4. NORMAL BACKGROUND VARIATION OF STRUCTURE

Introduction

4.1 This section illustrates several examples of normal morphological changes in the female reproductive tract that can complicate the evaluation of reproductive tissues from TG 407 studies. These alterations may be developmental in nature or simply reflect the normal physiology of the oestrous cycle. Artefacts caused by suboptimal sampling and/or sectioning of the reproductive organs may also occur. Oblique sections through epithelia, for example, can mimic focal areas of epithelial hyperplasia or squamous metaplasia. Similarly, inadequate ovarian sections may not be representative of the organ in terms of the follicular and luteal stages present.

4.2 An awareness of these normal background and artefactual changes is important in order to avoid erroneously labelling them as treatment-related. The situation is complicated by the fact that the incidence of many common spontaneous variations may be influenced by substances with endocrine activity. In TG 407 studies the normal background variation for the test animal population is based on five control animals per sex. Given this small group size, it is important that small increases in the incidence of spontaneous lesions are not over-interpreted as treatment-related.

4.3 As TG 407 studies use young, sexually mature non-mated adult rats, spontaneous age-related changes and alterations associated with pregnancy should not be encountered and are not discussed here.

Spontaneous changes

Figure 4.1 – Vagina: early metoestrus (rat, H&E). Polymorphonuclear cell infiltration (N) of the stratum germinativum. Neutrophils are the predominant cell type but eosinophils may also be observed. This is a normal feature of late oestrus/early metoestrus and should not be misinterpreted as vaginitis.
Figure 4.2 – Uterus: late oestrus (rat, H&E). A marked polymorphonuclear cell infiltration (N) of the endometrial glands may be observed during late oestrus/early metoestrus, reflecting the dominance of oestrogen during this part of cycle. This is a normal finding and should not be mistaken for endometritis.

Figure 4.3 – Uterus: early oestrus (rat, H&E). Early squamous metaplasia (SM) of the endocervix, affecting the luminal and/or glandular epithelium, may be occasionally observed in young control rats. This morphological alteration may also develop following treatment with oestrogenic compounds.

4.4 Cystic corpora lutea may be encountered as spontaneous findings in young rats. Following ovulation, a small, fluid-filled central cavity persists within the mass of luteal cells that forms the corpus luteum (Figure 4.4). Cystic corpora lutea should not be confused with ovarian luteal cysts, another occasional spontaneous finding in rodents. Luteal cysts form when tertiary and Graafian follicles fail to ovulate but undergo
luteinisation. The cystic cavity is typically large and surrounded small granulosa-like cells admixed with large, plump luteal cells (Montgomery and Alison, 1987). Increased numbers of luteal cysts may be observed following administration of compounds with gonadotrophic activity (Table 5.1, Section 5).

4.5 Cystic corpora lutea and luteal cysts must be differentiated from follicular cysts; these develop from secondary and tertiary follicles that fail to progress through folliculogenesis. Follicular cysts are fairly common spontaneous findings in aged rodents but are not typically observed in young rats. The cystic spaces are large but, unlike luteal cysts, the surrounding granulosa cells show no evidence of luteinisation. Follicular maturation arrest with follicular cyst formation may occur after dosing with antioestrogenic substances such as tamoxifen, raloxifene and CGS 18320B (Table 5.1, Section 5). Intrafollicular granulosa cell hyperplasia, characterised by infolding or papillary proliferation of the zona granulosa, may also be a feature of raloxifene-induced follicular cysts (Long et al, 2001).

4.6 Cysts of the ovarian bursa or rete ovarii may also be occasionally encountered in young rodents as spontaneous developmental lesions.
Common artefacts

Figure 4.6 – Normal skin (mouse, H&E). This may be inadvertently sampled from the perineum and included in histological sections of the vagina.

Figure 4.7 – Uterus: dioestrus (rat, H&E). Oblique sections (Ob) through the normal endometrial columnar epithelium (CE) should not be confused with foci of squamous metaplasia, a potential treatment-related effect.
Figure 4.8 – Ovary, prooestrus (rat, H&E). Proovulatory (Graafian) follicles (GF); the absence of free-floating primary oocytes within the follicular lumina is a sectional artefact.