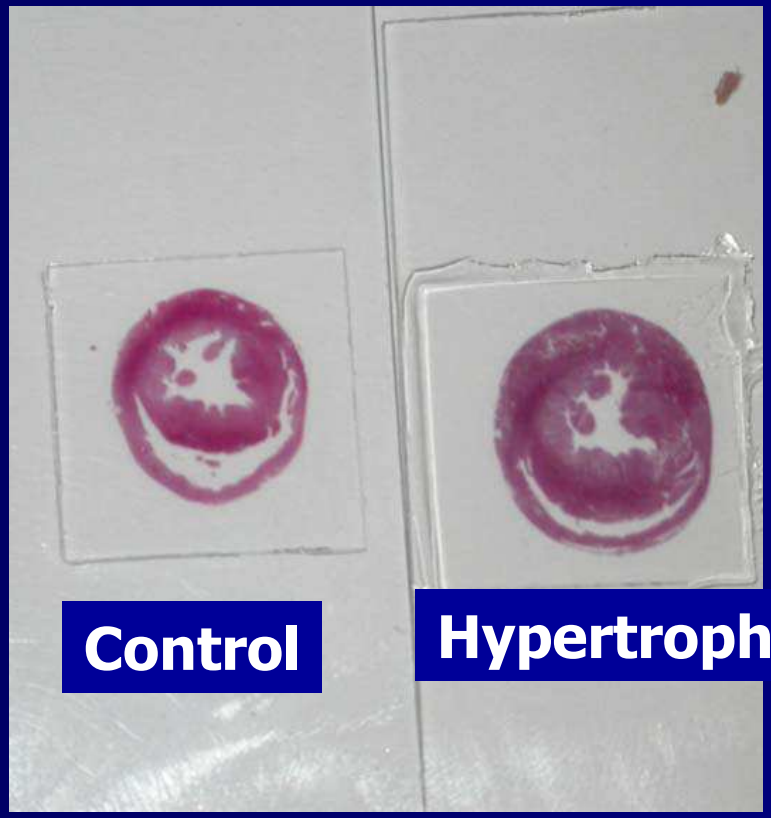
Fatty liver

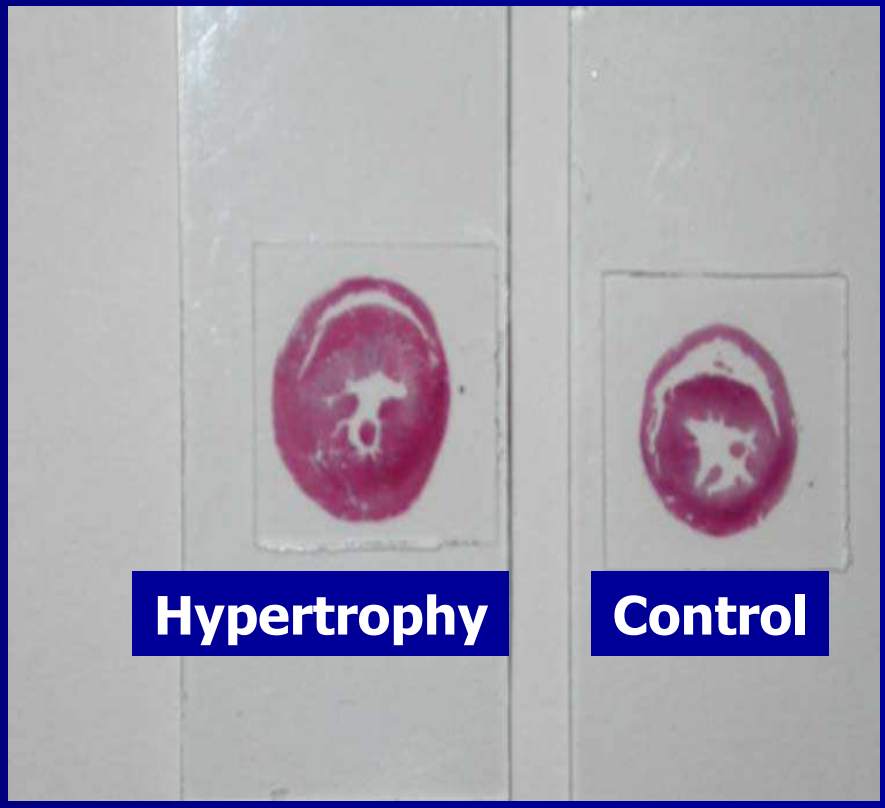
Abdominal fat

Phenotypic characteristics

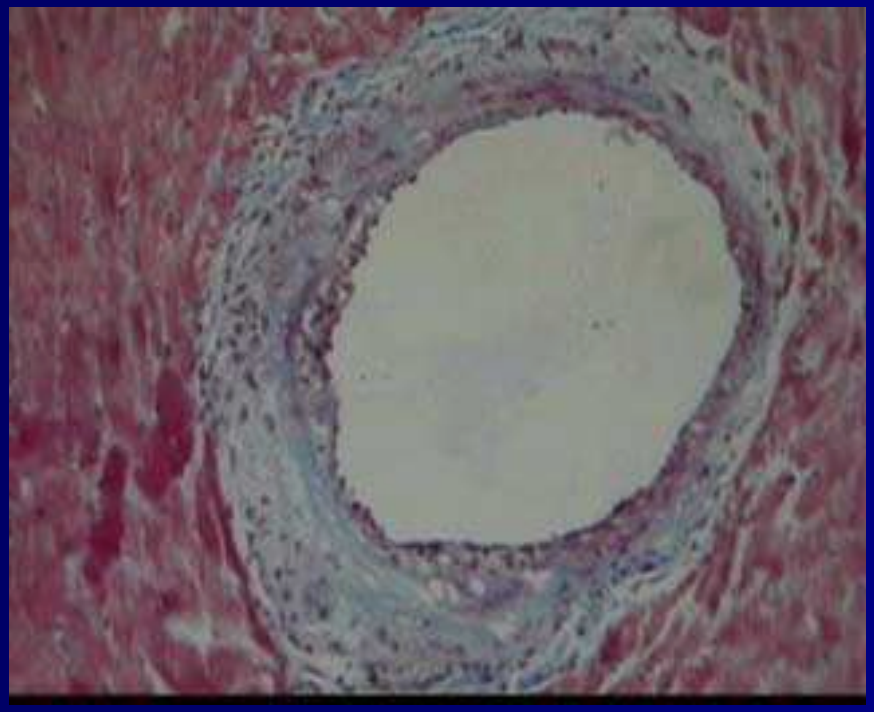
- Left ventricular dysfunction

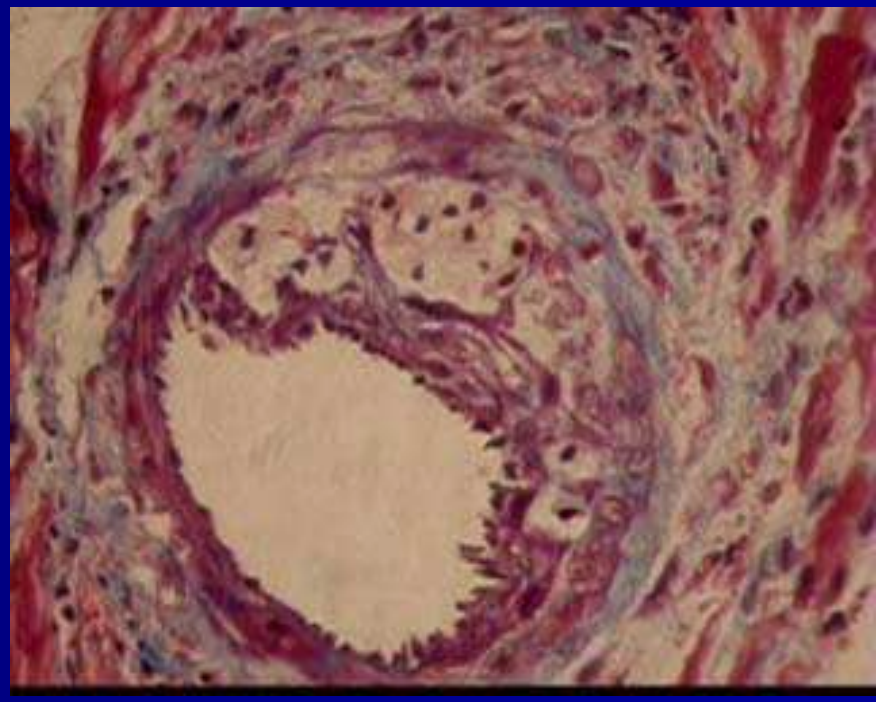
Left ventricular dysfunction





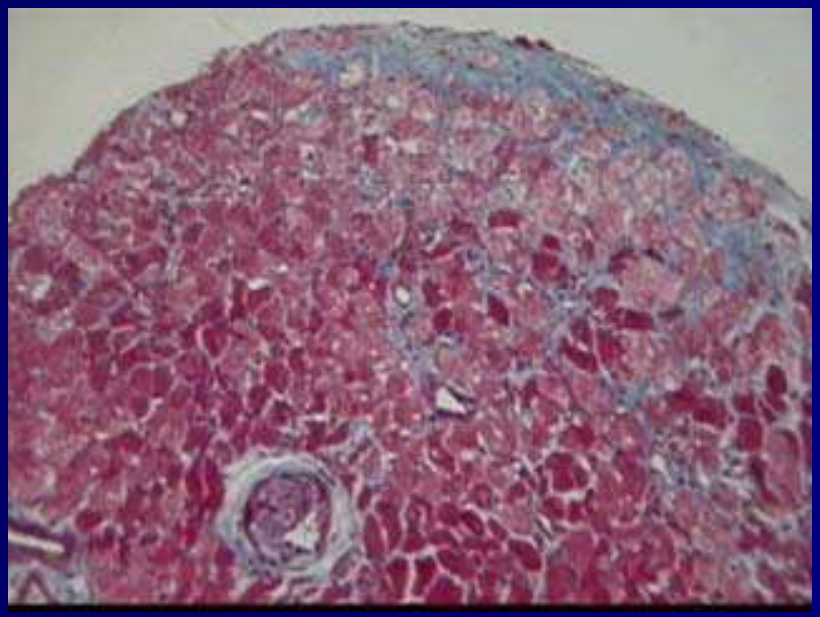
Heart

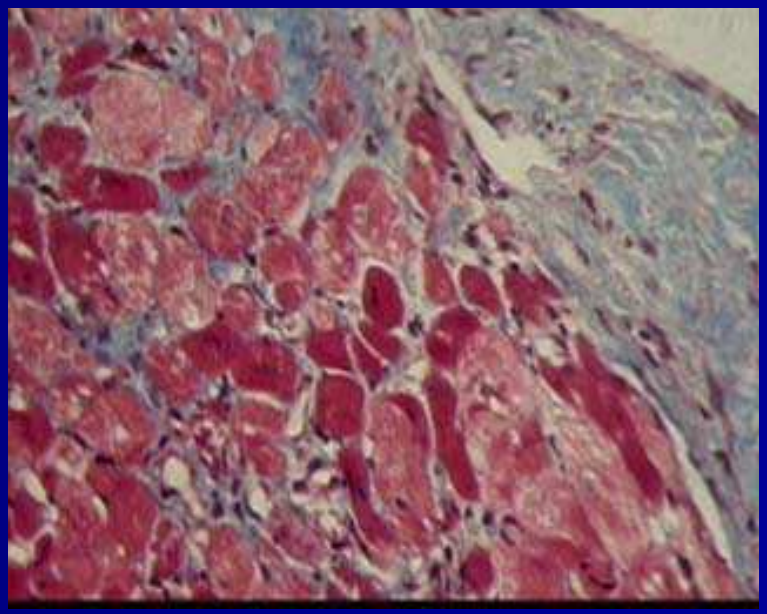




Heart - Atheromatous Plaque

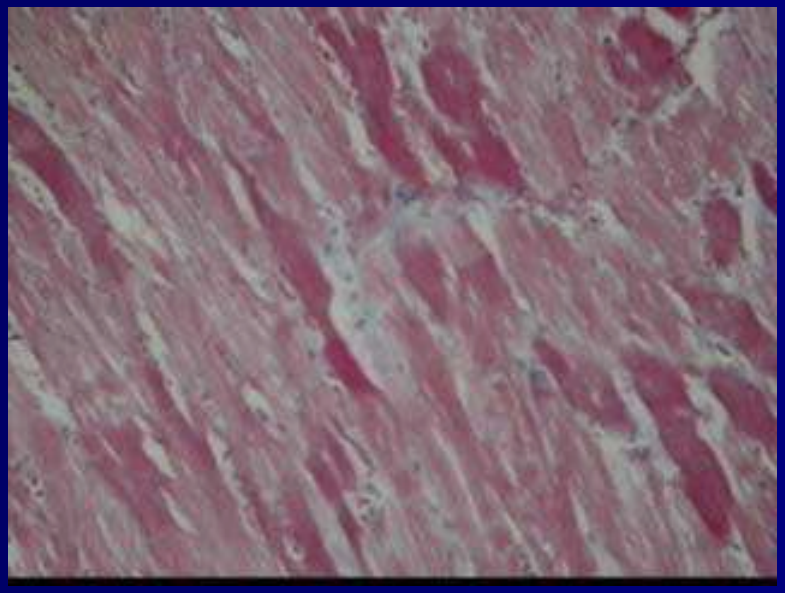
Heart

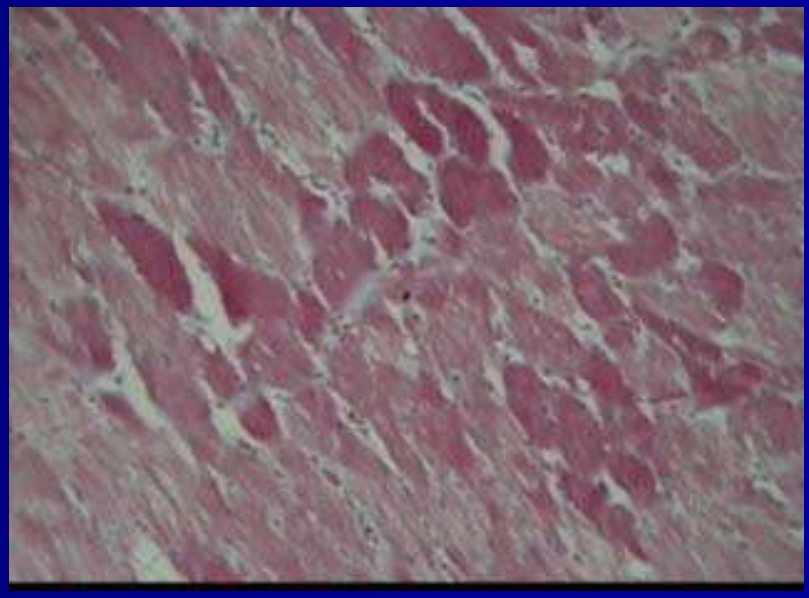




Endocardial fibrosis

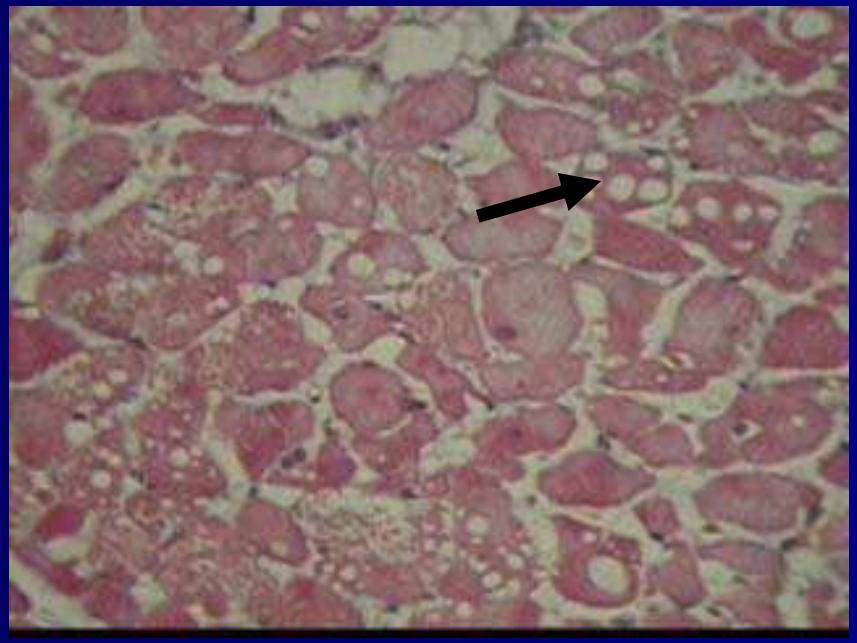
Heart

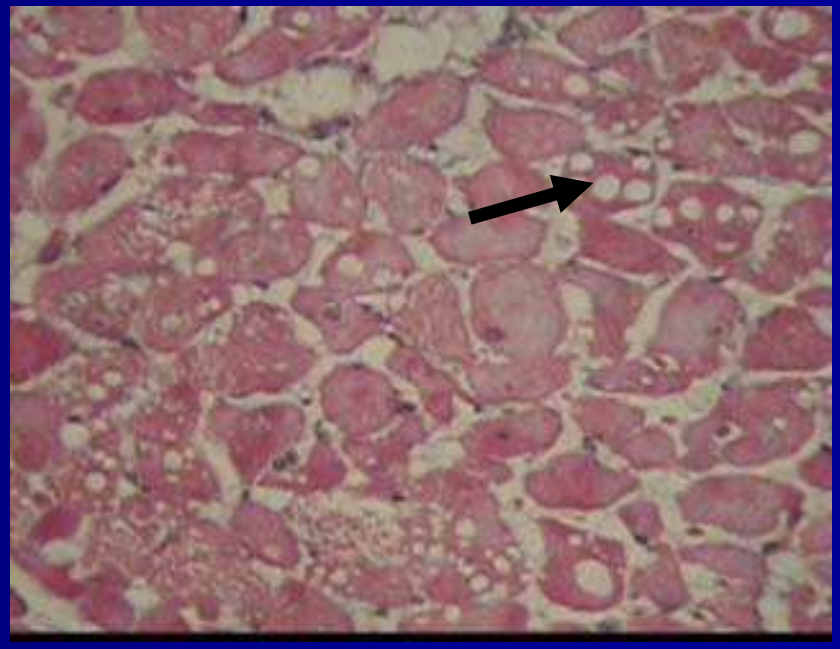




Left ventricle - Hypertrophied fibers

Heart



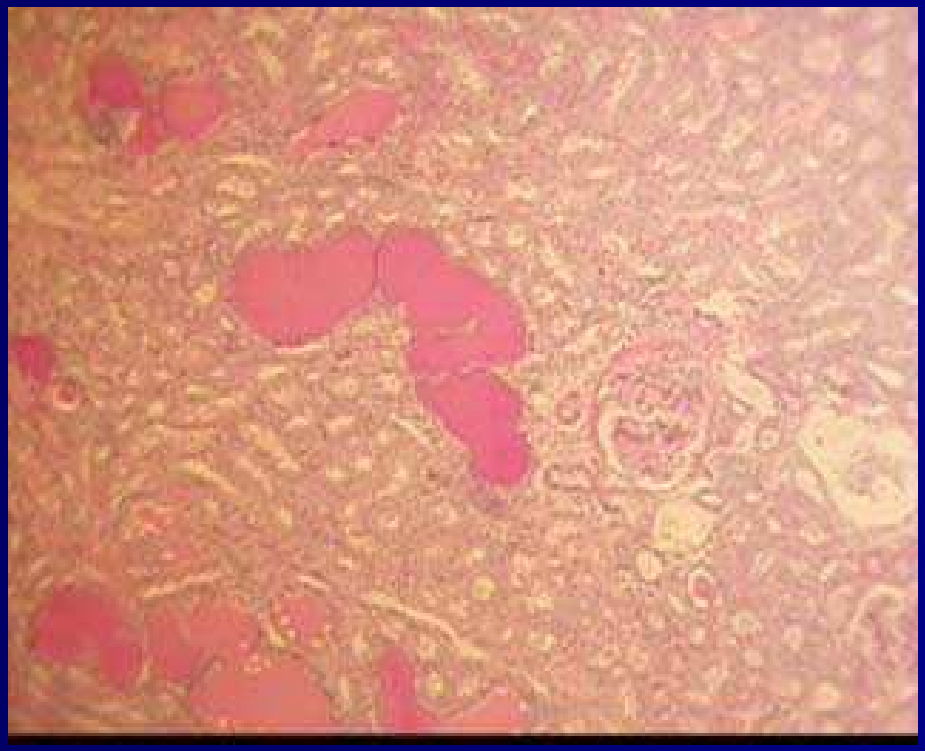


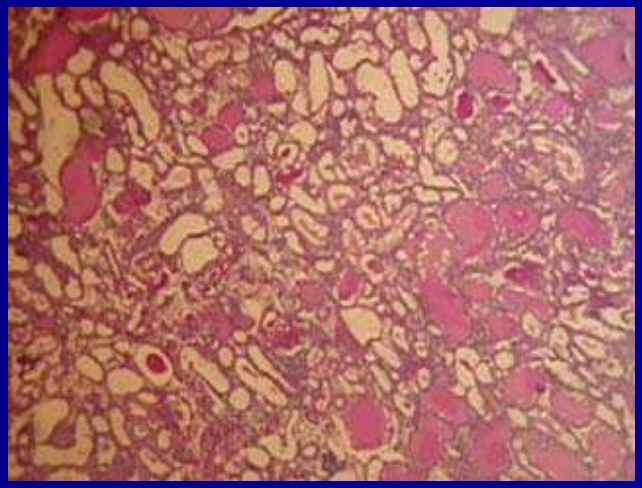
Myocardial vacuolations

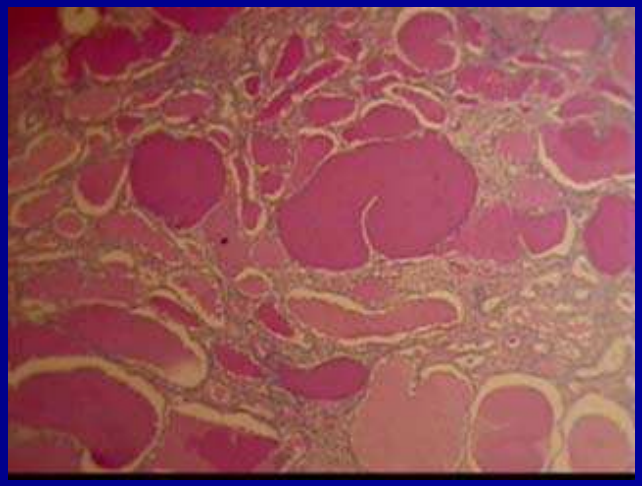
Phenotypic characteristics

- Nephropathy

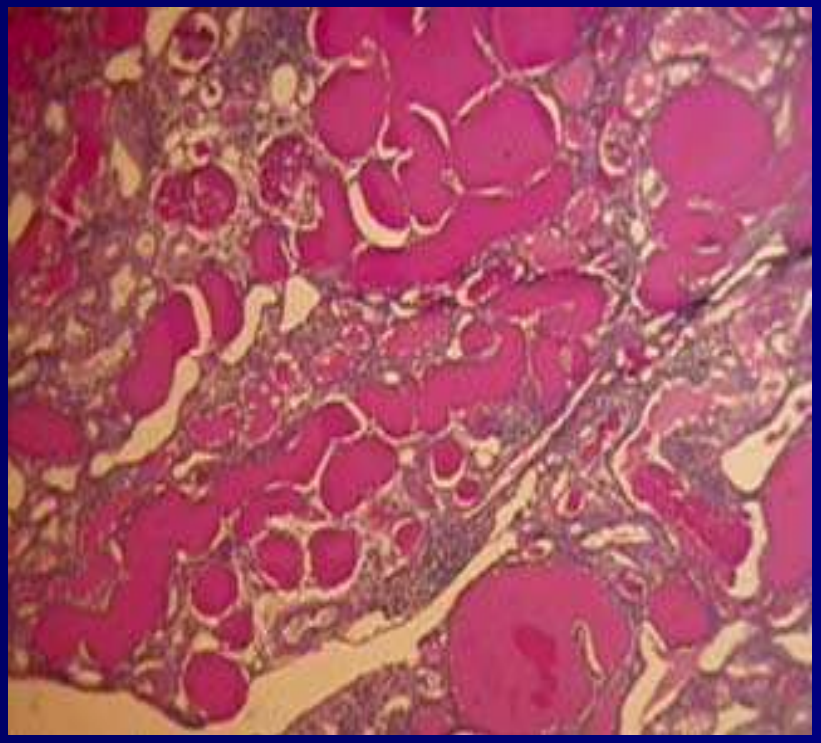
Nephropathy

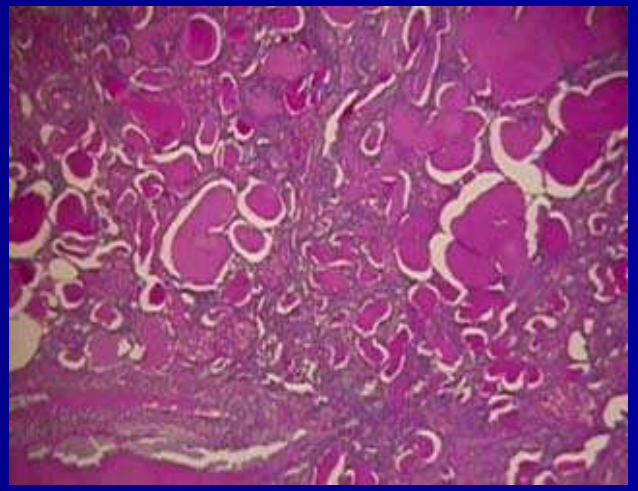


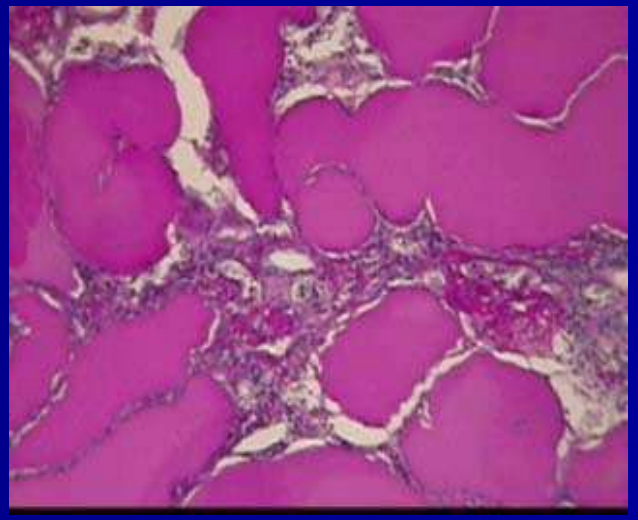




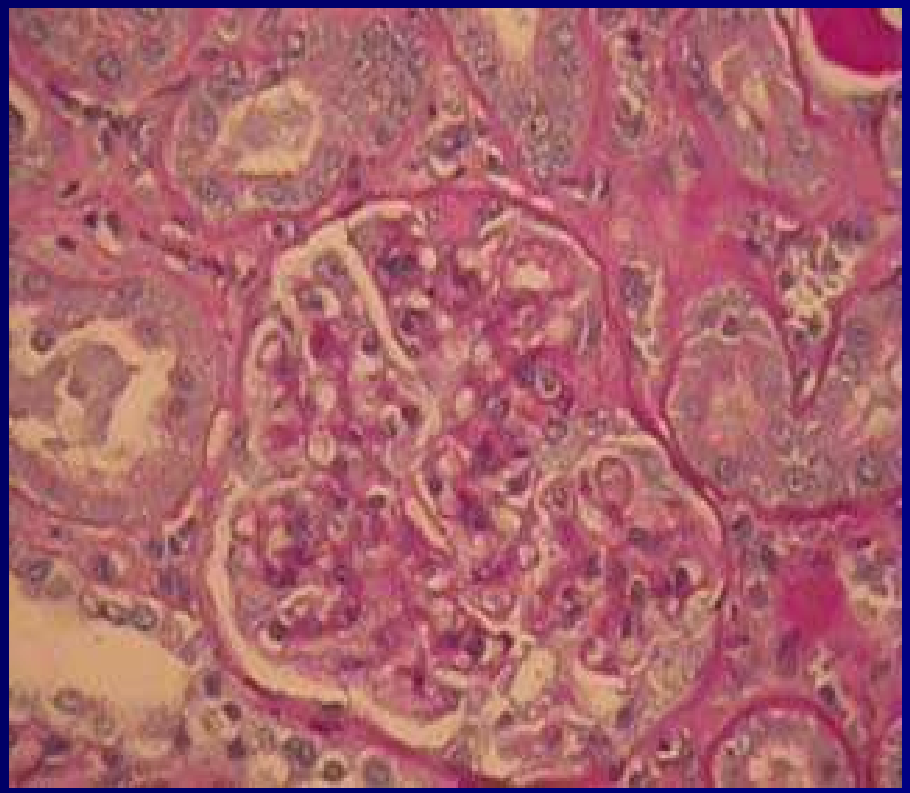
Nephropathy





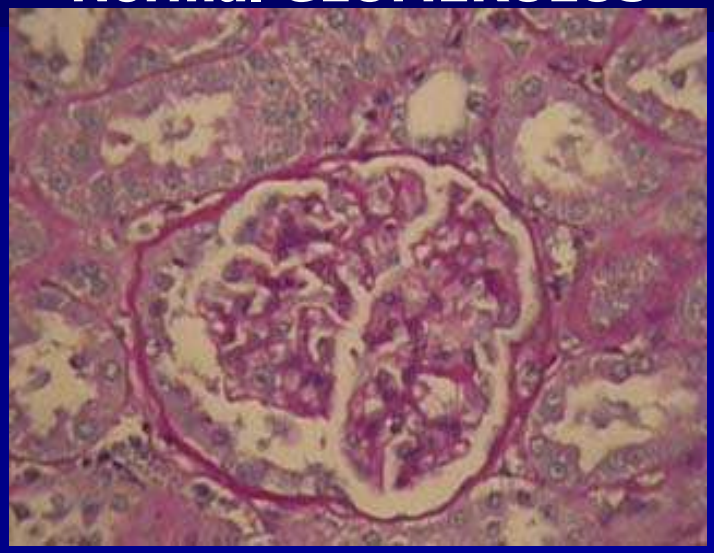


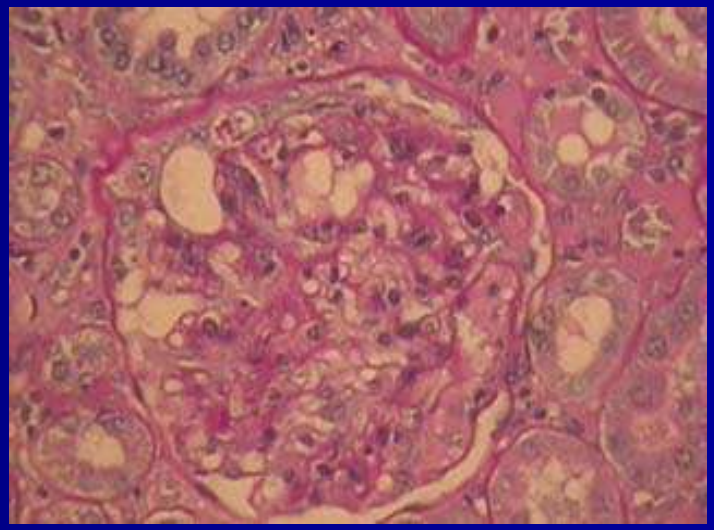
Nephropathy



Initial mesangial expansion

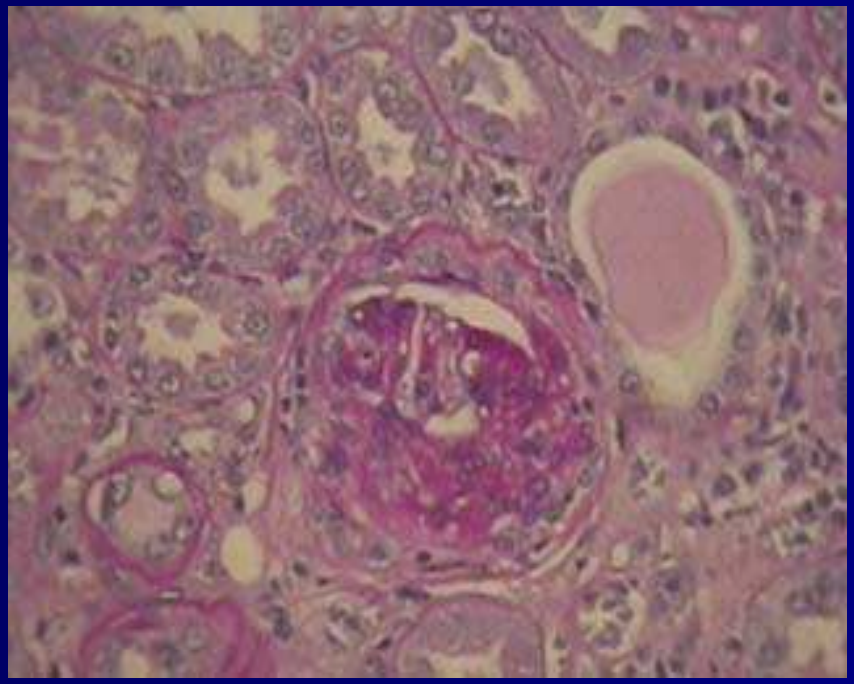
Normal GLOMERULUS

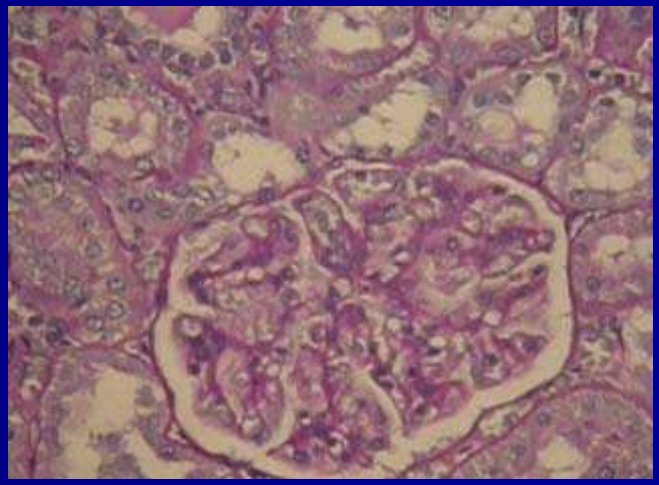


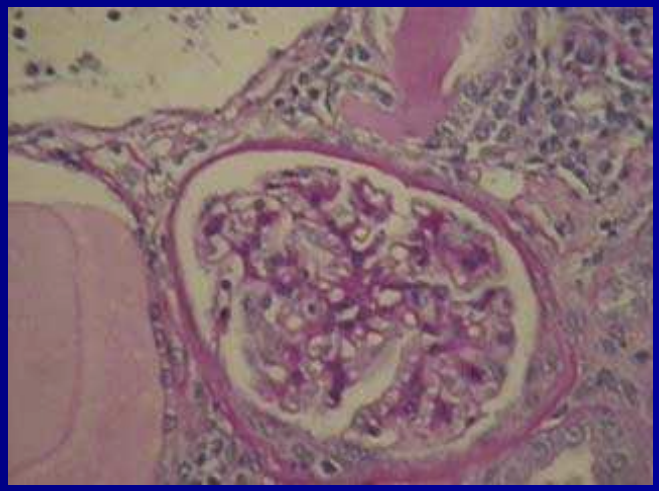


Initial mesangial expansion

kidney

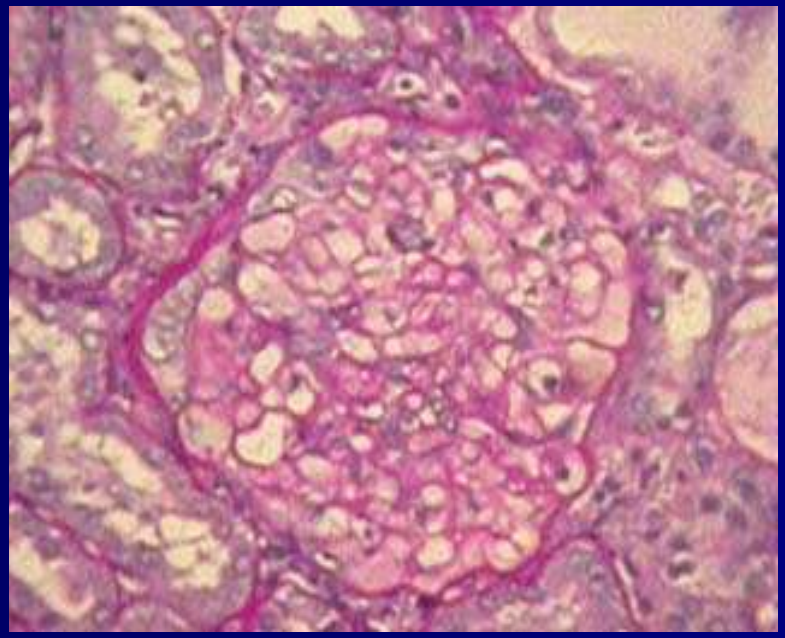


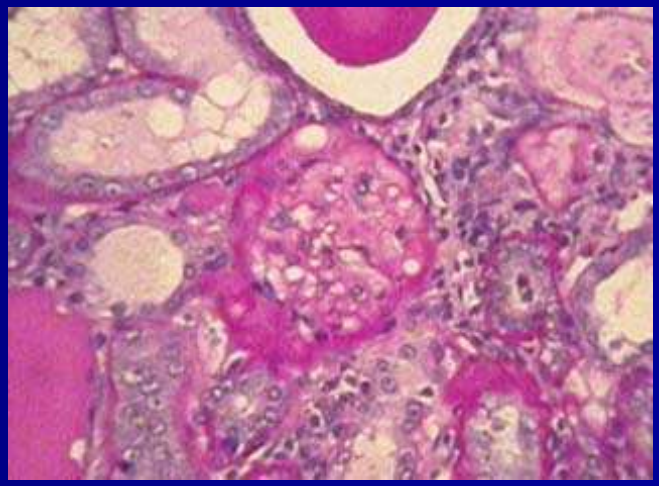


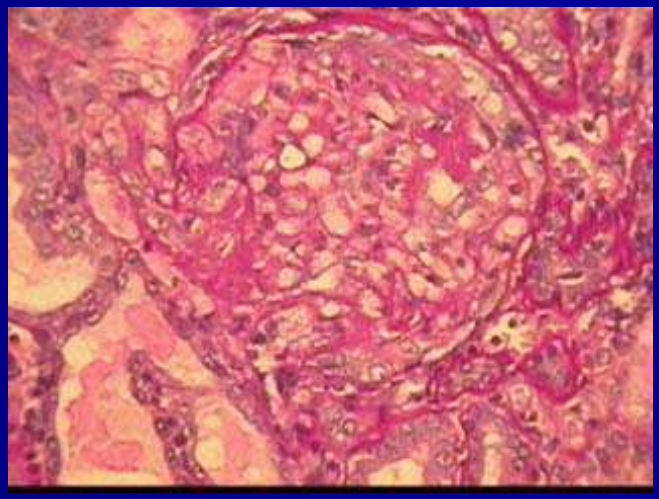


Segmental GN with crescent

kidney

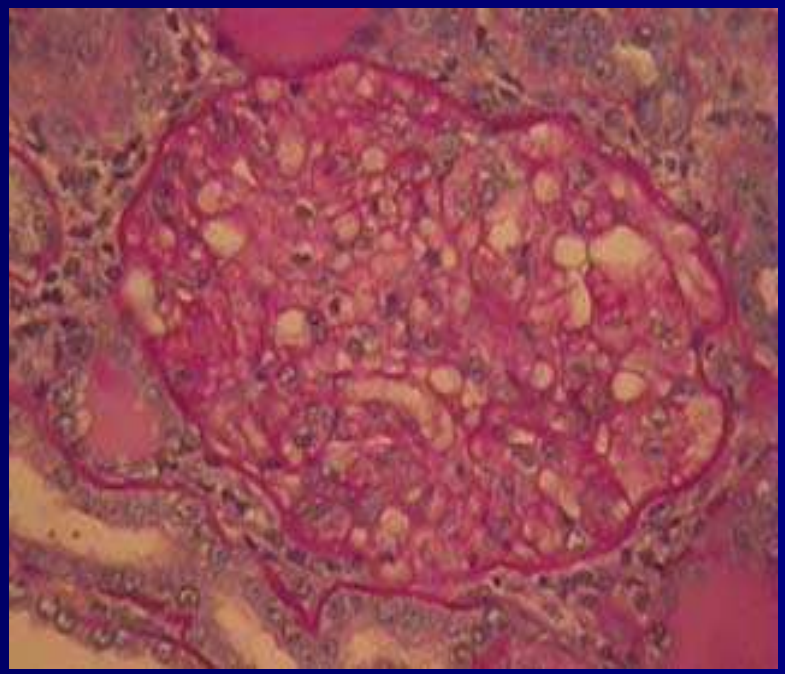


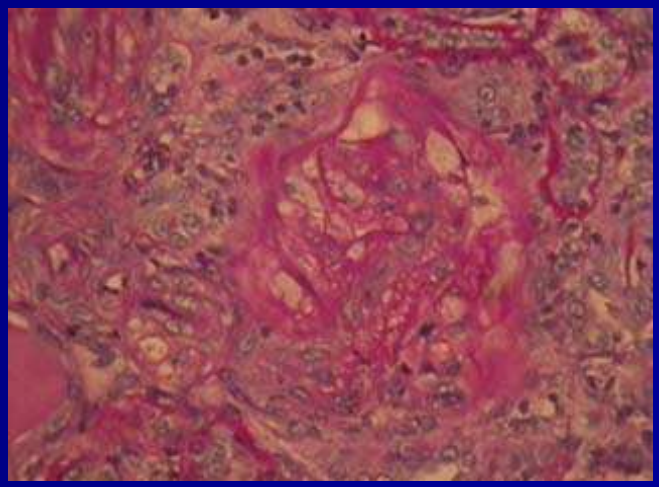


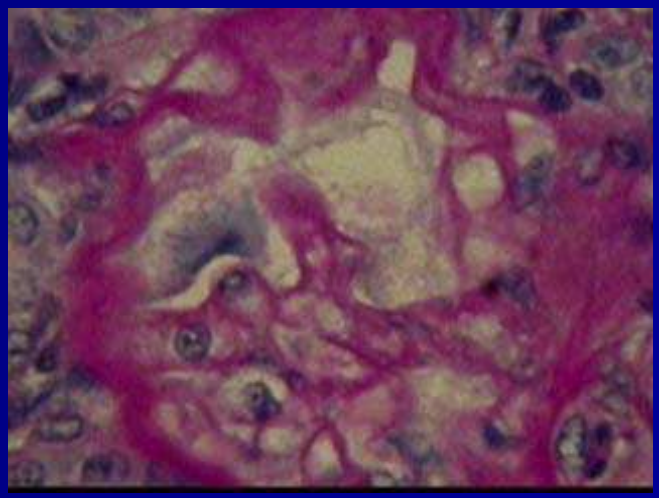


GLOBAL GN

kidney

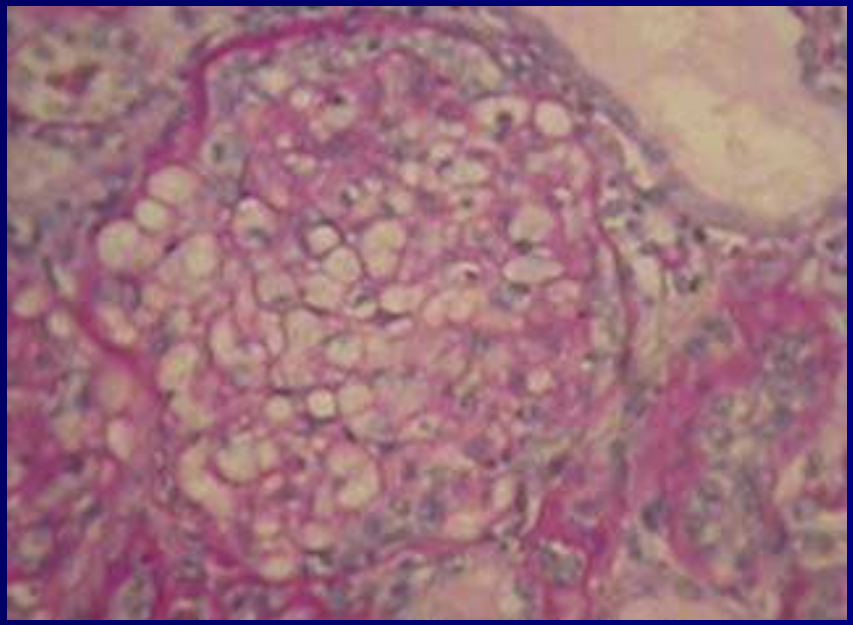




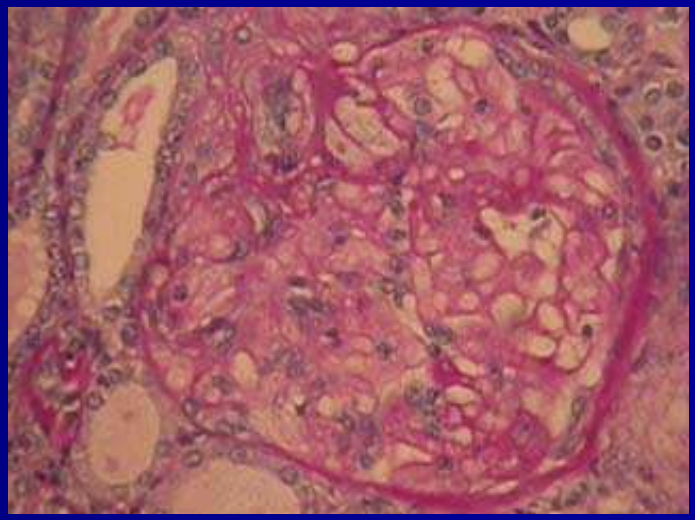


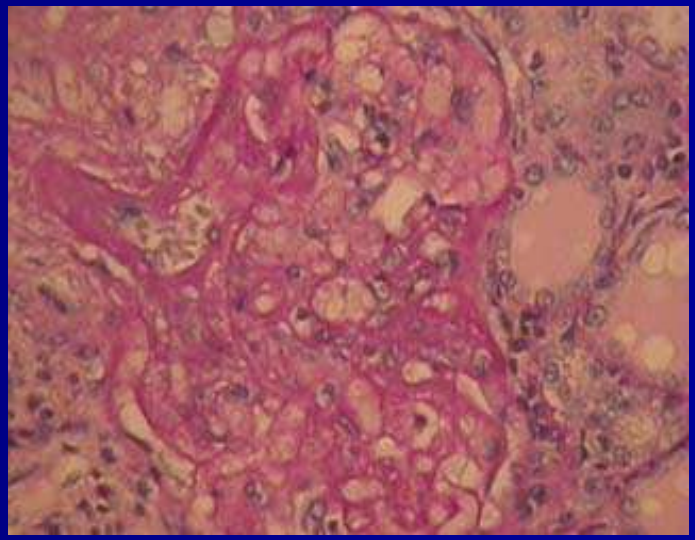
GLOBAL GN

kidney

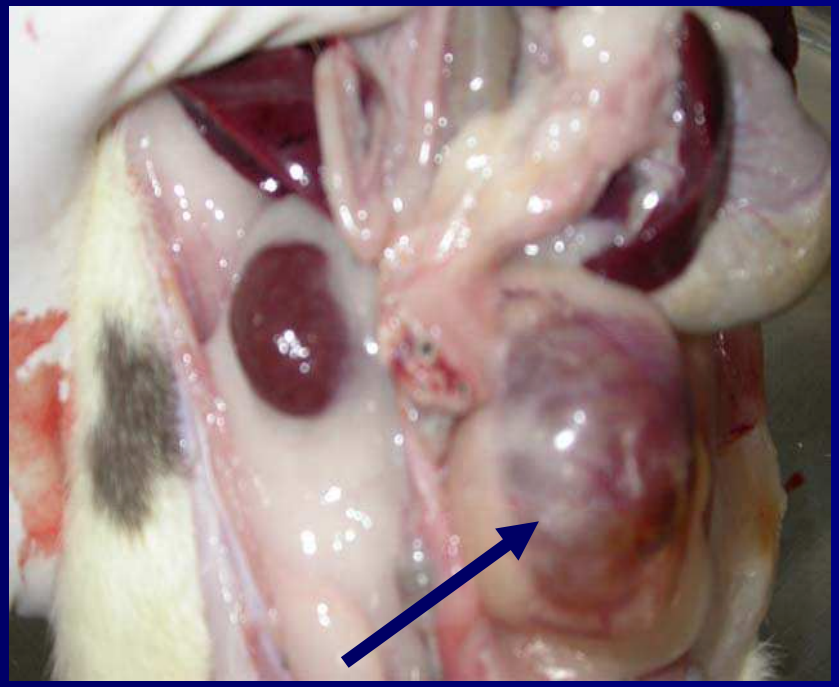


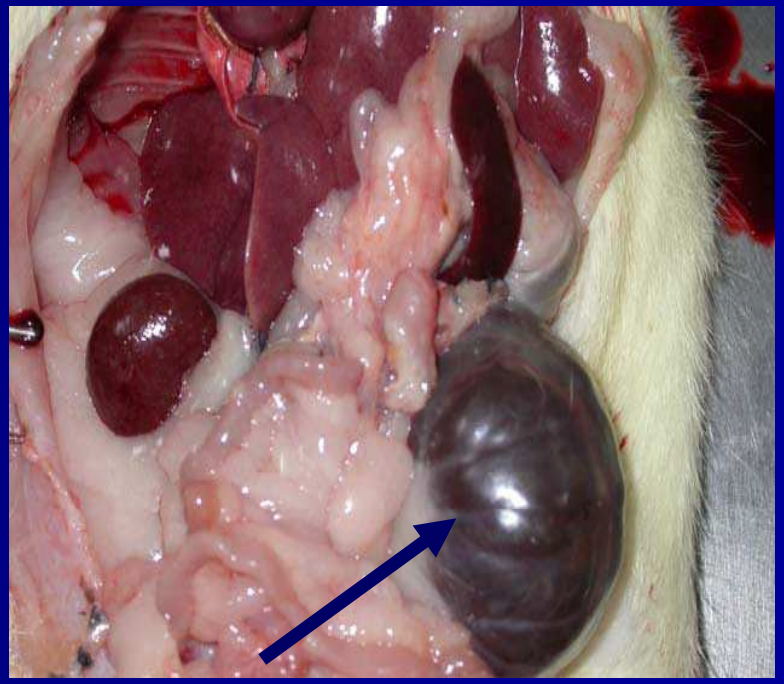
GLOBAL GN

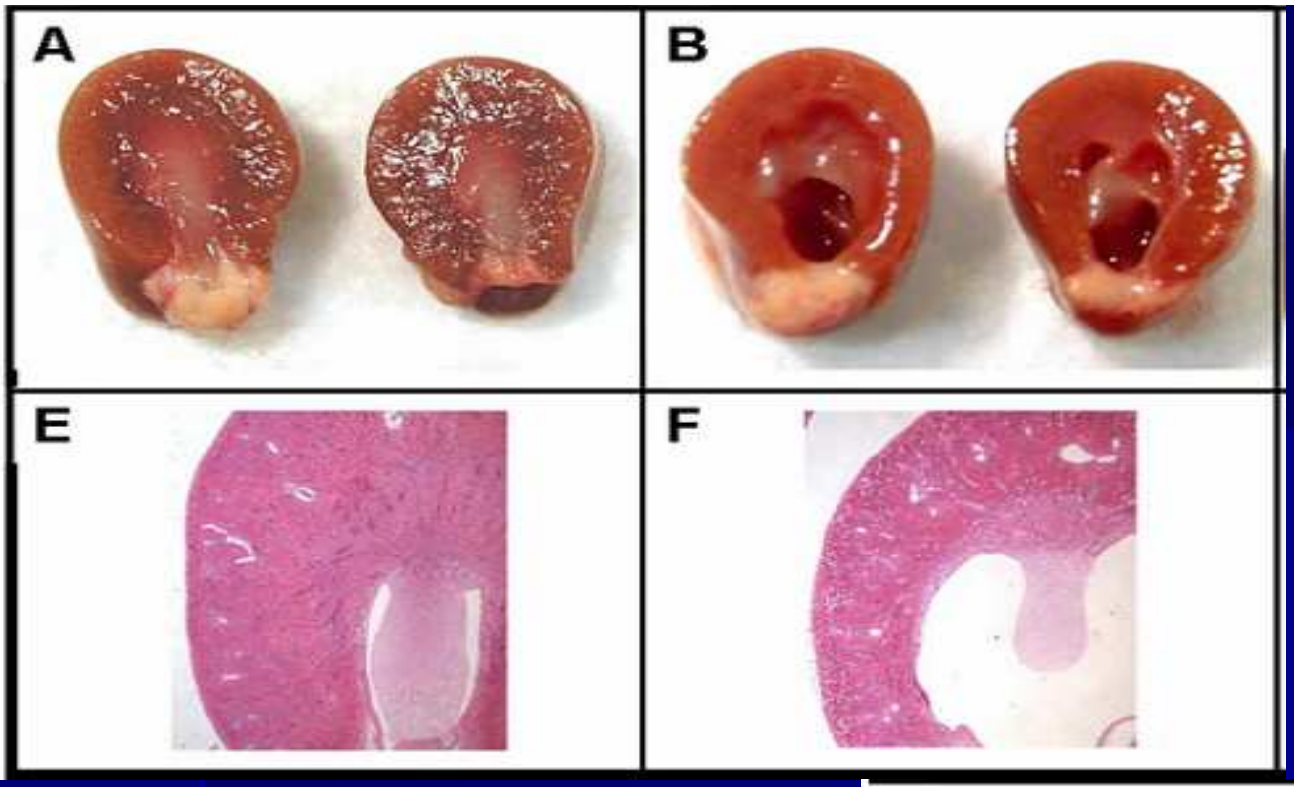




Hydronephrosis

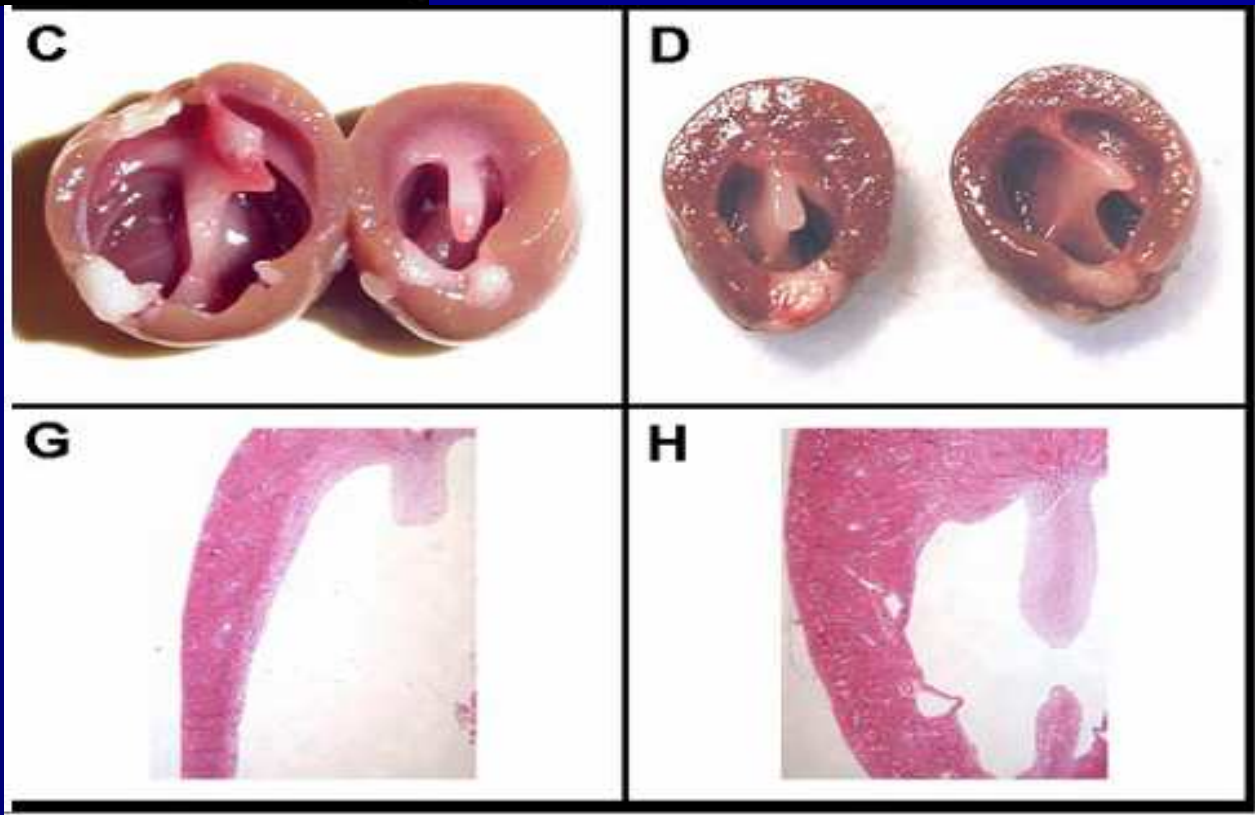






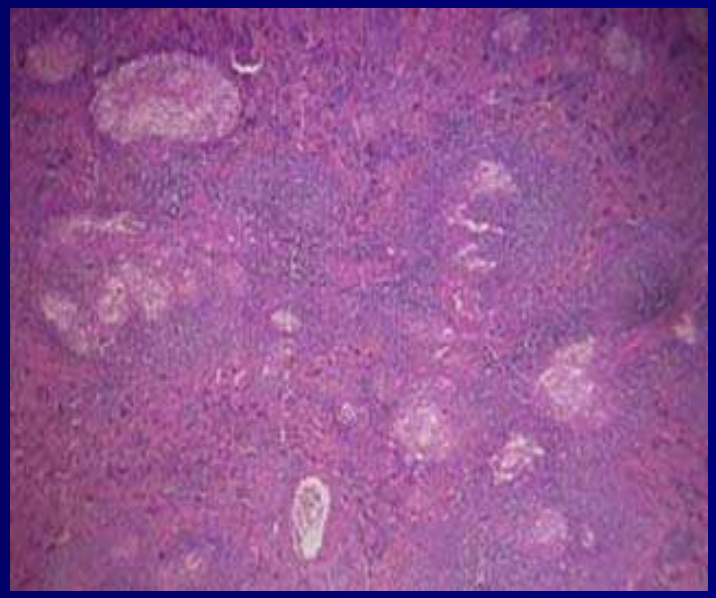
A & E: Sprague-Dawley
B & F: Lean ZDF rat

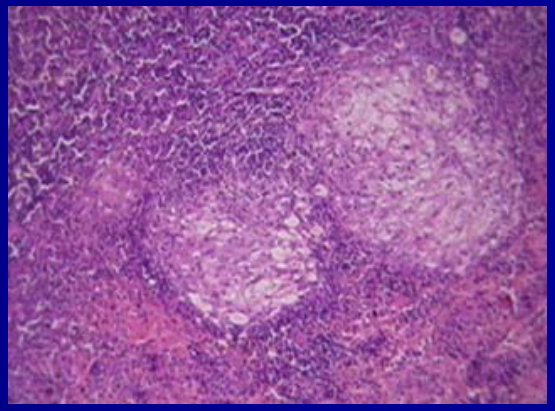
C & G: Zucker obese
D & H: ZDF obese

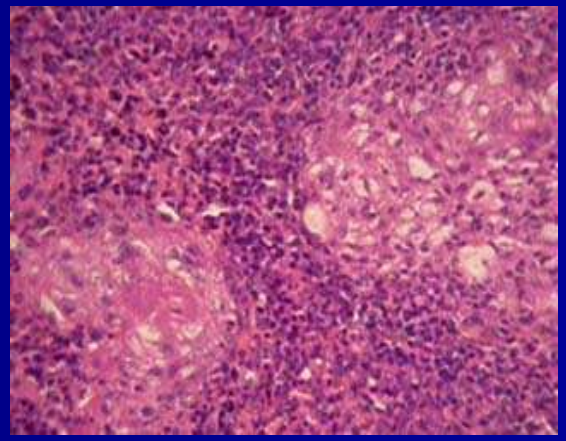


Marsh et al. 2007

Spleen -Atherosclerosis







ATHEROSCLEROSIS- SPLENIC VESSEL

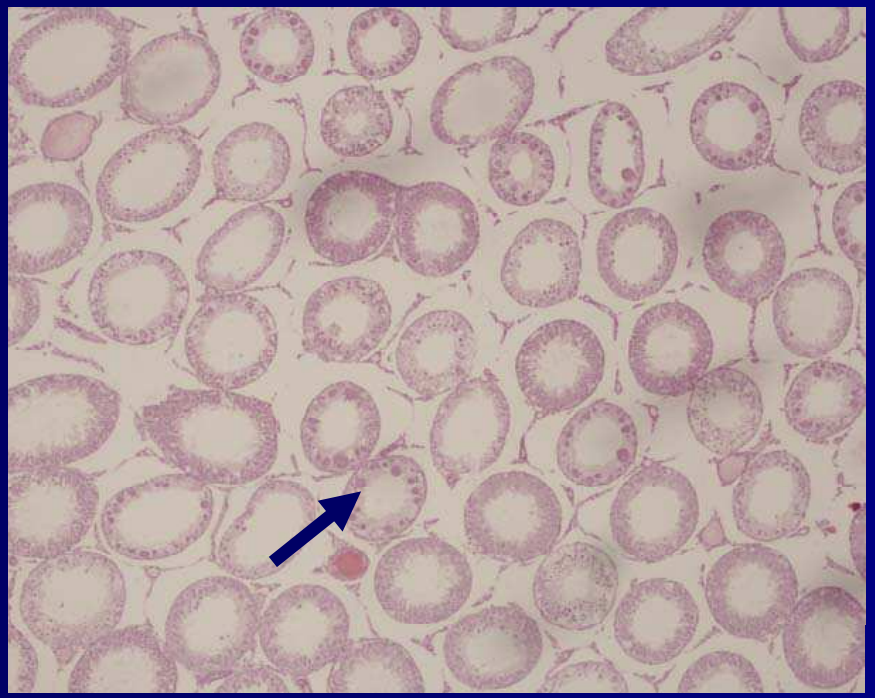
Zucker fa/fa Rats

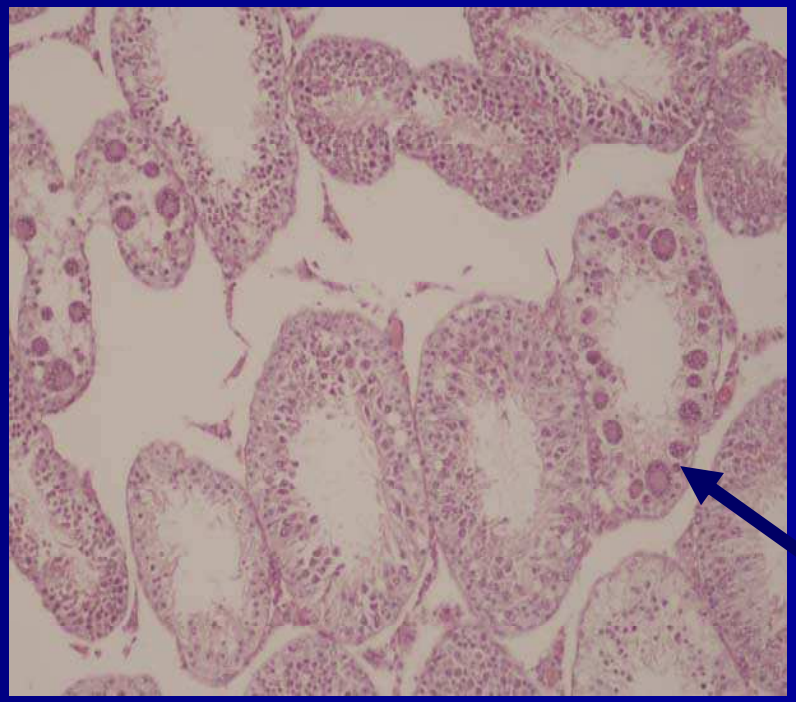
Zucker fa/fa Rats

- The fa gene – First described in obese ZDF rat
- Partially inbred strain – Resulted in development of Zucker fa/fa Rats which has the features of marked insulin resistance
- Frequently used in NIDDM, Obesity and hypertension

Zucker fa/fa rats - 3 months

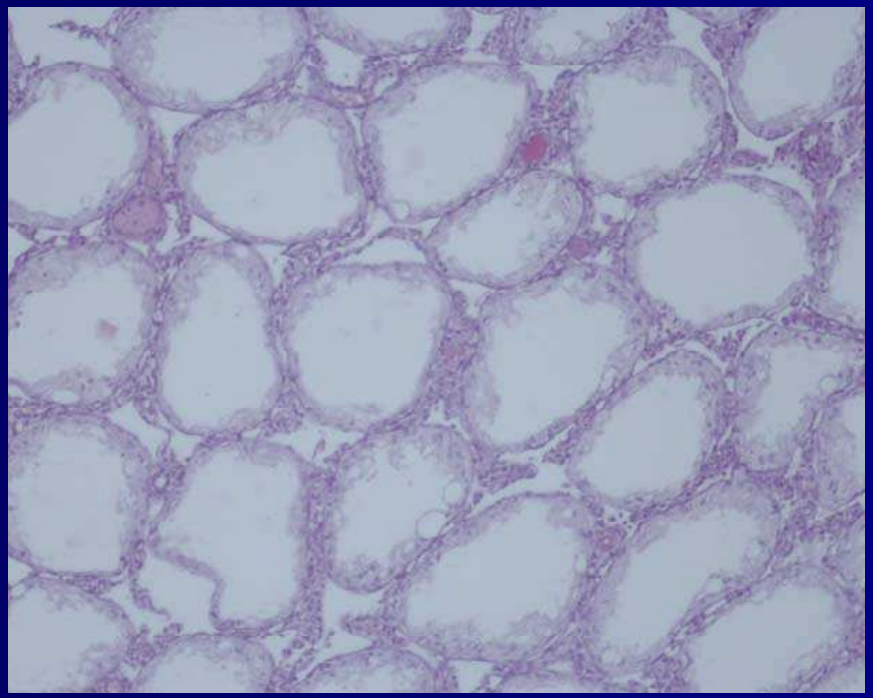
Testes

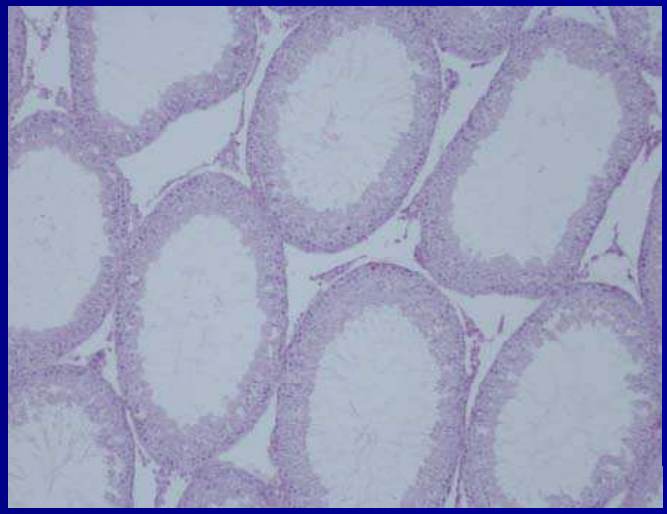


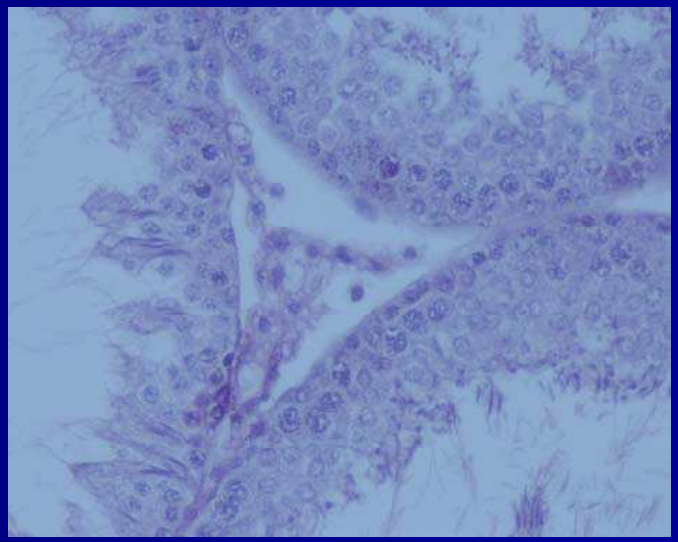


DEGENERATIVE CHANGES

Zucker fa/fa rats - 3 months



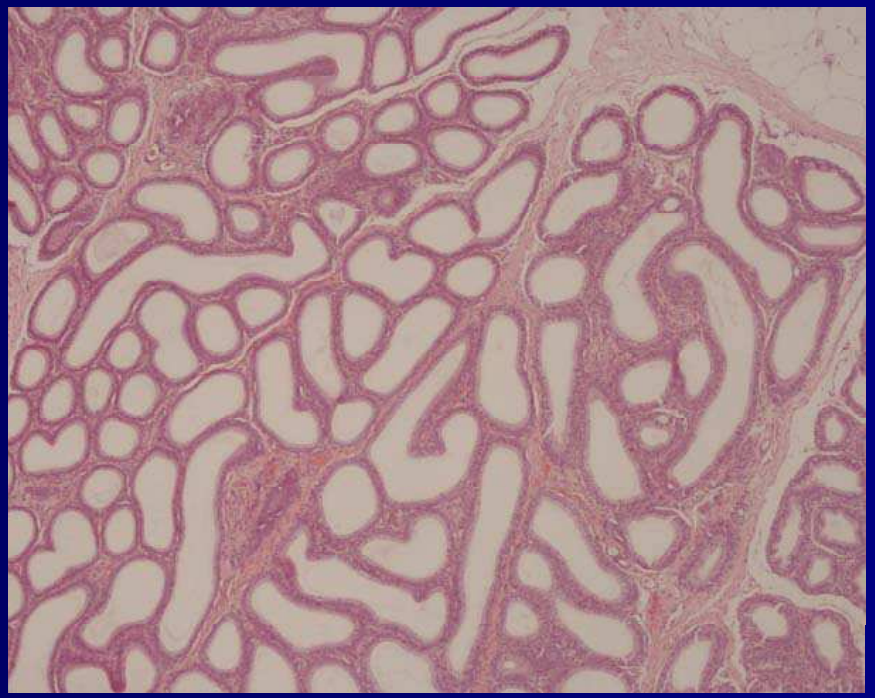


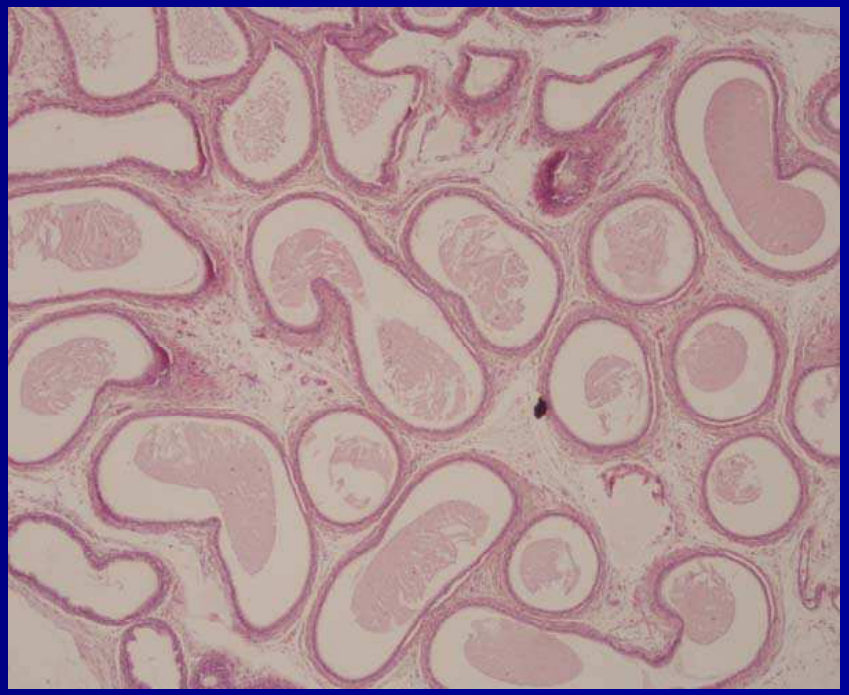


Advanced degenerative changes

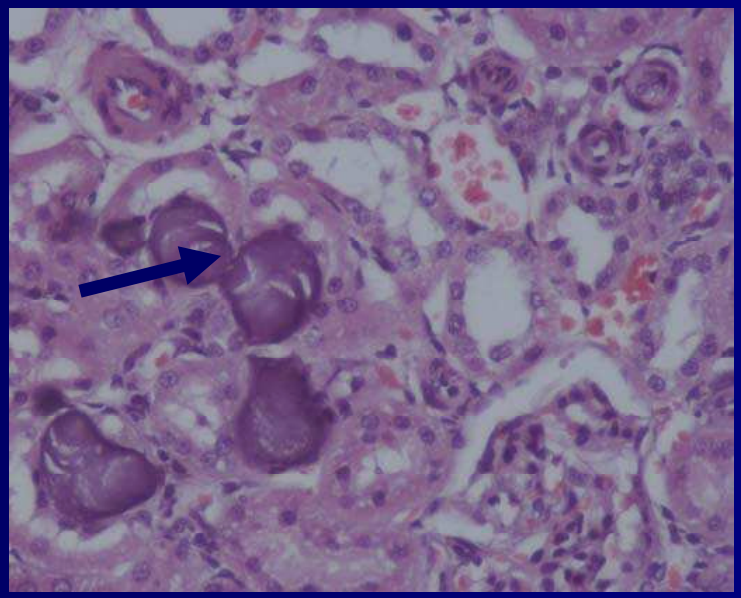
Zucker fa/fa rats - 3 months

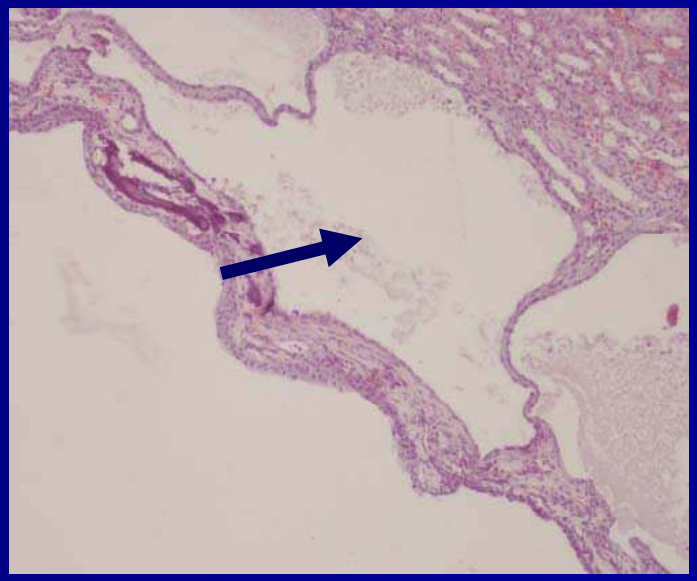
Aspermia -Epididymides





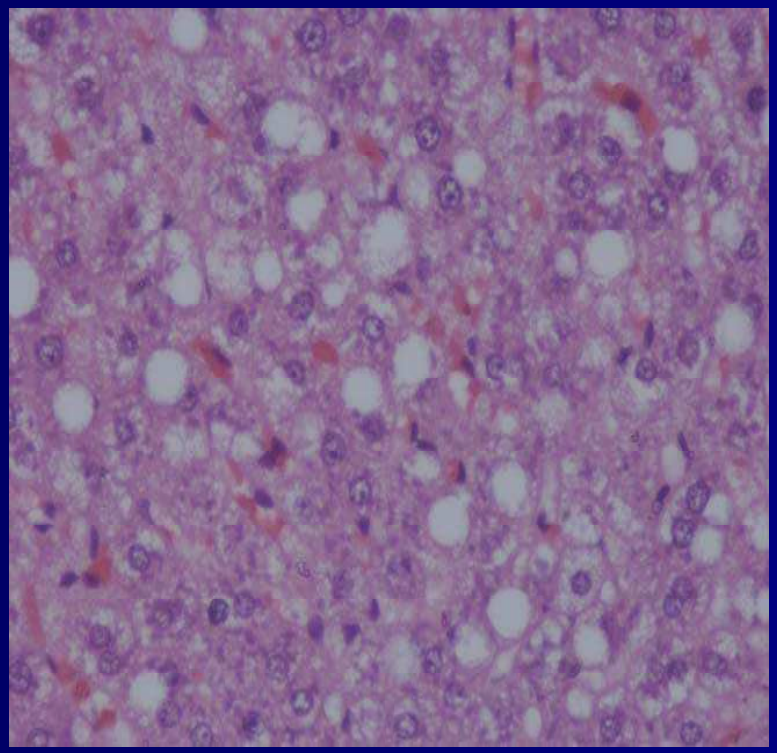
Zucker fa/fa rats - 3 months





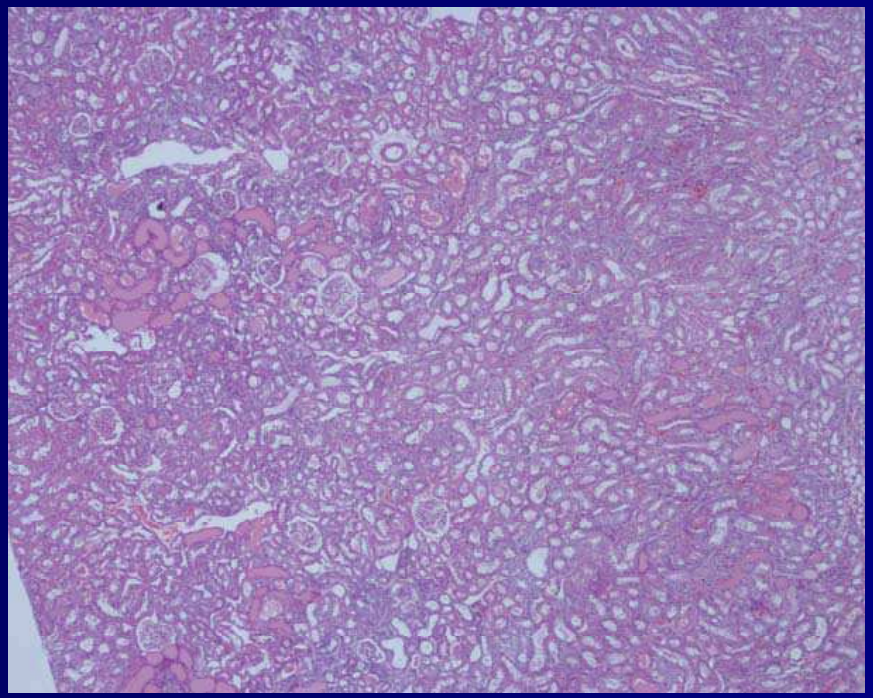
MINERALISATION AND DILATED TUBULES

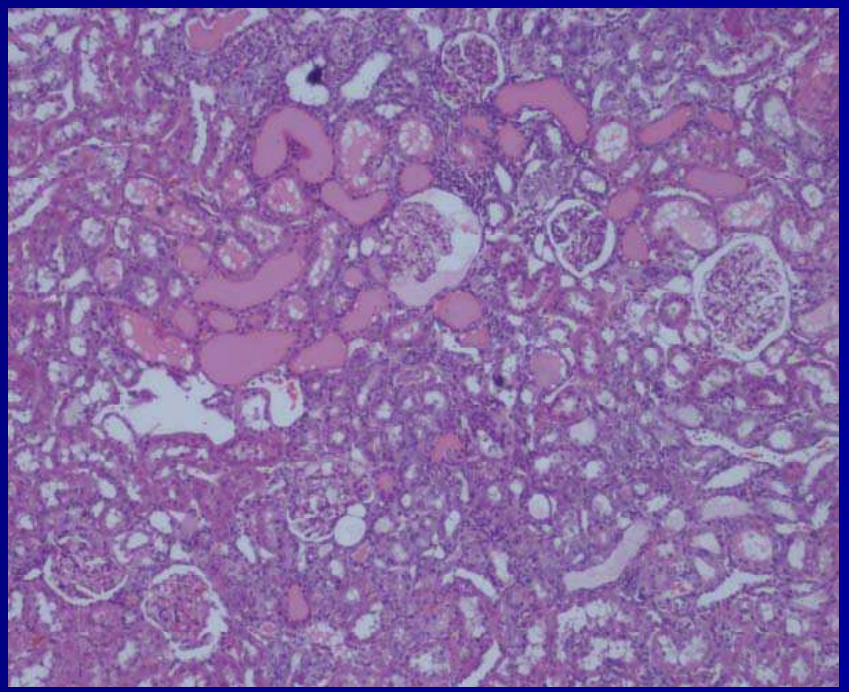
Zucker fa/fa rats - 3 months



LIPIDOSIS

Zucker fa/fa rats - 6 months



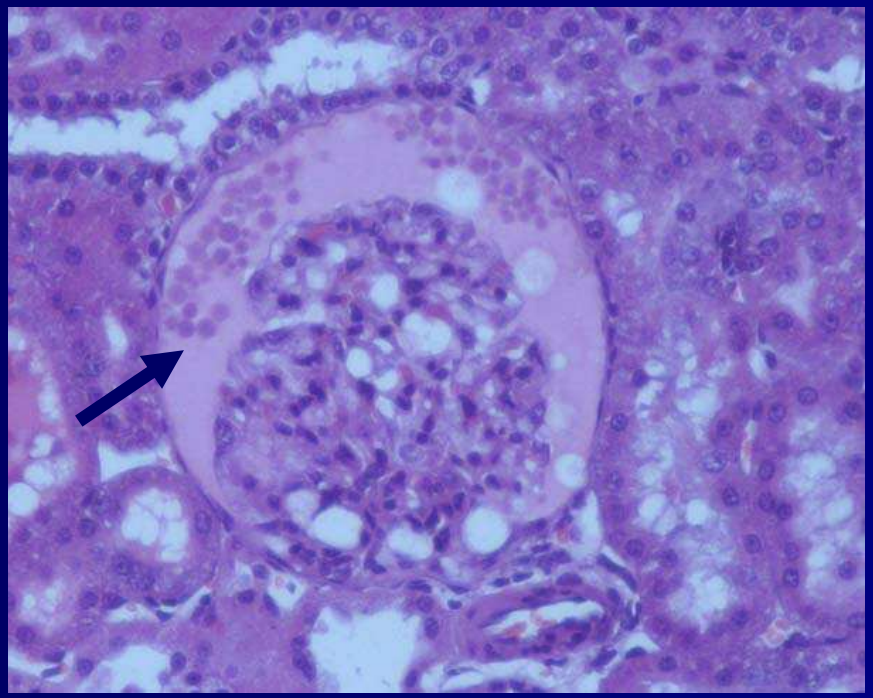


NEPHROPATHY

Zucker fa/fa rats - 6 months

Kidney

1



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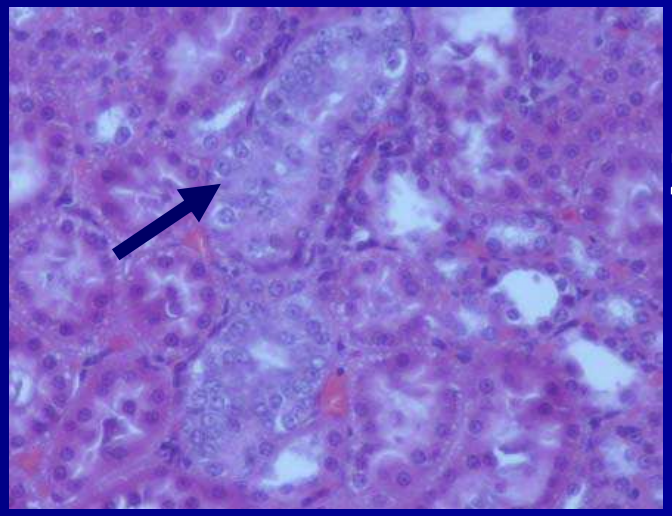

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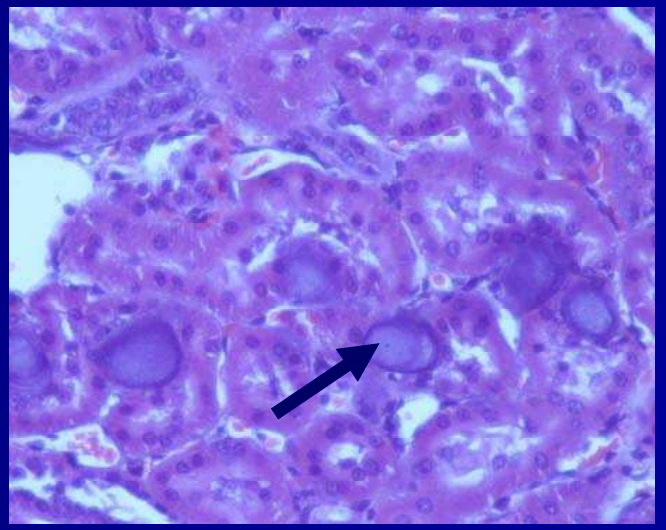
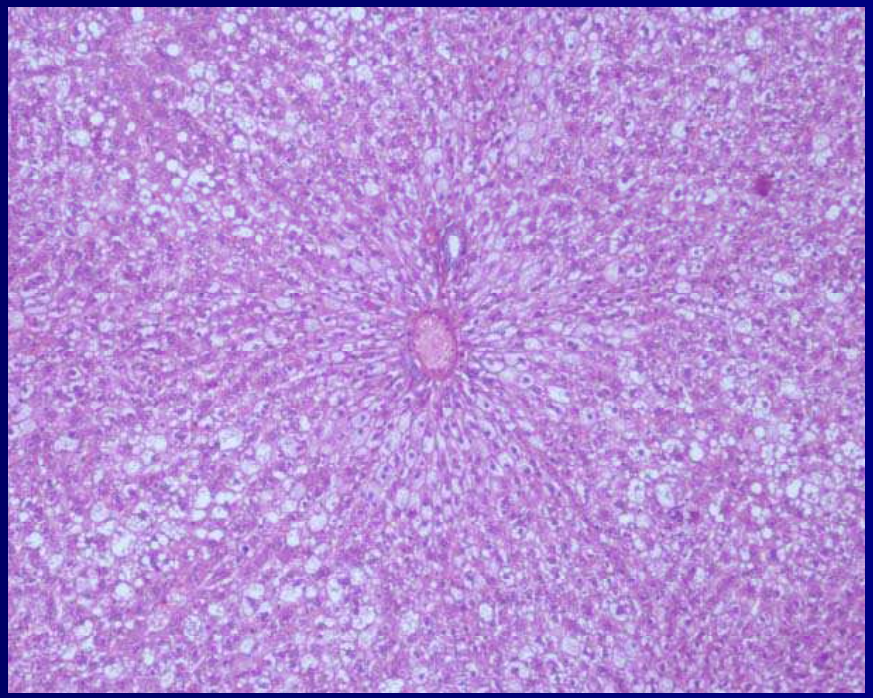


1- PROTEIN LEAKAGE
2- BASOPHILIC TUBULES
3- MINERALISATION

Zucker fa/fa rats - 6 months

Liver



LIPIDOSIS

Animal models in safety assessment

- Animal models of human diseases have been widely used in drug discovery
- Rarely utilized in toxicologic research and screening (except for transgenic models in carcinogenicity testing).
- The failure of preclinical toxicological studies to predict the adverse effects in humans is a major concern and has empahasized the need to search for better animal models for use in preclinical toxiclogy studies.

Healthy animals vs. Diseased

- Genetic and/or acquired Patho-physiological alterations associated with a particular disease may greatly exacerbate toxic responses to drugs in certain patient subsets
- These pre existing pathological conditions are usually not considered in preclinical safety assessment

Examples of disease states associated with increased risk for developing adverse drug reactions (ADRs)

Disease	Type of ADR
Diabetes mellitus	Drug induced fulminant liver failure
Rheumatoid disorders	Hepatotoxicity by NSAIDs
Viral infections	Idiosyncratic reactions to sulfa drugs

- Hence, if cellular stress caused by drugs or metabolites and the disease related effects are super imposed, then an individual can become sensitized to potential drug toxicity

- In fact, one of the reasons for incorrect prediction of toxic effects from preclinical toxicity studies has been attributed to the failure to consider preexisting pathological conditions in certain populations

- This obvious failure has even been called "ONE OF THE DEADLY SINS OF TOXICOLOGY".

- The failure of preclinical toxicological studies to predict the adverse effects in humans is a major concern

- This has emphasized the need to search for better animal models for use in preclinical toxicology studies.

why toxicologists have been reluctant to utilize non classical animal models in drug safety assessment ?

- The use of non conventional animal models is neither standardized nor required by regulatory authorities

- Inclusion of novel animal models within the existing test batteries might create new and unexpected findings which are difficult to interpret

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THANK YOU