

Proliferative Lesions of the Skin and Adnexa in Rats

M. G. EVANS,¹ M. E. CARTWRIGHT,² P. S. SAHOTA,³ AND C. B. CLIFFORD⁴

¹Pathology Associates International, Frederick, MD

²Merck Research Laboratories, West Point, PA

³Novartis Pharmaceuticals Corporation, Summit, NJ

⁴Charles River Laboratories, Wilmington, MA

INTRODUCTION

Laboratory rats have a broad spectrum of proliferative changes of the skin and adnexa that may be induced by carcinogenic stimuli. There is an ongoing lack of consensus regarding the nomenclature and histologic diagnostic criteria for classifying these neoplasms. This not only confounds comparisons of incidences among studies from different laboratories but, more importantly, may mislead those who must interpret the biological significance of skin tumors arising in carcinogenicity studies. Questions of whether or not tumors are truly malignant (such as basal cell carcinomas) or whether or not two neoplasms with different names (such as keratoacanthoma and inverted papilloma) may actually be the same entity are of more than academic or semantic importance. Only if such proliferative lesions are classified into biologically meaningful categories will statistical analyses comparing their incidences be relevant.

The system of classification and diagnostic criteria recommended in this *Guide* is based upon morphologic features visible in paraffin-embedded histologic sections stained with hematoxylin and eosin. Included are descriptive diagnostic criteria for skin/adnexa and for modified sebaceous glands (i.e., auditory sebaceous gland (Zymbal's gland), preputial/clitoral gland, and circumanal gland) invested in the skin. In general, structure and

classification follow the logical framework used by Botts et al. (2) and Riley et al. (14) in earlier *Guides*, with proliferative, benign, and malignant neoplasms discussed for each cell type. Care has been taken to avoid asserting diagnostic criteria for certain rare neoplasms, the existence of which have not been rigorously established in the rat.

Subclassification by histologic pattern within these categories is proposed only when there is evidence of significant differences in biologic behavior, such as malignant potential, for the different histologic variants. Classification of tumors arising from connective (soft) tissue elements are presented in a separate *Guide* by Greaves et al. (7).

An outline of the classification scheme for this *Guide* is presented in Table 1.

Table 1

CLASSIFICATION SCHEME OUTLINE

SKIN & ADNEXA

- I. Hyperplastic Lesions
 - squamous epithelium
 - sebaceous glands
- II. Neoplastic Lesions
 - A. Epithelial/Adnexal
 1. Squamous Cells

- keratoacanthoma
- papilloma
- carcinoma
- 2. Basal Cells
 - benign
 - malignant
- 3. Sebaceous Cells (non-specialized)
 - adenoma
 - carcinoma
- 4. Hair Follicle Components
 - trichoepithelioma
- B. Non-Epithelial
 1. Melanocytes
 - malignant melanoma (melanotic; amelanotic)
 2. Histiocyte or Histiocyte-like Cells
 - malignant fibrous histiocytoma*
 - histiocytic sarcoma*
 3. Schwann Cell
 - benign*
 - malignant schwannoma (neuri-lemoma/ neurosarcoma)*
 4. Blood Vessels
 - hemangioma*
 - hemangiosarcoma*
 - hemangiopericytoma*
 5. Fat, White (Brown)
 - lipoma (hibernoma)*
 - liposarcoma (malignant hibernoma)*
 6. Mononuclear Cells
 - mononuclear cell leukemia*
 - lymphoma*
- III. Miscellaneous Lesions
 - epidermal inclusion cyst

MODIFIED SEBACEOUS GLANDS

(Auditory Sebaceous Gland (Zymbal's Gland), Preputial/Clitoral Gland, and Circumanal Gland)

- I. Hyperplastic Lesions
 - glandular
 - squamous
- II. Benign Lesions
 - adenoma
 - papilloma
- III. Malignant Lesions
 - carcinoma

* Discussed in separate *Guides* covering other organ systems.

MORPHOLOGY

SKIN & ADNEXA

HYPERPLASIA (Figure 1 & 2)

Hyperplastic lesions may be generally classified as either squamous or sebaceous, although the two types may occur simultaneously. *Squamous hyperplasia* may include the epidermal surface or the epithelium lining hair follicles. It is usually most noticeable in the stratum germinativum, but all layers may be involved. Orthokeratotic or hyperkeratotic hyperkeratosis often accompanies squamous hyperplasia. *Sebaceous hyperplasia* is defined as an increased number of sebaceous cells in individual acini, causing an enlargement of the sebaceous gland. Squamous or sebaceous hyperplasia may precede neoplasia.

NEOPLASIA

SQUAMOUS CELLS

Keratoacanthoma (Figures 3 & 4)

The keratoacanthoma is a benign growth with a probable cell of origin being the squamous cell. It appears as a crater-like or flask-like invagination on histologic section, forming one to a few cystic spaces (often filled with keratinaceous debris) which communicate with the exterior by a pore. The growth typically involves the dermis and epidermis. Squamous epithelium is usually thick, and a prominent basal cell layer is usually seen adjacent to a keratin plug. Hyperkeratosis of squamous epithelium is commonly seen. The cutaneous horn is considered a variant of keratoacanthoma.

Squamous Cell Papilloma (Figure 5)

The squamous cell papilloma is a benign, exophytic growth of squamous epithelium. It has distinctive single to multiple papillar foldings lined by squamous epithelium peripherally and a fibrovascular stroma centrally. The squamous epithelium is well-differentiated, and variable degrees of necrosis, inflammation, ulceration, hyperkeratosis, or parakeratosis may be present (6, 8).

Squamous Cell Carcinoma (Figures 6 & 7)

The squamous cell carcinoma is an invasive neoplasm in which the dermis and subcutis are involved. Multiple and coalescing nests of malignant squamous cells are often seen, and individual malignant squamous epithelial cells are pleomorphic and have distinctive cytologic features such as enlarged nuclei and prominent nucleoli. These tumors may be non-keratinized or may have aggressive keratinization, with multiple keratin pearl

formation. These neoplasms often have necrosis, chronic inflammatory cell infiltrations, or fibrosis. Metastasis to lungs and regional lymph nodes may occur (6, 9).

BASAL CELLS

Basal Cell Tumor, Benign (Figure 8)

The benign basal cell tumor is an elevated skin nodule that is thought to arise from hair follicles. The cells have scant basophilic cytoplasm and a deeply staining basophilic nucleus. Differentiation into immature hair follicles or sebaceous glands is sometimes a feature of these neoplasms. Several different histologic patterns may be seen, including basal cells arranged in cords, fine ribbons, nests, or lobules.

Basal Cell Tumor, Malignant (Figures 9 & 10)

The malignant basal cell tumor is a mixture of basal cells that are usually pleomorphic. Mitotic activity is often prominent. Squamous or pilosebaceous differentiation may be variably present. Local invasion may be seen and variable degrees of inflammatory cell infiltration and necrosis are common. Metastasis to lymph nodes or lung is rare (19). Several histologic patterns have been described, including solid (which consists of an adenoid pattern with variable necrosis), cystic, keratotic, and basosquamous (21).

SEBACEOUS CELLS

Sebaceous Cell Adenoma (Figure 11)

The sebaceous cell adenoma is typically a well-defined exophytic mass that often contains multiple cystic areas. Mild compression of adjacent tissue is common at the periphery of the mass. The shape of individual lobules may be irregular, with basal cells peripherally and well-differentiated sebaceous cells centrally (6).

Sebaceous Cell Carcinoma (Figure 12)

The sebaceous cell carcinoma is a locally invasive neoplasm made of poorly-defined lobules of sebaceous epithelial cells. Cellular pleomorphism is greater among sebaceous cells of the sebaceous cell carcinoma than that of the sebaceous cell adenoma. Inflammation and necrosis are variable but are often present. Other cell types may be present, including squamous cells, abortive hair follicles, or basal cells (6, 21).

HAIR FOLLICLE CELLS

Trichoepithelioma (Figures 13 & 14)

The trichoepithelioma is a basal cell neoplasm that

has differentiation toward hair follicles which appear immature. The mass typically has a central lumen variably filled with keratin or poorly-defined hair shafts. The periphery of the mass contains basophilic cells. Keratin cysts with an abrupt transition zone from keratin to basal cells are a characteristic feature (12).

MALIGNANT MELANOMA

Melanotic Melanoma

The melanotic malignant melanoma is an invasive neoplasm that may be present in the dermis and is made of dense aggregates of melanocytes. The pinna and the anogenital region are predilection sites. A proliferative response of the connective tissue in areas of the tumor is often a feature. Cells contain dark brown pigmented granules (melanin) and have a round to oval nucleus with 1-2 nucleoli. The overall pattern may be spindle cell, epithelioid, highly anaplastic, or mixtures of these patterns. Nuclear pleomorphism and a high mitotic rate may be present, especially in larger tumors (5, 22).

Amelanotic Melanoma (Figure 15)

Amelanotic melanomas have been studied retrospectively in the F344/N strain of rats (20). Predilection sites include the pinna of the ear, eyelid, scrotum, and perineal area. Amelanotic melanomas are composed of spindle-shaped cells with interlacing fascicles that frequently are oriented perivascularly, features that differentiate them from Schwann cell tumors. Likelihood of metastasis increases with tumor size and is most frequent in pinnal amelanotic melanomas. Ultrastructural presence of pre-melanosomes and/or melanosomes, as well as lack of pericytoplasmic basal lamina, provide definitive identification.

MISCELLANEOUS LESIONS

Epidermal Inclusion Cyst (Figure 16)

The epidermal inclusion cyst, while not considered a hyperplastic or neoplastic lesion, is included in this discussion because its microscopic appearance can be difficult to differentiate from other proliferative lesions, such as the keratoacanthoma. The epidermal inclusion cyst, also called an epidermal cyst, usually occurs in older rats and is a round to oval nodular lesion. Microscopically, it consists of a solitary cystic space, the lumen of which is filled with variable amounts of concentrically layered keratin. The inner lining of the space is composed of simple squamous epithelium. Chronic inflammation may be present in and around the cyst, especially if the cyst wall has been ruptured.

MODIFIED SEBACEOUS GLANDS (Auditory Sebaceous Gland (Zymbal's Gland), Preputial/Clitoral Gland, and Circumanal Gland)

HYPERPLASIA

Hyperplasia of the modified sebaceous glands may be either of the glandular epithelium or of the squamous epithelium of ductules. *Glandular hyperplasia* appears as a focal increase in the number of sebaceous cells. The cytoplasm of hyperplastic sebaceous cells may stain more basophilic and may have a less foamy appearance to the cytoplasm than unaffected cells. *Squamous (or ductular) hyperplasia* is a focal increase in the thickness of squamous epithelium. This may result in folds of epithelium into the duct lumen.

BENIGN NEOPLASMS

Adenoma (Figures 17 & 21)

The adenoma of the modified sebaceous glands is a well-defined mass which may contain a variety of cell types, including sebaceous cells and basal cells, with mild compression of tissue adjacent to the periphery of the mass. Larger adenomas may contain necrosis and inflammation.

Papilloma

The papilloma appears as multiple papillary projections composed of stratified squamous epithelium overlying a vascular stroma.

MALIGNANT NEOPLASMS

Carcinoma (Figure 18-20, 22)

Carcinomas of the modified sebaceous glands are poorly-demarcated masses that invade surrounding tissues. Either the squamous or the sebaceous elements (or both) may appear malignant. Cellular pleomorphism and stromal proliferation are common.

DISCUSSION

In the rat, a variety of integumentary proliferative lesions may occur spontaneously or following exposure to carcinogens. A large number of these lesions originate from the cells of the epidermis, sebaceous glands, or hair follicle components. A given lesion may be limited to one or two cell types or may include a spectrum of cell types, each with varying degrees of differentiation.

Basal cell tumors, for example, are generally less heterogeneous than trichoepitheliomas. The hair follicle tumors, by contrast, frequently have a range of cellular and differentiation features that can make their diagnosis

especially challenging. Complex or poorly-differentiated hair follicle tumors may not easily fit into a rigorous classification scheme, as suggested by systematized classifications developed by others (13).

Other proliferative lesions in rat skin originate from the auditory sebaceous glands (Zymbal's glands), preputial/clitoral glands, or circumanal glands, all of which are modified sebaceous glands. Malignant tumors of the auditory sebaceous gland in particular must be carefully differentiated from squamous cell carcinomas of the head region. This gland is often not examined microscopically unless a lesion is noted during necropsy, a practice that may preclude determining the true incidence of auditory sebaceous gland neoplasms of various rat strains.

Certain proliferative lesions can be confused with cystic changes. For example, keratoacanthomas have some features in common with epidermal inclusion cysts (10). The implications for the carcinogenic potential of a test compound that causes keratoacanthomas may be different from a test compound that causes cystic changes, emphasizing the importance of an accurate diagnosis.

The incidence for all skin neoplasms in males and females, respectively, has been estimated to be 5.6% and 1.3% in untreated F344 rats; 7.7% and 1.9% in F344 rats administered corn oil by gavage (18); and 11.8% and 2.1% in 2-year old Sprague-Dawley rats (11). In both inbred Fischer rats and outbred Sprague-Dawley rats, males had a notably higher incidence of neoplasia than females (23). Historically, the frequency of spontaneous skin tumors in many rat strains has been considered to be relatively low (4, 5, 17).

Tumors of the specialized sebaceous glands have similarly low incidences. Auditory sebaceous gland tumors account for less than 1% of the spontaneous neoplasms of rats (1), while tumors of the preputial gland have a spontaneous incidence of less than 5% in this species (3, 15, 16). As with proliferative lesions of the skin, the incidence of lesions of the modified sebaceous glands can increase drastically due to the effects of chemical carcinogens.

The rarity of certain tumor types in the rat, such as *pilomatrixoma*, *trichofolliculoma*, and *tricholemmoma*, currently precludes the establishment of diagnostic criteria for these entities. One suggested approach to the diagnostic microscopic features of these tumors has been described by Zackheim et al. (21). Nevertheless, the existence of the three entities has not been rigorously established in the rat. Perhaps future editions of the *Guide* will contain criteria for these neoplasms based on examination of sufficient numbers of putative cases. Classifying the previously mentioned tumors (and including the trichoepithelioma) as "hair follicle/matrix tumors," without further subclassification, currently

seems to be an appropriate option in the context of most toxicologic studies. The paucity in the literature of these entities in the rat, except the trichoepithelioma, supports a cautious approach to the establishment of their diagnostic criteria.

RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA

SKIN & ADNEXA

HYPERPLASIA

Squamous Hyperplasia

1. May include epidermal surface and/or hair follicles
2. All layers of epidermis usually thickened, but is most noticeable in the basal layer
3. Inflammation may be present
4. Can progress to neoplasia
5. Can occur simultaneously with sebaceous hyperplasia, hyperkeratosis, and/or parakeratosis

Sebaceous Hyperplasia

1. Glands enlarged with increased numbers of sebaceous cells in individual acini
2. Can progress to neoplasia
3. Can occur simultaneously with squamous hyperplasia

NEOPLASTIC LESIONS

SQUAMOUS CELLS

Keratoacanthoma

1. Benign growth that appears as a crater-like or flask-like invagination in dermis and subcutis
2. Cystic downward growth of squamous epithelium with pronounced hyperkeratosis
3. May have prominent basal cell layer with thick squamous epithelium and dense, laminated keratin plug
4. Focal basal cell hyperplasia may be present
5. Proposed to arise from hair follicles
6. Cutaneous horn is a variant
7. May progress to squamous cell carcinoma

Squamous Cell Papilloma

1. Composed of proliferative squamous epithelium in distinctive papillar folds with central fibrovascular stroma

2. Well-differentiated epithelium
3. Hyperkeratosis (with or without parakeratosis) is usually present
4. May have inflammation or necrosis near surface
5. May develop into squamous cell carcinomas
6. Several variants - fibroepithelial, keratinizing, and non-keratinizing
7. Preceded by papillary hyperplasia

Squamous Cell Carcinoma

1. Invasive into dermis and subcutis; nests and fronds of neoplastic cells
2. Pleomorphic
3. Frequent mitoses in basal cell layer
4. Nuclei enlarged and have prominent nucleoli
5. Rarely metastasize to regional lymph nodes and lungs
6. Can be keratinized (keratin pearl formation) or non-keratinized
7. Variable necrosis, fibrosis, and inflammation
8. May arise from papilloma, keratoacanthoma, or trichoepithelioma

BASAL CELLS

Basal Cell Tumor, Benign

1. Usually arise from hair follicles
2. Elevated skin nodule
3. Histologic pattern variable - cords, ribbons, nests, or lobules
4. Usually have darkly staining, round to oval nucleus with scant basophilic cytoplasm
5. May differentiate into immature hair follicles or sebaceous glands
6. Collagenous stroma often present, which may be hyalinized

Basal Cell Tumor, Malignant

1. Pleomorphic mixture of basal cells with or without squamous or pilosebaceous differentiation
2. Keratin content variable
3. Locally invasive with associated areas of inflammation and necrosis
4. Rarely metastasize to regional lymph nodes or lungs
5. Solid variant may have adenoid structures with necrotic center
6. Cystic variant has cystic structures present and may contain watery or serous fluid
7. Keratotic variant has abrupt and complete formation of horn (keratin) cysts; granular cell layer is thin or absent
8. Basosquamous variant contains both basal cell and squamous cell components (rare)

SEBACEOUS CELLS

Sebaceous Cell Adenoma

1. Well-demarcated mass, may be lobular and extend from subcutis to basal cell layer of epidermis
2. May be exophytic
3. May contain multiple central cystic areas
4. Lobules composed of irregularly shaped acini that contain densely staining basal cells at the periphery and well-differentiated sebaceous cells and foamy cytoplasm at the center

Sebaceous Cell Carcinoma

1. Poorly formed lobules of sebaceous epithelium
2. Locally invasive; more likely to see inflammation and/or necrosis in this lesion than in adenoma
3. Majority of cells are of sebaceous type; may see nests of squamous cells, immature hair follicles, or foci of undifferentiated basal cells
4. Has greater pleomorphism among sebaceous cells than is seen in adenoma

HAIR FOLLICLE CELLS

Trichoepithelioma

1. Originate from pluripotential cells of epidermis or hair follicles
2. Basal cell neoplasm with differentiation toward hair follicle formation, but these structures appear immature.
3. Lumen present, surrounded by basophilic cells; lumen may contain keratin or aborted hair shafts
4. Characteristic horn/keratin cyst formation
5. Abrupt transition to keratinization; cysts are surrounded by concentric rings of flattened basaloid cells

MALIGNANT MELANOMA

Melanotic Melanoma

1. Appears as black dots or raised, firm, black nodules
2. Invasive neoplasm made of dense aggregates of melanocytes and melanophages with proliferation of loose connective tissue of dermis and subcutis
3. Overall pattern may be spindle cell, epithelioid, highly anaplastic, or a mixture of these patterns
4. Round or oval nuclei with 1-2 nucleoli
5. Cells contain dark brown pigmented granules (melanin)
6. Sites most often involved are external ear (pinna) and the anogenital region
7. Nuclear pleomorphism and high mitotic rate

Amelanotic Melanoma

1. Composed of spindle-shaped cells with interlacing fascicles oriented perivascularly
2. Pre-melanosomes and/or melanosomes present ultrastructurally
3. Lack pericytoplasmic basal lamina
4. Sites most often involved are external ear (pinna), perineal area, scrotum, and eyelid
5. Metastasize to regional lymph nodes and lung

MISCELLANEOUS LESIONS

Epidermal Inclusion Cyst

1. Not a hyperplastic or neoplastic lesion
2. Usually nodular and cystic
3. Cyst lined by simple squamous epithelium
4. Cystic space contains keratin, often in concentric layers
5. Inflammatory cells may be present in and around lesion, especially if cyst has ruptured
6. Must be differentiated from lesions with similar microscopic features, such as keratoacanthoma

MODIFIED SEBACEOUS GLANDS

(Auditory Sebaceous Gland (Zymbal's Gland), Preputial Gland, Clitoral Gland, and Circumanal Glands)

HYPERPLASIA

Glandular Hyperplasia

1. Usually focal
2. Lobular pattern retained with slight compression of adjacent tissue
3. Cytoplasm of affected cells usually more basophilic and less foamy than unaffected cells

Squamous (Ductular) Hyperplasia

1. Focal increase in thickness of squamous epithelium with formation of folds and papillary projections into duct lumen
2. Glandular proliferation may occur concomitantly

BENIGN NEOPLASMS

Adenoma

1. Well-demarcated with dilated lumina centrally containing variable amounts of secretions
2. Made of sebaceous cells, basal cells, and cells of intermediate morphology; usually seen as variably formed acinar or solid structures
3. Periphery may contain proliferative glandular tissue
4. Necrotic debris and inflammatory cells may be present, especially in larger adenomas

Papilloma

1. Multiple papillary projections
2. Stratified squamous epithelium covering cores of variably vascularized connective tissue

MALIGNANT NEOPLASMS

Carcinoma

1. Poorly circumscribed and may invade adjacent tissues
2. Consist of irregular acini or more solid sheets of malignant cells with cystic areas often filled with secretory material, keratin, or necrotic debris
3. Squamous and/or sebaceous components may be malignant, with the squamous portion often having more pleomorphism than the sebaceous portion
4. Rarely metastasize to regional lymph nodes or lungs
5. Stromal proliferation is common and may be atypical

REFERENCES

1. Altman NH and Goodman DG (1979). Neoplastic diseases. In: *The Laboratory Rat, Biology and Diseases*, Vol. 1. HJ Baker, JR Lindsey, and SH Weisbroth (eds). Academic Press, Inc., San Diego, CA, pp. 333-376.
2. Botts S, Jokinen MP, Isaacs KR, Meuten DJ, and Tanaka N (1991). Proliferative lesions of the thyroid and parathyroid glands, E-3 In: *Guides for Toxicologic Pathology*, STP/ARP/AFIP, Washington, DC.
3. Copeland-Haines D and Eustis SL (1990). Specialized sebaceous glands. In: *Pathology of the Fischer Rat*, GA Boorman, SL Eustis, MR Elwell, CA Montgomery, and WF MacKenzie (eds). Academic Press, Inc., San Diego, CA, pp. 279-293.
4. Curtis MR, Bullock FD, and Dunning WF (1931). A statistical study of the occurrence of spontaneous tumors in a large colony of rats. *Am. J. Cancer* 15:67-121.
5. Deerberg F, Knup R, and Rehm S (1986). Spontaneous epithelial tumors of the skin in Hab:WIST and DA:Han rats. *Z. Versuchstierkd.* 28:45-57.
6. Elwell MR, Stedham MA, and Kovatch RM (1990). Skin and subcutis. In: *Pathology of the Fischer Rat*, GA Boorman, SL Eustis, MR Elwell, CA Montgomery, and WF MacKenzie (eds). Academic Press, Inc., San Diego, CA, pp. 261-293.
7. Greaves P, Faccini JM, and Courtney CL (1992). Proliferative lesions of soft tissues and skeletal muscle in rats, MST-1. In: *Guides for Toxicologic Pathology*, STP/ ARP/AFIP, Washington, DC.
8. Hirose M (1989). Squamous cell papilloma, skin, rat. In: *Integument and Mammary Glands, Monographs on Pathology of Laboratory Animals*, TC Jones, U Mohr, and RD Hunt (eds). Springer-Verlag, New York, NY, pp. 15-19.
9. Hirose M (1989). Squamous cell carcinoma, skin, rat. In: *Integument and Mammary Glands, Monographs on Pathology of Laboratory Animals*, TC Jones, U Mohr, and RD Hunt (eds). Springer-Verlag, New York, NY, pp. 25-30.
10. Lake SG, Hart-Elcock L, Mueller RE, and Stuart BP (1989). Epidermal inclusion cyst, skin, rat. In: *Integument and Mammary Glands, Monographs on Pathology of Laboratory Animals*, TC Jones, U Mohr, and RD Hunt (eds). Springer-Verlag, New York, NY, pp. 130-133.
11. Lang PL (1992). *Spontaneous Neoplastic Lesions and Selected Non-Neoplastic Lesions in the Crl:CD BR Rat*. Charles River Laboratories, Wilmington, MA.
12. Mackawa A (1989). Trichoepithelioma, skin, rat. In: *Integument and Mammary Glands, Monographs on Pathology of Laboratory Animals*, TC Jones, U Mohr, and RD Hunt (eds). Springer-Verlag, New York, NY, pp. 56-63.

13. Mohr U, Bader R, Ernst H, Ettlin R, Gemhardt C, Harleman JH, Hartig F, Jahn W, Kaliner G, Karbe E, Kaufmann W, Krieg K, Krinke G, Kuttler K, Landes C, Mettler F, Morawetz G, Notman J, Puschner H, Quereshi S, Reznik G, Rittinghausen S, Tuch K, Urwyler H, Weisse G, Weisse I, and Zehnder J (1990). Tumor registry data base: Suggestions for a systematized nomenclature for pre-neoplastic and neoplastic lesions in rats. *Exp. Path.* 38:1-18.
14. Riley MGI, Boorman GA, McDonald MM, Longnecker D, Solleveld HA, and Giles HD (1990). Proliferative and metaplastic lesions of the endocrine pancreas in rats, E-1. In: *Guides for Toxicologic Pathology, STP/ARP/AFIP*, Washington, DC.
15. Reznik G and Reznik-Schuller H (1980). Pathology of the clitoral and preputial glands in aging F344 rats. *Lab. Anim. Sci.* 30:845-850.
16. Reznik G and Ward JM (1981). Morphology of hyperplastic and neoplastic lesions in the clitoral and preputial gland of the F344 rat. *Vet. Path.* 18:228-238.
17. Snell KC (1965). Spontaneous lesions in the rat. In: *The Pathology of Laboratory Animals*, WE Ribelin and JR McCoy (eds). CC Thomas, Springfield, IL, pp. 241-302.
18. Solleveld HA, Haseman JK, and McConnell EE (1984). Natural history of body weight gain, survival, and neoplasia in the Fischer 344 rat. *J. Natl. Cancer Inst.* 72:929-938.
19. Szabo E and Sugar J (1989). Basal cell carcinoma, skin, rat. In: *Integument and Mammary Glands, Monographs on Pathology of Laboratory Animals*, TC Jones, U Mohr, and RD Hunt (eds). Springer-Verlag, New York, NY, pp. 43-51.
20. Yoshitomi K, Elwell MR, and Boorman GA (1995). Pathology and incidence of amelanotic melanomas of the skin in F-344/N rats. *Toxicol. Pathol.* 23:16-25.
21. Zackheim HS, Zurcher C, Krutovskikh VA, and Troyanovsky SM (1990). Tumors of the skin. In: *Pathology of Tumours in Laboratory Animals, Vol. 1 - Tumours of the Rat*, V Turusov and U Mohr (eds). Oxford University Press, Oxford, UK, pp. 1-36.
22. Zurcher C and Roholl PJM (1989). Melanocytic tumors, rat. In: *Integument and Mammary Glands, Monographs on Pathology of Laboratory Animals*, TC Jones, U Mohr, and RD Hunt (eds). Springer-Verlag, New York, NY, pp. 76-86.
23. Zwicker GM, Eyster RC, Snells DM, and Gass JH (1992). Spontaneous skin neoplasms in aged Sprague-Dawley rats. *Toxicol. Pathol.* 20:327-340.

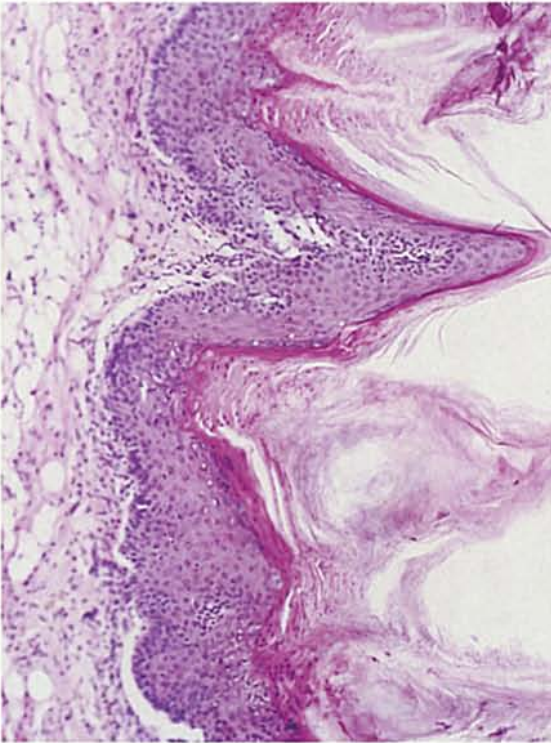


Fig. 1 – Squamous hyperplasia. Thickened epithelium with increased numbers of squamous epithelial cells (H&E).

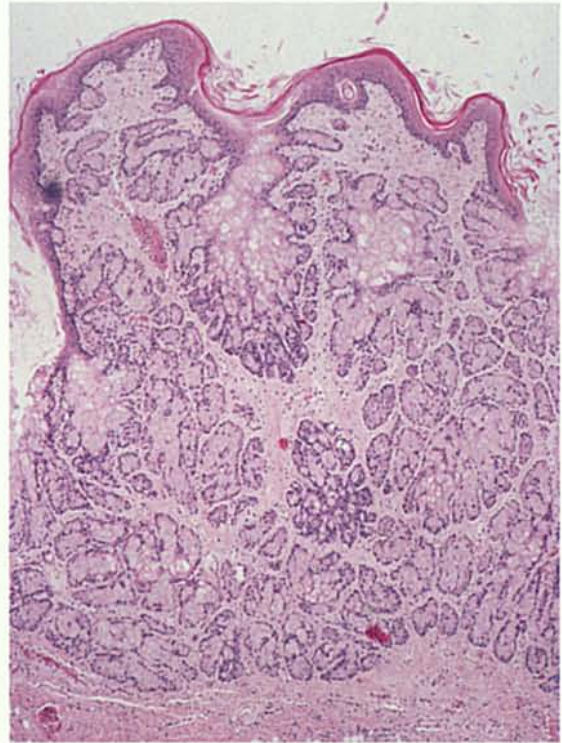


Fig. 2 – Sebaceous hyperplasia. Enlarged sebaceous glands with increased number of sebaceous cells in each acinus (H&E).

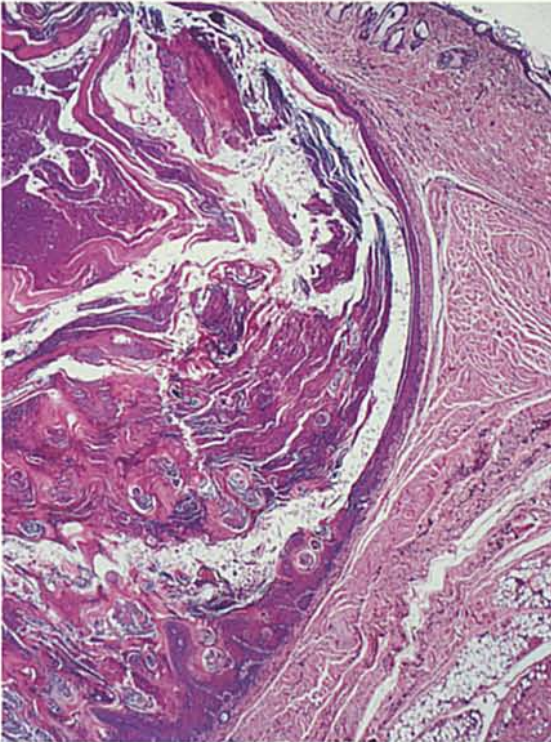


Fig. 3 – Keratoacanthoma. Portion of a crater-like mass filled with keratin and lined by prominent folds of squamous stratified epithelium and lumen (H&E).

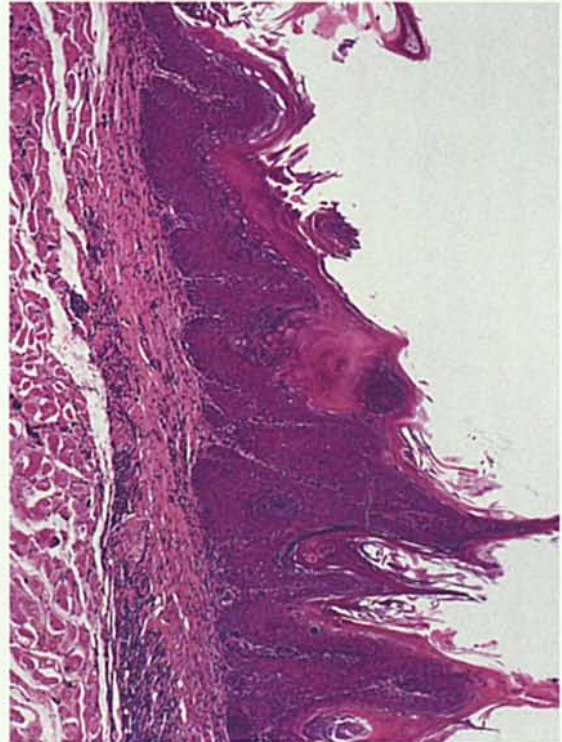


Fig. 4 – Keratoacanthoma. Higher magnification of squamous stratified epithelium of keratoacanthoma (H&E).

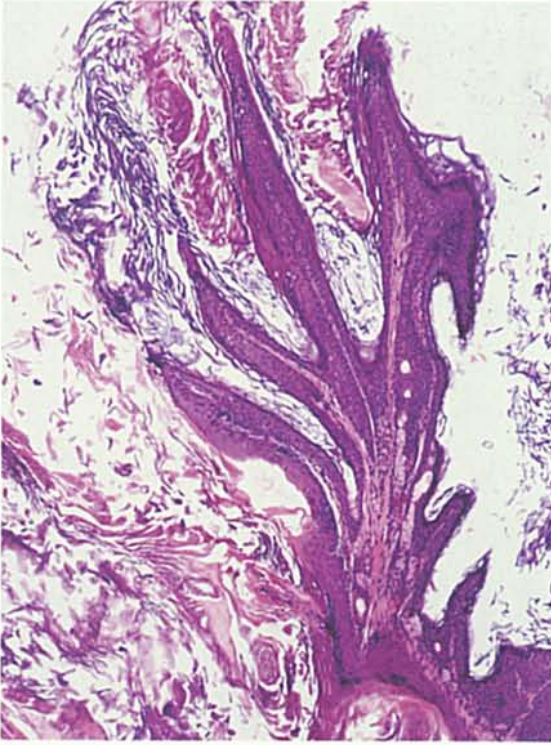


Fig. 5 – Squamous cell papilloma. Exophytic papillary projections of keratinized squamous stratified epithelium supported by fibrovascular stroma (H&E).

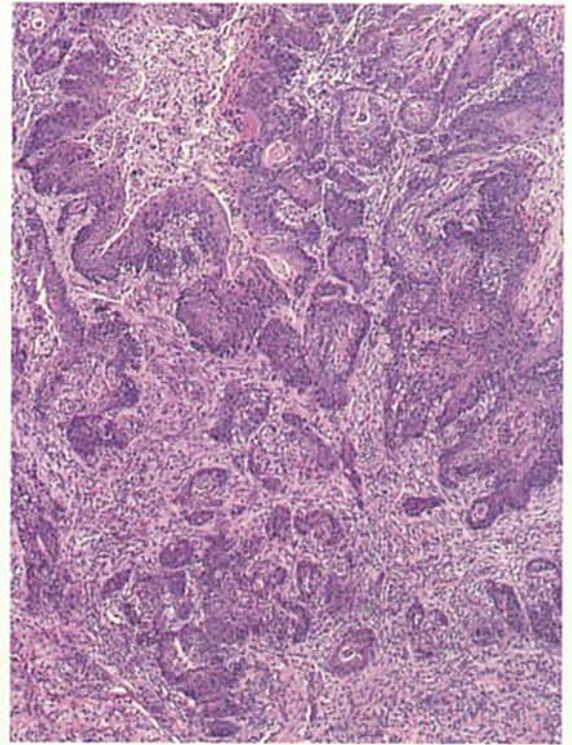


Fig. 6 – Squamous cell carcinoma. Cords and islands of pleomorphic squamous cells infiltrating the dermis (H&E).

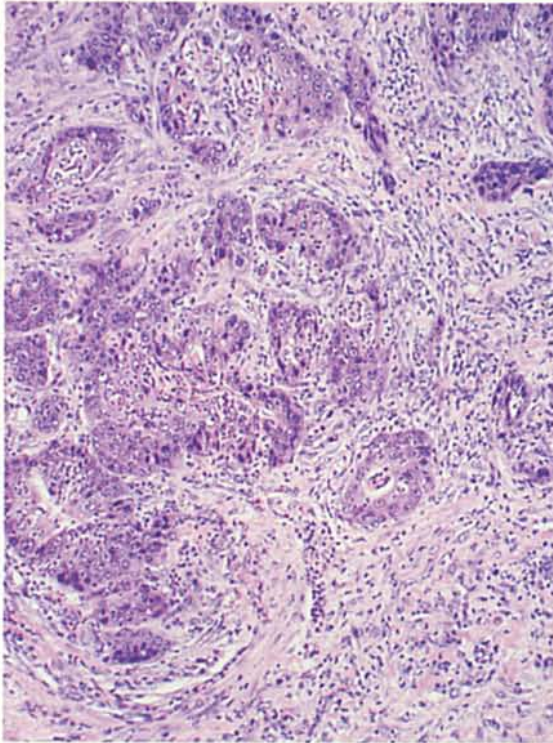


Fig. 7 – Squamous cell carcinoma. Higher magnification of Fig. 6, illustrating the infiltration of the dermis (H&E).

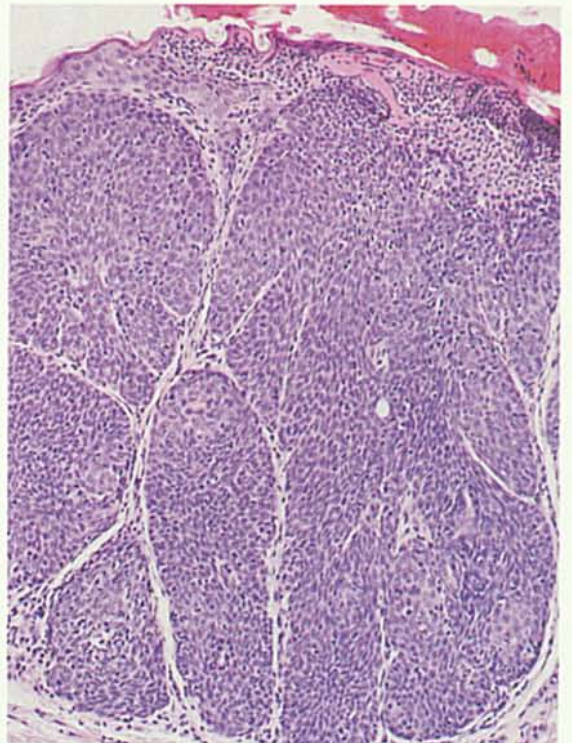


Fig. 8 – Basal cell tumor, benign. Lobules of basal cells without any evidence of invasion (H&E).

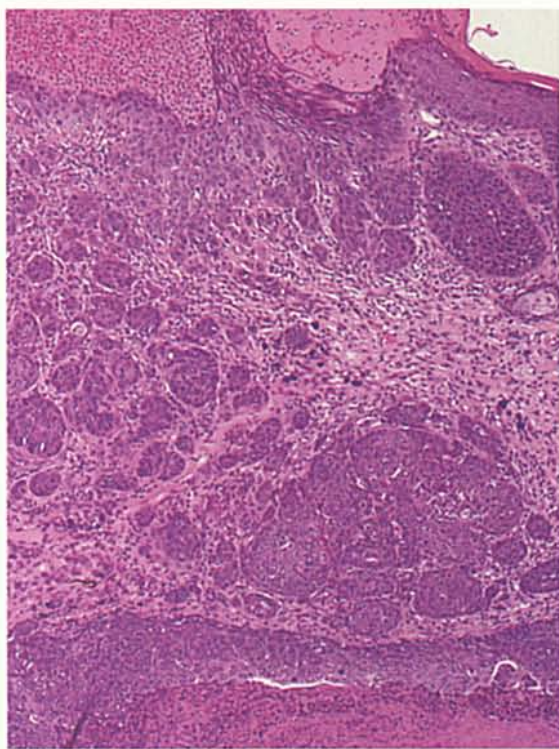


Fig. 9 – Basal cell tumor, malignant. Poorly-defined basal cell lobules and nests (H&E).

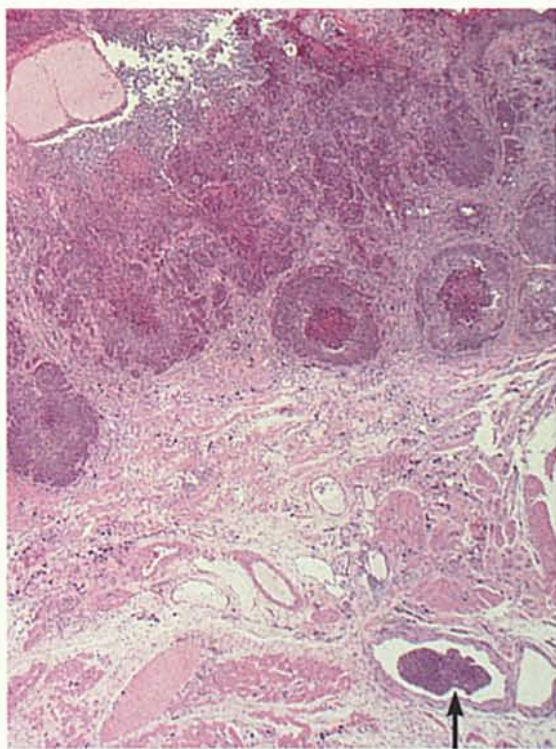


Fig. 10 – Basal cell tumor, malignant. Poorly-defined basal cell lobules and nests associated with comedo formation and lymphatic invasion (H&E).

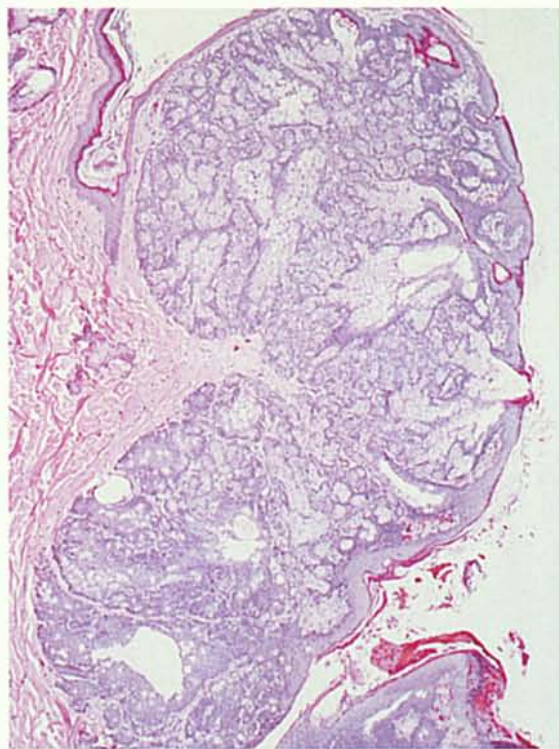


Fig. 11 – Sebaceous cell adenoma. Well-defined lobular mass with several cysts and mild compression of the adjacent tissue (H&E).

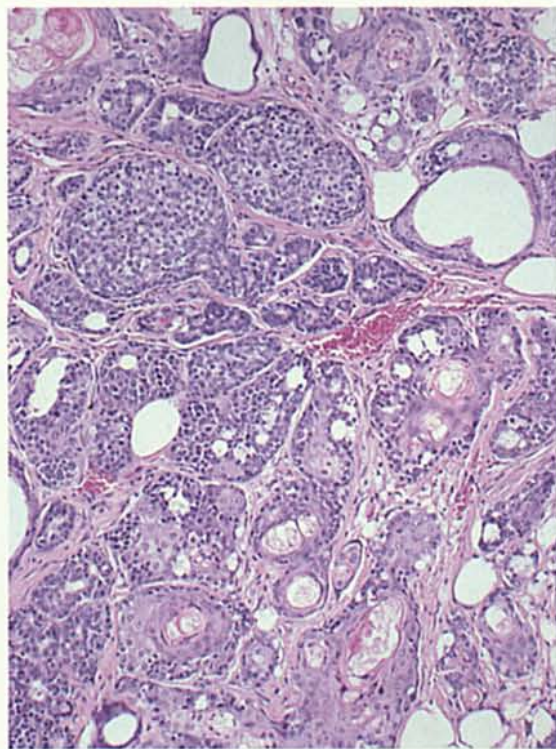


Fig. 12 – Sebaceous cell carcinoma. Irregular lobules composed of sebaceous and basal cells with dermal invasion (H&E).

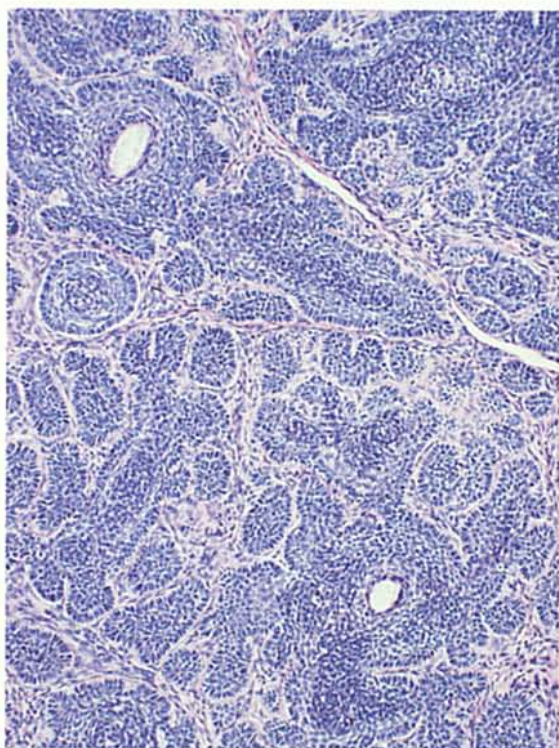


Fig. 13 – Trichoepithelioma. Cuboidal to columnar basal cells differentiating into immature hair follicles with nuclear palisading (H&E).

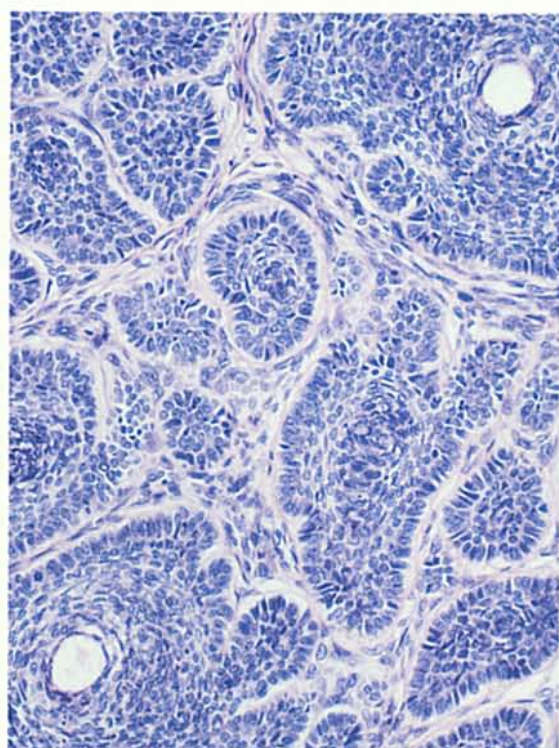


Fig. 14 – Trichoepithelioma. Higher magnification of Fig. 13 (H&E).

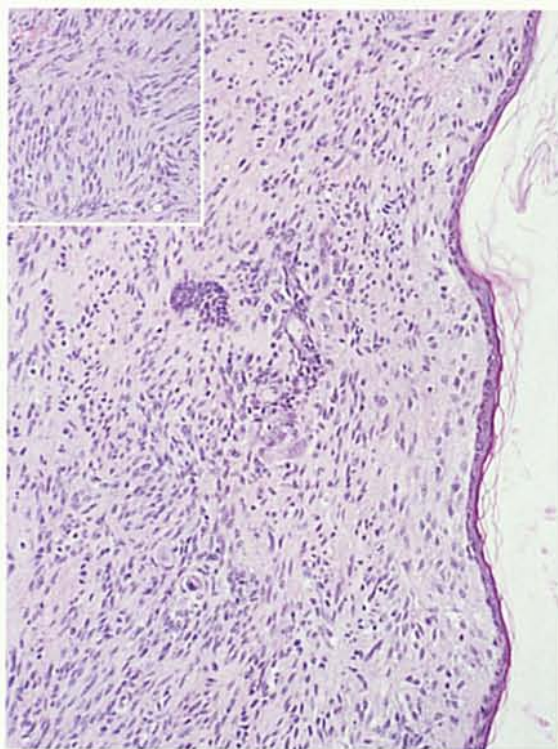


Fig. 15 – Amelanotic melanoma, pinna. Interlacing fascicles of spindle-shaped cells (inset) (H&E).

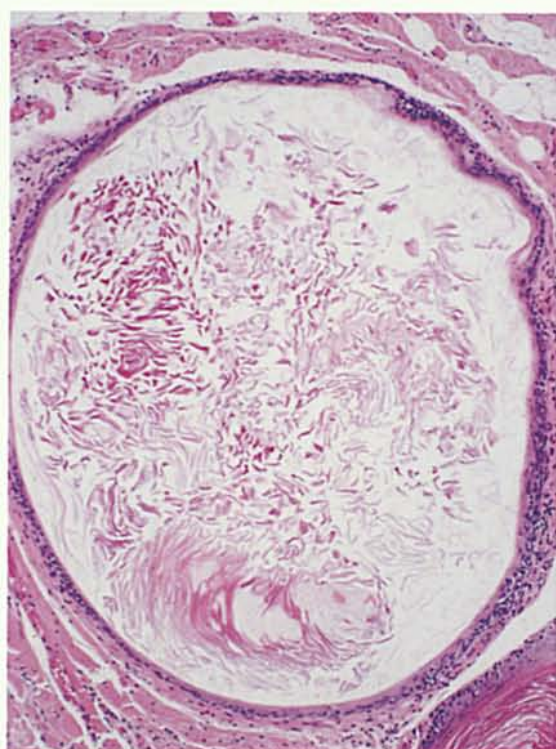


Fig. 16 - Epidermal inclusion cyst. A solitary cystic space filled with keratin and lined by simple squamous epithelium (H&E).

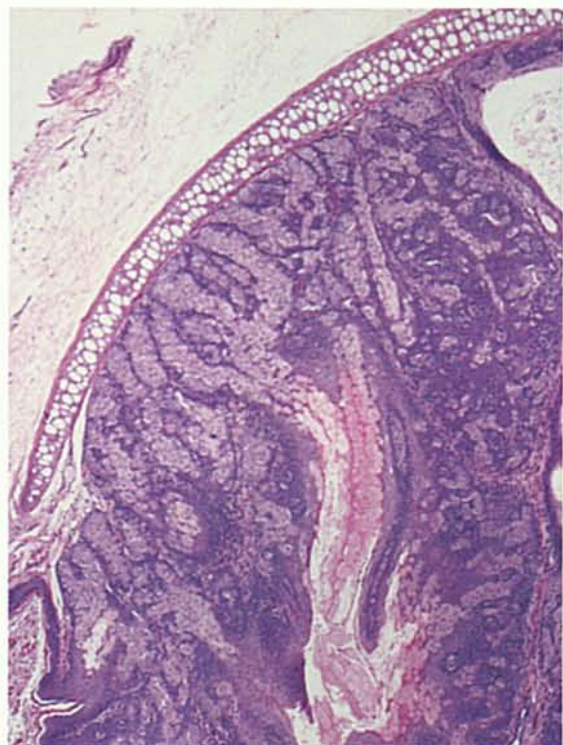


Fig. 17 – Adenoma, auditory sebaceous gland (Zymbal's gland). Well-differentiated sebaceous acini with mild compression of the adjacent tissue (H&E).

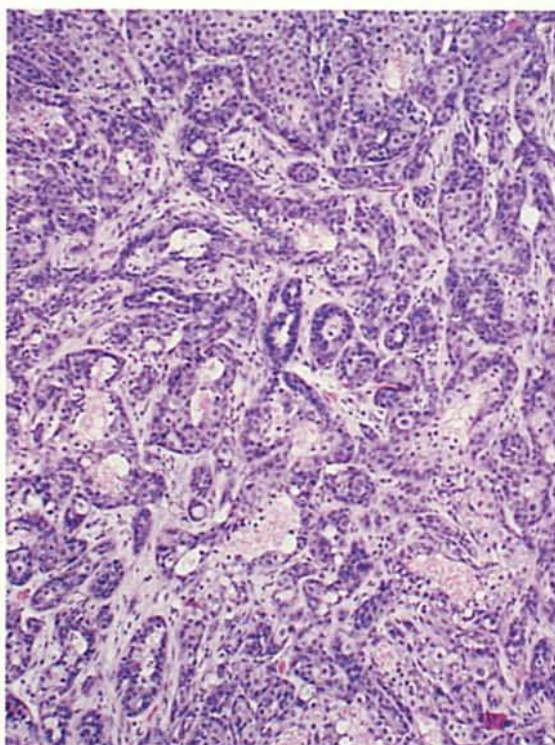


Fig. 18 – Carcinoma, auditory sebaceous gland (Zymbal's gland). Sebaceous acini of irregular shapes and sizes (H&E).

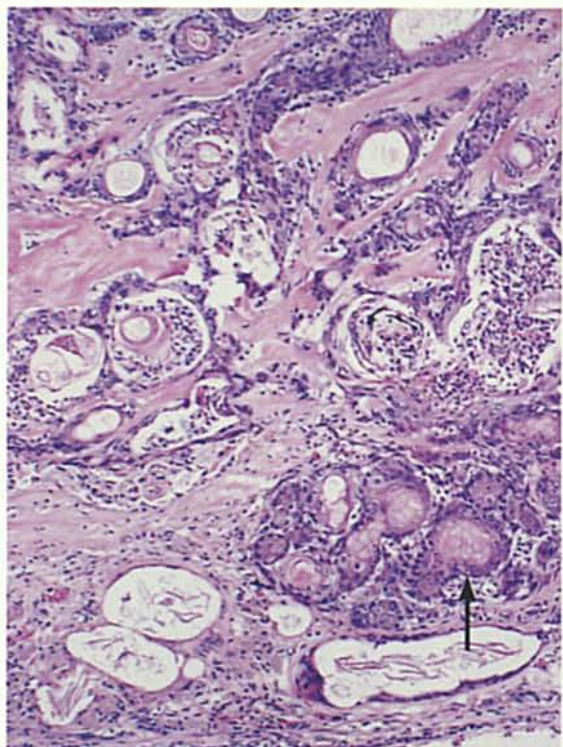


Fig. 19 – Carcinoma, auditory sebaceous gland (Zymbal's gland). Irregular sebaceous acini with invasion of the adjacent tissue (arrow) (H&E).

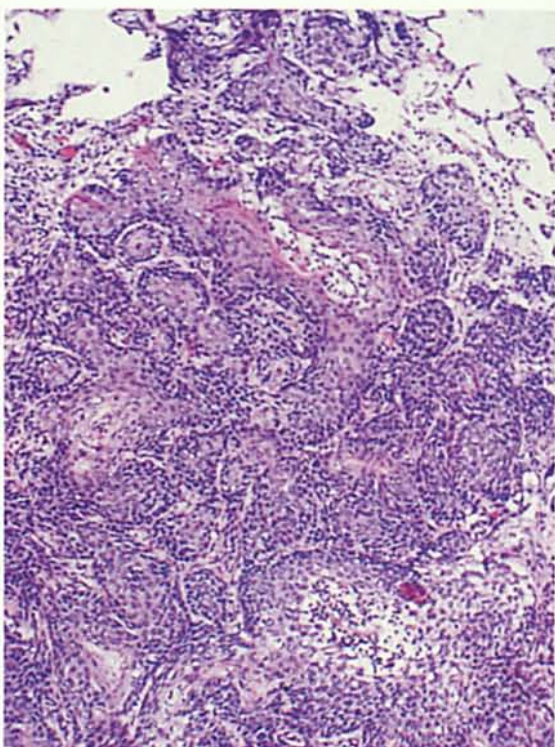


Fig. 20 – Pulmonary metastasis associated with carcinoma of the auditory sebaceous gland (Zymbal's gland) (H&E).

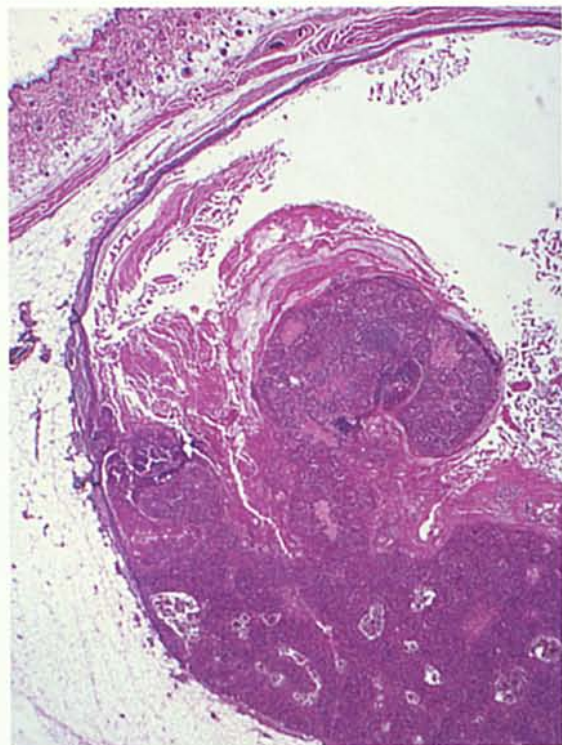


Fig. 21 – Adenoma, preputial gland. Well-defined mass (H&E).

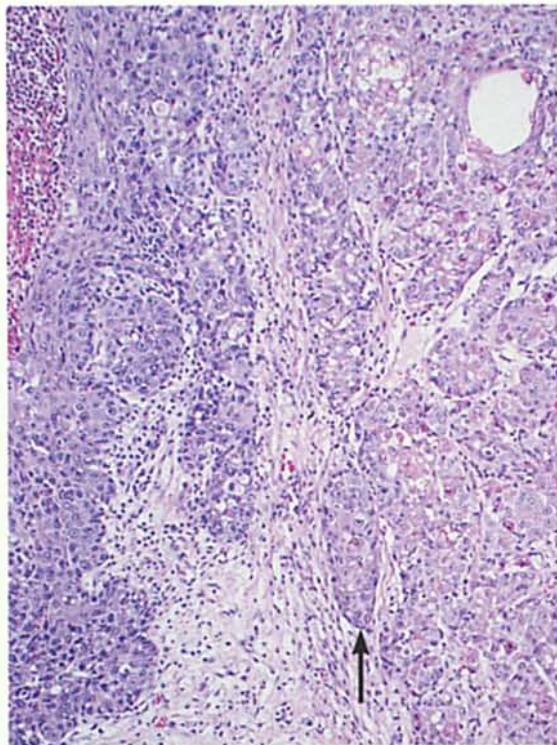


Fig. 22 – Carcinoma, preputial gland. Irregular acini and invasion of the adjacent tissue (arrow) (H&E).