CONTINUING EDUCATION IN TOXICOLOGIC PATHOLOGY
REPRODUCTIVE SYSTEM

ORGANIZED BY SOCIETY FOR TOXICOLOGIC PATHOLOGY IN INDIA (STPI)

OCTOBER 29-31, 2010

The Atria Hotel, # 1, Palace Road, Bangalore - 560 001
Non proliferative lesions of Male reproductive system in rats

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Aurigene Discovery Technologies Limited
Bangalore, Hyderabad, Kuala Lumpur
End result - Disruption of spermatogenesis
Spermatogonia death
Spermatogonia degeneration

Progression of Drug-Induced Testicular Toxicity, Daniel Morton, *Toxicol Pathol* 1999; 27; 380
Pachytene spermatocyte death
Round spermatid death
Round spermatid death
Syncitial cells
Loss of Germ Cell Layer
Meiotic germ cell death
Meiotic germ cell death
Vitamin A deficiency

(e) Cross section of a seminiferous tubule, 10 days after retinol-acetate treatment, showing B spermatogonia in mitosis.

(f) Cross section of seminiferous tubules 41 days after retinol acetate treatment, all in epithelial stage XII.

The Origin of the Synchronization of the Seminiferous Epithelium in Vitamin A-Deficient Rats after Vitamin A Replacement, ANS M.M. VAN PELT1 and DIRK G. DE ROOIJ, BIOLOGY OF REPRODUCTION 42, 677-682 (1990) 677
Detection of cell death

Spermatogonia (thin arrows), primary spermatocytes in different stages (thick arrows) and round spermatids (arrowheads) are TUNEL-positive. A giant multinucleated cell derivative from round spermatids (white arrow) is also positive.

Structural alterations in the seminiferous tubules of rats treated with immunosuppressor tacrolimus, Breno H Caneguim, *Reproductive Biology and Endocrinology* 2009, 7:19
Testes - Germ cell toxicity

- Almost and always - Cell specific and Stage specific
- Death is predominantly through apoptosis
  - Spontaneous or induced
- Cell death and phagocytosis can be complete within 24 hours - Cell depletion
- **Spermatogonia** death in stage XI-XIV and stage I
- Stem cell spermatogonia are less vulnerable
  - Early stages - base of tubule
  - Later stages - round up and slightly displaced from base of tubule
  - Stains heavily
  - Busulfan, Bleomycin
- Phagocytosed by sertoli cells
- No clear example of arrest of cell
- Temporary arrest – Vitamin A deficient rats - A1 spermatogonia
- Short duration, reversal on retinol administration, synchronisation
Testes - Germ cell toxicity

- **Primary spermatocyte** degeneration
  - 2 Methoxy Ethanol, Dinitropyroles

- Preleptotene spermatocytes – Base of tubules
  - Pyknotic and densely stained

- Leptotene and zygotene spermatocytes – no reports

- Pachytene spermatocyte - Easy to identify - Stage VII
  - Cells shrink, unstained crescentic intracellular space around portion of surface or full

- Spermatocyte degeneration in metaphase of second meiotic division – Stage XIV
  - Seen on normal animals
  - Characteristic feature - both chromosome and spindle fibers stain intensely
  - Microtubule destructing agents - Colchecine, Vinblastine, Taxol

- **Round spermatids** – Step 7 at Stage VII
  - Developing acrosome - pyknotic, distorted, irregularly infolded nucleus
  - Cytoplasm intensely stained as degeneration progresses
  - Acrosomal contents less heavily stained
  - Multinucleate syncytium (Symplast, multinucleate giant cell) – less rapidly phagocytosed by sertoli cells
  - Ethane methane sulphonate, Methyl Chloride
Testes - Germ cell toxicity

- Elongating spermatids- Step 19-Stage VII
  - Characteristic shape
  - Position near tubular lumen
  - Increase in density of entire cell
  - Boric acid, Dibromo Acetic acid

- Blood vessels damage - irreversible
  - Cadmium Chloride, 5 Hydroxytryptamine, Histamine

- Sertoli cells are highly resistant for cell death

- slow cycling stem cell spermatogonia more resistant than differentiating (committed) spermatogonia

- spermatogonia basal compartment (outside the blood-tubule barrier) are exposed to any xenobiotic that enters the interstitial fluid, spermatocytes, which also undertake DNA synthesis and meiotic division are protected by blood testis barrier
Sperm retention
Sperm release defect
Spermatid retention – Stage VIII
Spermatid retention – Stage XII
Residual body defects
Sperm release defects

- Retention of step 19 spermatids in stage VIII-XII
  - Luminal
  - Basal
  - Can it be in any other stage?
- Retained spermatids per sertoli cell
- Defect in spermatid or defect in sertoli cell
  - Even good spermatozoa can be retained and phagocytosed—Hormone deprivation
- Residual bodies
- Decent and phagocytosis—stage 9-11
  - Stage 12 with spermatid retention?
- Formation and behaviour of residual body can be altered
  - Abnormal shape, size
  - Tubular lumen and epididymal lumen
Sertoli Cell Vacuolation
Tubular Vacuolization
Sertoli Cell

- Sustentacular cell or Nursing cell
  - Blood testes barrier - tight sertoli - sertoli junction
- Vacuolation – Single or Multiple or Microvacuolation
  - Dilatation of smooth endoplasmic reticulum
  - Fixation artifact - osmotic shrinkage at basement membrane
- Rate of phagocytosis differ throughout the cycle or is affected by treatment
- Death and depletion of sertoli cells is rare - ischemia
  - Pthalaate esters, 2,5 hexanedione, 1,3 dinitrobenzene - first affected
- Number of unique structures and functions of sertoli cell are targets - Protein and fluid secretion, cytoskeletal alterations, metabolic disturbances
Germ cell exfoliation
Focal exfoliation
Sertoli and Germ Cell exfoliation

- Shearing of sertoli cell cytoplasm by cytoskeletal disrupting agents
- Loss of adhesion b/n sertoli cell and germ cell
- Breakage of intercellular bridges
- Effect of prolonged treatment
- Trauma, handling and cutting of testis before fixation

- Hormones of lack of hormones do not affect spermatogenesis by speeding up or retarding germ cell development
Morphometry

Fig. 3. Diameter of the seminiferous tubule, and volume of the epithelium and the lumen per unit length of seminiferous tubule at various stages of the cycle. Each value represents the mean of four animals (± SEM).

<table>
<thead>
<tr>
<th>Stages</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
<th>IX</th>
<th>X</th>
<th>XI</th>
<th>XII</th>
<th>XIII</th>
<th>XIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>13.7</td>
<td>5.3</td>
<td>2.3</td>
<td>4.9</td>
<td>6.8</td>
<td>7.5</td>
<td>20.9</td>
<td>7.6</td>
<td>3.0</td>
<td>3.2</td>
<td>3.0</td>
<td>8.7</td>
<td>6.2</td>
<td>6.8</td>
</tr>
<tr>
<td>SE</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.5</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.5</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>
*Total number of seminiferous tubules examined was 9672; one testicular cross section per rat.


Fig. 4. Number of various categories of cells per unit length of the seminiferous tubule at successive stages of the cycle. There is no significant difference in cell number for a given category between any two stages.
Normal Stage XIV
Tubular contraction- Stage XIV
Testicular Atrophy
Sertoli only tubules - Agenesis
Focal Tubular Atrophy
Testis - Oligospermia
Sertoli only tubules
Rete Testis – Cellular debris
Dilated Rete

Theophylline-treated rat testis with sperm stasis (S) within the rete testis. The tubular atrophy (A) vascular inflammation (V) of testicular vessels.

Overview of Male Reproductive Pathology, George L. Foley, *Toxicol Pathol* 2001; 29; 49
Semineferous tubule

- Atrophy/contraction
- Reduction in overall diameter of tubule
  - Germ cell depletion
  - Reduced secretion of seminiferous tubule fluid - Sertoli cell (1 µL/hour)
  - Varies with stage of spermatogenesis - Testosterone dependant
  - Fluid secretion - Presence of elongating and elongated spermatids

- Tubular dilation
- Increase in overall diameter of tubule
  - Increased secretion by sertoli cell?
  - Reduced expulsion of fluid from tubule - contractile peritubular cells
  - Reduced reabsorption of fluid by the epithelial cells of rete and efferent ducts
  - Obstruction of outflow

- Inspissated sperm granulomatous inflammation
Semineferous tubule

- Vacuolation
- Focal tubular atrophy
- Oligospermia
- Mineralisation
- Sertoli only tubule
  - Cadmium, Ischemia, Serotonin, histamine
- Necrosis involves Leydig cells and peritubular cells

- Dilated rete
  - Obstruction
  - Cellular debris
Leydig cell Hypertrohy/plasia
Leydig cells

- **Atrophy**
  - Reduced LH secretion

- **Hypertrophy/Hyperplasia**
  - increased stimulation by LH
  - Qualitative
  - Only in marked changes

- **Degeneration and necrosis is rare**
  - Ethane dimethasone sulphonate, Lansaprazole
  - Regeneration thro fetal type Leydig cells

- **Tissue resident macrophages- 20% of interstitial space**
# Table 2.—Cell-specific toxicants of the male reproductive tract.

<table>
<thead>
<tr>
<th>Target cell</th>
<th>Toxicant</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leydig cell</td>
<td>Ethanedimethane sulfonate</td>
<td>Leydig cell necrosis with secondary germ cell death and depletion and atrophy of secondary sex organs</td>
</tr>
<tr>
<td></td>
<td>Lansoprazole</td>
<td>Inhibition of testosterone synthesis with secondary Leydig cell tumor induction</td>
</tr>
<tr>
<td>Sertoli cell</td>
<td>Phthalate esters, 2,5-hexanedione</td>
<td>Sertoli cell vacuoles with secondary germ cell death and exfoliation</td>
</tr>
<tr>
<td>Spermatogonia</td>
<td>Busulfan, bleomycin</td>
<td>Spermatogonial death with secondary depletion of post spermatogonial germ cells</td>
</tr>
<tr>
<td>Spermatocytes</td>
<td>2-methoxyethanol, dinitro pyrroles</td>
<td>Spermatocyte death with secondary depletion of post spermatocyte germ cells</td>
</tr>
<tr>
<td>Round spermatids</td>
<td>Ethylmethane sulfonate, methyl chloride</td>
<td>Spermatid death with secondary depletion of post spermatid germ cells</td>
</tr>
<tr>
<td>Elongated spermatids</td>
<td>Boric acid, dibromoacetic acid</td>
<td>Retention and phagocytosis of step 19 spermatids, abnormalities in released sperm</td>
</tr>
<tr>
<td>Testicular blood vessels</td>
<td>Cadmium chloride</td>
<td>Endothelial necrosis with secondary ischemic necrosis of all cell types</td>
</tr>
<tr>
<td></td>
<td>5-hydroxytryptamine, histamine</td>
<td>Reduced blood flow, with secondary anoxic damage ranging from oncotic necrosis of the seminiferous epithelium to germ cell apoptosis and depletion</td>
</tr>
<tr>
<td>Epididymal epithelium</td>
<td>α-chlorohydrin (high doses)</td>
<td>Inhibits fluid resorption and causes edema of the caput resulting in sperm granulomas</td>
</tr>
<tr>
<td></td>
<td>Methyl chloride</td>
<td>Epithelial necrosis resulting in sperm granulomas</td>
</tr>
<tr>
<td></td>
<td>Carbendazim</td>
<td>Efferent duct necrosis resulting in sperm granulomas</td>
</tr>
<tr>
<td>Epididymal sperm</td>
<td>α-chlorohydrin (low doses), deoxychlo-ro-glucone</td>
<td>Inhibition of glycolysis resulting in sperm immotility</td>
</tr>
<tr>
<td>Vas deferens</td>
<td>Guanethidine</td>
<td>Inhibition of ejaculation due to adrenergic ganglion blockade resulting in rupture of vas-epididymal junction and sperm granulomas</td>
</tr>
<tr>
<td>Prostate and seminal vesicles</td>
<td>Flutamide</td>
<td>Androgen receptor blockade resulting in secretory inhibition and atrophy</td>
</tr>
<tr>
<td></td>
<td>Finasteride</td>
<td>Inhibition of dihydrotestosterone production from testosterone resulting in secretory inhibition and atrophy</td>
</tr>
</tbody>
</table>

Dianne M. Creasy, Pathogenesis of Male Reproductive Toxicity, Toxicol Pathol 2001; 29; 64
Reversibility

- Spermatogenesis: Generally reversible as spermatogonial cell population is relatively resistant- Dormant for long period of time
- Leydig cells damaged- irreversible
- Sertoli cell injury- mild- fully reversible
- Sertoli cell destroyed- regeneration not possible
  - Do not divide in adults
  - Markedly resistant
- Epididymis- Granuloma is not reversible
- Prostate, Seminal vesicles generally reversible
- Dependant on site and severity of insult
### Incidence of Nonneoplastic Lesions in Historical Control Male and Female Fischer-344 Rats from 90-Day Toxicity Studies


#### TABLE I.—Incidence of nonneoplastic lesions in control male and female Fischer-344 rats.

<table>
<thead>
<tr>
<th></th>
<th>Feed</th>
<th>Inhalation</th>
<th>Gavage</th>
<th>Combined incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 80 M (%)</td>
<td>n = 79 F (%)</td>
<td>n = 40 M (%)</td>
<td>n = 40 F (%)</td>
</tr>
<tr>
<td>Urogenital system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney #Ex=†</td>
<td>80</td>
<td>79</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>77 (96.3)</td>
<td>17 (21.5)</td>
<td>29 (72.5)</td>
<td>4 (10.2)</td>
</tr>
<tr>
<td>Mineralization</td>
<td>0</td>
<td>72 (91.1)</td>
<td>0</td>
<td>29 (74.4)</td>
</tr>
<tr>
<td>Urinary bladder #Ex=</td>
<td>80</td>
<td>79</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Mineralization, suberosal</td>
<td>2 (2.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ovary #Ex=</td>
<td>0</td>
<td>79</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Cyst, bursa</td>
<td>−</td>
<td>9 (11.4)</td>
<td>−</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Cyst, follicle</td>
<td>−</td>
<td>1 (1.3)</td>
<td>−</td>
<td>0</td>
</tr>
<tr>
<td>Uterus #Ex=</td>
<td>0</td>
<td>79</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Dilation, horn</td>
<td>−</td>
<td>7 (8.9)</td>
<td>−</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Decidual reaction</td>
<td>−</td>
<td>2 (2.5)</td>
<td>−</td>
<td>0</td>
</tr>
<tr>
<td>Clitoral gland #Ex=</td>
<td>0</td>
<td>79</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>Inflammation, mononuclear cell</td>
<td>−</td>
<td>26 (32.9)</td>
<td>−</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Preputial gland #Ex=</td>
<td>80</td>
<td>0</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Inflammation, mononuclear cell</td>
<td>25 (31.3)</td>
<td>−</td>
<td>1 (2.5)</td>
<td>10 (31.3)</td>
</tr>
<tr>
<td>Granuloma</td>
<td>0</td>
<td>−</td>
<td>1 (2.5)</td>
<td>−</td>
</tr>
<tr>
<td>Prostate gland #Ex=</td>
<td>80</td>
<td>0</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Inflammation, suppurative</td>
<td>1 (1.2)</td>
<td>−</td>
<td>0</td>
<td>−</td>
</tr>
<tr>
<td>Inflammation, mononuclear cell</td>
<td>2 (2.5)</td>
<td>−</td>
<td>0</td>
<td>−</td>
</tr>
<tr>
<td>Testis #Ex=</td>
<td>80</td>
<td>0</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Atrophy, seminiferous tubule</td>
<td>2 (2.5)</td>
<td>−</td>
<td>1 (3.3)</td>
<td>−</td>
</tr>
<tr>
<td>Hyperplasia, interstitial cell</td>
<td>1 (1.3)</td>
<td>−</td>
<td>0</td>
<td>−</td>
</tr>
</tbody>
</table>
### Table II.—Summary of testicular lesions in control male rats used for subchronic inhalation or oral toxicity studies in 1990.

<table>
<thead>
<tr>
<th>Testicular Lesions</th>
<th>Number of Study</th>
<th>Inhalation</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular lesions</td>
<td>Number of rats:</td>
<td>Number of rats with testicular atrophy:</td>
<td></td>
</tr>
<tr>
<td>Early minimal changes</td>
<td>10 10 10 10 10 10</td>
<td>3/10 3/10 2/10 4/10 1/10 1/10</td>
<td>1/1</td>
</tr>
<tr>
<td>EGB/degeneration, mature spermatids, stages I–VIII</td>
<td>— 3/3 2/2 2/4 1/1 1/1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>EGB/degeneration, elongated spermatids, stages IX–XIV</td>
<td>— 3/3 2/2 2/4 1/1 —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mature spermatid retention, stages IX–XIV</td>
<td>— 3/3 2/2 2/4 1/1 —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Early moderate changes</td>
<td>2/3 1/3 1/2 2/4 1/1 —</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Depletion, mature spermatids, stages I–VIII</td>
<td>2/3 1/3 — 3/4 1/1 1/1</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Depletion, round spermatids, stages I–VIII</td>
<td>— — — 3/4 —</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Depletion, elongated spermatids, stages IX–XIV</td>
<td>— — — —</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Advanced changes</td>
<td>— 1/3 — 2/4 —</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Degeneration, spermatocytes, stages IX–XIV</td>
<td>— 1/3 — — —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Degeneration, meiotic spermatocytes, stage XIV</td>
<td>1/3 — — —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Spermatid giant cell formation</td>
<td>1/3 — — —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sertoli cell only, 1–10 seminiferous tubules</td>
<td>1/3 — 1/2 1/4 1/1 —</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Round cell only, stages I–VIII</td>
<td>1/3 — 1/2 — —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Unilateral testicular atrophy</td>
<td>1/3 — — —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Epididymal lesions</td>
<td>— 2/10 7/10 3/10 3/1 3/10 2/10 1/1</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Exfoliated degenerative germ cells, epididymides</td>
<td>2/10 4/10 2/10 — — —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Oligospermia (decreased sperm density), epididymides</td>
<td>— — 1/10 — —</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Spermatic granuloma, epididymides</td>
<td>1/10 — — 1/10 —</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Figure 2.—Absolute organ weights for left testis (A) and epididymides (B) and relative organ weights for seminal vesicles (C) and ventral prostate (D) in rats fed AL or FR for two or six weeks. Solid bars are ad libitum feeding, open bars are food restricted; error bars = standard error of the mean.

Effects of Food Restriction on Testis and Accessory Sex Glands in Maturing Rats, SABINE REHM, TACEY E. WHITE, EIAS A. ZAHALKA, DINESH J. STANISLAUS, ROGELY W. BOYCE, AND PATRICK J. WIER, Toxicologic Pathology, 36: 687-694, 2008
**Food Restriction**

**Figure 3.** Degeneration of pachytene spermatocytes (arrows) in stage VII of the rat spermatogenic cycle. PAS reaction.

**Figure 4.** Step 19 spermatid retention and phagocytosis by Sertoli cells (arrow), as shown in stage XI of the rat spermatogenic cycle. PAS reaction.

**Figure 5.** Degeneration and loss of germinal epithelium, bilateral in a rat FR from twelve to eighteen weeks of age. PAS reaction.

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**Effects of Two Weeks of Feed Restriction on Some Common Toxicologic Parameters in Sprague-Dawley Rats**

STUART EVIN, D' AVIDSE MLERA, 'N D ZADOKR UBEN, *Toxicol Pathol* 1993; 21; 1

**Effects of Food Restriction on Testis and Accessory Sex Glands in Maturing Rats**

Post Mortem changes

Time-Dependent Changes in Post-Mortem Testis Histopathology in the Rat, Bronwyn H. Bryant and Kim Boekelheide, *Toxicol Pathol 2007; 35; 665*
Background lesions

- Fixation and tissue preparation artifacts very common
- Altered temperature of the testis
- Trauma
- Testis forced into inguinal canal and scrotum—restraint
- Stress
- Food restriction
- Common lesions
  - Atrophic tubules – 1-3 contracted tubules having only sertoli cells
  - Tubular vacuolation
  - Degeneration of germ cells
  - Syncitial germ cells
  - Spermatid retention/delayed spermiation
  - Diffuse germ cell degeneration/depletion or total tubular atrophy affecting one or both testis
Epididymis - Oligospermia
Epithelial Vacuolation
Epithelial Vacuolation
Atrophy
Sperm Granuloma
Epididymis

- Blood epididymal barrier not as strong as blood testis barrier
- Weight is a very sensitive method of detection of alterations
- Atrophy, Oligospermia, Cellular debris
  - Degenerating cells and residual bodies
- Sperm granuloma
  - More common in epididymis than testes
- Epithelial changes
  - Vacuolation-direct toxic effect - α Chlorohydrin, Methyl Chloride or secondary to reduced androgenic stimulation
  - Inflammation
- Disruption of sperm maturation-TCDD, - α Chlorohydrin
  - Only when toxicant has direct effect on sperm in epididymis
  - Reduced sperm motility
  - Reduced motile sperms
  - Increase in morphologically abnormal sperms
Normal Prostate
Prostate - Atrophy
Prostate - Hypertrophy
Prostate – MNC infiltration
Seminal Vesicles & Coagulation gland
Prostate and Seminal Vesicles

- Highly androgen dependant
- Weight is more sensitive than histology
  - Atrophy
  - Hypertrophy
  - Inflammation
  - Flutamide, Finasteride, 17-20 Lyase inhibitors
References

- http://vetmed.illinois.edu/~rexhess/Pubs.html
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- Histopathology of Preclinical Toxicity Studies, 2007, Greaves
- Fundamentals of Toxicologic Pathology, 2009, Haschek
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Lokesh
Charamanna
Nischita

Aurigene Senior Management

Murali Ramachandra, Vice President-Preclinical Biology
Thank You

Aurigene, Bangalore HQ

Picture of the Atrium. The building has a curved hallway and circular atrium designed to maximize the use of wind tunnels in the area. The use of natural wind and light are consistent with our support for the environment.