6th STPI conference, a Continued Education program on
'Toxicologic pathology of nervous and musculoskeletal system'
at Pune on 21-23 October 2016

"Rare Spontaneous & induced lesions of the musculoskeletal system" (& some other tissues ☺)

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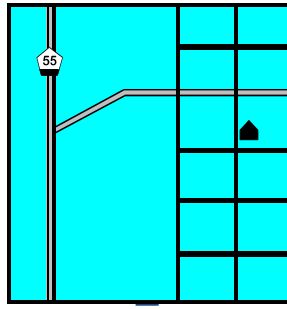
1: published and „nearly" full data available under http://www.eurotoxpath.org/publications/form_cdrom.php?id=cetp2013

The aims of this presentation are to:

- Sensitize you to induced lesions you might experience in future
- Broaden your anticipation for pharmacological vs safety findings
- See a lot of macro-, histological and electrone microsc. pictures
- Induce a challenging discussion
- **Entertain you**

This is your road-map you have to survive



Introduction

Induced lesions in the musculoskeletal & soft tissue system (with some deviations ;-)))

- To start Positive: Angiotensin Converting Enzyme II Inhibitor (vessels)
- ß2 Agonists (muscle)
- Phospho-diesterase type IV Inhibitors (bone)
- Matrix Metalloproteinase Inhibitors (joint & muscle)
- Vascular Endothelial Growth Factor Receptor 1 Antagonist (joint, bone & a surprise)
- A “NVM” tour through some rare spontaneous lesions: Embryonal Rhabdomyosarcoma, Hibernoma, Liposarcoma; (and their importance)

Take home message

Your questions, please open end

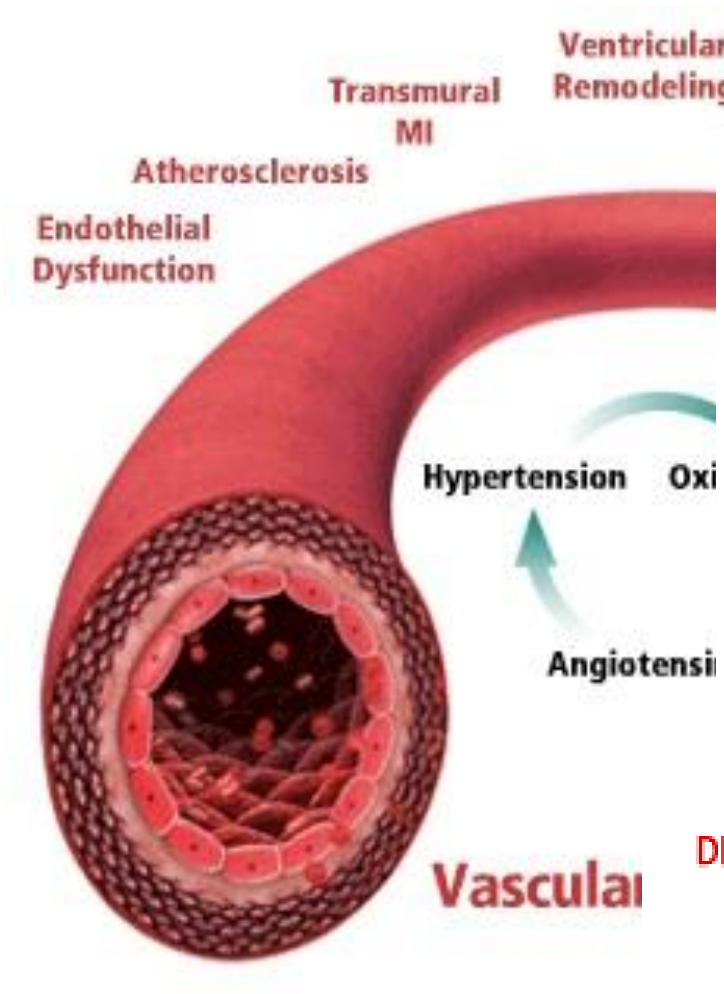
Some orientation

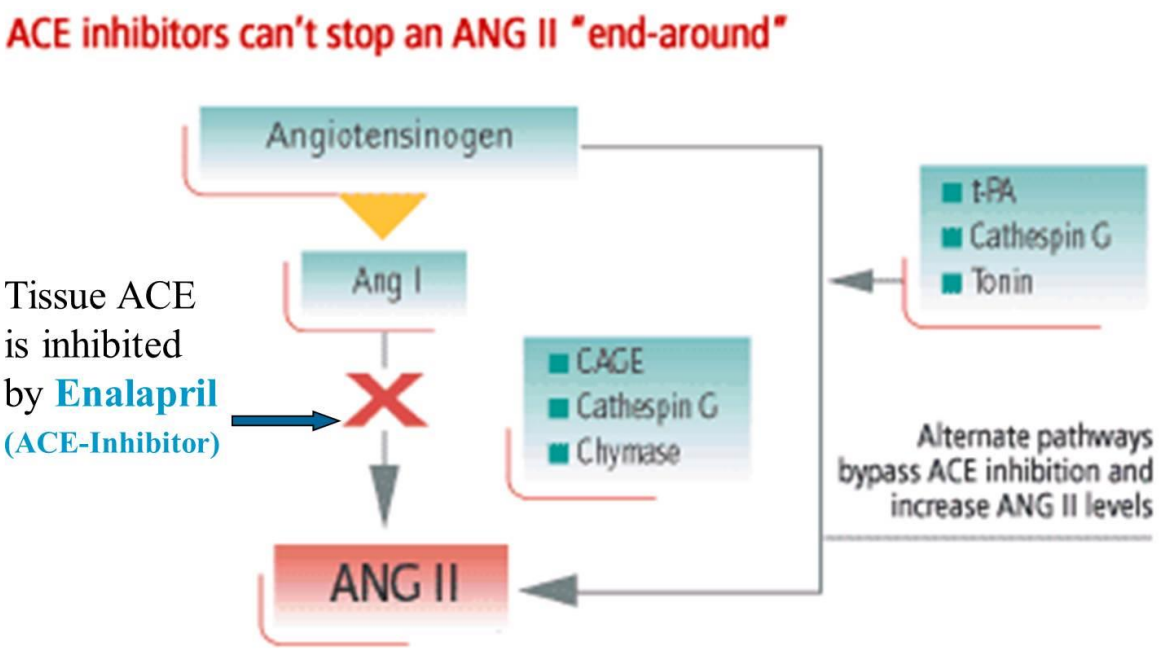
Compound class	
Indication	
Mechanism of Action	
Mater. &Meth., relev. Studies	
Histopatholog. side effect	
Mechanism of side effects	
Relevance to humans	
References	

Angiotensin Converting Enzyme II Inhibitors

Angiotensin Converting Enzyme Inhibitors

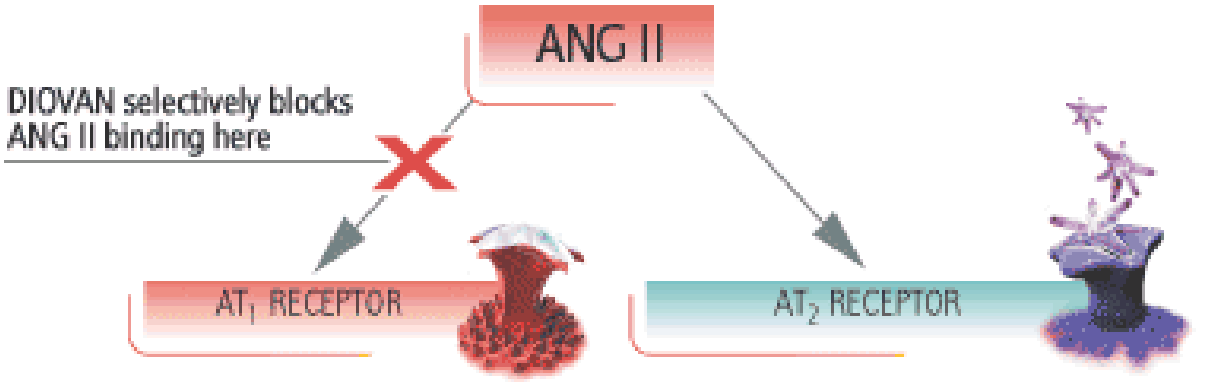
Indication	Cardio-Vascular System. AT II Receptor antagonists are usede in the treatment of hypertension (high blood pressure), diabetic nephropathy (kidney damage due to diabetes) and congestive heart failure.
Mechanism of Action	**Angiotensin II receptor antagonists**, also known as **angiotensin receptor blockers (ARBs)**, **AT_1-receptor antagonists,** are modulating the renin–angiotensin system.
Mater. & Meth., relev. Studies	See extra slides
Histopathological side effect	See extra slides
Mechanism of side effects	Reverse lesions of a cardiovasluar disease model by pharmacological combination therapy
Relevance to humans	**Hypertension** has long been associated with increased cardiovascular risk. But now, hypertension is emerging as a **"key player"**—along with oxidative stress and angiotensin II—in an insidious process occurring in the vasculature that causes daily vascular damage





DIOVAN: *Selectively* blocks ANG II like no ACE inhibitor can

Angiotensin II receptor antagonists, also known as **angiotensin receptor blockers (ARBs)**, **AT_1-receptor antagonists,** are modulating the renin–angiotensin system. Their main uses are in the treatment of hypertension (high blood pressure), diabetic nephropathy (kidney damage due to diabetes) and congestive heart failure.



Study Design

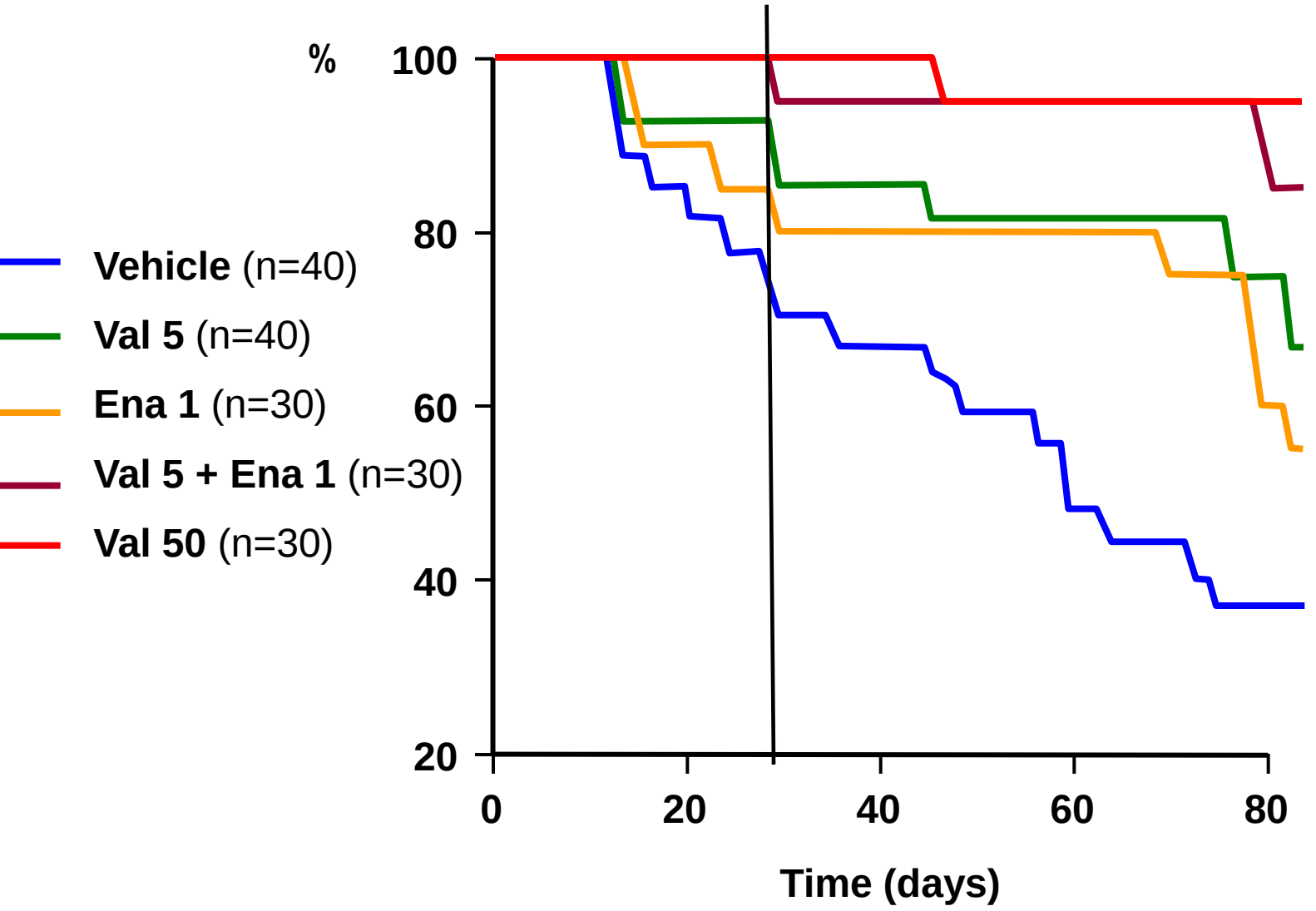
- Spontaneously hypertensive rats (SHR) treated with a NO-synthase inhibitor (L-NAME)

- **Treatment groups** (12 animals each):
  - Vehicle, placebo treatment ("Real sick" control)
  - High dose Valsartan (50mg/kg b.w.)
  - Low dose Valsartan (5 mg/kg b.w.)
  - Low dose Enalapril (1 mg/kg b.w.)
  - Combination low dose Valsartan / low dose Enalapril
  - Healthy WKY rats (no treatment at all)

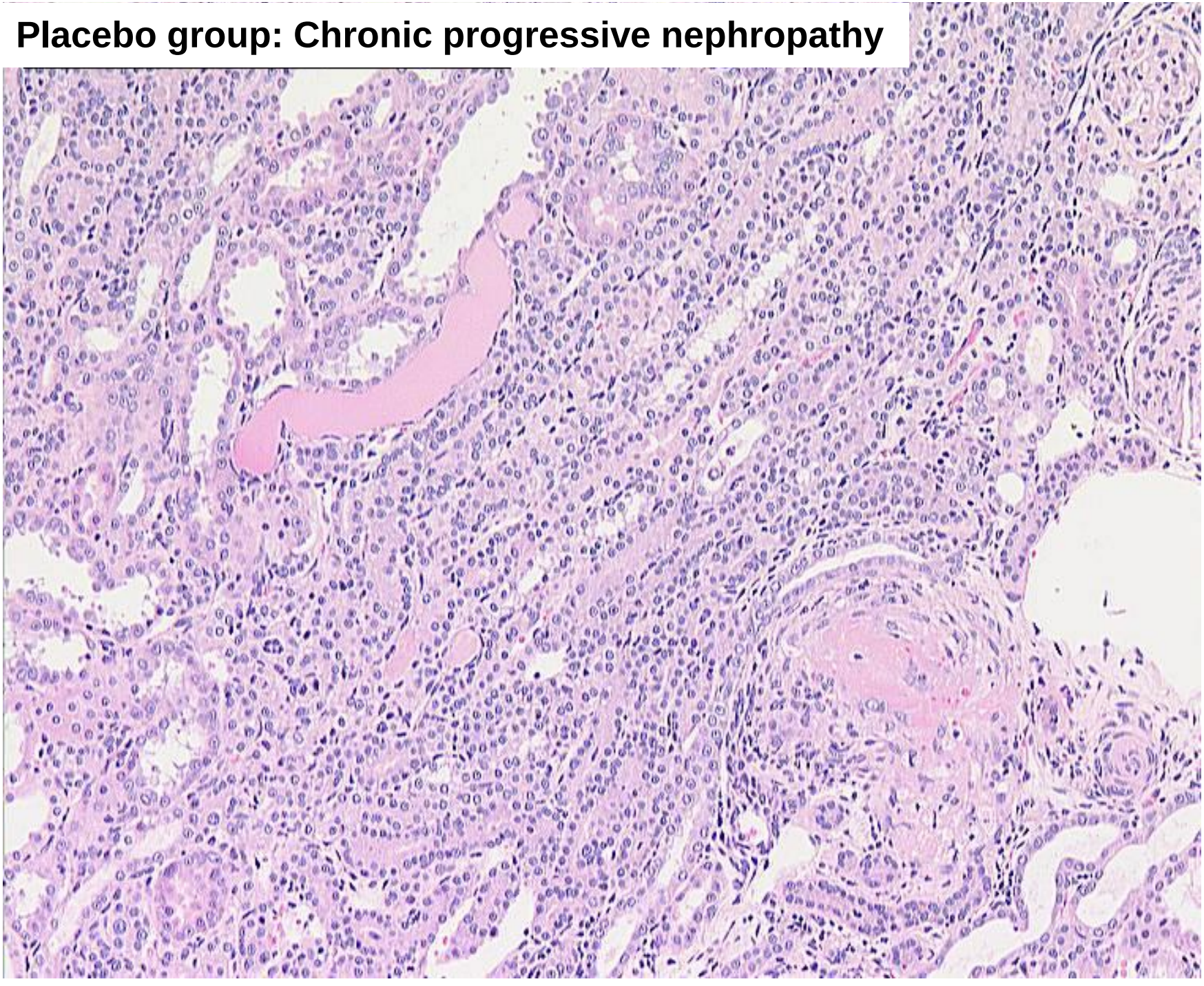
Read outs

- Survival and clinical signs
- Body & organ weights
- Clinical Pathology for Kidney Markers (Plasma & Urine)
- Endothelial function (ex vivo)
- The endothelium function in aortic ring
- Maximal coronary flow (in isolated perfused hearts)
- Maximum coronary vasodilatation
- Coronary reserve
- **Histopathology of Kidney, Heart and Aorta (coded)**
- **Metabonomic Profile in Deep frozen blood samples**

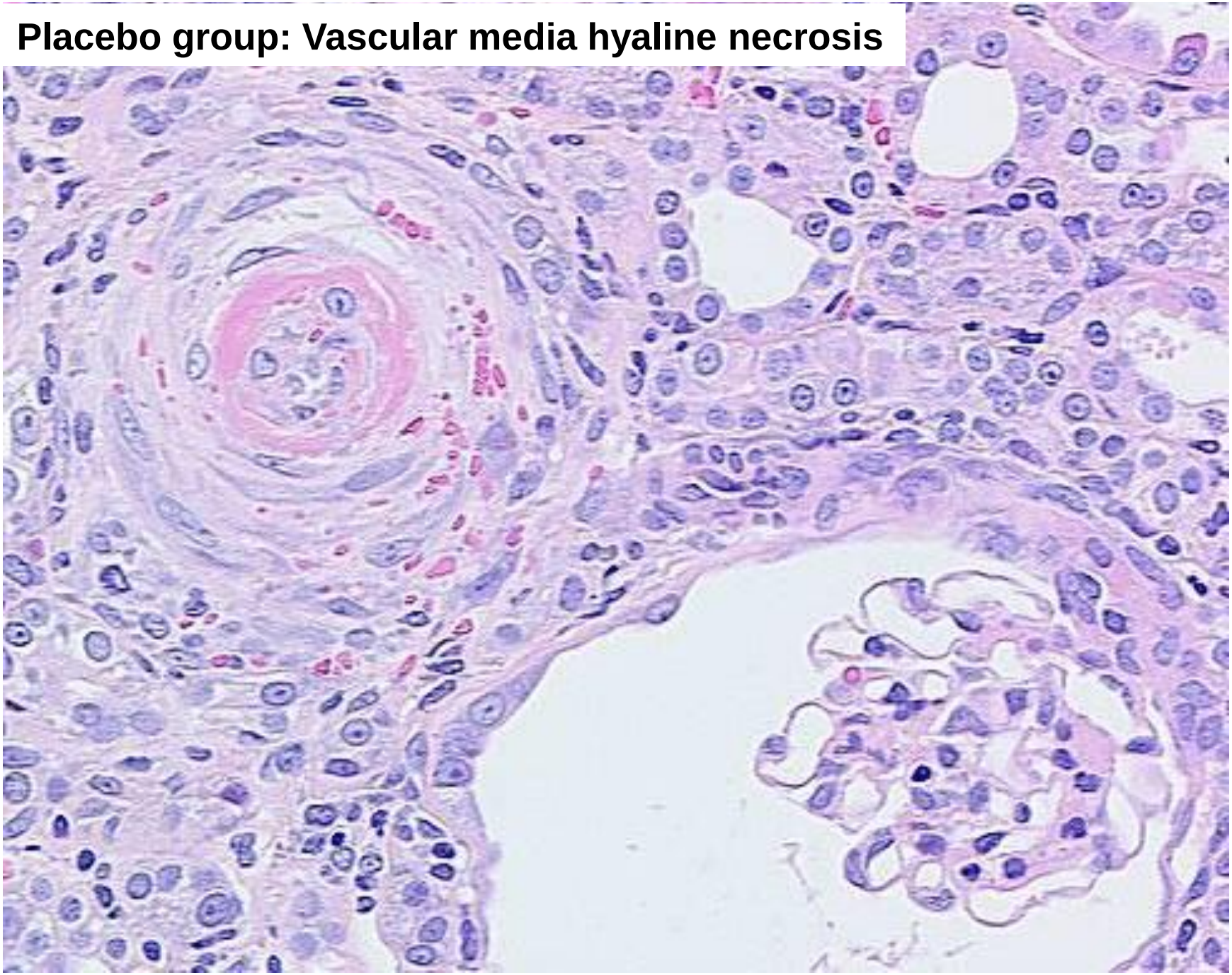
Survival rate



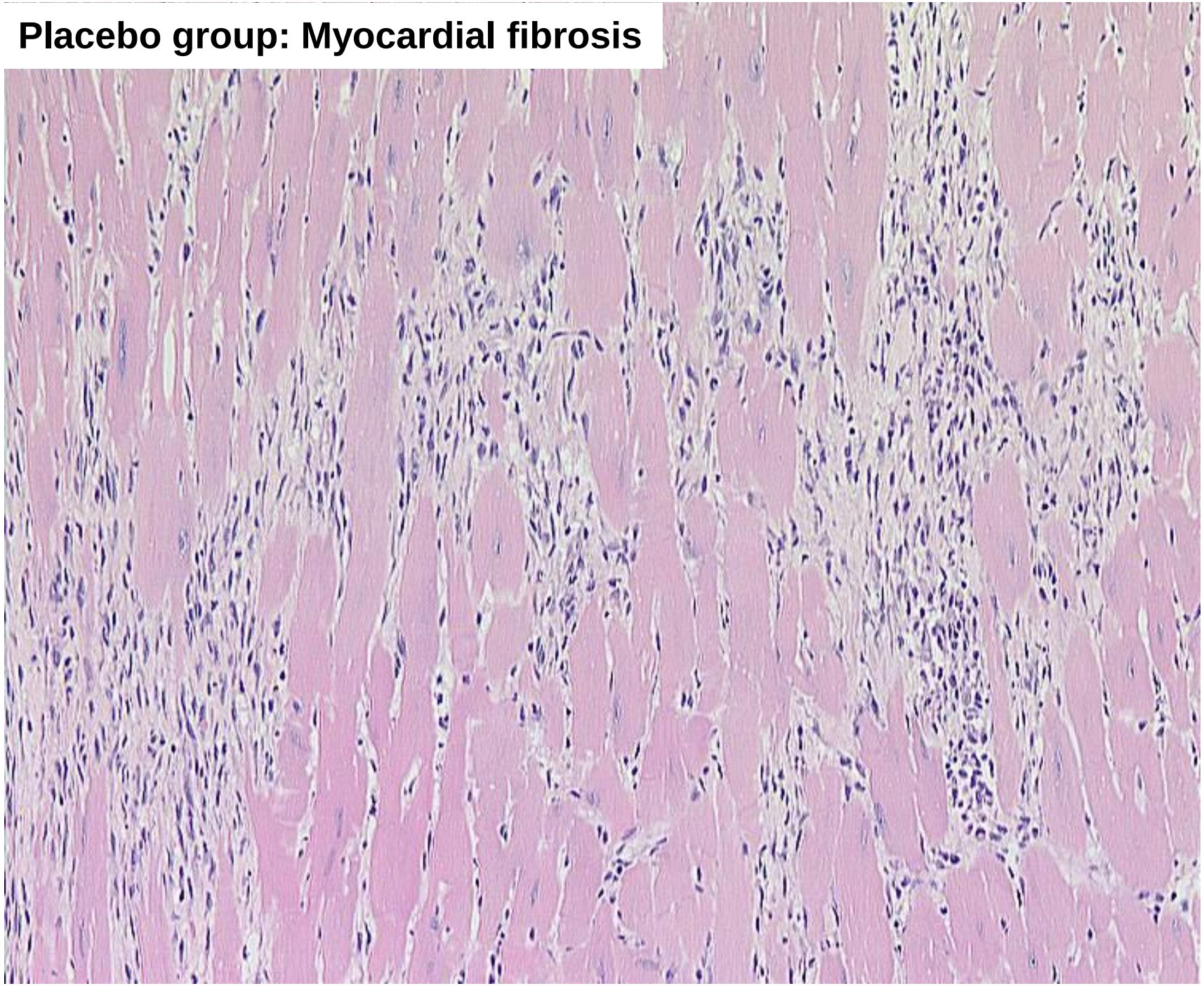
Placebo group: Chronic progressive nephropathy

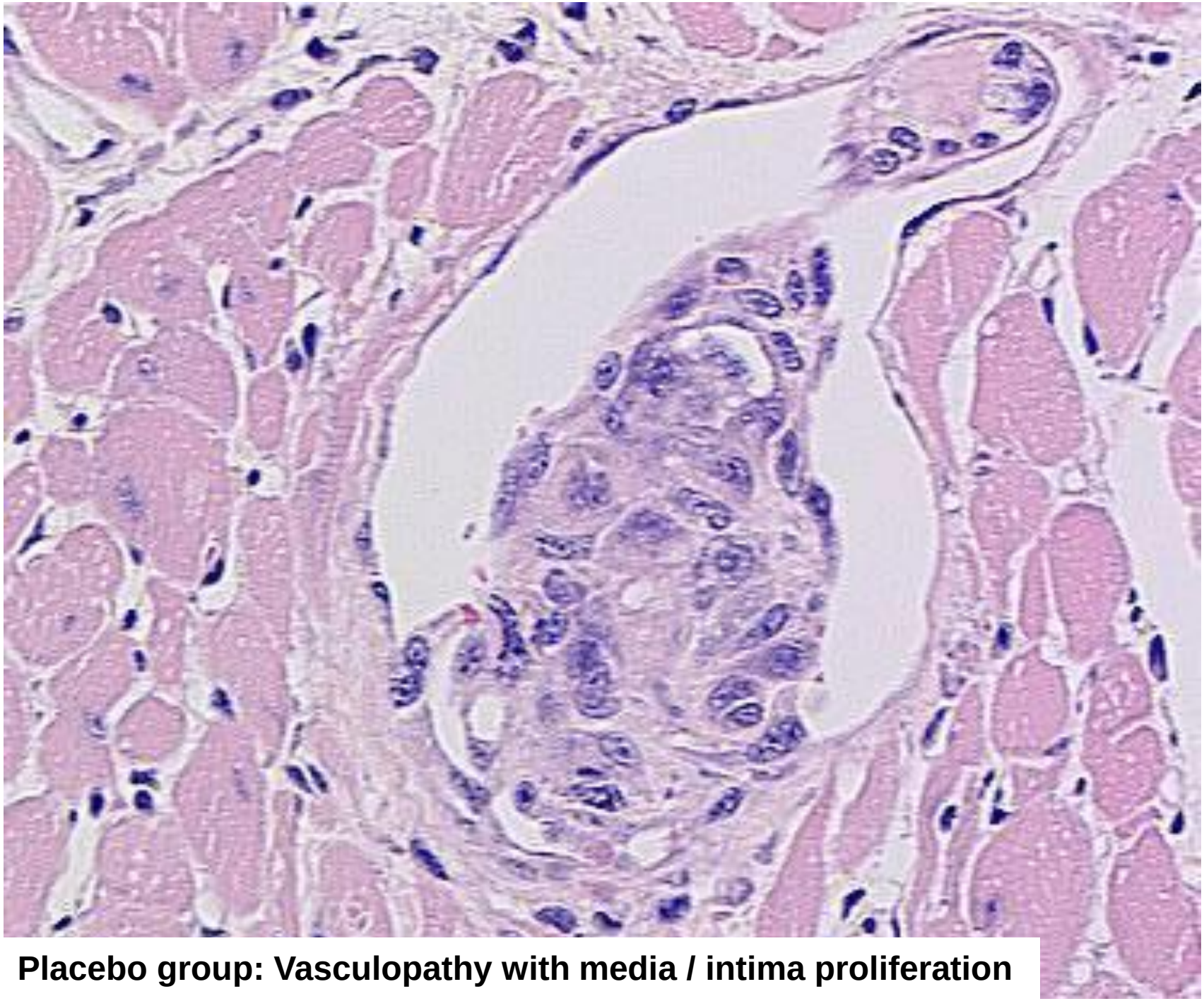


Placebo group: Vascular media hyaline necrosis



Placebo group: Myocardial fibrosis





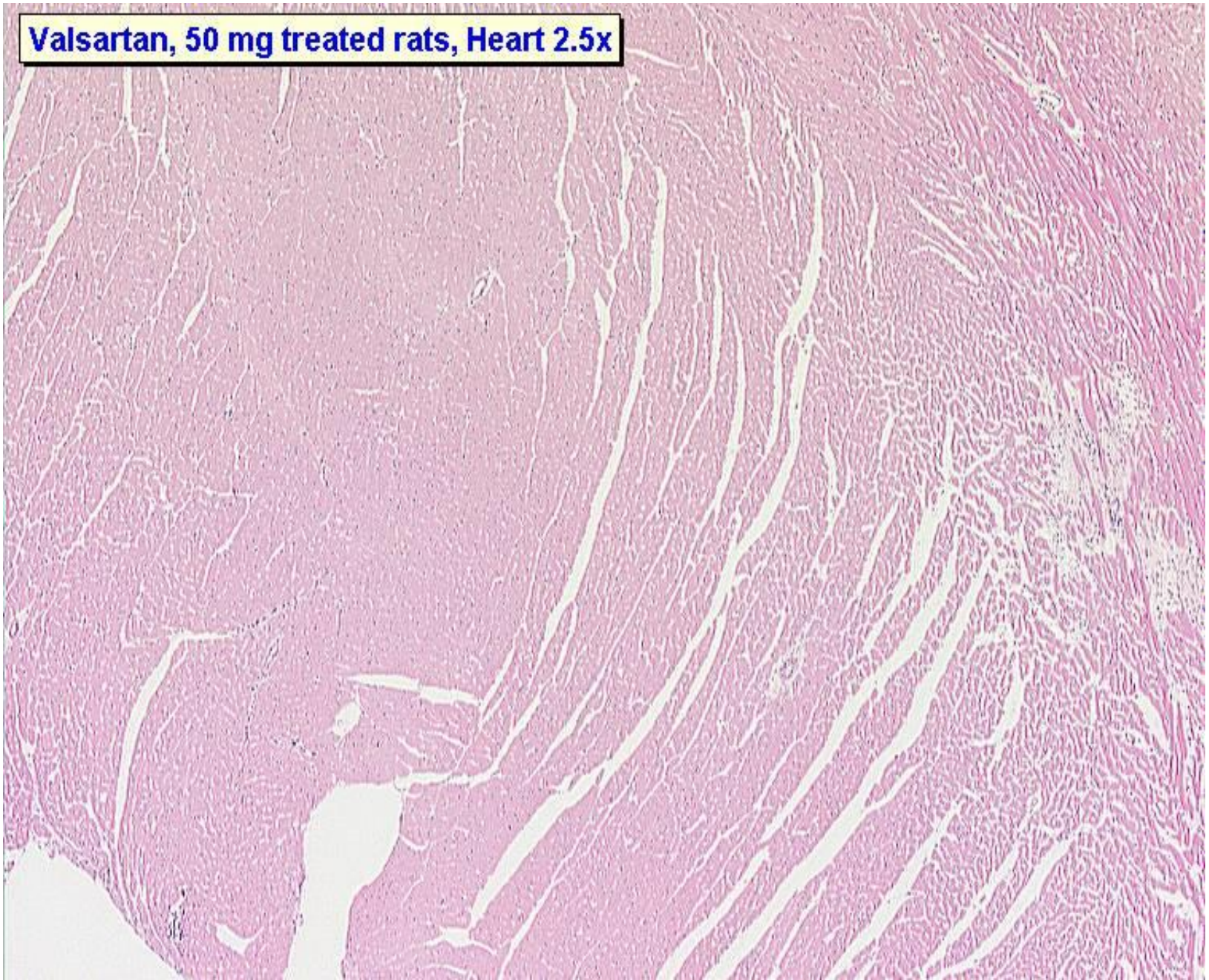
Placebo group: Vasculopathy with media / intima proliferation

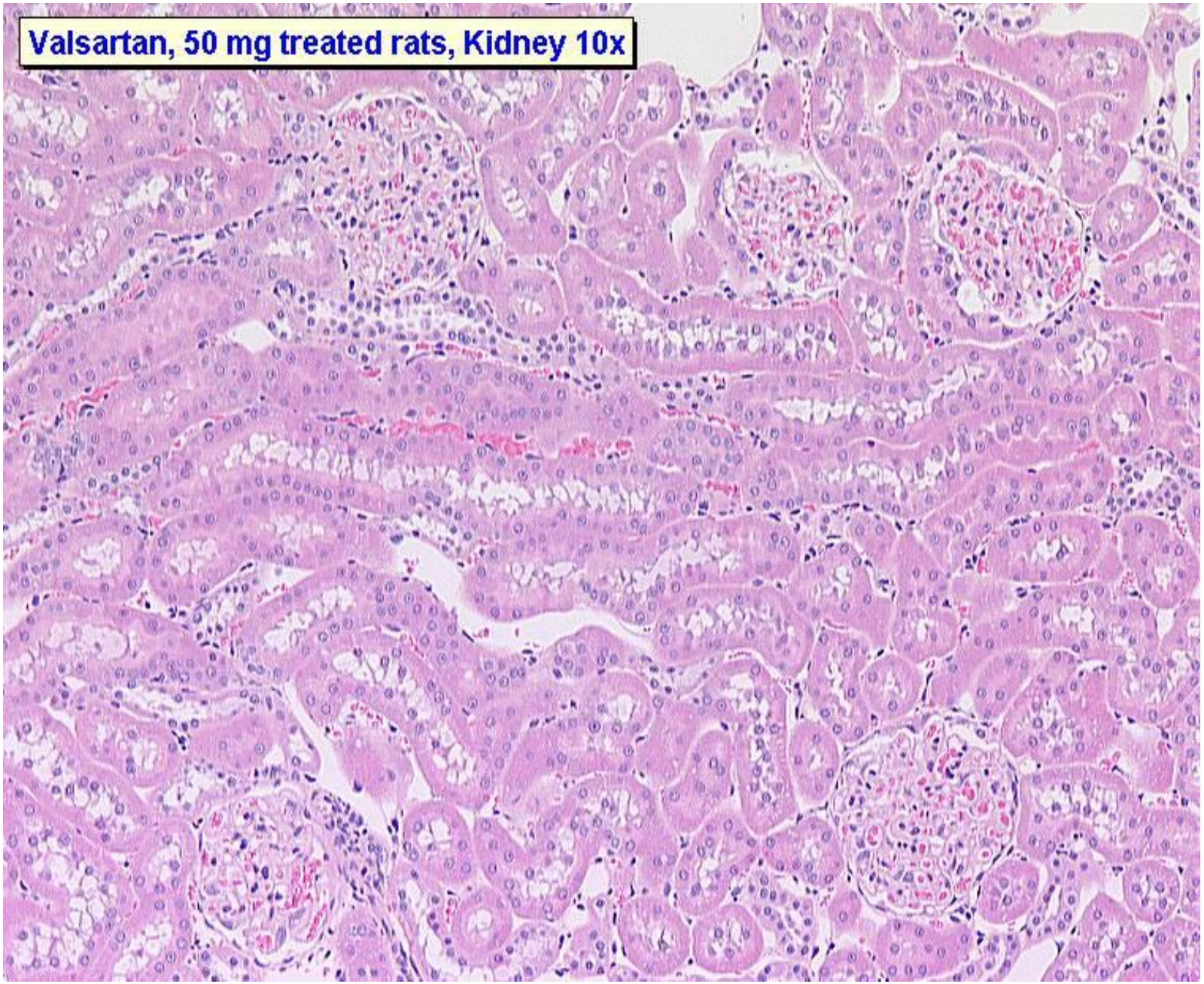
Results of histopathology, control SHR-rats:

Severe chronic progressive nephropathy (CPN)

Myocardial fibrosis with lymph-histiocytic infiltrates

Vasculopathy with proliferation of medial and intimal cells


Valsartan, 50 mg treated rats, Heart 2.5x


Valsartan, 50 mg treated rats, Kidney 10x

Results of histopathology

Mono-therapies of Enalapril (1 mg) or low dose Valsartan (5 mg) showed only minimal beneficial effects.

Mono-therapy of Valsartan **high dose** (50 mg) exhibited a clear reduction of the lesion severity in the kidneys, heart and vessels.

Severity grades of histopathological lesions

	WKY	Vehicle	Valsartan 5	Enalapril 1	Val 5 - Ena 1	Valsartan 50
Vascular media hyaline necrosis	**0.2**	**2.00**	**2.00**	**2.09**	**1.64**	**1.36 ***
Media myocyte degeneration	**0.0**	**1.62**	**1.20**	**0.73**	**0.64 * # b**	**1.27**
Chronic progressive nephropathy	**0.0**	**3.50**	**2.90**	**2.82**	**1.00**	**1.00**
Myocardial fibrosis	**0.0**	**2.25**	**1.60**	**2.45**	**1.00 * # b**	**1.64 ***
Cardiac myocyte degeneration	**0.0**	**2.25**	**2.00**	**2.09**	**0.82**	**1.27**
Vasculopathy **media / intima proliferation**	**0.0**	**0.87**	**0.60**	**1.09**	**0.27 b**	**0.27**
Overall mean	**0.02**	**2.10**	**1.72**	**1.90**	**0.88 ***	**1.15**

$p<0.05$ *vs vehicle; # vs Val 5; b vs Ena 1

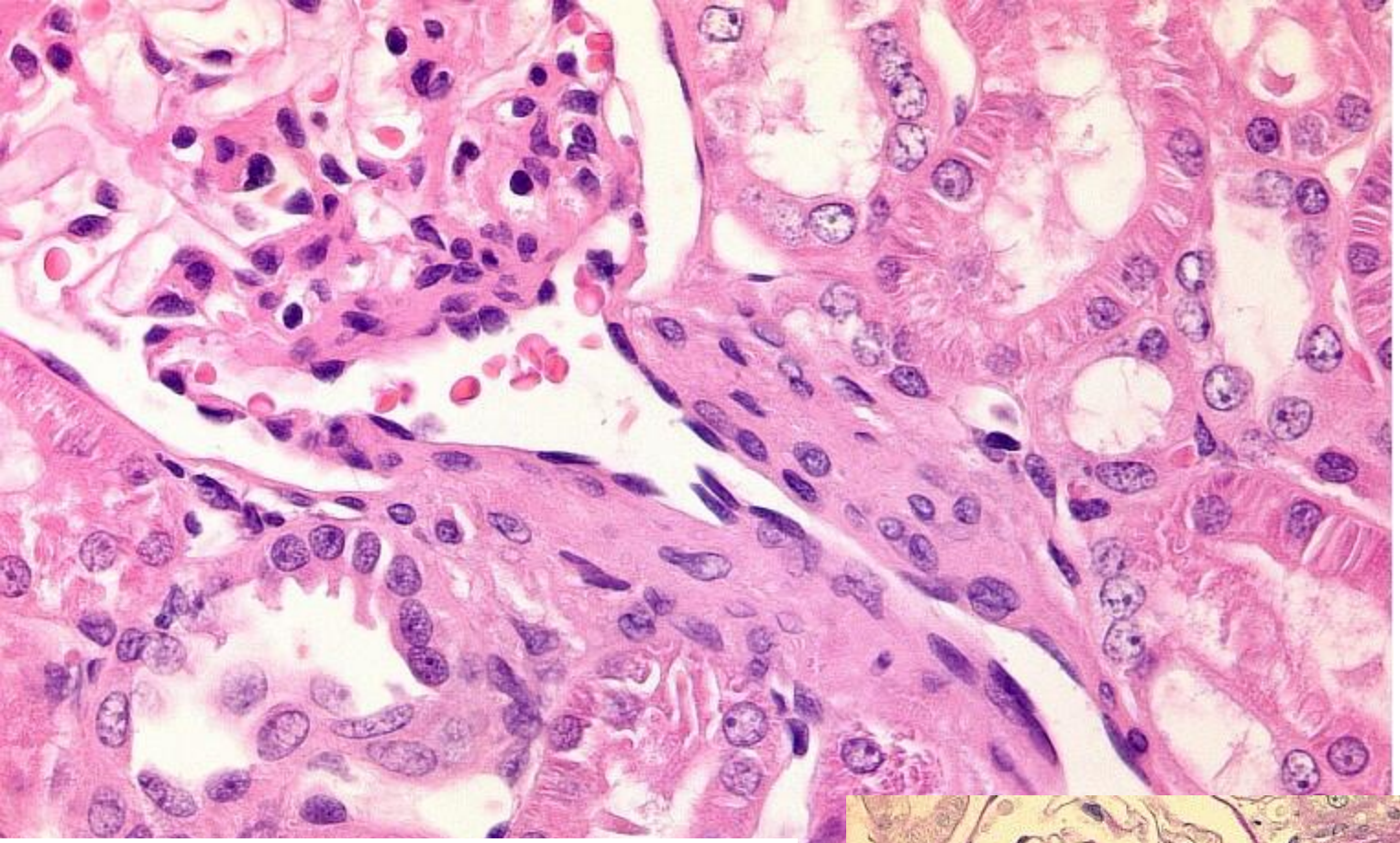
Conclusions

Combination therapy of the low dose Valsartan (5 mg) with Enalapril (1 mg) proved to be the most effective therapy in many parameters.

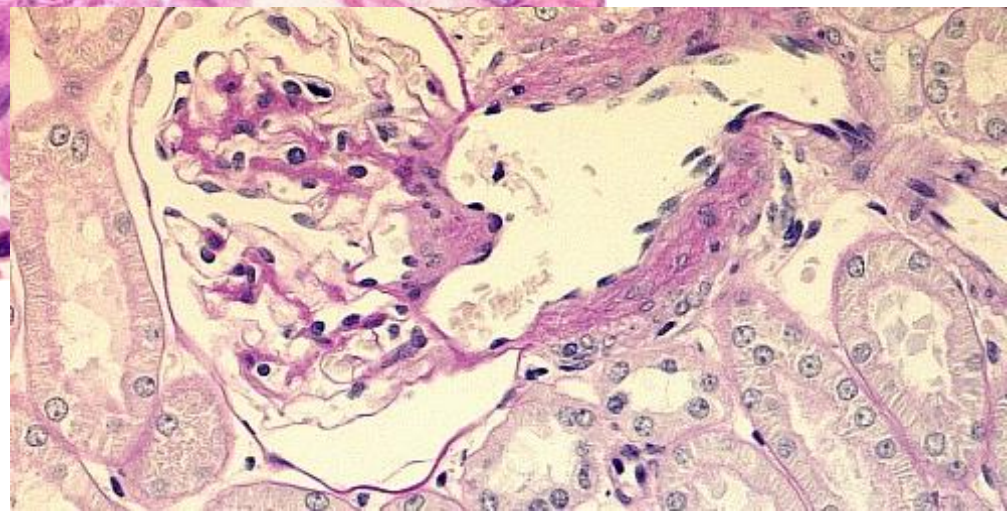
Overall efficacy of the combination Valsartan 5 mg & Enalapril 1 mg is comparable to the high dose mono-therapy Valsartan (50 mg).

Reference: Low Dose Combinations of Valsartan and Enalapril Improves Histopathology, Endothelial Dysfunction and Coronary Reserve in Spontaneously Hypertensive Rats. M. de Gasparo, P. Hess. M. Clozel, E. Persohn, P Germann, D. Roman, JP Clozel , R.L. Webb. J. Cardiovascular. Pharmacol. 40, 789-800, 2002

A glance to the dog



Kidney, dog, ACE inhibitor treatment. Vas afferens and vas efferens are thickened 2- to 4-fold when compared with the normal control dogs. H&E & PAS



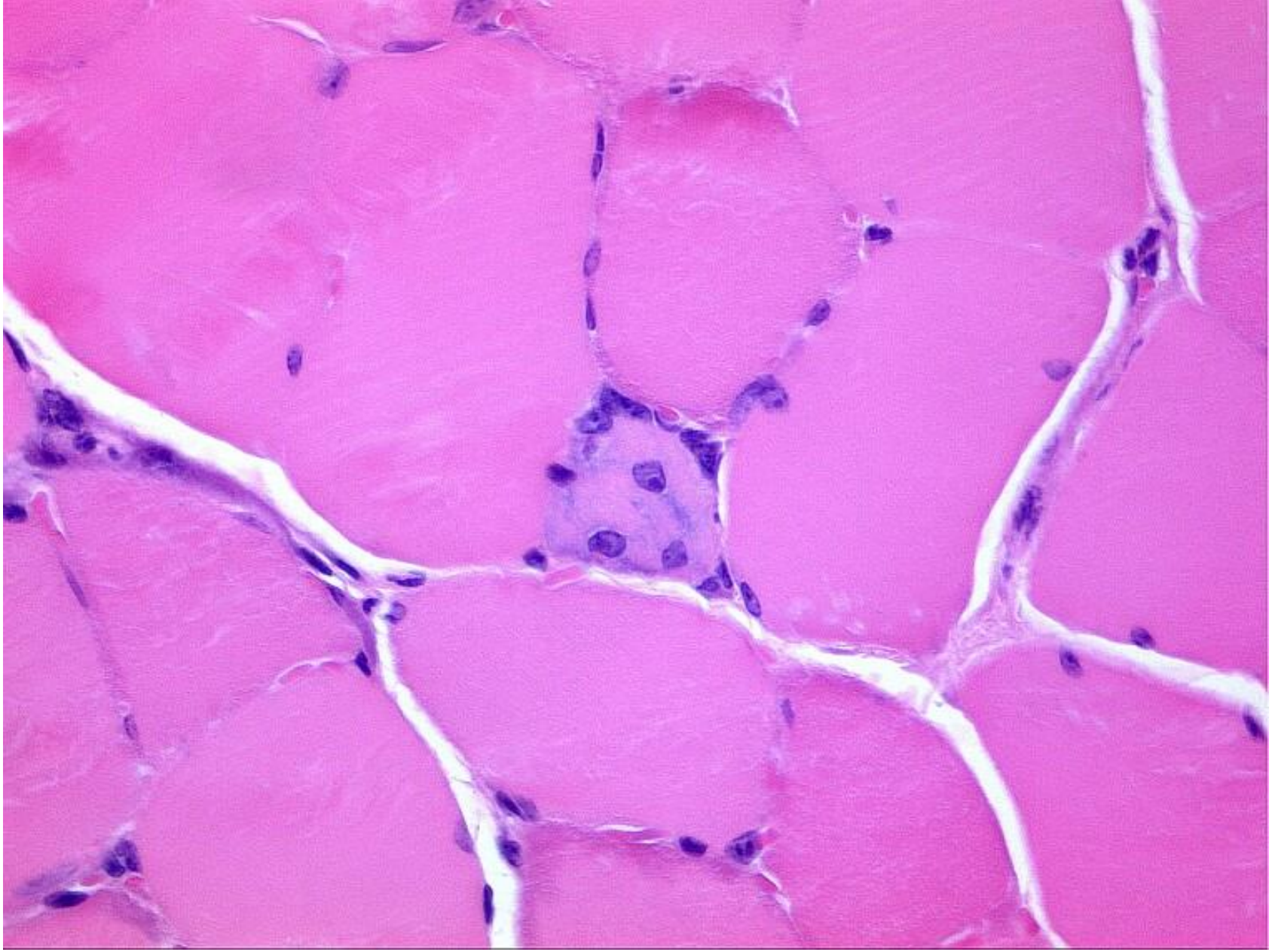
ß2 Agonists (muscle)

ß2 Agonists

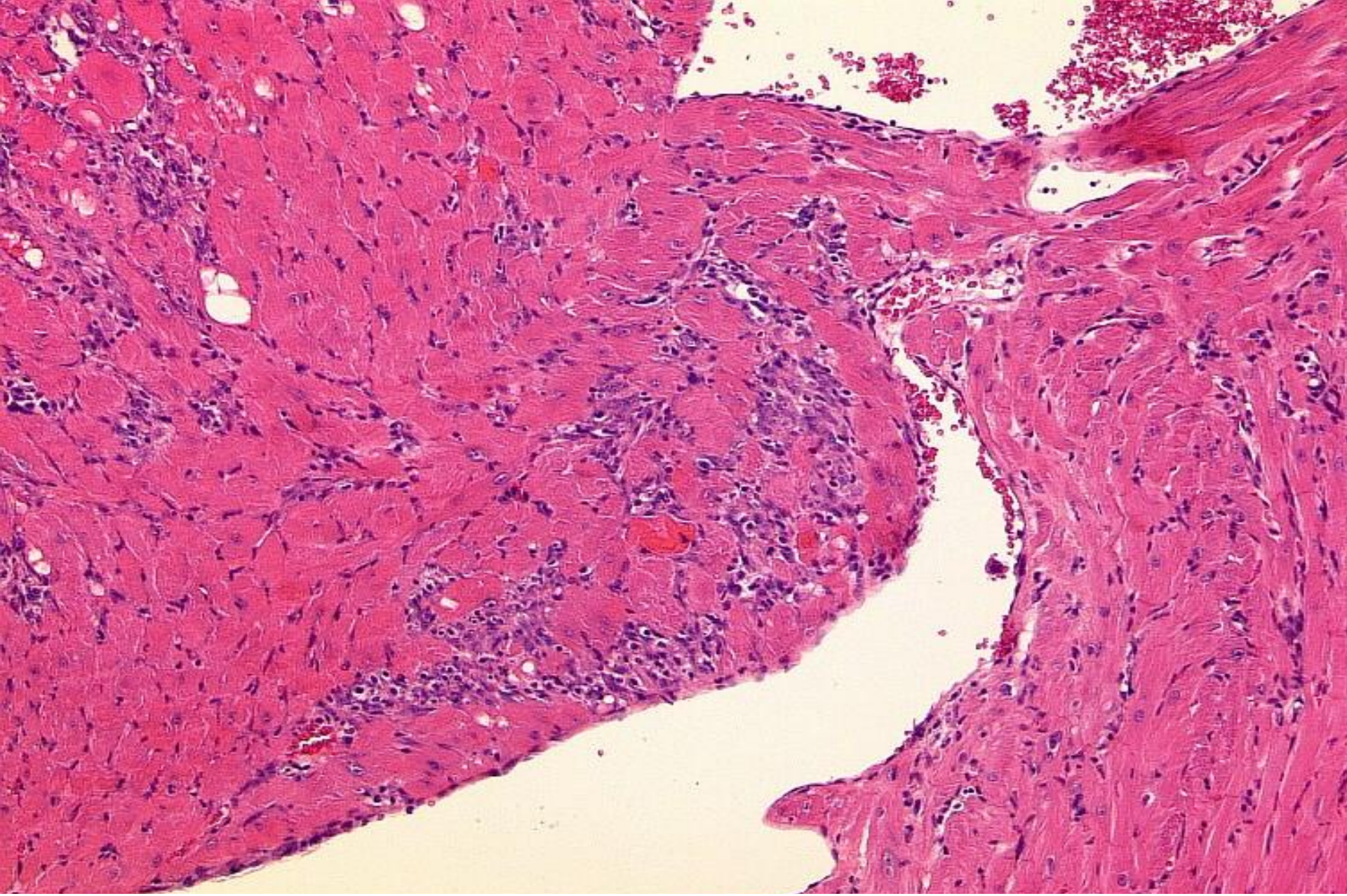
Indication	β_2-adrenegic receptor agonists (stimulating agents) are used to for the treatment of bronchospasms in patients with bronchial asthma
Mechanism of Action	β-sympathomimetic substances induce a positive chronotrope, inotrope and dromotrope effect in the heart via stimulation of the cardiac β_1-receptors.
Mater. &Meth.	Rat, 13 weeks treatment, once daily oral application

ß2 Agonists

Histopatholog. side effect	Histologically, skeletal muscle fibers were hypertrophied and there was multifocal necrosis with inflammatory infiltrates, mainly macrophages. Additional lesions were observed in the heart. Focal inflammatory infiltrates (mainly macrophages), granulation tissue and fibrosis were present, most pronounced subendocardially in the left ventricle and septum. Similar to the rat, foci with myodegeneration were also observed in the skeletal muscles
Mechanism of side effects	It is suggested that the adenylate cyclase is activated, which leads to an increase in cAMP content. After treatment with Isoprenalin an increased DNA-content and an enhanced incorporation of radiolabelled thymidine were reported (Greaves 2000), which indicates that besides hypertrophy there is also hyperplasia. The focal myodegeneration seen in rats treated with formoterol may partially be a consequence of the hypertrophy. Since similar lesions have been seen in mice without hypertrophy, other factors must play a role as well. It is described in the literature that overstimulation of the receptors in the muscle leads to spasms, which may induce ruptures of muscle fibers and subsequent inflammatory and reparative processes (Van Vleet et al. 2002).



Rat, skeletal muscle, terminal sacrifice after treatment with formoterol for 13 weeks: hypertrophy of muscle fibers, post-necrotic regeneration;



Rat, heart, terminal sacrifice a. treatment with formoterol for 13 weeks: necrosis, granul. tissue;

ß2 Agonists

Relevance to humans	A link also exists between the hypertrophy of the skeletal muscle and the pharmacological effects of the β_2-agonists. This has been misused in sport as well as in meat production. The mechanism is not fully understood.

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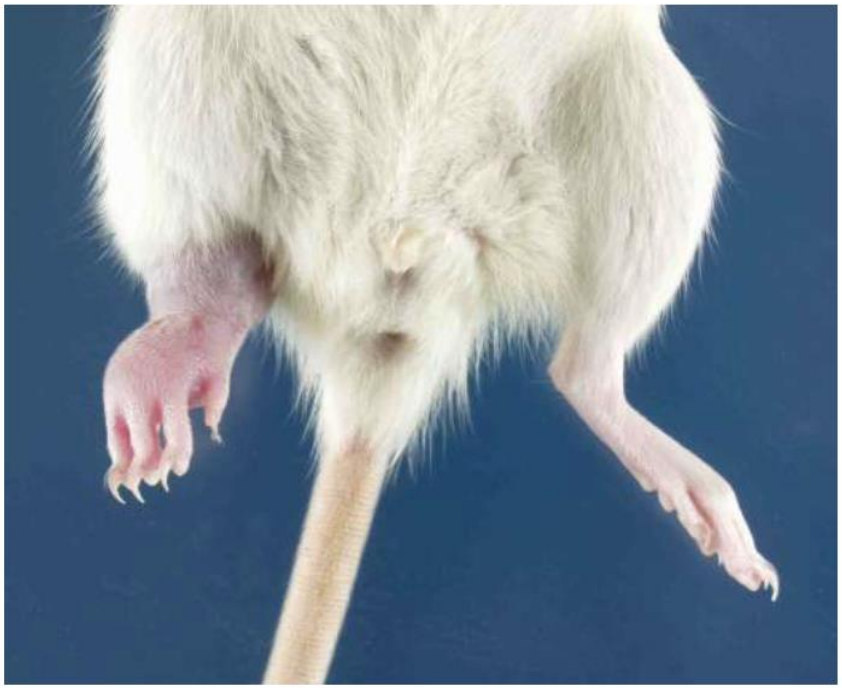
Van Vleet JF, Ferrans JF, Herman E (2002) Cardiovascular and skeletal muscle systems. In: Haschek WM, Rousseaux CG, Wallig MA (eds) Handbook of toxicologic pathology, volume 2, Academic Press San Diego, p 434

Phospho-diesterase type IV Inhibitors (bone)

Phospho-diesterase type IV Inhibitors

Indication	Asthma, Psoriasis, Atopic Dermatitis: PDE3i: heart failure, PDE4i: chronic obstructive pulmonary disease (COPD); PDE5i: pulmonary arterial hypertension, erectile dysfunction
Mechanism of Action	Inhibition of selective isoenzymes to prolong or enhance effects mediated by cAMP or cGMP in target tissue /cells
Mater.& Met. relev. Studies	Findings in the skeletal system in toxicity studies in rats
Histopatholog. side effect	
Mechanism of side effects	
Relevance to humans	
References	



- mainly hindlimbs, often unilateral
- paws are thickened
- skin reddish or bluish discoloration
- rapid onset
- fast reversibility
- transient

10th European Congress of Toxicologic Pathology
September 11th – 14th 2012, Stresa, Italy

Histopathological Effects on the Skeletal System of Rodents after Administration of Phosphodiesterase Inhibitors

Anke Heuser[1], Ursula Junker[2], Itai Bab[3]

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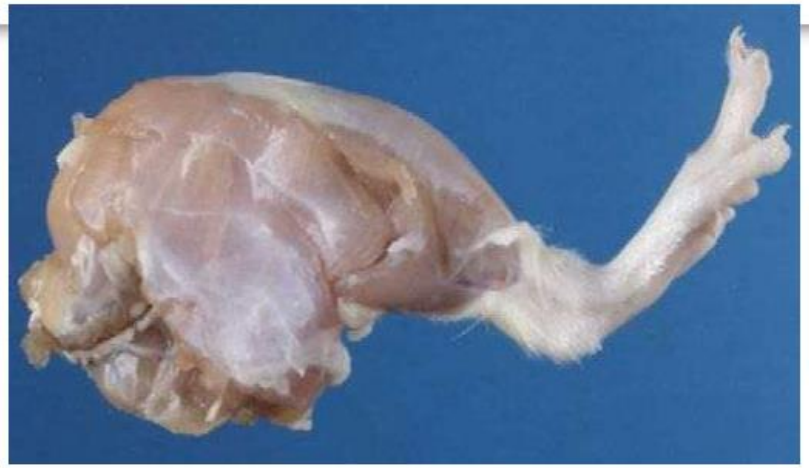
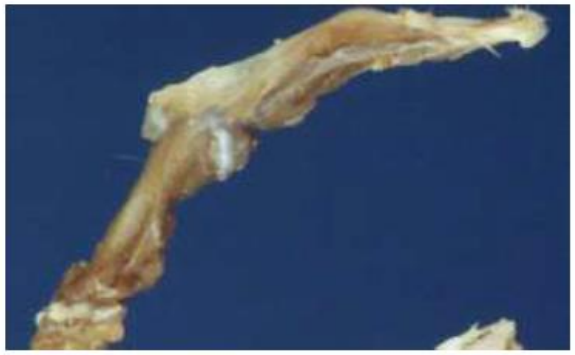
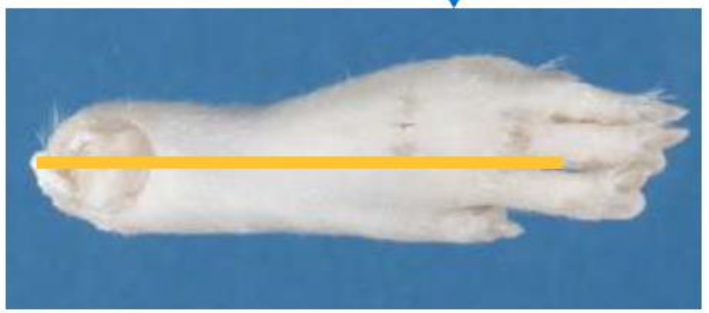
[2] Novartis Pharma AG, Basel, Switzerland
[3] The Bone Lab, The Hebrew University, Jerusalem, Israel

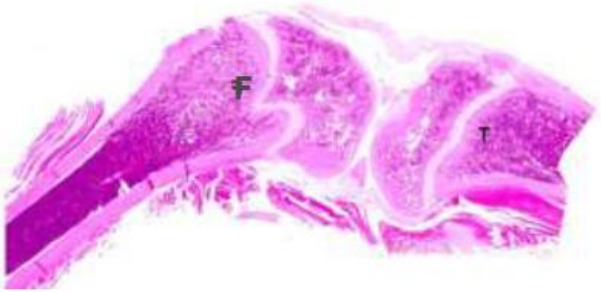
Standard section
Stifle joint



Additional section at
distal tibia/metatarsus



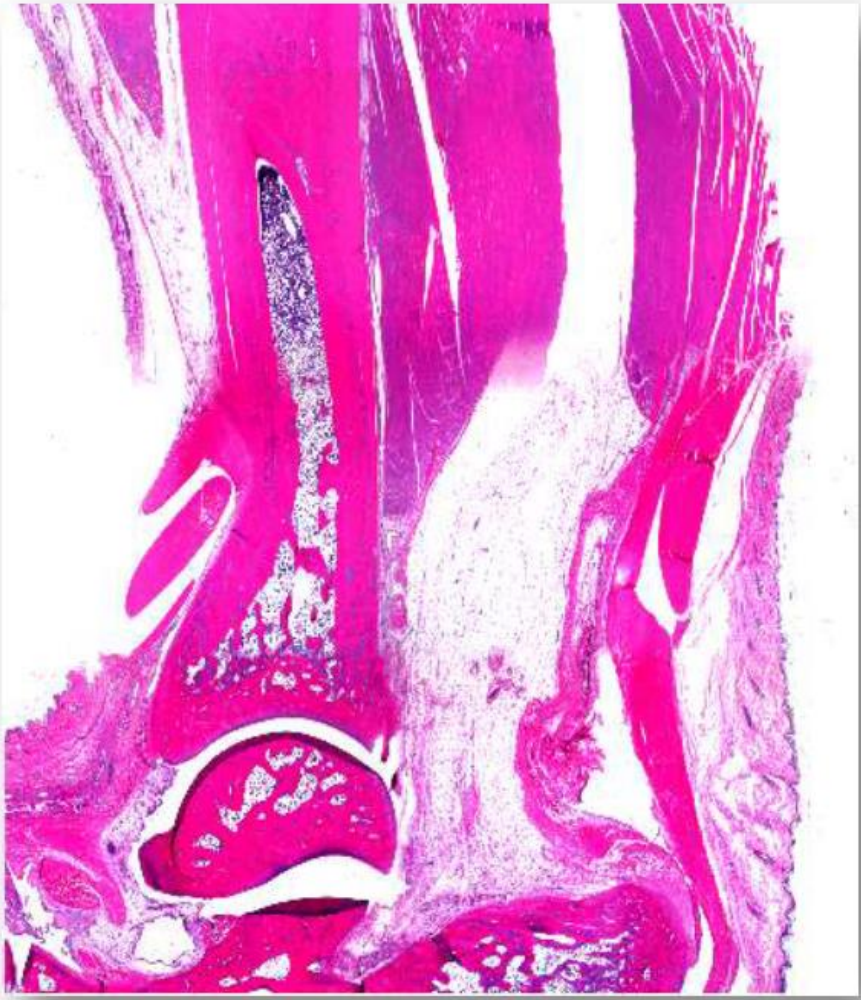




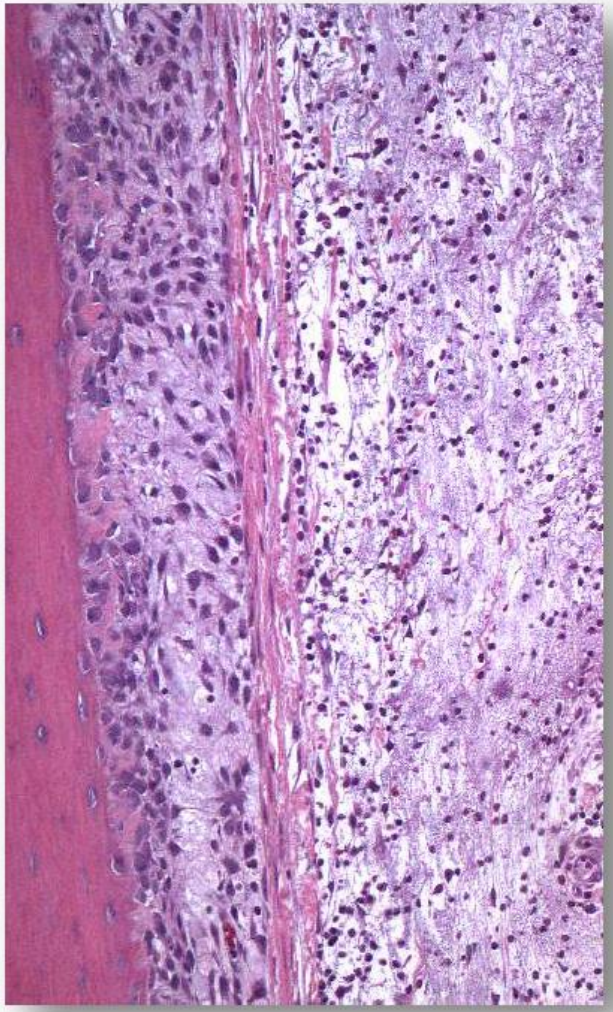
Histology: Massive inflammatory edema in soft tissue around distal tibia, tarsal joint and Achilles tendon

Treated

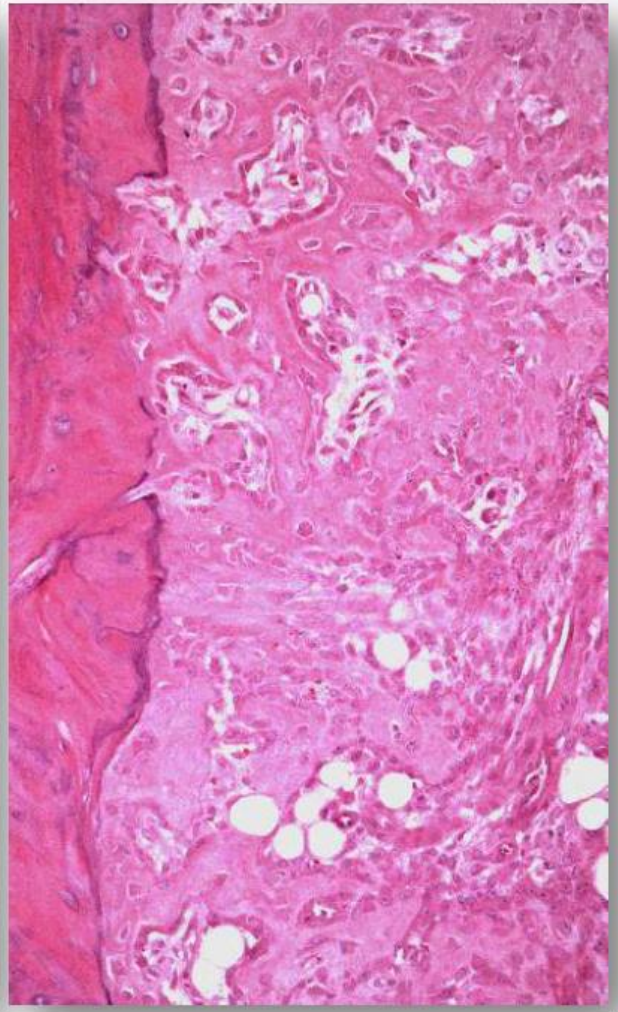
Control



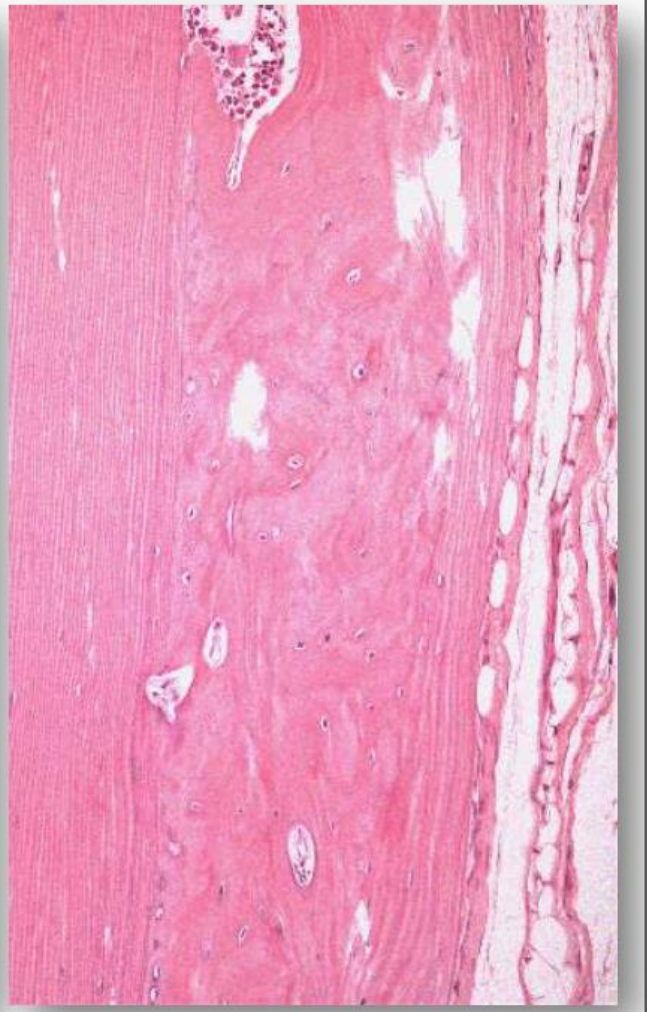
Periosteal thickening, osteoblast differentiation and new bone formation



Periosteal thickening
Proliferation of osteoblasts



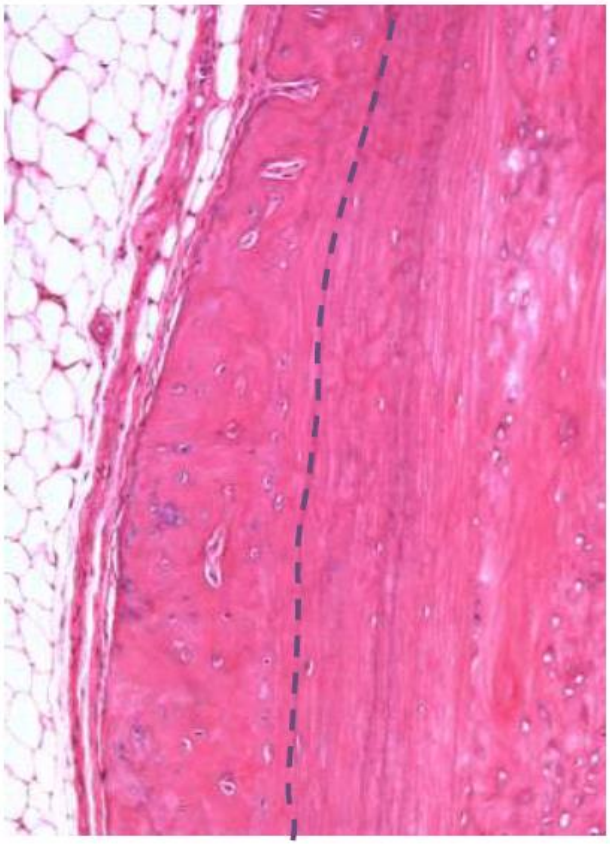
Formation of woven bone
2 days after onset of clinical findings

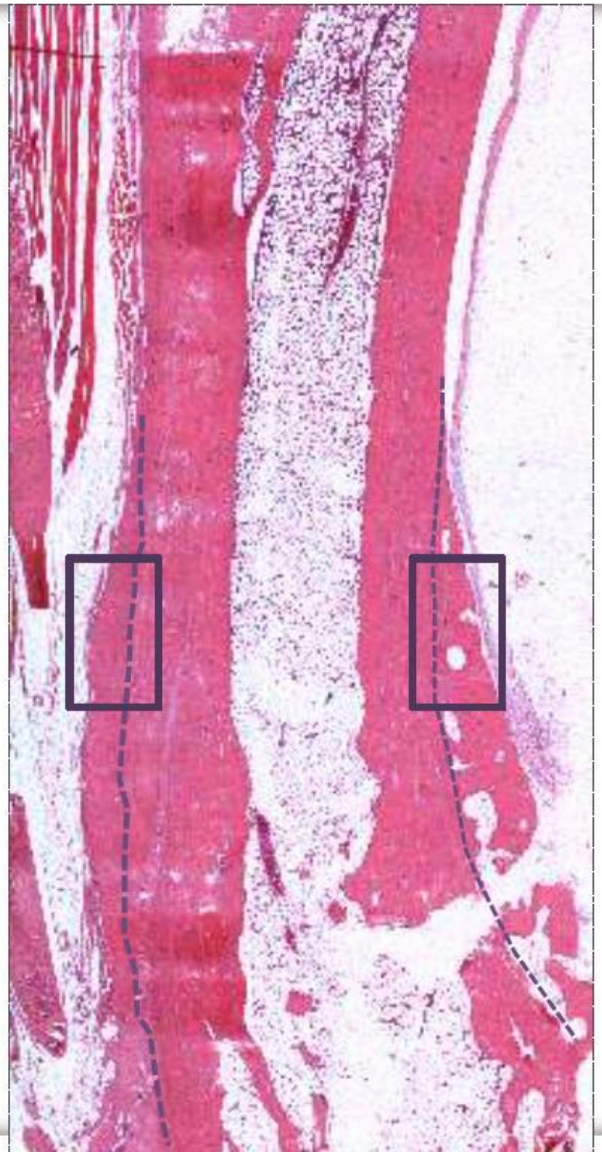


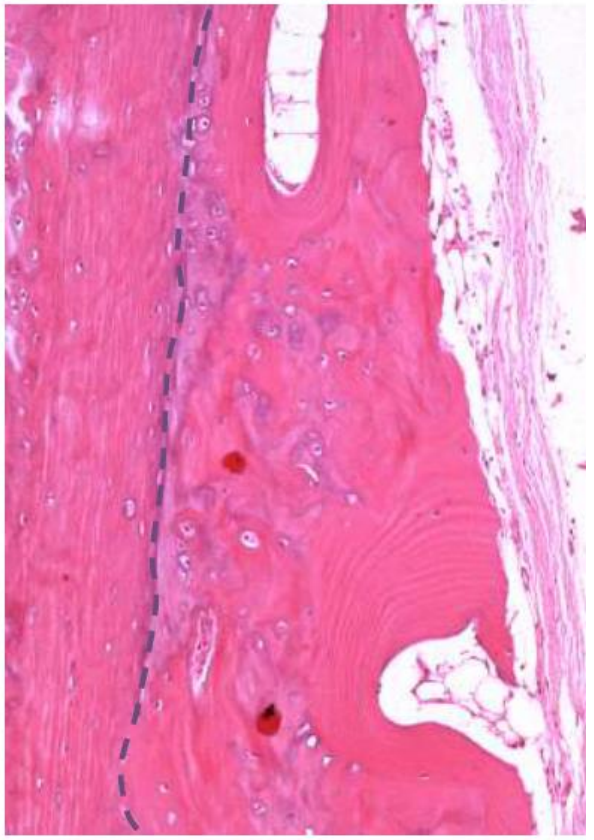
Remodlling to lamellar bone
8 weeks after onset of clinical findings (week 2 to 3)

Mild hyperostosis at distal tibia

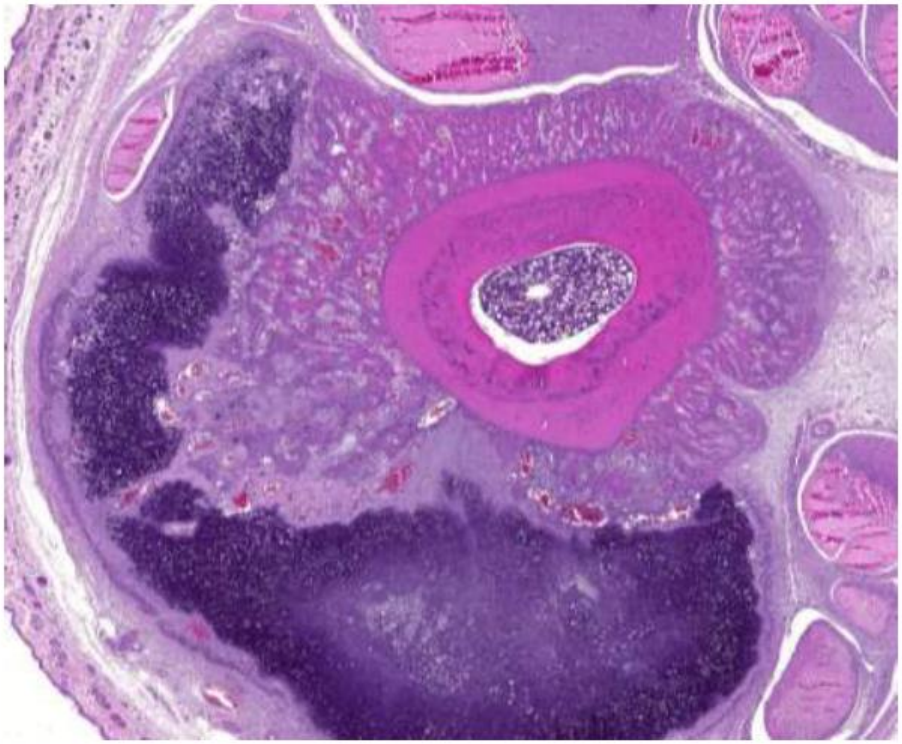
Compound: PDE4i *(mid dose)*
Clin. Obs.: not observed
Necropsy: Day 84



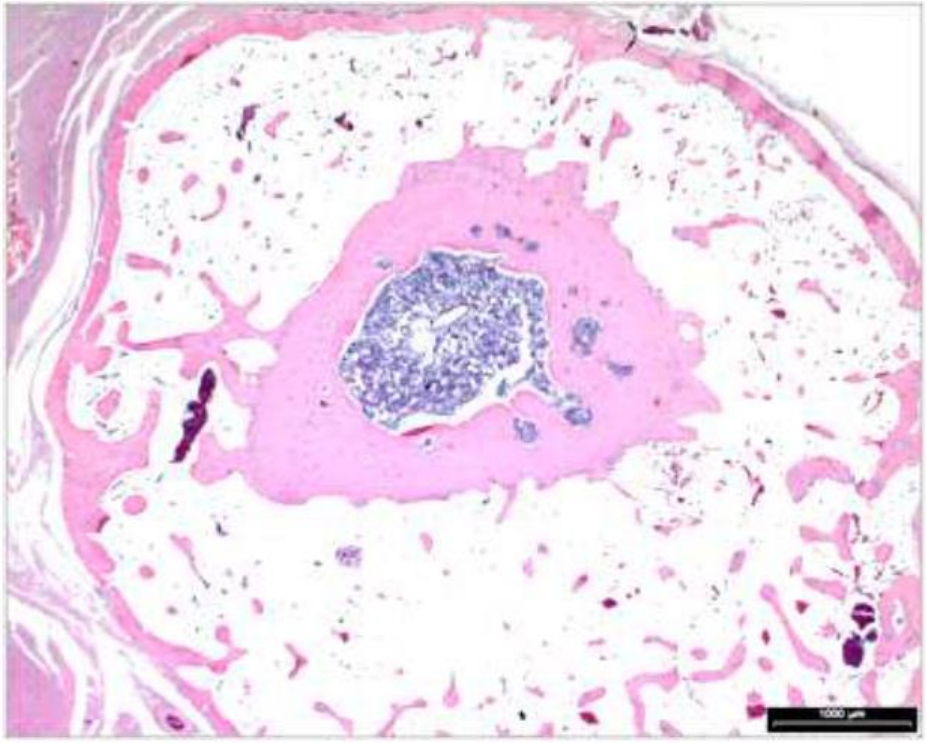




Second shell of bone with bone marrow cavities around pre-existing tibia

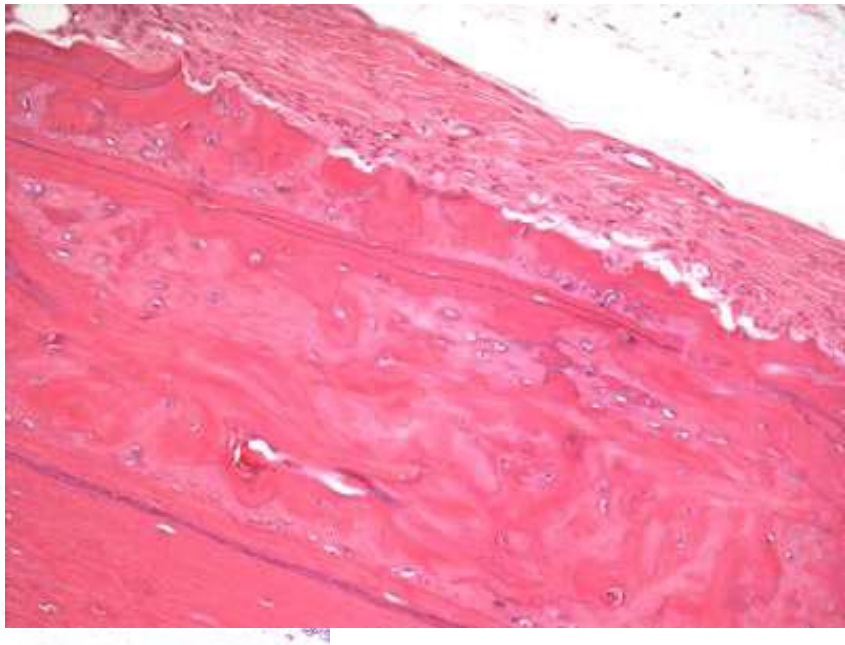


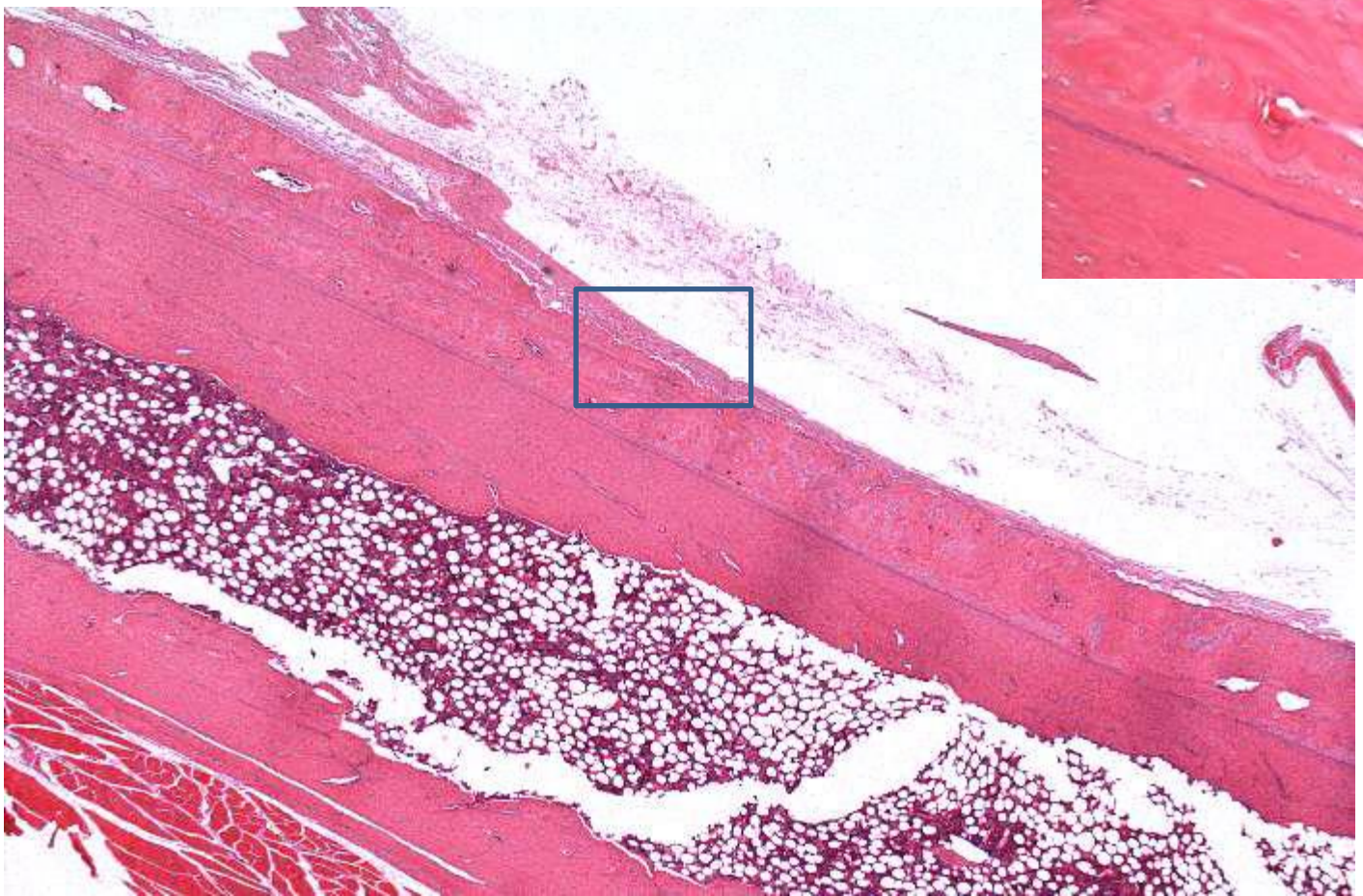
Compound: PDE3/4i *(high dose)*
Necropsy: Day 47



Compound: PDE3/4i *(high dose)*
Necropsy: Day 109

Under long-term treatment different episodes of new bone formation were observed





Compound: PDE3/4i (high dose)
Clin. Obs.: Day 41-43
Necropsy: Day 95

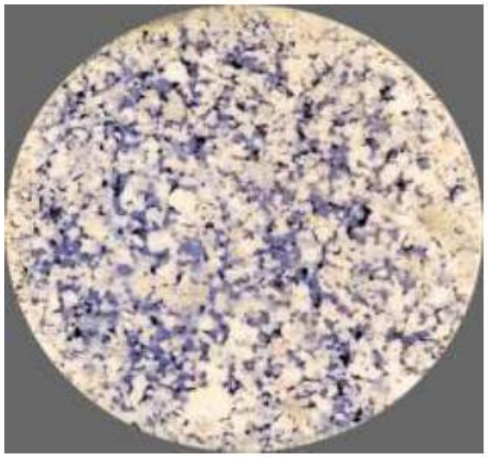
Summary of Findings

- *Affected Species* : Rats (not in mice, hamsters, dogs)
- *Distribution pattern:*
  - Unilateral or bilateral
  - Hindlimbs >> Forelimbs
  - No preference for right or left!
- *Predilection site:* Distal tibia (Trimming)
- *Histology:* Different stages
  - Acute transient inflammation in soft connective tissue (repeated episodes)
  - Periosteal new bone formation, partly islets of cartilage
  - Remodelling of newly formed woven bone to lamellar bone
- *No Reversibility*
  - Mild changes: Incorporation into cortical bone
  - Moderate-severe changes: Second bony shell with bone marrow
- *End-stage lesion*: mature bone, no indication of dysplasia or neoplasia

Effect of PDE4 inhibitors on bone tissue

➢ *In vitro*

- cAMP↑ in osteoblastic cells enhance their bone forming activity
- PDE4 inibitors increase osteoblasto-genesis and inhibit osteoclast-like cell formation



Osteoblasts differentiating from rat bone marrow cells. Alkaline Phophatase stain.
http://www.ucl.ac.uk/cdb/research/arnett/gallery_bone1

➢ *In vivo*

- Restoration of bone mass or enhancement of new bone formation

Denbufylline	*Walker256/carcinoma bearing rat*
Pentoxifylline + Rolipram	*Mouse model of bone induction (rhBMP-2) and normal male mice*
Rolipram	*OVX rat model*

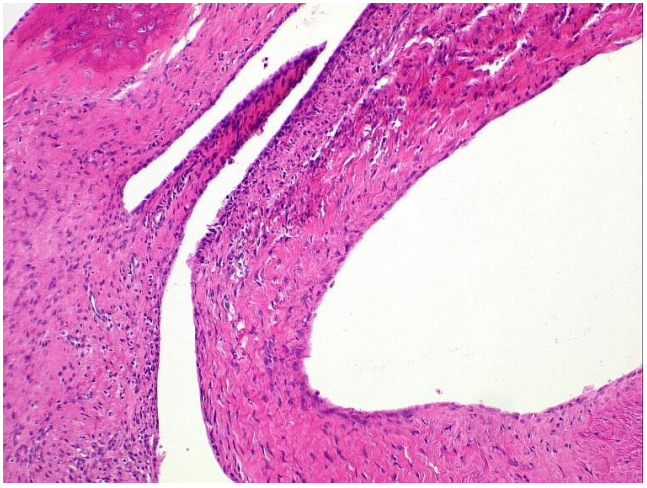
J Bone Miner Res (1997),12:172-8; *Jpn J Pharmacol. (1999)*79 :477-83. *Biochem Pharmacol*, (1997), 54:613-7.,
J Bone Miner Metab. (2004). 22 :329-34. Bone (1997), 30: 589-93; Bone (200). 27:811-7 ; J Bone Miner Res. (2002): 17:249-56.

Matrix Metalloproteinase Inhibitors

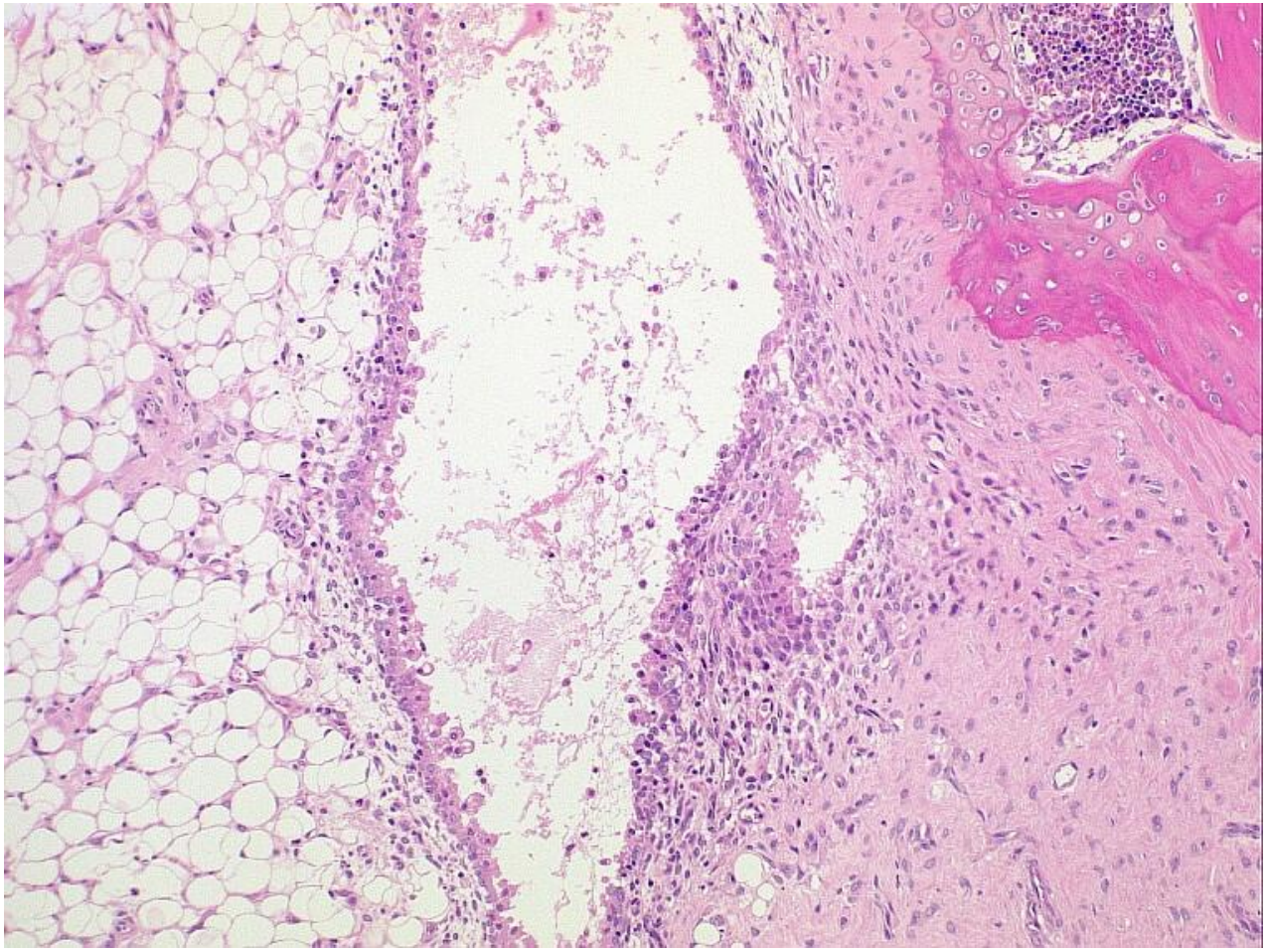
Matrix metalloproteinase inhibitors (MMPI´s)

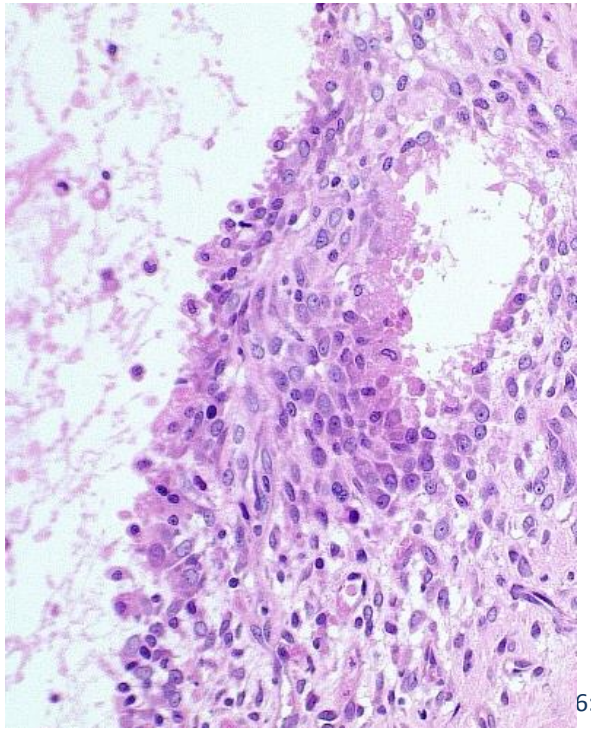
Indication	Cancer, Inhibition of MMP activity inhibits tumor invasion and metastasis.
Mechanism of Action	Activity of the MMPs under normal physiological conditions is strictly controlled. Altering this equilibrium of MMP activity affects the process of cellular invasion by modulating extracellular matrix (ECM) turnover and the adhesive and motile properties of neoplastic cells.
Histopatholog. side effect	Severe tendinitis and arthritis: **Inflammatory cell infiltration and fibrosis around the tendons and exudate within the articular space of the knee joints as well as synovial cell proliferation**. Abnormal endochondral ossification was also observed in femur and tibia, and a myopathy with fiber degeneration or necrosis and inflammatory cell infiltration affected the skeletal muscles.
Mechanism of side effects	The mechanism of inducing the inflammatory and degenerative side effects is most likely due to the broad inhibition of matrix metalloproteinases including those responsible for the physiological mechanism of collagen remodeling such as collagenase-1. In fact at the level of joints, collagenase-1 maintains the homeostasis between collagen production and degradation allowing the proper joint function and movement.

(MMPI´s)

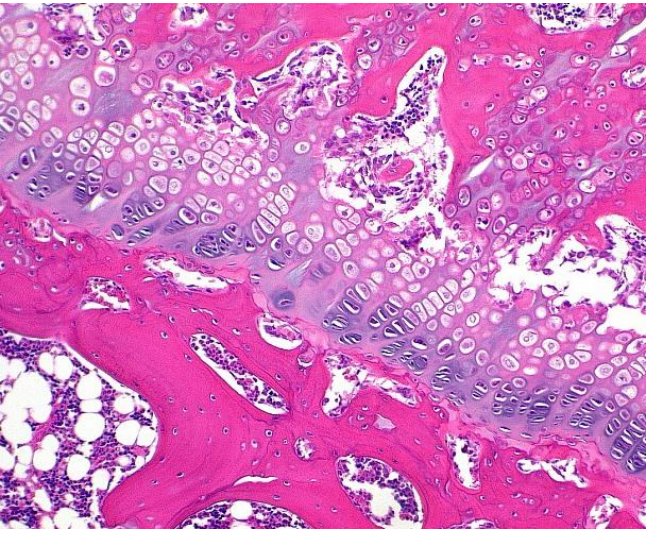


Rat, femur, normal knee joint with synovial space, vehicle (DMSO/PEG300). H&E, lens x10

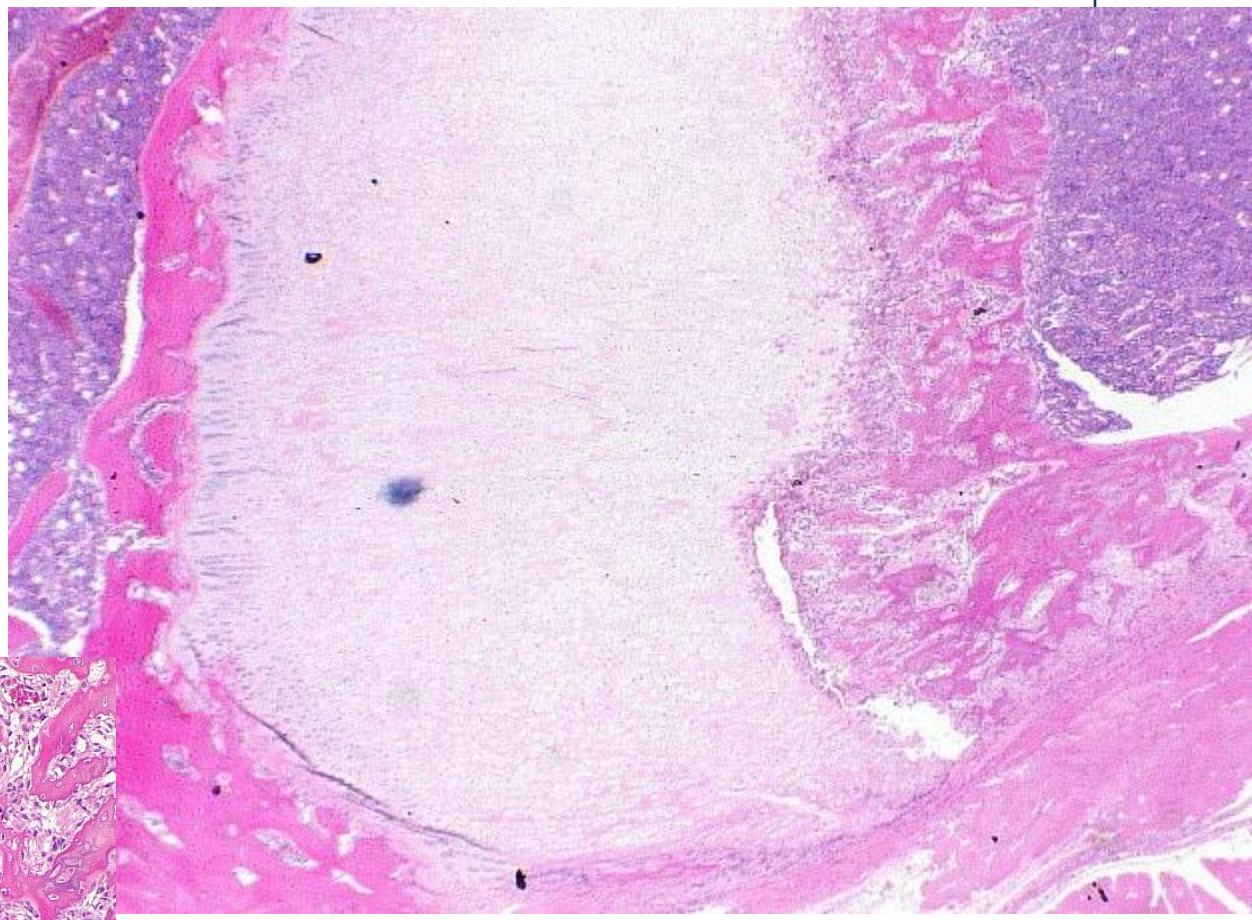


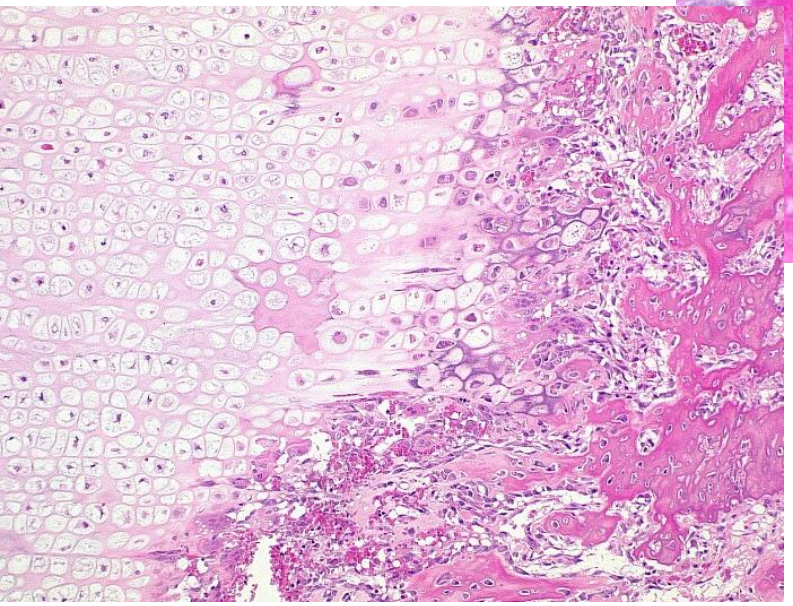


Rat, femur, knee joint, inflammation and fibrosis of the synovia and subsynovial tissue; CGS 27023A 140 mg/kg/day for 21 days duration. H&E, lens x10 and x20.

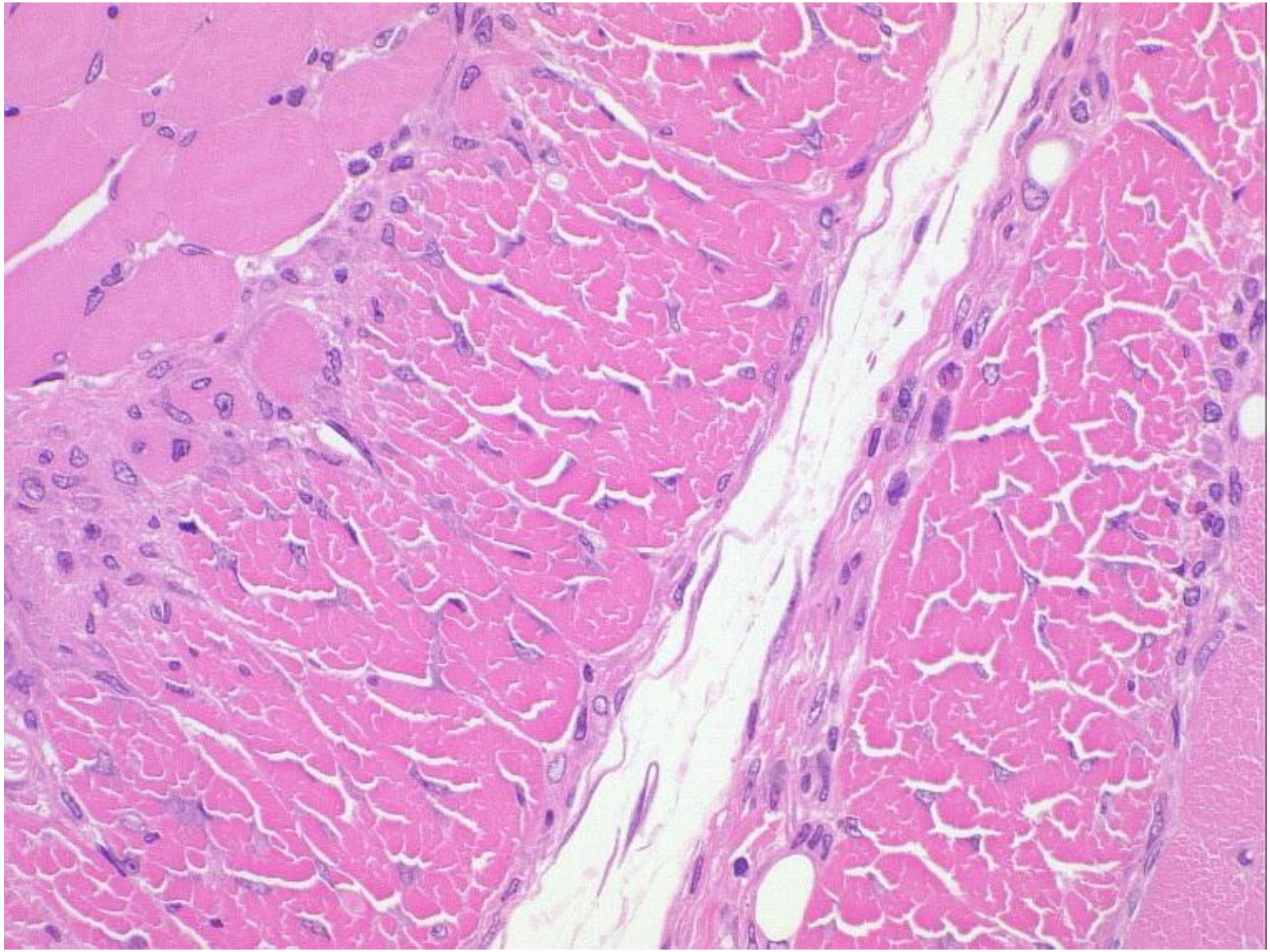


Rat, femur, normal growth plate; vehicle (DMSO/PEG300). H&E, lens x10.





Rat, femur, increased growth plate cartilage width due to chondrocyte proliferation and arrest of mineralization; CGS 27023A 140 mg/kg/day for 21 days duration. H&E, lens x2 & x10.



(MMPI´s)

Rat, skeletal muscle, myopathy with degeneration and necrosis of myofibers, CGS 27023A 140 mg/kg/day for 21 days duration. H&E, lens x40.

Matrix metalloproteinase inhibitors (MMPI´s)

Mater. &Meth., relev. Studies	Marimastat and CGS 27023A (two synthetic MMPI) were given by continuous infusion, using an osmotic mini pump model implanted subcutaneously, to male Wistar rats for a period up to 21 days. Marimastat was given at the dose of 10 mg/kg/day, CGS 27023A at the dose of 140 mg/kg/day. At the end of the treatment period, animals were killed under anesthesia of pentobarbital and limbs of animals of controls and each treatment group were collected and fixed with 10% neutral buffered formalin. The sections from muscles, tendons and bones were stained
Relevance to humans	The toxicity observed in animals has been recorded in humans as well. The most common side effects were a syndrome of musculoskeletal pain and stiffness, often starting in the small joints of the hands and progressing to the arms and shoulders, mainly at tendon-insertion points Two main toxicities were observed: a widespread, self-limiting maculopapular rash and mild to moderate arthralgias and myalgias which did not appear to be dose-related. These side effects, mostly related to the inhibition of collagenase-1, were the cause of the interruption of the clinical development of all MMPIs under investigation.

References- Andersen IC, Shipp MA, Docherty AJP, Teicher BA (1996) Combination therapy including a gelatinase inhibitor and cytotoxic agent reduces local invasion and metastasis of murine Lewis lung carcinoma. Cancer Res 56: 715-718; Brown PD, Giavazzi R (1995) Matrix metalloproteinase inhibition: a review of anti-tumor activity. Ann Oncol 6: 967-974 ; Hajitou A, Sounni N, Devy L, Grignet-Debrus C, Lewalle JM, Li H, et al. (2001) Down-regulation of vascular endothelial growth factor by tissue inhibitor of metalloproteinase-2: effect on in vivo mammary tumor growth and angiogenesis. Cancer Res 61: 3450-3457 ; Nelson AR, Fingleton B, Rothenberg ML, Matrisian LM (2000) Matrix metalloproteinases: biologic activity and clinical implications. J Clin Oncol 18: 1135-1149 ; O'Byrne EM, Parker DT, Roberts ED, Goldberg RL, MacPherson LJ, Blancuzzi V, et al. (1995) Oral administration of a matrix metalloproteinase inhibitor, CGS 27023A, protects the cartilage proteoglycan matrix in a partial meniscectomy model of osteoarthritis in rabbits. Inflamm Res 44 (Suppl 2): S117-118

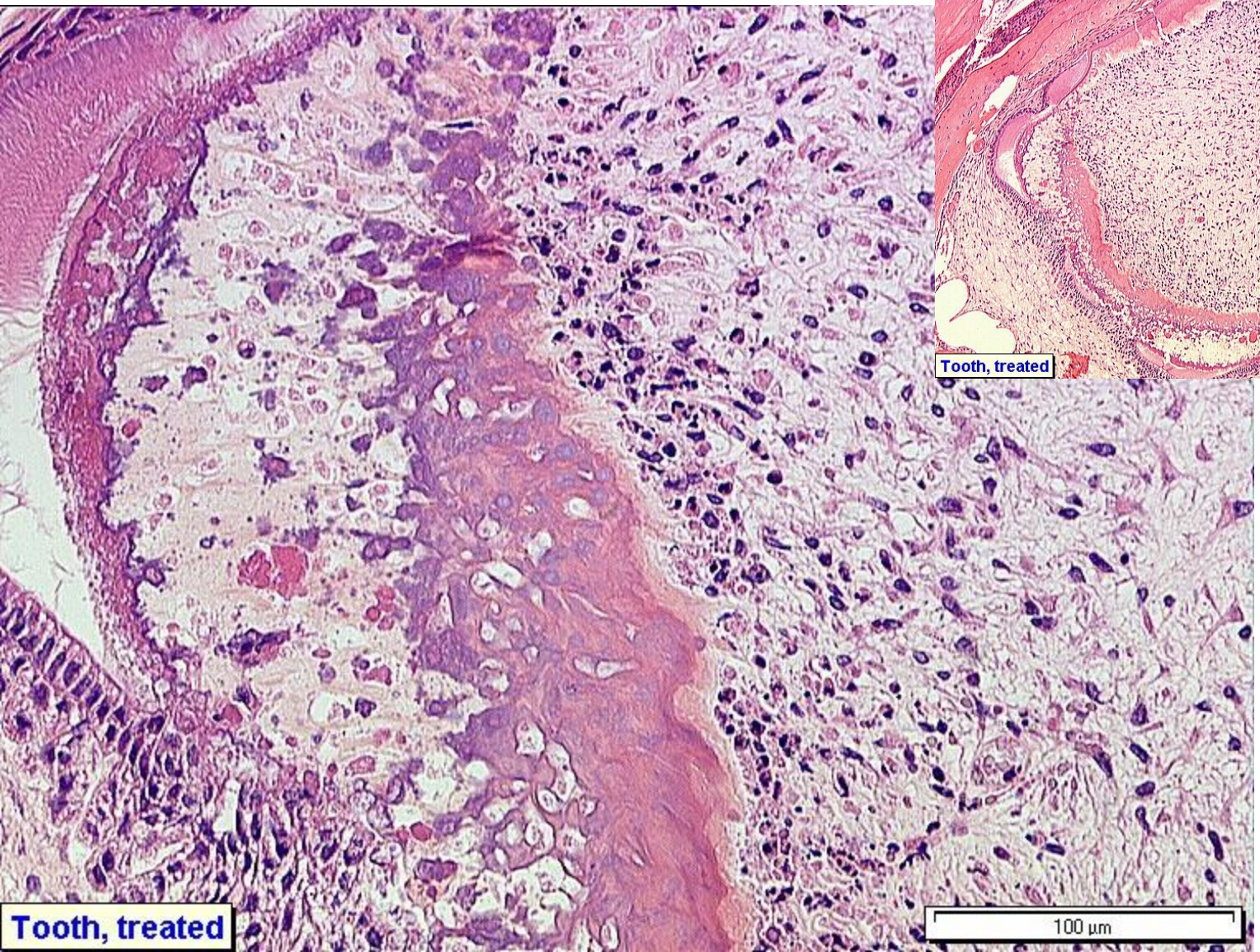
Vascular Endothelial Growth Factor Recep. 1 Antag.

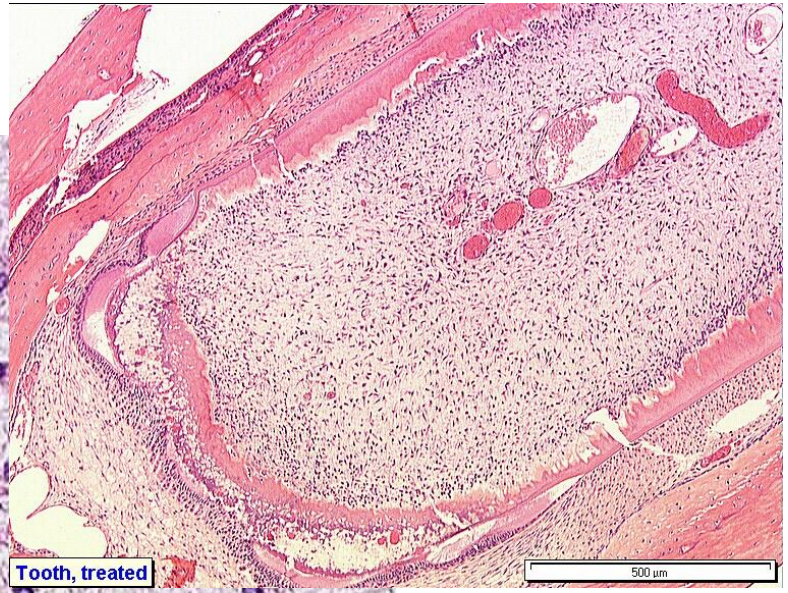
Vascular Endothelial Growth Factor Receptor 1 Antagonists	
Indication	Cancer
Mechanism of Action	Inhibition of VEGF-induced angiogenic signals will selectively target the tumor-associated vessels, since cell division of endothelial cells in the normal vasculature is a very rare event except during growth and repair.
Mater. &Meth., relev. Studies	Lesions are from a 26-week exploratory toxicity study in rats and the compound was given once daily by gavage, starting at the age of 6 weeks

VEGF inhibitors

Femur (epiphyseal growth plate); rat sacrificed in poor health condition after oral administration of 100 mg/kg body weight/day for 12 weeks of a VEGF-receptor inhibitor: Lack of endochondral ossification and enlargement of the epiphyseal growth plate, H&E, lens x5.

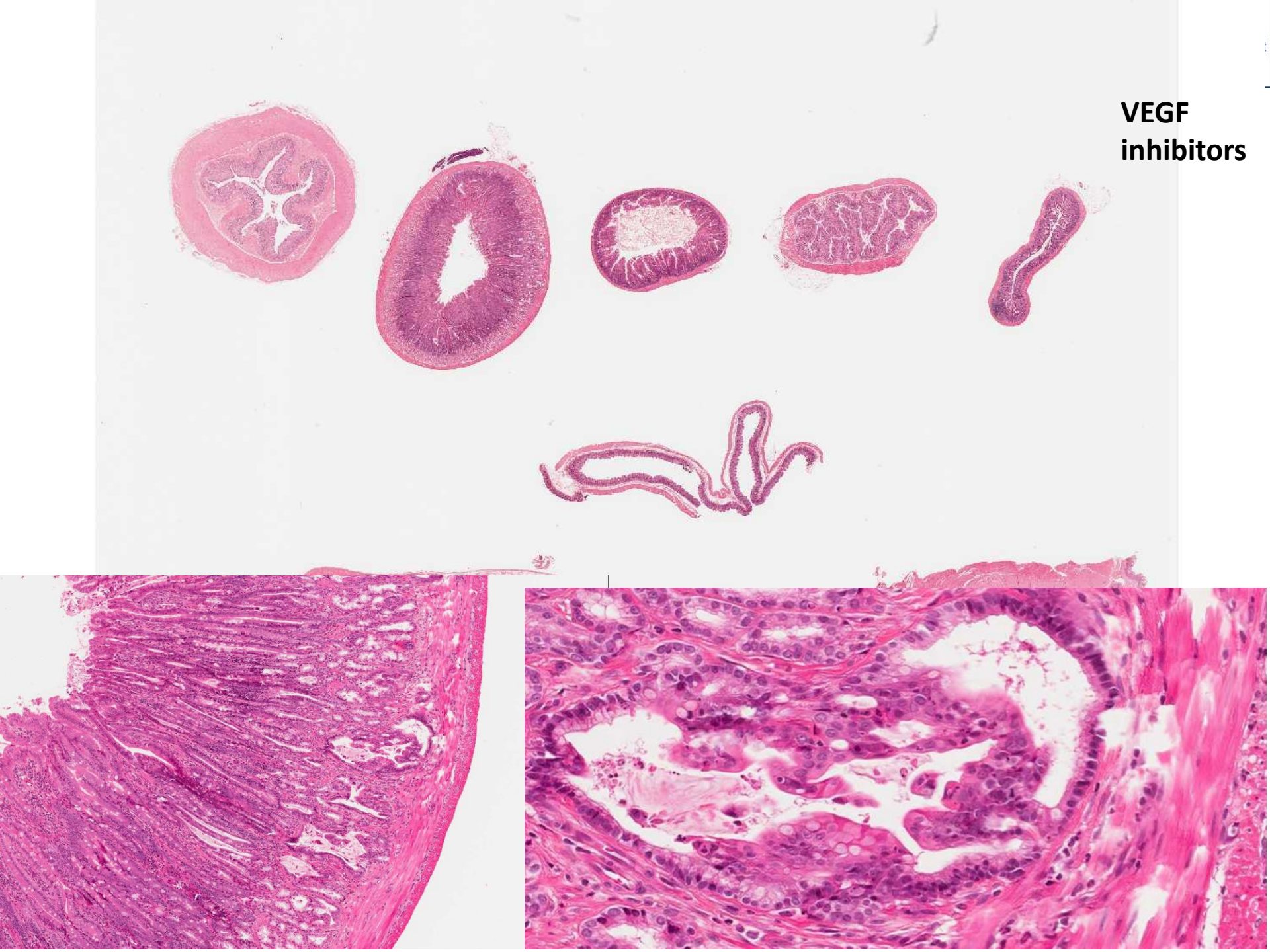
VEGF inhibitors





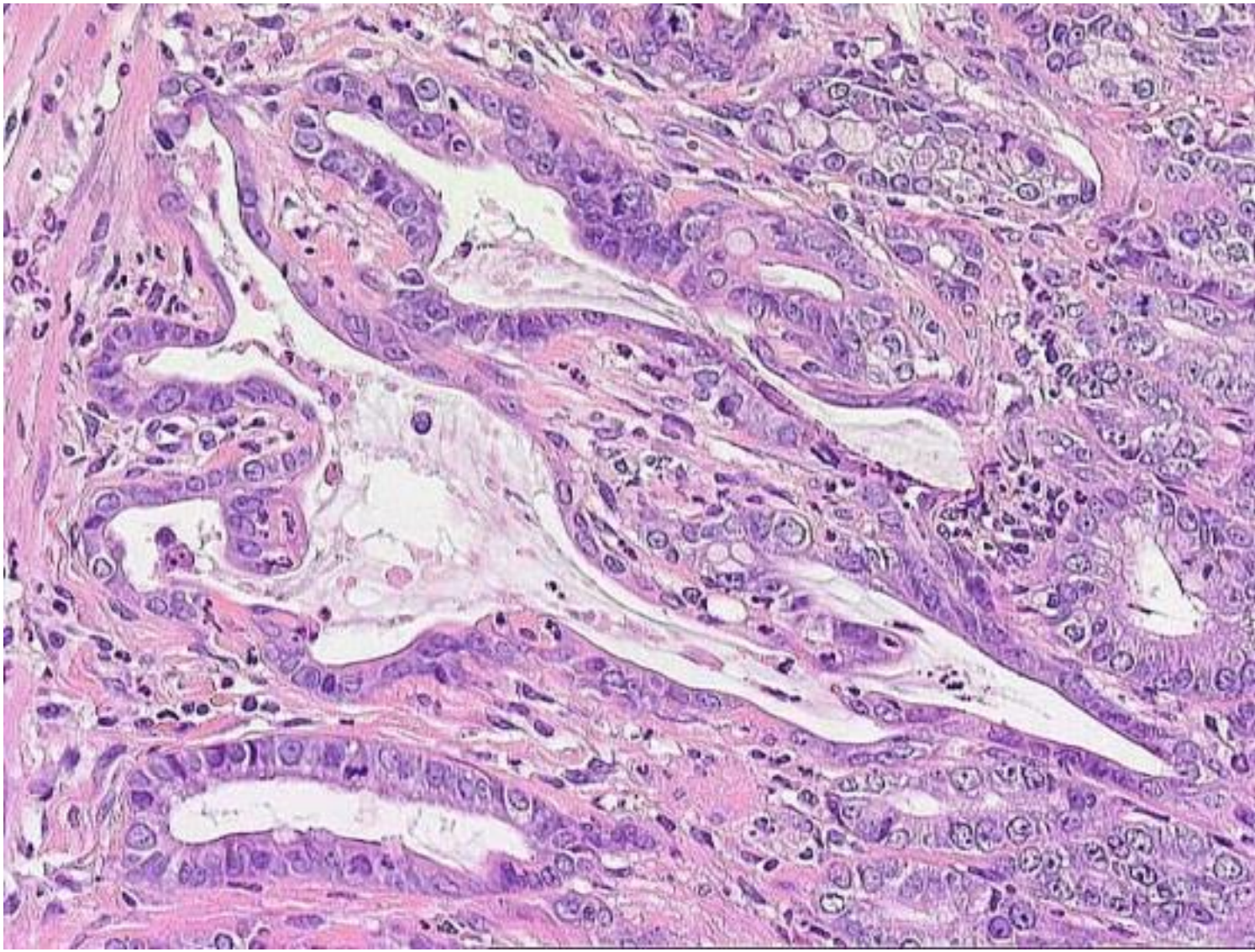
Sorry,
I need to show you this !!!

VEGF inhibitors



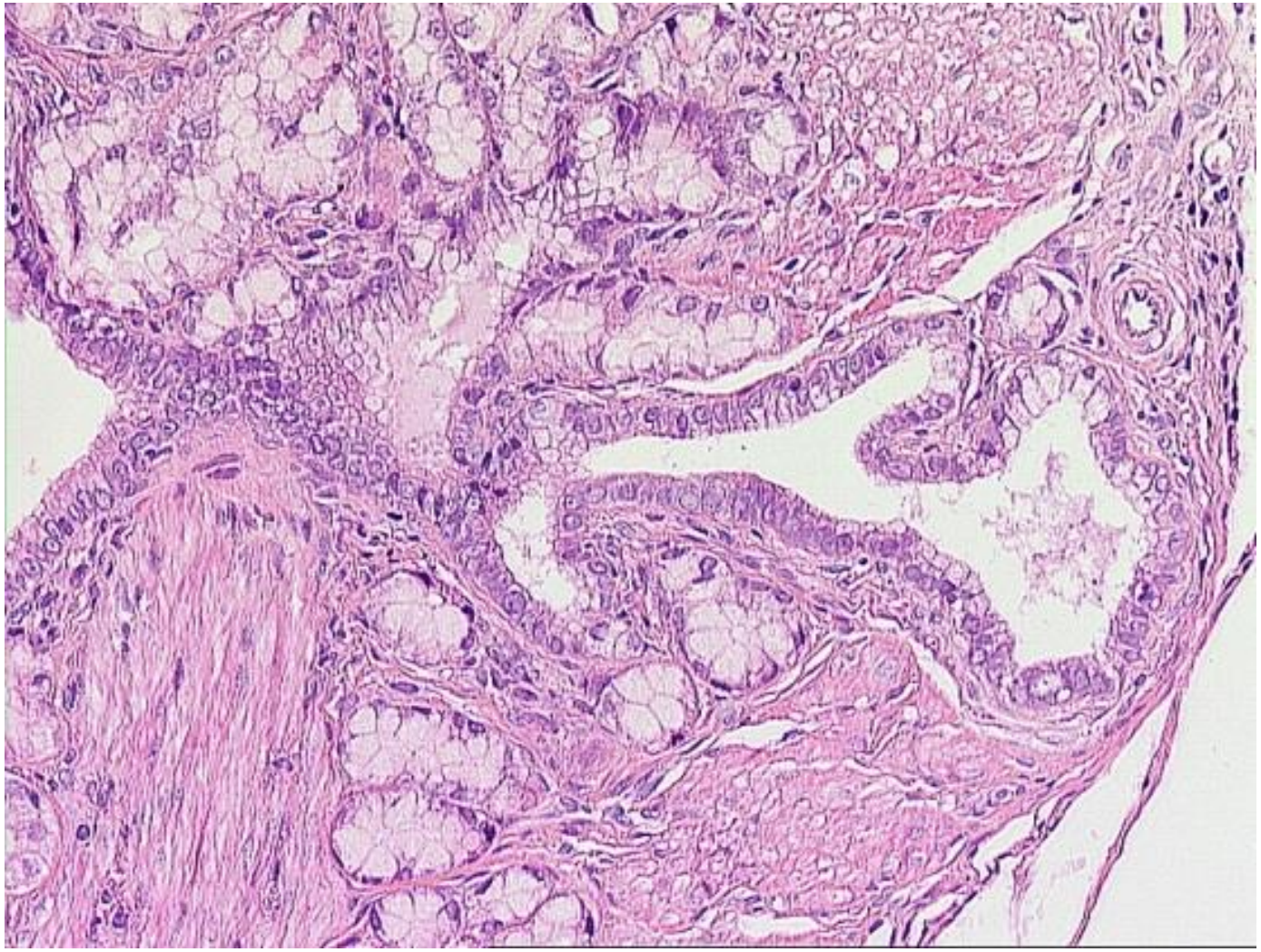
VEGF inhibitors

Duodenum;
Epithelial hyperplasia of the mucosal glands into the submucosa, H&E, lens x20;
High mitotic index, dysplastic cell morphology, glandular structure still maintained, inflammatory reaction;



After 13 week recovery

Clear signs of regression of the epithelial hyperplasia and of the infiltration of the mucosal glands into the submucosa and muscle layers; the layer of Brunner's glands is completely restituted, H&E, lens x20



Vascular Endothelial Growth Factor Receptor 1 Antagonists	
Histopatholog. side effect	In the long bones (femur) lack of endochondral ossification and moderate to marked enlargement of the epiphyseal growth plate was found. Insufficient qualitative and quantitative dentine formation due to degeneration/ necrosis of odontoblasts was observed in the incisor teeth The duodenum was markedly increased in diameter and incisor teeth were discolored or broken. The duodenum showed diffuse epithelial hyperplasia of the mucosal crypts / glands with invasion into the muscular layers. After a recovery period of 13 weeks the lesions in the duodenum were still present, but accompanied by clear signs of regression of the epithelial hyperplasia and infiltration of the mucosal glands into the submucosa and muscle layers. This regression could be confirmed immunohisto-chemically by a reduction of cells stained positive with the proliferation marker Ki67. .

Vascular Endothelial Growth Factor Receptor 1 Antagonists	
Mechanism of side effects	Related to mechanism of action
Relevance to humans	The effects on the duodenum have so far only been observed in rats, but not in mice or dogs, and might be species-specific. Careful monitoring is required in clinical trials. The effects on teeth are not relevant for adult humans, since the rodent incisors, which are growing throughout the animal's life, are morphologically different from teeth in other species. Effects on bone growth are also not expected to occur in adult humans, where epiphyseal plates are no longer present
References	Keshet E, Ben-Sasson SA (1999) Anticancer drug targets: approaching angiogenesis. *J Clin Invest* **104:** 1497-1501; Marks PA, Rifkind RA, Richon VM, Breslow R (2001) Inhibitors of histone deacetylase are potentially effective anticancer agents. *Clin Cancer Res* **7:** 759-760; Matter A (2001) Tumor angiogenesis as a therapeutic target. *Drug Discov Today* **6:** 1005-1024

Know we will go into NVM !!!

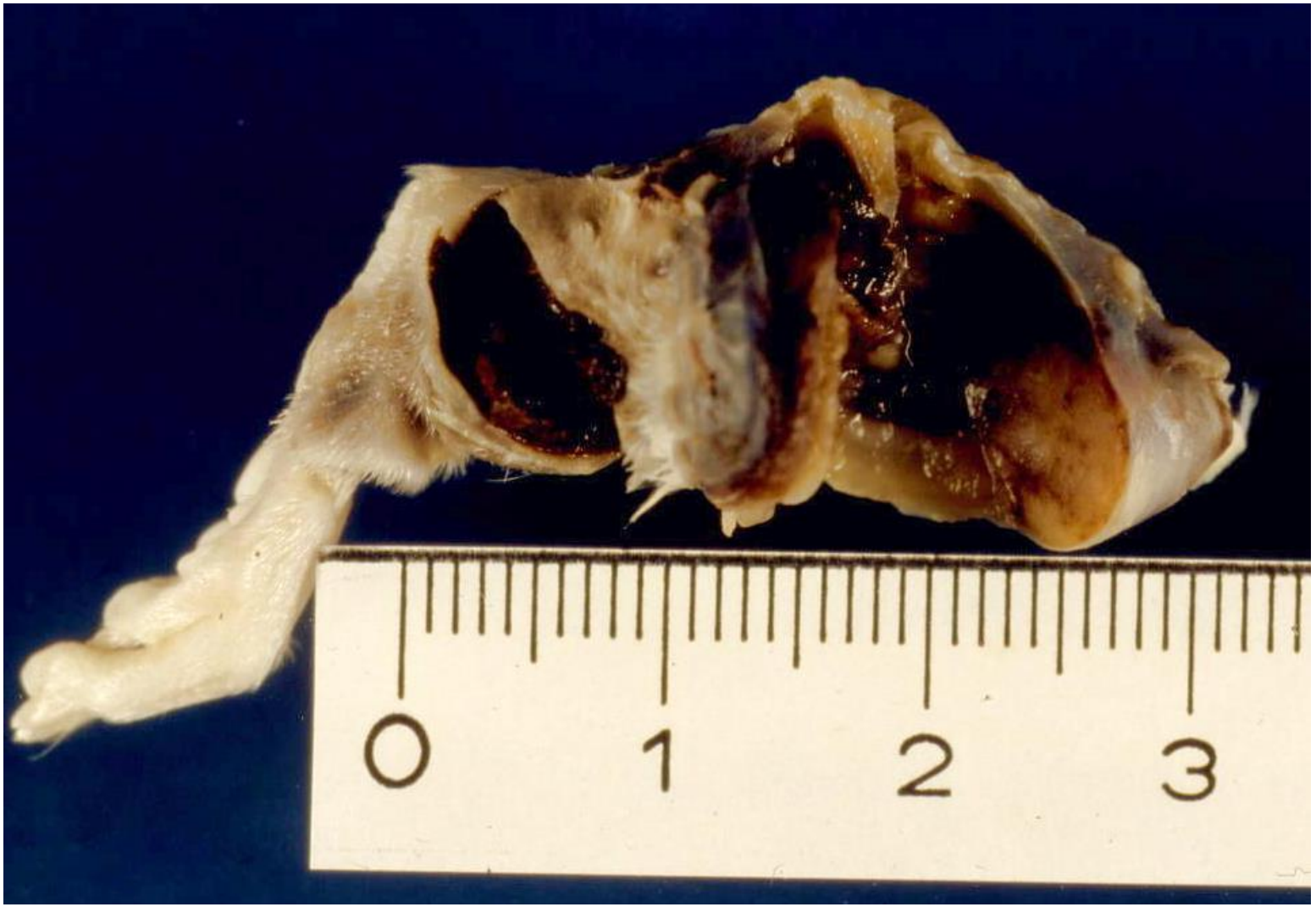
(near video mode)

Three rare spontaneous lesions of the muscolo-skeletal system& soft tissue

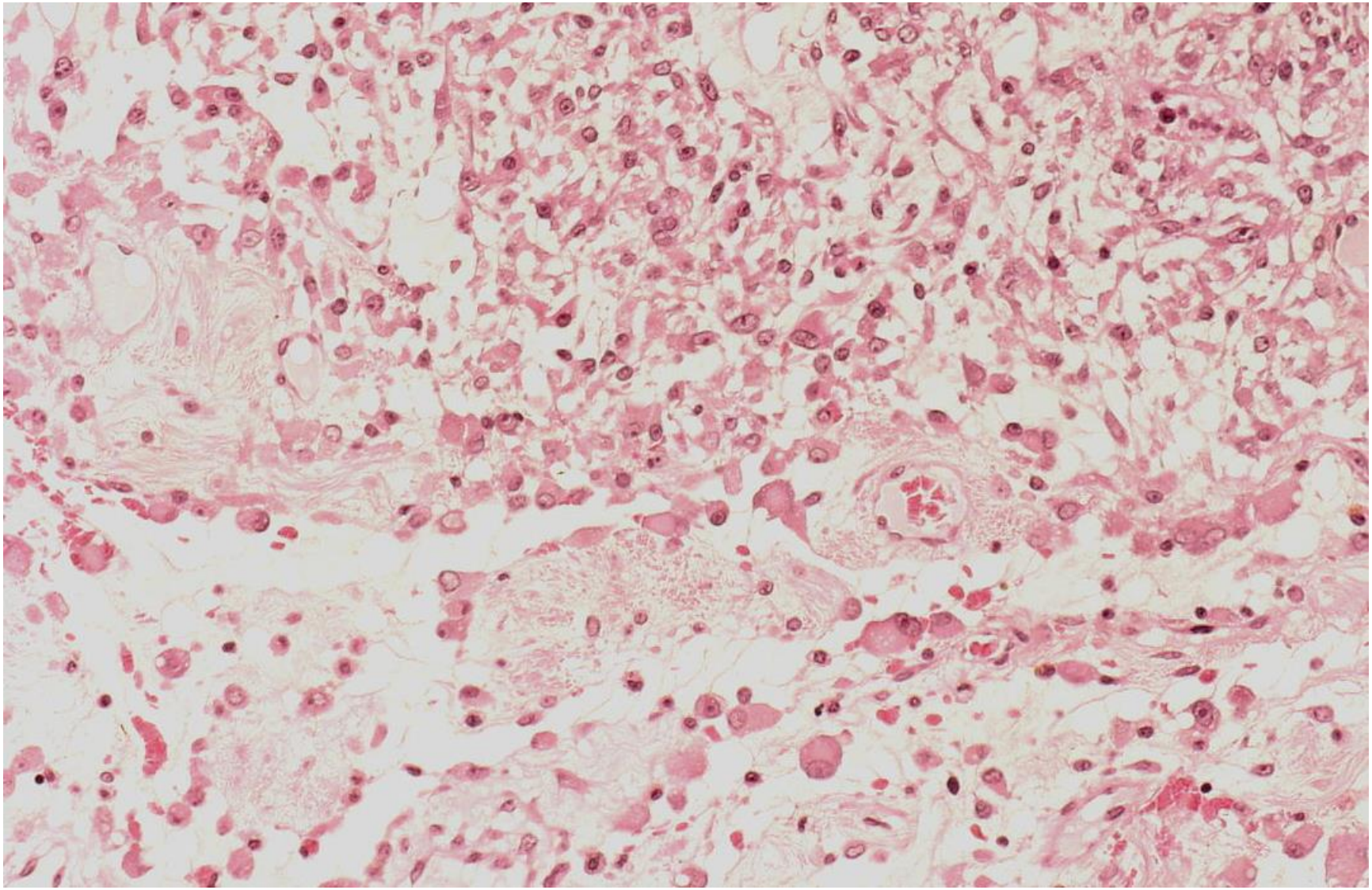
Embryonal Rhabdomyosarcoma
Myxoid Liposarcoma
Hibernoma

Three rare spontaneous lesions of the muscolo-skeletal system& soft tissue

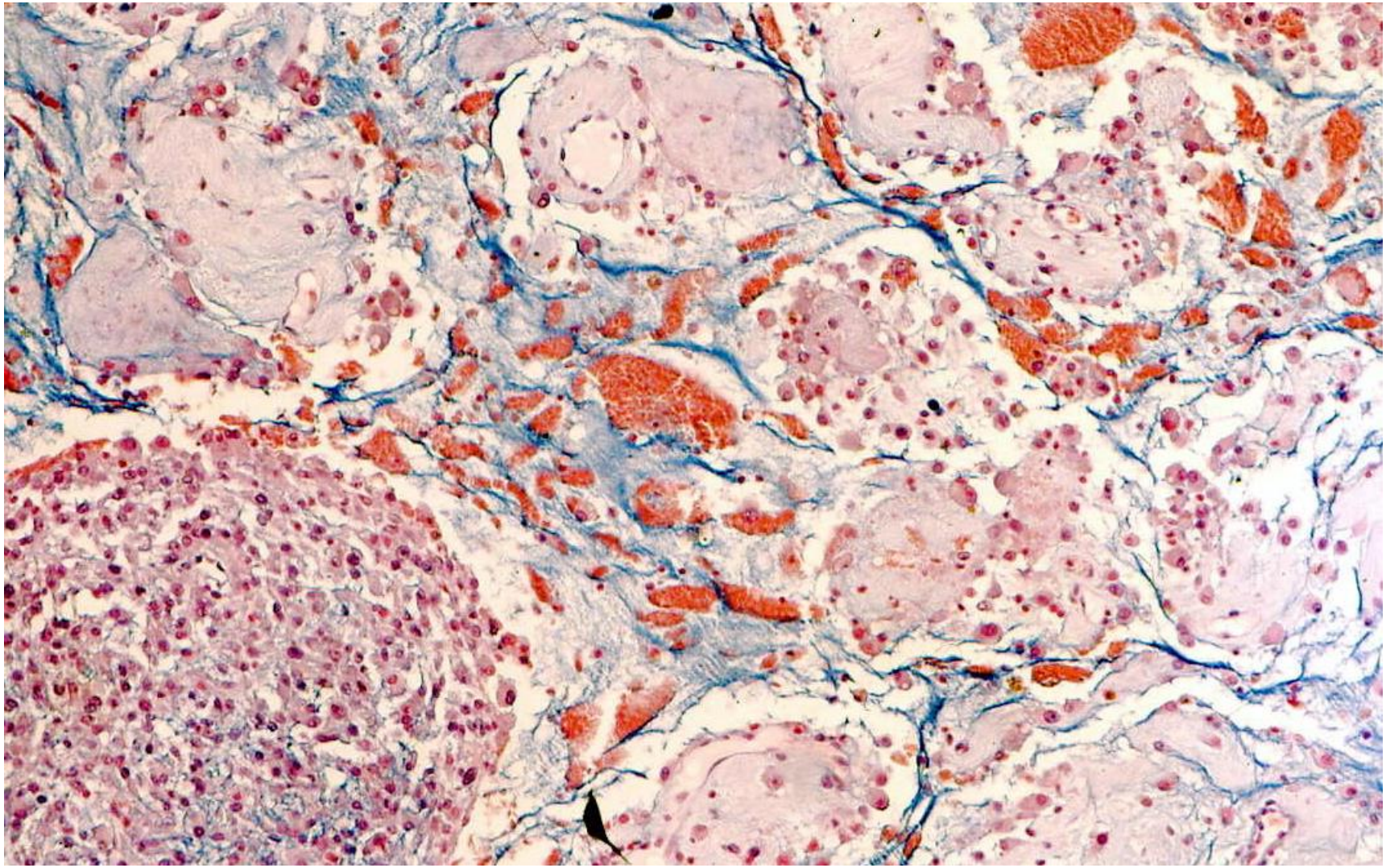
Embryonal Rhabdomyosarcoma



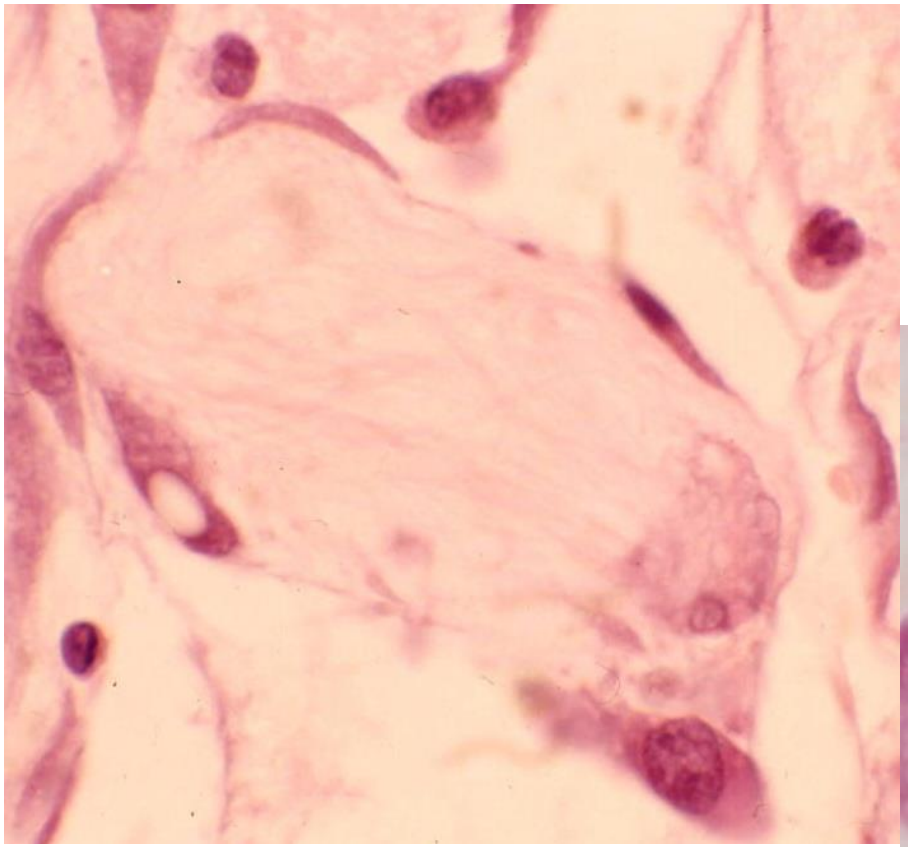
Embryonal Rhabdomyosarcoma

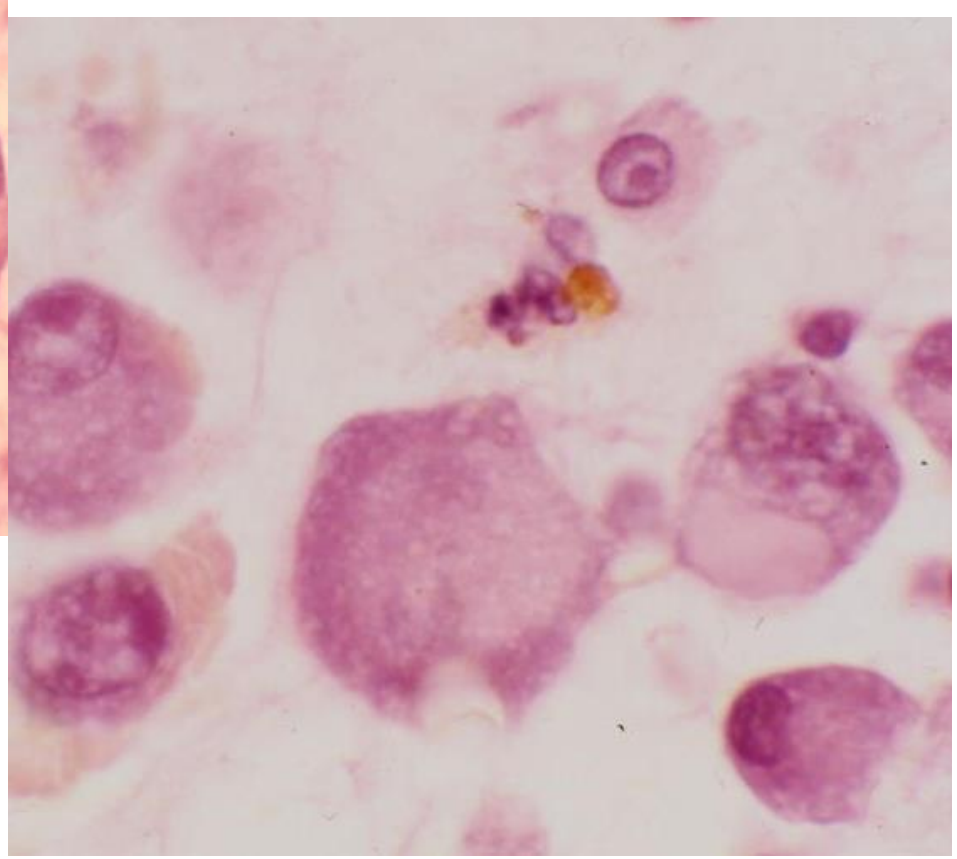


Embryonal Rhabdomyosarcoma

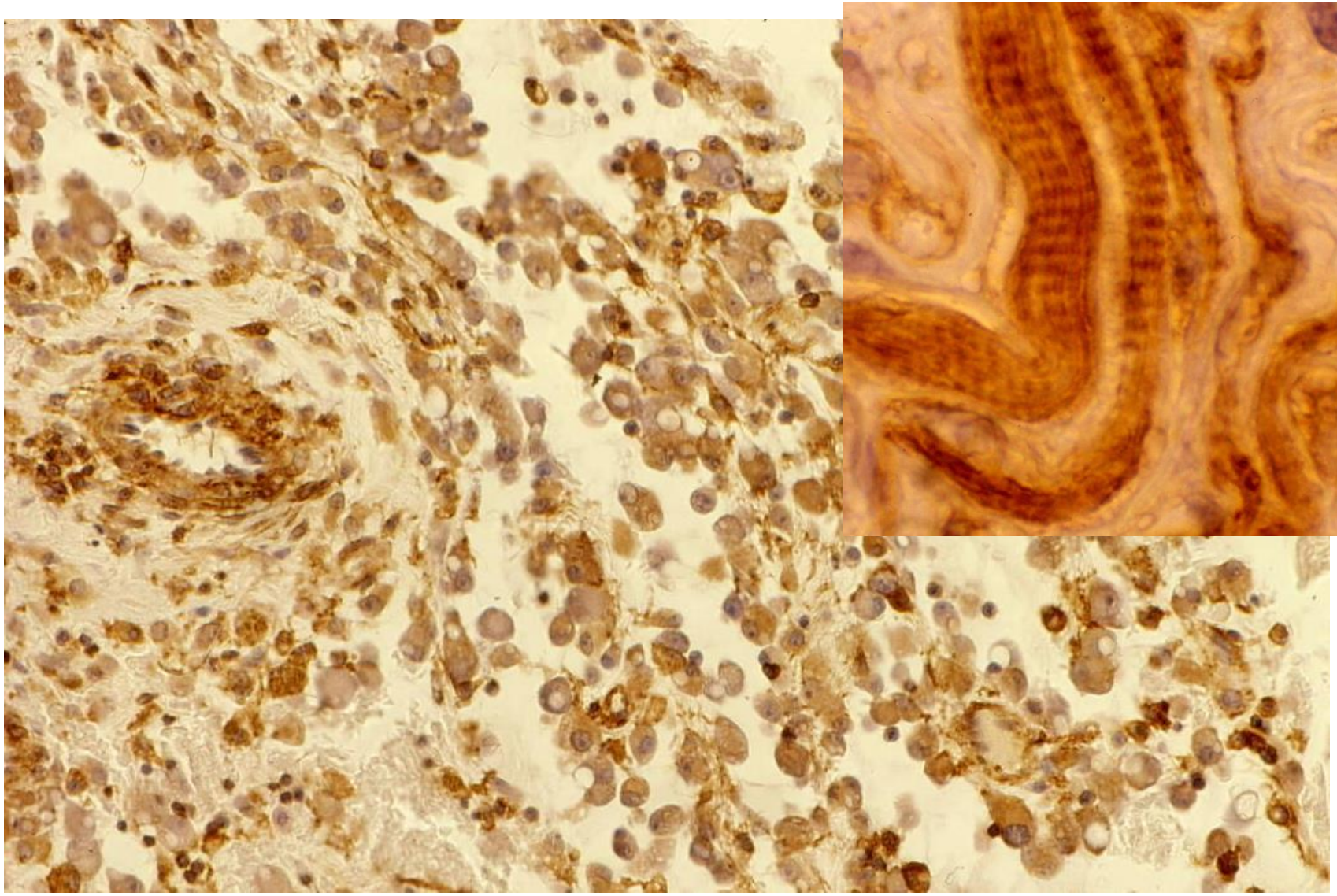


Embryonal Rhabdomyosarcoma, PAS & Alcianblau

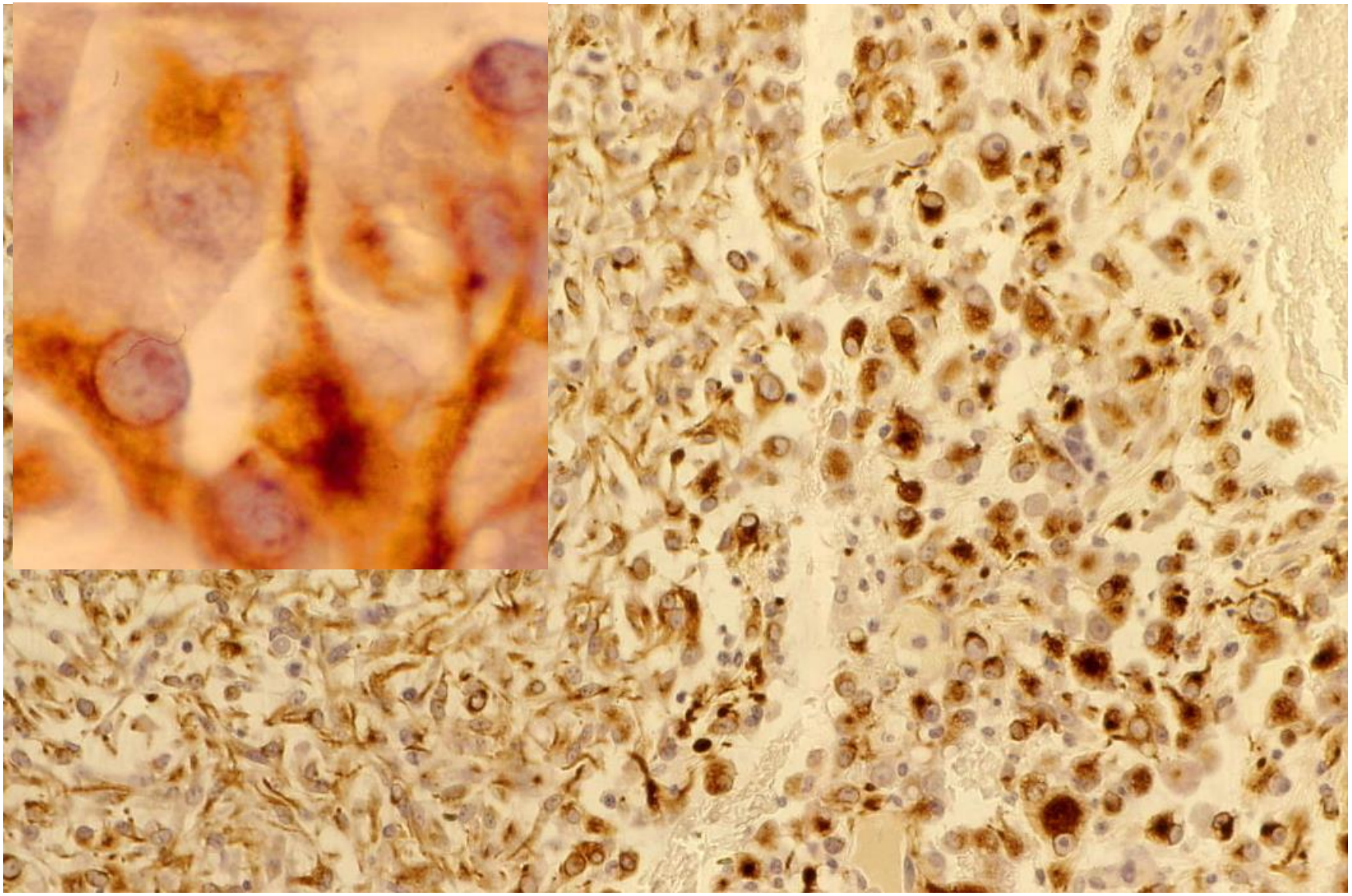




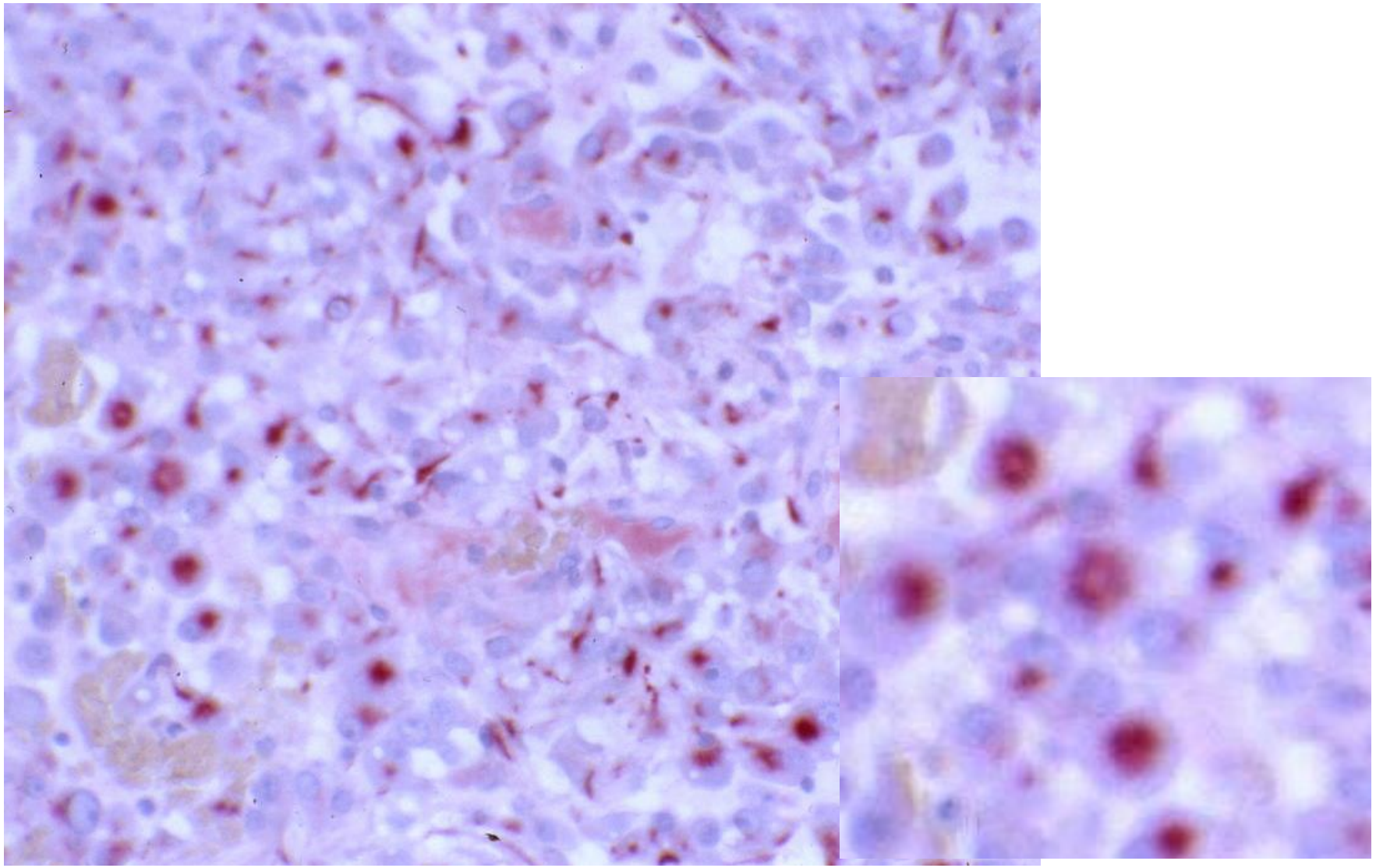
Embryonal Rhabdomyosarcoma



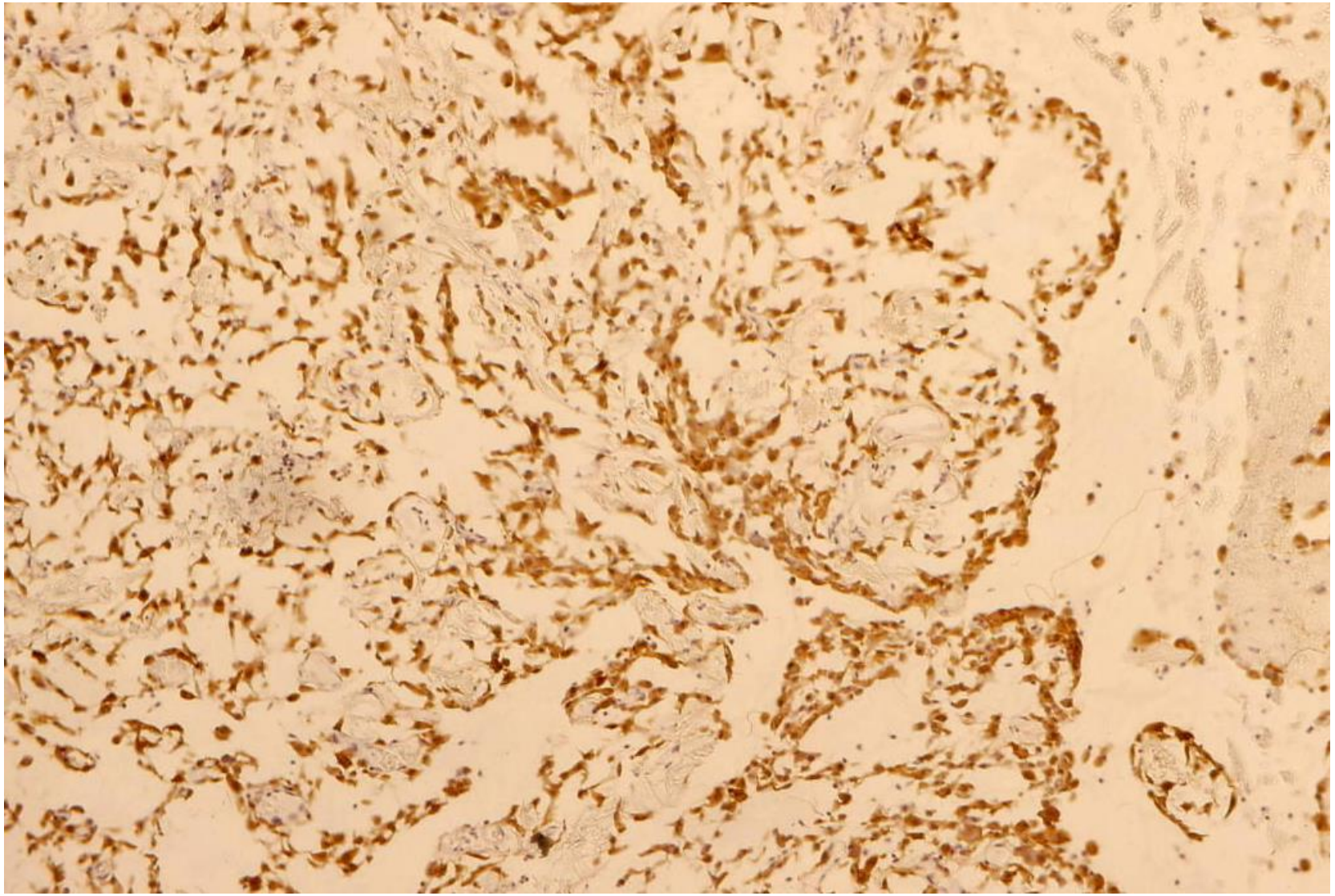
Embryonal Rhabdomyosarcoma, Aktin



Embryonales Rhabdomyosarcoma, Desmin

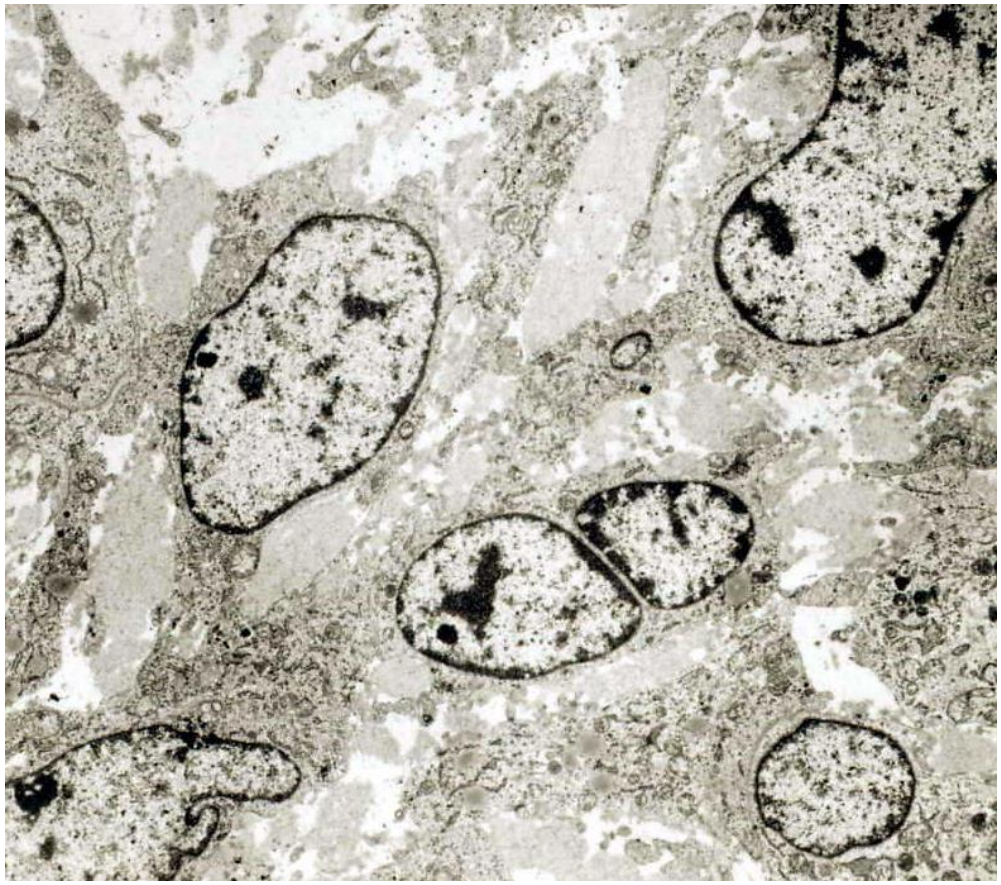


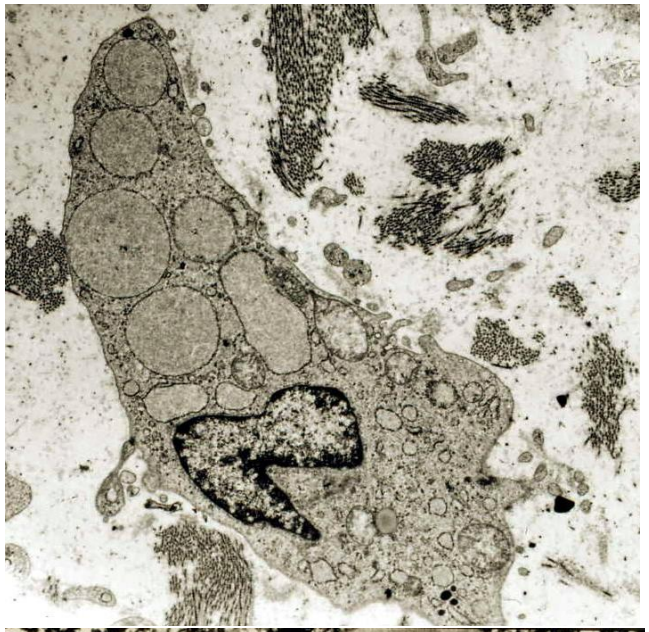
Embryonal Rhabdomyosarcoma, Myoglobin

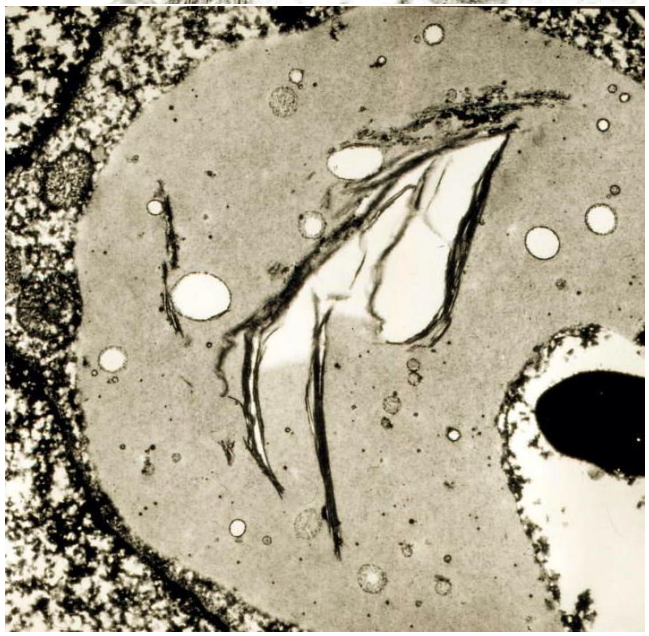


Embryonal Rhabdomyosarcoma, S100

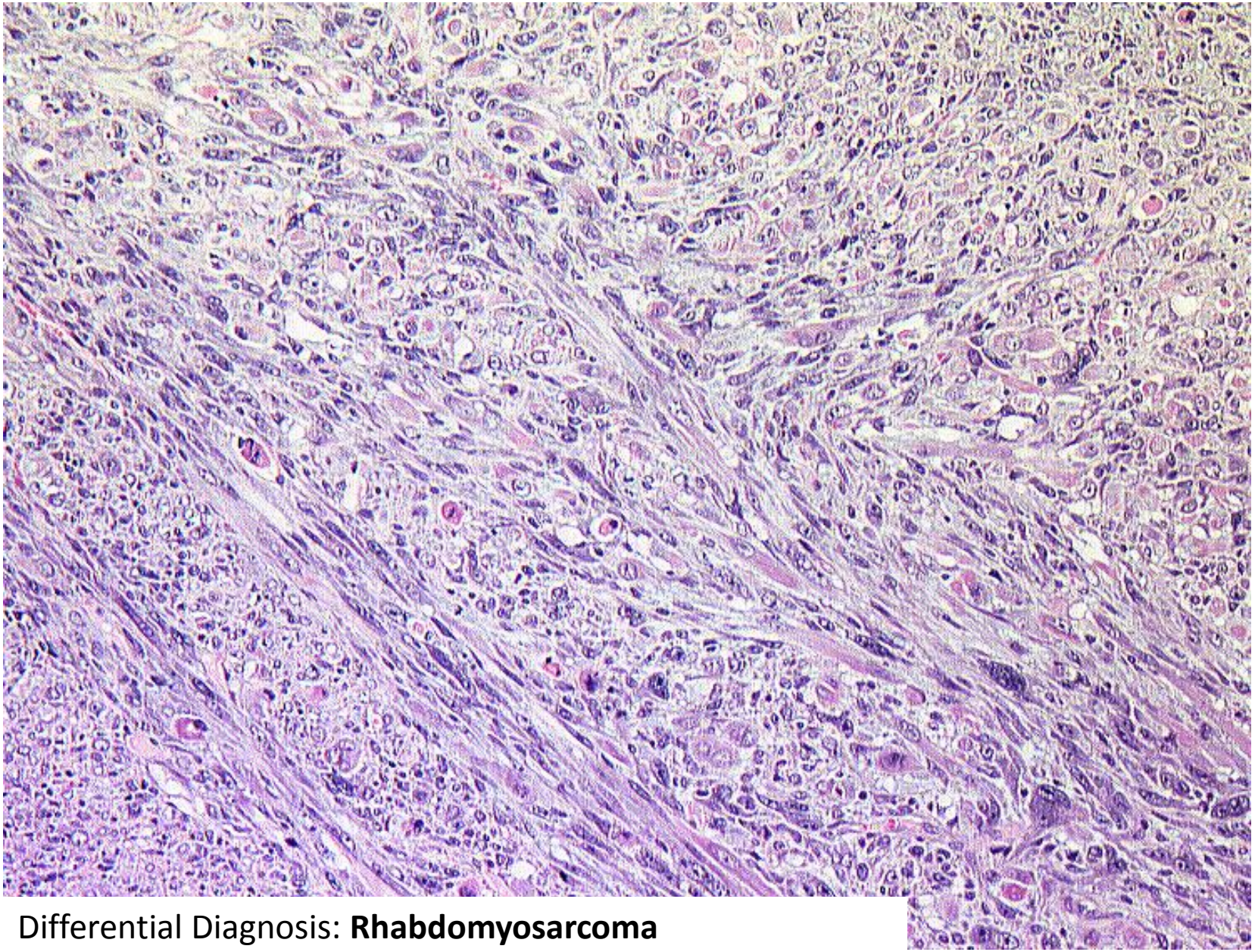
"Rare Tumours in Laboratory Animals ", Paul-Georg Germann







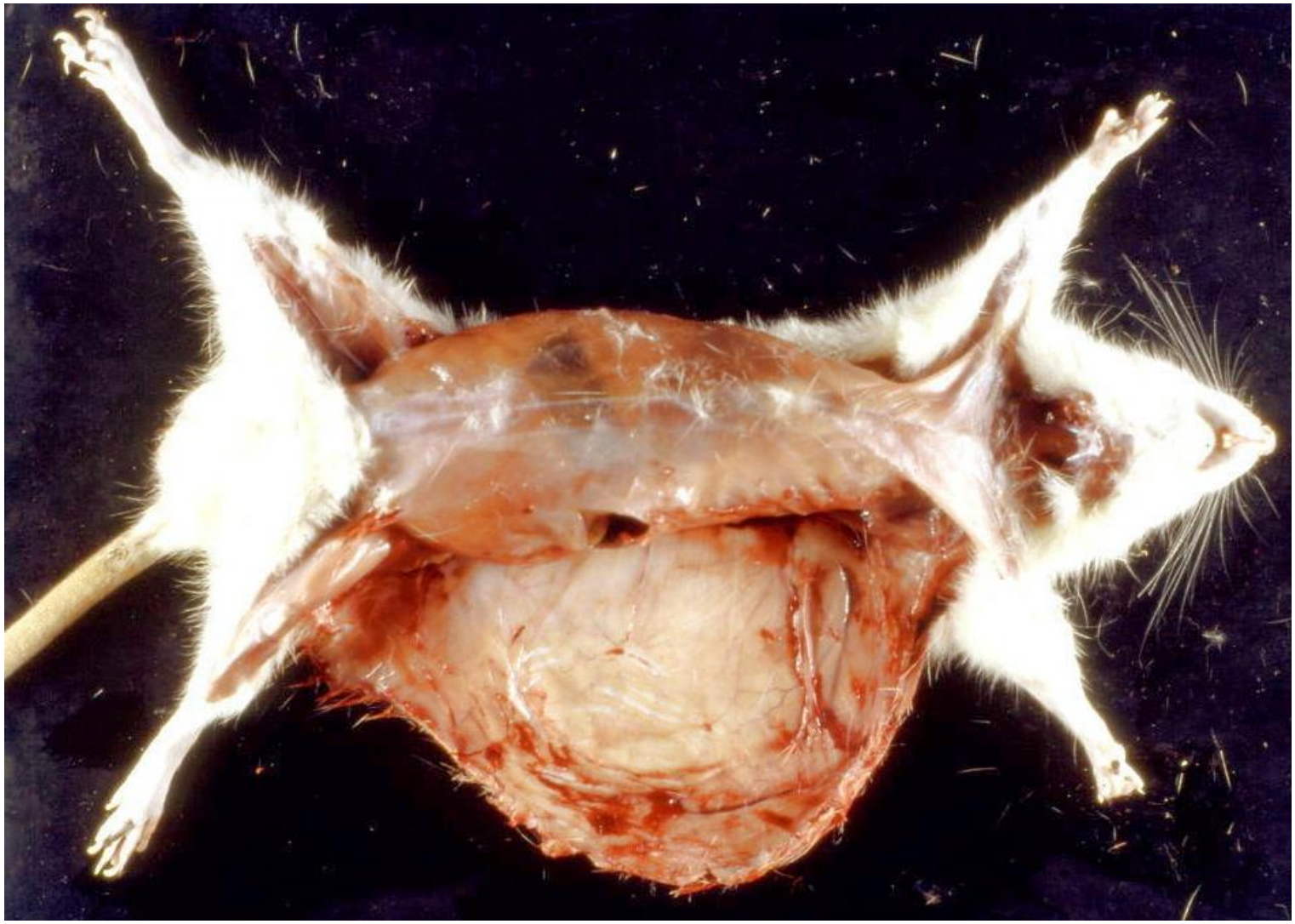
Embryonal Rhabdomyosarcoma



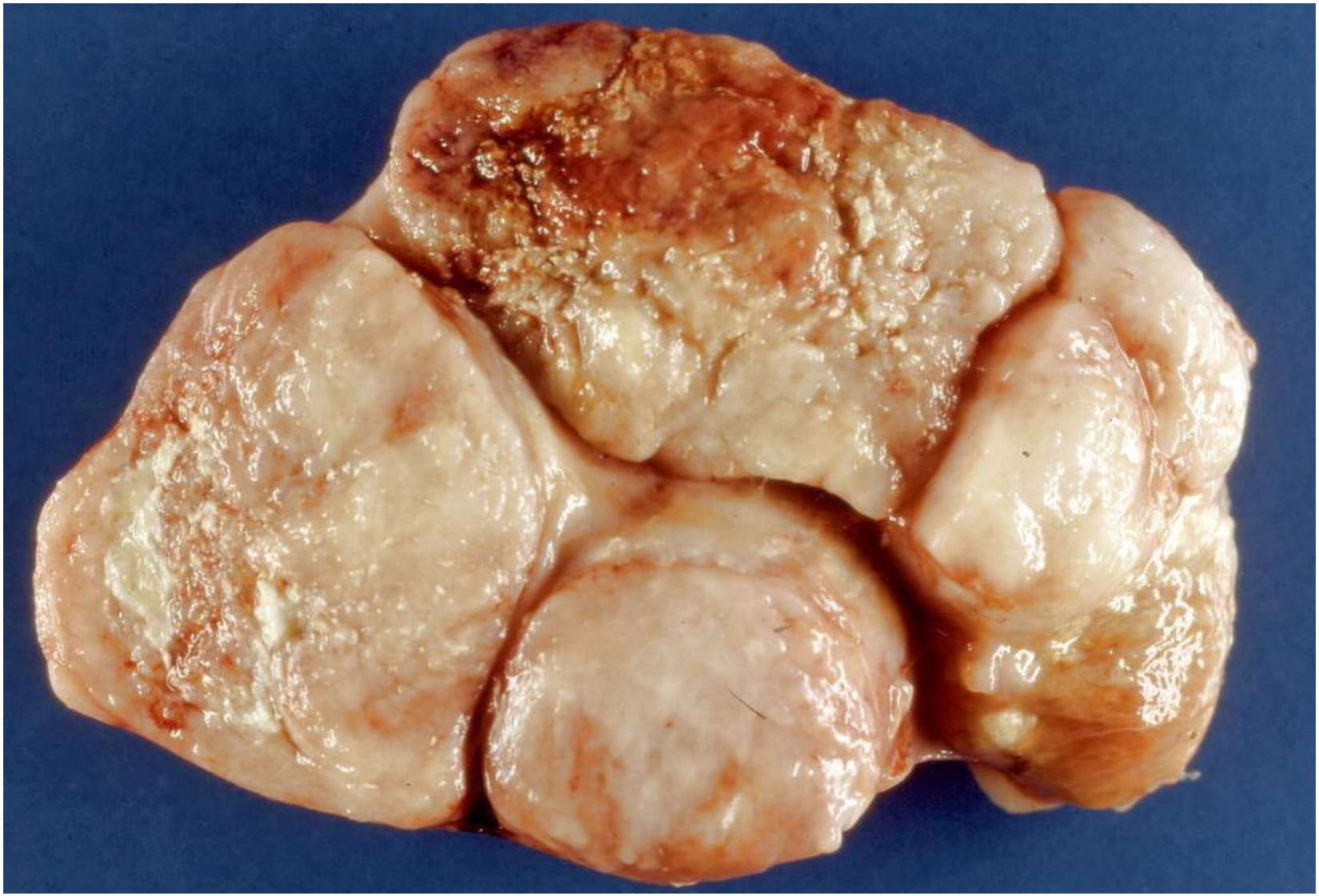
Differential Diagnosis: **Rhabdomyosarcoma**

Three rare spontaneous lesions of the muscolo-skeletal system& soft tissue

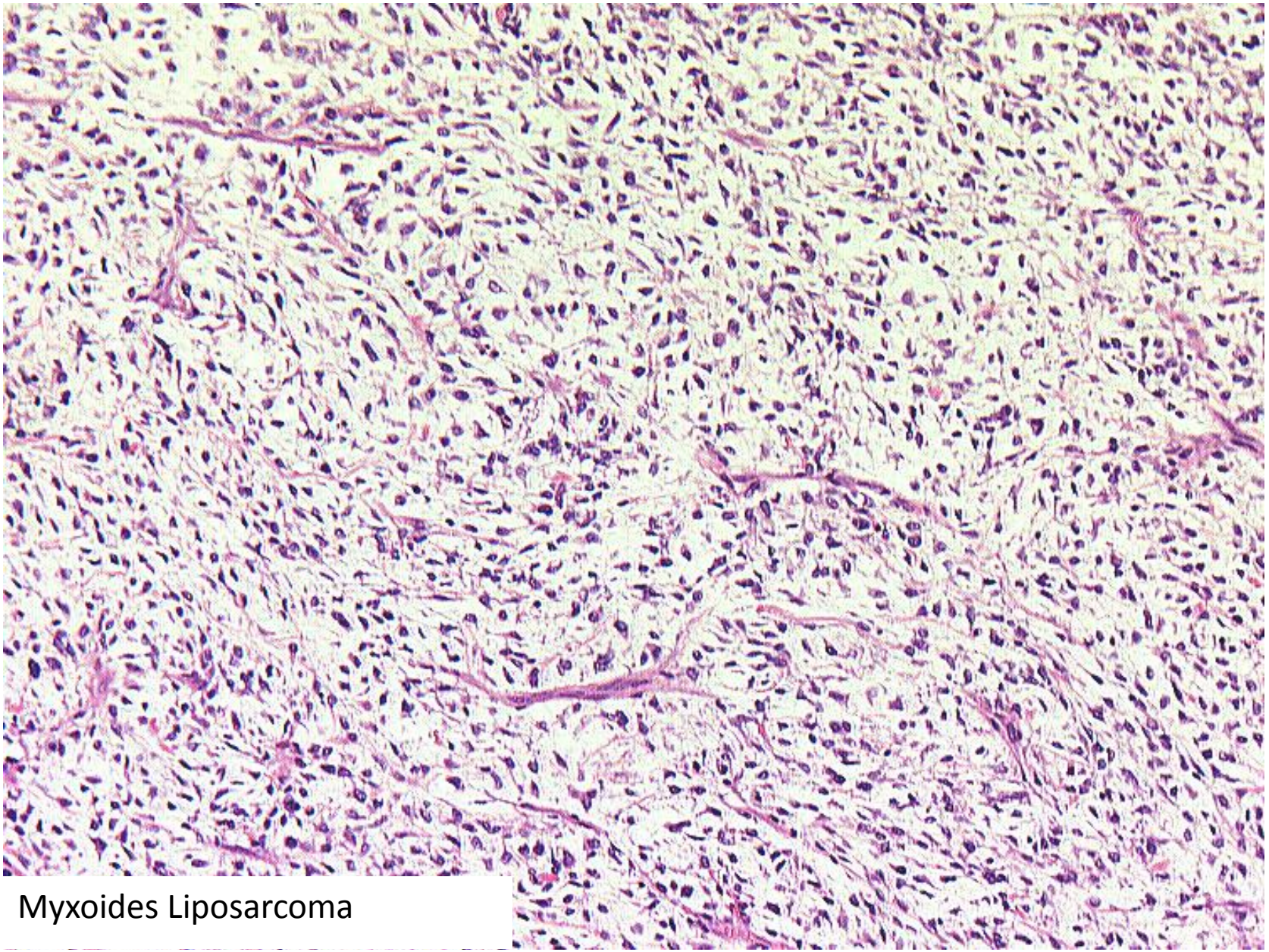
Myxoid Liposarcoma



Myxoid Liposarcoma

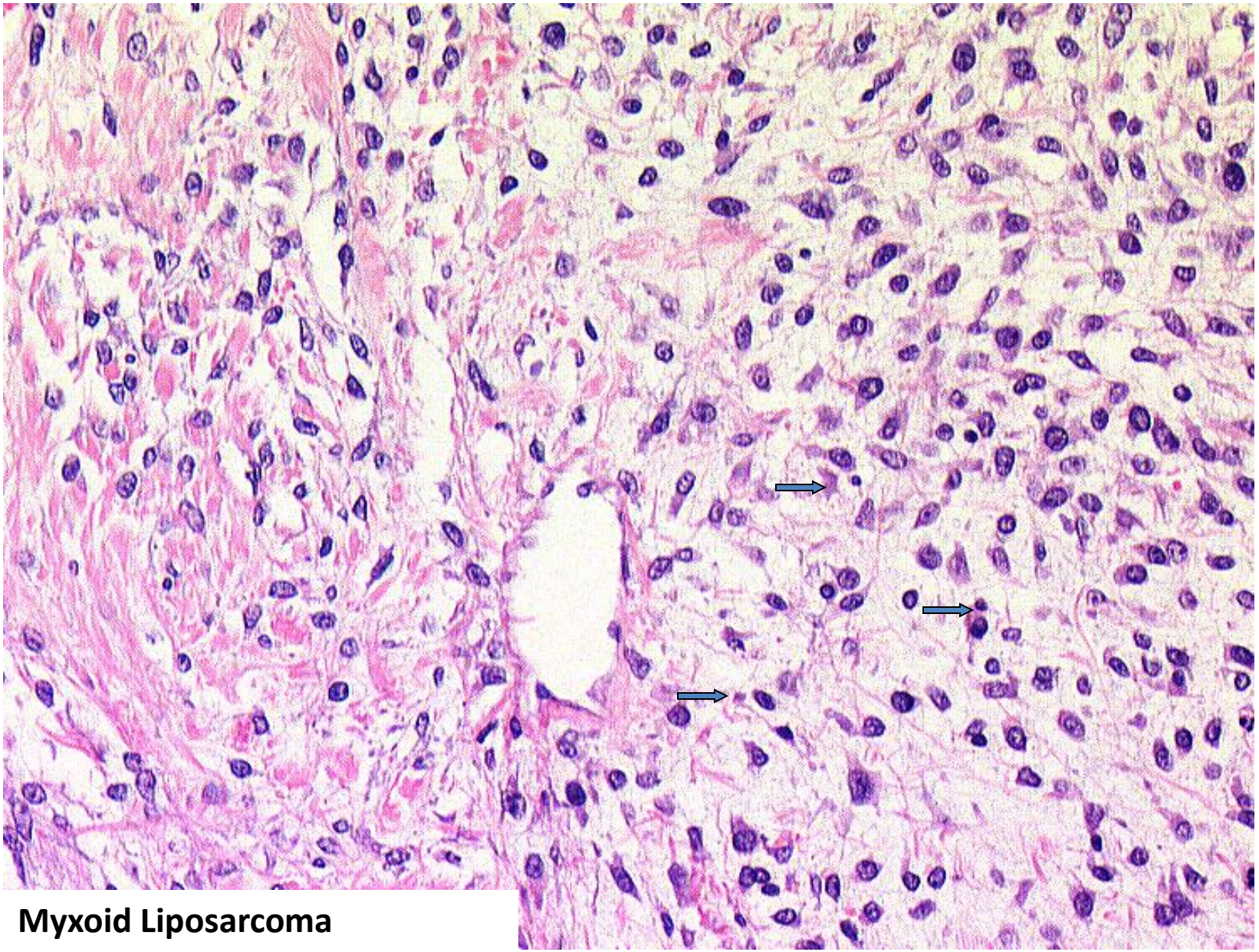


Myxoides Liposarcoma

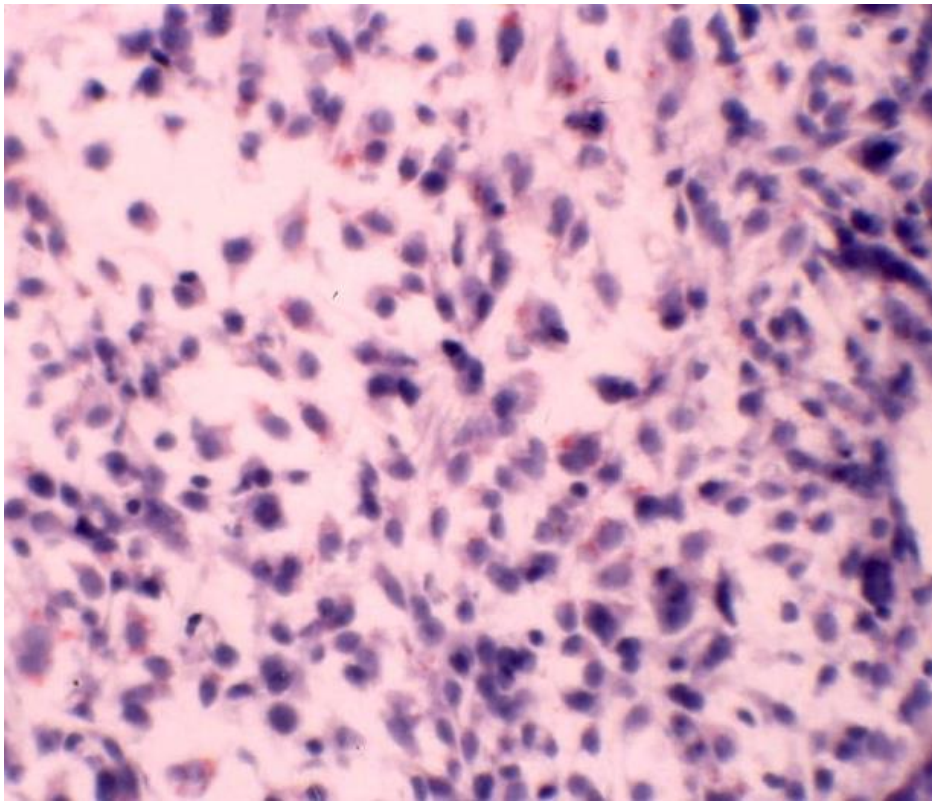


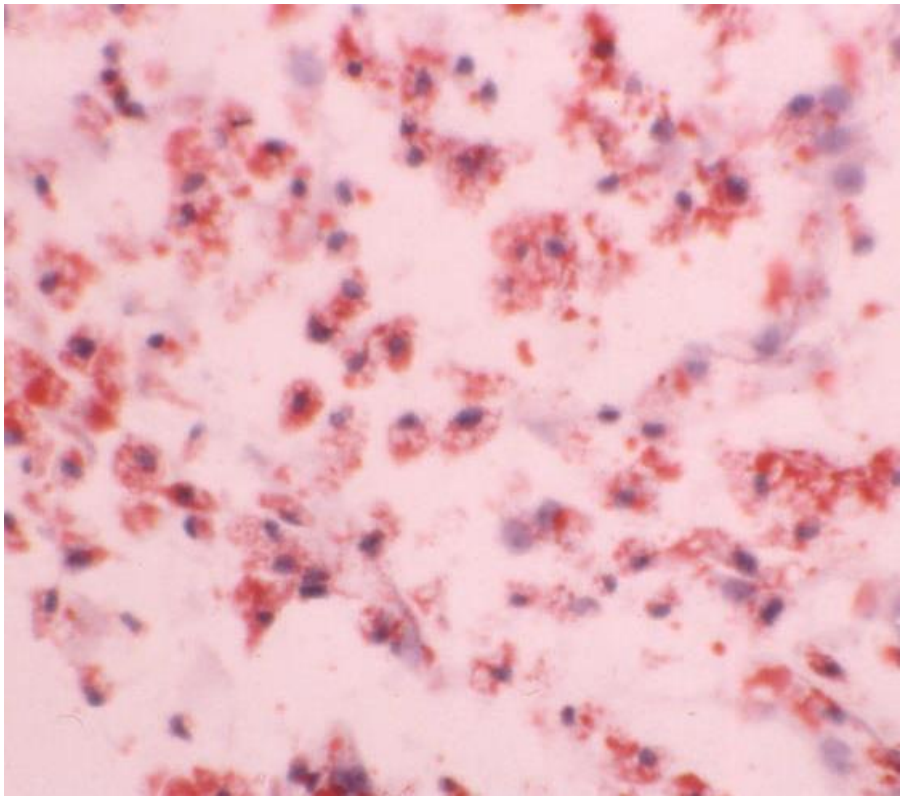
Myxoides Liposarcoma

"Rare Tumours in Laboratory Animals ", Paul-Georg Germann



Myxoid Liposarcoma

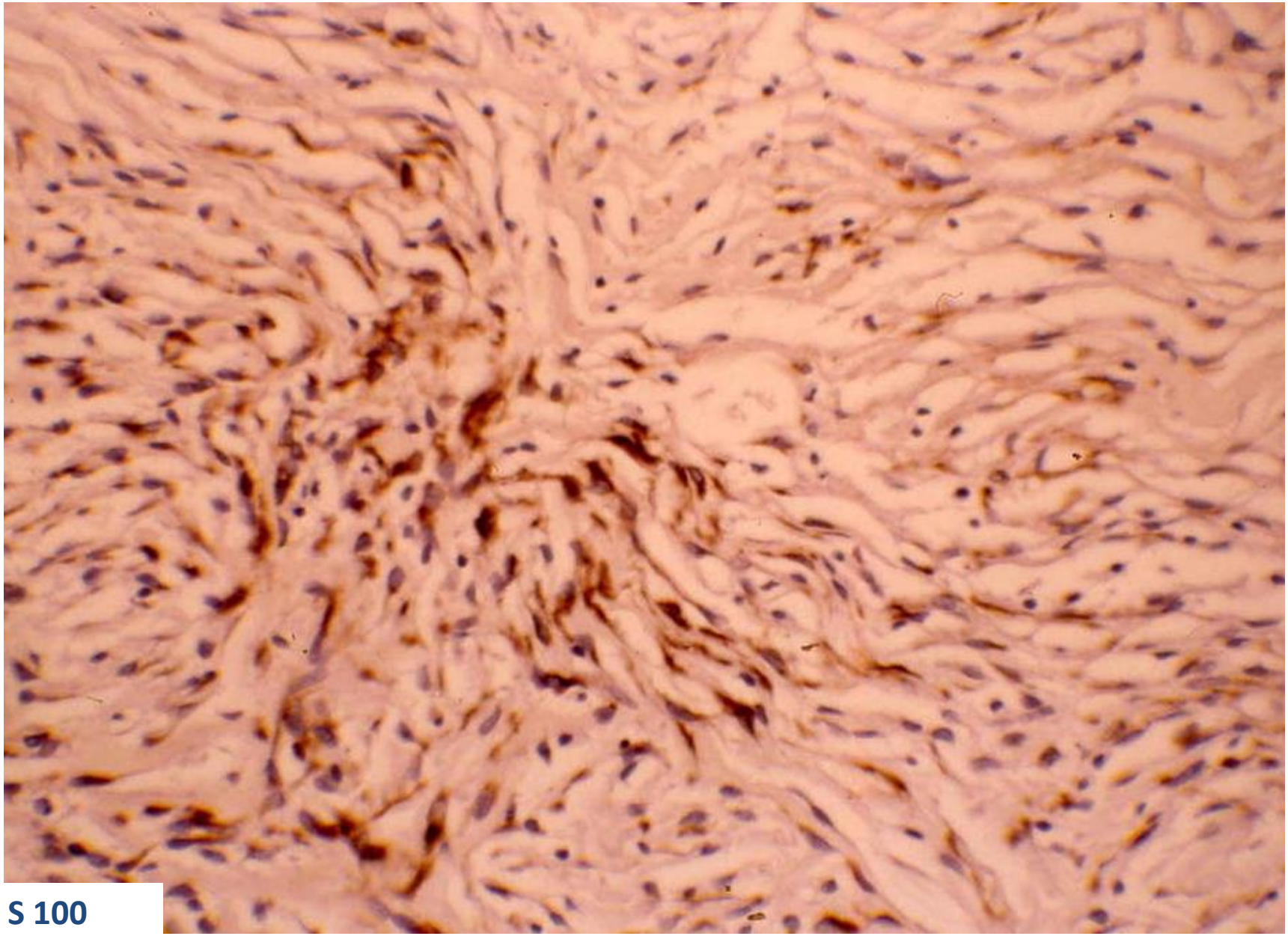




Fat stain: Oil red

Myxoid Liposarcoma

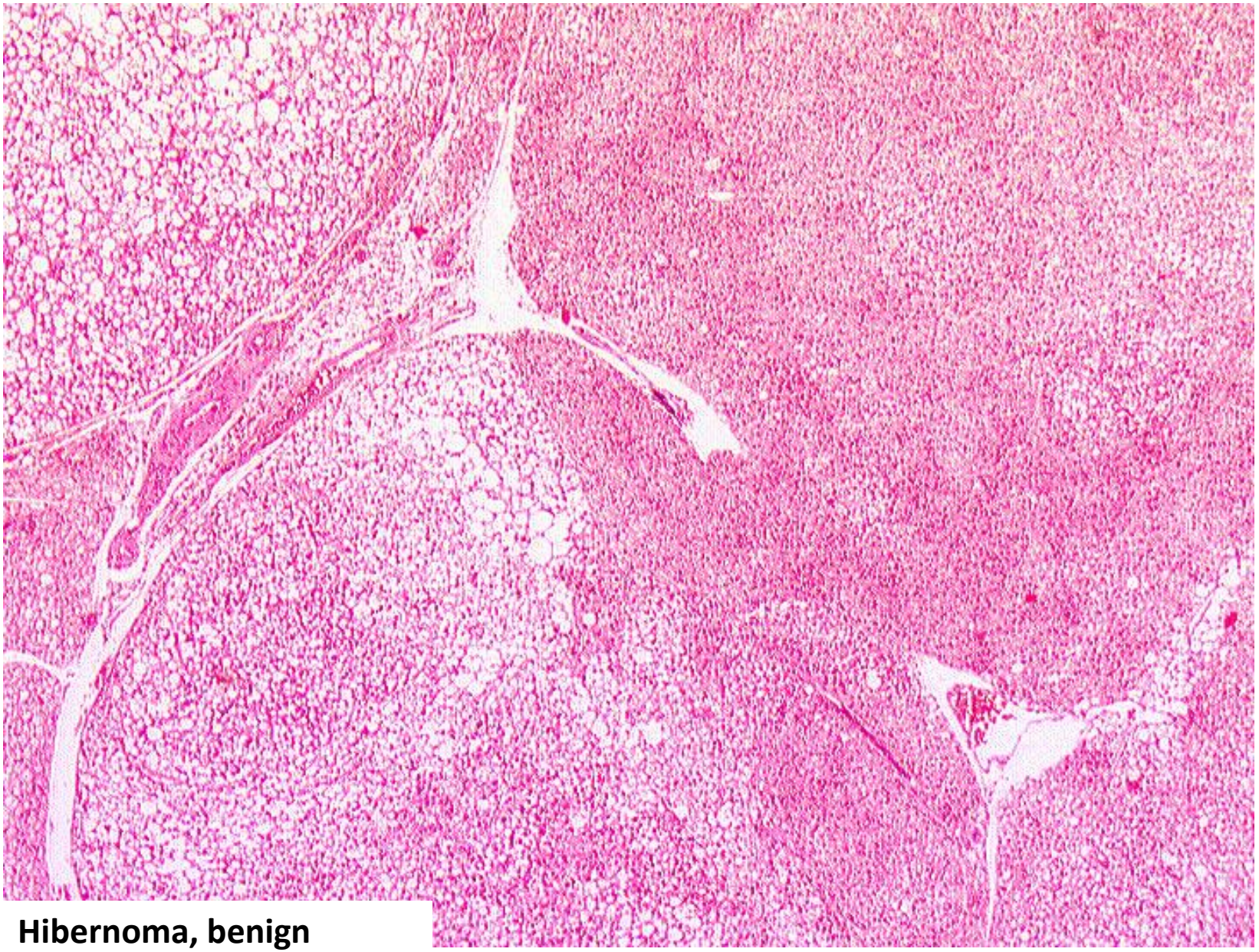
Liposarcoma (other case)



S 100

Three rare spontaneous lesions of the muscolo-skeletal system& soft tissue

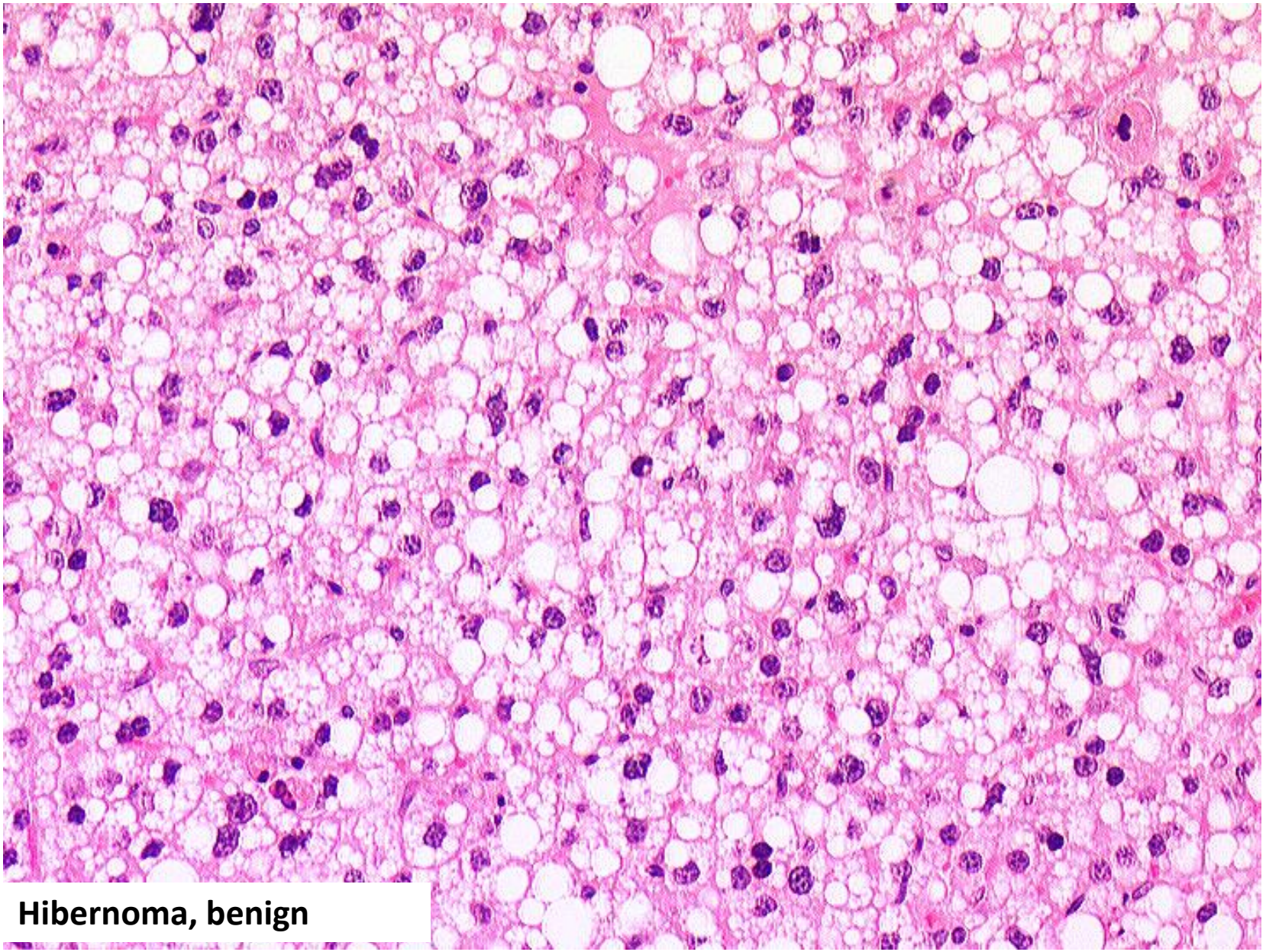
Hibernoma



Hibernoma, benign

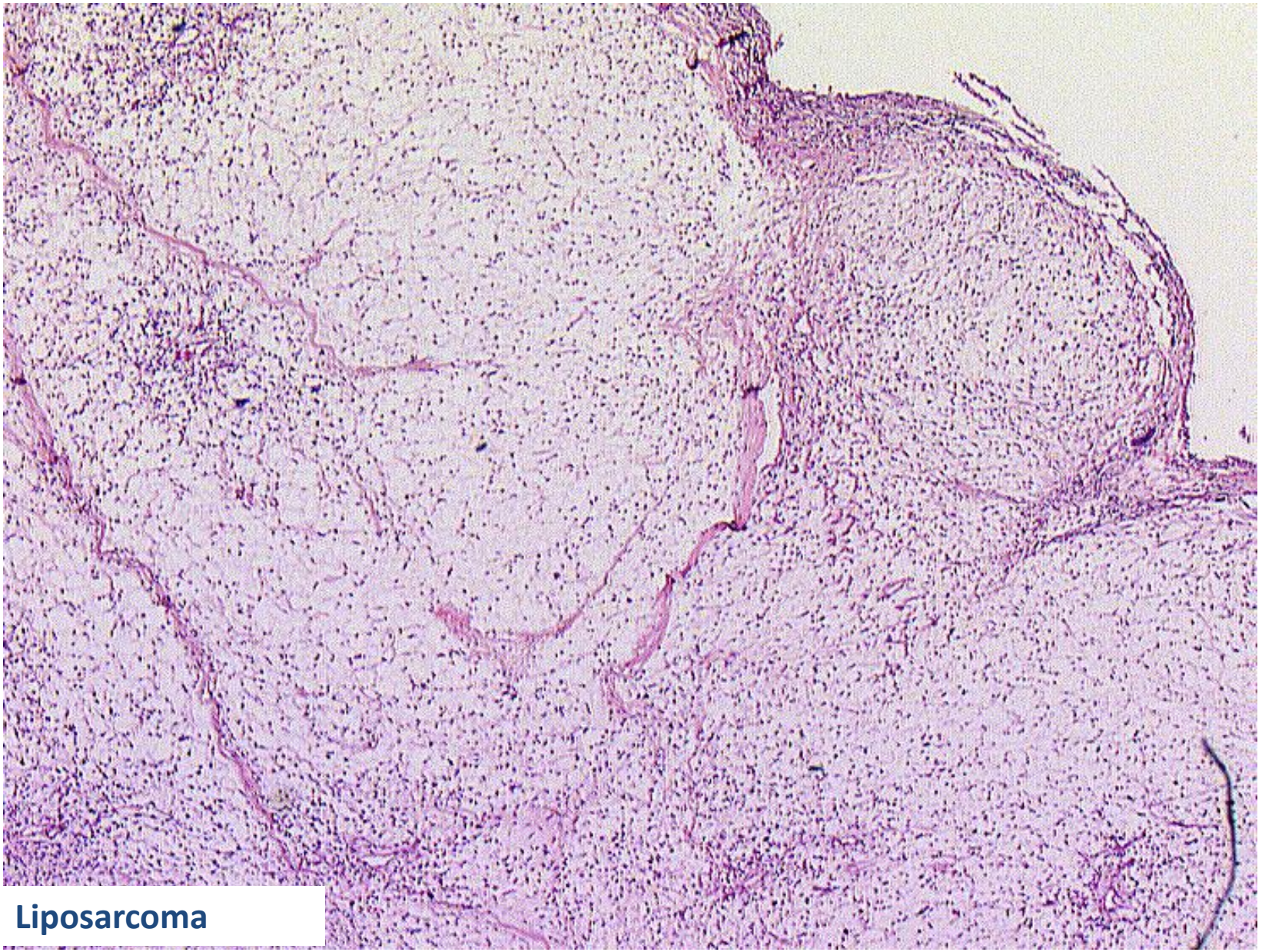
"Rare Tumours in Laboratory Animals ", Paul-Georg Germann

Hibernoma, benign

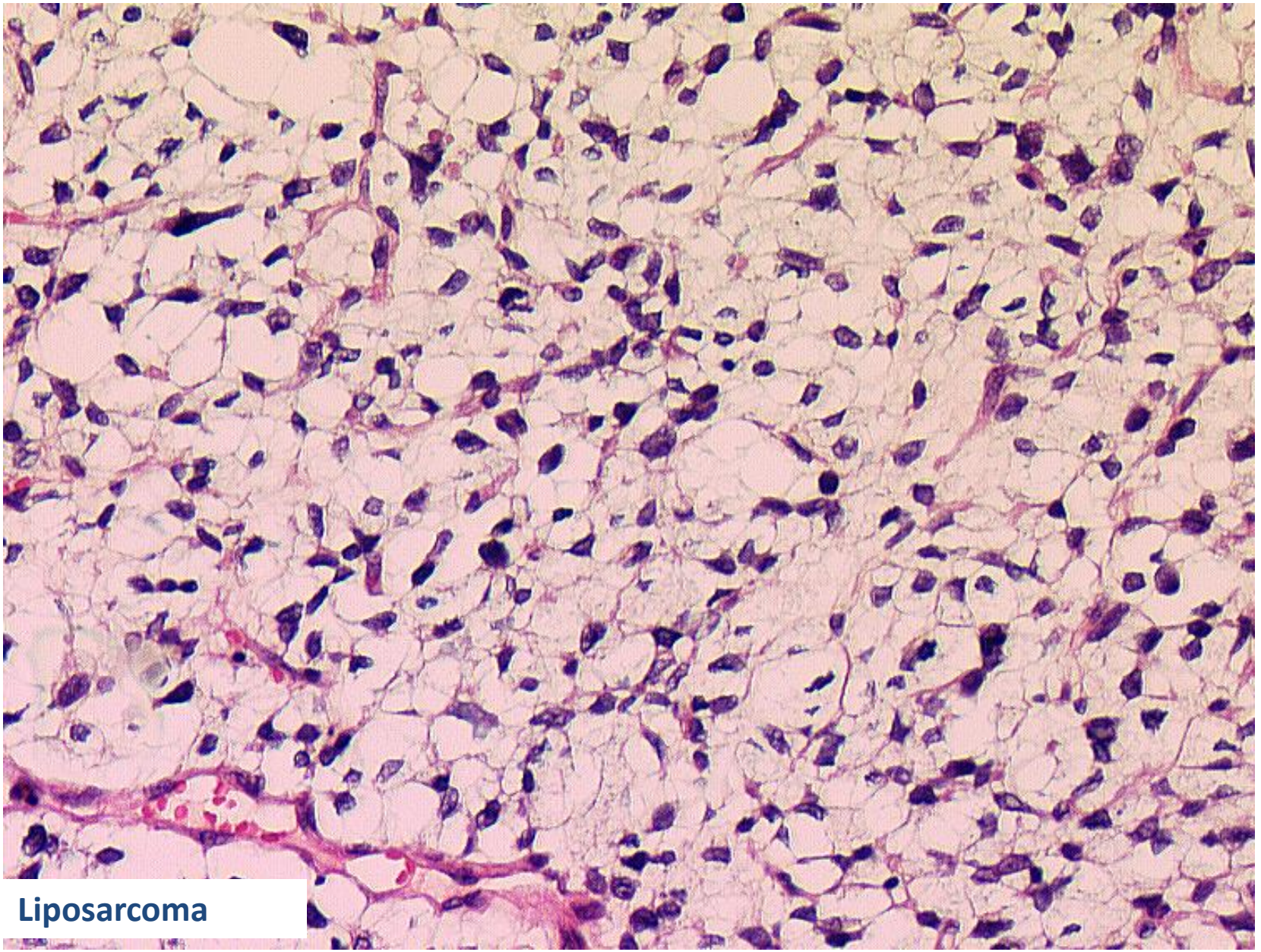


Hibernoma, benign

Differential diagnosis: Liposarcoma



Liposarcoma



Liposarcoma

Why I am showing you these spontaneous cases ?

Brown adipose tissue and effects on the morphology

E. Atzpodien, R. Neff, T. Singer, M. Albassam, B. Lenz

F. Hoffmann-La Roche Ltd.

10th European Congress of Toxicologic Pathology
Stresa, September 11 – 14, 2012

1: Compound class: PPARγ agonist

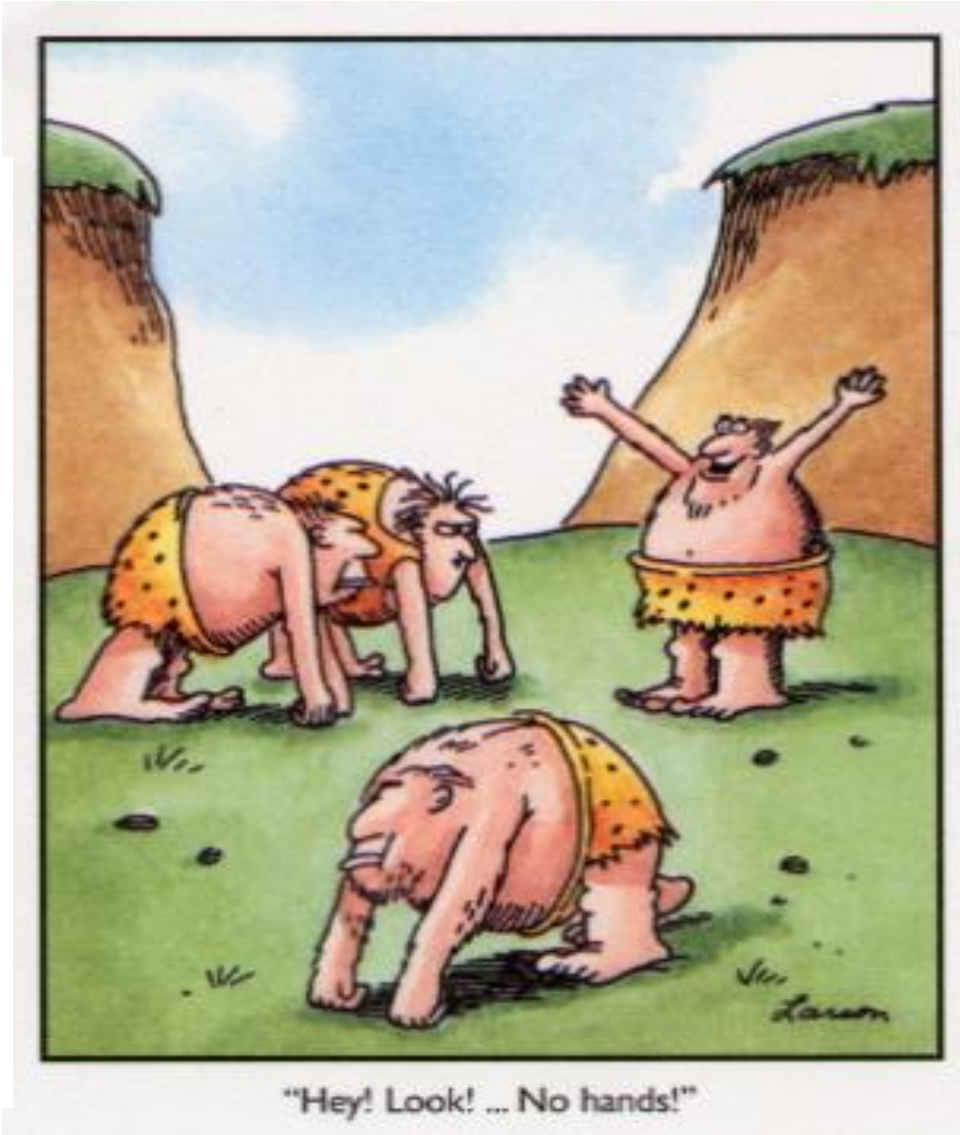
2: Diagnostic Criteria http://www.goreni.org/

I promised you pictures:

You have seen in total **70 pictures,** from macro to electrone microscopy !

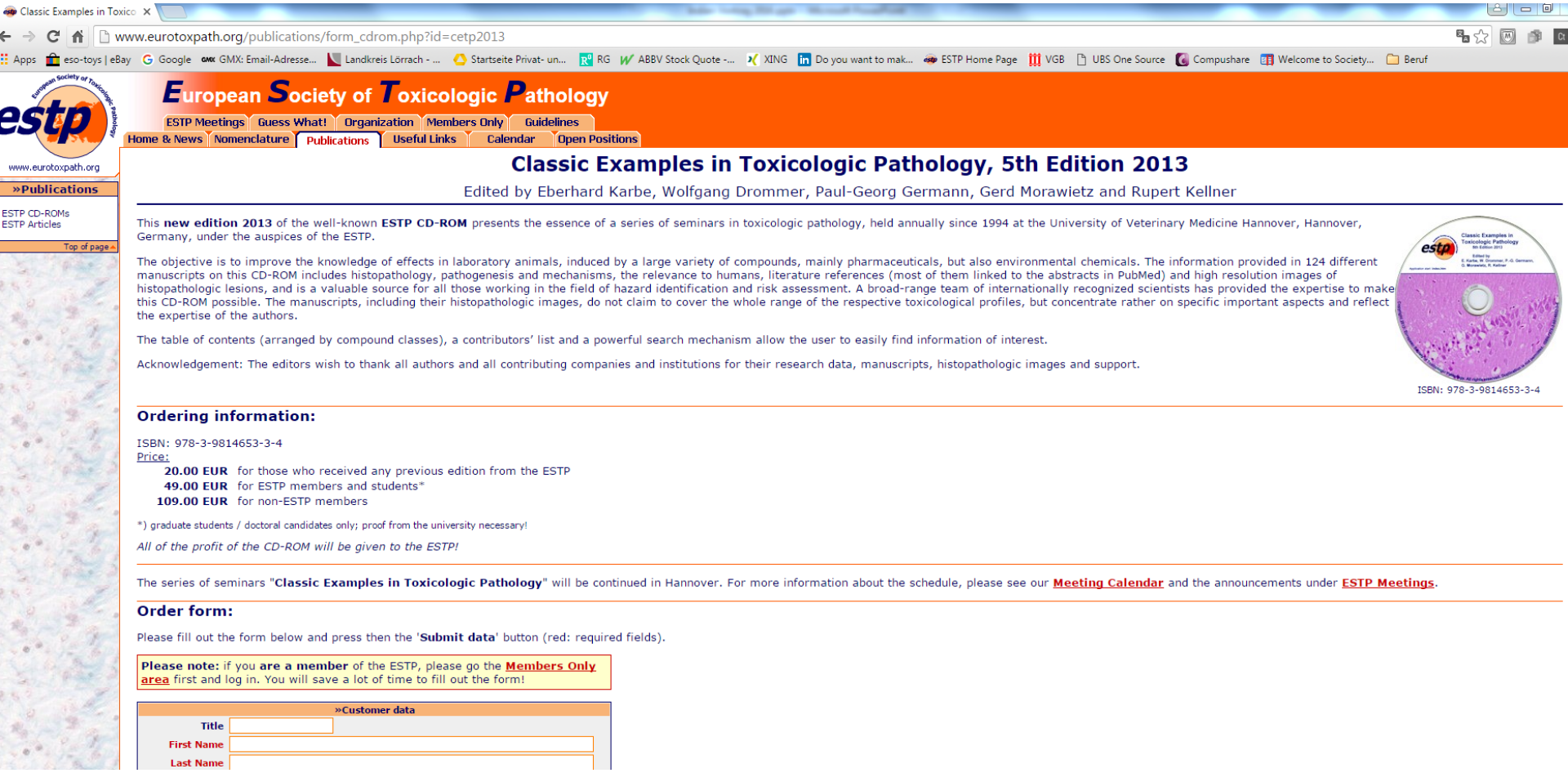
Take home message:

- **Differentiate between safety & pharmacology related effects**
- **Be curious, develop yourself**
- **Livelong learning is key**
- **Have fun with all what you do !**



"Hey! Look! ... No hands!"

Acknowledgement



Classic Examples in Toxico

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Classic Examples in Toxicologic Pathology, 5th Edition 2013

Edited by Eberhard Karbe, Wolfgang Drommer, Paul-Georg Germann, Gerd Morawietz and Rupert Kellner

This **new edition 2013** of the well-known **ESTP CD-ROM** presents the essence of a series of seminars in toxicologic pathology, held annually since 1994 at the University of Veterinary Medicine Hannover, Hannover, Germany, under the auspices of the ESTP.

The objective is to improve the knowledge of effects in laboratory animals, induced by a large variety of compounds, mainly pharmaceuticals, but also environmental chemicals. The information provided in 124 different manuscripts on this CD-ROM includes histopathology, pathogenesis and mechanisms, the relevance to humans, literature references (most of them linked to the abstracts in PubMed) and high resolution images of histopathologic lesions, and is a valuable source for all those working in the field of hazard identification and risk assessment. A broad-range team of internationally recognized scientists has provided the expertise to make this CD-ROM possible. The manuscripts, including their histopathologic images, do not claim to cover the whole range of the respective toxicological profiles, but concentrate rather on specific important aspects and reflect the expertise of the authors.

The table of contents (arranged by compound classes), a contributors' list and a powerful search mechanism allow the user to easily find information of interest.

Acknowledgement: The editors wish to thank all authors and all contributing companies and institutions for their research data, manuscripts, histopathologic images and support.

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The series of seminars "**Classic Examples in Toxicologic Pathology**" will be continued in Hannover. For more information about the schedule, please see our **Meeting Calendar** and the announcements under **ESTP Meetings**.

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