Adrenal Gland, Cortex, X-Zone – Atrophy

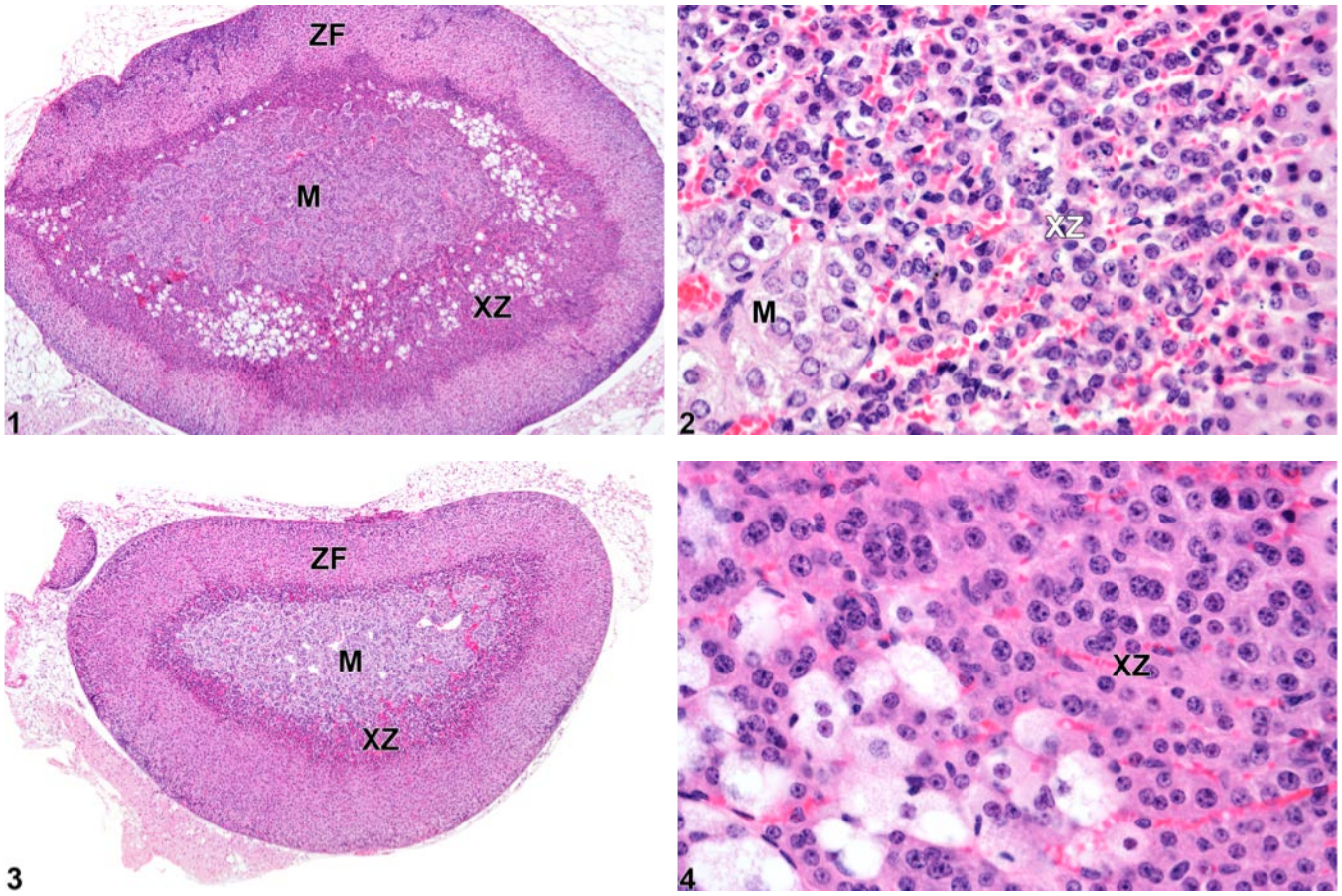
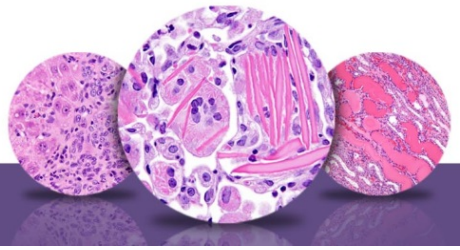


Figure Legend: **Figure 1** Adrenal gland, Cortex, X-zone - Normal in a female B6C3F1/N mouse from a subchronic study. Adrenal gland with moderate numbers of vacuolated cells in an age-matched control virgin female is shown for comparison with Figure 3. M = medulla, XZ = X-zone, ZF = zona fasciculata. **Figure 2** Adrenal gland, Cortex, X-zone - Normal in a female B6C3F1/N mouse from a subchronic study (higher magnification of Figure 1). Adrenal gland in an age-matched control virgin female is shown for comparison with Figure 4. M = medulla; XZ = X-zone. **Figure 3** Adrenal gland, Cortex, X-zone - Atrophy in a virgin female B6C3F1/N mouse from a subchronic study. There is acceleration of X-zone (XZ) regression characterized by narrowing of the X-zone compared with Figure 1. M = medulla, ZF = zona fasciculata. **Figure 4** Adrenal gland, Cortex, X-zone - Atrophy in a virgin



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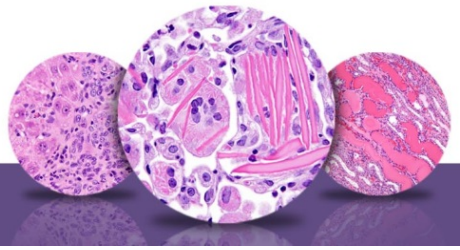
female B6C3F1/N mouse from a subchronic study (higher magnification of Figure 3). There is increased degeneration and necrosis of the X-zone (XZ) cells compared with Figure 2.

Comment: The X-zone appears a few days after birth in mice of both sexes and is fully developed by weaning. The X-zone is located at the junction of the cortex and the medulla and is populated by cells with more eosinophilic cytoplasm than those of the zona fasciculata (Figure 1 and Figure 2). In male mice, the X-zone regresses at puberty (by about 5 weeks of age). In females, the X-zone persists for several weeks past puberty and then regresses more gradually in nulliparous females or more rapidly at first pregnancy. The extent of X-zone development and the rate of involution can also vary with mouse strain.

Normal regression (involution) of the X-zone in females of many mouse strains, including the B6C3F1 strain, progresses in morphologically distinct stages. The onset of regression begins with vacuolization of scattered constituent cells (Figure 1 and Figure 2). As regression continues, the number of vacuolated cells progressively increases until virtually all X-zone cells are affected. In later stages, the vacuolated X-zone cells undergo degeneration and necrosis, with subsequent overall X-zone architectural collapse, condensation, and eventual disappearance. A common end-stage sequela is the residual accumulation of pigment-laden cells in the perimedullary area formerly occupied by the X-zone. In males, X-zone regression is similar except that it usually occurs without vacuolization.

The function of the X-zone is unknown. Its normal development and regression are mediated by gonadal and thyroid hormones, so factors that alter levels of these hormones can affect the X-zone. For example, gonadectomy prolongs the persistence of the X-zone in female mice and prepubertal male mice and can cause the reappearance of the X-zone in postpubertal males. Administration of androgens like testosterone is followed by rapid disappearance of the X-zone in female mice. Administration of certain other chemicals can also affect the X-zone, resulting in asynchronous deviations, such as accelerated regression (Figure 3 and Figure 4) in treated groups compared with age-matched concurrent controls (Figure 1 and Figure 2).

Recommendation: Adrenal cortical X-zone regression is a normal physiologic process, and its various stages are often incidental findings in mice of both sexes and at various ages. Features of normal X-



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zone regression stages (e.g., vacuolization, degeneration) and its end-stage sequelae (e.g., X-zone collapse, fibrosis, and pigment-cell accumulation) should not be mistaken for pathologic lesions. Thus, physiologic X-zone regression should not be diagnosed when it occurs in a similar, age- and sex-appropriate manner in both the control and treated mice in a given study. Abnormally accelerated (rapid) regression or, conversely, excessively lengthy persistence of the X-zone can be effects of treatment with various chemicals and exogenous hormones. However, in these cases, the X-zone morphology of treated animals will not be distinctive or exhibit pathognomonic pathologic features. Instead, the existence of a toxic effect manifests only as a disparity in the appearance (temporal stage) of the X-zone in treated animals compared with normal, age- and sex-appropriate concurrent study controls. For these reasons, X-zone toxicity in treated animals cannot be diagnosed in isolation but must be evaluated in the context of the physiologic temporal stage occurring in the study controls.

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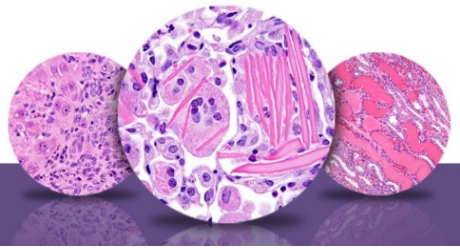

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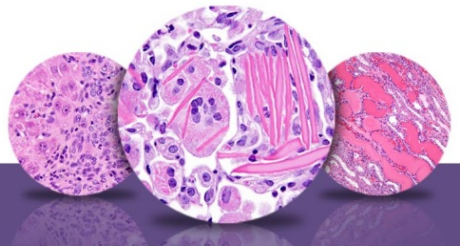

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