EXTRAGENITAL CHORIOCARCINOMA IN THE MALE *

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Choriocarcinoma of the male is usually primary in the testis. Only rarely does it originate in other situations. Two possibilities exist as to extragenital origin, namely, from elements of teratomas or from embryonal rests of the urogenital fold. Dickson [1] and others have contended that they come from totipotent cells capable of forming trophoblastic tissue which can produce various structures including fetal chorionic tissue. Blastomeres may become dissociated wherever germinal epithelium is found. Arey [2] explained that due to limitation of lateral expansion by the dorsal body wall, the enlargement of the growing mesonephric tubules necessitates longitudinal growth on each side of the dorsal mesentery. Thus the urogenital fold ultimately extends from the sixth cervical to the second sacral segment. The ridge becomes divided into a lateral mesonephric fold and a median genital fold, the anlage of the genital gland. Hence there is a distinct possibility that the primary focus of a choriocarcinoma may be located at the hilum of the lung as a remnant of the urogenital fold persisting in the region of the thoracic segments.

Symeonidis,[3] Prym,[4] and others have emphasized the importance of careful examination of the testes in cases of choriocarcinoma supposedly of extragenital origin. Symeonidis was skeptical of extragenital origin in any case, referred to possible accessory abdominal testes as a source, and maintained that even if derived from a teratoma the tumor originates in trophoblastic tissue.

In Prym's [4] case there were lesions distributed as are metastases of testicular tumors and with a microscopic picture like choriocarcinoma. Because he found a scar, peculiar in its structure and vascularization, in the right testis, he assumed that a primary choriocarcinoma in that testis had undergone spontaneous retrogression. It is said that uterine choriocarcinoma may regress, but in such instances the original diagnosis may have been incorrect. Even if this is true, Prym had no proof that the testicular scar was due to healing of a neoplasm. Nevertheless, these observations indicate the importance of most careful examination of the testes for either tumor or scar in all cases thought to have originated in a situation other than testis. This includes complete study of the genital tract, with serial block sections of the testes.

Adherence to these rigid criteria excludes many cases reported as

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extragenital choriocarcinomas. Among these is that of Bonn and Evans.[5] In this case the primary site was uncertain because a small scar was demonstrated in one testis. Although this scar may possibly have resulted from regression of a tumor, it seems more likely to have been due to an injury sustained 20 years before when the patient was kicked by a horse. Other probable cases * of primary extragenital choriocarcinoma, excluded because of uncertainty about the thoroughness of the examination of the testes, are those reported by Ritchie,[6] Lambert and Knox,[7] Hammarskjöld,[8] Arendt,[9] and Becker.[10] In all of these there were mediastinal teratomas and choriocarcinomatous metastases.

The number of cases, accepted as authentic, varies in different reports. If, however, strict criteria are adhered to and negative serial block sections of the testes considered essential, only 7 of the cases recorded in the literature furnished conclusive proof of an extragenital origin. To these is added the case reported in this paper, making a total of 8 unquestionably proved cases of primary extragenital choriocarcinoma in the male.*

1. Krassnianskaya.[11] Age 72 years. Primary either at hilum of left lung or in retroperitoneal tissue. A pure choriocarcinoma with multiple metastases. No gynecomastia. Testes showed no microscopic change. Aschheim-Zondek test not done.

2. Kantrowitz.[12] Age 22 years. Primary in the superior mediastinum. A complex teratoma in the superior mediastinum with choriocarcinomatous metastases in the lungs. No gynecomastia. Testes showed interstitial cell hyperplasia. Aschheim-Zondek test positive.

3. Fenster.[13] Age 27 years. Primary in retroperitoneal tissue. Pure choriocarcinoma with metastases to lungs and liver. Bilateral gynecomastia. Testes were normal. Aschheim-Zondek test not done.

4. Gerber.[14] Age 23 years. Primary in retroperitoneal tissue, overlying right ileopsoas muscle. Pure choriocarcinoma with metastases to lungs, liver, spleen, and kidneys. No gynecomastia. Testes showed no microscopic change. Aschheim-Zondek test not done.

5. Weinberg.[15] Age 70 years. Primary in urinary bladder. A pure choriocarcinoma with metastases to most of the viscera. No gynecomastia noted. Marked interstitial cell hyperplasia and tubular atrophy in the testes. Aschheim-Zondek test positive.

6. Erdmann, Brown, and Shaw.[16] Age 45 years. Primary in retroperitoneal tissue, posterior to left kidney. Pure choriocarcinoma with metastases to lungs. Enlargement of breasts, considered to be fibroadenomas, probably gynecomastia. Aschheim-Zondek test negative.

7. Hyman and Leiter.[17] Age 57 years. Pure choriocarcinoma, primary in urinary bladder. Bilateral orchiectomy performed. No autopsy. Testes showed no abnormality. Bilateral gynecomastia. Aschheim-Zondek test positive.

8. Laipply and Shipley. Age 21 years. Primary site was a complex teratoma of the superior mediastinum. Choriocarcinomatous metastases in many organs. Testes

* Since this paper was submitted for publication, Plenge[20] has reported a probable case, primary in the retroperitoneal region, and Stowell *et al.*[21] have described a well established case, primary in the region of the pineal gland.

showed marked atrophy, tubular fibrosis, and interstitial cell hyperplasia. Bilateral gynecomastia present. Aschheim-Zondek test positive.

In the above indisputable cases the primary sites were mediastinum (2), urinary bladder (2), retroperitoneal (3), and in 1 case either in the hilum of the lung or in the retroperitoneal tissue. In all instances the disease was fatal. The duration of life after onset of symptoms varied from 2 weeks to 15 months (average 5½ months).

Secondary changes in the breasts and testes are not uncommon in cases of choriocarcinoma. The enlargement of the breasts is usually bilateral and may be the first sign associated with such a tumor. The increase in size results from proliferation of ducts and stroma (Fig. 5). Definite gynecomastia was noted in 3 of the above 8 accepted cases, was doubtful in 1, and absent in 4. In the doubtful case [16] a diagnosis of adenofibroma was made on one breast which was removed prior to the patient's death. It seems possible that gynecomastia could have been mistaken for such a tumor.

The testicular changes include atrophy of the entire organ, fibrosis and hyalinization of the seminiferous tubules, and hyperplasia of the interstitial cells of Leydig (Figs. 6 and 7). Such features were noted in 7 of the 8 accepted cases. Similar changes have been observed in primary teratomas of the testes and in many other conditions such as senility, tuberculosis, cryptorchidism, and hermaphroditism. Houghton [18] described similar testicular alterations in a case of well differentiated malignant mediastinal teratoma.

Report of Case *

A white male, 13 years old, was first admitted to Mount Sinai Hospital, Cleveland, Ohio, in January, 1936. For 8 months he had had pain, intermittent in character, in the region of the left nipple. He was well nourished and normally developed. There was diffuse pulsation of the entire upper one-half of the thorax. Tactile fremitus and resonance were diminished over the upper third of the left lung. A tumor was located and removed from the superior mediastinum (Fig. 1). It extended laterally between the lobes of the left lung and was adherent posteriorly to the pericardium. Gross examination of the specimen revealed an irregularly nodular mass which weighed 385 gm. and measured 13 by 12 by 8 cm. Except in one area, 1 cm. in diameter, the mass was completely encapsulated. The bulk of the tumor was solid, with a few irregularly distributed cysts containing gelatinous and grumous material. Microscopic examination revealed it to be a complex teratoma. There were no trophoblastic elements and there was no evidence of malignant change. The following structures were identified: skin, hair, glands (sebaceous, serous, mucous, and salivary), mucous membrane (like that of upper respiratory tract and colon), brain, ganglia, nerves, smooth and skeletal muscle, fibrous connective tissue, fat, cancellous bone, and cartilage.

The patient recovered and was apparently well until July, 1942, 6½ years after

* We are indebted to Dr. S. O. Freedlander for permission to publish this case and to Dr. B. S. Kline for making available the gross specimen, microscopic sections, and photograph (Fig. 1) of the surgical specimen.

the operation. At this time a routine roentgenogram of the chest, taken on examination for entrance into the Navy, revealed a mediastinal tumor with multiple metastases to the lungs. In October, 1942, he was given 30 deep x-ray treatments to the lungs. The metastases increased in size during the treatments. In January, 1943, the patient was admitted to Lakeside Hospital. At this time physical examination revealed an emaciated white male, 21 years old. His temperature was 38°C.; pulse, 105; respirations, 24; blood pressure, 115/65 mm. of Hg. The breasts were increased in size, firm, and nodular. A spherical, firm nodule, 2 cm. in diameter, was present in the subcutaneous tissue of the right upper quadrant of the abdomen. The testes, which were present in the scrotum, were abnormally small. Secondary sex characteristics were well developed.

Laboratory Examination. Urine: trace of albumin, an occasional white blood cell and granular cast. Blood: 16,500 white blood cells, 2.07 million red blood cells, 36 per cent hemoglobin (Sahli), negative Kline exclusion test. Hormone assays; results given in Table I.

Soon after hospitalization the patient's condition was recognized as hopeless. Testosterone propionate (25 mg. per day) was given for 1 week in a futile attempt to depress the growth of the tumor. Because of the insistence of relatives he was given several blood transfusions. On his 11th hospital day the patient developed signs of bronchopneumonia. His temperature, which had varied between 36.7° and 38°C., rose to 39.5°C. Sulfadiazine was given without effect. He died on his 17th hospital day, 7 years after the teratoma was removed from the mediastinum.

Autopsy (no. 8014, performed by Dr. J. C. Sherrick) revealed a circumscribed tumor in the superior mediastinum and metastatic tumors in subcutaneous tissues of anterior abdominal and posterior thoracic walls, left deltoid muscle, lungs, right parietal pleura, diaphragm, liver, kidneys, jejunum, ileum, thoracic and abdominal lymph nodes, and greater omentum. Other important diagnoses were gynecomastia, fibrosis and interstitial cell hyperplasia of testes, and bronchopneumonia.

The mediastinal tumor (Fig. 2) was slightly to the left of the midline. It was spherical in shape, completely encapsulated, and measured 6 cm. in diameter. It was in large part solid but contained scattered cysts filled with translucent, yellow, gelatinous material. Near the periphery there were a few small, soft, hemorrhagic foci. Microscopically its complex nature was indicated by the presence of skin, fat, fibrous connective tissue, smooth muscle, hyaline cartilage, cancellous bone, salivary gland, ganglia, and mucosa, submucosa, and muscularis of bronchus and stomach. In addition, there were cell masses having the structure of a choriocarcinoma. Syncytia and cells of Langhans' type, which normally make up the trophoblastic covering of the chorionic villi, were present (Figs. 3 and 4). Such groups of cells could be located macroscopically by associated hemorrhage and necrosis. The metastatic tumor was similar at all sites. The nodules varied from 1 to 3 cm. in diameter, were sharply circumscribed, and in most instances dark red. Microscopically they contained syncytial and Langhans' cells. The red discoloration was due to recent hemorrhage. Small foci of necrosis were common.

Microscopic examination of the breasts revealed proliferation of ducts and stroma. The ducts were lined with stratified columnar epithelium. The periductal connective tissue was loosely arranged and sparsely infiltrated with lymphocytes (Fig. 5).

In order to exclude a primary testicular tumor, serial sections of the testes were made. The sections were cut at 6 μ and every tenth section was mounted. No tumor or scar was identified. This examination, therefore, excluded any lesion in the testes greater than 0.06 mm. in diameter. Both organs were small, weighing 7 and 6 gm. There was no spermatogenesis. The seminiferous tubules were small and hyalinized. The interstitial cells were markedly increased in numbers (Figs. 6 and 7).

Comment

During life the presence of gynecomastia and small testes suggested to the clinician the possibility of a feminizing tumor. For this reason hormone assays of the urine were done. The results were striking and

Table I

Hormone Assays on 24-Hour Urine Specimens

	Gonadotropin (chorionic type) in mouse units per 24 hrs.	Estrogen in international units per 24 hrs.	17 ketosteroid mg. per 24 hrs.	Pregnanediol mg. per 24 hrs.
Present case	300	750 or more	27	2 or more
Normal male	0	75 or less	25	0.1
Normal nonpregnant female	0	50 to 300 (ovulation)	12	45 (in luteal phase)
Teratoma of testis	Elevated	Not known	Not changed	Not known
Late pregnancy	6000	10,000	Not changed	30 to 40
Choriocarcinoma of uterus	200,000 to 1,000,000	Elevated	Not changed	Not known

probably diagnostic of choriocarcinoma. A comparison of the hormonal findings in this case with those in normal persons and related conditions is given in Table I.

In this case there is no way of determining whether the mediastinal tumor present at autopsy represents the growth of a small portion of the original teratoma left at the operation 7 years prior to death or the growth of another tumor of similar and subsequent origin.

The presence of chorionic gonadotropin in the urine along with increased excretion of estrogens and of pregnanediol is similar to the hormonal alteration which occurs in pregnancy. It may be presumed that these hormones or their precursors were elaborated by the chorionic tissue of the tumor.

Atrophy of the testicular tubules and gynecomastia were undoubtedly due to the large amount of circulating estrogen. A contributory stimulus to the enlargement of the breast may have been added by progesterone.

No exact quantitative method was used to determine the number of Leydig cells in the testes. It was estimated, however, that these cells were increased in number. The examination of a large number of sections of the testes to some extent decreases the error inherent in such an estimation. An actual increase in the number of testicular interstitial cells could be due either to direct stimulation by chorionic gonadotropin or to increased luteinizing hormone secreted by the anterior lobe of the pituitary gland in response to the high level of circulating estrogen. The work of Collins [19] indicates that Leydig cell hyperplasia may occur in cases without carcinoma and in the absence of known excess of luteinizing hormone or estrogen. From his work it is also apparent that hyperplasia of the interstitial testicular cells is associated with atrophy and fibrosis of the tubules but that tubular fibrosis and atrophy may occur without a significant change in the number of Leydig cells.

SUMMARY

Review of the literature discloses only seven well established cases of extragenital choriocarcinoma in males. In the additional case reported in this paper a complex teratoma originating in the thorax of a boy, 13 years old, was removed surgically. Seven years later he died of either a recurrence or an independent teratoma with choriocarcinoma in the tumor and widespread choriocarcinomatous metastases. Gynecomastia, testicular atrophy, and hyperplasia of the interstitial cells of Leydig were associated. Hormonal alterations resembled those of pregnancy.

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[*Illustrations follow*]

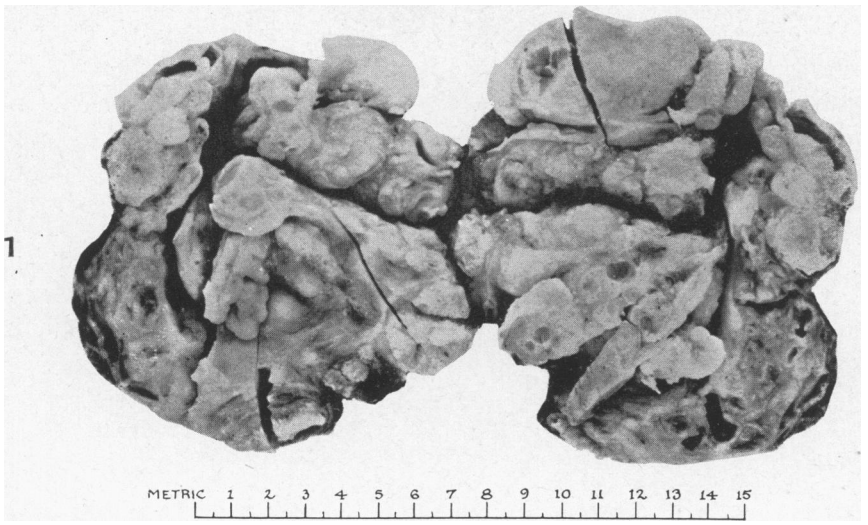
DESCRIPTION OF PLATES

PLATE 154

FIG. 1. Tumor removed from upper mediastinum, 7 years before patient's death. This was a complex benign teratoma. The metric scale which is reproduced is for comparison with Figure 1 only.

FIG. 2. Sections of lungs with mediastinal teratoma attached to medial aspect of upper lobe of left lung. Multiple hemorrhagic metastatic choriocarcinomatous nodules in both lungs.

1



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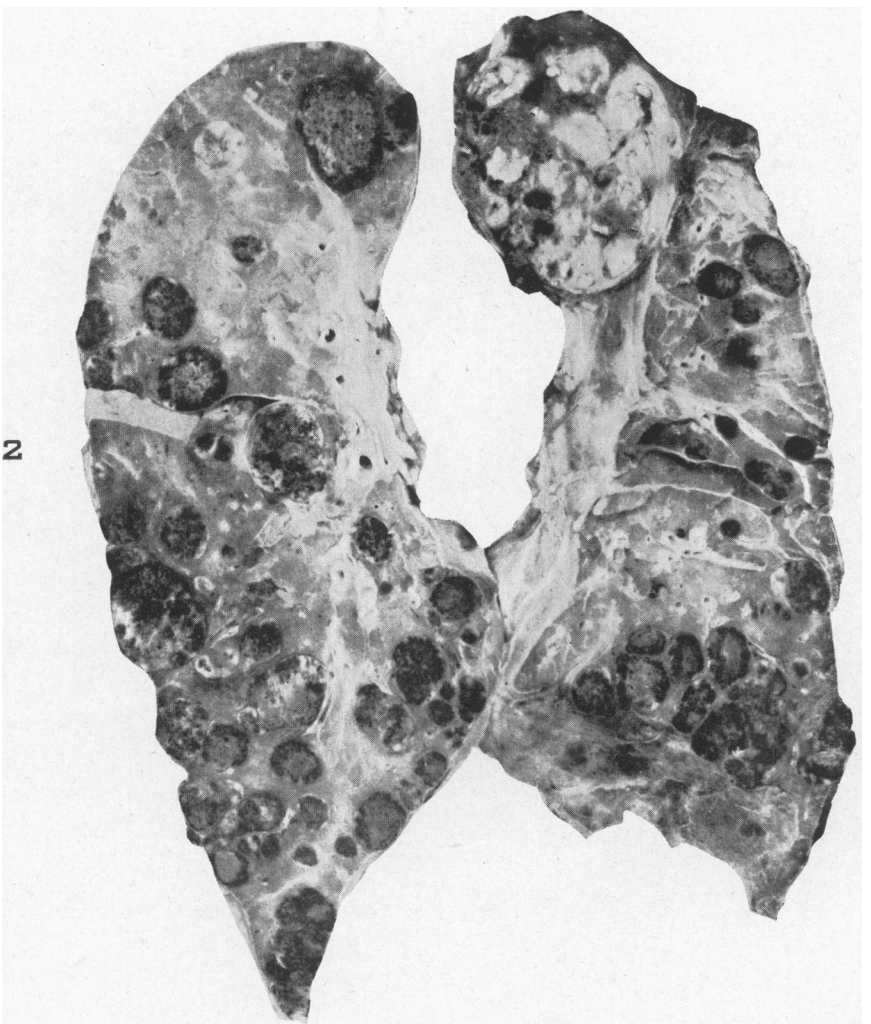
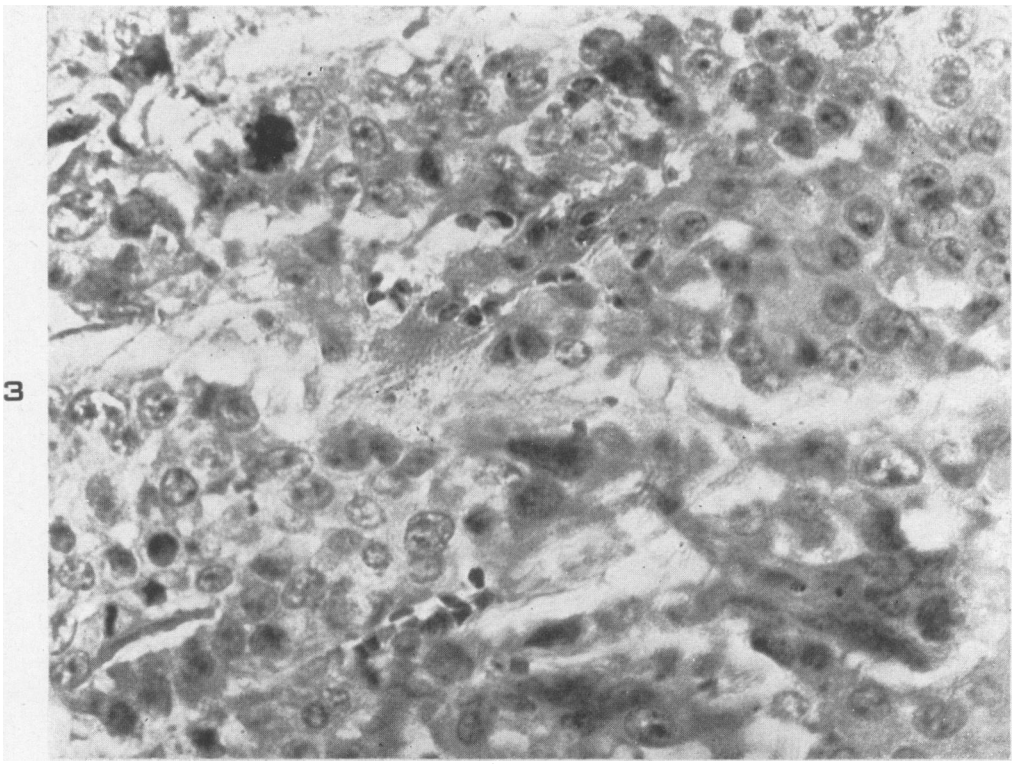


PLATE 155

FIG. 3. Pulmonary metastasis with syncytia, many cells of Langhans' type, and mitotic figures. Hematoxylin and eosin stain. × 538.

FIG. 4. Pulmonary metastasis. Discrete syncytia and groups of Langhans' cells are evident. Hematoxylin and eosin stain. × 582.



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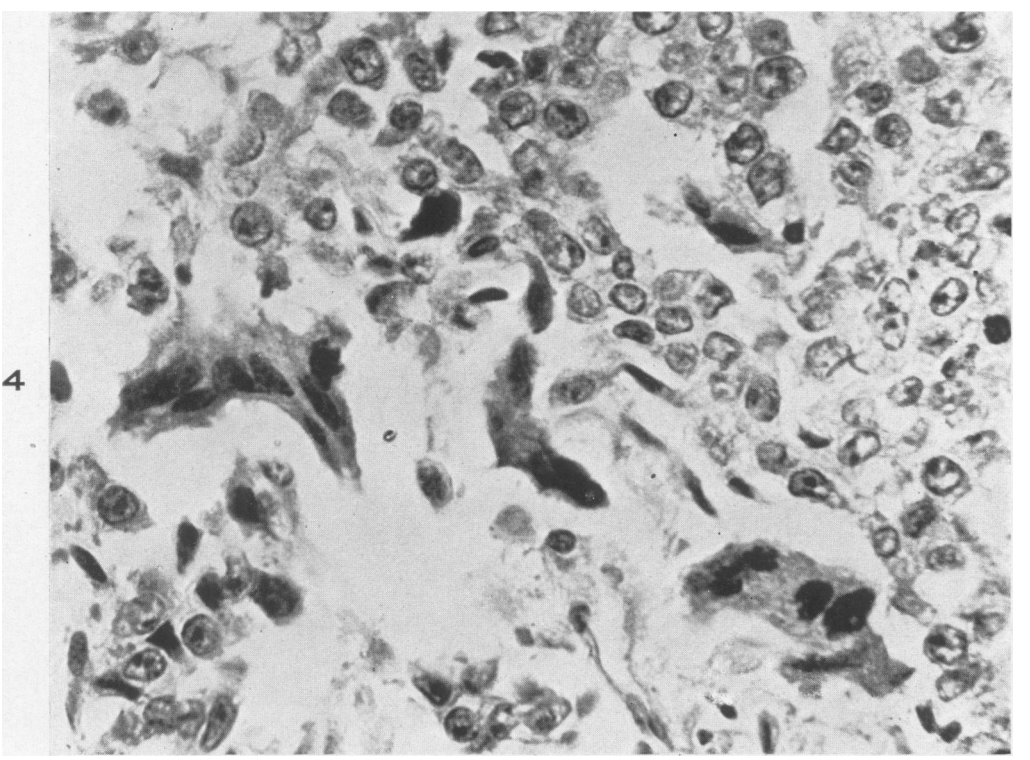


4

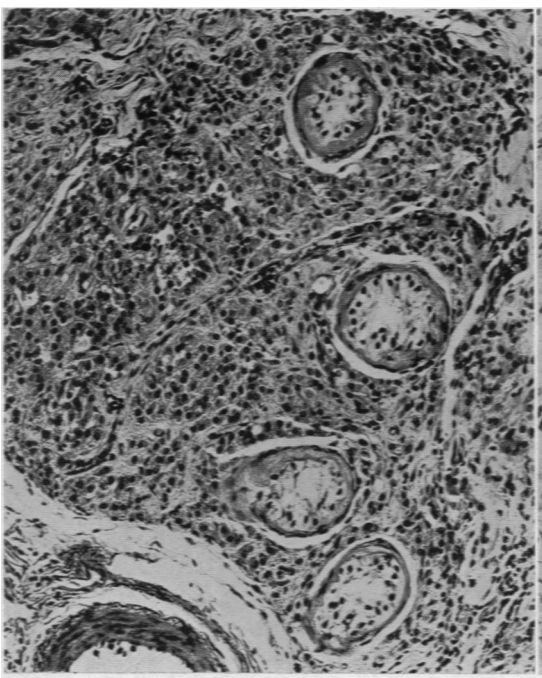
PLATE 156

FIG. 5. Ducts of breast are increased in number and lined with stratified columnar epithelium. Loose cellular periductal connective tissue is infiltrated with lymphocytes. Hematoxylin and eosin stain. × 94.

FIG. 6. Atrophy and hyalinization of seminiferous tubules and hyperplasia of interstitial cells of testis are evident. Hematoxylin and eosin stain. × 140.

FIG. 7. Marked hyperplasia and pleomorphism of interstitial cells of testis. Hematoxylin and eosin stain. × 140.

5



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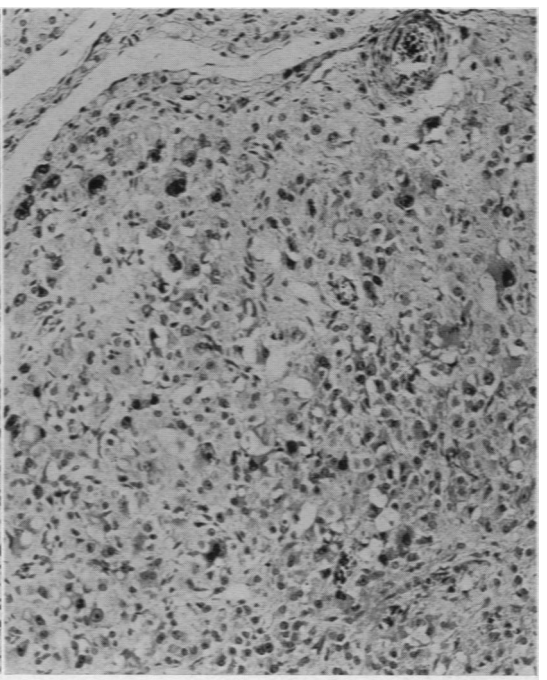

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Laipply and Shipley

Extragenital Choriocarcinoma in the Male