

2.1 Introduction

Germ cell tumors are a varied group of benign and malignant neoplasms derived from primordial germ cells [1–10, 11–15] (Table 2.1 and Fig. 2.1). They occur in a variety of sites, both gonadal and extragonadal, the latter in midline locations as the sacrococcygeal, retroperitoneal, mediastinal, cervical, and pineal regions (Tables 2.2 and 2.3). *Teratoma* is the leading fetal and neonatal neoplasm in several reviews [9, 10, 12, 14, 16, 17] (Table 1.1). Most germ cell tumors of the fetus and infant are histologically benign and are diagnosed as either mature or immature teratomas (Table 2.2). *Yolk sac tumor*, second in frequency, occurs alone or in combination with a teratoma. Although yolk sac tumor of the cervix or vagina is the subject of a few case reports, yolk sac tumor of the infant testis is more prevalent and is the most common germ cell tumor arising from this organ [2, 4, 8, 20]. To my knowledge, neither yolk sac tumor nor teratoma of the ovary has been reported during the first year of life [7, 14].

The *World Health Organization (WHO) classification of germ cell tumors* is the basis for most contemporary classifications [2, 6, 10] (Table 2.1). According to this classification, germ cell neoplasms are divided into eight histologic types: *dysgerminoma*, *yolk sac tumor*, *embryonal carcinoma*, *polyembryoma*, *choriocarcinoma*, *teratoma*, *gonadoblastoma*, and *germ cell sex cord tumor* [6]. Moreover, *gonadoblastoma*, a neoplasm typically occurring in dysgenetic gonads, is included in this category of germ cell tumors, although granulosa and Sertoli cells are found in addition to germ cells [2, 5, 6, 19] (Fig. 2.30).

Table 2.1 WHO classification of germ cell tumors

1. Dysgerminoma
Variant – with syncytiotrophoblast cells
2. Yolk Sac Tumor (Endodermal Sinus Tumor)
Variants
Polyvesicular vitelline tumor
Hepatoid
Glandular (“endometrioid”)
3. Embryonal Carcinoma
4. Polyembryoma
5. Choriocarcinoma
6. Teratomas
(a) Immature
(b) Mature
Solid
Cystic (dermoid cyst)
With secondary tumor (specify type)
Fetiform
(c) Monodermal
Struma ovarii
Carcinoid
Mucinous carcinoid
Neuroectodermal tumors (specify type)
Sebaceous tumors
Others
Mixed (specify types) ^a
7. Gonadoblastoma
Variant – with dysgerminoma or other germ cell tumor
8. Germ Cell Sex Cord, Stromal Tumor
Variant – with dysgerminoma or other germ cell tumor

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^aFor example, immature teratoma + yolk sac tumor

Fig. 2.1 Origin of germ cell tumors; *indicates inclusion of dysgerminoma and seminoma (Reprinted from Teilum [5]. With kind permission of © Lippincott, 1976; From Isaacs [10, 15], with permission)

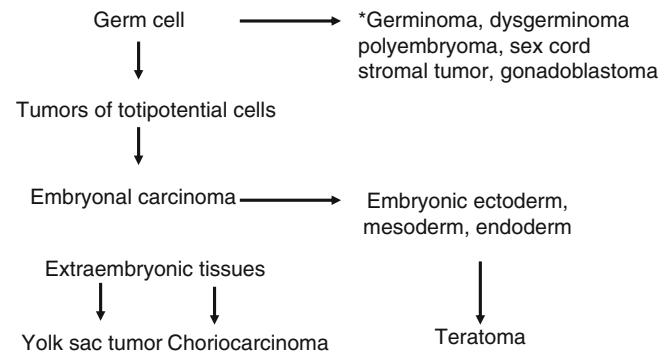


Table 2.2 Fetal and neonatal teratomas ($n=534$)

Location	Number	Sex histology	Survival (%)	Female	Male	NS	M I	NS	YST ^a
Sacroccygeal	214 (40.1) ^b	134	40	40	106	108	–	22	67
Intracranial	71 (13.3)	32	34	5	6	56	7	2	11
Cervical	70 (13.1)	34	35	1	26	43	–	–	66
Palatal and nasopharyngeal	41 (7.7)	18	17	1	27	12		2	56
Cardiac	40 (7.5)	18	15	6	8	15		2	75
Fetus-in-fetu ^c	25 (4.5)	11	14	7	21	3		1	96
Gastric	14 (2.6)	3	11	–	7	7		–	100
Orbital	13 (2.4)	10	3	–	8	4		1	85
Mediastinal	13 (2.4)	7	5	–	4	9		–	69
Facial	8 (1.5)	6	2	1	7	1		–	87
Placenta	8 (1.5)	4	4	–	6	2		–	75
Miscellaneous ^d	17 (3.2)	7	10	–	11	6		1	76
Overall survival	335 (63 %)								

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Abbreviations: I immature teratoma, M mature teratoma, NS not specified, YST yolk sac tumor

^aOverall incidence of yolk sac tumor 6 %; survival of fetuses and neonates with yolk sac tumor 39 %

^b() = percent

^cFetus-in-fetu: retroperitoneum 18 (72 %); hard palate 2 (20 %); 1 each undescended testis, scrotal sac, intrahepatic, attached to ovary, sacroccygeal

^dMiscellaneous: tongue, tonsil, retroperitoneum, eye, mesentery, ileum, testis, vulva, anorectal area

Table 2.3 Clinicopathological features of fetal and infant germ cell tumors

Tumor	Clinical findings	Pathological findings
Teratoma	Mass at site of origin, e.g., sacroccygeal and cervical areas	Mature: tissues derived from the 3 germ layers; Immature: immature tissues mostly neuroglial and neuroepithelial elements: GFAP +, NSE +, S-100 +
Fetus-in-fetu	Fetiform mass occurs most often in retroperitoneal area	Mature tissues; vertebral axis and long bones present; heart and brain absent
Yolk sac tumor	Mass at site of origin, testis and sacroccygeal areas main sites; ±association with a teratoma	Six histologic patterns; reticular and papillary most common ones in infants, netlike and papillary formations, perivascular Schiller-Duval bodies; PAS+ hyaline droplets; α-FP+ cytoplasm
Gonadoblastoma	Gonadal dysgenesis, 46XY or 45X0/46XY karyotypes; flecks of calcification on imaging studies	Malformed gonad(s), e.g., streak ovary, with small, tan calcified nodules; large germ cells encircled by smaller round, darkly staining Sertoli and/or granulosa cells forming microfollicles with hyaline bodies and foci of calcification
Embryonal carcinoma ²	Mass; usually not associated with a teratoma in infants	Poorly differentiated, malignant tumor with large primitive embryonal-appearing epithelial cells with vesicular nuclei and characteristic large nucleoli; solid, papillary, and glandular patterns; cytokeratin +, NSE +, placental alkaline phosphatase and NSE +; HCG, and α-FP variable staining
Polyembryoma	Gonadal or sacroccygeal mass; found in combination with yolk sac tumor	Tiny embryoid bodies with 2 cavities separated by a 2–3 cell layer embryonic disc; α-FP, hCG +, and α1-antitrypsin +
Choriocarcinoma	Mass (s), widespread metastases on imaging studies; severe bleeding tendencies; increased serum and urinary hCG	Soft, hemorrhagic, necrotic mass(es); cytotrophoblasts and giant syncytiotrophoblasts with cells intermediate between the two; hCG+, cytokeratin +, α-FP

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Abbreviations: α-FP alpha-fetoprotein, GFAP glial fibrillary acidic protein, hCG human chorionic gonadotropin, NSE neuron-specific enolase, PAS periodic acid-Schiff reaction

2.2 Cytogenetics

Nonrandom structural aberrations most often involving chromosomes 1 and 12 have been described in germ cell tumors [21]. The chromosomal patterns of malignant ovarian and testicular germ cell tumors are alike, and thus, these tumors are similar and may have the same origin and pathogenesis. The cytogenetic anomalies described are a hypertriploid/hypotetraploid chromosome number, presence of $i(12p)$, and overrepresentation of chromosomes [3, 21–23]. Investigations in extragonadal and testicular germ cell tumors show that they arise mitotically from either a somatic or a germ cell [22, 23].

Transcription factors GATA-4 and GATA-6 are expressed in pediatric yolk sac tumors and in teratomas [22, 23]. They play critical roles in mammalian yolk sac differentiation and function. GATA-6 is expressed not only in most yolk sac tumors but also in nonmalignant tissues including gut and respiratory epithelium, sebaceous cells, and neuroepithelium in mature and immature teratomas. GATA-6 can be used to identify yolk sac components in pediatric germ cell tumors. In addition, it is expressed in specific tissues in teratomas [22, 23].

2.3 Teratoma

Teratoma is defined as a true tumor composed of multiple tissues foreign to, and capable of growth in excess of, those characteristic of the part from which it is derived [10].

However, it is sometimes difficult to make a distinction between teratomas and structures that result from abortive attempts at twinning. An even progression can be traced from normal twins to conjoined twins, parasitic twins, fetus-in-fetu, and teratoma [10]. Careful studies reveal a break in the progression from an oriented, longitudinal, partially symmetrical structure of a twin to the jumbled, disordered, irregular growth of a teratoma in which one, two, or three tissues predominate [10]. Despite the apparent progression from twins to fetus-in-fetu to teratomas, some investigators feel that this relationship does not exist. The distinction is based primarily on the fact that teratomas are capable of independent growth, whereas structures included under malformations are limited in their potentiality for growth to a rate similar to the part of the body they resemble [10].

Teratomas are observed in several locations at birth, but the most common ones are the sacrococcygeal, cervical, and retroperitoneal areas [1–4, 7, 12, 14, 15, 17] (Table 2.2) (Figs. 2.2, 2.3, 2.4, and 2.10). Other locations are the brain, anterior mediastinum, stomach, heart and pleura, pharynx, base of the skull, upper jaw, gonads, pelvis, liver, and subcutaneous tissue [3, 4, 7, 10, 15, 24–28] (Figs. 2.5, 2.6, 2.8, 2.9, 2.10, 2.11, and 2.12). Intracranial teratomas are not uncommon in the fetus and newborn [14, 27]. The types of tissues found in fetal and infant teratomas are practically the same regardless of the site of origin [10, 15].

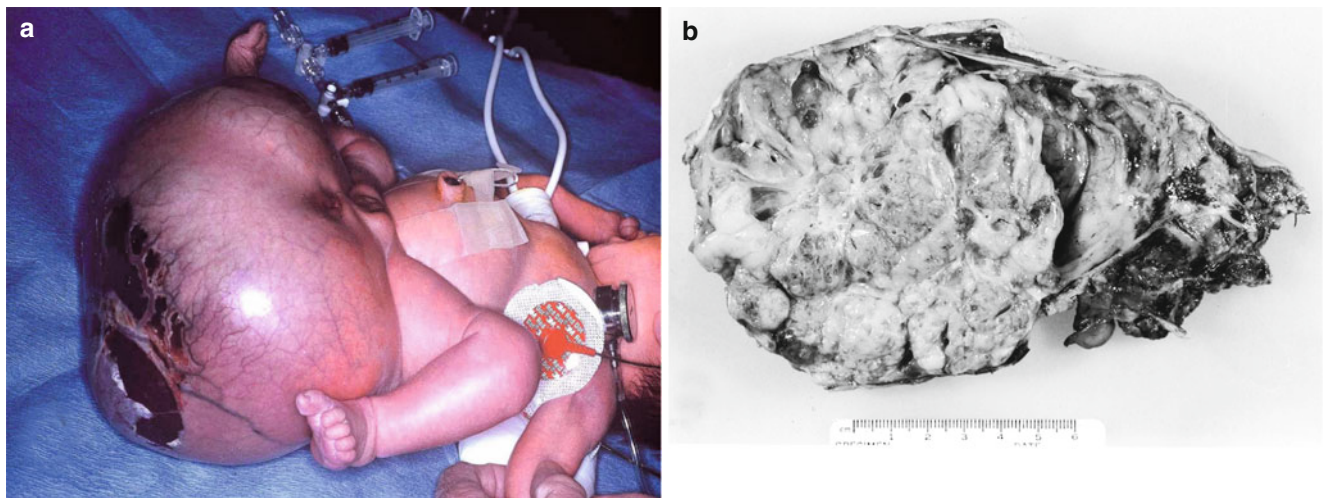


Fig. 2.2 Solid sacrococcygeal teratoma. Sonography at 30 weeks gestation revealed a large abnormality in the sacral region. Shortly before delivery, fetal distress was noted and a cesarean section was performed. (a) The 4.4-kg female was born at 37 weeks gestation with a huge sacrococcygeal tumor. (b) The tumor excised at 1 day of age weighed 1.5 kg (1/3rd the baby's birth weight) and measured 15 × 13 × 10 cm.

The bisected tumor with a variegated solid and cystic appearance. Skin partially covers the periphery of the specimen. Microscopically, the tumor consists of immature neuroglial elements in addition to a variety of mature tissues typically found in these teratomas (see Figs. 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, and 2.22) (Reprinted from Isaacs [15], with kind permission of © Springer-Verlag, 2002)

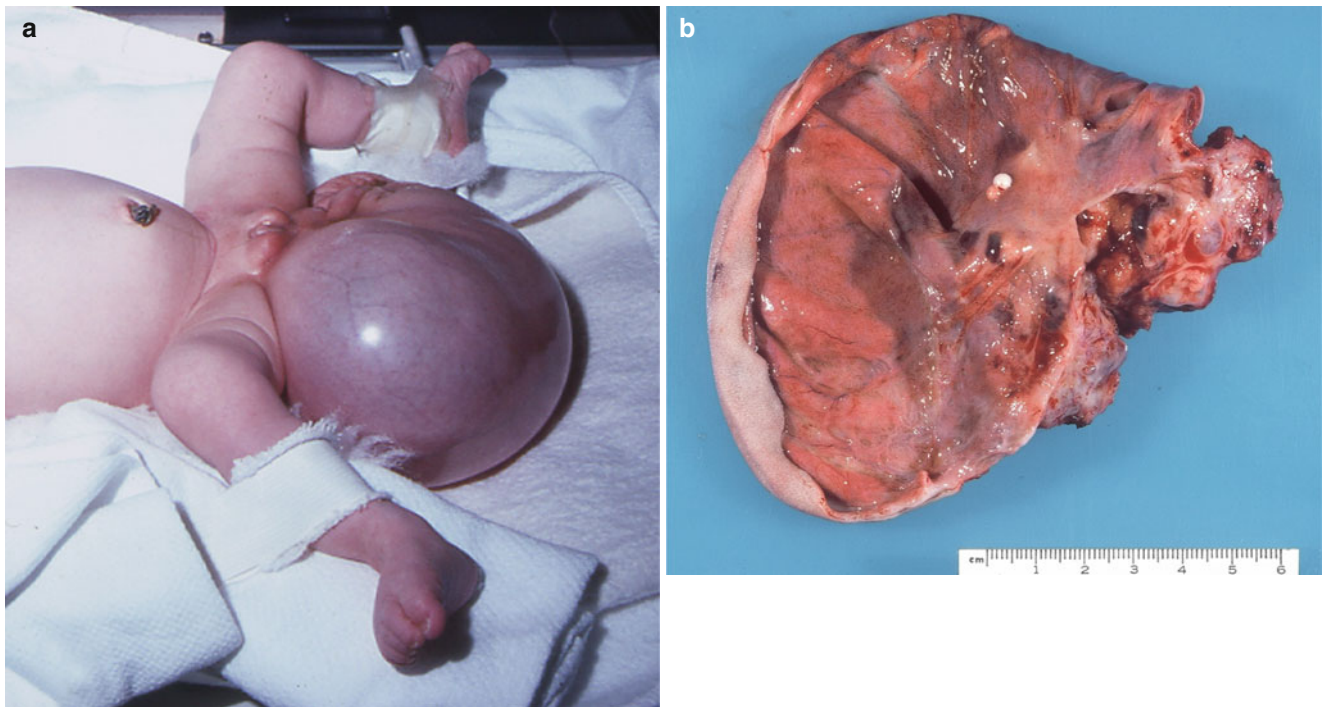


Fig. 2.3 Cystic sacrococcygeal teratoma. (a) 12-day-old, 4.5-kg female, product of a full-term gestation, was delivered by cesarian section because of dystocia. The external genitalia and anus are displaced anteriorly by the mass. (b) Gross specimen, 1,090 g, $18.5 \times 12.4 \times 9.8$ cm,

consisted mostly of a large cyst partially covered by skin. The cyst was filled with 900 ml of clear fluid which was drained prior to removal. Microscopically, the teratoma consisted of both mature and immature tissues (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

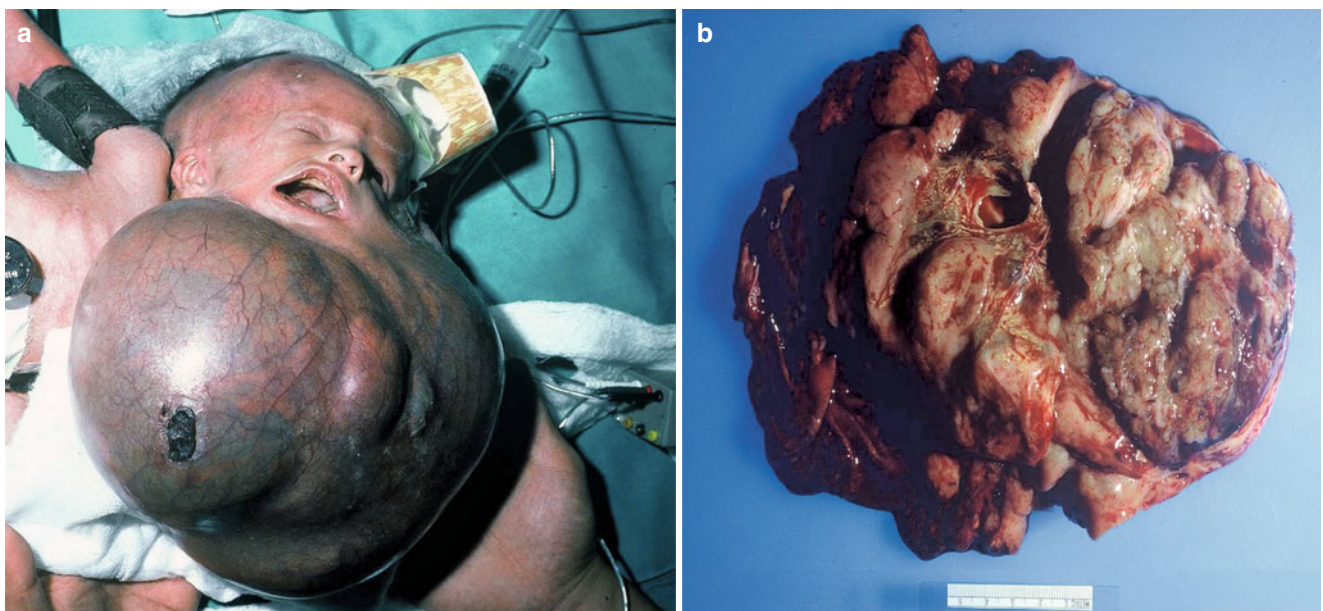


Fig. 2.4 Thyrocervical teratoma. (a) 2-week-old male with a gigantic teratoma arising from the neck producing maternal dystocia. (b) The specimen weighed 1,184 g, measured $24 \times 15 \times 8$ cm, and consisted of

both mature and immature neural tissue in addition to cartilage, respiratory, and gastrointestinal epithelium (Reprinted from Tumors Isaacs [15]. © Springer-Verlag, 2002)

Fig. 2.5 Pharyngeal teratoma with great distortion of the facial region. **(a)** Lateral view of the body surface. **(b)** Sagittal section through the midline showing the extent of the tumor (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

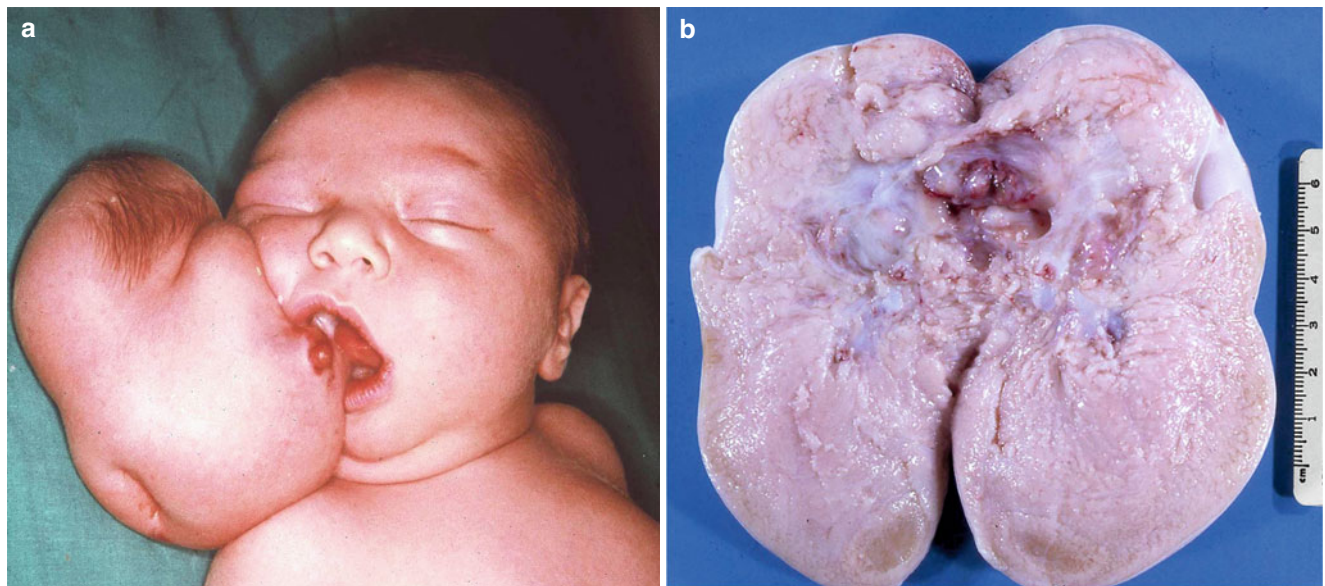
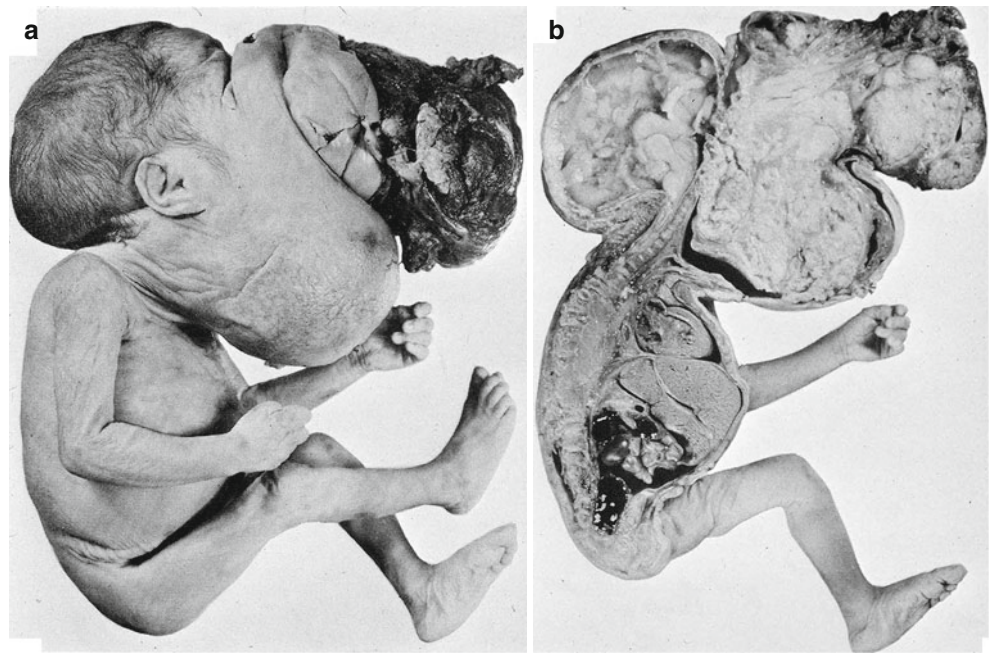


Fig. 2.6 Epignathus. **(a)** 4-day-old, full-term male infant with a solid teratoma attached to the right side of the hard palate. **(b)** The specimen consists mostly of fat. There is an appendage-like protrusion sticking out on the left side. The central nodular area is composed of mature tissues consisting of brain, gastrointestinal tract, and bone. Although

the tumor is suggestive of “fetus-in-fetu” microscopically, neither a well-defined vertebra nor structural organization of the tissue components were found (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

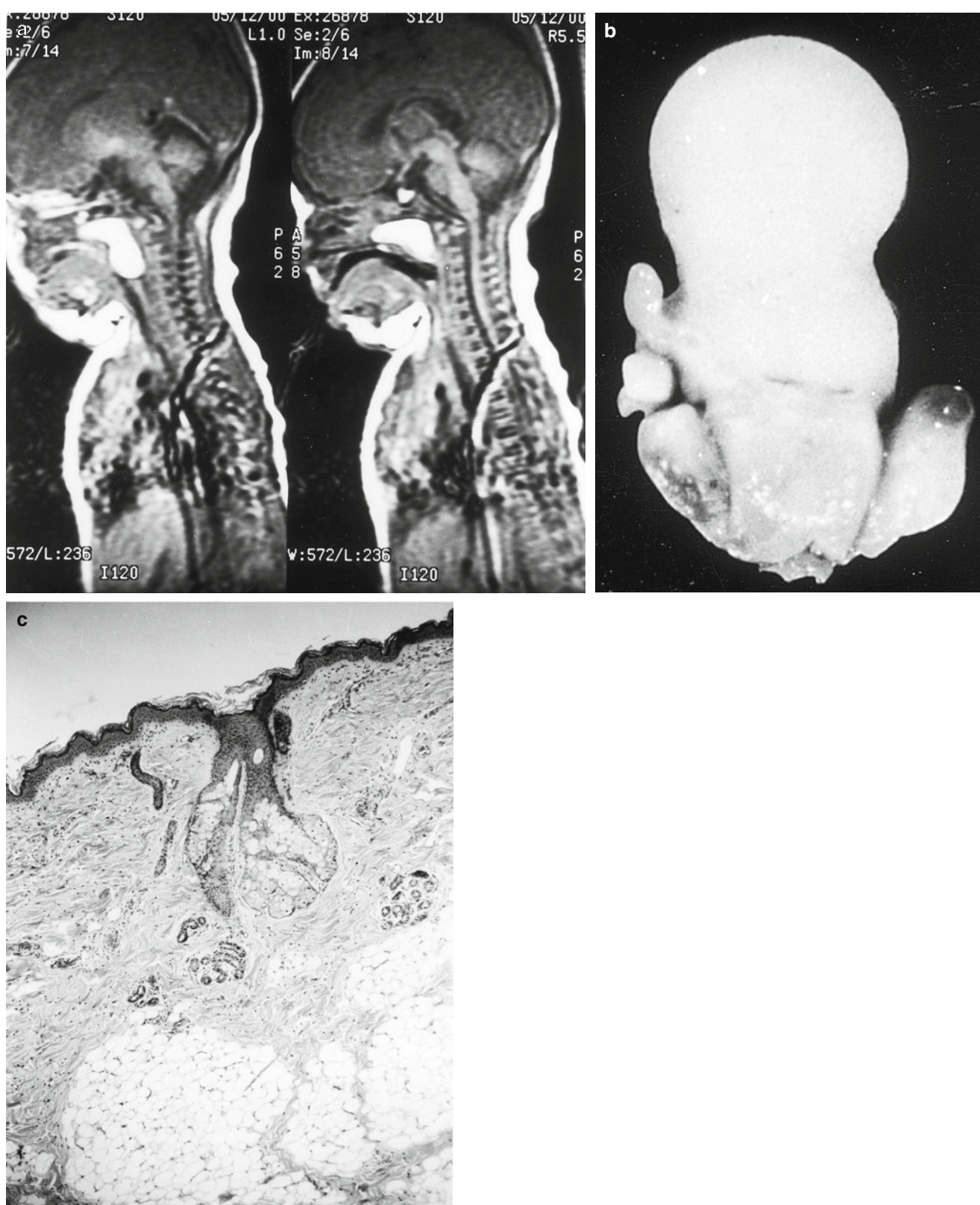


Fig. 2.7 Nasopharyngeal dermoid ("hairy polyp"). Intermittent respiratory distress related to positioning of the infant was noted shortly after birth. Laryngoscopy revealed a fingerlike projection protruding from and obstructing the nasopharynx. (a) Radiograph shows a bright white mass within the nasopharynx and oropharynx with signal

characteristics of fat. (b) The polyp consists only of skin with hair follicles, fat, and cartilage, which is not shown. (c) Histologically the polyp consists only of skin with hair follicles, fat and cartilage, not shown in this field. (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

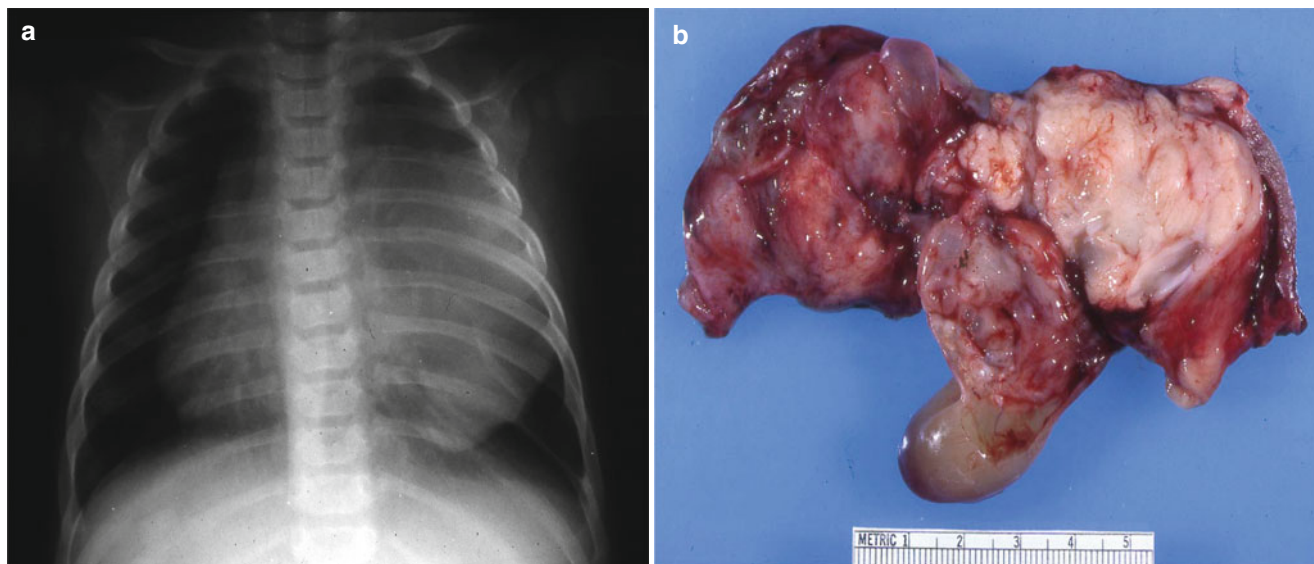


Fig. 2.8 Mediastinal teratoma. 4-month-old male was evaluated for an upper respiratory infection. A mediastinal mass was discovered on a chest radiograph. **(a)** Chest radiograph shows the mass occupying the

right thoracic cavity. **(b)** The teratoma is attached to the thymus and consists of both mature and immature tissues (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

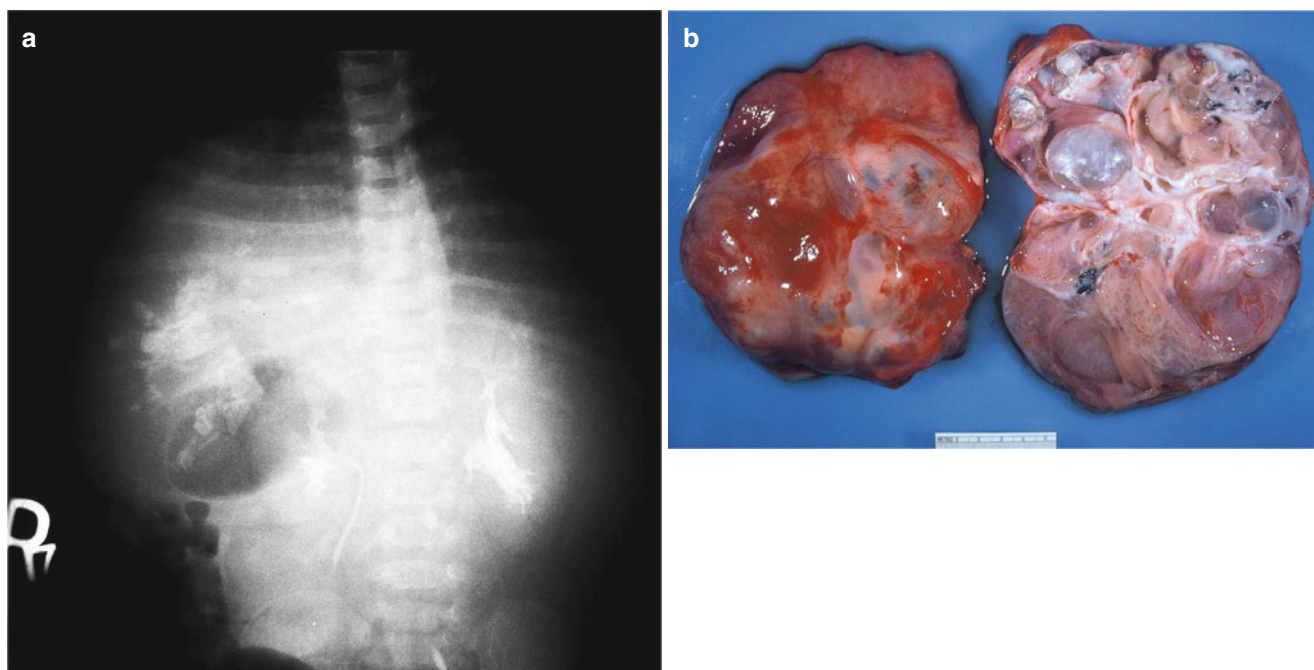


Fig. 2.9 Gastric teratoma. 4-month-old male with a history of constipation, progressive abdominal distension vomiting, feeding problems, and an abdominal mass. **(a)** Intravenous pyelogram reveals a tumor arising from the lesser curvature of the body of the stomach. **(b)** The cystic and

solid tumor measures 16×14 cm and contains immature neuroglial tissue, skin, choroid plexus, gastrointestinal and respiratory epithelium, and cartilage (Reprinted from Isaacs [15], © Springer-Verlag, 2002)

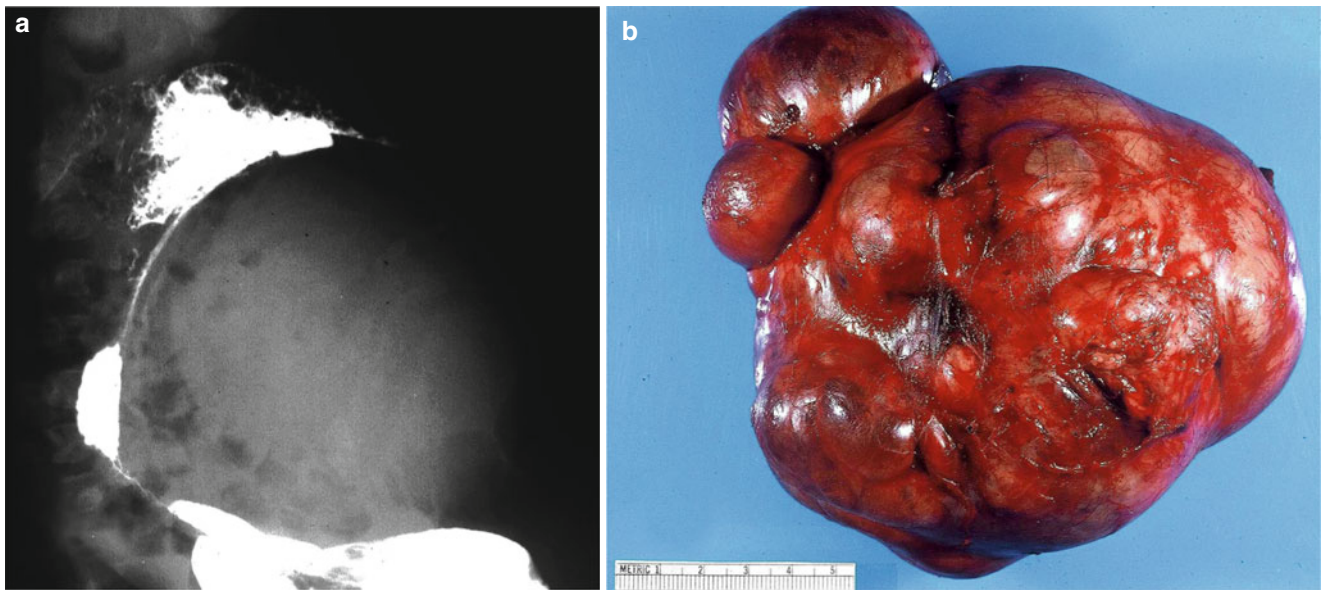


Fig. 2.10 Retroperitoneal teratoma. The patient was a 2-month-old male with a history of constipation, progressive abdominal distension and an enlarging abdominal mass since birth. **(a)** Abdominal imaging reveals compression of the intestine by a large retroperitoneal mass

situated anterior to the spine. **(b)** The specimen, 799 g, 15×15×6 cm, consists of solid and cystic areas. Both mature and immature tissue elements are present histologically (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

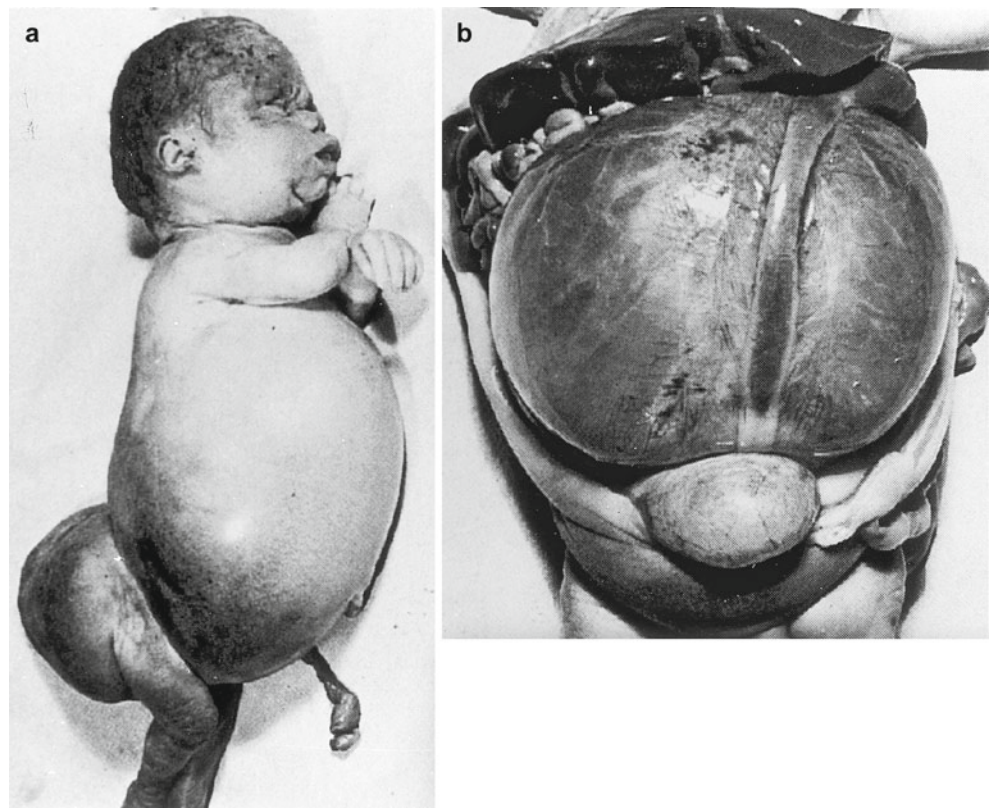


Fig. 2.11 Newborn female infant with combined pelvic and retroperitoneal immature teratoma. **(a)** External appearance. **(b)** Large tumor with overlying sigmoid colon. The bladder is distended as a result of urethral obstruction. The teratoma consists of both mature and immature neuroglial elements (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

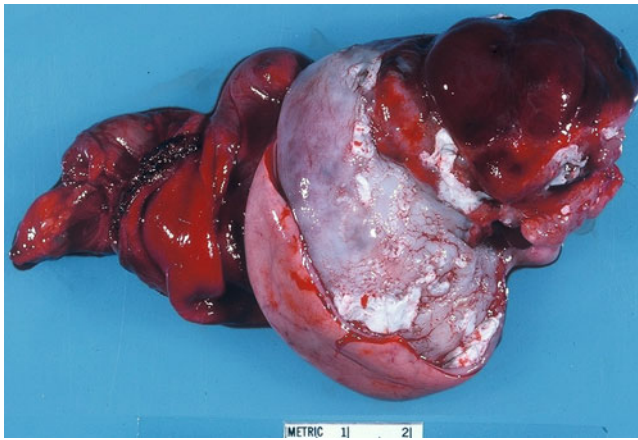


Fig. 2.12 Immature teratoma of the testis. The patient is a 1-year-old male operated on because of bilateral inguinal hernias and what was thought to be a left-sided hydrocele. Instead, an enlarged testis was found that measures 7.5×5×3.5 cm. The cut surface of the testis reveals a tumor composed of skin, sebaceous material, hair, and multiple cysts. In addition to skin, bone, and gastrointestinal tract epithelium, immature neuroglial elements are present histologically (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

2.3.1 Clinical Findings

Teratoma is the leading germ cell tumor of the fetus and infant typically presenting as an obvious mass with signs and symptoms referable to the location of origin [10, 12, 14, 15] (Table 2.3). Half of childhood teratomas are congenital, and in some series, they are the most common tumor overall [4, 7, 10, 13, 16–18] (Table 1.1). They are discovered as unexpected or incidental findings on routine prenatal or neonatal imaging studies, in a stillborn, as a mass during a newborn physical examination or later on during a routine follow-up visit or for some other unrelated clinical problem. Although a teratoma is defined as benign histologically, it may cause death if vital structures are involved or if the airway is compromised [7, 10, 15, 24, 25, 28] (Fig. 2.6).

Significant congenital anomalies are associated with certain types of teratomas [10, 15, 28, 29]. They depend on the site of the primary tumor and vary considerably in their appearance and extent. For example, single or combined malformations of the genitourinary tract, rectum and anus, and vertebra and caudal spinal cord are found in some patients with sacrococcygeal teratomas [10, 29]. Large, disfiguring cleft palate defects occur in newborns with extensive cranial, palatal, and nasopharyngeal neoplasms [4, 10, 28].

Several unique clinical presentations associated with large space-occupying congenital teratomas are described. They include nonimmune fetal hydrops; respiratory distress and/or hemoptysis resulting from a mediastinal teratoma compressing or eroding into the airway; polyhydramnios occurring with epignathus and cervical tumors because the fetus cannot swallow amniotic fluid; stillbirths resulting

from intracranial teratomas and maternal dystocia (difficult delivery) caused by large intracranial, pharyngeal, cervical, and sacrococcygeal teratomas; and gigantic exophthalmos and massive hydrocephalus secondary to orbital and cranial teratomas, respectively [10, 12, 15] (Table 1.2). Failure to establish respirations due to airway obstruction or compression may be the initial finding in a newborn with a nasopharyngeal, tonsillar, palatal, cervical, or mediastinal teratoma [10, 15, 25, 28] (Figs. 2.4, 2.5, and 2.6). Some palatal (epignathic), thyrocervical, and nasopharyngeal teratomas are so large that they are not resectable and cause death by asphyxia at birth [10, 15, 28] (Fig. 2.6).

2.3.2 Pathology

Teratomas are composed of tissues representing each of the three layers derived from the embryonic disc [1, 2, 4, 6, 10] (Table 2.3 and Figs. 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, and 2.19). Endodermal components are the least common, but at times, intestinal or gastric mucosa is remarkably well developed and may be surrounded by muscle layers. Ectodermal components, especially brain tissue, make up a large portion of most teratomas that are present at birth and are more prominent in these than in such tumors discovered later in life. This is particularly true of the sacrococcygeal group. The tissue of these tumors for the most part resembles neuroglia (Figs. 2.14 and 2.15), although ganglion cells and cavities lined by cells simulating ependyma and choroid plexus are not uncommon [10, 15] (Figs. 2.13, 2.20, 2.21, and 2.22).

The *immature teratoma* consists primarily of embryonic-appearing neuroglial or neuroepithelial components, which may coexist with mature tissues. They may display a worrisome histologic appearance because of their hypercellularity, nuclear atypia, and increased mitotic activity (Figs. 2.21, 2.22, 2.23, 2.24, and 2.25). In most instances, immature teratomas, high grade or otherwise, occurring in the fetus and infant are considered benign and associated with a favorable prognosis [10, 15, 30]. The presence of microscopic foci of yolk sac tumor rather than the grade of immature teratoma, per se, is the only valid predictor of recurrence in pediatric immature teratomas at any site [10, 15] (Fig. 2.26). Therefore, grading of immature teratomas in the young child is not required at any site [10, 15, 30].

The neuroectodermal components of a teratoma are variably immunoreactive for one or more neural markers including GFAP, NSE, S-100, neurofilament protein, synaptophysin, nerve growth factor receptor, glial filament protein, myelin basic protein, and polysialic acid [10] alpha-fetoprotein (α -FP) (Fig. 2.28e); immunoreactivity in immature teratomas is generally confined to hepatic tissue, intestinal type epithelium, and yolk sac tumor, if present [10]. DNA ploidy,

Fig. 2.13 Mature teratoma with skin, neuroglial tissue, and choroid plexus. Most teratomas contain these tissues, which were found in tumors described in Figs. 2.2, 2.3, 2.4, 2.5, 2.6, 2.8, 2.9, 2.10, 2.11, and 2.12 (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

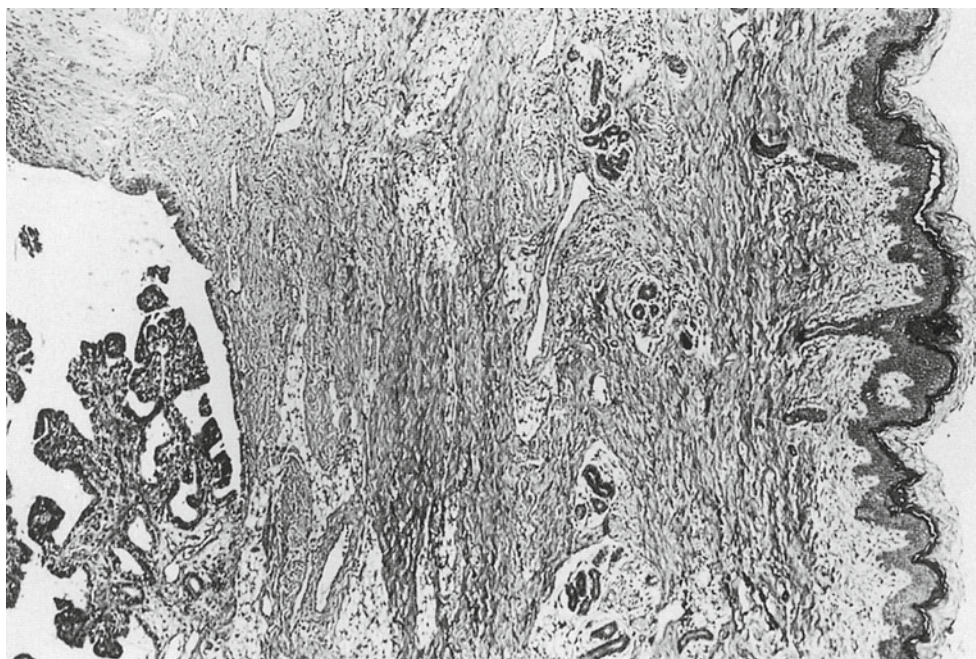
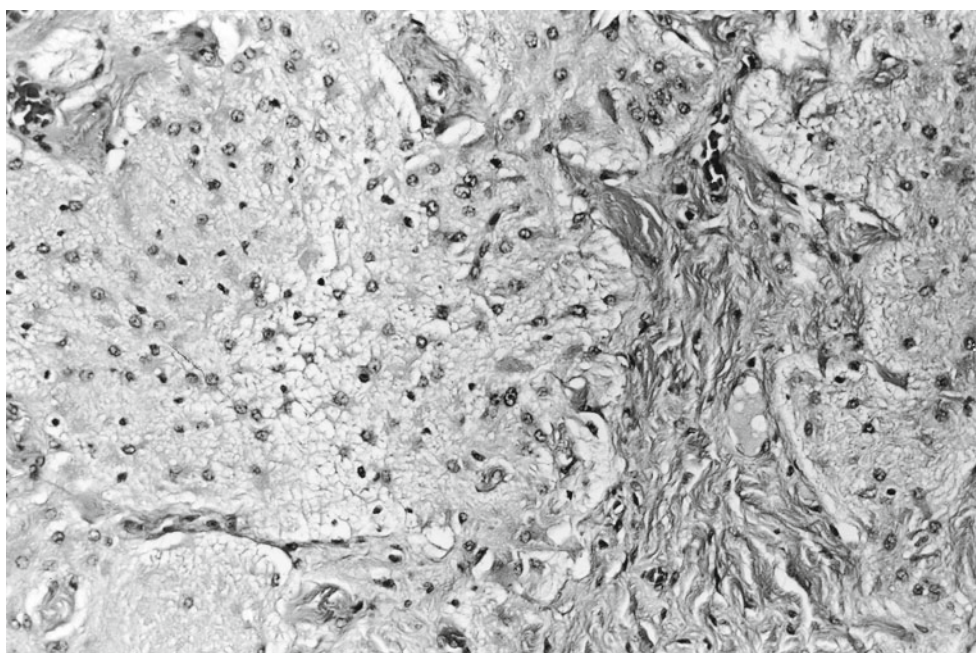


Fig. 2.14 Neuroglial tissue is found often in both mature and immature teratomas. Section taken from a mature teratoma of the testis (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)



p53 and ret expression in teratomas are discussed by Herrmann et al. [31]. Occasionally, tissues other than neural in origin such as nodular renal blastema are found in the immature teratoma [4, 10] (Fig. 2.20).

Epidermis and dermal structures including hairs and sebaceous and sweat glands and fairly well-developed teeth are generally present (Figs. 2.13 and 2.17). Varieties of epithelium

include columnar, pseudostratified, stratified, ciliated and nonciliated, secretory and nonsecretory. Glands in addition to those derived from the skin include salivary, thyroid, pancreas, adrenal, and others. Tissues resembling kidney, liver, and lung are uncommon. Mesodermal components as fat, cartilage, bone, and muscle are present in almost all congenital teratomas [10, 15] (Figs. 2.13, 2.15, and 2.16).

Fig. 2.15 Photomicrograph of a mediastinal teratoma composed of neuroglial tissue with cysts lined by a variety of epithelium in addition to cartilage and salivary gland (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)



Fig. 2.16 Mature sacrococcygeal teratoma with small intestine and cartilage components (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

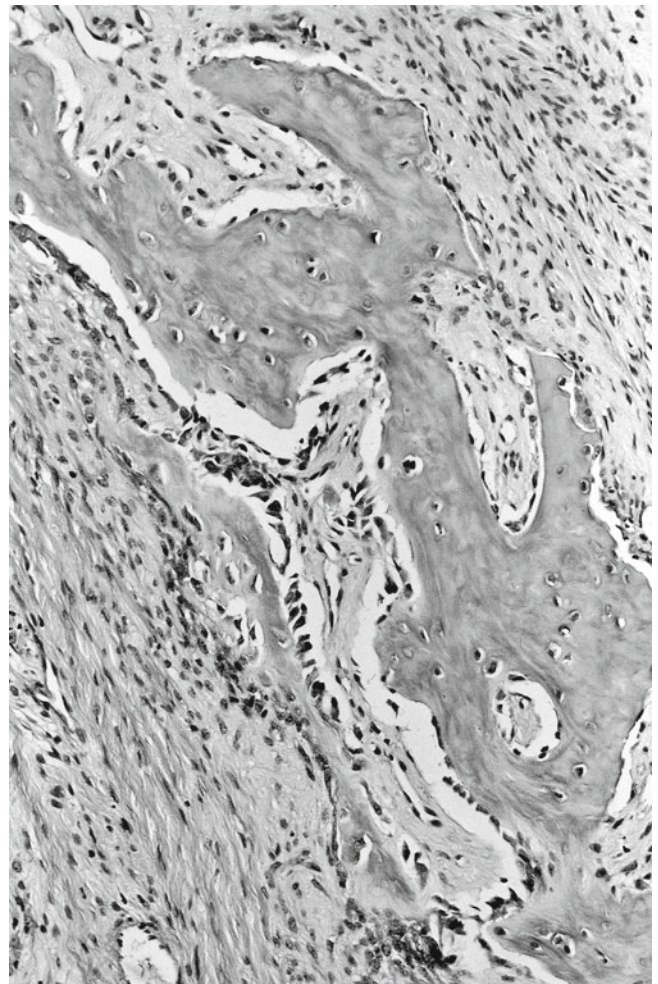


Fig. 2.17 Bone from a testicular teratoma. Bone is present frequently in mature teratomas (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

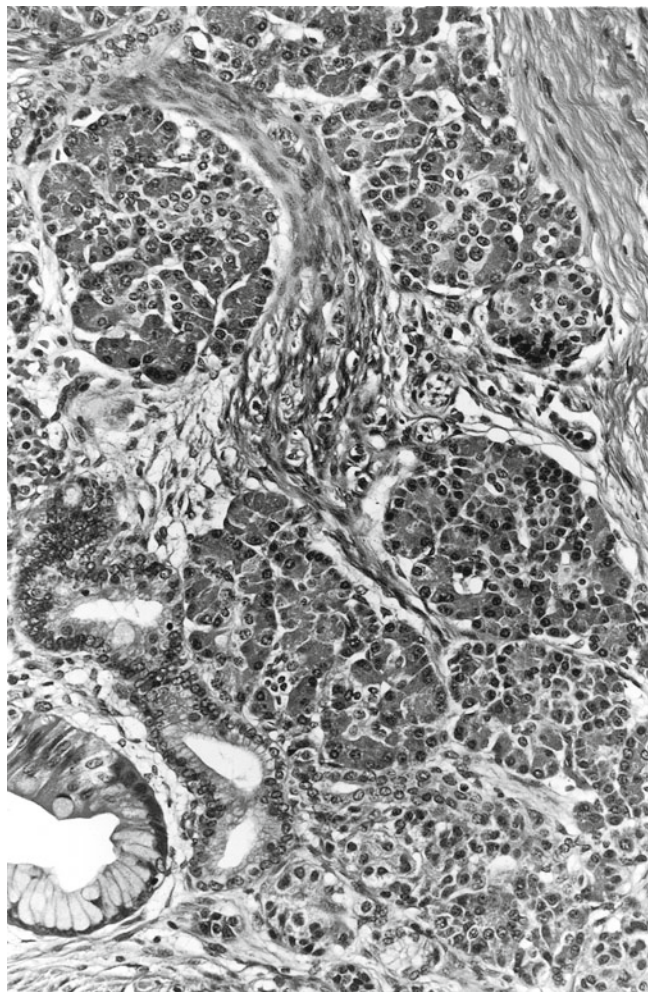


Fig. 2.18 Mature sacrococcygeal teratoma with pancreas (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

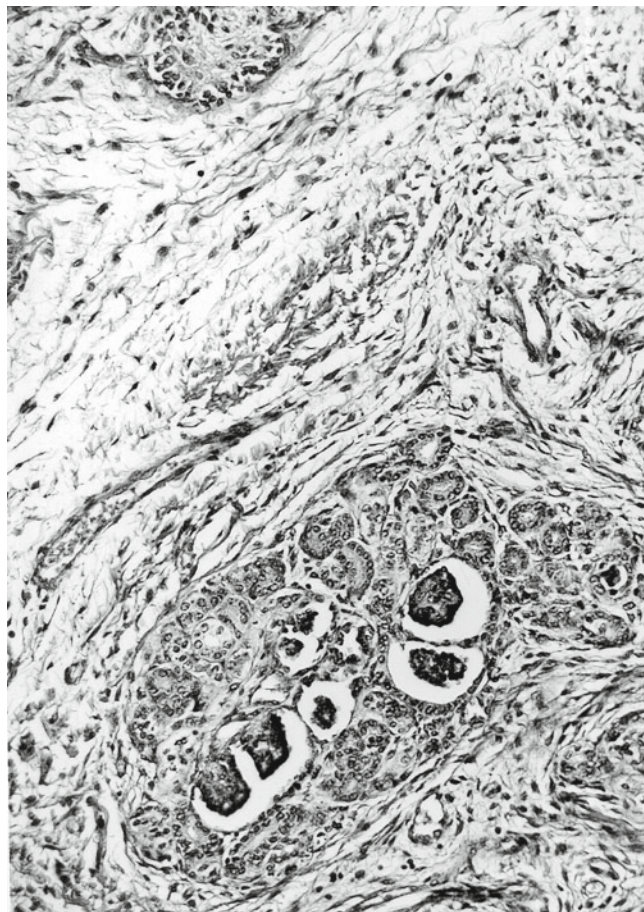


Fig. 2.20 Nephrogenic tissue is an uncommon component of teratomas; section taken from an immature mediastinal teratoma (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

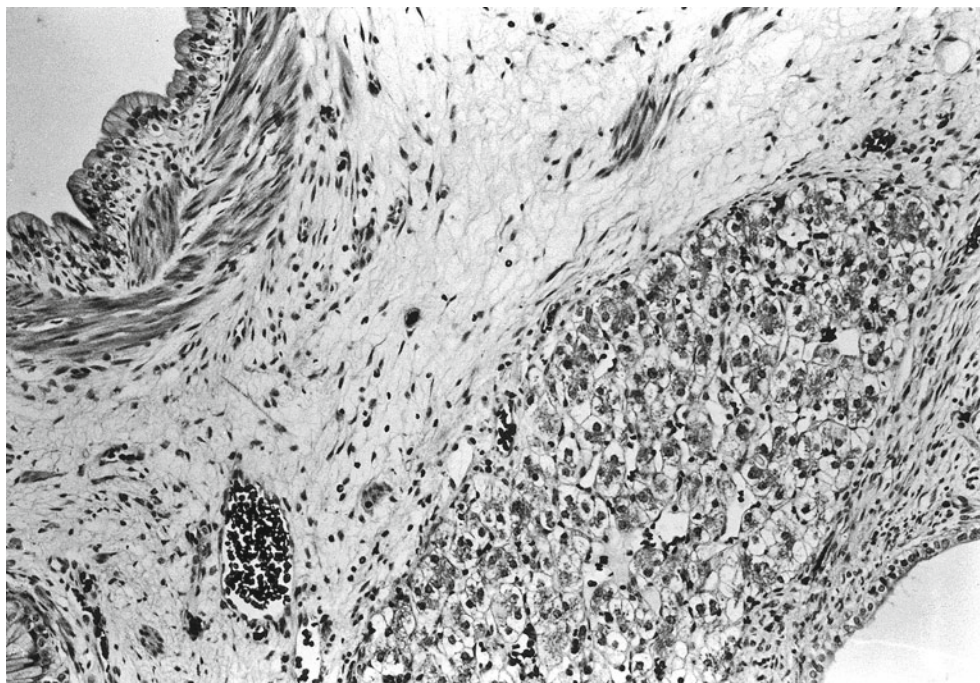


Fig. 2.19 Mature sacrococcygeal teratoma with liver and primitive gut (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

Fig. 2.21 Immature cerebellar teratoma with ependymal rosette neuroglial elements. The main component of immature teratomas regardless of location are neuroglial elements, which may be derived from brain germinal matrix, ependyma, choroid plexus, or retina. The presence of immature neuroglial elements in a fetal or infant teratoma is not considered malignant in contrast to adult teratomas (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

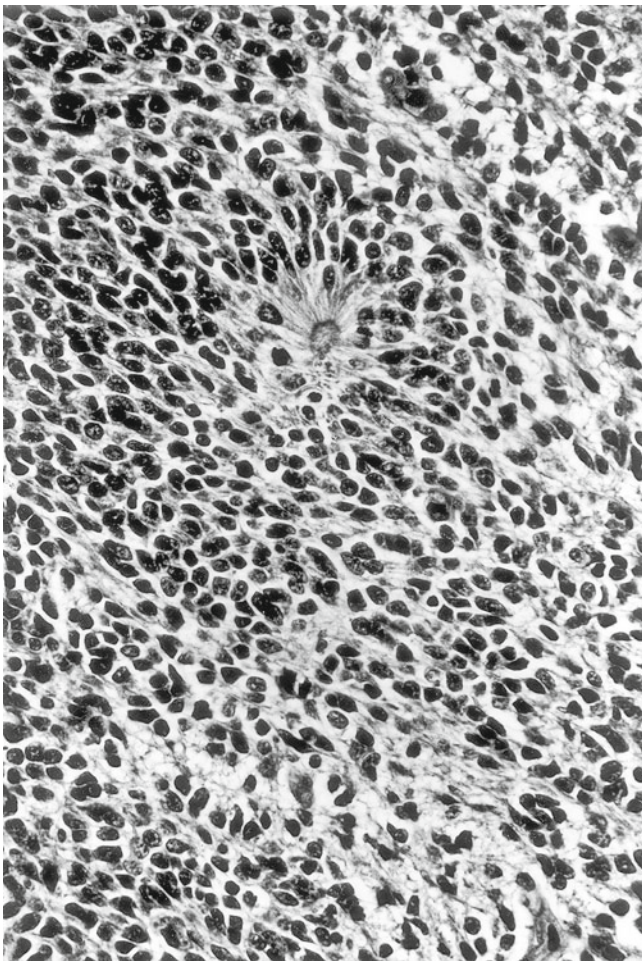
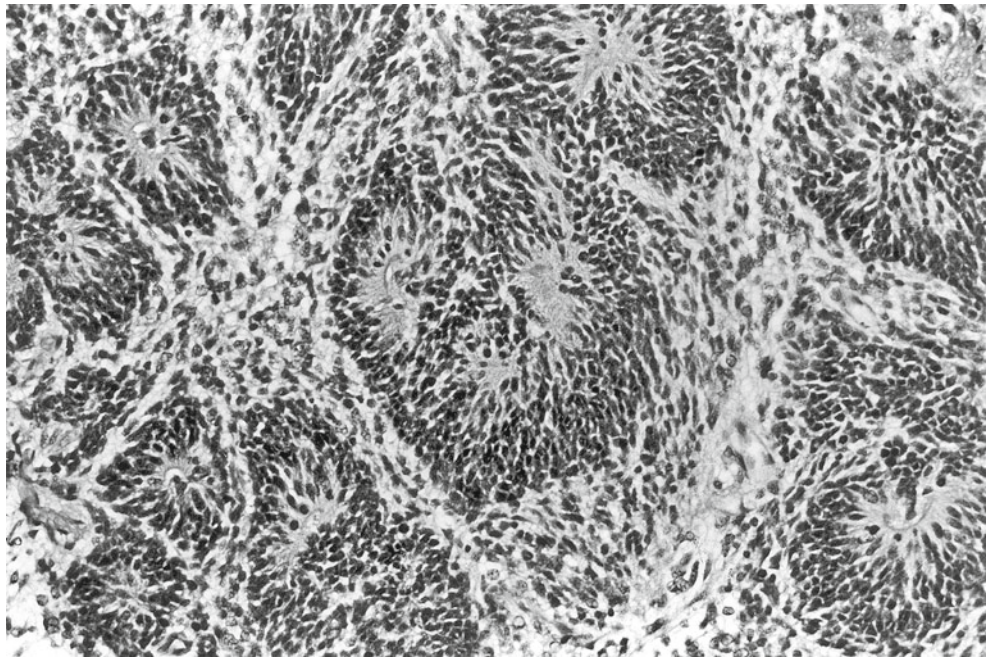


Fig. 2.22 Higher magnification of an ependymal rosette showing foot processes (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

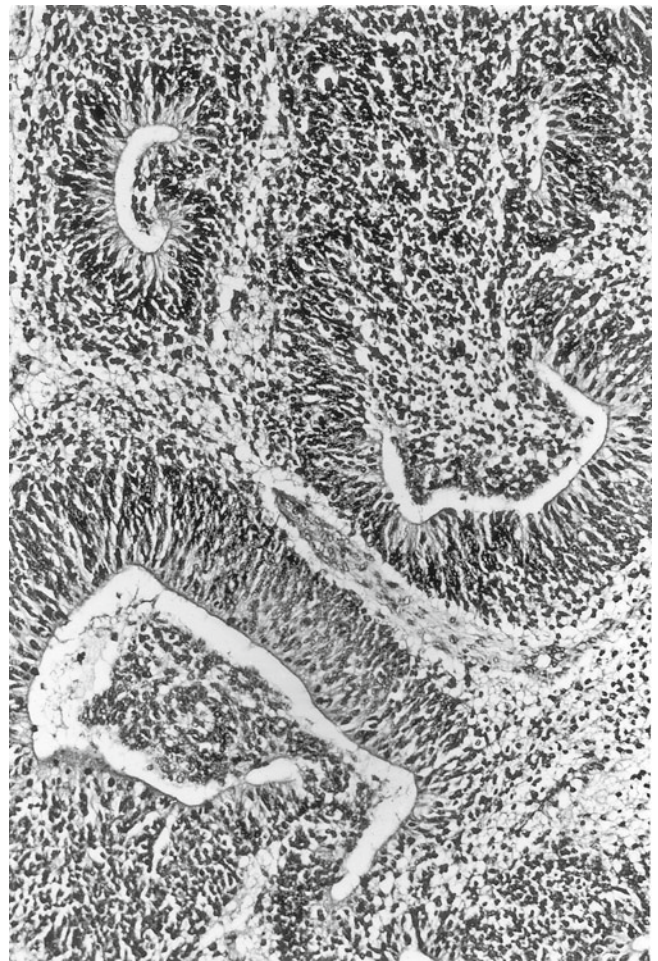


Fig. 2.23 Immature cervical teratoma with neuroepithelial elements forming primitive ependymal-like canals, which are present also in other immature teratomas, for example, Figs. 2.8 and 2.9, respectively (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

Fig. 2.24 Immature cerebellar teratoma with germinal matrix-like cells having the appearance of a small cell malignant tumor. In addition, the hypercellular, small dark round cells resemble those of PNETs, neuroblastoma, and medulloblastoma. Immature neuroglial elements blend imperceptively with adjacent mature neural tissues which are helpful in distinguishing them from malignant cells (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

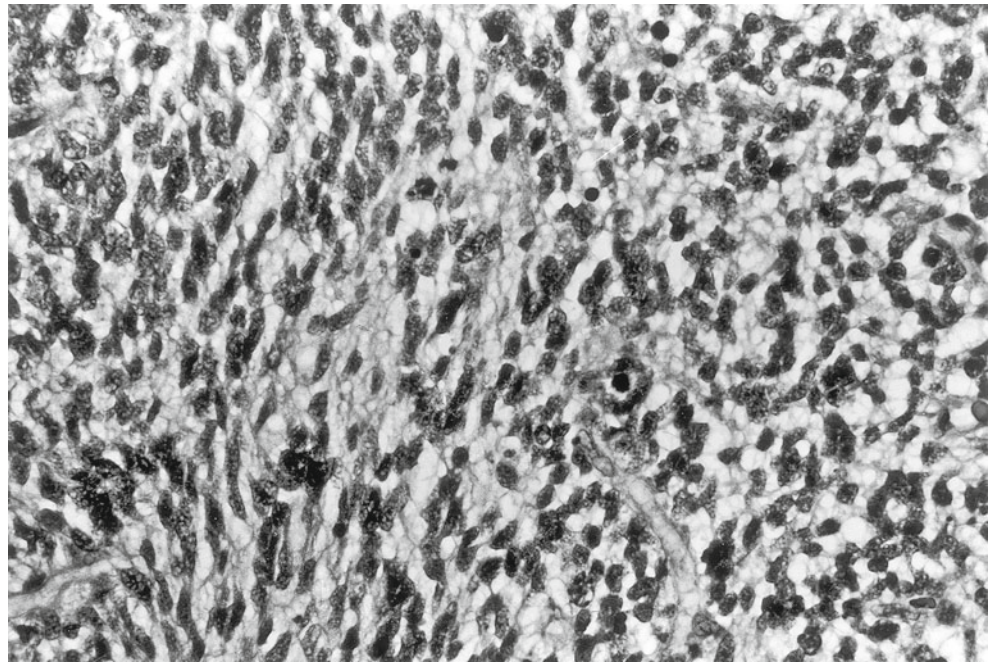


Fig. 2.25 Immature cerebellar teratoma with a pigmented structure suggestive of an optic cup. Heavily pigmented epithelium, resembling retina, is present along the *right* margin of the vesicle (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

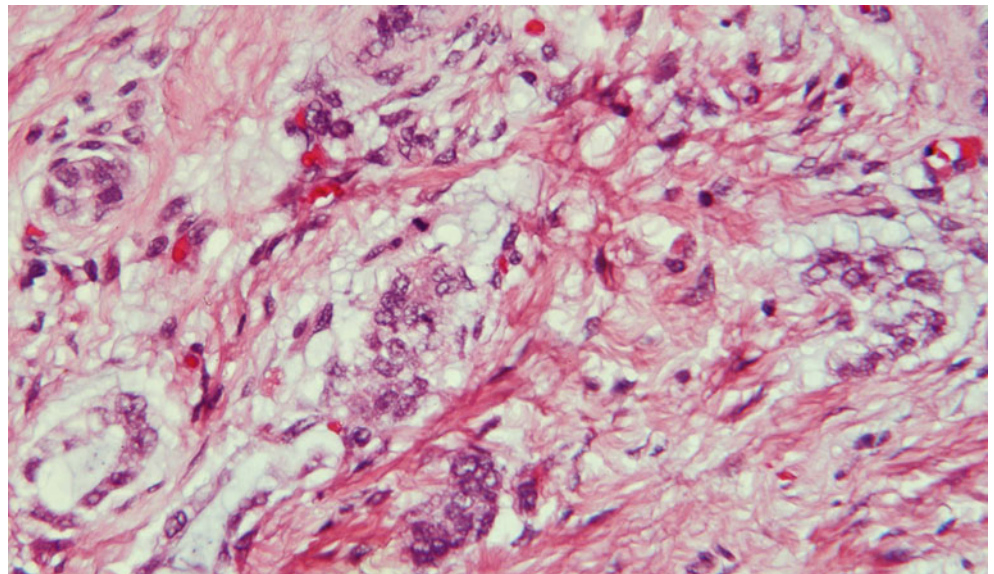
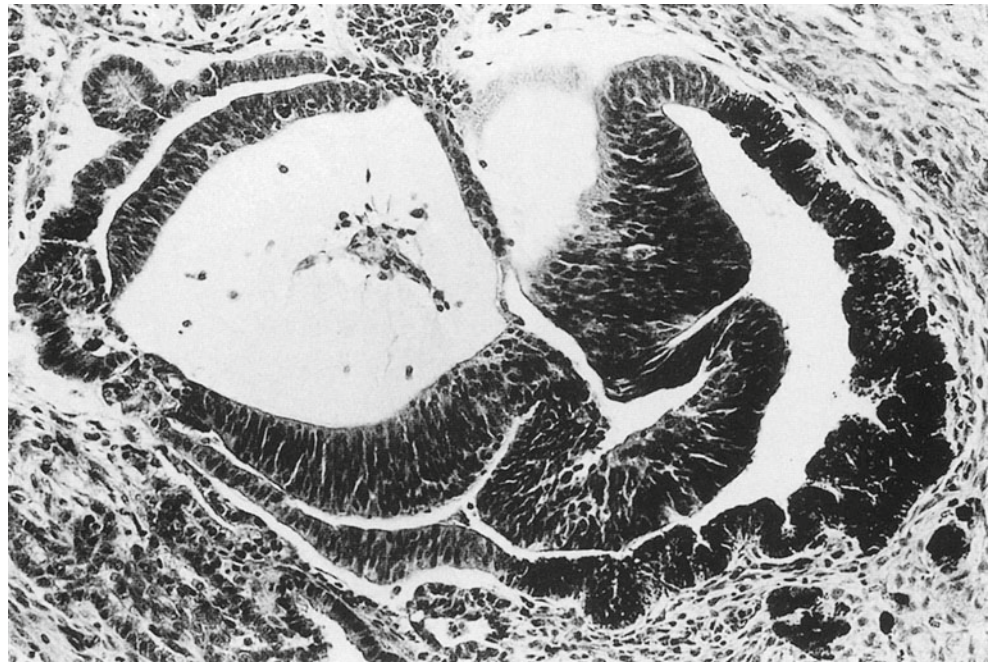


Fig. 2.26 Subtle yolk sac tumor components in an immature sacrococcygeal teratoma removed from a 6-day-old male. Small clusters of bubbly yolk sac tumor cells are scattered throughout. If not diligently searched for, these small foci of malignant cells can be missed easily. The tumor cells stain positively for α -fetoprotein (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)



2.4 Fetus-in-Fetu

Fetus-in-fetu is a strange congenital condition in which a fetiform mass with an axial skeleton and vertebral column is enclosed within the body of its host [10, 15, 32, 33] (Fig. 2.27). Most occur within the retroperitoneum as a single fetiform mass. Less common locations are the pelvis, mesentery, cranial cavity, scrotum, undescended testis, oral cavity, and sacrum. Both fetus-in-fetu and teratoma may coexist in the same individual, and a family history of twinning, as high as 18 %, is present in some patients with both entities [10, 14, 32, 33].

Fetus-in-fetu is detected readily on routine prenatal sonograms. Diagnosis is established on imaging studies by demonstrating a diminutive vertebral column and other parts of a skeleton [10, 14, 33]. The most common imaging and clinical finding is an abdominal retroperitoneal mass (Fig. 2.27). Other

presenting signs in the patient are abdominal distension, feeding difficulty, vomiting dyspnea, and rarely jaundice [10, 14].

The fetiform mass is anencephalic, acardiac, and showing various degrees of organ system differentiation and deformity. Well-formed limbs, vertebra, gut, and various other organs are noted on gross dissection and on prior imaging studies [10, 32, 33] (Fig. 2.27). Microscopic examination shows recognizable organs in various stages of development, mostly mature and sometimes immature tissues (e.g., neuroglial and renal) derived from the three germinal layers. Reported cases of fetus-in-fetu in the neonate thus far have been shown to be histologically benign initially [10].

Treatment of the fetus-in-fetu is surgical resection, which results in cure. There are case reports of patients who had yolk sac tumor recurrences several years after the original surgery [14].

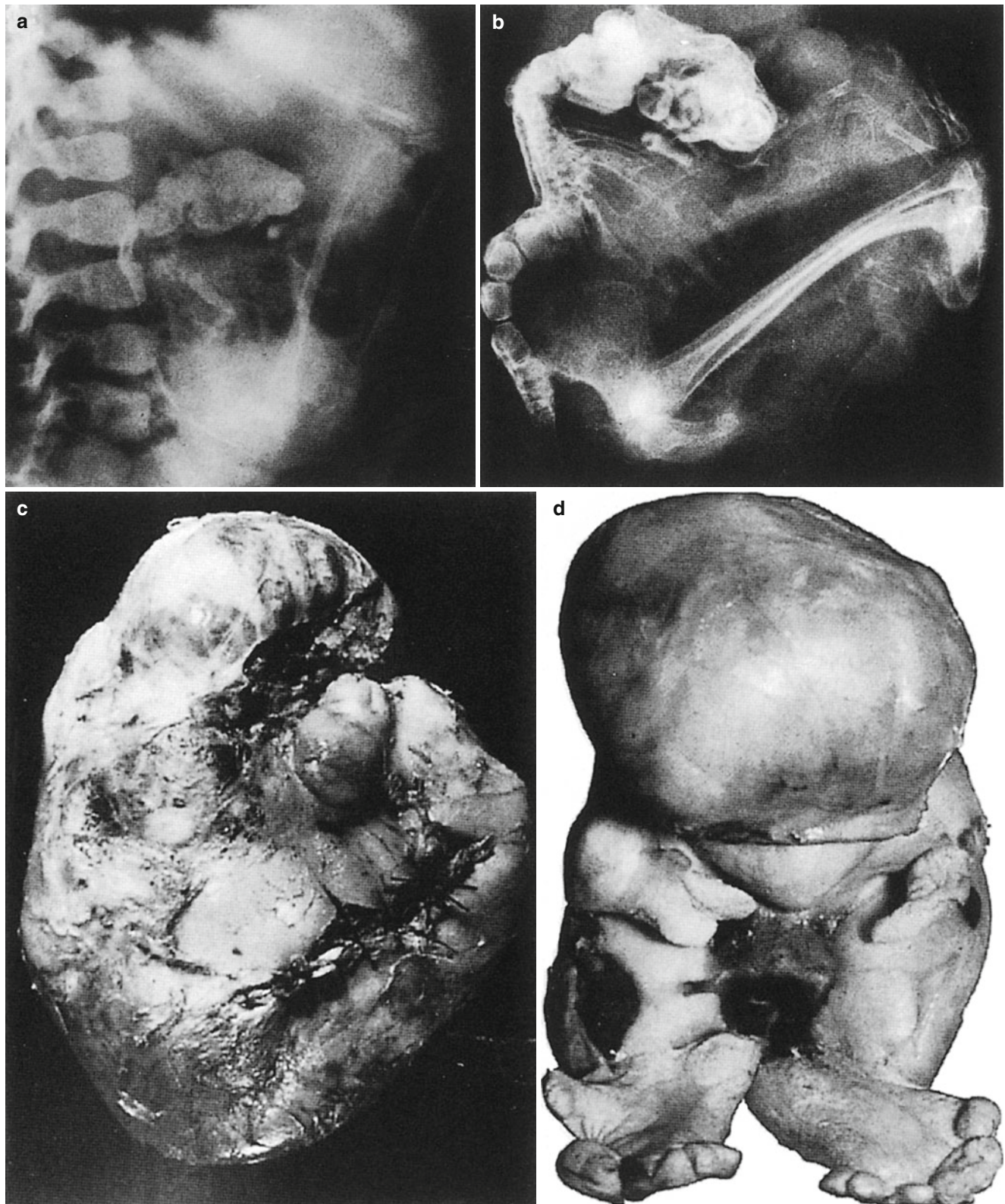


Fig. 2.27 Fetus-in-fetu. Radiographs of a retroperitoneal mass resembling a fetus in a 1-year-old child. (a) Before removal from the abdomen. (b) After removal. (c) External surface of the mass shown in (a). (c) Before removal of the outer covering. (d) After removal of outer covering. (e) Sagittal section shows well-developed vertebra, spinal nerves, base of skull, and cystic replacement of the brain. The large

black convoluted structure is intestine filled with blood. Heart was not identified. (f) Cross section of intestine showing the presence of all muscle layers. Auerbach's plexus appears identical with that of normal intestines (Reprinted from Isaacs [10]. © Mosby, 1997. With kind permission)

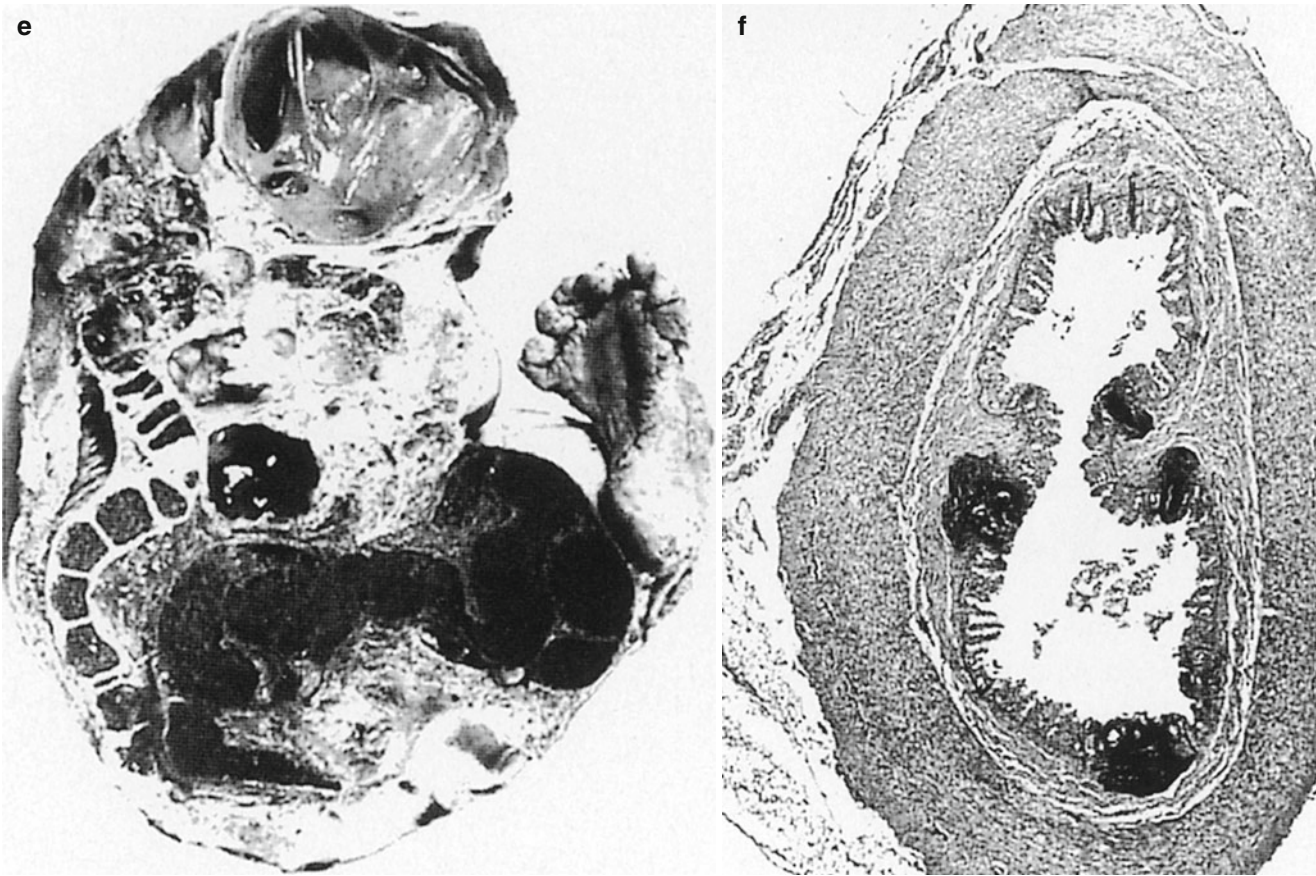


Fig. 2.27 (continued)

2.4.1 Prognosis

Most teratomas diagnosed in infants are classified microscopically as mature [10, 14]. The immature teratoma, with or without a mature component, is second in frequency [7, 10, 14]. In the fetus and neonate teratomas, mature and immature tissues occur about equally depending on the gestational age [10, 14]. The sacrococcygeal area is associated with the highest incidence of malignancy, in the form of yolk sac tumor [1, 7, 14, 15] (Table 2.4). The frequency of yolk sac tumor in sacrococcygeal teratomas is approximately 10 %; however, the values range from as low as 2.5 to 20 % [10, 12, 14, 15]. The presence of immature neuroglial elements in infant and fetal teratomas has no bearing on prognosis [10, 12, 14, 15].

Table 2.4 Location and patient survival with various types of teratomas (n=534)

Location	Survival
Sacrococcygeal	44/214 (67) ^a
Cervical	46/70 (66 %)
Intracranial	8/71 (11)
Oro-nasopharyngeal	23/41 (56)
Cardiac ^b	30/40 (75)
Gastric	11/14 (79)
Mediastinal ^c	9/13 (69)
Facial	7/8 (87.5)
Fetus-in-fetu	24/25 (96)
Teratoma recurrence rate	29/534 (5)
Overall survival	335/534 = 63 %

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^aPercent

^bMost cardiac teratomas were situated in the pericardium

^cMediastinal teratomas outside of the heart and pericardium

2.5 Yolk Sac Tumor

Yolk sac tumor (endodermal sinus tumor) is the leading malignant germ cell tumor in infants and children [2, 8, 10, 14, 15] (Tables 2.2 and 2.3). More arise from the sacrococcygeal area than from any other location during the first year of life where it adversely affects the prognosis [14]. Less common primary sites in this age group are the testis, pelvic retroperitoneum, and vagina but, practically, never the ovary [2, 10].

Yolk sac tumors have a slimy, pale tan-yellow gross appearance with grayish-red foci of necrosis and small cyst

formations. Generally, they are very soft and mushy falling apart upon removal [10, 15]. When the testis is involved, most of it is replaced by tumor, leaving a barely recognizable light tan, thin rim of parenchyma (Fig. 2.28).

Six or more histologic patterns are recognized [2, 4–6, 10]. The *papillary* form consists of papillary projections with or without the perivascular endodermal sinus structures (Schiller-Duval bodies) (Figs. 2.28b and c). The *reticular* pattern shows tumor cells arranged in a network situated about spaces containing vacuolated pink-staining material (Fig. 2.28d). The *solid* pattern shows mostly solid nests of cells. The rare

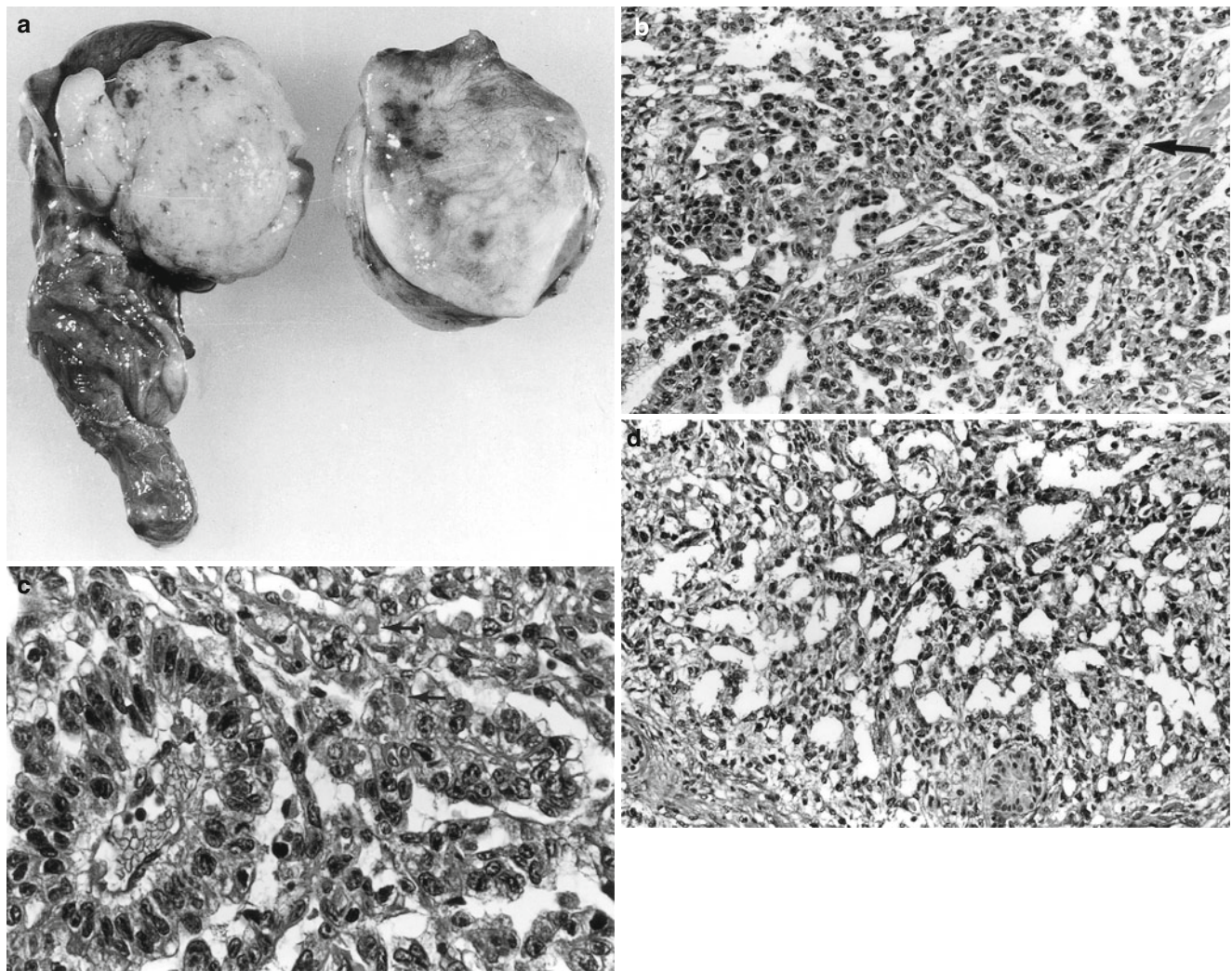


Fig. 2.28 Yolk sac tumor of the testis. (a) 11-month-old male with a scrotal mass. The bisected testicular tumor and attached spermatic cord. (b) Photomicrograph reveals the characteristic papillary pattern of yolk sac tumor with perivascular endodermal sinus structures (Schiller-Duval bodies) (*arrow*) in a solid pattern background. (c) Higher magnification of one of the endodermal sinus structures showing the relationship of the central blood vessel with surrounding tumor cell. Droplets of hyaline staining material representing α -fetoprotein are present (*arrows*). (d) Histological section showing the reticular (*netlike*)

pattern. Two small, testicular tubules are present near the lower margin of the photograph. Tumor cells react with α -fetoprotein. (e) Embryoid body of the polyembryoma variant. 1-year-old male with a yolk sac tumor of the testis. The embryoid body, upper right corner, resembles a tiny embryo consisting of two vesicles resembling yolk sac and amniotic cavities separated by a 2–3 cell layer embryonic disc. (f) Yolk sac tumor hepatoid variant consisting of fetal-like liver cells (Reprinted from Isaacs [15]; With kind permission of © Springer-Verlag, 2002)

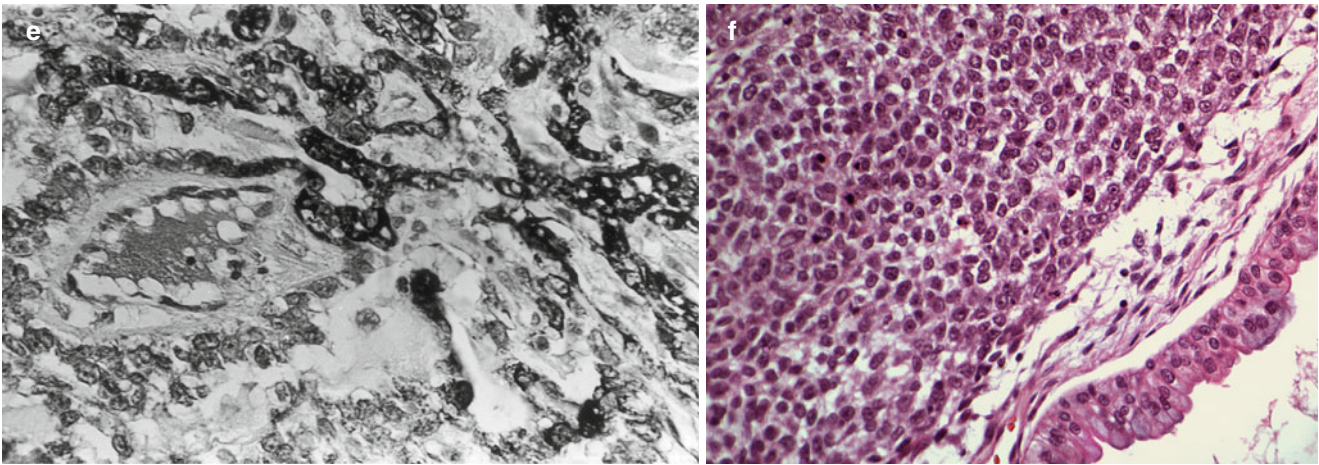


Fig. 2.28 (continued)

Table 2.5 Average normal serum alpha-fetoprotein levels in the newborn and infant

Age	Mean $\pm$ SD (ng/ml)
Premature	134,734 $\pm$ 41,444
Newborn	48,406 $\pm$ 37,718
Newborn 2 weeks	33,113 $\pm$ 32,503
Newborn 1 month	9,452 $\pm$ 12,610
2 weeks 1 month	2,654 $\pm$ 3,080
2 months	323 $\pm$ 278
3 months	88 $\pm$ 87
4 months	74 $\pm$ 56

Wu et al. [33]. With kind permission of © Nature Publishing Group, 1981

polyvesicular vitelline variant displays hourglass-like vesicles with constrictions (blastocyst yolk sac vesicles with constrictions described by Teilum) embedded in a cellular mesenchymal background [5]. A unique variation of the solid pattern is the *hepatoid* pattern, which derives its name from the

histologic observation that the cells resemble fetal liver cells, suggesting hepatocellular differentiation by the tumor [6, 8] (Fig. 2.28f). The *endometrioid-like* variant occurs in the ovary in girls over 11 years of age and is characterized by gland-like formations lined by tall clear cells similar to the early secretory endometrium [34]. There is also a more primitive *glandular* form [34].

Intra- and extracellular hyaline droplets are present in most yolk sac tumors. The droplets are periodic acid-Schiff (PAS) positive, diastase resistant, and variably reactive with α -FP, which is a useful biologic marker present in the serum of these patients [2, 6, 10, 14, 15] (Fig. 2.28e). α -FP can be used also to monitor for the presence of recurrence and/or metastases and the effect of chemotherapy [10, 14, 15]. It is important to note that normally, serum α -FP levels are markedly elevated in the newborn attaining normal levels around 4 months of age [35] (Table 2.5).

The main sites of yolk sac tumor metastases are the lungs and liver (Fig. 2.29a–c).

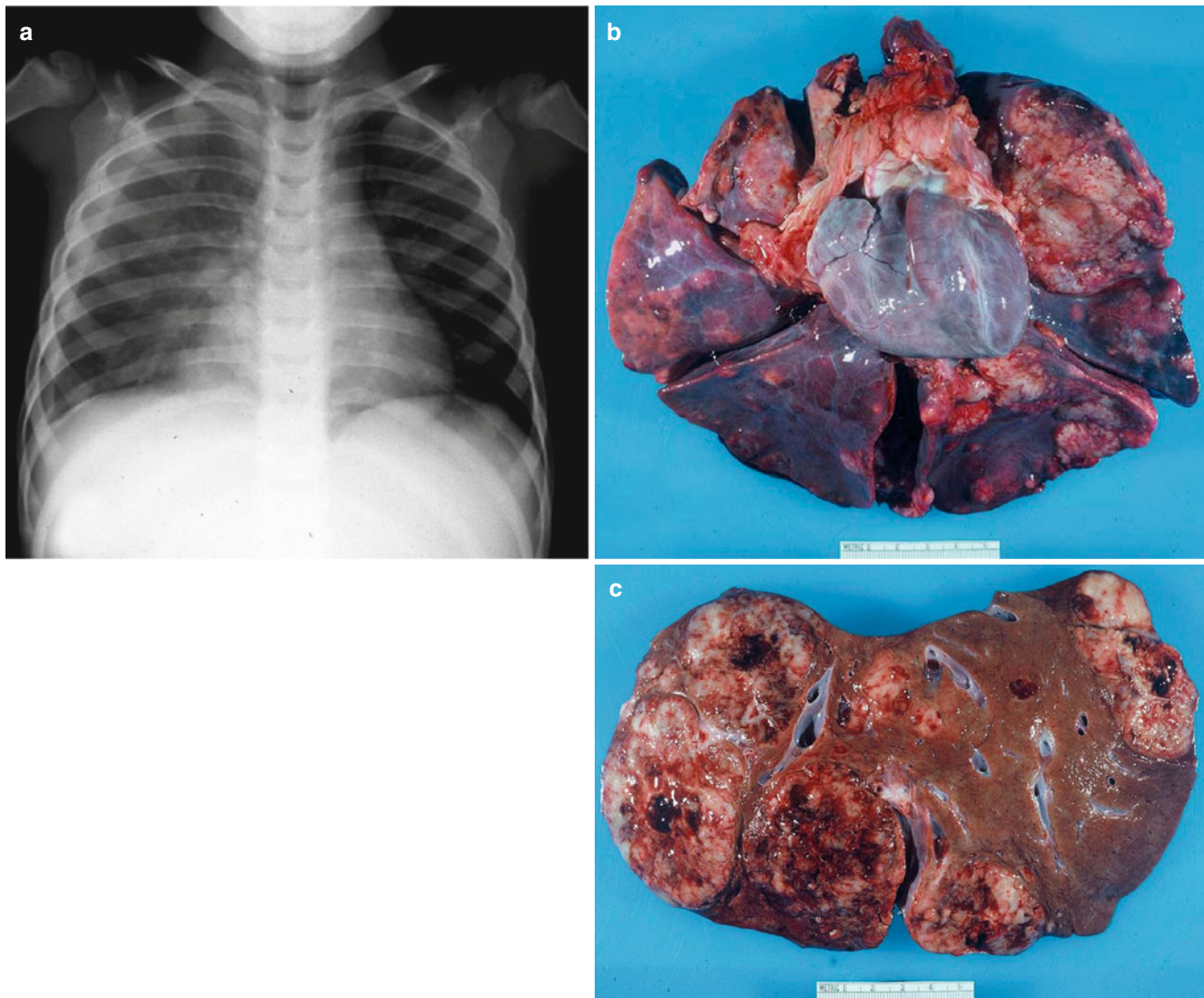


Fig. 2.29 Sacrococcygeal teratoma with yolk sac tumor metastases. Yolk sac tumor is the primary malignant component of sacrococcygeal teratomas; the malignancy occurs in approximately 5–10 % of sacro-

coccygeal tumors. (a, b) Lung metastases. (c) Liver metastases (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

2.6 Gonadoblastoma

Gonadoblastoma usually arises from within a dysgenetic gonad, but there are a few case reports of this tumor occurring in apparently normal testes or streak ovary [4–6, 10, 15, 36–38] (Table 2.3) (Figs. 2.30a, b and 2.31). Grossly, the tumor consists of one or more small, firm, tan nodules, which may be single or multiple, characteristically containing flecks of calcification visible on imaging studies. Gonadoblastoma has a distinctive appearance consisting of large germ cells surrounded by smaller immature cells of darkly staining, immature cells of sex cord derivation (Fig. 2.31a, b). The latter are round, darkly

staining Sertoli cells or granulosa cells forming microfollicles and containing hyaline bodies and calcium deposits [4, 6, 10, 15, 36–38]. In addition stromal Leydig or lutein cells may be present around the follicles. Gonadoblastoma practically always occurs in individuals having a karyotype with a Y chromosome [10, 37, 38].

It is regarded as an in situ malignancy from which germinoma and other malignant germ cell tumors arise [2, 8, 10, 37, 38]. It is neither locally invasive nor does it metastasize. Gonadectomy is recommended for young children with mixed gonadal dysgenesis because of not only the increased risk of gonadoblastoma and germinoma but also the virilizing effects of residual testicular tissue [3, 10, 15].

Fig. 2.30 Gonadoblastoma arising from a dysgenetic gonad. The patient was a 7-year-old, 45X0/46XY child with ambiguous genitalia. **(a)** The *left side* of the field beneath the tunica albuginea shows the morphologic features of a “streak gonad,” that is, ovarian stroma without either oocytes or developing follicles. Several tumor microfollicles with focal calcifications are present. **(b)** Higher magnification reveals microfollicles composed of nests of large clear germ cells and smaller, *dark round to oval* Sertoli cells. Some cell nests contain round spaces filled with hyaline staining material. According to Teilum, gonadoblastoma recapitulates the structure of the fetal gonad [5]. Calcifications form in the microfollicles which can be appreciated grossly by a gritty sensation on section and also on imaging studies (Courtesy of Rob Newbury, M.D., Department of Pathology, Rady Children’s Hospital, San Diego; Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

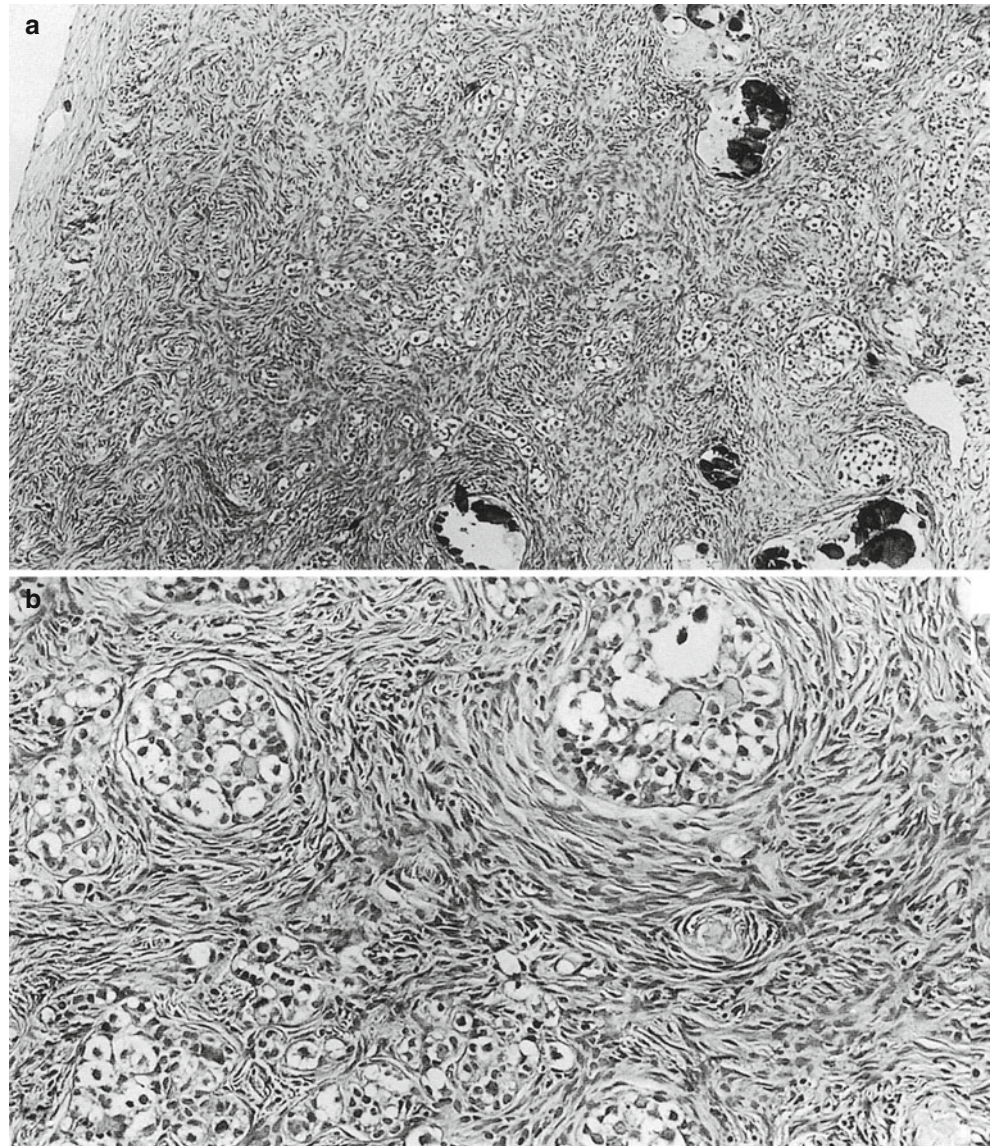
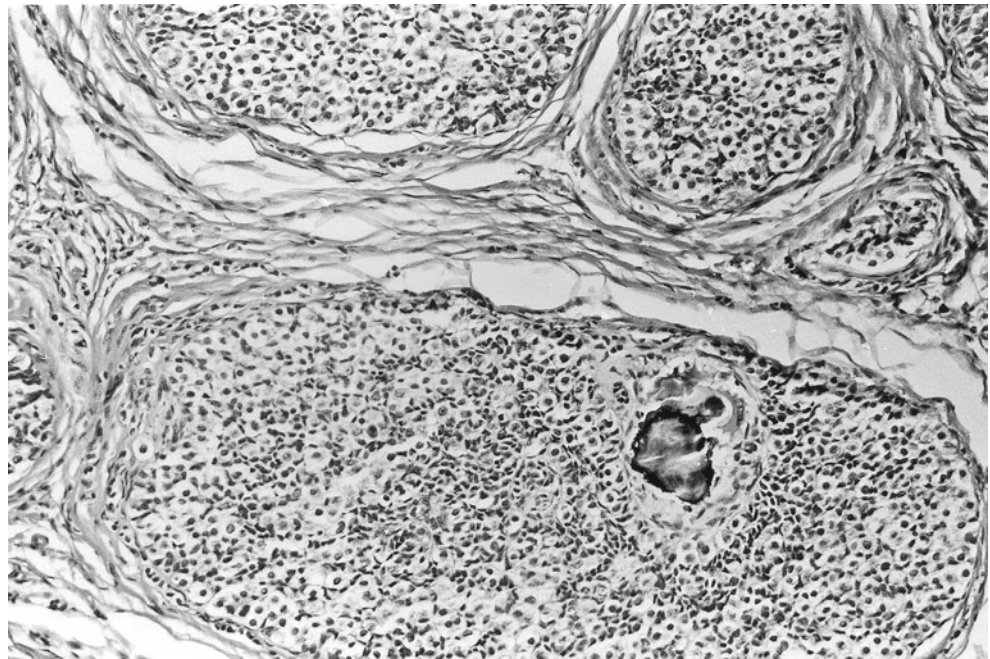


Fig. 2.31 Gonadoblastoma arising from a dysgenetic gonad. The patient was a dysmorphic 4-month-old child with tetralogy of Fallot, ambiguous genitalia, and a karyotype of 45XO/46XY. During a bilateral herniorrhaphy, an undescended “streak” gonad, measuring 2 × 1.3 cm, was found on the right side and an undescended immature testis, 1.5 × 1.5 cm, was noted on the left. Tumor was present only in the streak gonad. The photomicrograph shows an early stage of gonadoblastoma consisting of nests of large germ cells and smaller, dark round to oval Sertoli cells situated in lobules surrounded by fibrous ovarian stroma. A focus of calcification is present (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)



2.7 Embryonal Carcinoma

Embryonal carcinoma is extremely rare in infants [8, 10, 15, 39] (Tables 2.2 and 2.3). It is far less common occurring alone or in association with a teratoma than yolk sac tumor. In the past, many yolk sac tumors were called embryonal carcinomas which resulted in the confusion in the terminology of these two tumors [10]. Grossly, embryonal carcinoma has a variegated cut surface with white tan-gray to yellow soft areas with extensive hemorrhage and necrosis.

Microscopically, embryonal carcinoma consists of a poorly differentiated tumor composed of large, primitive, embryonal-appearing epithelial cells, resembling those of the embryonic disc, with characteristic large nucleoli growing in solid, papillary, and glandular patterns [4, 6, 8, 10, 15, 39] (Fig. 2.32). Tumor cells are immunoreactive with cytokeratin, placental alkaline phosphatase, and NSE and usually negative for EMA [6]. Human chorionic gonadotropin (HCG) and α -feto-protein staining are variable [6]. Electron microscopy is not helpful for the diagnosis.

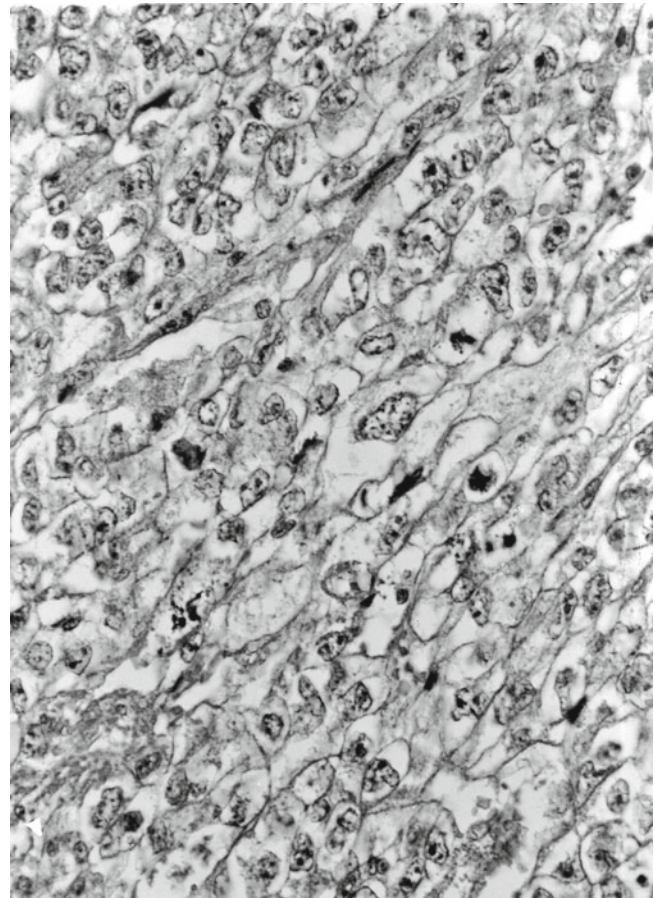


Fig. 2.32 Presacral teratoma with embryonal carcinoma and yolk sac tumor. The patient was a 1-year-old female with a large presacral mass. Microscopically, the tumor contained neuroglial tissue, cysts lined by squamous and respiratory epithelium, and nodules of cartilage. In addition, there was a malignant germ cell tumor component composed of both yolk sac tumor (mainly) and focal embryonal carcinoma. The latter consists of sheets of large, pleomorphic, anaplastic, epithelial cells with vesicular nuclei and prominent nucleoli (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

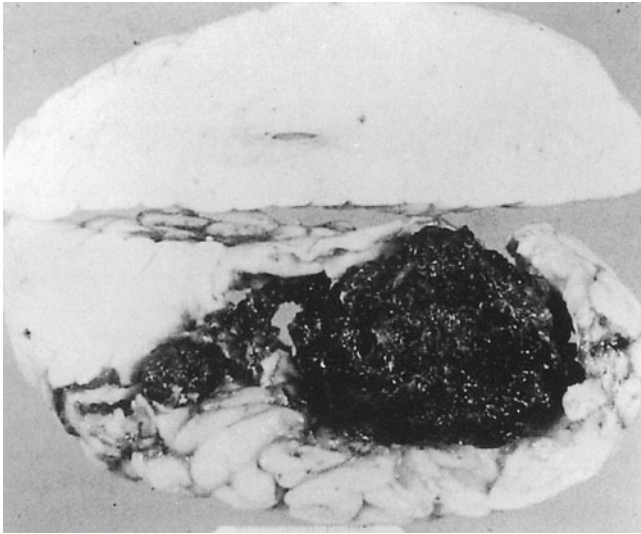


Fig. 2.33 Choriocarcinoma in the brain of a newborn, presumably a metastasis presumably from a placental primary. A large hemorrhagic tumor mass occupies half of one cerebral hemisphere (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

2.8 Polyembryoma

Polyembryoma is a very uncommon, unusual germ cell tumor of the gonads characterized by the presence of embryoid bodies, which resemble developing presomite embryos [5, 6, 10, 15] (Table 2.3). Microscopically, the embryoid bodies are similar to tiny embryos composed of two vesicles resembling yolk sac and amniotic cavities separated by a two or three cell layer embryonic disc (Fig. 2.33). The yolk sac and hepatic elements of the embryoid body are immunoreactive for α -FP and α -1-antitrypsin and the syn-

cytotrophoblastic component with HCG [6]. In the Children's Hospital Los Angeles review, two infants had yolk sac tumors of the testis with minor polyembryoma components [10, 12, 15].

2.9 Dysgerminoma and Choriocarcinoma

Primary dysgerminoma (germinoma) has not been described in infants either alone or in combination with a teratoma [2, 10, 12, 14, 15]. *Choriocarcinoma*, however, can present in the first year of life either as metastases secondary to a placenta choriocarcinoma [10, 14, 40–43] (Figs. 2.33 and 2.34a–c) or as a primary tumor arising in a variety of locations such as liver, lung, brain, kidney, and maxilla [10, 40–43] (Table 2.3). Choriocarcinoma practically never occurs in association with a teratoma during the first year of life [10].

Infantile choriocarcinoma becomes symptomatic at a mean age of 1 month [42]. Symptoms with decreasing frequency are anemia, failure to thrive, hepatomegaly, hemoptysis, or respiratory failure. Signs of precocious puberty may be present. HCG levels are diagnostically markedly elevated in all patients tested. The most common extraplacental site is the liver followed by the lung, brain, and skin [42, 43]. Maternal choriocarcinoma develops in slightly more than half the women; since 1989, practically all have survived following chemotherapy. Without appropriate treatment, the disease in the infant is rapidly fatal and death occurs on average within 3 weeks from first presentation [40–42]. However, in a recent study, 18 % of patients achieved a sustained remission after multiagent cisplatin-based chemotherapy and delayed or primary tumor resection [42].

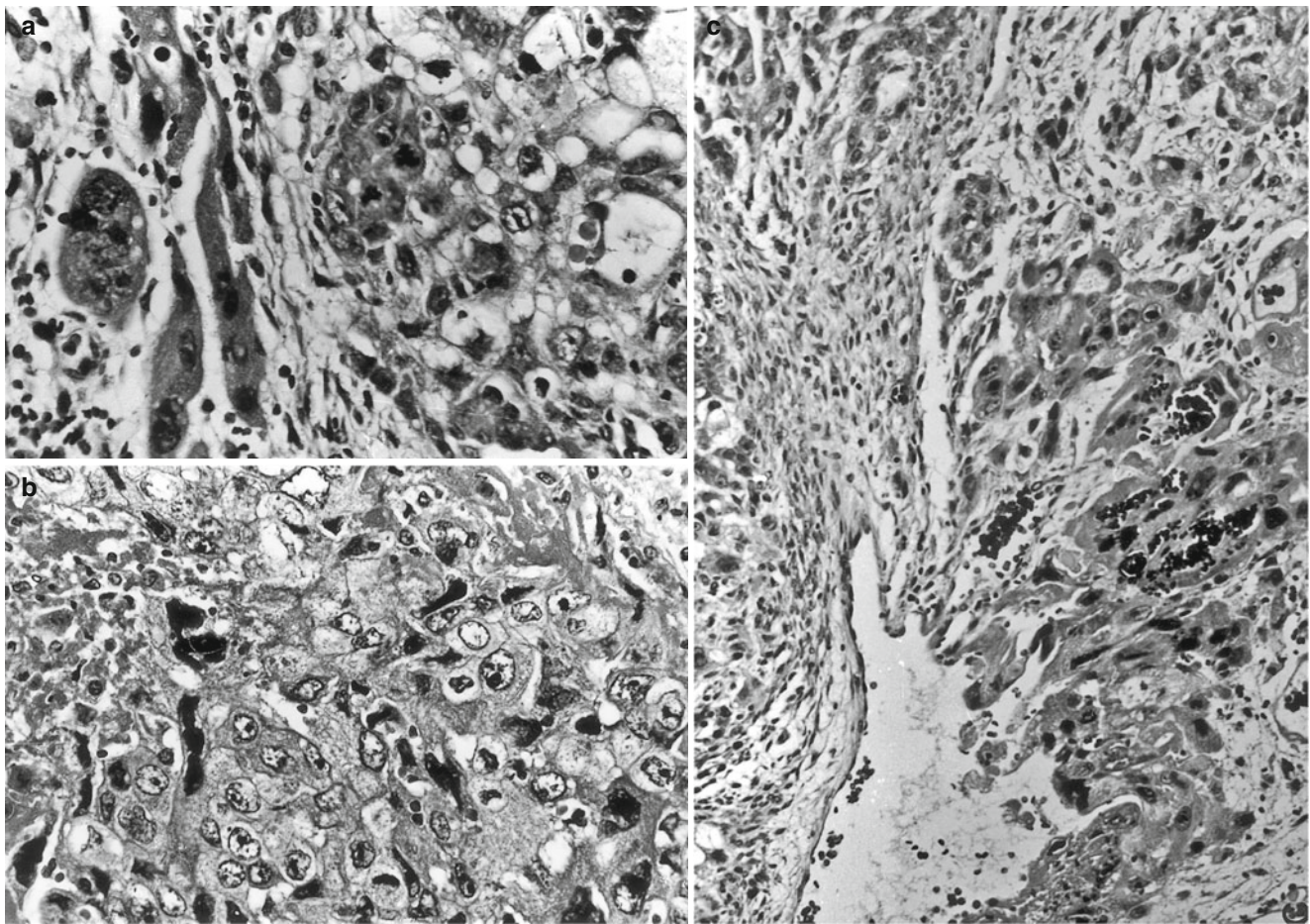


Fig. 2.34 Choriocarcinoma. (a) Cytotrophoblasts occupy the left half of the field; giant, elongated, multinucleated syncytial trophoblasts are situated on the *right*. (b) Cytotrophoblasts with large vesicular nuclei, prominent nucleoli, and vacuolated to granular cytoplasm. Necrosis is

present. (c) Tumor cells invading and lining up along vascular channels. Foci of necrosis and vascular invasion are characteristic features of choriocarcinoma (Reprinted from Isaacs [15]. © Springer-Verlag, 2002)

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