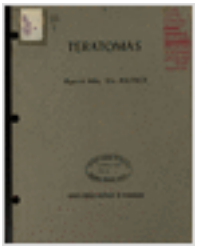

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TERATOMAS

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ARMED FORCES INSTITUTE OF PATHOLOGY

ATLAS OF TUMOR PATHOLOGY

Section III—Fascicle 9

TERATOMAS

by

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I am indebted to Dr. Harold Stewart for his critical appraisal and helpful suggestions. Col. Thomas C. Jones, V.C., U.S.A., contributed the specimen of a malignant teratoma of the ovary in a cow (see p. 12). Figure 2 is from the Armed Forces Institute of Pathology, Washington, D. C.

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Rupert A. Willis

TERATOMAS

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TERATOMAS

NOMENCLATURE

SYNONYMS AND RELATED TERMS: Teratoma (Gr. and Lat.); bidermoma; cholesteatoma of ovary; compound ovarian tumor; dermoid; dermoid cyst; dysembryoma; embryoma; epignathus; "fetus in fetu"; hairy cyst; mixed cyst; "mixed teratoid tumor"; monodermoma; "parasitic fetus"; teratoblastoma; teratoid tumor; tridermoma. A teratoma may mistakenly be called a tumor of the tissue that predominates in its structure (for example, ovarian goiter for a teratoma of the ovary). For the synonyms of Malignant Teratomas see that section.

A teratoma is a true tumor or neoplasm composed of multiple tissues foreign to the part in which it arises. Teratoma is the most suitable name for this class of tumor; its literal meaning—"a malformation which is also a true tumor"—is very appropriate. Particular tumors can then be designated benign teratoma or malignant teratoma according to their structure or behavior. This is the simplest terminology and is all that is necessary.

The names teratoblastoma and teratoid tumor have no advantages over teratoma and are clumsier. Teratocarcinoma, now a prevalent substitute for "malignant teratoma containing epithelial elements," is an unnecessary and unsatisfactory term: it may be supposed to imply carcinomatous change in the epithelial components of the teratoma, whereas in most teratomas malignancy is not restricted to any particular component but is a property of the whole tumor (see the discussion of Malignant Teratomas).

Dermoid cyst is a frequently used synonym for benign cystic teratomas of the ovary or other sites. It is an unfortunate term for three reasons: (*a*) the same name (or epidermoid cyst) is applied—and correctly so—to sequestration skin-lined cysts of the skin, cranial cavity, and other parts, and these cysts are quite unrelated to teratomas; (*b*) the simplest benign teratoma usually contains several or many other tissues besides skin; and (*c*) in some so-called "dermoid cysts," the main cyst is lined wholly or mainly, not by skin, but by nervous, respiratory, or alimentary tissue, or by mixtures of these.

Embryoma is a particularly bad name; it affirms that a teratoma represents an embryo, a hypothesis which, though still widely held, is certainly erroneous (see the section on Hypotheses of the Origin of Teratomas).

DEFINITION

A teratoma is a true tumor; i.e., unlike a simple malformation, it has powers of progressive growth in both benign and malignant forms. Teratomas can and should be distinguished from non-neoplastic malformations of all kinds, whether relatively simple heterotopias of particular tissues or complex malformations such as double monsters or imperfect twins, which lack neoplastic attributes. This distinction needs to be specially emphasized, for many kinds of malformations have been confused with teratomas by one writer or

another. Sequestration dermoid cysts of the skin or cranial cavity, branchial cysts, enterogenous cysts, and many other developmentally misplaced and supernumerary parts and tissues (Albrecht's "hamartomas")—all of these constitute masses of multiple kinds of tissues in the wrong places; but they are non-neoplastic masses, quite unrelated to teratomas, and they will not be considered further here.

Teratomas contain multiple tissues of kinds foreign to the part. In this they differ from mixed tumors peculiar to particular regions. A mammary fibroadenoma, even when its fibromatous component undergoes cartilaginous or bony change, is not a teratoma, because its components are clearly derived from indigenous mammary tissue. A nephroblastoma of the kidney, even when some of its cells become rhabdomyoblastic, is not a teratoma, because it is derived from and composed of embryonic tissue which is specifically renal in nature. This and other mixed embryonic tumors of viscera may show aberrant differentiation of their young plastic tissues, but they do not contain completely exotic tissues, such as respiratory, alimentary, dental, or central nervous tissues, all of which are common in teratomas. So also, the mixed tumors of the endometrium are not teratomas because, although they may develop such tissues as cartilage and muscle, these are not truly exotic, but are derivable by metaplasia from the endometrium itself. The same applies to tumors of other mesenchymal tissues, in which aberrant differentiation has taken place, e.g., bone or cartilage in soft tissue growths; such tumors have sometimes been referred to as "mesenchymomas."

CLASSIFICATION

Teratomas form a single class of tumors, within which, however, there is a wide range of structure and behavior.

Structural subdivision into cystic and solid types, or into monodermal, bidermal, and tridermal forms, according to the number of "germ-layers" represented in their component tissues, is quite artificial and serves no useful purpose.

Behavioristic subdivision into benign and malignant teratomas is of value and can usually be made on structural grounds; benign teratomas are composed wholly of mature, fully differentiated tissues, while malignant ones almost always contain in addition embryonic tissues of variable degrees of immaturity. However, even this distinction is not clear-cut; a few borderline tumors occur in which, although the tissues appear "benign" and fully differentiated, they are not completely quiescent but are multiplying and may later show accelerated growth and malignant behavior.

INCIDENCE

Age.—Teratomas of various sites are discovered at ages which show plainly that most, if not all, of these growths take origin early in embryonic development. Most sacrococcygeal, retroperitoneal, cervical, intrapericardial, and intracranial teratomas are known to have been present at birth or are discovered in early childhood. Ovarian, testicular, and mediastinal teratomas are discovered at rather later average ages, but still in early adult life, the average ages for these three sites being about 33, 30, and 27 years respectively. Since many of these growths are very large and clearly of long duration when first discovered, and since many cases of congenital teratomas in these situations have been observed, there is little doubt that the gonadal and mediastinal teratomas also arise at an early period of development. The delay in the discovery of the ovarian and mediastinal tumors is readily understood; they are usually benign and slow growing and are so situated that they are unlikely to cause symptoms until they attain considerable size.

The group of malignant testicular teratomas is an apparent exception to the rule that teratomas arise during early development; although situated in an organ where they are likely to be discovered before they have attained great sizes, most of them do not make their clinical appearance until the third decade or later. However, cases do occur in which enlargement of the testis has been noticed since childhood or for many years before the onset of rapid malignant growth; and there is also a well known group of cases in which bulky, highly malignant metastases develop from small unsuspected primary testicular teratomas, the structure of which, at the time they are examined, may appear well differentiated and "benign." It is therefore possible that teratomas of the testis, like those of other sites, take origin during early development, and that, having usually lain dormant during childhood and adolescence, they grow actively as malignant tumors in early adult life. This change of behavior may be connected with the general endocrine or metabolic state of the bearer, or possibly with local injury or inflammation.

Sex.—Apart from the genital organs themselves, there are distinct sex differences in the frequency of teratomas of various sites. Retroperitoneal, presacral, and coccygeal teratomas appear to be a little more frequent in females than in males. On the other hand, intracranial teratomas are commoner in males; this applies particularly to pineal teratomas, of which almost all those reported have been in boys. While mediastinal teratomas affect the sexes nearly equally, malignant members of this group are usually in males.

Site.—Teratomas arise, in order of frequency, in ovaries, testes, anterior mediastinum, retroperitoneal region, presacral and coccygeal regions, pineal and other intracranial sites, neck, and abdominal viscera other than the

gonads. (See the fascicles corresponding to these anatomic sites.) Ovarian teratomas outnumber all the rest put together. It is a striking fact that, with relatively few exceptions, teratomas occur in tissues which developmentally occupy median, or nearly median, preaxial positions. This fact suggests that their genesis is in some way related to disturbances emanating from the embryonic axis of the body.

Species.—In mammals teratomas have rarely been recorded except in man and the horse. Jackson and Brues described a transplantable ovarian teratoma of the mouse. I have seen two examples of cystic teratomas of the dog's ovary, one of which was benign, and the other, very fully studied by Dr. C. L. Oakley of London, though consisting mainly of well differentiated tissues, produced cellular peritoneal metastases. The Armed Forces Institute of Pathology in Washington has a specimen of malignant ovarian teratoma from a 2-year-old Hereford cow. It is 20 cm. in diameter and weighs 5,700 gm., containing a great variety of both well differentiated and embryonic tissues. Teratomas are quite common in the testes of young horses, in which they may be found unexpectedly following gelding operations (Willis and Rudduck); they are almost all of benign type, composed of fully differentiated tissues, including skin, teeth, respiratory and alimentary epithelia, central nervous tissue, nerves and ganglia, cartilage, bone, adipose tissue, and muscle; and they are sometimes multiple and bilateral (figs. 1, 25).

Avian teratomas have occurred spontaneously in the testes of cocks, and have also been evoked experimentally by injections of zinc or copper salts in these organs (Michalowsky; Falin; Bagg). Further study of this remarkable result is needed before assessing its possible significance for mammalian pathology.

HYPOTHESES OF THE ORIGIN OF TERATOMAS

This is not the place for a detailed critique of the numerous speculations which have been indulged in regarding the nature and histogenesis of teratomas.* The most popular of these, expressed in the name "embryoma," has been that these growths represent distorted fetuses, derived either from included twins of the bearers or from parthenogenetic proliferation of the bearers' own germ cells. This view is clearly erroneous for the following reasons: the common sites of teratomas are not the sites of parasitic twins; most teratomas are known to arise during early stages of development when their bearers have no mature germ cells capable of parthenogenesis; proper topographical study of teratomas shows that, unlike most amorphous fetuses,

* For other hypotheses on the origin of teratomas, particularly regarding the germ cell and the seminomas, see Fascicle 32, "Tumors of the Male Sex Organs."

they show no signs of a vertebrate axis or of regional relationship of parts, even when they contain highly organized structures, i.e., they are fundamentally non-fetiform; and, finally, the view that they represent embryos completely ignores the important fact that they are true neoplasms, with powers of independent progressive growth which have never been observed in either "amorphi" or parasitic twins.

The genesis of teratomas is still far from understood, but it will be clarified by increasing knowledge of the chemistry of early embryonic growth, the chemistry of the "organizers" or growth hormones which determine the orderly sequences of normal development, and the mutual influences of growing plastic tissues on one another. As has already been suggested, the site distribution of teratomas points to the operation of growth disturbances emanating from the primary axis—the notochord and contiguous structures which are derived by invagination of tissue at Hensen's node in the early embryo and which constitute the primary organizer. Experimental embryologists have shown that the blastulas deprived of their primary organizer regions, or blastomeres removed from pregastrular embryos, can grow and differentiate into a variety of tissues, but do so in a chaotic manner and without forming an axis or defined organs. Perhaps teratomas represent areas of tissue which during early embryonic development escaped from the action of the primary organizer; and perhaps knowledge of the chemistry of this escape may bring with it an understanding also of the neoplastic qualities of teratomas.

GROSS

Teratomas vary greatly in structure according to the variety of the tissues which they contain and according to whether they are benign or malignant.

Benign teratomas are usually grossly cystic, showing one or more large cysts into which the solid components project in the form of one or more small or large eminences; and, on cutting into them, many of their fully differentiated tissues are easily recognized by the naked eye—skin, hairs, teeth, bone, cartilage, adipose tissue, etc. (pl. I, figs. 2–5, 7–14, 17). The contents of the common skin-lined cysts are sebaceous matter, often associated with shed hairs or flakes of keratin; and in some cases the sebaceous material consists of numerous spherical "butter-balls," formed by mechanical agitation. As much as 10 gallons of sebaceous fluid has been seen in one tumor. In some teratomas, the main cavity is not lined by skin but by alimentary or respiratory mucosal tissue or by central nervous tissue, and therefore contains not sebum, but mucoid secretions or clear watery cerebrospinal fluid. The grossly cystic character of most benign teratomas is simply a consequence of the continued accumulation of their cutaneous or other secretions.

Figure 1A-B. Multiple bilateral teratomas in a horse's testes. Natural size. A.F.I.P. Acc. Nos. 219005-1 and 219005-2.

Figure 2. Skiagram of a "dermoid cyst," showing several teeth socketed in a mass of bone. (From the Armed Forces Institute of Pathology.) A.F.I.P. Acc. No. 72520.

Figure 3. Photograph of a benign cystic ovarian teratoma, showing an irregular intracystic eminence. Natural size. See figure 8. (From Willis, R. A., "A further study of the structure of teratomata." J. Path. Bact., 45:49-65, 1937.) A.F.I.P. Acc. No. 219005-5.

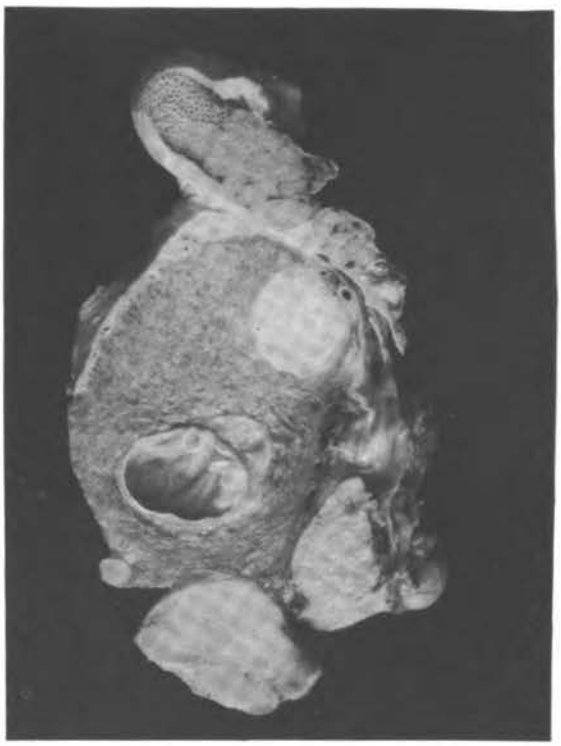


Fig. 1A.

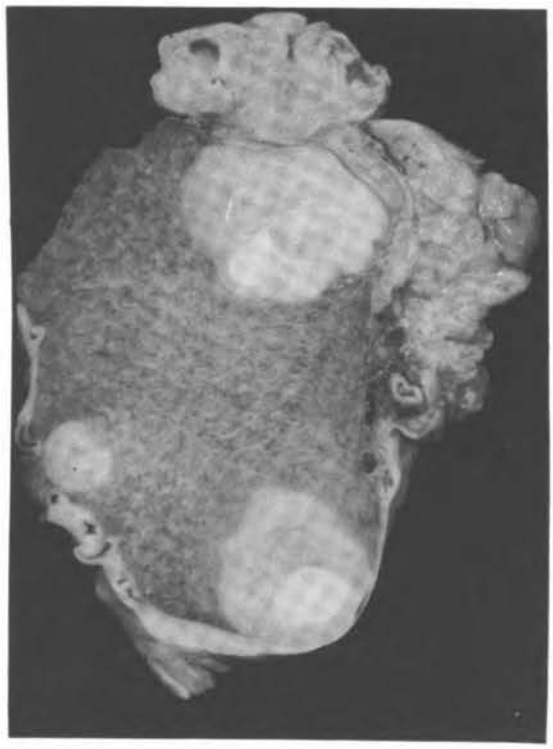


Fig. 1B.

Fig. 2

Fig. 3

Figure 4. "Dermoid cyst" of ovary, bisected to show a skin-covered eminence and numerous hairs projecting into the cyst. FT, Fallopian tube. Natural size. A.F.I.P. Acc. No. 219005-45.

Figure 5. "Dermoid cyst" of ovary, opened to show a skin-covered eminence and a densely matted mass of hair. Two-thirds natural size. A.F.I.P. Acc. No. 219005-46.

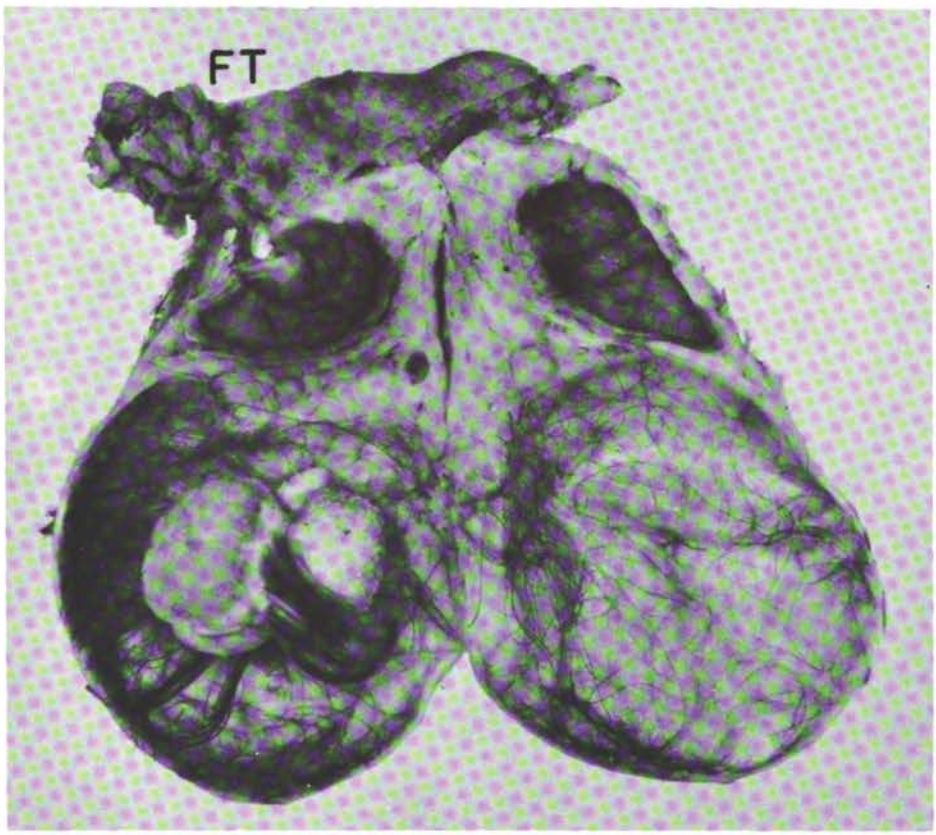


Fig. 4

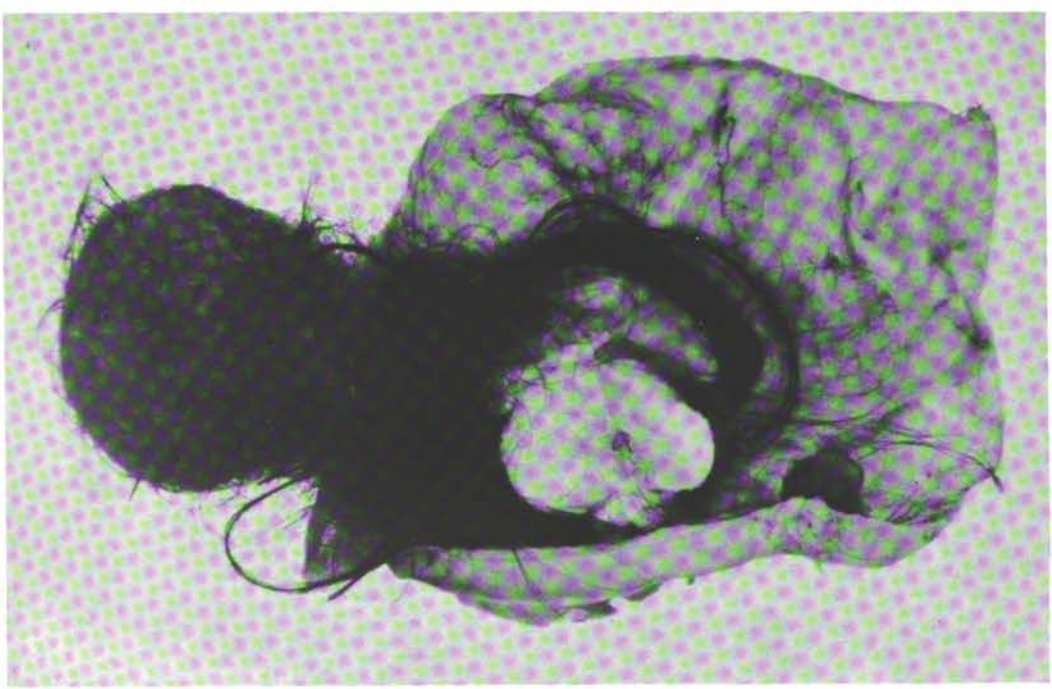


Fig. 5

Figure 6. Malignant teratoma of testis. Slightly reduced. A.F.I.P. Acc. No. 219005-19.

Figure 7. Section of a small ovarian "dermoid cyst" containing a skin-clothed eminence. X 8. A.F.I.P. Acc. No. 219005-4.

Figure 8. Section of eminence in figure 3, showing an unerupted tooth and some bars of cartilage. X 5. A.F.I.P. Acc. No. 219005-6.

Fig. 6

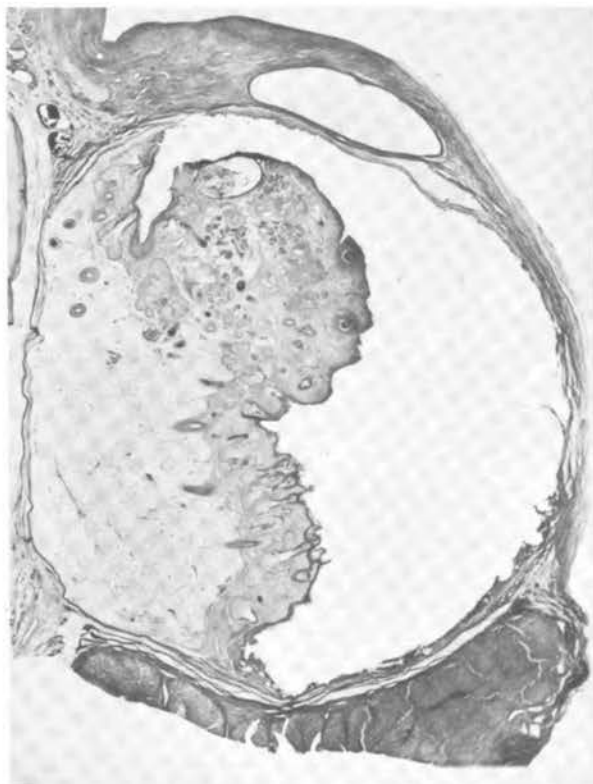


Fig. 7

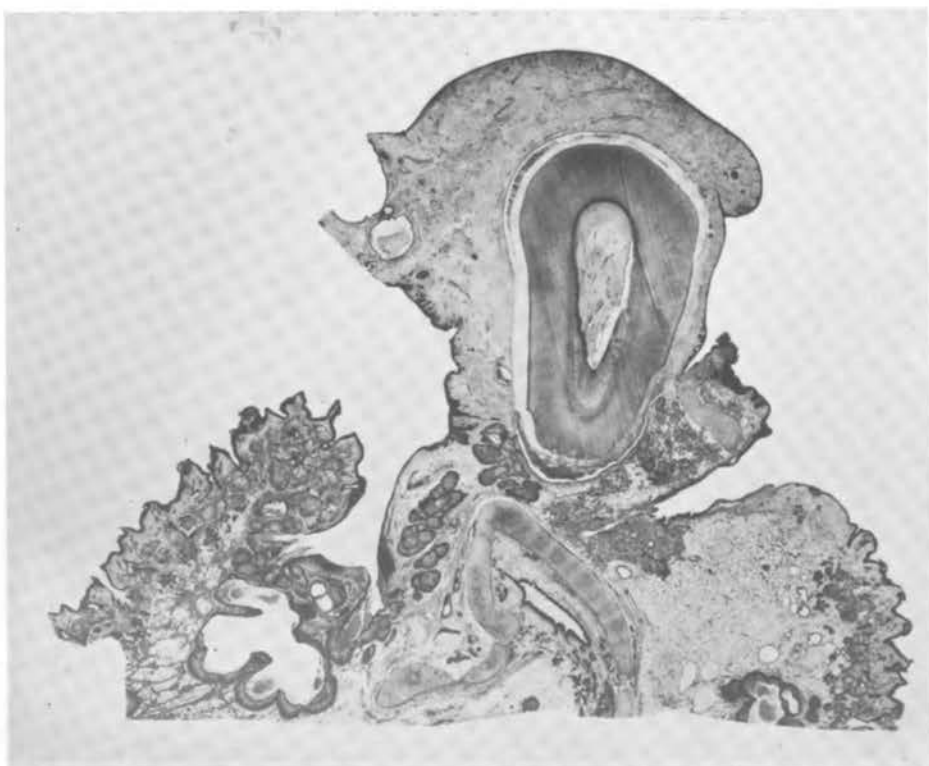


Fig. 8

Figure 9. Section of a benign cystic tooth-bearing teratoma of ovary (see diagram in figure 10). X 4½. A.F.I.P. Acc. No. 219005-7.

Figure 10. Diagram of topography of tissues shown in figure 9:

Epidermis with hairs and appendage glands	Heavy line
Bone	Solid black
Cartilage	Close stippling
Central nervous system	N and hatching
Connective and adipose tissue	Widely spaced stippling
Main cyst	E
Tooth	T
Paradental epithelial residues	X
Cysts lined by respiratory epithelium	R
Cyst lined by alimentary epithelium	A
Layer of ovarian tissue	O

(From Willis, R. A., "The structure of teratomata." J. Path. Bact., 40:1-36, 1935; and from Willis, R. A., "Pathology of Tumours," p. 945. London: Butterworth & Co., Ltd., 1948.) A.F.I.P. Acc. No. 219005-8.

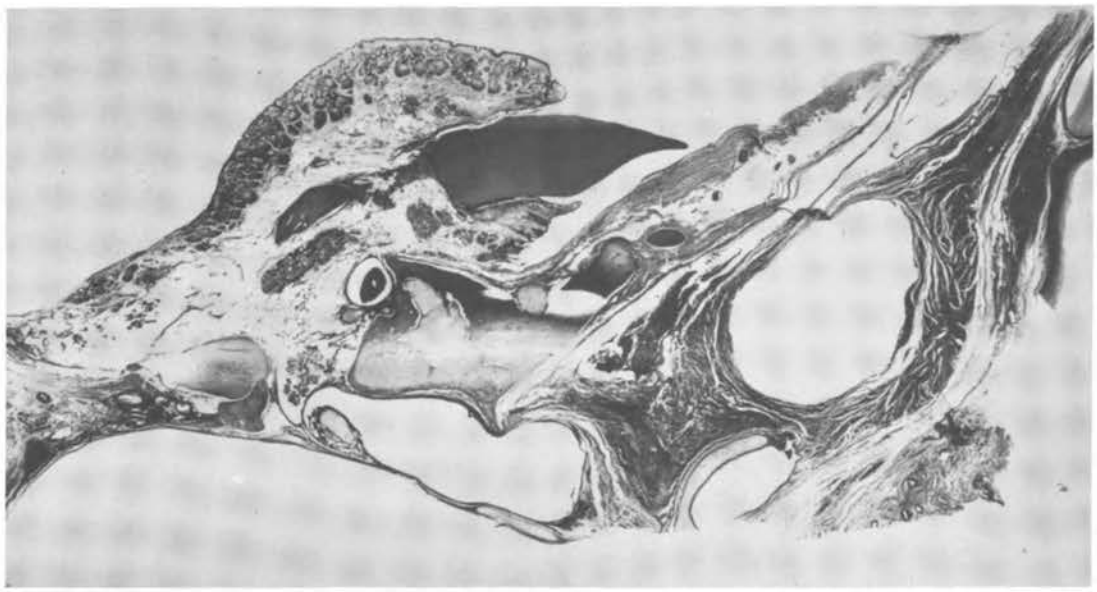


Fig. 9

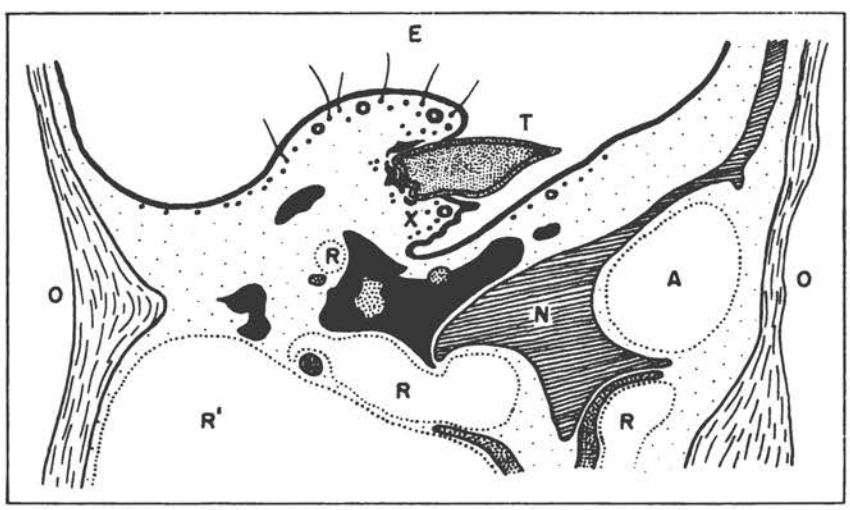


Fig. 10

Figure 11. Section of a benign ovarian teratoma, containing a skin-covered eminence, a tooth, and a mass of bone with a tooth socket. X 5. A.F.I.P. Acc. No. 219005-9.

Figure 12. Ovarian teratoma consisting of a main cyst into which projects a large partly cystic and partly solid eminence. Teratomas of this type may contain immature tissues and may be malignant. Natural size. A.F.I.P. Acc. No. 219005-10.

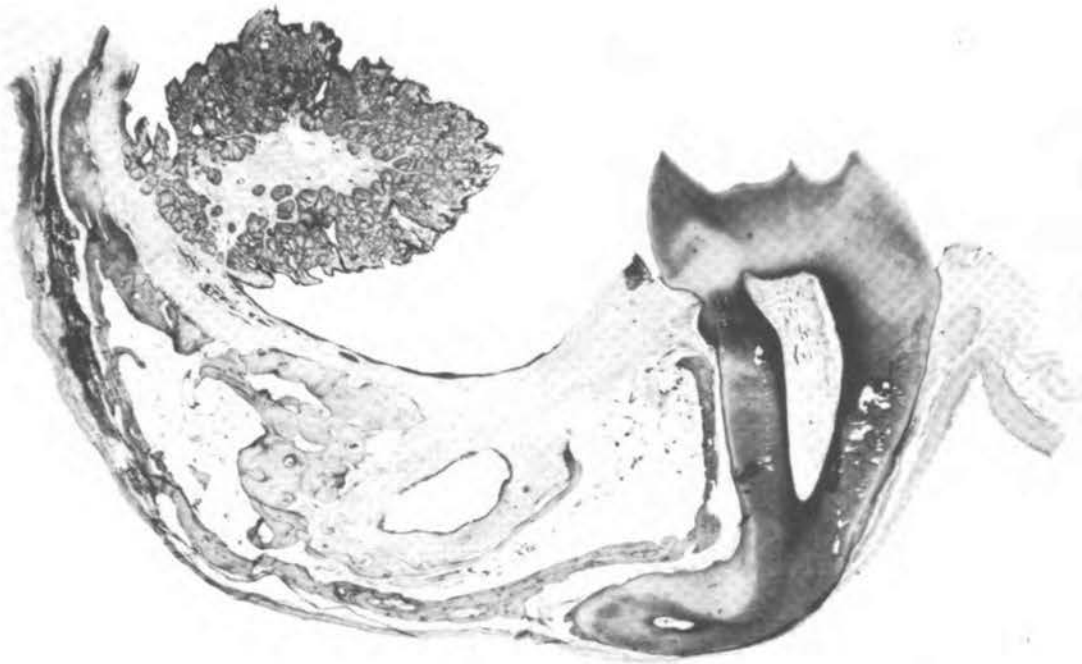


Fig. 11

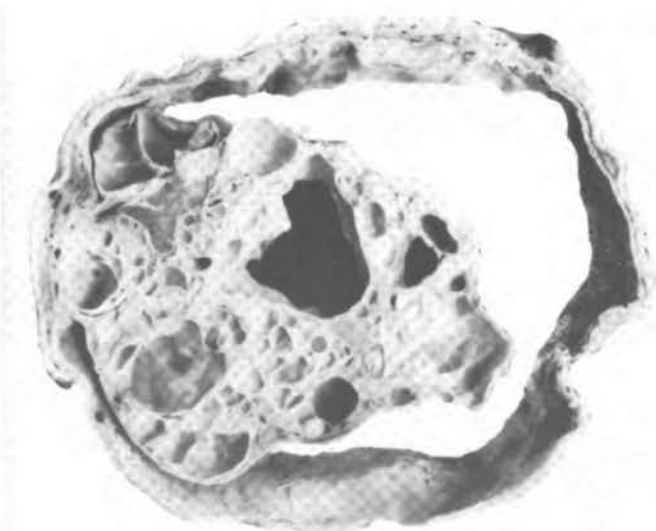


Fig. 12

Figure 13. Section of the tooth-containing part of the teratoma shown in plate IB (see diagram in figure 14). X 5. A.F.I.P. Acc. No. 219005-15.

Figure 14. Diagram showing components of figure 13. N, Nervous tissue; Q, skin-lined cavity; R, respiratory cavities; P, pulp tissue; D, layer of odontoblasts and dentine (black); E, enamel; L, residues of dental lamina; bone in black. (From Willis, R. A., "The structure of teratomata." J. Path. Bact., 40:1-36, 1935.) A.F.I.P. Acc. No. 219005-16.

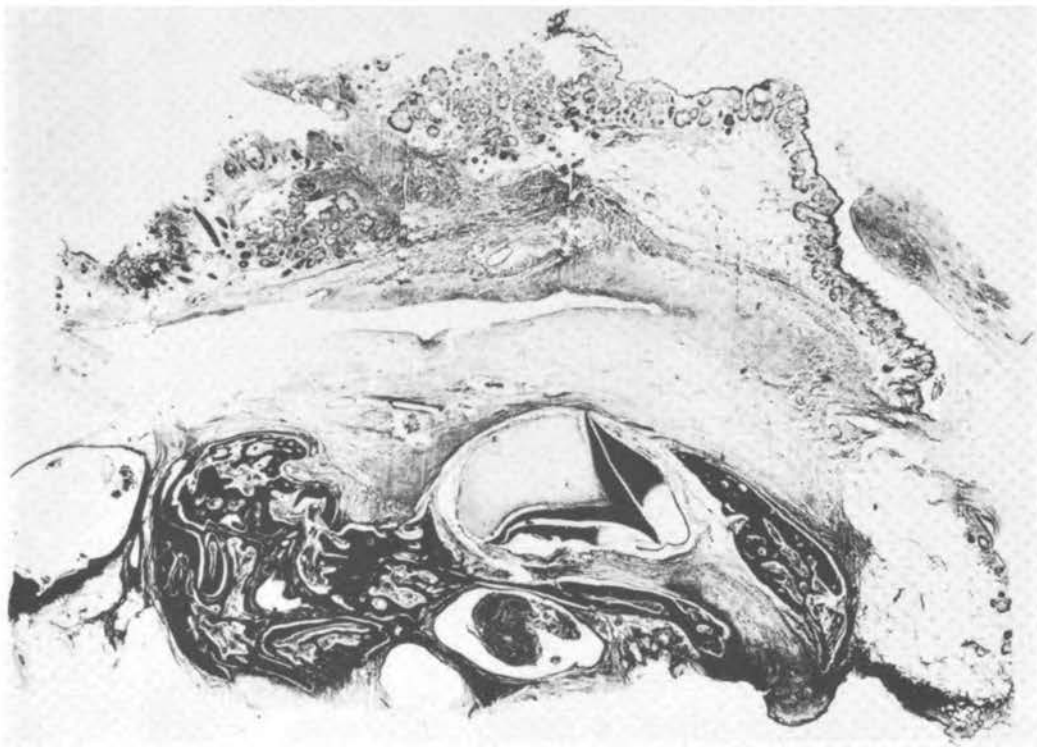


Fig. 13

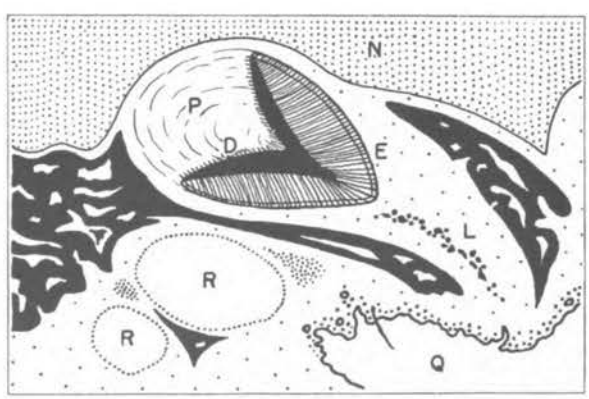


Fig. 14

Figures 15 and 16. Intrapericardial teratoma attached to the aortic trunk. 15. Intact, 16. Cut surface: T, teratoma; H, heart; A, aorta; P, pulmonary artery; L, lungs. (Figure 15 is from Willis, R. A., "Pathology of Tumours," p. 951. London: Butterworth & Co., Ltd., 1948.) A.F.I.P. Acc. Nos. 219005-17 and 219005-18.

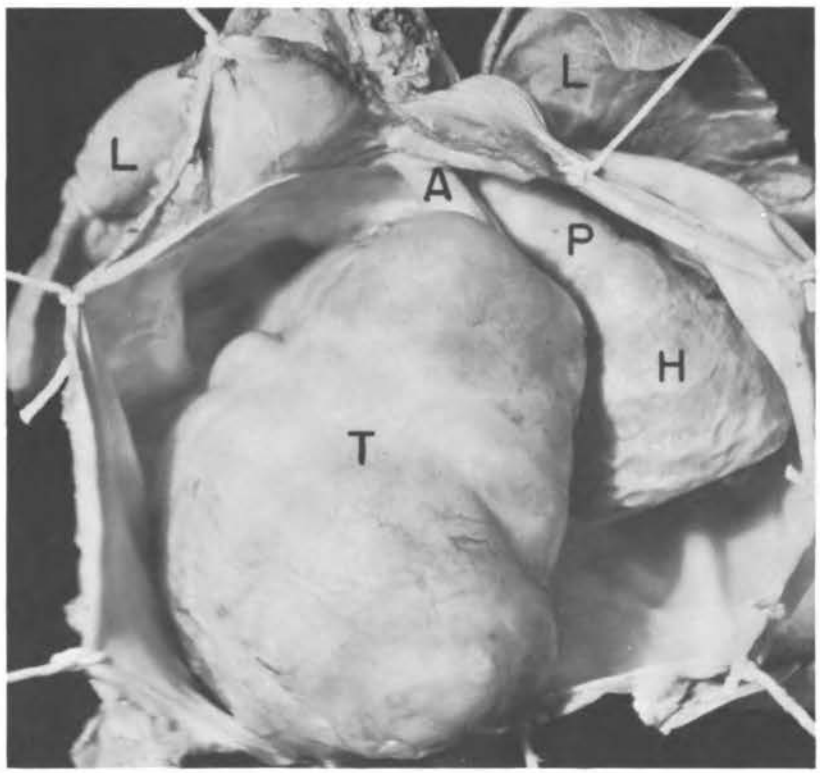


Fig. 15

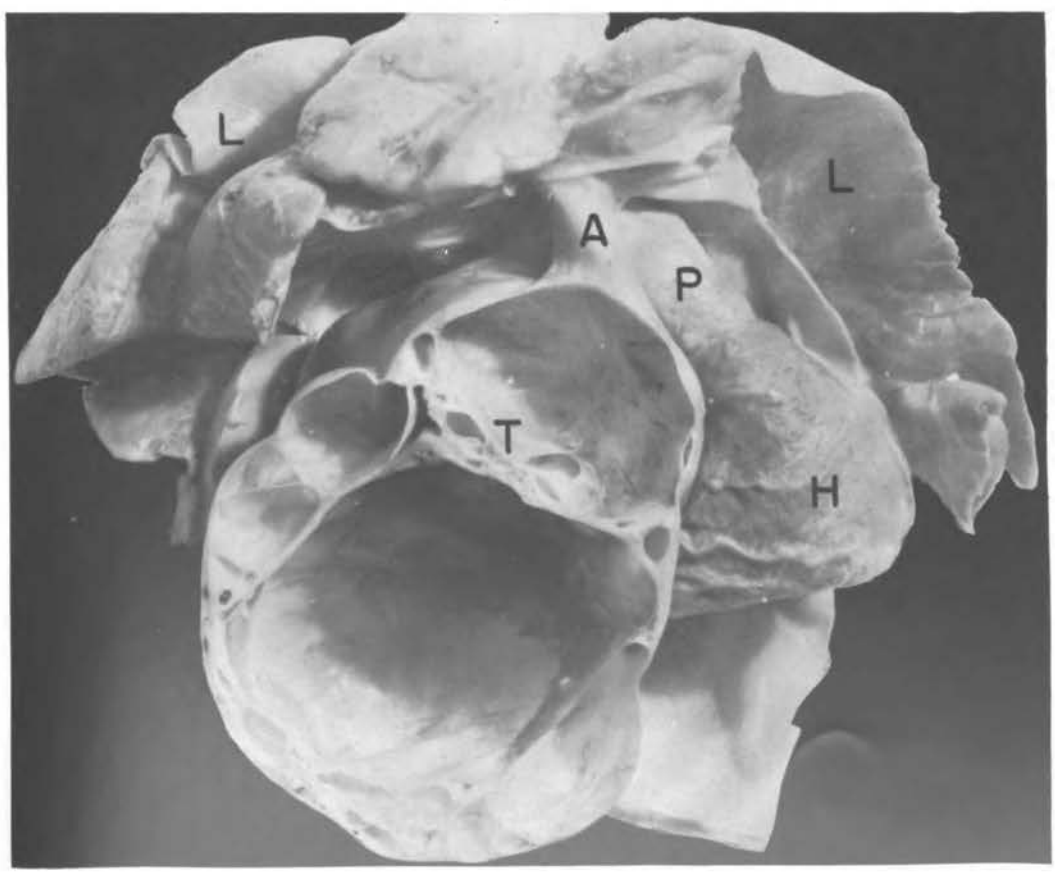


Fig. 16

Figure 17. Section of a "dermoid" eminence in an ovarian teratoma, clothed by skin and containing adipose subcutaneous tissue, epithelial cysts, and masses of cartilage and bone. Dotted lines denote the pedicle of attachment to the cyst wall. X 4½. A.F.I.P. Acc. No. 219005-3.

Figure 18. Section of a malignant teratoma of ovary, showing the heterogeneous, solid and cystic tissues. X 10 (further enlarged X 1 1/3 from the original photograph). A.F.I.P. Acc. No. 219005-20.

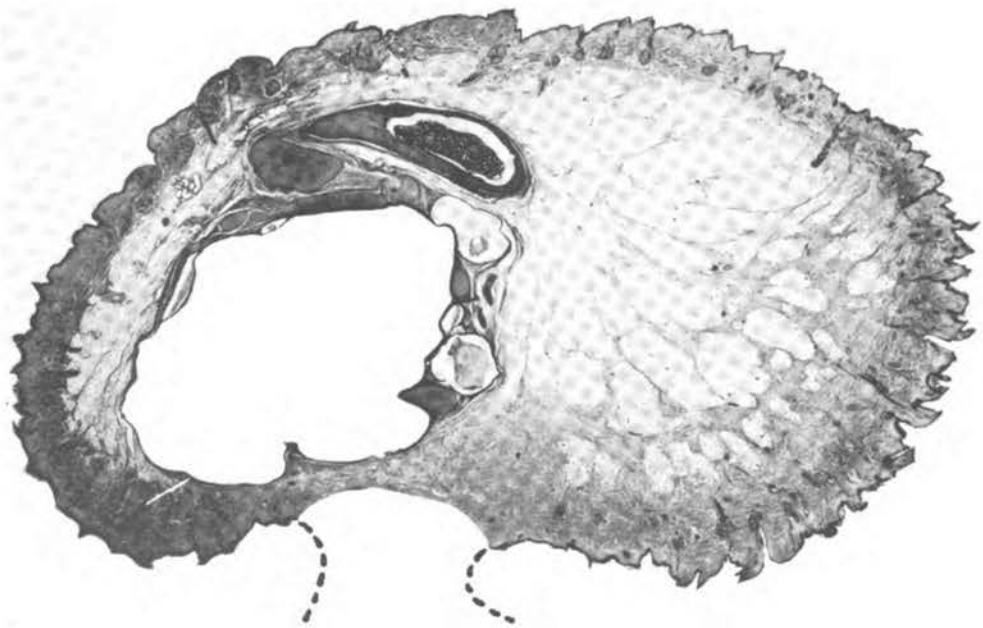


Fig. 17

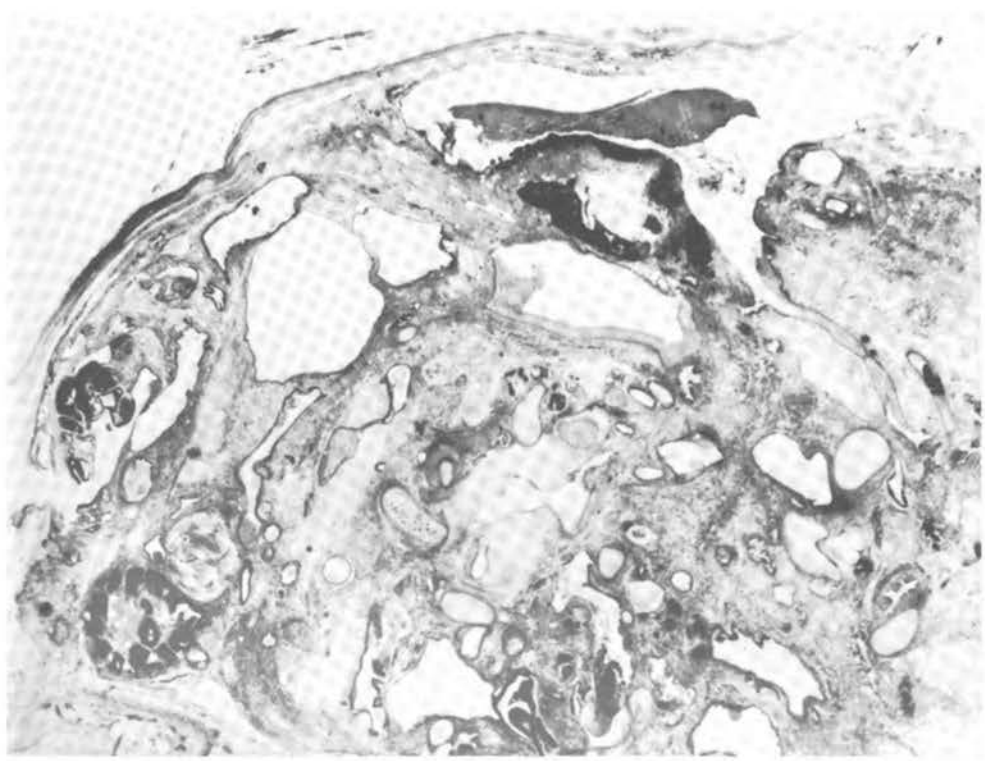


Fig. 18

Figure 19. Section of a malignant teratoma of testis in a predominantly cystic area. X 4. A.F.I.P. Acc. No. 219005-22.

Figure 20. Cross section of half of brain-stem which has been bisected in the median plane (MM), showing the aqueduct of Sylvius (AA) greatly distended by an extension of a malignant teratoma of the pineal region. X 4½. A.F.I.P. Acc. No. 219005-23.

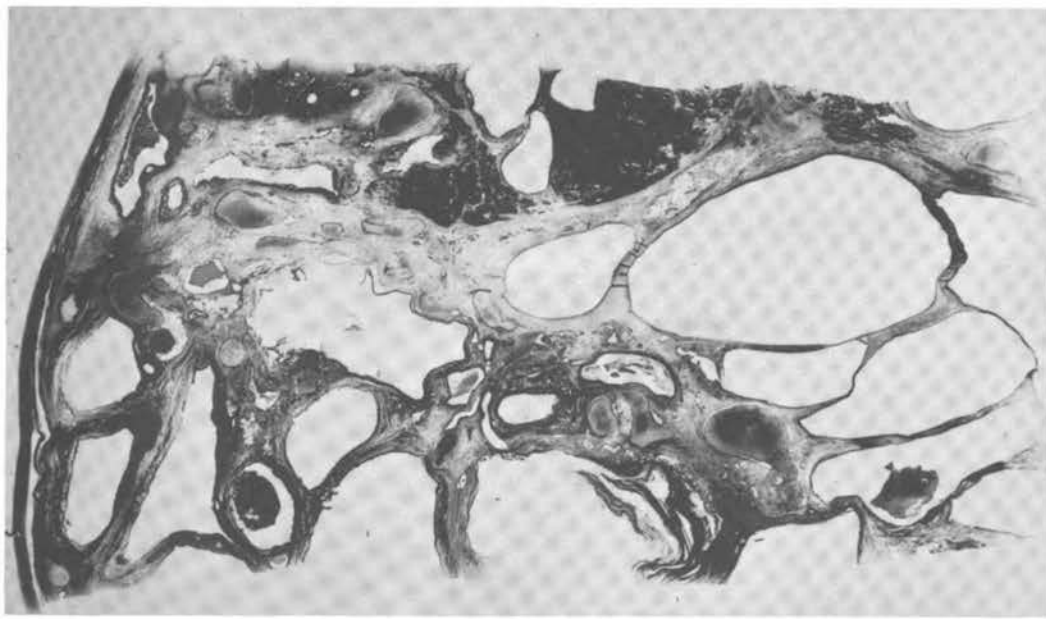


Fig. 19

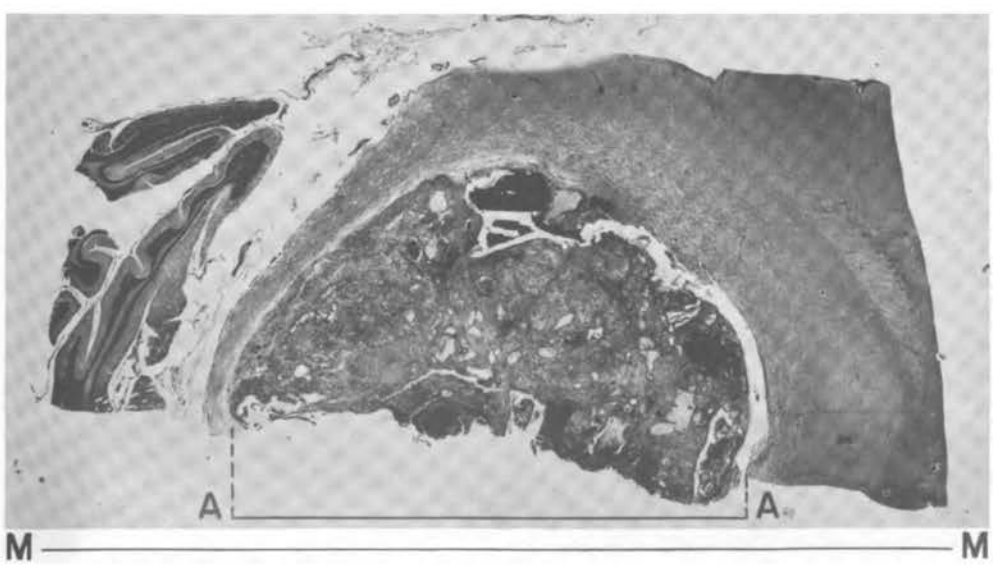


Fig. 20

Plate I. Diagrams Showing Structure of
Four Slabs of a Mediastinal Teratoma
(slightly reduced)

Epidermis, hairs, and skin glands.....

Central nervous tissues.....

Main mass of nervous tissues with
ependyma-lined cavity ..... N

Choroid plexus..... C

Cartilage.....

Bone.....

Respiratory glandular cavities.....

Alimentary glandular cavities..... A

Renal tissue.....

Tooth (see also figures 13, 14, 23)..... T

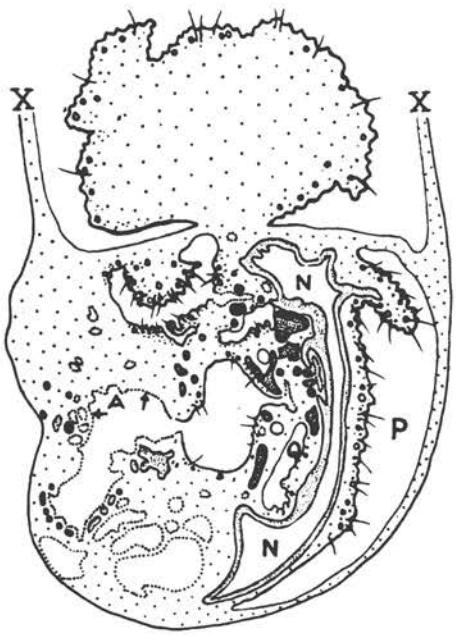
Main cyst wall..... X

Skin cavities, P and Q (pl. IA, B, C), continuous
with main cavity as indicated by arrow (pl. ID).....

Tag of adherent thymus..... Th

Cavity partly lined by endometrium-like tissue..... Z

(From Willis, R.A., "The structure of teratomata." J. Path. Bact., 40:1-36, 1935.) A.F.I.P. Acc. Nos. 219005-11-14.



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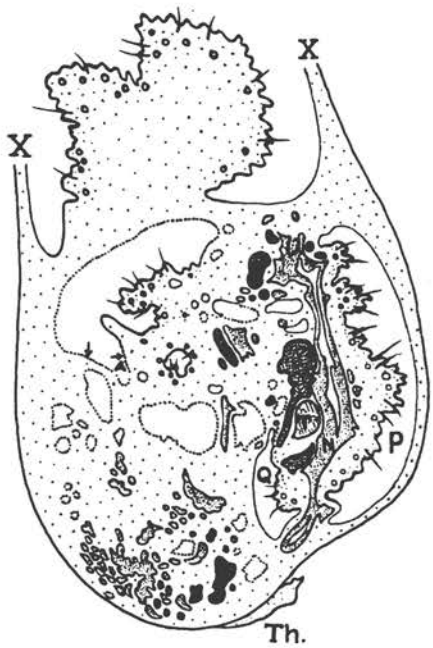

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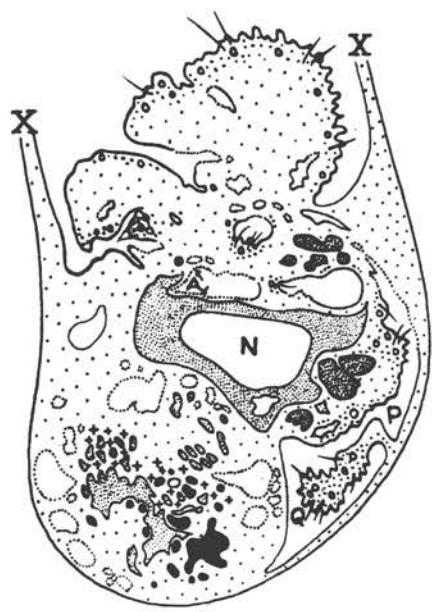

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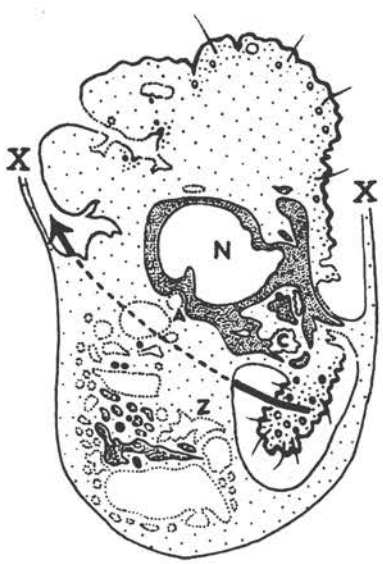

D

Plate I

Malignant teratomas, containing as they do much actively growing, imperfectly differentiated tissue, also frequently show mixtures of such tissue with better differentiated elements. They are often finely polycystic. Most of them are thus heterogeneous in appearance (figs. 6, 18–20), even when they are predominantly solid; and spicules of bone, nodules of cartilage, or small cutaneous or mucoid cysts may be recognizable in the solid areas. Areas of necrosis or hemorrhage are often present as well; and the "chorionepitheliomatous" type of teratoma is conspicuously hemorrhagic.

This is the place to insist that adequate study and comprehension of the structure of a complex tumor like a teratoma necessitates orderly examination of all parts of it to ascertain its topography. The ideal procedure would be complete serial section and reconstruction, but this is practicable only with very small growths. With large growths, a compromise which is adequate for most purposes is to cut the tumor up into properly oriented numbered blocks for microsections, and, when microscopic study of these has been completed, reconstruct maps of the slices to show the nature and distribution of the component tissues. Such reconstructions, examples of which are shown in plate I and figures 10 and 14, are essential to a proper understanding of the composition and anatomy of teratomas. In particular they show conclusively the non-fetiform character of these tumors.

HISTOLOGIC

Tissue Components.—The tissues of teratomas are adult or embryonic, mature or immature. The fully mature tissues of benign teratomas closely resemble their normal counterparts and are easy to recognize. But malignant teratomas contain embryonic tissues of all degrees of immaturity, the recognition of which often demands much experience and a good knowledge of embryonic histology. This is especially so when, as is often the case, embryonic and mature tissues are mingled. This mixture of differentiating tissues of all ages is one of the most striking structural characters of malignant teratomas. It must be emphasized here that the imperfectly differentiated tissues of malignant teratomas are not merely anaplastic but truly embryonic; they reproduce indefinitely structures which, though neoplastic, closely correspond to all stages of embryonic and fetal development (figs. 26, 27, 29, 34–38).

Skin, including hairs, sebaceous and sweat glands, and occasionally pigmented areas or moles, is a very common component (figs. 7, 11, 17). Stratified epithelium of oropharyngeal type, associated with lymphoid tissue or with mucous and mixed glands, and respiratory pseudostratified epithelium (fig. 21) is of frequent occurrence. So also are teeth (figs. 2, 8, 9, 11, 13, 23, 36), which are usually solitary or few, but sometimes number dozens or even hundreds. Intestinal epithelium and glands (fig. 43) are often present, while gastric and pancreatic tissues are less frequently seen. Liver and lung tissue

(fig. 22) have rarely been seen. In malignant teratomas any of these tissues may be found in varying stages of immaturity.

Nervous tissue is present in at least 80 percent of all teratomas. In benign growths it occurs as masses of neuroglial tissue (figs. 24, 32, 33), usually devoid of but sometimes containing nerve cells, and with or without ependyma-lined cavities; small or large spaces lined by fringes of choroid plexus (fig. 24), or peripheral nerve bundles and ganglia of sympathetic type may also be seen (fig. 25). Occasionally, small masses of well differentiated cerebellar (see figure 45 in Fascicle 18, "Tumors of the Mediastinum") or cerebral cortex are present. In malignant growths, all degrees of immaturity of these tissues are seen, a specially prominent component often being neuroepithelial tubules and plaques consisting of a thick layer of darkly-staining, cellular tissue closely resembling that of the ependymal and mantle zones of the early embryonic nervous system (figs. 26, 27, 34). Ocular tissue is sometimes present in the form of heavily pigmented epithelium resembling that of the ciliary body or of pigmented embryonic neuroepithelium (fig. 27); well developed retinal tissue has not been seen.

Thyroid tissue is occasionally present in ovarian teratomas, in which it sometimes forms the bulk of the growth. Ovarian teratomas containing thyroid tissue have been called ovarian goiter, struma ovarii, ectopic ovarian thyroid, and thyroid tumor of the ovary. In a number of reported cases of "ovarian goiter," other heterotopic tissues have not been discovered; therefore, their teratomatous nature cannot be regarded as proved. However, since many "ovarian goiters" have been shown to be teratomatous, and since several cases have been reported in which the other teratomatous elements were found only by painstaking search, it is probable that all "ovarian goiters" are really teratomas with thyroid tissue predominating. Needless to say, other types of polycystic ovarian tumors in which the tissue may in parts morphologically only resemble thyroid tissue, should not be called "ovarian goiters." Thyroid tissue is extremely rare in teratomas other than ovarian.

Renal tissue with glomeruli and tubules has been seen occasionally in teratomas (fig. 28); and in one case of the writer's, a mass of immature renal tissue resembling that of a nephroblastoma was present (fig. 29). Gonadal and other genital tissues have rarely been recorded, and in most, perhaps all, cases the identifications are doubtful.

Cartilage and bone in all stages of formation are frequent components (figs. 8, 9, 11, 13, 17); so also are adipose tissue (figs. 17, 33), connective tissues, blood vessels, and, in malignant growths, undifferentiated embryonic mesenchyme (fig. 35). Hemopoietic tissue is sometimes represented by bone marrow in masses of bone and by lymphoid tissue associated with oropharyngeal, respiratory, or intestinal epithelia; but well differentiated spleen

or lymph nodes have rarely, if ever, been observed. Tissue resembling notochord has occasionally been reported, but its identity is doubtful.

Nonstriated muscle is a frequent component, especially around cavities lined by alimentary or respiratory epithelia. Striated muscle (fig. 30) is plentiful in some teratomas, and may be abundant and well differentiated in tumors in which central nervous tissue and nerves are scanty or absent. This raises the question of whether or not the muscle fibers are innervated; study of this point is needed. In some malignant teratomas, especially of the testis, immature striated muscle has been so predominant that the tumors have been called "rhabdomyosarcomas." Most teratomatous striated muscle is clearly of skeletal type; cardiac muscle has rarely been recorded, and its identification is doubtful.

Teratomatous "chorionepithelioma." While very occasionally chorionepithelioma-like appearances are seen around areas of necrosis or hemorrhage in seminomas, most "chorionepitheliomas" of the testis are undoubtedly teratomas, since other teratomatous tissues are frequently to be found in parts of them. The nature of the "chorionepitheliomatous" tissue in teratomas has been the subject of much discussion. Many pathologists support the view, first put forward by Schlagenhaufer in 1902, that this tissue is truly chorionic in nature and that it arises from actual trophoblastic components of teratomas. Other pathologists, while admitting the strength of the evidence favoring this view, are not wholly convinced of its correctness and wonder if this tissue may be "chorionepitheliomatous" only in appearance, just as are some anaplastic and necrotic growths of other kinds; e.g., carcinomas of liver, stomach, or urinary bladder. The very high production of gonadotrophic hormone by many teratomatous "chorionepitheliomas" is a powerful argument for their truly chorionic nature: the Aschheim-Zondek reaction is often strongly positive at a titer far in excess of that accompanying any other class of tumor, and gynecomastia has frequently been observed. (See, for examples, Prym; Roth; Symeonidis.) However, hormonal disturbances do accompany testicular tumors of other kinds, and still further investigation of these is needed. It is noteworthy that well differentiated placental tissue has not been described in a teratoma; and also that "chorionepithelioma" rarely, if ever, develops in teratomas other than testicular.

Seminoma and teratoma. Many American writers have accepted Ewing's view that the common seminoma of the testis is essentially teratomatous, an "embryonal carcinoma" or "one-sided development of a teratoma." The present writer dissents from this view on grounds which are fully set forth elsewhere (Willis, 1948), but which are briefly the following: (1) The structural evidence for the origin of seminoma from the seminiferous epithelium appears to him to be clear and indubitable; (2) the great majority of ordinary

seminomas, even small ones, when carefully studied in serial sections, shows no signs of heterotopic teratomatous tissues; (3) teratoma and seminoma sometimes coexist in one testis, in which case careful topographic study usually shows them as distinct and separate tumors or affords evidence that they were probably so originally; (4) undifferentiated teratomatous epithelium of the kind shown in figure 38 has often been called "embryonal carcinoma" and confused with seminoma; and (5) seminoma and teratoma differ strikingly in their age incidence, species incidence, and metastatic behavior; seminomas appear on an average more than a decade later than teratomas; they are a common testicular tumor of dogs, while testicular teratomas have been found only in horses; blood-borne metastases occur later and less frequently from seminomas than from teratomas. Hence, in spite of the widely held idea that seminoma is a kind of teratoma, it will not be discussed further here. (See Fascicle 32, "Tumors of the Male Sex Organs.")

Tissue Correlations.—Although teratomas are devoid of a true vertebrate axis and of regional distribution of parts, the arrangement of the various tissues in them is not entirely chaotic but shows many characteristic associations of particular tissues similar to those of normal histology. Skin shows normal relationships of dermis and epidermis, respiratory epithelium is usually accompanied by cartilage, cavities lined by alimentary epithelium are often encircled by smooth muscle, masses of central nervous tissue are often surrounded by meninges-like membranes and by cartilage or bone, and teeth show normal relationships of enamel and dentine and are often set in bony sockets. These relationships show the operation in teratomas of inductive influences of one growing tissue on another, similar to those which determine dependent differentiation in normal organogenesis. Such tissue correlations are especially evident in teratomas with highly organized parts (see that section).

Histogenesis in Teratomas.—Malignant teratomas, containing many kinds of embryonic tissues at different stages of maturity and in different spatial relationships, provide an interesting field for the study of the genesis and differentiation of various tissues. Such study shows, for example, that neuroepithelium takes origin from a simple epithelium which, like early embryonic ectoderm, is plastic and can produce also epidermis and dental epithelium. It is therefore not surprising to find that in the linings or cavities in teratomas, nervous tissue, skin, and teeth are often seen in abrupt continuity (figs. 31–34).

Teratomatous teeth, like normal ones, arise from tooth germs which develop from downgrowths of dental-shelf epithelium from cavities lined by ectoderm; dental papillae develop in relation to characteristic enamel organs with abundant stellate reticulum; and paradental residues of dental shelf tissue persist in the peridental connective tissue around the fully formed

teeth (figs. 36, 37). In young teratomas the teeth are frequently unerupted, but in older growths they erupt into the neighboring epithelial cavities from which they originally sprang (figs. 13, 14).

Epidermis, oropharyngeal, and respiratory epithelia are often seen in continuity in teratomas, and may clearly arise from a common precursor. Pancreatic tissue is usually connected with intestinal cysts, and gastric and pancreatic tissue frequently occur together.

Malignant teratomas often contain plentiful embryonic mesenchyme, in which all stages in the development of connective, adipose, skeletal, and muscular tissues can be traced (fig. 35).

HIGHLY ORGANIZED STRUCTURES

Digits have been seen mainly in retroperitoneal and sacral teratomas. They show nails, phalanges, and metacarpals (or metatarsals—it is uncertain which), and in a few cases recognizable carpals (or tarsals) have also been present. None of the "limbs" described in teratomas deserves this title; digits and carpals are the most that have been demonstrated, and although pieces of bone proximal to these have been called "radius," "pelvis," etc., these identifications are imaginary.

Intestine, possessing all coats and an Auerbach's plexus, is sometimes found with free coils and attached mesentery projecting into a celomic cavity. Such coils end blindly and become distended with mucus.

Highly organized nervous structures. Masses of central nervous tissue in teratomas are often highly organized, in that they contain cavities lined by ependyma and choroid plexus and filled with clear cerebrospinal fluid, and are surrounded by meninges-like sheaths. Occasionally a small area of such tissue has the typical architecture of cerebellar or cerebral cortex. Sympathetic ganglia and nerves in some teratomas are as perfectly developed as their normal counterparts (fig. 25).

MALIGNANT TERATOMAS

SYNONYMS AND RELATED TERMS: Teratoma malignum (Lat.): "embryoma"; embryonic carcinoma; teratoblastoma (Adami); teratocarcinoma. Chorionepithelioma and embryonal carcinoma of the testis are specific terms for malignant tumors developing in teratomas of the testis.

The various main sites of teratomas show distinct differences in the incidence of benign and malignant growths. In the human ovary, most teratomas are of the benign "dermoid cyst" variety; relatively few of them are malignant, solid or polycystic tumors. Conversely, in the human testis, most teratomas when first discovered are malignant; and benign tumors form only a small minority. Most retroperitoneal, presacral, and mediastinal teratomas are benign and cystic, and only a few of them are, or become, malignant. Many

Figure 21. Ciliated respiratory epithelium in a mediastinal teratoma. (Iron hematoxylin stain.) X 1000. (From Willis, R. A., "Pathology of Tumours," p. 956. London: Butterworth & Co., Ltd., 1948.) A.F.I.P. Acc. No. 219005-24.

Figure 22. Lung tissue in a teratoma of the brain. X 120. A.F.I.P. Acc. No. 219005-25.

Figure 23. Tooth in a mediastinal teratoma shown in plate IB and figures 13 and 14. X 30. A.F.I.P. Acc. No. 219005-26.

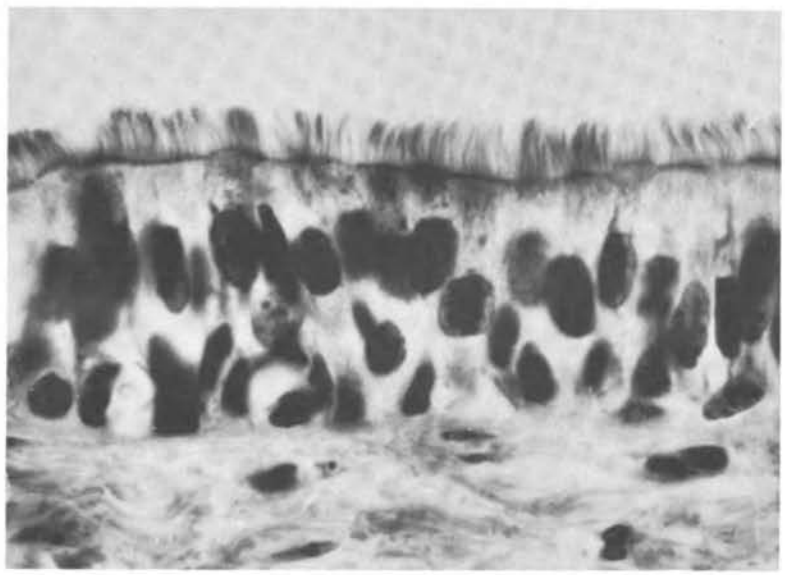

Fig. 21

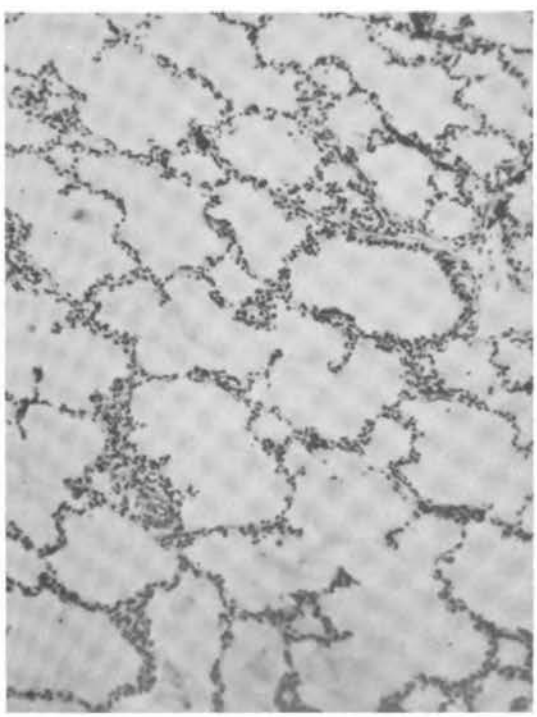

Fig. 22

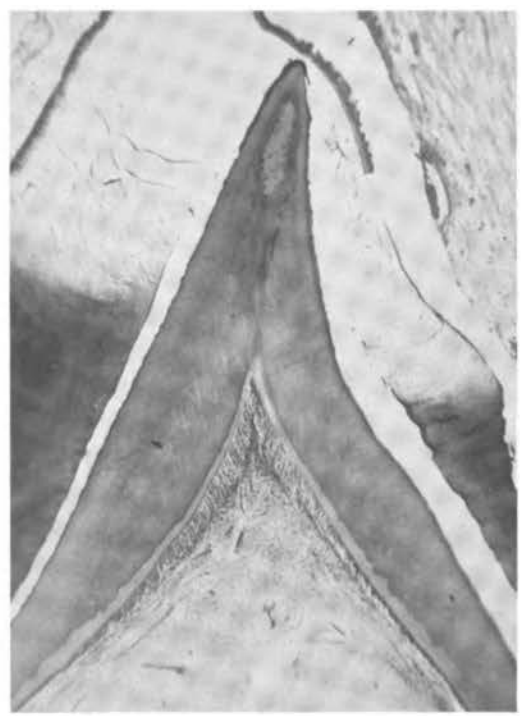

Fig. 23

Figure 24. Cavities lined by central nervous tissue (N) and choroid plexus in a retroperitoneal teratoma. X 100. (From Willis, R. A., "The structure of teratomata." J. Path. Bact., 40:1-36, 1935.) A.F.I.P. Acc. No. 219005-48.

Figure 25. Sympathetic ganglionic tissue in a teratoma of a horse's testis. X 144. (From Willis, R. A., and Rudduck, H. B., "Testicular teratomas in horses." J. Path. Bact., 55:165-171, 1943; and from Willis, R. A., "Pathology of Tumours," p. 974. London: Butterworth & Co., Ltd., 1948.) A.F.I.P. Acc. No. 219005-49.

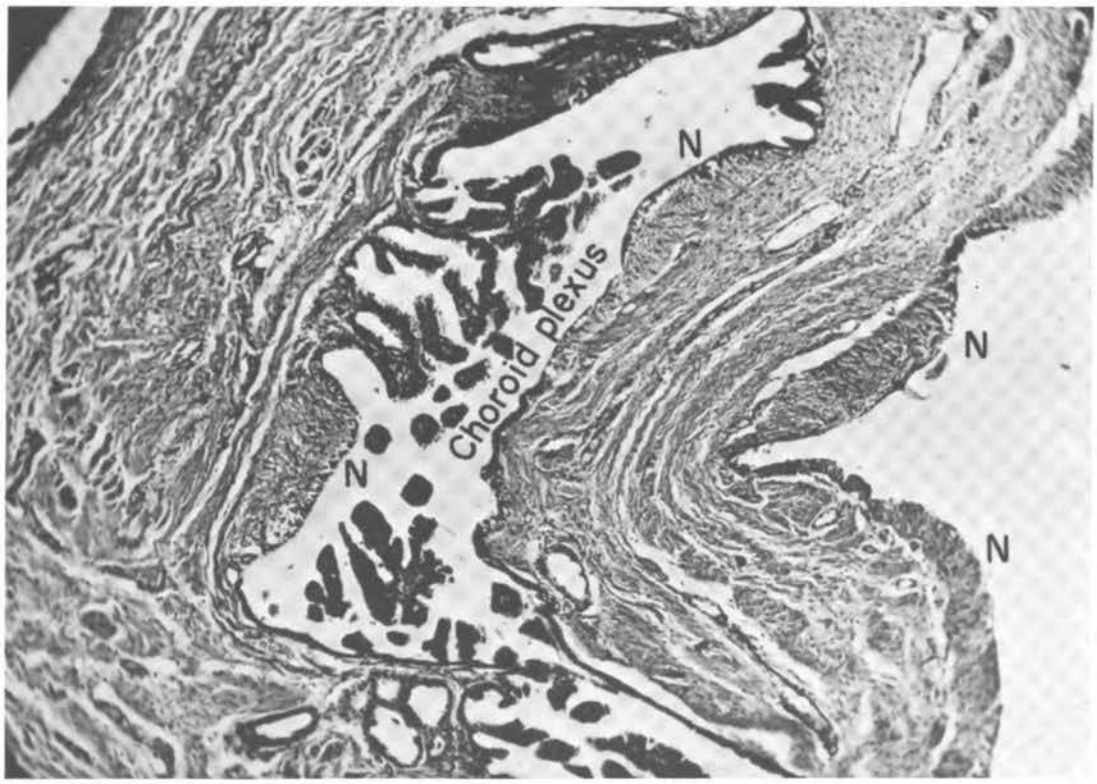

Fig. 24

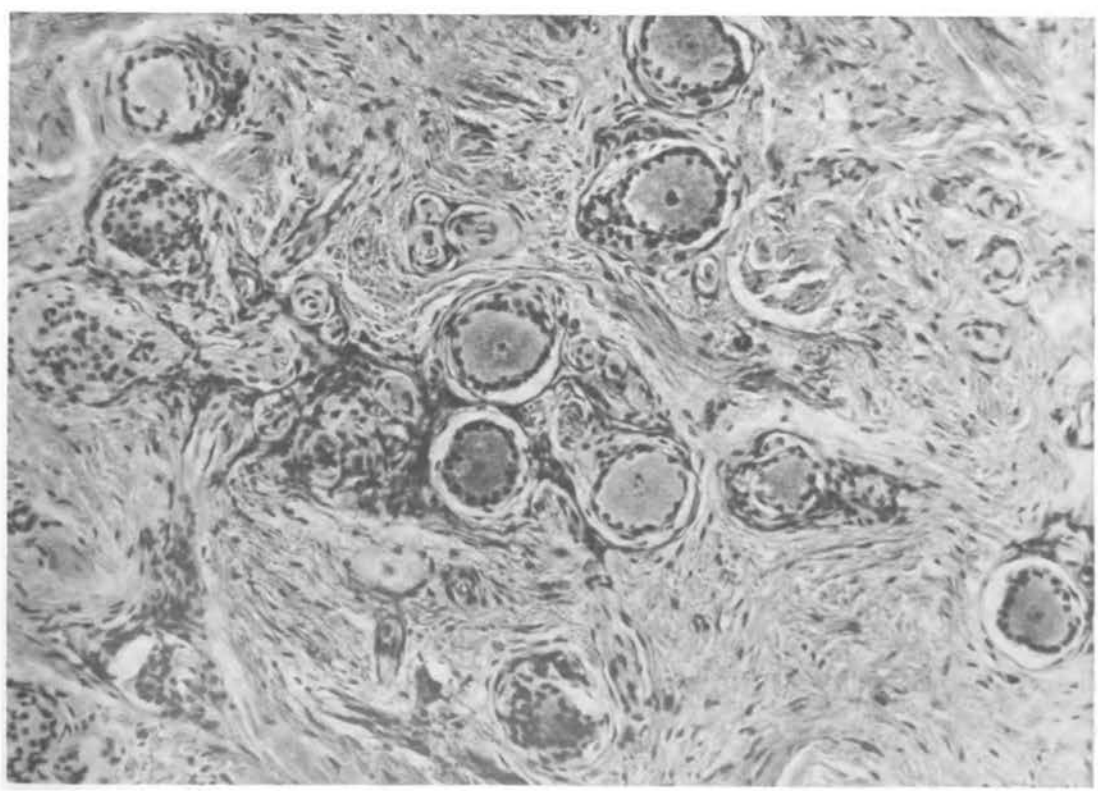

Fig. 25

Figure 26. Early ependymal differentiation in a neuroepithelial canal in a teratoma of the testis. X 360 (further enlarger X 1 1/3 from the original photograph). A.F.I.P. Acc. No. 219005-28.

Figure 27. Small cavity in a cerebral teratoma, lined partly by embryonic nervous tissue and partly by deeply pigmented ocular epithelium. X 120 (further enlarged X 1½ from the original). (From Willis, R. A., "Pathology of Tumours," p. 959. London: Butterworth & Co., Ltd., 1948.) A.F.I.P. Acc. No. 219005-31.

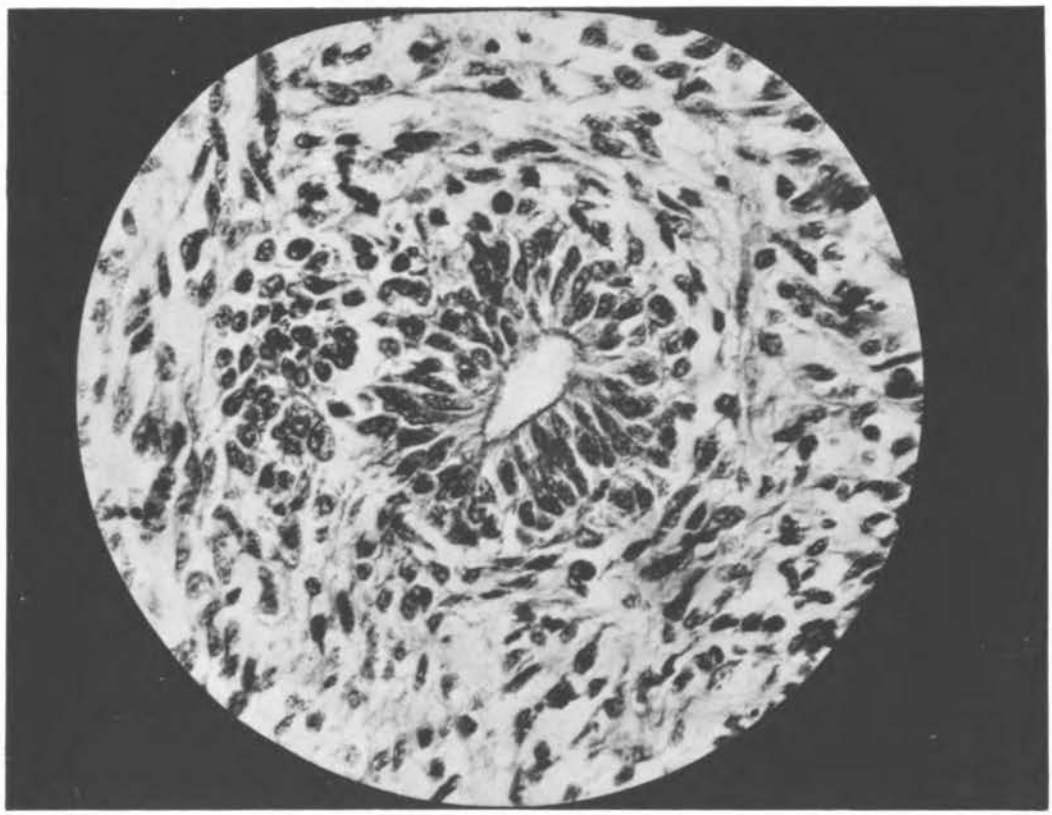

Fig. 26

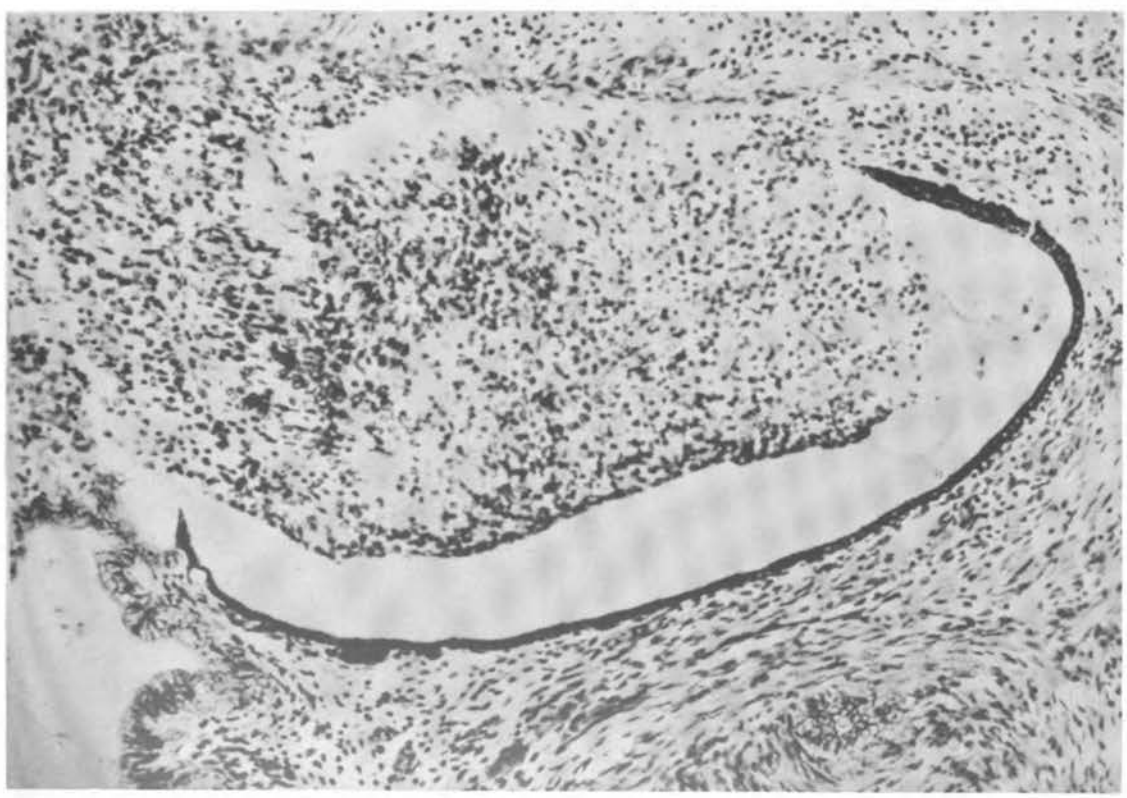

Fig. 27

Figure 28. Renal tissue in a retroperitoneal teratoma. X 100. (From Willis, R. A., "The structure of teratomata." J. Path. Bact., 40:1-36, 1935.) A.F.I.P. Acc. No. 219005-31.

Figure 29. Immature renal tissue, like that of a nephroblastoma, in a retroperitoneal teratoma. X 50. (From Willis, R. A., "The Pathology of Tumours," p. 960. London: Butterworth & Co., Ltd.) A.F.I.P. Acc. No. 219005-32.

Figure 30. Striated muscle fibers in a retroperitoneal teratoma. X 375. (From Willis, R. A., "Pathology of Tumours," p. 961. London: Butterworth & Co., Ltd., 1948.) A.F.I.P. Acc. No. 219005-33.

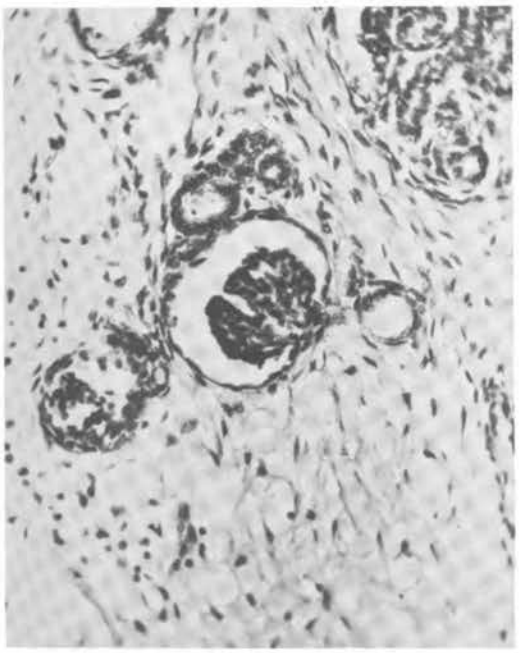

Fig. 28

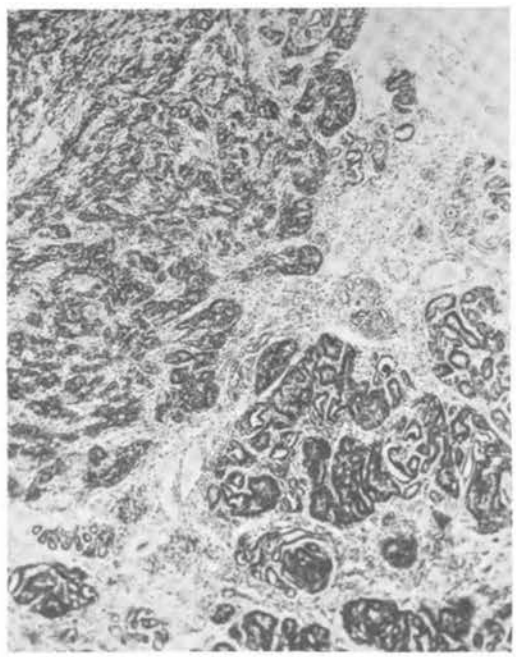

Fig. 29

Fig. 30

Figure 31. A keratinized focus of squamous epithelium abruptly continuous with neuroglial tissue in the lining of an ovarian "dermoid cyst." X 48. A.F.I.P. Acc. No. 219005-34.

Figure 32. Respiratory epithelium abruptly continuous with neuroglial tissue in the cavity of an ovarian teratoma. X 55. A.F.I.P. Acc. No. 219005-35.

Figure 33. An abrupt junction of glandular epithelium and neuroglial tissue in an ovarian teratoma. X 60. (From Willis, R. A., "A further study of the structure of teratomata." J. Path. Bact., 45:49-65, 1937.) A.F.I.P. Acc. No. 219005-50.

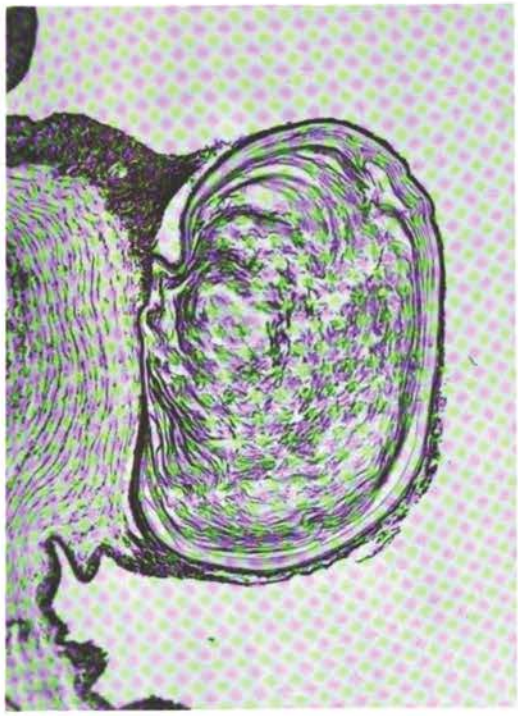

Fig. 31

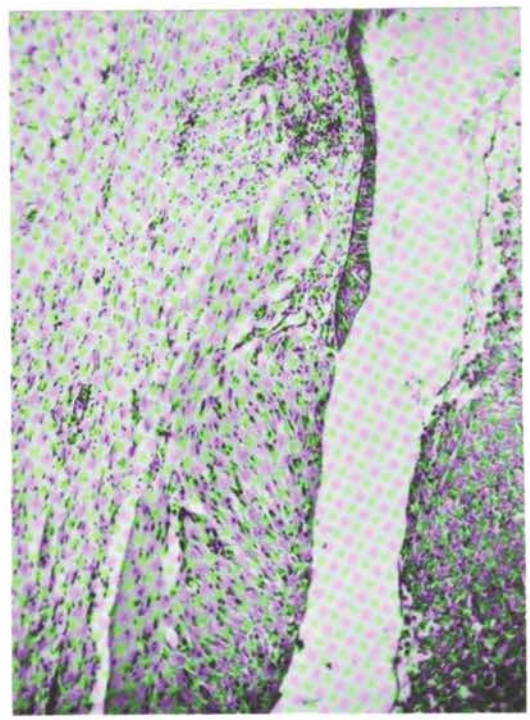

Fig. 32

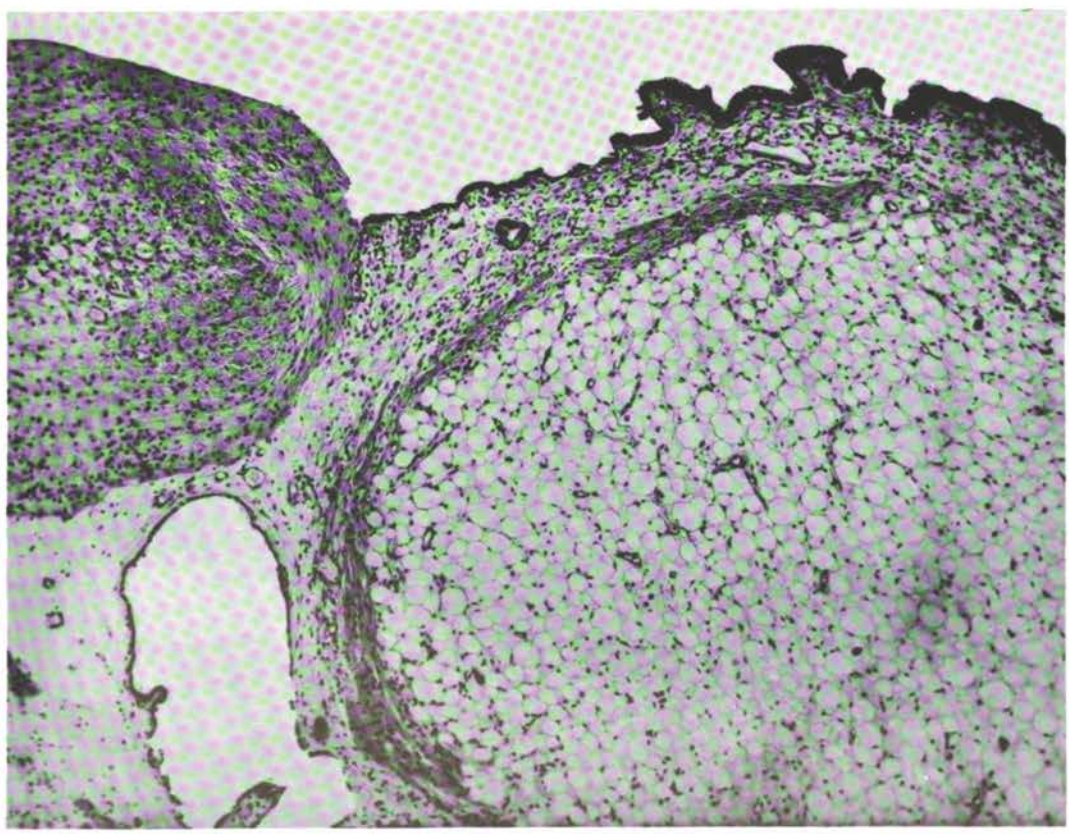

Fig. 33

Figure 34. Young stratified epithelium and embryonic nervous tissue continuous with one another in a malignant ovarian teratoma. X 90. (From Willis, R. A., "Pathology of Tumours," p: 965, London: Butterworth & Co., Ltd., 1948.) A.F.I.P. Acc. No. 219005-51.

Figure 35. Early differentiation of smooth muscle from undifferentiated mesenchyme around young glandular structures in a malignant teratoma of the testis. X 200. (From Willis, R. A., "The structure of teratomata." J. Path. Bact., 40:1-36, 1935.) A.F.I.P. Acc. No. 219005-52.

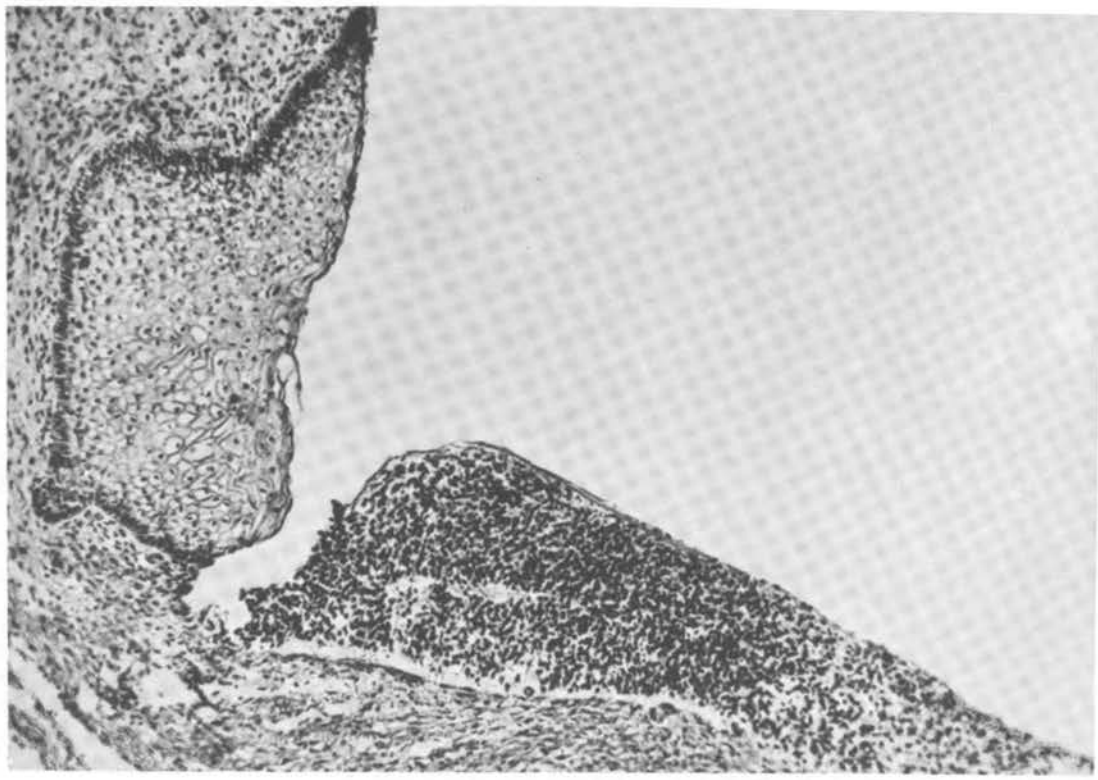

Fig. 34

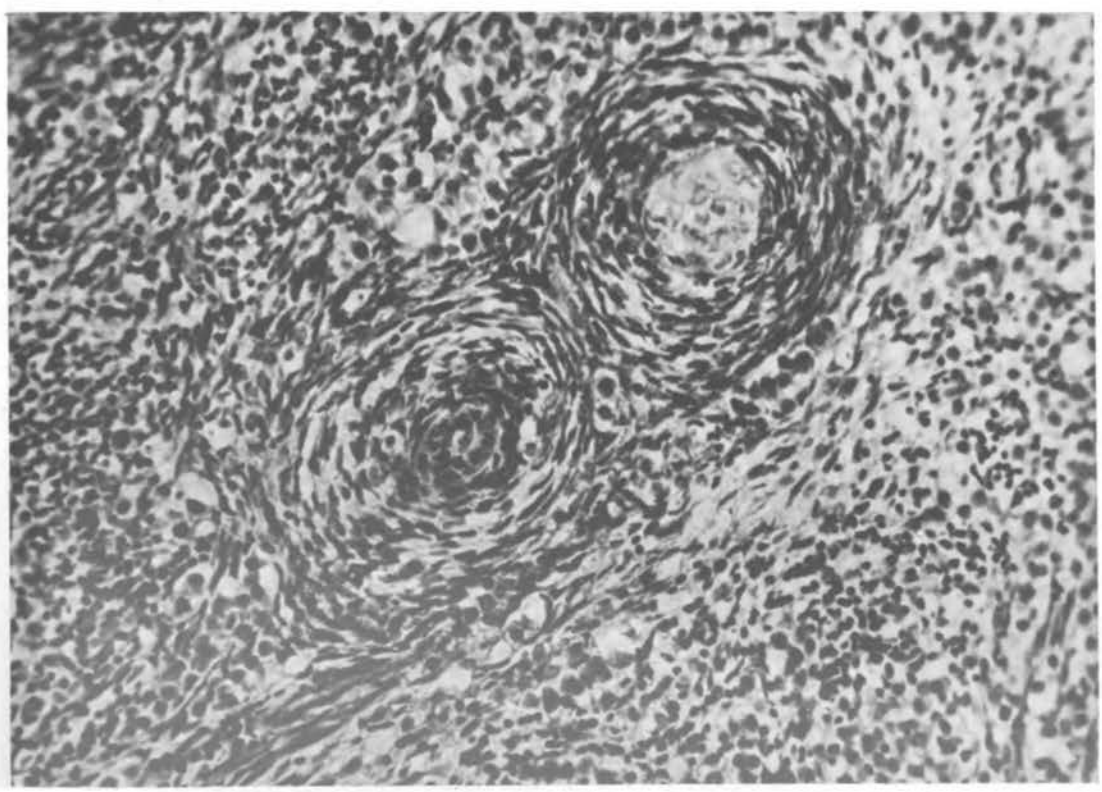

Fig. 35

Figure 36. Immature tooth rudiment surrounded by a mass of stellate reticulum (S) in a teratoma of the brain. X 60. A.F.I.P. Acc. No. 219005-38.

Figure 37. Residues of dental lamina connected with the stellate reticulum (S) of a tooth rudiment in a teratoma of the brain. X 60. A.F.I.P. Acc. No. 219005-39.

Figure 38. Undifferentiated embryonic epithelium (often called "embryonal carcinoma"), a frequent component of malignant teratomas of the testis. X 110. A.F.I.P. Acc. No. 219005-41.

Figure 39. Area of infiltrating adenocarcinoma in an otherwise benign ovarian teratoma. X 100. (From Willis, R. A., "Pathology of Tumours," p. 971. London: Butterworth & Co., Ltd., 1948.) A.F.I.P. Acc. No. 219005-45.

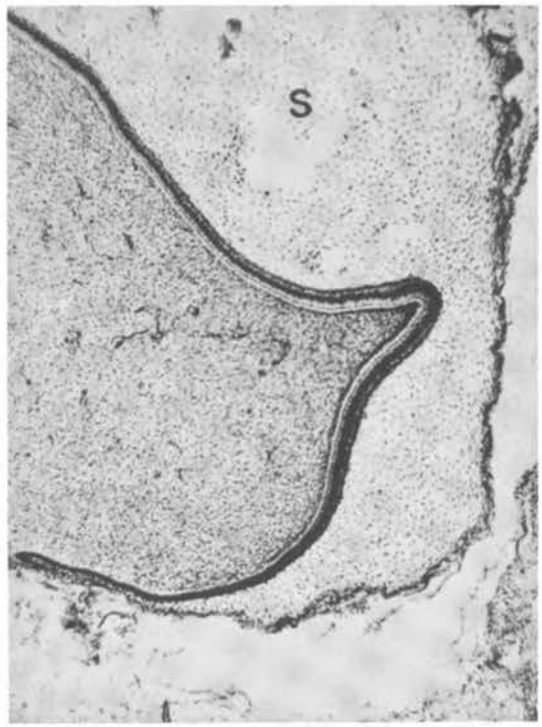

Fig. 36

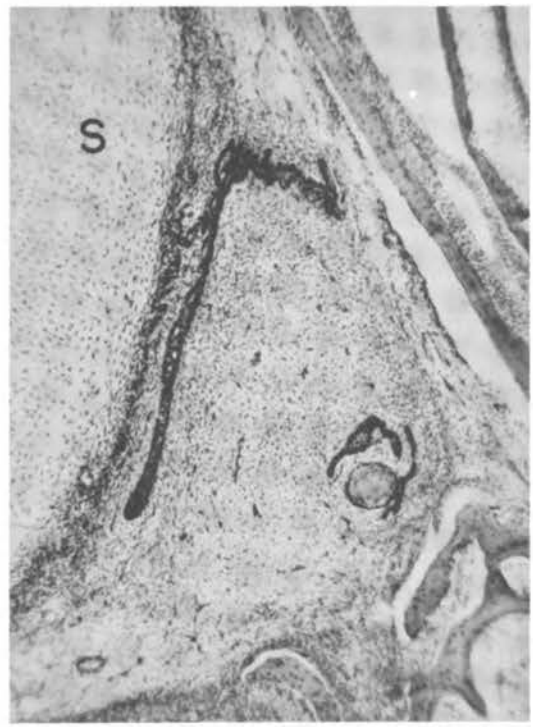

Fig. 37

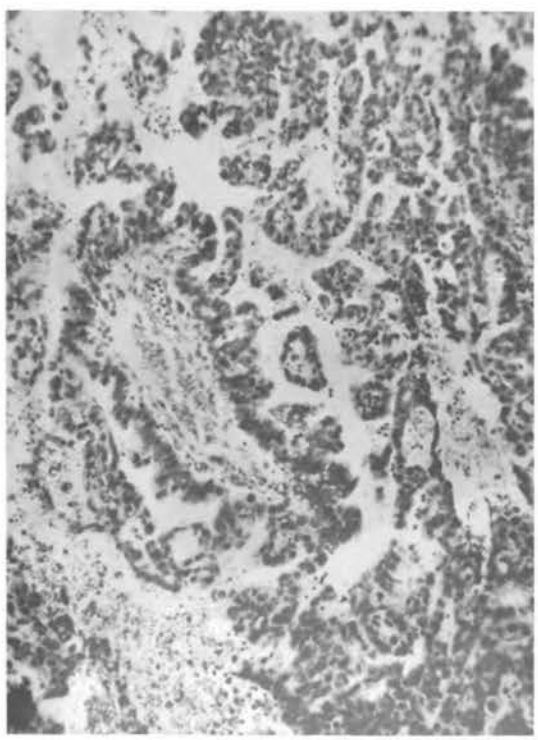

Fig. 38

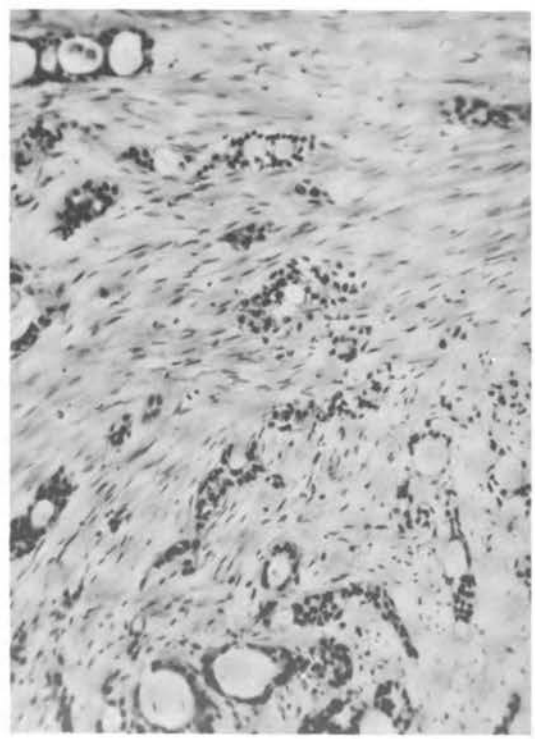

Fig. 39

Figure 40. Hyperplastic epidermis in part of an ovarian "dermoid cyst," which elsewhere showed squamous cell carcinoma. X 10. (See also figures 41 and 42.) A.F.I.P. Acc. No. 219005-42.

Figure 41. Papillomatous epidermis from the same specimen as figure 40. X 10. A.F.I.P. Acc. No. 219005-43.

Figure 42. Squamous cell carcinoma from the same specimen as figures 40 and 41. X 80 (further enlarged X 1½ from the original photograph). (From Willis, R. A., "A further study of the structure of teratomata." J. Path. Bact., 45:49-65, 1937, and from Willis, R. A., "Pathology of Tumours," p. 969. London: Butterworth & Co., Ltd., 1948. A.F.I.P. Acc. No. 219005-44.

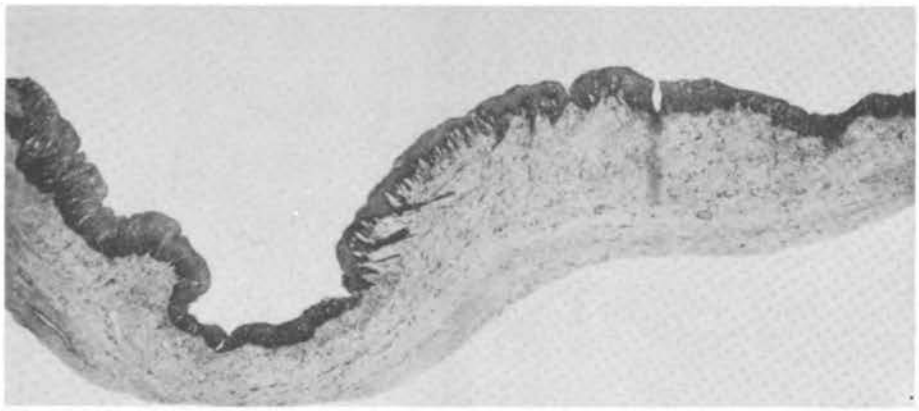

Fig. 40

Fig. 41

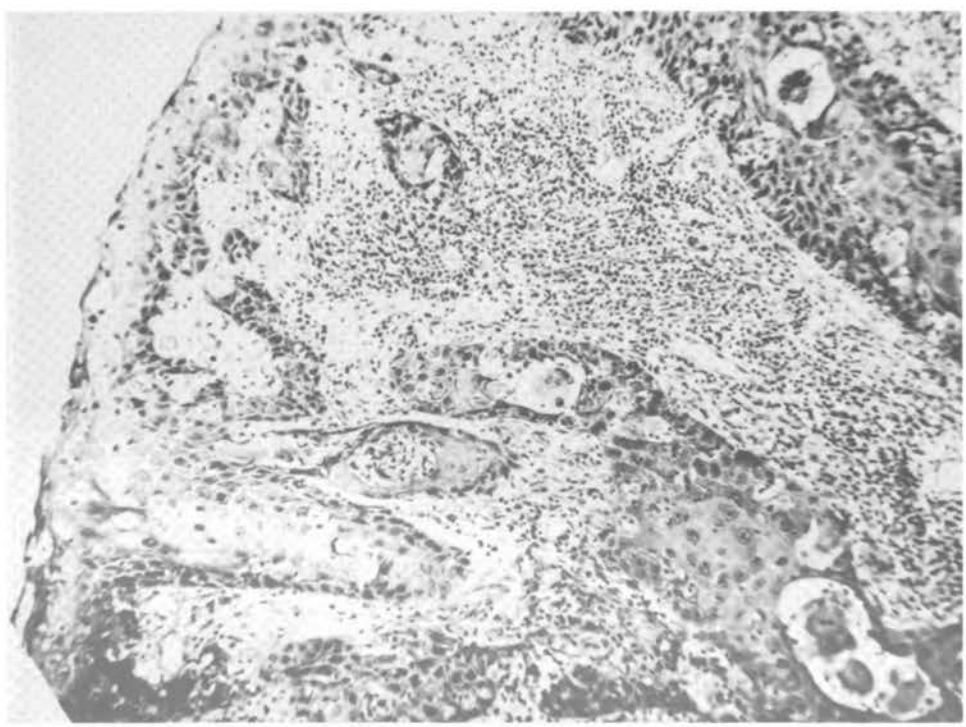

Fig. 42

Figure 43. Section of wall of an ovarian "dermoid cyst," partly lined by intestinal mucosa (EE), whence an argentaffinoma ("carcinoid") (CC) invades underlying muscularis (MM). (See also figures 44 and 45.) A.F.I.P. Acc. No. 219005-46.

Figures 44 and 45. Enlarged views of figure 43, showing the characteristic structure of argentaffinoma. X 40 and X 55. (Figures 44 and 45 from Stewart, M. J., Willis, R. A., and de Saram, G. S. W., "Argentaffine carcinoma (carcinoid tumour) arising in ovarian teratomas: a report of two cases." J. Path. Bact., 49:207-212, 1939; figure 44 also from Willis, R. A., "Pathology of Tumours," p. 971. London: Butterworth & Co., Ltd., 1948.) A.F.I.P. Acc. Nos. 219005-47 and 219005-48.

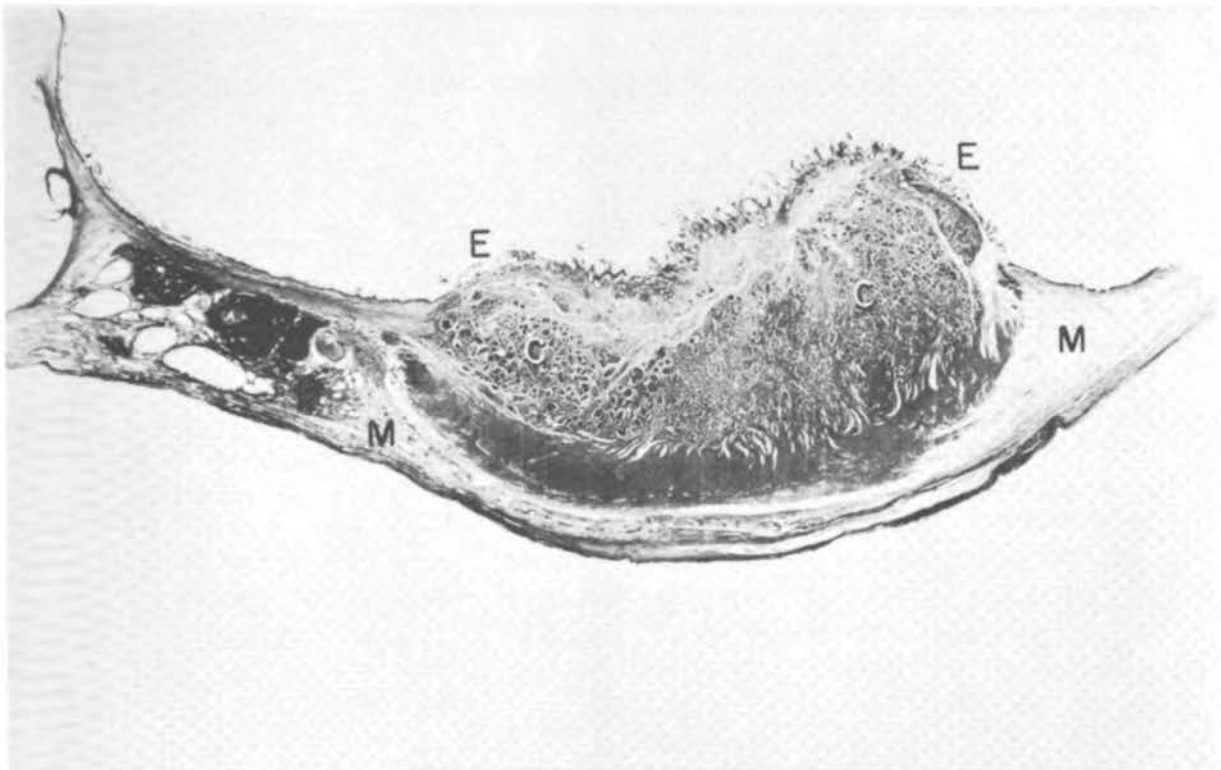

Fig. 43

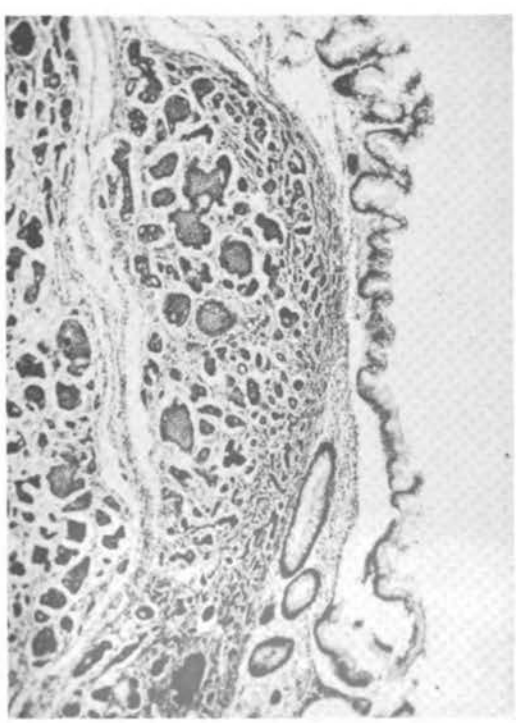

Fig. 44

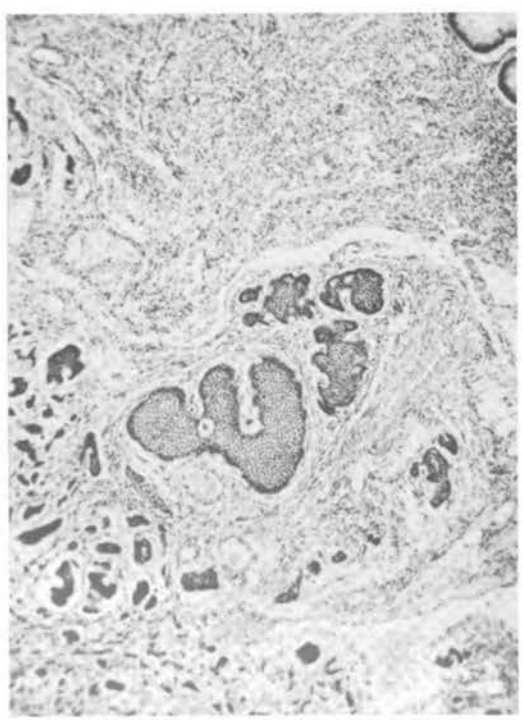

Fig. 45

intracranial teratomas, perhaps the majority of them, are actively growing and malignant.

Malignancy and metastatic proclivities are of three distinct kinds in teratomas:

(1) Total malignancy of embryonic teratomas. This is the usual kind of teratomatous malignancy, as in most testicular teratomas. The gross appearance is frequently solid or finely polycystic, while histologically, a mixture of differentiating tissues of all ages is characteristic. All the immature tissues are actively growing and share in the malignant qualities of the tumor, and metastases in lymph nodes, lungs, or elsewhere are often of composite structure (Bosse; Herzog; Houghton; Steinert; Zerman). However, since the most immature elements are likely to be the first to disseminate, it is not surprising to find that in many cases metastatic growths are less heterogeneous than their parent primary growth, and that they sometimes consist only of highly undifferentiated cellular tissue with no structural evidence of its teratomatous nature (fig. 38). In a remarkable group of cases (Craver and Stewart; Michel; Prym; Roth; Symeonidis), small relatively well differentiated teratomas of the testis, unsuspected clinically, were found accompanying large, rapidly growing, undifferentiated, often chorionepithelioma-like metastases in the retroperitoneal lymph nodes or elsewhere; and in a few such cases, the small primary growths had disappeared, leaving only a fibrous scar in the testis. The only feasible explanation of these remarkable cases appears to be that in each of them the primary focus was originally an actively growing one containing undifferentiated elements, that some of these escaped as emboli by the lymph or blood stream, and that, while these later grew actively as metastatic tumors, the tissues of the primary growth in the meantime underwent maturation to a fully differentiated form or suffered total retrogression.

(2) Malignancy of one component only of a previously benign teratoma. This is most often squamous-cell carcinoma of the skin of a benign cystic teratoma (Masson and Ochsenhirt; figs. 40–42). Rarely, it is adenocarcinoma of a glandular component (fig. 39), or argentaffinoma of the intestine (Gabrilove; Stewart, Willis, and de Saram; figs. 43-45). It is possible also that melanoma or sarcomas of various types may occasionally arise in a particular tissue of a teratoma; but in few, if any, of the reported instances is this interpretation certain.

(3) Peritoneal dissemination of relatively benign teratomatous tissues. In occasional cases, following rupture of benign "dermoid cysts" of the ovaries, multiple cystic implants of the teratomatous skin have developed in the peritoneal cavity (Randall and Lawrence). Rarer still is the peritoneal dissemination of well differentiated neuroglial tissue (Helmke) or thyroid tissue (Emge; Morgen; Shapiro) from a relatively benign ovarian teratoma.

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