Pathology of the Adrenal Gland

R.R. Maronpot
maronpot@me.com

Photomicrographs courtesy of the National Toxicology Program (http://ntp.niehs.nih.gov)
Pathology of the Adrenal Gland

- Normal histology & physiology
- Hyperplasia
  - Cortex
    - Subcapsular
    - Cortex
  - Medulla
- Neoplasia
  - Cortex
    - Subcapsular
    - Cortex
  - Medulla
Mouse Adrenal
• Adrenals are 25% heavier in females
• No clearly visible zona reticularis in mice
X-Zone

Female Mouse Adrenal

- Unique to mouse
- Appears a few days after birth
- Fully developed at weaning
Growth and Involution of the X Zone

- In females, the X zone increases in size with a maximum at about 9 weeks and regresses gradually in virgins and rapidly upon the first pregnancy.
- In males, the X zone disappears at puberty (5 wks) without undergoing vacuolization.
- Gonadectomy of prepubertal male and female delays involution by several months.
- Hysterectomy causes the X zone and zona fasiculata to degenerate.
X-Zone at 9 Weeks
Female Mouse Adrenal
Fatty vacuolation of early involution
Nearly complete involution of X-zone
Normal male mouse does not have an X-zone
Lipogenic Pigment in a Swiss Mouse Adrenal

Occurs in rats and mice
Lipogenic Pigment

- Ceroid pigment
- In cortical cells at corticomedullary junction
- Age-related & occurs due to large amount of lipid in adrenal gland
- May be associated with X zone in female mice
Deposition of ceroid pigment may be exacerbated by treatment (Female B6C3F1 – tricresylphosphate)
B6C3F1 mouse treated with tricresylphosphate
Cytoplasmic vacuolization
(Multifocal)

Can be associated with increased ACTH secretion

High P450

Female SD
Female SD
Cortex Cytoplasmic Vacuolation (Diffuse)

Harlan SD Male  90-Day study – p-Chloro-A,A,A–trifluoro toluene
Cytoplasmic Vacuolization (Diffuse)
The vacuoles consist of microvesicular and macrovesicular cytoplasmic fat.
Discrete foci of fatty change can occur
Cortical Cysts

Rarely seen

B6C3F1 mouse
Cystic Degeneration

Control female SD

Cystic degeneration

Medullary hyperplasia
Cystic degeneration vs. Focal fatty change
Cystic Degeneration with Hemorrhage

Male F344 Na chlorate
Adrenal Cortical Atrophy

- Decreased thickness of cortical layers
- PCB118 High dose female SD
Lipogenic pigment also present.
Cortex necrosis

B6C3F1 mouse treated for 90-days with 1-bromopropane (water disinfection byproduct)
Vascular Ectasia

Male F344 treated with codeine

(Differential Dx = Hemangioma)
Chronic inflammation

B6C3F1 mouse treated for 90-days with 1-bromopropane (water disinfection biproduct)
Chronic inflammation

B6C3F1 mouse treated for 90-days with 1-bromopropane (water disinfection biproduct)

- X-zone involution
- Mixed inflammatory cell infiltrate plus mineralization
Accessory Cortical Nodule

Common in mice
2-14% incidence in past NTP studies
Accessory cortical nodule

Untreated male B6C3F1 mouse in a 2-year study
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Subcapsular Hyperplasia

B6C3F1 mouse treated for 90-days with Na bromate (water disinfection byproduct)
Subcapsular Hyperplasia

- Common, age-related in mouse adrenals
  - 60 to 90% incidence; first seen at about 4 months
- Type A spindle cells, Type B polygonal cells, or mixed population of Type A and Type B
- Scattered aggregates (usually Type A cells)
- Focal nodules (usually Type B cells)
Type A spindle cells

Type B polygonal cells
Type A spindle cells

Type B polygonal cells
Subcapsular hyperplasia (Type B cells)

Vehicle male B6B3F1 mouse in a chronic study
Cortical Hyperplasia

Female SD

Dioxin-related study
Cortical hyperplasia - focal increased number of basophilic cells
Cortical Hypertrophy
(Treated Female SD)

Cellular enlargement; may be associated with hyperplasia but not in this example.
Cortical Hypertrophy

(Vehicle male B6C3F1)
Medullary Hyperplasia

Vehicle female SD
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# NTP Historical Control Data

## Adrenal Tumors

(Incidence > 1 %)

<table>
<thead>
<tr>
<th>Species &amp; Tumors</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>F344 Rat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex Adenoma</td>
<td>1.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Benign Pheochromocytoma</td>
<td>13.6%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Malignant Pheochromocytoma</td>
<td>15.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>B6C3F1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex Adenoma</td>
<td>6.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Benign Pheochromocytoma</td>
<td>0.3%</td>
<td>1%</td>
</tr>
<tr>
<td>Malignant Pheochromocytoma</td>
<td>0.2%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>
Subcapsular Adenoma

High dose female B6C3F1

Subcapsular hyperplasia also present
Well circumscribed nodule of poorly differentiated cells
Subcapsular Adenoma

A more typical example consisting of mostly Type B cells

Treated male B6C3F1
Subcapsular Adenoma

A more typical example consisting of mostly Type B cells

Treated male B6C3F1
Subcapsular hyperplasia (Type B cells)

Vehicle male B6B3F1 mouse in a chronic study
Subcapsular Carcinoma

High dose female B6C3F1 N-methylolacrylamide study
Subcapsular Carcinoma

Consistently of predominantly Type A spindle cells
Cortical Adenoma

Low dose male B6C3F1
Cortical Adenoma

Low dose
male B6C3F1
Cortical Adenoma

Low dose
F344 male
Cortical Carcinoma
Benign Pheochromocytoma in a Mouse
Epinephrine

Chromagranin

Catecholamine (tyrosine hydroxylase)

Phenylethanolamine-N-methyltransferase
Benign Pheochromocytoma

Treated male F344

Male F344
Pheochromocytoma

- Benign pheochromocytoma
- Malignant pheochromocytoma
  - Penetrates capsule or blood vessels
  - Extreme pleomorphism
- Complex pheochromocytoma
  - Contains neural elements
Malignant Pheochromocytoma

Penetrates capsule

Low dose male F344
Malignant Pheochromocytoma

Penetrates capsule

Low dose male F344
Malignant Pheochromocytoma

Cellular pleomorphism
F344 Rat from Chronic Urea Study
Complex Pheochromocytoma

- Adrenal medullary sympathoblasts can develop into:
  - Pheochromocytes, neuroblasts, ganglion cells, Schwann cells, neurofibrils
- Neural component less than 80%
- If neural component is 80% or greater, diagnosed as neural tumor:
  - Neuroblastoma, ganglioneuroma, paraganglioma, Schwannoma
Complex Pheochromocytoma

Treated male B6C3F1
Complex Pheochromocytoma

High dose male F344 in water disinfection byproduct study
Neuroblastoma

Low dose F344 male
Neuroblastoma
Neuroblastoma

156 Week-old Male B6C3F1 – Lifetime study
Ganglioneuroma

High dose male F344
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Thank you for your attention