ARRHENOBLASTOMA

A MALIGNANT OVARIAN TUMOR ASSOCIATED WITH ENDOCRINOLOGICAL EFFECTS

EDGAR H. NORRIS, M.D.

Department of Pathology, University of Minnesota

Only since the year 1930, chiefly through the writings of Robert Meyer and Emil Novak, has our attention been called to the observation that certain of the malignant ovarian neoplasms appear to produce hormones which may be biologically active and clinically important. Since that time a few more examples have been reported; but, probably because one observer sees so few of these cases, our ideas unfortunately have not become very well defined.

At the outset it needs to be emphasized that any significant investigation of the ovarian tumors belonging to this group demands that the problem be approached from many widely differing points of view. Questions of genetics, ontogeny, embryology, sex determination, sex differentiation, intersexuality, oncology, histologic pathology, endocrinology, clinical medicine, and operative surgery are all, as a necessary consequence, inseparably joined in the consideration of each individual case. Many of these subjects are young in years and limited in their scientific scope; none has attained epistemological accuracy. It is not strange, therefore, that many hazy ideas should be encountered and caution is necessary because, owing to the inexactness of some of our fundamental concepts, many seemingly tenable premises may be found to be quite incorrect, and many attractive conclusions may fail of substantiation in the light of more complete knowledge. With this note of admonition well in mind, sound progress can be expected.

At one time all tumors were thought of as autonomous growths; they were considered, by definition, to be functionless, semiparasitic lesions whose effects upon the host were always indirect. Within the quarter century just past this notion has been wholesomely modified. Today we recognize a definite group of neoplasms which are characterized by functional activity and by ability to affect profoundly the physiology of the body through the formation of hormones. These are particularly those benign adenomatous tumors which
take origin from the endocrine glands. Among these are the acidophil adenomas of the hypophysis, the primary hyperplasias of the parathyroid, the cortical and chromaffin adenomas and the primary hyperplasias of the adrenal, and the islet tumors of the pancreas. In the case of these, every possible proof has been brought to demonstrate their secretory activity and to incriminate them in the production of profound physiological disturbances.

As regards the tumor with which the present paper is concerned, however, the conception expressed by Robert Meyer was particularly novel because it joined endocrine function with tumors of a high degree of malignancy. In fact, further study has indicated that the more undifferentiated these tumors are, the more constant may be their biologic effects. Occasionally the human ovary is the site of origin of such new growths. Among the large variety of ovarian tumors, however, there are only two types which seem regularly to be associated with endocrinological effects; these are the arrhenoblastoma and the granulosa-cell carcinoma.

In recent years the functional activity of certain malignant tumors arising from other ductless glands has been demonstrated; and it should be pointed out that the effects of these are quite different from the cachexia so frequently seen associated with malignancy. Thus carcinoma of the adrenal cortex, carcinoma of the islands of Langerhans, and the chorionepitheliomas of both the testis and uterus have been shown to produce physiologically active hormones. These observations constitute an important corollary to the thesis of Meyer regarding the secretory activity of the arrhenoblastoma and the granulosa-cell carcinoma of the ovary. The present paper records a case of arrhenoblastoma and will attempt an analysis of the general subject. In another communication a similar study of the granulosa-cell carcinomas will be made.

The case about to be described is of particular importance because of the long period through which the patient was observed, because of the careful clinical and laboratory studies which were made, and finally because a complete post-mortem examination has provided the opportunity to investigate all of the tissues.

**Case Report**

*Clinical History, Physical Findings, Laboratory Studies, and Course:* The patient was a married white woman, aged thirty-one years at the onset of her illness and thirty-four years at the time of her death. Her health had always been excellent; an attack of cystitis in January 1933 being the only illness mentioned. She had never been pregnant.

Her father had died of multiple sclerosis; her mother, still living, had had two attacks of manic depressive insanity. One brother and four sisters were living and well. Two sisters had had exophthalmic goiter; one sister was dead.

The present illness started in March 1933, when the patient began to feel tired and nervous. In May 1933 she consulted a physician because of generalized edema of a few days' duration, beginning in the face and spreading over the body and legs. The blood pressure was reported as 150/80; the urine contained a slight amount of albumin and a few erythrocytes. In June 1933 the blood pressure was reported as 180/90, a severe glycosuria had developed, and a fine papular rash had appeared on the body. On insulin and a diet the patient "had become stronger, had started to gain weight, had lost most of her edema except that of the face, and had seemed to be improving generally. August 2, 1933, she
ARRHENOBLASTOMA, MALIGNANT OVARIAN TUMOR

had become irritable and forgetful, had repeated phrases over and over, and had talked in a peculiar, high-pitched voice." 1 At this time she was referred to the Mayo Clinic where the following physical findings were recorded, a diagnosis made, and surgical treatment exhibited.

"The patient was 5 feet, 2 inches (157.5 cm.) in height. She weighed 105 pounds (47.6 kg.), but her usual weight was 130 pounds (59 kg.). Her face was swollen and moon-like. There were multitudes of comedones and pustules over the back and chest. On the upper lip there was a growth of fine hair. The external genitalia were normal and the clitoris was not enlarged. The appearance of the face suggested pituitary basophilism, but there was no obesity, and the hirsutism was not sufficient to attract attention. The blood pressure was 150 systolic and 100 diastolic. Examination of the ocular fundi and roentgenograms of the skull gave negative results. The urine was normal on analysis. The value for hemoglobin of the blood was 12.3 gm. per 100 c.c. (79 per cent). Erythrocytes numbered 3,610,000 per cubic millimeter of blood. The value for blood sugar was 154 mg. per 100 c.c. The value for plasma chlorides was 524 mg. per 100 c.c. On a diet containing 108 gm. carbohydrate, the woman's urine remained sugar-free without her taking insulin. She was over-active mentally, rambled a great deal in her speech, but had fair memory, orientation and insight. A definite diagnosis was not made. She was dismissed two weeks after admission, with instructions to continue with the diet prescribed, and to return in a few months for further observation.

"The patient returned in January, 1934. In the interim her condition had greatly improved in most respects, her face appeared less swollen, the acne had disappeared, and her mental status was practically normal. She complained, however, that her legs were weak and that she could not trust herself when walking. The blood pressure was 116 mm. of mercury systolic, and 76 diastolic. The urine contained no sugar. She stated that after she had left the Clinic, the hair of her scalp had fallen out, and then gradually returned, but it was gray. For two or three months she had not menstruated. As she seemed to be improving, she was advised to follow the régime prescribed on her previous examination.

"The patient remained in fair health until March, 1934. Her general physical and mental status were essentially as they had been at her first visit. Her face was again swollen, the skin was sallow and dry, and the hair of the scalp was streaked with gray. In addition to the acne, there was brownish pigmentation of the knuckles and feet. A few ecchymotic areas were present on the legs, but striae were not present. There was no unusual hirsutism except for the presence of a slight down on the upper lip. There was profound muscular weakness, especially of the legs, and as a result the gait was of steppage type. The external genitalia and clitoris were still normal.

"The blood pressure was 158 mm. of mercury systolic, and 96 diastolic. The urine contained 4.56 per cent sugar. The value for blood sugar was 234 mg. for each 100 c.c. of blood. More extensive studies, made on the blood, showed the values for chlorides, sodium, potassium, total base, calcium and phosphorus to be reduced. The carbon dioxide-combining power was definitely and persistently elevated . . . blood volume was low, and there was an unexplained low oxygen content and saturation of both arterial and venous blood. The value for hemoglobin was 11.1 gm. per 100 c.c. and erythrocytes numbered 3,500,000 per cubic millimeter of blood.

"On the patient's usual diet, which contained 111 gm. of carbohydrate, 65 gm. of protein, and 152 gm. of fat, 40 to 45 units of insulin were required to keep the urine sugar-free.

"A diagnosis of suprarenocortical syndrome was made, and bilateral hyperplasia, rather than tumor was suspected.

"May 22, 1934, bilateral exploration of the suprarenal glands, through posterolumbal extraperitoneal incisions, revealed marked enlargement of both suprarenal glands; each gland measured approximately 7 cm. in length, 3.5 cm. in width, and about 8 mm. in thickness. 2

1 This and the following quotation have been taken from the paper of Walters, Wilder and Kepler (1934), who reported this case as an instance of cortical hyperplasia of the adrenal gland (Case 2 of their 1934 communication). It is most fortunate that we have the record of their thoroughgoing clinical and metabolic studies.

2 But these measurements are almost identical with those given in Cunningham's Anatomy as normal for adult suprarenales!
Tumors were not seen or felt. A portion, 2 cm. in diameter, was removed from the left suprarenal gland, and a somewhat larger portion, 3 × 2 cm., was removed from the right gland. Microscopic examination of the excised tissue disclosed hyperplasia of the cortex.

"Postoperative convalescence was normal. The patient regained strength. Her blood pressure returned to normal, 124 mm. of mercury systolic and 62 diastolic. Much of the swelling of the face, and the acne, disappeared. The urine became sugar-free without insulin, and remained so even after the diet had been increased to 250 gm. carbohydrate, and later when no dietary restrictions were imposed. The values for carbon dioxide-combining power and plasma chlorides became normal and the potassium content increased markedly."

This postoperative clinical improvement continued for a few months. The swelling then returned in the face, neck, shoulders, and arms; this was a brawny swelling which did not pit. On Nov. 13, 1934, the patient came under the care of Dr. E. L. Lundquist of Minneapolis. She became psychotic and finally violently insane and had to be confined in a psychopathic hospital.

On Feb. 4, 1935, the patient was removed from the psychopathic hospital by her family. At this time there was an extensive growth of long hair on the face. Some of this hair was an inch in length; it was present on the upper lip and on the chin, and extended up onto the lateral parts of the face. There was a dark pigmentation of the skin. Because of her mental condition the patient had to be kept in restraint and to be tube fed.

On March 13, 1935, x-ray therapy was given over the thymic area, although no abnormal shadow could be demonstrated in this region roentgenographically. Five days after this treatment the patient became rational and cooperative. During the following month, six more x-ray treatments were given. Large abscesses developed in the gluteal region and were drained. On April 17, 1935, the condition had improved so much that the patient was discharged from the hospital. She remained fairly well until Sept. 17, 1935, when she began to feel nervous, her skin became dark, and swelling reappeared. Further x-ray irradiation over the thymic area was given. On Oct. 8, 1935, an abscess, which discharged pus and necrotic fat, was opened in the right knee region. General improvement continued and on Feb. 25, 1936, the patient was able to come to the doctor's office. For a number of months she was almost entirely normal and visited with friends and enjoyed living. On May 25, 1936, sugar, 3 +, was found in the urine. The further course, as recorded, was as follows.

June 2, 1936: 1 + sugar and a trace of albumin in the urine.
Aug. 5, 1936: No sugar and no albumin in urine; no insulin had been given.
Aug. 20, 1936: More swelling of face, darkening of skin and nervousness. X-ray treatments given over thymic area.
Sept. 4, 1936: No sugar and a trace of albumin in urine.
Sept. 16, 1936: General symptoms improved.
Dec. 15, 1936: More general symptoms and more x-ray irradiation over thymic region, without evident benefit.
Jan. 30, 1937: Entered hospital because of severe pain in the right lower chest region and nausea and vomiting. Hemoglobin 48 per cent; leukocytes 8,300.
Feb. 24, 1937: An exploratory laparotomy was done. The liver was found to be very large and to contain many tumor nodules. The abdomen contained a large amount of ascitic fluid in which some blood cells were present. Tissue was removed from the liver.
April 3, 1937: The patient died after an illness which had extended through four years.

Autopsy (A-37-739): The body (embalmed) is well developed and fairly well nourished, 158 cm. in length and weighing about 110 lb. Hypostasis is evident over the posterior parts. There is a marked edema of both lower extremities and of the left labium majus; the face is swollen and moon-like. There is an old puckered scar on the lateral surface of the right knee; a similar scar on the surface of the right buttock; bilateral healed surgical scars in the posterolumbar regions; a partially healed surgical wound in the right upper abdomen. There is a contracture of the right knee. The skin over the anterior part of the neck and mid-chest region is deeply bronzed. The skin of the face is much darker than
that of the lower portion of the trunk and there is a brownish pigmentation on the backs of the hands and feet. A considerable growth of hair is present on the upper lip and on the chin. The hair of the scalp is about 1½ to 2 inches in length, is gray, and somewhat coarse.

The peritoneal cavity contains no excess fluid. The omentum is adherent to the recent operative scar. The appendix is 2 cm. in length, bulbous, and hangs over the pelvic brim. The diaphragm reaches the 3d rib on the right, the 4th rib on the left.

The pleural and pericardial cavities contain no excess fluid and no adhesions.

In the superior mediastinum and extending down into the anterior mediastinum, is an irregular nodular mass measuring 9 cm. in the longitudinal axis, 7 cm. in transverse width, and 5 cm. in maximal anteroposterior extent, and weighing 105 gm. The nodules of the mass partially surround the great vessels. The mass is firm but on section shows cyst-like areas in which some necrotic tissue is present; other portions show extensive hemorrhagic infiltration. This mass occupies the thymic region and no grossly recognizable thymic tissue can be identified.

FIG. 1. TYPICAL GROSS SECTION THROUGH THE LIVER

The grayish white areas are tumor metastases. At the right side of the figure the hepatic parenchyma is almost completely replaced by tumor tissue.

The heart weighs 275 gm. There is no gross evidence of disease of the valvular or mural endocardium, nor of the epicardium or myocardium. The root of the aorta shows no atherosclerosis. The coronary orifices are normally patent; the coronary trunks show no evidence of thickening of their walls and no narrowing of their lumens.

The right lung weighs 300 gm. the left 325 gm. Both are narrowly adherent along their anterior margins to the mediastinal mass. With the exception of a few small areas in which tiny tumor-like nodules are felt, crepitation is normal throughout. On section no increased amount of fluid and no pus can be expressed from either lung. Multiple tiny nodules, grayish in color and of a waxy appearance, are scattered near the surface of the right lung. Similar nodules, but fewer in number, are found in the left lung; the largest of these measures 6 mm. in diameter. Almost all of these nodules are close to the visceral pleural surfaces.

The spleen weighs 50 gm.; its capsule is smooth. The pulp is firm and the malpighian corpuscles are not apparent.

The liver edge is located 15 cm. below the xiphoid in the midline, and 12 cm. below the costal margin in the right midclavicular line. The falciform ligament is displaced so far to the left that it lies parallel with the left costal margin. The liver weighs 5,500 gm. Through the capsular surface of the liver multitudinous tumor nodules of variable size are
EDGAR H. NORRIS

seen. On section a large percentage of the nodules are found to be discrete, rounded in outline, and grayish white in color; the largest of these measures 3.5 cm. in diameter and they are so numerous as to be almost confluent (Fig. 1). The gallbladder contains 30 c.c. of thick bile and no concretions. The bile ducts are normal.

The esophagus, stomach, small bowel, and large bowel show no gross lesions. The pancreas is grossly normal.

The right adrenal (Fig. 2a) is much flattened, apparently by pressure of the liver; it has an abnormally irregular outline, appearing as though a partial resection of one edge and pole had been performed. The weight is 7.5 gm. and the dimensions are $7.5 \times 3 \times 0.7$ cm. The cut surface shows no gross lesion. The left adrenal (Fig. 2b) appears quite normal in its general form and no evidence of operative removal of tissue can be recognized; this adrenal weighs 11 gm. and measures $7 \times 3.2 \times 1.5$ cm. The cut surface shows two grayish white, waxy, round tumor nodules in the substance of the gland, measuring 5 mm. and 4 mm. in diameter respectively (Fig. 10).

**FIG. 2. RIGHT (a) AND LEFT (b) ADRENAL GLANDS**

Each gland was sectioned to obtain a block for microscopic study prior to being photographed. Note the abnormally irregular outline of the right adrenal (a).

The right kidney weighs 90 gm., the left 80 gm. Their capsules strip with ease, leaving smooth surfaces. The cut surfaces show normal markings. On the capsular surfaces of both kidneys are several tiny grayish tumor nodules. The renal pelves, ureters, and urinary bladder show no gross lesions.

The uterus is small and infantile in type; it measures $5.5 \times 3 \times 2$ cm. in its maximal diameters. On section a small clot of blood is found in the cavity of the cervix. The uterine tubes are grossly normal.

The right ovary (Fig. 3a) is irregular in outline because of the presence of a small ovoid tumor nodule, $15 \times 12 \times 11$ mm., which protrudes from the surface. The purplish-gray color of the nodule contrasts sharply with the pale adjacent ovarian tissue. The peritoneal surface of the nodule is smooth and on section it is found to be sharply outlined (Fig. 3b). The right ovary with the tumor nodule weighs 4.8 gm. Exclusive of the tumor nodule it measures $3.5 \times 2.2 \times 1.5$ cm. The left ovary (Fig. 3c) weighs 3.5 gm. and measures $3.5 \times 2 \times 1.2$ cm. Both ovaries are hard to palpation, white in color, and have the pitted, nodular surfaces characteristic of the gonads from an elderly woman. Except for
ARRHENOSPLASTOMA, MALIGNANT OVARIAN TUMOR

The presence of the primary tumor in the right ovary the cut surface has a uniform structural appearance. The cut surface of the left ovary shows the presence of a small yellow body, which measures 3 X 2 mm. in diameter, and several tiny follicular cysts.

The thoracic and abdominal aorta shows no gross lesion. There is a large thrombus tightly filling the left iliac vein and extending for 5 cm. into the inferior vena cava. There are no enlarged lymph nodes.

The mammary glands are small and flat but show no other gross abnormality on inspection from without. Section shows the presence of a very small amount of breast tissue.

The scalp and calvarium are normal. On the inner surface of the dura, over the vertex of the brain, are multiple petechial hemorrhages.

The brain weighs 1,400 gm. A few petechial hemorrhages are present in the pia arachnoid, especially over the upper surface of the cerebral hemispheres. Serial sections through the brain fail to demonstrate any gross lesion. The cerebral cortex, however, appears thinner than normal; in most places it measures from 2 to 4 mm., while in a few places it reaches a maximum thickness of 8 mm.

The thyroid gland weighs 21 gm.; its capsular surface is smooth and on the cut surface the tiny, colloid-filled follicles are just visible; no adenomas are seen.

Three parathyroid glands were found and these weigh 25, 35, and 40 mg. respectively.

The hypophysis weighs 450 mg. and is grossly normal.

The pineal body weighs 180 mg. and is grossly normal.

**Microscopic Findings.** The free surface of the right ovary, away from the tumor, is covered by a single layer of columnar germinal epithelial cells. Immediately below the germinal epithelium lies the fibrocellular stroma. This appears quite normal and shows some variation of density and cellularity from field to field. Very few follicles are recognizable; such as can be identified appear as tiny circles made up, on the average, of from 8 to 12 cells. Certain follicles are scarcely recognizable and are evidently undergoing atrophy. Only one follicle of moderate size, made up of about 50 cells, is seen. Oogonia are rarely present (Fig. 6). The blood vessels appear normal. A number of small corpora albicantia are present.

Apparently the small rounded primary tumor arose within the ovary, for its free surface

---

**FIG. 3. RIGHT AND LEFT OVARIAS**

In a is shown the gross appearance of the right ovary; the dark primary tumor nodule is seen protruding from the right-hand side of the figure. In b is shown the sectional appearance of the right ovary; note the sharply outlined margins of the dark tumor nodule and the relatively homogeneous character of the ovarian tissue. The gross appearance of the left ovary is shown in c. Note the scarred and pitted surface.
Fig. 4 (above) shows the cords and masses of epithelium and the general structural pattern. In the lower part of this figure the cells are less intimately related and the structure suggests a sarcoma. Fig. 5 (below) shows the character of the cells and their hyperchromatic nuclei.

is covered by a continuous layer of flattened germinal epithelial cells just beneath which is a narrow zone of fibrous ovarian stroma. This zone completely surrounds the tumor nodule and can be identified around the deep surfaces as well as over the free surfaces. It is made up of tissue which is more fibrous (less cellular) than most of the ovarian stroma elsewhere. Thus a definite, continuous, rather dense pseudo-capsule surrounds the tumor. In contrast to the tall columnar germinal epithelium over the ovary in general, that which covers the tumor nodule is made up of cuboidal or flattened cells.
ARRHENOBLASTOMA, MALIGNANT OVARIAN TUMOR

Fig. 6 (left), a section from the right ovary, shows the presence of a small follicle containing an oögonium. This is the most nearly normal follicle in the right ovary. Fig. 7 (right), an area from the left ovary, shows numerous follicles. One is in good condition; two others are degenerate.

The ovarian tumor is made up of cords, and more particularly of block-like masses, of epithelial cells; these cords and masses are very irregular in size and shape (Fig. 4). The epithelial portions are separated by narrow bands of fibrous connective tissue in which many large capillary-like vessels are present; nothing suggestive of the interstitial cells of the testis is found. The epithelium of the tumor shows no tendency to form follicles, tubules, or glandular structures. In some parts the epithelial cells are packed closely together but elsewhere they are less intimately associated and the structure is less dense. In these less dense parts the cytological arrangement simulates a loose syncytium and the structure does not make a good epithelium (Fig. 4).

The epithelial cells of the tumor have little cytoplasm; the nuclei are relatively large, irregular in outline, and of variable chromatic density (Fig. 5). In general, however, they tend to be hyperchromatic.

The findings in the non-neogenic left ovary are quite different from those in the opposite organ. The covering germinal epithelium is tall and columnar in type and the stroma has a slightly more fibrous structure than is usual for the ovary of a middle-aged female. A considerable number of follicles are present (Fig. 7); some of these appear to be in good condition but many are atresic. One recently formed corpus luteum is present (Fig. 8), and several other corpora lutea in stages of involution are found. There are numerous corpora albicantia (Fig. 9). Two small cyst-like follicles are present whose walls are lined with a rather well formed stratum granulosum. Deep within the substance of the left ovary are three tiny round, metastatic, tumor-like nodules similar in structure to the primary tumor in the right ovary and to the metastatic lesions in the other organs (Fig. 9).

Examination of numerous blocks from the cerebrum, basal nuclei, pons, cerebellum, and spinal cord show no microscopic evidence of disease.
Fig. 8 (left) shows an area from a recent corpus luteum, the edge of which is near the bottom of the figure. In the lower half of the area shown in Fig. 9 (right) part of a metastatic lesion is seen; at the upper edge is a portion of a corpus albicans.

On the inner surface of the dura mater are separate, non-confluent areas which show hemorrhagic extravasation. These hemorrhages are located in the looser fibrous tissue which makes up the innermost layer of the dura and the extravasated blood separates the fibers of this stratum. The hemorrhages are recent, for the blood corpuscles are well preserved and no pigment is seen. Otherwise the dura and its vessels appear normal.

The cardiac muscle shows no pathologic lesion.

Except for small metastatic tumor nodules and the local pressure effects produced by these, the pulmonary parenchyma is normal.

There are a few small patches in the peripheral part of the kidney cortex in which the glomeruli are completely sclerosed and the adjacent tubules atrophied. Some of the preglomerular arterioles show a moderate degree of subintimal and muscular hyalinization. Hyalin casts are present in some collecting tubules. Otherwise the kidney parenchyma is normal. Several tiny subcapsular tumor nodules are present.

The liver parenchyma is greatly disrupted by the presence of multitudinous metastatic tumor nodules of variable size. The larger masses show central necrosis and locally they have completely destroyed and replaced the liver cords. The smaller masses of tumor tissue show no necrosis, but in the remaining liver parenchyma associated with these are evidences of many stages of fatty metamorphosis and degenerative changes leading toward necrosis of the hepatic tissue.

Metastatic implants of the tumor are present in the liver, lung, kidney, left adrenal, left ovary, and in the mediastinum. With the exception of the mediastinal mass the histological structure of the metastases in these other organs is alike. As compared with the primary tumor the metastatic lesions tend to be somewhat denser and the cells, being more compactly arranged, show less tendency to be distributed loosely. Irregular solid cords and masses of epithelium constitute the general pattern and these are separated from one another by delicate strands of connective tissue. Certain of the larger metastatic masses
In Fig. 10 (above) note the presence of two metastatic tumor nodules. No tissue of the adrenal medulla is shown in this section. Two types of cortical cells can be seen; the dark gray denser areas represent the acidophil cells and the very irregular distribution of these among the more numerous pale cells is clearly indicated. The area shown in Fig. 11 (below) corresponds to that at the left edge of the left-hand metastatic nodule shown in Fig. 10. Note the erosion of the wall of the vein and the presence in the vein of two malignant emboli.

have centers in which the cells have loosened up; this is interpreted as a tendency toward central necrosis and it is not a common or usual structural feature. Except for the mediastinum, it is only in certain of the larger metastatic nodules found in the liver that any considerable degree of necrosis is present. Such minor differences as are noted in the microscopic patterns found in the several organs seem best accounted for on the basis of the environmental differences presented by the organs invaded. In Fig. 11 the tendency of the tumor to erode into vessels and to metastasize through the blood stream by the formation of malignant emboli is clearly shown.

Larger and more extensive areas of complete necrosis are found in the tissue of the mediastinal mass than in any of the other places which the tumor has invaded. There are other areas from this region, however, in which mitoses are numerous (Fig. 12) and in which the tumor cells are larger and have less hyperchromatic nuclei than the cells of the primary tumor or those making up any of the other metastatic lesions. These larger cells
FIG. 12. SMALL AREA FROM THE MEDIASTINAL METASTASIS

Note the relatively large cytoplasmic bodies of these cells; also the larger and less dense nuclei. One mitosis is seen to the right of the center. This figure should be compared with Fig. 5.

appear younger and more active than those of the primary tumor (Fig. 5) or of any other metastases. However, the cells are here grouped together to form patterns which are similar to those observed elsewhere. Apparently the roentgen therapy had both a necrotizing and a stimulating effect upon this neoplasm.

In the spleen the malpighian corpuscles are very small and poorly organized. The pulp cords and sinusoids appear normal and there is no excessive accumulation of blood in either. The trabeculae appear slightly more numerous than normal, but there is no tendency toward fibrosis. A normal amount of pigment is present.

There is a very marked atrophy of both the glands and the stroma of the endometrium with considerable endometrial fibrosis; this atrophy is of the senile type (Fig. 13). The myometrium and blood vessels are normal.

Each breast presents the same histological picture. The lobules and ducts show an extreme degree of atrophy of the senile type. There is almost complete fibrous replacement of the interlobular adipose tissue and much of the connective tissue is hyalinized (Fig. 14).

There is a moderate but definite atrophy of all the tissues of the scalp—epidermis, hair follicles, sweat glands, sebaceous glands, and corium.

With the exception of the two metastatic tumor nodules in the left adrenal, the structure of the right and left glands is similar. The medullary cells appear normal in number and in cytological characteristics (Fig. 15). Two types of cortical cells are present. The majority of the cortical cells stain poorly with eosin; their cytoplasm has a spongy, foamy-like structure. Fine eosin-staining fibrils make a delicate network in the cell bodies of these pale cells and surround tiny droplets which take no color with the routine stains. Although many of these clear cells are much larger than normal cells of the adrenal cortex, their nuclei for the most part do not show a corresponding enlargement. The nuclei of these pale cells are irregular in outline and appear crenated (Figs. 15 and 16). With Scharlach R these cells take a strong stain for fat. With Nile blue sulphate most of them stain pink, others take varying light shades of blue, while a few show both pink and blue droplets.

The second type of cortical cell takes a good eosin stain. The cells of this type show
In the section of endometrium note the fibrous stroma and small number of glands. The mammary gland section shows the atrophied ducts and fibrous (partially hyaline) stroma which has replaced the adipose tissue.

wide variations in size. Some of them are extremely large and have nuclei which are proportionately enlarged (Figs. 15 and 16). With routine stains the acidophilic cytoplasm is seen to be finely granular. With Nile blue sulphate most of these cells have a dark blue color; with Scharlach R they stain lightly or very incompletely.

All manner of transitional stages between these two cell types appear to be present.

In the pancreas neither the islands of Langerhans nor the general parenchyma show any recognizable pathologic changes.
Figs. 15 and 16. The Right Adrenal Gland

Just to left of the center of the area shown in Fig. 15 (above) is a narrow strip of medullary tissue. To the right of this are mostly large pale cells and to the left mostly acidophil cells. Fig. 16 (below) is a high power photomicrograph of the two cells shown in the center of Fig. 15; the one above is an acidophil cell, the one below a pale cell.
ARRHENOBLASTOMA, MALIGNANT OVARIAN TUMOR

In the hypophysis, an excessive number of small colloid masses are scattered throughout the anterior lobe (Fig. 17), many more than are encountered normally. In the peripheral portions of the anterior lobe multiple small areas of necrosis are seen. The sinusoids are unusually dilated in places but they contain few blood corpuscles (Fig. 18). Many of the basophils show degranulation and hyalinization of their cytoplasm (Figs. 18 and 19); this is the characteristic hyaline change of Crooke seen regularly in pituitary basophilism. Only a few basophils are found in the posterior lobe and some of these also show the hyalinization of Crooke. There is no obvious change in the acidophil and chromophobe cells. However, there are a few small islands or clusters of chromophobes which might be considered as tiny adenomas (Fig. 20). Upon following these islands through serial sections they are found to join up with a larger mass of similar cells; these islands therefore represent irregular bud-like branches from a small chromophobe adenoma. The cells making up these islands are smaller than ordinary chromophobes and they resemble the cell characteristically found in chromophobe adenomas. The posterior lobe and the pars intermedia are normal."

The pineal shows no pathologic lesion. In the thyroid the follicles are uniformly filled with colloid and they show a normal range of variation in size. The follicular epithelium is very low and flattened—almost pavement in type. The interfollicular stroma is normal and no lymphocytic infiltration is seen.

The three parathyroids show almost identical structure. The parenchyma is made up for the most part of clear chief cells with a few small vesicular cells. There are about 1 per cent of large pale oxyphiles and these are present as scattered individual cells; very few small clusters (islands) of oxyphiles are seen.

A careful search of numerous blocks from the thymic region failed to reveal any definite thymic tissue. Apparently the mediastinal metastasis has completely replaced and destroyed the thymus. In the sections from the tumor in this region a number of concentric, calcified nodules are present; these are interpreted as the remains of calcified Hassall's corpuscles. It is most remarkable that the only regional (extra-organic) metastasis of this tumor should localize in the superior and anterior mediastinum. The only reasonable explanation of this finding appears to be that this also represents an organic metastasis—metastasis to the thymus.

THE CLINICO-PATHOLOGICAL FEATURES OF THE ARRHENOBLASTOMA

Definition: Because of the infrequency with which examples of this tumor are encountered, it may be well to preface our more particular discussion by an attempt to define the arrhenoblastoma as a clinico-pathological entity. The term arrhenoblastoma originated with Robert Meyer and etymologically signifies a tumor which makes like a male ("arrhenos" meaning male). This name, arrhenoblastoma, is useful for the designation of a small but highly interesting group of malignant ovarian tumors in which, through the action of what is thought to be the hormone produced by the tumor, defeminizing or masculinizing effects become manifest in the host. The term is not intended to include cases of ovario-testis or instances of true or pseudo-hermaphroditism; neither are cases of spontaneous defeminization without ovarian tumors nor cases in which partial defeminization results from castration or other cause to be included. While it is admitted that other conditions may cause functional and anatomic changes similar to those produced by this tumor, if the term arrhenoblastoma is to have useful significance, it must be rigidly limited to that small group of ovarian tumors which are associated with clinical signs of defeminization or masculinization. Thus, as we shall point out, the term

---

3 For this description of the findings in the hypophysis, I am indebted to Dr. A. T. Rasmussen; Dr. Rasmussen's observations are included as a quotation from his report.
arrhenoblastoma must, in the present state of our knowledge, refer to a clinico-pathological condition; uncommonly can the term be used as more than a presumptive clinical diagnosis and less commonly can it be employed for a diagnosis based solely upon histologic study. Arrhenoblastoma is a worthwhile term which etymologically carries definite significations; practically it must be applied only when both the clinical and the pathological observations justify its use.

**Incidence:** The arrhenoblastoma is a rare tumor, but the physiologic effects which are associated with its presence give to it a signal importance. The figures thus far available as to the relative serial incidence of the lesion are valueless.

Meyer has assembled 26 cases which he has regarded as instances of the arrhenoblastoma on the basis of their histologic structure; but in 8 of these no evidence of masculinization had developed. It is doubtful, as we shall indicate later, when we consider the pathology of this tumor, whether these 8 cases can properly be included among the arrhenoblastomas.

In 1933, Taylor, Wolfermann and Krock reported the first case in the American literature under the title "Arrhenoblastoma of the Ovary." In 1921, Moots had described a case under the title "Lateral Partial Glandular Hermaphroditism," concerning which the following pathologic diagnosis and statement were made: "Fibroblastic sarcoma of embryonic testis. The (tumor) mass may have been an ovotestis with the ovarian stroma completely obliterated by sarcomatous process." The prominent clinical signs of masculinization, the prompt postoperative relief of these, and the histologic structure of the tumor leave little doubt that, although Moots did not recognize the case as such, he should probably be credited with having made the earliest record of an arrhenoblastoma in the American literature.

In 1930, Popoff reported a case of testicular tubular adenoma of the ovary; although amenorrhea was the only conspicuous symptom, Meyer has been willing to include Popoff's case among the arrhenoblastomas. I have carefully studied the original case report as presented by Popoff and am unable to agree that it should be so regarded. Popoff clearly states in his summary: "A case is described of a tubular adenoma of the ovary which occurred in a woman free from any signs of hermaphroditism." If Meyer can be lenient enough to accept this case of Popoff's as one of arrhenoblastoma, we should be the more critical of his own cases which have been reported with far less detail.

In 1933 Büttner reported a case and, as a part of his contribution, tabulated the findings in 25 cases from the literature. This tabulation was brought up to date in 1936 by Baldwin and Gafford and 34 cases were accounted for. Other cases have been reported by Phelan (1934), Maxwell (1937) and Depuy (1937).

The world's medical records thus appear to include only 37 cases which have been, or which may be, in retrospect, interpreted as arrhenoblastomas. More critical analysis of these, however, and the application of the definition which we have just annunciated reduces the number to 28. The addition of our case makes a grand total of only 29 reported cases which have been recognized and made to pass more or less rigid combined clinical and morphologic tests.
Figs. 17–20. Anterior Lobe of the Hypophysis

Fig. 17 (above, left) shows the general structure of the gland and the presence of a large number of colloid masses. Fig. 18 (above, right) note the dilated sinuses and three basophils which show the degranulization of Crooke. Fig. 19 (below, left) is a high-power view showing the structure of the two basophils in the upper part of Fig. 18. Note the sparseness of granules and the hyaline character of the cytoplasm. Fig. 20 (below, right) shows islands of small chromophobe cells, representing the sectioned appearance of bud-like branches from a chromophobe adenoma.
Age: The arrhenoblastoma appears to be more prevalent in the third and fourth decades. The reported cases range between the sixteenth and sixty-sixth years. Too few cases have been studied, however, to allow much importance to be attached to the limitations here set upon age distribution.

Clinical Symptoms and Signs: As yet it seems useful to keep in mind a clear distinction between those symptoms which arise from the loss of feminine qualities and those which are due to the development of definite male characteristics. So far as the individual is concerned, the former are negative changes and may be grouped under the term defeminization, while the latter are positive alterations to be described as signs of masculinization. Possibly in the future, when our notions of sex and intersexuality have been better defined, this distinction may become one of little or no importance; this because evidence is rapidly accumulating to indicate that most of the accepted features of separate sex qualification are arbitrary and apparent rather than real and of fundamental significance.

(1) Signs and Symptoms of Defeminization: Commonly the earliest symptom has been a persistent amenorrhea with sterility. The breasts and the endometrium atrophy and the genitalia, with the exception of the clitoris, are normal or somewhat hypoplastic. The uterus tends to become infantile and the unaffected ovary small.

(2) Signs and Symptoms of Masculinization: Some degree of hirsuties is apparently a constant finding. A mustache, a beard, and often a generalized growth of hair on the face is usual. The hair may grow so actively as to necessitate daily shaving. The distribution of the hair over the pubis, the perineum, the lower abdomen, and around the nipples is of the masculine type. There may be a generalized abnormal and excessive development of hair over the body. There is, however, a tendency for the scalp hair to fall out and to be short. An extensive acne is a common symptom and the skin tends to become rough and darker than normal (hyperpigmentation). "The facial expression is masculine, due to the coarse features and bushy eyebrows. There is an enlargement of the larynx, resulting in a lowering of the pitch of the voice. The skeleton is heavy and there is an inversion of the normal 'pelvis-to-shoulders ratio' of the female. The musculature is correspondingly affected. The clitoris is hypertrophied in most longstanding cases" (Taylor, Wolfermann and Krock, 1933).

(3) General Symptoms and Signs: There is regularly a loss in weight, but at times abnormal deposits of fat may occur over the body. Nervous symptoms of variable type and intensity are usual; the psyche may be altered but the heterosexual libido may remain unchanged until late in the disease. The pelvic tumor may be very large or very small and such pain as may be noticed is produced by pressure of the growing neoplasm or by secondary metastases. There are no constant changes in the blood, although a secondary anemia is frequently observed.

Hormone Effects: The Aschheim-Zondek test is negative. As indicated by our case, it is likely that there may be a considerable imbalance of the other hormones; hyperglycemia and glycosuria may appear and disappear at irregular intervals and the blood pressure and other clinical signs may fluctuate most remarkably. Szathmáry (1934) noted an absence of estrin
ARRHENOBLASTOMA, MALIGNANT OVARIAN TUMOR

in the urine before operation; three months after operation this had returned to normal.

Clinical Course and Prognosis: In general the course is continuous and progressive. The manifestations may be interrupted, however, and periods of symptomatic exacerbation and quiescence may alternate. Such an intermittent course is probably best explained by attributing the fluctuant variations to endocrine imbalance or disharmony. Untreated cases go on to death from malignant metastases.

Treatment: Surgical removal of the tumor is the indicated therapeutic resource. The primary growth is regularly unilateral and the affected ovary should, if possible, be removed without disturbing the other pelvic organs. The arrhenoblastoma is evidently very sensitive to radiotherapy (our case) and irradiation may be useful in the management of postoperative recurrences. Radiotherapy should not be employed, however, prior to operation, or prior to demonstration of metastatic implants, for the rays may destroy the tissue of the good ovary and thus prevent refeminization. When radiotherapy is employed it should be exhibited in maximal dosage for, as indicated in our case, the rays may have a stimulating effect upon the neoplasm.

Postoperative Course: After surgical removal of the tumor the normal female characteristics return in a most dramatic fashion (Moots, 1921; Kleinhaus, 1930; Krock, 1933; Phelan, 1934; Szathmáry, 1934); normal pregnancy has occurred following operation in a number of the reported cases (Meyer, 1932; Phelan, 1934). If there is a postoperative recurrence of the tumor, remasculinization may occur. In his discussion of a recent paper by Novak and Long (1933), Krock made some very significant remarks regarding the case reported in 1933 by Taylor, Wolfermann and Krock. He said: "The patient experienced a complete return to normal femininity after operation. Fifteen months later, recurrent nodules removed from the omentum showed on section spindle-cell sarcoma and areas of cartilage-like tissue. This brings up the question as to whether or not arrhenoblastoma of the ovary is a pathologic entity or whether it is merely a modified teratoma in which growth of functioning sex-directing cells has taken place at the expense of the other tissue elements usually found in these tumors. It also shows that these tumors are more malignant than is usually considered" (Krock).

Clinical Diagnosis: In a previously normal female, the appearance of signs of defeminization and the development of outspoken masculine characteristics should certainly suggest arrhenoblastoma as a clinical possibility. The early clinical recognition of this lesion will, however, probably always be difficult. Notwithstanding, a careful analysis of the various signs and symptoms should at least make it possible to mention arrhenoblastoma along with not more than six other diagnostic possibilities. The conditions to be considered in differential diagnosis are as follows:

(1) Pregnancy: The association of a growing pelvic tumor with amenorrhea naturally suggests pregnancy. It needs to be emphasized that degrees of masculinization of the female patient not uncommonly accompany gestation. The Aschheim-Zondek test may be relied upon to differentiate between pregnancy and arrhenoblastoma.

(2) Postclimacterium: The decreasing prominence of female charac-
teristics which commonly follows the menopause is well known and when this is associated with hypertrichosis (Halban, 1925) the possibility of the presence of an arrhenoblastoma may need to be considered. Such symptoms at this period of life, unless a palpable ovarian tumor can be identified, are probably best never regarded as due to an arrhenoblastoma.

(3) Tumors of the adrenal cortex (adenoma or carcinoma): Excess of the heterosexual hormone of the adrenal cortex may produce a clinical state which is very like that generated by the activity of an arrhenoblastoma. Sexually mature women cease to menstruate, exhibit marked hirsuties, may develop a voice of male timbre and present an hypertrophied clitoris (Broster and Vines, 1933). If the adrenal tumor is of large size it may be palpated or demonstrated in the roentgenogram. As yet information to be gained from chemical metabolic studies is too uncertain to aid in the practical clinical differentiation of these two lesions. Too much reliance upon such evidence may lead to mistakes like that made in our case.

(4) Cushing's syndrome (polyglandular syndrome): The clinical manifestations of this condition are of such nature as to give the greatest difficulty in the differential diagnosis. In the polyglandular syndrome, all or more commonly certain of the following symptoms and signs may be grouped together to constitute the clinical picture; painful adiposity, atrophic striae, hirsuties, amenorrhea, sterility, hypertension, glycosuria, osteoporosis, dusky or florid facies, a tendency to bruise easily, and erythrocytosis. This symptom complex, in the present state of our knowledge, especially if the syndrome is incompletely developed, may be impossible to separate from that produced by an arrhenoblastoma.

(5) Diabetes of bearded women: This syndrome was described by Achard and Thiers in 1921. It is characterized by hypertrichosis of the face, obesity, glycosuria with decreased carbohydrate tolerance, hypertension, and usually amenorrhea. It is possible that this combination of symptoms is not other than an incompletely developed Cushing's syndrome.

(6) It appears that degrees of masculinization of the female patient may not infrequently be found in the entire absence of either ovarian, pituitary, or adrenal lesions. Such cases are as yet poorly understood but they are now supposed to find their explanation in some endocrine disturbance, and it may be that instances of this type will ultimately come to be interpreted on the basis of intersexuality.

Pathology: Most previous reports on cases of the arrhenoblastoma have been based upon the study of surgically removed tumors of the ovary. Such information as we have had, therefore, pertains for the most part to the primary lesion, to the affected ovary, to the gross inspection of the other pelvic organs at operation, and to those externally recognizable clinical changes which we have already reviewed. It is unfortunate that no report on the findings in any of the ductless glands was included in Spielman's study of an autopsied case. On the basis of the general anatomic findings in our case, it becomes possible to extend considerably our conceptions of this disease. Apparently it is the first case to be reported which, having run an uninterrupted course and come to autopsy, has had a microscopic study of all the organs. In the "case report" we have already described the gross and
microscopic lesions found in each organ. It remains to correlate critically our findings with those of others. In this connection it must be pointed out that in the past there seems to have been much wishful and chaotic thinking in an attempt to interpret the primary tumor and its pathogenesis. Our efforts will be directed toward a simplification of the descriptive terminology and toward a correlation of the findings on justifiable embryologic grounds.

Regularly only one of the ovaries is involved by this tumor. The opposite, non-neogenic ovary is commonly smaller than normal for the age of the patient; it may have the appearance of the gonad from a much older woman. Attention should be called, however, to the fact that the histologic findings in the non-neogenic ovary of our case indicate the continuance of fairly normal ovarian function; from the morphologic point of view this ovary had not been physiologically suppressed.

The arrhenoblastoma is definitely a malignant tumor, having both the tendency to invade and to metastasize. In general, however, the malignancy is not of high grade, for the tumor tends to grow slowly and recurrences and metastases appear late. The primary tumor may attain huge proportions or it may be of inconspicuous size as in our case. Grossly this neoplasm may be solid or cystic in its constitution; if cystic, it may resemble the ordinary multilocular serous cystadenoma, and the solid fleshy portions may be few and scattered so that numerous blocks may be required before the structural identity of the tumor can be ascertained. It needs to be emphasized repeatedly that no hard and fast line of separation can be drawn between the ordinarily recognized groups of ovarian tumors. The ovarian cystadenomas, teratomas, carcinomas and sarcomas blend by ill defined gradients one with another, and even different parts of the same tumor may frequently present structural patterns typical of these various groups. Consequently, having in mind our clinico-pathological definition of the arrhenoblastoma, I am strongly of the opinion that, whenever defeminizing signs or symptoms are associated with one of these neoplastic types, the condition may properly be regarded as an arrhenoblastoma. It is probable that in such cases the careful study of many tissue blocks will reveal areas in which the histologic pattern will conform rather well to certain of those patterns found in the more readily recognized cases.

**Histology and Pathogenesis of the Arrhenoblastoma**

Meyer has seen fit to divide the arrhenoblastomas into three distinct groups on the basis of their histologic structure, as follows:

1. Adenoma tubulare testiculare: This group is typified by the tumor described by Pick (1905) and so named because of a supposed similarity in structure to an adenoma which develops in the testes of men. As will shortly be pointed out, the descriptions and figures presented by Pick and by Meyer are not at all convincing that the structure of the lesions included under this name are any more like embryonic testis than they are like embryonic ovary. Furthermore, Meyer (1931) has illustrated his article with photomicrographs of a so-called adenoma tubulare testiculare of the ovary which indicate, as he himself states, that the structure of tumors of this class may vary within the
widest limits. He further points out that even in the same tumor different areas may present quite different types of structural pattern: some parts show irregular tubules, which most certainly, from the illustrations offered, have little resemblance to seminal tubules; other parts show rudimentary epithelial cords; still others have a sarcoma-like structure. Surely there is no good and sound anatomic reason for designating a tumor of such mixed histologic structure by a name of such definite morphological significance.

Meyer states that the tumors which he has seen fit to place in this first group only occasionally cause any signs of masculinization.

(2) Atypical group: Under this heading Meyer has included those neoplasms of sarcoma-like structure “but with rudimentary cords or consisting of irregular tubules which only rarely resemble seminal tubules.” Thus Meyer uses the same descriptive language for the members of this group as he used for the first. And, surprising as it may seem, the illustrations which he cites bear the caption “adenoma tubulare testiculare” and are the identical ones used to show the structural patterns of his first group.

Meyer found evidence of marked masculinization in the majority of the cases included in this second group.

(3) Intermediate group: Morphologically the tumors of this group resemble structurally those of group one in some areas and those of group two in others. Meyer offers two figures to illustrate the histological appearance of this group; but these are not differentially distinguishable from patterns shown for the two preceding groups. The patients included in this third group “showed a slighter degree of masculinization than the others” (of group two).

It is my opinion that these groups as arranged by Meyer cannot be recognized as separate and distinct morphologic classes. Meyer made a great and lasting contribution when he so energetically called our attention to the hormonal effects of these malignant neoplasms, but he has added only confusion and frustration by his efforts to classify these lesions morphologically. It appears that he has been influenced by two forces; from one side, the necessity of including in his classification all the cases in which signs of defeminization or masculinization were present, and, from the other side, the desire to make structural patterns conform to a theoretical conception of the tumors’ origins. As anatomical morphologists, we must heartily disparage such efforts, for they can do no more than cast our science into disrepute. There is nothing to be gained by straining at the collar in an effort to make function conform to structure, or to force the reconciliation and pigeon-holing of histologic findings in accordance with preconceived theories of genetics. Thus for example in the case presented by Taylor, Wolfermann, and Krock we come upon this; “...the tubules are lined with a single layer of atypical columnar to cuboidal epithelium without basement membrane. Cellular detritus and coagulated material have collected in some of the lumens, and in a few, definite pear-shaped forms, suggesting atypical spermatozoa, can be made out.” Nothing in their description or illustration of these tubules suggests the possibility of spermatogenesis and their interpretation is certainly wishful and directed by the effort to force gender upon their tumor.

It is most important for us, however, both from the point of view of the
endocrinologist and from that of the morphologic pathologist, to understand
the likely embryologic background of the arrhenoblastoma. For this reason
several paragraphs concerned with the development of the human sex glands
have been interpolated. In this connection I have studied the human embryos
and fetuses in the collections of the Department of Anatomy of the University
of Minnesota and many of those of the Carnegie Institution at Baltimore. In
general my observations accord with the findings of Wilson (1926) and
Fischel (1930).

**Histogenesis of the Human Sex Glands:** The tissue destined to go into the
formation of the human sex glands can first be recognized in embryos 7 mm.
in length. The site of origin of the sex gland may first be identified by a
regional increase in the size of the epithelial cells which line the body cavity
over the medial aspect of the mesonephros; together these cells are referred
to as the germinal epithelium. Just beneath this single layer of germinal ep­
ithelial cells is a mass of embryonic connective tissue which does not differ
morphologically from the connective tissue in other parts of the embryonic
body. The primary sex cells have wandered in from the region of the hind
gut (where they appear to have been localized originally) and have become
scattered in the germinal epithelium and in the underlying connective tissue
(Politzer, 1933; Hamlett, 1935). Thus the primordial human sex gland is
made up of a layer of modified celomic epithelial cells (germinal epithelium)
which covers the free surface of the gland and a mass of underlying embryonic
connective tissue, through both of which tissues the primary sex cells are
scattered. The glomeruli and tubules of the mesonephros lie just lateral to
the body of the sex gland and the connective tissue which surrounds these
mesonephric structures blends, with no line of separation, with the connective
tissue of the gland.

A stratification of the germinal epithelial cells occurs and a condensation
of the connective tissue just below the germinal epithelium begins, but a zone
of loose connective tissue remains between this denser tissue and the adjacent
Wolffian body.

Through further condensation of the connective tissue and through the
differentiation and rearrangement of the cells, epithelial cords are developed
in the sex gland. From these cords the follicles of the ovary *or* the tubules
and interstitial cells of the testis are developed. Ultimately there is little
morphologic difference between the cells of the overlying germinal epithelium
and those of the epithelium of the sex cords below. Apparently it is the
presence of the germ cells which determines the type of differentiation.

The differential and specific identity of the testis may be recognized in
embryos of about 15 mm. in length and that of the ovary in a slightly later
developmental stage. The testis may first be recognized by the persistence
of a layer of relatively loose embryonic connective tissue between the germinal
epithelium and the sex cords; this layer is the primordium of the tunica al­
buginea. If the sex gland is to become an ovary this layer does not form and
the sex cords are immediately adjacent to the germinal epithelium. Whereas
in the developing testis the sex cords become more definite, develop lumina,
and finally become the seminal tubules, in the ovary the sex cords become
broken up into a large number of epithelial balls (primordia of follicles), each
of which contains one or more primitive ova. Whereas in the developing testis there is a considerable amount of inter-tubular tissue (interstitial cells), in the early ovary the amount of connective tissue between the cords is minimal. Finally, in the depth of the sex gland, of both male and female, near the mesonephric structures, there appears another condensation of the mesenchyma; this condensation develops in situ and at first is entirely separate from the sex cords on one side and from the Wolffian elements on the other. This mesenchymal condensation is the primordium of the rete and shortly the cells of this condensation become arranged in a plexus of anastomosing cords. The cells of the rete are similar to epithelial cells but they are not so closely packed as are the cells in most epithelia. In the male sex gland the rete cords develop lumina and become united at one end with the testicular tubules and at the other end with the mesonephric structures. In the ovary the rete cords regularly atrophy and do not go on to the formation of tubules.

Thus the ovary and testis are, up to a certain period of development, exactly alike. Through the developmental emphasis of certain characters, the indifferent reproductive gland is transformed into the sexually differentiated organ.

Pathogenesis of the Arrhenoblastoma: With the foregoing review in mind, we are in a position to consider Meyer's theory regarding the possible mode of origin of the arrhenoblastoma. In the cases thus far reported the structural constitution of the individual tumors, and even that of different parts of the same tumor, has varied from the picture of undifferentiated sarcoma, through conditions typified by poorly developed epithelium and irregular epithelial cords or masses, to pictures in which some poorly formed tubules or gland-like structures are found. There can be little doubt that this tumor seems to follow a general pattern similar to that outlined in the early development of the sex gland. There seems, however, to be no justifiable morphological or genetic reason for deriving this neoplasm from any particular part of the primitive sex gland. The arrhenoblastoma should be looked upon as a malignant ovarian tumor whose morphologic picture more or less corresponds to certain, some, or all of the varying structural conditions found in the indifferent stage of the sex gland's development. Therefore, because of the variable structure of these tumors, there is as yet no reason to attempt a subdivision of the group on the basis of their histologic pathology.

The derivation of the arrhenoblastoma from embryonic cell rests in the hilus region of the ovary is an interesting theoretical conception, but there seems to be little direct evidence to support the notion. Apparently the primary lesion in our case originated in the cortical or subcortical zone of the ovary. We have shown that the rete cords are just as characteristically a part of the early female gonad as they are of the testis of a similar developmental period. Because these rete cords atrophy in the normal course of ovarian development and persist in the male to form a portion of the testicular structure, is no reason to suppose that they produce a specific sex hormone. Indeed, from the point of view of probable secretory function there seems more reason to derive the arrhenoblastoma from any other part of the developing gonad; and from the point of view of the tumor's histology it might as well find its origin in one part as another.
Because of the above observations I am unable to agree with the statements and inferences of Novak (1933), when he says, "... the rete ovarii, which is not only a mere analogue, but the actual homologue of the male testis. To put it another way, every woman shelters within the medulla of the ovary a potential testis. Under certain conditions this undifferentiated male tissue may become active, and its male endocrine influence may override the primary female tendency, with the production of various degrees of intersexuality." Neither can I accord with the assertions by Taylor, Wolfermann and Krock (1933) that these tumors "show male characteristics histologically as well as clinically," and that "the finding of rudimentary testicular cells in the tumor microscopically confirms the diagnosis."

It is doubtful if the pathologist can make more than a presumptive diagnosis of this tumor. He might, however, suspect the probability of a defeminizing syndrome whenever he encounters, in his study of an ovarian neoplasm, any of the microscopic pictures described above. Pathologic investigation has not as yet progressed far enough to justify the final diagnosis of arrhenoblastoma without a knowledge of the presence of the characteristic clinical syndrome.

Intersexuality and Hormonal Pathology: In order to understand the deranged hormonal state present with the arrhenoblastoma it is necessary to consider briefly the subjects of sex determination and sex differentiation. It is now generally accepted that the matter of sex determination dates from the moment of fertilization and that sex is determined by the chromosomal pattern established through the union of a particular spermatozoon with an ovum. The spermatozoa are of two kinds—one kind carrying an X chromosome and the other carrying a Y chromosome. The ova are all alike in that each is equipped with an X chromosome. Thus in fertilization the constitution of an XX pattern determines femaleness and the constitution of the XY pattern determines maleness. So it is that with fertilization the general sex tendency of the individual is settled. It appears, however, that only the tendency is determined by the chromosomal pattern, for the matter of sex differentiation seems thenceforth to be turned over to the endocrine glands. One other factor may also influence sex differentiation, and that depends upon the orderly or disorderly embryologic development of the body in general and of the gonads and genital apparatus in particular. Orderly development results in the usual anatomic picture and disorderly development gives rise to a variety of anomalous conditions such as gonadal aplasia or hypoplasia, the ovario-testis, cryptorchidism, embryological rests, and abnormalities in the morphogenesis of the extra-gonadal parts of the internal and external genital organs. This group of anomalous developmental conditions which results in the production of hermaphroditic or pseudo-hermaphroditic types must, therefore, be kept in mind whenever the intersexual state produced by an arrhenoblastoma is being considered. Moreover, certain of these, notably the cryptorchid testis and the ovario-testis, seem to be responsible for more or less constantly associated, general, pathological hormonal effects.

Whereas the conditions just considered are not common, and whereas they may more or less distort the picture of sex differentiation, disturbances in the function of the endocrine glands are common and they may profoundly affect
the degree and character of sex differentiation. Indeed I am strongly of
the opinion that here is to be found the physiological explanation of inter-
sexuality. Normally the distinctive sex attributes—the type of external and
internal genitalia, the features of body contour and hair distribution, the
quality of the voice and certain peculiar psychic characters—are differentially
well enough developed to make the recognition of male or female an easy
matter. It needs to be emphasized, however, that, with the possible exception
of the gonads, these sex attributes are not characters of absolute difference
in the two sexes. Such differences as appear even between the most distinc-
tively developed males and females are never more than relative; the
differences are not those of kind but are rather those of degree.

Many observations among human beings who have been castrated or in
whom pathologic changes in certain of the endocrine glands have appeared,
have shown that the germ cell impulse and the chromosomal pattern are not
all important in the matter of sex differentiation. Moreover, even the type
of gonad is not the sine qua non of maleness or femaleness. The female char-
acters may be well developed in cases where the only gonad is a testis. Ex-
periments on parabiosis, observations on “freemartins” (Lillie, 1916), and
the phenomenon of the Crew hen offer irrefutable evidence that sex differentia-
tion and degrees of intersexuality are matters of endocrine function. There
appears, therefore, to be a quantitative balance between the male and the
female sex tendencies in every individual, which at a certain point can be
overturned depending upon changing hormonal relationships.

That a primary ovarian neoplasm of such undifferentiated state and one
which apparently corresponds to so early a genetic stage should regularly
produce a potent male sex hormone is more than remarkable. Although the
observation seems well established, speculation as to which cells are account-
able for the secretion, or as to whether the hormone is derived from a tumor
which had its origin in some cell rest supposed to be made up of male directed
cells, is valueless. Some future investigator may attempt the isolation of
the hormone from this tumor and demonstrate its physiologic activity.

Histological Evidences of Dejeminisation: The changes which we have
described in the endometrium, in the mammary glands, and to a lesser degree
in the ovaries from our case are clearly those to be expected in normal women
after the menopause. They show the condition of histologic structure ex-
pected in the senile period. The findings in the ovaries are of special im-
portance in the light of the recent experiments on parabionts. It is well
established that the continuous introduction of either male hormone from an
adult male parabiont or the frequent injection of adult testicular extract
into the body of a sexually mature female will regularly suppress ovarian
function and will lead to atrophy of the follicles. Experimental work of this
character has a very direct bearing upon the endocrinological problems pre-
sented by the arrhenoblastoma. That the effects produced in the ovaries of
the parabiotic experimental animals are similar to those found in the non-
neogenic ovaries of clinical cases of arrhenoblastoma provides a strong argu-
ment that a substance is produced by the arrhenoblastoma which either is
the male sex hormone, or something very like it. It needs to be emphasized,
however, that the suppression of ovarian function in the non-neogenic gonad
of our case was far from complete. Corpora lutea were present and not all of the follicles were atresic.

The atrophic changes in the mammary glands of our case might be ascribed to the roentgen therapy, inasmuch as these were closely adjacent to the mediastinal area irradiated. This, however, seems an unlikely explanation, for the atrophic changes in the endometrium are at least of equal degree. Moreover, these atrophic effects in the ovarian, mammary, and endometrial tissues are similar to those found in other cases of arrhenoblastoma in which no radiation had been used. It seems justifiable, therefore, to consider these changes as a part of the disease process.

Pathology of the Endocrine Glands: Our case is apparently unique in so far as it is the only one in which all of the ductless glands have been submitted to careful microscopic examination. Possibly the most important contribution from this case is concerned with the findings in these glands.

Recently Crooke (1935) and Rasmussen (1936) have shown that the cases of Cushing’s syndrome are not, as was originally believed, regularly associated with a basophil adenoma of the hypophysis; on the other hand, they have demonstrated the constant presence of degranulation and hyalinization of the basophils in these cases. As far as is known today, a variable degree of hyalinization of the basophils of the hypophysis is the only constant anatomic change associated with Cushing’s syndrome. That the hypophysis from our case of arrhenoblastoma should show the same histologic picture is most significant.

The microscopic findings in the cells of the adrenal cortex are no less striking, but are much less amenable to interpretation, for we lack studies on the adrenal which are comparable to those of Rasmussen and Crooke on the hypophysis. The marked hypertrophy of both the acidophil and pale cells of the cortex is easily evident, but so far as I can learn this bit of microscopic pathology still resists interpretation (Broster and Vines, 1933).

The extreme quiescent state of the thyroid, as shown histologically, is remarkable; but the association of this structural state with the changes in the other ductless glands is possible of no more than speculative interpretation.

In spite of the hyperglycemia and glycosuria, the negative findings in the pancreas and islands of Langerhans are not of noteworthy significance.

That the thymus should apparently be absent, because of the regional metastatic invasion, needs emphasis and calls for further study to determine whether the resultant thymoprivic condition might have any relationship with the clinical picture.

Finally the apparently normal parathyroids and pineal deserve mention.

Summary and Conclusions

1. A case of arrhenoblastoma is reported in which the clinical, laboratory, and post-mortem findings are recorded.

2. Of the large variety of ovarian tumors there are only two types which seem regularly to be associated with endocrinological effects; these are the arrhenoblastoma and granulosa-cell carcinoma.

3. The world’s medical records include 38 cases which have been, or which
may be, in retrospect, interpreted as arrhenoblastomas. More considered opinion with the application of more or less rigid combined clinical and morphologic tests has reduced this number to a grand total of only 29 reported cases.

4. The name arrhenoblastoma is useful for the designation of a small but highly interesting group of malignant ovarian tumors in which, through the action of what is thought to be the hormone produced by the tumors, defeminizing or masculinizing effects become manifest in the hosts. The term arrhenoblastoma must, in the present state of our knowledge, refer to a *clinico-pathological* condition; practically the term must be applied only when both the clinical and the pathological observations jointly justify its use.

5. The signs and symptoms of an arrhenoblastoma may be divided into three groups: those of defeminization, those of masculinization, and a group of general signs and symptoms. These may include amenorrhea, sterility, atrophy of breasts, endometrium and genitalia, hirsuties, baldness, hyperpigmentation, coarse features, low-pitched voice, hypertrophy of clitoris, masculine body contours, abnormal deposits of fat, psychic alterations, pelvic tumor, and malignant cachexia.

6. The general course of the disease is continuous and progressive, and untreated cases go on to death from malignant metastases. However, periods of symptomatic exacerbation and quiescence may alternate.

7. Early surgical removal of the tumor is the indicated therapeutic resource. The immediate postoperative result is good and the symptoms disappear if the tumor can be removed. The symptoms may return if the tumor recurs.

8. The differential diagnosis of arrhenoblastoma is difficult. The conditions which need to be differentiated are pregnancy, postclimacterium, tumors of the adrenal cortex, Cushing's syndrome, the diabetes of bearded women, and a poorly defined group of cases in which degrees of masculinization appear in the absence of ovarian, pituitary, or adrenal lesions.

9. There is no justifiable reason for the subdivision of this group of tumors on the basis of their variable histologic structure.

10. There seems to be no justifiable, morphological or genetic reason for deriving this neoplasm from any particular part of the primitive sex gland. Pathogenetically the arrhenoblastoma should be looked upon as a malignant ovarian tumor whose morphologic picture more or less corresponds to certain, some, or all of the varying structural conditions found in the indifferent stage of the sex gland's development.

11. The physiologic state present with an arrhenoblastoma is best explained on the basis of intersexuality. Intersexuality is thought to find its explanation in disturbances or disharmonies in the function of the endocrine glands.

12. Concerning the endocrine glands, significant pathologic alterations have been found in the ovary, the hypophysis, the adrenal cortex, the thymus, and the thyroid (?).

NOTE: Thanks are due H. W. Morris for the photographic work in this paper.
ARRHENOBLASTOMA, MALIGNANT OVARIAN TUMOR

BIBLIOGRAPHY


ALLEN, E.: Sex and Internal Secretions, Baltimore, Williams and Wilkins Co., 1932.


