Arrhenoblastoma

William A. Day
University of Nebraska Medical Center

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

Part of the Medical Education Commons

Recommended Citation
https://digitalcommons.unmc.edu/mdtheses/655

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.
ARRHENOBLASTOMA

OF THE

OVARY

WILLIAM A. DAY

SENIOR THESIS

PRESENTED

TO THE

COLLEGE OF MEDICINE

UNIV. OF NEBR.

OMAHA

1938
INDEX

INTRODUCTION 1
CLASSIFICATION 2
PATHOLOGY 6
SYMPTOMATOLOGY AND DIAGNOSIS 11
TREATMENT AND PROGNOSIS 18
EMBRYOLOGY 20

THE GONAD

The Indifferent Stage
Internal Sexual Transformations
The Testis
The Ovary

THE ADRENAL

ETIOLOGY 33
PATHOLOGICAL PHYSIOLOGY 37
BIBLIOGRAPHY 46
INTRODUCTION

The term arrhenoblastoma is derived from the Greek term 'arrhenoe' which means male, and blastoma which means to germinate. This is the name given by Robert Meyer (15) to certain tumors of the ovary, probably derived from tissue which is primarily testicular. These tumors simulate, to a certain extent, the normal tissue of the testis and also have the peculiar effect of defeminization and masculinization of the patient.

Various terms have been used to describe this growth, among which are adenoma testiculare tubulare, used by Pick when he described the first case reported in 1905. Other names are defeminizing and masculinizing tumors, fibroblastic sarcoma of embryologic testis by Moots (61), luteoma, aberrant adrenal cortex tissue, ovarian hypernephroma and others.

While this is a rather rare tumor, it may be present more commonly than is recognized, and it presents an interesting clinical picture which may also be of value in the study of genetics and sex determination as well as the still incomplete field of endocrinology.
CLASSIFICATION

Novak and Gray (25) classify the arrhenoblastoma as one of the group of tumors of dysontogenetic origin along with the disgerminoma, granulosa cell carcinoma and the Brenner type tumor.

The classification of this group of tumors within themselves is based on the differences in the microscopic pathological picture and most of the work has been done by Robert Meyer (29). Other authors such as Spielman (33), Phelan (28), Behrend and Levine (4), Novak and Gray (25), McLester (19), Taylor, Wolfermann and Krock (34) and Baldwin and Gafford (3) follow in general his classification.

He divides the tumor into three different classes as follows:

(a) the typical group which simulates most closely true testicular tissue.
(b) the completely atypical group which shows no cord formation and have a sarcomatous appearance.
(c) the intermediate group which shows a mixture of the two types.

A brief discussion of the pathological classification is given as follows by Geist (12):

The typical adenoma testiculare ovarii is usually a small tumor, firm, encapsulated or embedded in the
ovarian structure and composed of regular tubules with a small circular lumen, lined by a layer of cuboidal cells, supported in dense connective tissue. In one case reported by H. O. Neumann, the presence of cells resembling the interstitial cells of the testicle made the resemblance to the true testicular adenoma of the male gonad very striking.

In the atypical group the tumor pattern varies markedly from the pure tubular or partly tubular and partly cellular-like growth of the intermediate type. In the main the tumor is solid with a few atypical tortuous tubular areas, or areas of convoluted solid cords of cells. These cell cords can at times be recognized as composed of cells resembling the more sarcomatous appearing elements that may form the bulk of the growth. The stroma may become sarcomatous. There are evidences of cyst formation with epithelial lining and even papillae, and Beuttner and Meyer have described mucinous epithelium.

The intermediate group of tumors, which showed various stages of transition from the tubular adenoma to the atypical form, with masculinization in varying degrees, are larger growths that the typical ones, reaching the size of an adult head, and are unilateral. They have a lobulated surface, are encapsulated, smooth and may infiltrate the surrounding structures. On section
they are soft, medullary like, yellowish growths with a marked tendency to undergo regressive changes. Hemorrhage, necrosis and liquifaction are present, and in some instances true cysts with an epithelial lining may be present. Some of these tumors may simulate cysts and their true identity may be extremely difficult to establish. The tubules are irregular, their lumina varying in size and contour. Some of the epithelial cells undergo fatty degeneration.

Others such as Novak and Long (26), Mueller (22), Fleming (11), Baldwin and Gafford (3) and McLester (19) have brought up the question as to whether or not this is but a special type of teratoma.

They base their conclusions on the fact that there has been found in certain of the tumors, tissue which does not normally occur in the gonad, either testis or ovary. Instances of this are the finding of mucous producing epithelium with typical goblet cells by McLester (19), poorly formed spicules of bone, apparently produced by metaplasia of connective tissue without intervening cartilage formation, by Baldwin and Gafford (3) and areas of cartilage-like tissue in the metastatic nodules in the case of Taylor, Wolfermann and Krock, referred to by Novak and Long (26).

Fleming (11) also refers to two cases in which the hilum of the ovary was definitely not involved in
the tumor formation.

However, we will follow Meyer's classification in this paper, not disputing the fact that it may be but a special form of teratoma. We believe that this will be of advantage in discussing the associated symptomatology and also the not yet clear underlying hormone factors involved.

Meyer (20) believes that these are but three different types of a single neoplasam having a common origin. He bases this on the variation of morphology in the intermediate group between that of the completely typical and completely atypical groups.
PATHOLOGY

A more detailed discussion of the pathology, gross and microscopic, according to the classification of R. Meyer, is interesting, especially in regard to the discussion of conflicting opinions of various authors as to the similarity and perhaps homology, of the tumor to the normal testis. A brief description of the uterus and other genital organs will also be given.

This tumor is generally unilateral, Novak and Gray (25), but there may be several of them of small size located in one ovary, as was the case of Gnassi (14) in which there were four of them about .5 cm. in size. They vary from this case up to much larger single tumors, that of Taylor, Wolfermann and Krock measuring 20 x 20 x 18 cm. and weighing 990 gm., the one of Behrend and Levine (4) weighing 1,030 gm., and Spielman's (33) being 9.5 x 6 x 4.5 cm. and Phelan's (28) measuring 6 x 3 1/2 cm.

It is from the descriptions of the above tumors and also from Geist (12), Novak and Gray (25), Novak and Long (26), Baldwin and Gafford (3) and Popoff (29) that the following description is based upon.

The tumor is generally smooth, lobulated and encapsulated in a fibrous, opaque capsule. It is greyish in color but may have yellowish streaks on the surface or
the entire tumor may have a yellow tinge.

It is classed as a solid tumor but is prone to undergo cystic degeneration due to hemorrhage and necrosis. On section it may or may not show cysts, varying in size from .5 cm. up to 6 cm.

The cut surface is opaque, greyish or yellow and may be divided into lobules by thin connective tissue septa, extending from the capsule into the base of the tumor, which may undergo a moderate degree of hyalinization. It may show varying amounts of hemorrhagic foci. It is soft to the touch and is moist and glistening. There are no corpora lutea or follicular cysts.

The microscopic picture varies considerably but in general it can be said to be made up of two types of cells, (1) the cuboidal, roughly spheroidal or columnar cells with acidophilic nuclei which enter into the tubule or cord formation and are found to a large extent in the typical type of tumor of Meyer's classification.

Transitional cells of the two types suggests however, that these are but phases of a single basic cell according to McLester (19).

The large cuboidal cells have a pale, finely granular, acidophilic cytoplasm and strongly acidophilic nucleus with darkly stained chromatin granules and one or occasionally, two, heavily stained nucleoli. There
are frequently found inclusion bodies which appear as small eosin-stained, occasionally rather refractive globules. The fat which is found in the tumor is practically always found in this type of cell, within the cytoplasm, appearing as thin crescents, partially outlining a vacuole or globules of unstained material or in the form of a delicate circlet.

This cell is thought to be identical or similar to the interstitial cells of Leydig by Gnassi (14), McLester (19) and Geist (13) and to the early seminiferous tubules or medullary cords by Behrend and Levine (4) and Novak and Gray (25).

Popoff (29) in his discussion states that they resemble the interstitial cells which originate in the embryonal ovary and testis among the medullary or sex cords, but should not be confused with the interstitial cells of Leydig. He bases his opinion upon the appearance of the fat in the cells which suggests local fatty degeneration of the epithelial ingredients of the cords, rather than the fatty infiltration that is found in the mesenchymal cells of Leydig.

These cells are arranged to form gland like tubules or acini, sometimes in single layers and sometimes they proliferate to form many layers and almost completely occlude the lumen, which may vary considerably in size. The basement membrane is not very definite
but there is a close relationship to the accompanying blood vessels which generally show a perivascular lymphocytic infiltration. This relationship is suggestive of an endocrine function of these cells. These cells in this arrangement are generally considered to be the homologue of the seminiferous tubules of the testis.

In other places no attempt at tubule formation is present but they appear as isolated nests of cells.

Varying amounts of mitotic figures were reported, but no spermatozoa were described in any case.

The other type of cell, fusiform, with hyperchromatic nuclei and scanty cytoplasm, has no definite arrangement and is more sarcomatous in nature, although they may be arranged in irregular bundles or whorls, or imperfectly convoluted cords, slightly suggestive of the early sex cords. These cells resemble embryonic fibroblasts, with many mitotic figures, and some evidence of changes into the cell type described first. McLester (19) thinks that these may represent the mesodermal tissue from which the interstitial cell is said to arise.

In patients where this tumor is found, especially those of the atypical and mixed types, where there is defeminization and masculinization, the opposite ovary is small, greyish and sclerotic.

The uterus and tubes are atrophied and infantile in type with the cervix long and conical. The vagina
may be atrophied and constricted with an hypertrophy of the clitoris.
III. Atypical Tumors.

A. Mostly Solid Forms with Atypical Tubular Portions.

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. Halban</td>
<td>31</td>
<td>1 child; regular menses, then irregular following birth of child; amenorrhea 14 years, then mild bleeding.</td>
</tr>
<tr>
<td>21. Wagner</td>
<td>25</td>
<td>Premature birth 3 years ago; amenorrhea for 9 months.</td>
</tr>
<tr>
<td>22. Kleinhaus</td>
<td>31</td>
<td>Nulliparous</td>
</tr>
<tr>
<td>23. Krause</td>
<td>41</td>
<td>Diabetes mellitus; death post pneumonia.</td>
</tr>
<tr>
<td>24. Geissler</td>
<td></td>
<td>Menarche at 13, menses regular; beginning hair growth following struma operation.</td>
</tr>
<tr>
<td>26. Baldwin &amp; Gafford</td>
<td>24</td>
<td>Menarche at 14, regular; increased flow for 8 mo., 8 months before surgery; amenorrhea since.</td>
</tr>
</tbody>
</table>

B. Solid Forms.

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>27. Sellheim</td>
<td>47</td>
<td>Several healthy children; age 43, amenorrhea.</td>
</tr>
<tr>
<td>28. Bingle-Schultze</td>
<td>47</td>
<td>4 children; regular menses; irregular 5 years; amenorrhea at 35; polycaesthesia; enlarged thyroid; glycosuria.</td>
</tr>
<tr>
<td>29. Mathias</td>
<td>19</td>
<td>Amenorrhea for 3 years; normal menses prior to surgery.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Clinical Data</th>
</tr>
</thead>
</table>

Signs of masculinism. Course; return to feminism.

- Beard; baldness; hirsutism; deep voice; large clitoris; small breasts.

- Masculine habitus; deep voice; hirsutism.

- Amenorrhea; masculine body; voice deeper; beard; breasts feminine. Again arose by recurrence.

- Hypertrichosis; clitoris similar to penis.

- Amenorrhea; virile body; regular menses; voice higher; hair type; beard; hirsutism type of hair closer to feminine.

- Hirsutism, face and body; Menses in 5 weeks; feminine deep voice; clitoris enlarged; voice in 3 months. Largely; uterus small.

- Amenorrhea; atrophy of breasts; hirsutism; baldness; enlarged clitoris.

- Menses started in 1 month, profuse; transfusion; reoperated 4 mo later for uterine fibroids.

- Beard; hair over body; short scalp hair; deep voice; enlarged clitoris.

- Complete femininism.

- Beard; marked hair on body; male habitus.

- 3 years later, absolute femininism; body hair disappeared; beard gone; polycaesthesia gone.

- Beard; masculine habitus; Married 4 years later, 1 child voice change; enlarged clitoris.

- Beard and body hair; amenorrhea.

- Operation for incarcerated myomatous uterus; death in 3 weeks.
<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popoff</td>
<td>31</td>
<td>1 birth; regular menses; missed one period, had one period, then amenorrhea.</td>
</tr>
<tr>
<td>Meyer (Cupei)</td>
<td>16</td>
<td>Regular menses, now irregular.</td>
</tr>
<tr>
<td>Meyer (Univ. Clinic)</td>
<td>33</td>
<td>Menses regular, then bleeding for 4 months, amenorrhea for 9 months.</td>
</tr>
<tr>
<td>Meyer (Sauer)</td>
<td>66</td>
<td>Regular menses; last period at 53 years.</td>
</tr>
<tr>
<td>Meyer (Mackenrodt)</td>
<td>35</td>
<td>4 children; menses regular at beginning, amenorrhea for 5 yrs. following birth of first child; continuous bleeding for 9 months.</td>
</tr>
<tr>
<td>Meyer</td>
<td>31</td>
<td>1 child; regular menses, irregular at 53, amenorrhea 2 years later.</td>
</tr>
<tr>
<td>Meyer</td>
<td>36</td>
<td>Irregular periods for 6 months.</td>
</tr>
<tr>
<td>Spielman</td>
<td>26</td>
<td>Regular menses, amenorrhea for 3 years; nulliparous; scanty periods for 6 months.</td>
</tr>
<tr>
<td>Novak &amp; Long</td>
<td>20</td>
<td>Onset of menses at 13, 2 normal periods, then amenorrhea for 13 months, scanty periods for 3 mo.</td>
</tr>
<tr>
<td>Szathmary</td>
<td>25</td>
<td>Para 2; menarche at 13, regular menses; signs for 2½ years, then amenorrhea.</td>
</tr>
</tbody>
</table>


Feminine habitus; deep voice; small breasts. Regular menses; voice higher.

Amenorrhea; small breast; voice; deep hoarseness. Death from recurrence.

Feminine habitus; hoarseness for 1½ years. Voice clear 14 days postoperative.

Voice deeper; hair on arms and legs. Hair disappeared; voice unchanged.

Amenorrhea; menopausal maliminate. Return of regular menses.

Male facies; deep voice. Regular menses.

Amenorrhea; hirsutism; small breasts; enlarged clitoris; infantile uterus; almost complete absence of oestrin. Died unoperated; basilar hemorrhage, pneumonia.

Harsh voice, enlarged clitoris. Operated; menses for 3 mo., then recurrence with death.

Hirsutism; enlarged clitoris; deep voice; small breasts. Gained 35 pounds in 3 mo.; feminine habitus; growth of breasts; masculine form; hair on face decreased; less hypertrophy of clitoris; voice and larynx the same; breasts larger.
The following table is taken from Baldwin & Gafford (8).

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Tubular Adenoma Testiculare, Pick.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Mature Forms.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Pick</td>
<td>34</td>
<td>1 abortion; 3 healthy children; menses always irregular; continuous bleeding for months.</td>
</tr>
<tr>
<td>2. Shickele</td>
<td>26</td>
<td>Nullipara; profuse menses, almost hemorrhages.</td>
</tr>
<tr>
<td>3. Neumann</td>
<td>32</td>
<td>Menarche at 13; menses regular; at 20 irregular; amenorrhea for 14 years.</td>
</tr>
<tr>
<td>4. Berner</td>
<td>23</td>
<td>Menses originally regular, then every 14 days, then amenorrhea for 19 years.</td>
</tr>
<tr>
<td>5. Blair Bell</td>
<td>16</td>
<td>Menarche at 14, regular; somewhat enlarged thyroid; amenorrhea for 5 years.</td>
</tr>
<tr>
<td>B. Partly Carcinomatous Forms.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Meyer</td>
<td>43</td>
<td>Three children</td>
</tr>
<tr>
<td>7. Meyer</td>
<td>47</td>
<td>Nullipara; regular menses, frequent and profuse for last year.</td>
</tr>
<tr>
<td>8. Neumann</td>
<td>53</td>
<td>6 children, 2 abortions; amenorrhea for 7 years; slight bloody discharge for 4 months.</td>
</tr>
<tr>
<td>9. Meyer, (Priebsch)</td>
<td>44</td>
<td>1 child, 2 abortions; regular menses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs of masculinism</th>
<th>Course; return to feminism</th>
</tr>
</thead>
<tbody>
<tr>
<td>None; feminine habitus</td>
<td>5 births following operation.</td>
</tr>
<tr>
<td>Amenorrhea; male facies; hirsutism; large clitoris; decreased libido.</td>
<td>Return of menses; loss of beard; return of feminine fat pads; clitoris unchanged; sex normal.</td>
</tr>
<tr>
<td>Changed voice; enlarged clitoris; amenorrhea; beard; hirsutism.</td>
<td>6 months postoperative, loss of beard, clitoris smaller.</td>
</tr>
<tr>
<td>Light beard, male type of hair distribution; enlarged clitoris.</td>
<td>Symptoms similar to menopause; hair fell out; voice somewhat higher.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feminine habitus</th>
<th>Feminine habitus</th>
<th>Feminine habitus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Death 1½ years postoperative from recurrence.</td>
</tr>
<tr>
<td>None; feminine habitus</td>
<td>None; feminine habitus</td>
<td>Died with carcinoma cachexia.</td>
</tr>
</tbody>
</table>
SYMPTOMATOLOGY AND DIAGNOSIS

The most interesting and definite syndrome found with this condition is the defeminization and masculinization which is most marked accompanying the atypical type of tumor and is found in nearly all of them. It is inconsistently found with the intermediate type and but seldom found with the typical type or adenoma tubulare testiculare. For the incidence of these symptoms relative to the type of tumor, see the accompanying chart which is taken from an article by Baldwin and Gafford (3). The description of the symptom complex was taken from the same articles referred to under the discussion of the pathology.

Aside from these symptoms, about the only other manifestations are pain, which is sometimes absent, and palpation of the tumor mass.

It is convenient to divide the symptoms into defeminization and masculinization, one probably due to a lack of hormones from the ovary and the other due to an excess of the male hormones produced by the tumor. The former will be discussed first.

Amenorrhea is most consistently found and may have a sudden onset, thus simulating pregnancy, or it may begin by first an irregularity with a decrease in flow, followed later on by a complete amenorrhea. This
is generally accompanied by an atrophy of the uterus, both in gross size and in the thickness and character of the endometrium. Also there is almost a complete absence of the female sex hormone cycle by the Frank-Goldberger test as reported by Spielman (33).

There is generally also an atrophy of breast tissue due to a decrease in fat deposition and also a decrease in size of the glandular substance. With this there is also a disturbance in other typically feminine fat deposits. The hips and buttocks lose their fat and become more angular with prominent illia and tuberosities of the femur, the face loses its rounded features and becomes more sharp and masculine in appearance. The neck becomes thinner with a more prominent musculature and larynx.

In the genital organs, besides the atrophy of the uterus, there is a constriction and shortening of the vaginal canal which sometimes becomes so small that it will barely admit the examining finger. The labia majora atrophy. The ovary of the opposite side becomes small, grey and sclerotic. There is generally no loss of libido if it has once been established, but there may be considerable decrease of it, especially of the tumor is quite advanced or masculinization has proceeded to a marked degree.
Among the masculinizing symptoms, hirsutism with hypertrichiasis is commonly found, the hair taking on a masculine distribution. There may be a falling out of hair on the head with temporal baldness as is found typically in men, which was quite marked in the case of Maxwell (23).

There is apt to be a prominent, coarse beard, distributed over the cheeks, chin, upper lip and neck. It may be so heavy as to require shaving every day or two. There is a varying amount of hair over the chest, shoulders, back, arms and legs. The pubic hair assumes a typically male distribution and may extend nearly to the umbilicus along the linea alba.

There is generally an hypertrophy of the clitoris and it may assume almost masculine proportions, with a well defined prepuce and glans, and markedly erectile. In the case reported by Spielman it was 4 cm. long.

If it occurs early in life there may be distinct changes in the skeletal system with an inversion of the "shoulder to pelvis" ratio as reported by Taylor, Wolfermann and Krock (34), and "the gate of a male stride instead of the mincing steps of the female", Geist (12).

The musculature becomes hard and more like that
of a male.

There is an hypertrophy of the larynx with a noticeable prominence of it and a deepening of the voice, or it may assume the cracked character found in puberty.

These are the most constant and dependable symptoms, the laboratory not being of much value. They may show a slight lowering of the basal metabolic rate but this is not very constant. Blood and urine findings may be of value in determining disturbances in glucose metabolism, which is generally upset in pituitary adenomas. The hormone findings are not of much value as they are not only difficult and expensive to run and not very dependable in results, unless one is especially equipped, but also are hard to interpret in the correct manner with our present limited knowledge of their action.

The diagnosis of this special tumor is rarely made in the typical type until after microscopic examination. With the other two types, however, we are confronted with a rather difficult problem in differential diagnosis between them and two other conditions, namely adenoma or hyperfunction of the adrenal cortex and basophilic adenomas of the anterior lobe of the pituitary, as these occasionally give rise to quite
similar clinical pictures.

Age is one important factor as the arrhenoblastoma has not been reported as occurring before puberty while the other two often occur then with precocious puberty and masculinization.

In the article by Goldzieher and Koster (13), some good differential points are given.

The hirsutism found in hyperfunction of the adrenal cortex is very similar to that of the arrhenoblastoma and may not give us any assistance. In adenoma of the pituitary it is generally of a soft, silky, lanugo type and is more prominent over the cheeks and upper lips, rarely over the chin or neck.

In arrhenoblastoma there is seldom any obesity, in fact there is the opposite, a loss of fat. This is also found in adrenal tumors, but with a diffuse hyperplasia or small adenomata of the cortex the fat is restricted to the trunk, with massive thighs and upper arms, while the forearms, legs, hands and feet are of normal proportions. They also have a characteristic bull neck and pulpy face. In the pituitary dysfunction, there is a deposition of abdominal fat in the form of a dependent fold which often covers the genitalia like an apron. The extremities are involved to a lesser degree.

Blood pressure determinations may be of value
as hypertension is seldom present in arrhenoblastoma while it is often present in hyperfunction of the adrenal cortex, where it is constantly high and not of the paroxysmal type found to be present in pituitary adenoma.

Likewise, glycosuria or hyperglycemia may be present in the others but seldom is it found in arrhenoblastoma.

The fact that these two conditions are so similar to arrhenoblastoma, especially that of hyperfunction of the adrenal cortex, may account for the small number of these tumors reported in the literature and a review of the symptomatology and pathological specimens may reveal more of them. This was especially noticeable in a report by Glynn (15), entitled, "A comparison between ovarian 'hypernephroma' and luteoma and suprarenal hypernephroma, with comments on suprarenal virilism."

In this article there were 14 cases reported, including Pick's adenoma tubulare testiculare, nine of which showed "suprarenal virilism". The tumors were classified as luteoma or ovarian hypernephroma, apparently due to displaced adrenal cortex tissue. Pathologically they were described, "the cytoplasm was usually clear, or contained many vacuoles or fat or both."
Fibrous tissue stroma of varying amounts and gland like lumina in some cases". This is quite similar to the pathological description of arrhenoblastoma.
TREATMENT AND PROGNOSIS

The treatment of this tumor is primarily operative, with the removal of only the affected ovary, as it is but rarely that the condition is bilateral. In case there is also some involvement of the other ovary, only partial bilateral oophrectomy should be done, as it is necessary that there be some ovarian tissue left in order to have a return of normal feminine characteristics, according to Taylor, Wolfermann and Krock (34).

This return generally occurs, as is seen in the table listing the cases collected by Baldwin and Gafford (3), the menses generally returning within from four to eight weeks. In the case of Gnassi (14), there had been an amenorrhea for twenty years previous to extirpation of the tumor, but menstruation began after removal.

Pregnancy with normal delivery and the mother nursing the child may occur as in the case of Phelan (28) and Popoff (29). Geist (12) states that pregnancy occurred in the cases reported by Sedlaczek, Mathias and Neumann also.

There is generally a retrogression of hirsutism, the hair falling out and becoming softer and finer, with a return to the normal female distribution.

Anatomical changes such as hypertrophy of the
larynx and clitoris, are more or less permanent and do not return as completely to the normal female type.

As to the prognosis following removal, there is some controversy, especially as regards the malignancy of the growth, but it is generally considered good unless there is some evidence of metastasis or direct invasion.

Geist (12) states that while these tumors may present the histologic signs of malignancy, many of the patients have been successfully operated upon and permanently cured. He further states that Strassmann reported thirteen cases and all but one were malignant.

However, Taylor, Wolfermann and Krock (34) state that while these tumors are primarily malignant, this is usually relatively benign as recurrence and metastases do not usually make their appearance before six to seven years. They state that prophylactic deep X ray therapy does not seem to be indicated but in event of recurrence it should be of value because of the marked sensitivity of germinal epithelium to destruction by radiation.
EMBRYOLOGY

According to most authors it is of advantage to clearly understand the embryology of the ovary in order to explain the formation of this tumor. Since this is so closely related to the embryology of two other structures, the testis and the suprarenal gland cortex, these will also be covered. This is necessary in relating other clinical syndromes similar to that of the arrhenoblastoma, namely tumors and hyperplasia of the suprarenal cortex.

The general discussion of the embryology of these structures is adapted from Arey (2), modified and strengthened by the opinions of various other authors.

THE GONAD

The Indifferent Stage

During about the sixth week of foetal life, which corresponds to about a 5 mm. embryo, there arises a longitudinal genital fold in the urogenital fold, produced by a thickening of the peritoneal epithelium. This lies mesial to the mesonephric fold and parallel to it. There is also an inner epithelial mass, derived from an ingrowth of the superficial germinal epithelium.

The theory of the continuity of germ plasm of Weismann, and the site of origin of the primordial germ cells, as discussed by Arey (2), is not of paramount importance to the question in hand and so will not be discussed in detail. However, Schiller (32), Novak
and Long (26), who quote Fishel, Novak and Gray (25) and Novak (24), agree with Arey (2) that even before the genital ridge has begun to form and in the 3.5 mm. embryo, these primordial germ cells originate in the dorsal endoderm of the hind gut and migrate through the mesenterium to invade the gonad from the hilus. The previous view that they originate from proliferations of the germinal epithelium is now not generally accepted.

The genital ridge shortens and is constricted from the mesonephroi with the formation of the primitive gonadal mesentery.

During this time it is impossible to determine by histologic examination whether the gonad will develop into an ovary or a testis. However, it is now generally accepted that the sex of the offspring is predetermined by the chromosomal variations in the germ cells, or the genes contained within them, according to Novak and Long (26), Schiller (33) and R. Meyer (20). The normal mechanism is given as follows:

(a) Mesenchyme determined in the female direction, invading ovula, differentiation of granulosa.

(b) Mesenchyme determined in the male direction, invading spermatogonia, differentiation of Sertoli cells.

While the gonad is sexually predetermined,
these authors also maintain that it has the potential faculty for developing in either the male or female direction, that is, are primarily bisexual.

Lillie, quoted by Popoff (29), states, "theoretically we would have to assume that the male zygote contains female as well as male factors, but the male zygote may not be capable of such extensive transformation as the female."

This must be kept in mind when studying the further development and differentiation of the gonad into testis and ovary, as we will see that there are many homologous structures formed, those degenerating which are not significant to the particular sex of the foetus.

An interesting example of the bisexuality of the foetus is shown in the development of the free-martin in animals. As defined by Popoff (29), a free-martin is a female which is born a co-twin with a normal male of cattle, goats or pigs, having the internal reproductive organs of the male type and the external reproductive organs of the female type." This is thought to be primarily a female, which later, through the hormonal action of the male co-twin, circulating through both animals in a common circulation, later transforms the embryonic ovary into a testis.
On the other hand, Halban, quoted by Novak and Long (26) believes that the zygote is primarily male, female or hermaphrodite, and that the gonads exercise only a "protective" and not a formative influence in sex differentiation.

Internal Sexual Transformations

The Testis

When the embryo has reached a length of about 13 mm., at about the 10th week of foetal life, the gonads undergo certain changes which indicate that it is to become a testis. The differentiating changes which mark it as an ovary do not occur until about a week later. It is from the beginning of this stage that the relationship to our subject starts, as we will see the direct connection between the two types of development.

From the surface epithelium of the prospective testis, branched and anastomosing strands of cells appear, radially arranged, converging toward the mesorchium. There are two theories as to the exact mode of formation of these cords, one stating that they arise by a direct condensation of a loose inner epithelial mass, diffusely proliferated from the surface epithelium, and another stating that the strands grow directly inward from the surface epithelium.
This point is as yet not definitely settled, but does not have a direct bearing upon our subject.

These testis cords, as they are called, after converging toward the mesorchium, organize the dense primordium of the rete testis, which develops in contact with the mesonephroic tubules, and later begins to unite with them to form the passage way for the sperm.

Beneath the covering epithelium, is a loose layer of tissue, separating it from the testis cords, and termed the tunica albuginea. Connective tissue sheaths form septula, surrounding the future testis tubules, the testis cords, and extend from the tunica albuginea to the mediastinum testis.

The testis cords are composed chiefly of indifferent cells, and a few larger germ cells, which gradually arrange themselves within the connective tissue sheath as a many layered epithelium.

During the seventh month, central cavities begin to appear and extend toward the rete testis to meet lumina which have arisen there also.

Early spermatogonia are formed from the primordial germ cells but later the sustentacular cells of Sertoli are also derived from them. The interstitial cells of Leydig, which are probably hormonal in function, develop from the cells of the mesenchymal stroma. These are large pale cells which lie between
the testis tubules in the unspecialized connective tissue.

At about the tenth week, when the differentiation of the gonad is beginning, the mesonephric tubules are also undergoing certain changes. Degenerative reduction in the number of tubules occurs, until there are but about eight to fifteen left, which project against the adjacent primordium of the rete testis, and at about the third month, begin to unite with them. By the end of the sixth month the lumina of the rete testis and the cranial mesonephric tubules are continuous. The mesonephric tubules are transformed into the efferent ductules of the epididymis, which later coils and becomes known as the lobules of the epididymis. A few tubules of the cranial group comprise the cystic appendix of the epididymis. The caudal group of mesonephric tubules is vestigial but persists as the blindly ending coiled tubules called the paradidymis and aberrant ductules.

The mesonephric duct then undergoes changes which transform it into the duct of the epididymis, ductus deferens and the ejaculatory duct.

In this manner the genital system of the male is developed.

The Ovary

It is not until about a week after the gonad
has shown changes which indicate that it is to become a testis that it first shows the changes which it follows in becoming an ovary.

Those which occur first are very similar to the ones which occur in the formation of the testis. In the hilus there is a compact cellular mass, near the mesovarium which forms the rete ovarii, the homologue of the rete testis. At this stage, about the eleventh week, there is no homologue of the testis cords formed. The rete, according to Arey (2), Novak (24) and Fishel, quoted by Schiller (32) is mesenchymal in origin, and is composed of undifferentiated cells, derived from the tissues of the primitive gonad. Popoff, (29) who reported his case in 1930, stated that there were two views, the one presented above, supported by Allen, Meyer, Felix, Kingsbury and Wilson, and the other one which stated that the rete was of Wolffian origin and supported by Miholkovics, Saint-mont, Winiwarter, Balfour and Wallort. At that time the former view was quite definitely established, and can be accepted now in view of the later support.

At about three months, there is a proliferation of cells giving rise to thick plain cellular cords, which ramify and anastomose and are homologues of the testis cords. There is no formation of a lumen
in them and they do not unite with the rete ovarii, but converge toward it and form the so-called "medullary cords" which then atrophy, although portions of them may persist, according to Long and Gray (25), even till adult life, especially in the region of the rete ovarii. Along with this atrophy of the medullary cords, there is also a degeneration of the young ova in the medulla, leaving only a stroma of fibrous tissue.

At this time there is beginning a second proliferative wave from the germinal or coelomic epithelium, or a modification of gonadal mesenchyme in loco, or both, a point which has not yet been definitely established according to Novak and Gray (25). This forms the cords of Valentin-Pfluger, or Pfluger's "egg tubes" as they are sometimes called. Arey (2) states that in man this is always a homogeneous mass and shows no cords growing in from the epithelium, as in other mammals.

This second proliferative wave, likewise degenerates at about the time of birth and is followed by a third one. It is from these cells that the cortical zone and the definite ovary are formed, with ova and their surrounding Graffian follicles.

Thus we see that the ovary goes through the
same steps as the testis in its development. Later additional changes designate it as an ovary, and as aptly expressed by Novak and Gray (25), "the distinctive female histologic characteristics are developed over the fossil remains of the male apparatus" and "every woman shelters within the medulla of the ovary a potential testis". Novak (24) quotes Witschi, "the medulla of the gonad is the 'determiner' of masculinity in the germ cell, just as the cortex is the 'determiner of femaleness, a view which is supported by a wealth of biologic evidence."

Popoff (29) gives an interesting discussion of the differential sex development in connection with the formation of a free-martin, previously mentioned. To repeat, and complete his quotation of Lillie, "theoretically we would have to assume that the male zygote may not be capable of such extensive transformations as the female, owing to the embryologic fact that the male gonad never forms normally any homologue of the cords of Pfluger in the female, i.e. of the ovarian cortex, whereas the female does form the homologue of the seminiferous tubules before the cords of Pfluger begin to arise." Popoff continues, "An additional reason for the stability of the male gonad is that since the early sex differentiation of the female presumably takes place solely under zygotic control,
while differentiation of the male is controlled by sex hormones, the introduction of female substance into the male system is without effect on the growth of the testis. The primary action of the sex hormones is the inhibition of the growth of germinal epithelium. Thus the introduction of male substance into the female system may overcome zygotic influence and suppress the growth of the cortex."

This makes us wonder then, as it did Novak and Long (26) if a female is a person with a primarily female zygote, one with an ovary, or one with the physical and psychic characteristics which one associates with woman. They place the determination of sex on an endocrine basis.

We must continue and consider the transformations undergone by the mesonephric tubules in the female, corresponding to those in the male. The cranial tubules become the cystic "vesicular appendages", a rudimentary structure homologous to the appendix of the epididymis, and associated with the tubal fringes or broad ligaments. Other of the tubules often unite with the rete ovarii, which may canalize some time before birth, and form the epoophoron which also atrophies but may persist to adult life, along with the mesonephric ducts which persist as the ducts of the
epoophoron. The caudal group forms the paroophoron, which generally disappears entirely by birth, or a few days afterward.

The rete ovarii, homologue of the rete testis is the structure which is definitely related to the formation of the tumor under discussion. As Popoff (29) describes them, they are the epithelial formations seated in the hilum of the ovary and extending into the mesovarium on one side and into the medullary substance on the other side. They present themselves in the form of solid epithelial buds and sometimes in the form of ramifying canals lined with cuboidal, or more seldom, with cylindric epithelium, are furnished with a delicate basement membrane and sometimes have smooth muscle around them.

While it is a vestigial structure it is distinctly male in nature and cells in this region retain male capacities and may give rise to tumors with distinctly masculinizing tendencies, according to Meyer as quoted by Novak and Gray (25). The degeneration has progressed to such an extent that all of the primary germ cells of this region have degenerated, so there is no spermatogenesis according to Schiller (32).
THE ADRENAL

A short discussion of the embryology of the adrenal will be given owing to the proximity of its anlage to the primitive gonad, and also the similarity of the clinical syndrome produced by hyperfunction of its cortex, to that of the tumor under discussion.

The medulla is composed of chromaffin cells which descend from the coeliac plexus of the sympathetic system. About the seventh week masses of these cells begin to invade the median side of the cortical primordium and thus gain their central position.

The cortex, according to Arey (2) is derived, at about the fifth week, from ingrowing buds of peritoneal mesothelium, on each side near the dorsal mesentery and between it and the urogenital fold.

According to Saphis and Parker (31) it is derived from the coelomic epithelium of the urogenital fold, which later separates into cortex and gonad. At any rate they originate very close to each other, which explains the presence of aberrant adrenal cortical tissue anywhere along the original preformed urogenital anlage.

It then divides into three characteristic histologic layers which may not be complete till birth or afterwards.
ETIOLOGY

When we speak of the etiology of neoplastic growths in general, it is quite a controversial subject and one which is rather difficult to prove.

However, in this tumor the etiology is quite well accepted, as far as the structures from which it originates is concerned, but we are still at a loss to explain the exciting factor or factors as this is probably in the still unfathomed realm of endocrinology. Speculations, which seem quite reasonable, can be made, but cannot be proven.

When Pick first described his "adenoma testiculare tubulare", in 1905, which is now classified as a typical type of arrhenoblastoma by Meyer (20), he thought that it was from an ovotestis, in which the testicular portion had undergone neoplastic growth. Meyer, however, doubts this and is supported by most of the present day authors in presenting his viewpoint, Geist (12), Spielman (33), Behrend and Levine (4), Novak and Gray (25), Taylor, Wolfermann and Krock (34), Novak (24) and Popoff (29).

They do not believe that this tumor originates in an ovotestis because none of the patients in which it has occurred have shown any early signs of pseudohermaphroditism as are almost always found when
there is an ovotestis present. Furthermore, this
tumor never occurs in children but always after puber-
ty and generally before the menopause. However, there
is probably a close similarity to the hormone distur­
ances accompanying the two conditions.

Meyer's (20) theory, which is quite generally
accepted, is that this tumor arises from a prolifera­
tion of the cells of the medullary cords of the first
proliferation which remain quiescent in the region of
the rete testis and probably from the rete testis it­
self.

As we have seen in the embryology of the
ovary, it passes through the same stages of develop­
ment as the testis does, but the medullary cords and
the rete ovarii, which remain active in the male go­
nad and form the seminiferous tubules and rete testis,
undergo atrophy and remain as vestigial structures in
the hilum of the ovary. They do, however, retain the
potentialities of further development which is brought
about by a yet undetermined stimulus, probably hormonal.

Authorities on sex reversal, according to Pop­
off (29), have arrived at three rather definite conclu­
sions. (1) that the testes are markedly stable while
the ovaries possess a certain instability, (2) that the
right ovary exhibits testicular transformations more
often than the left one, and (3) that in sex reversal or hermaphroditism in which an ovotestis is present, the spermatogenic tissue occurs most commonly median to the ovarian position.

In the discussion of free-martins by Popoff (29), he believes that the gonad is primarily female, which is changed into a testis by the hormonal action of the male co-twin through the common foetal circulation.

It is quite evident that there is a disturbance in hormone action which will be further discussed later, and this probably has a definite place, not only in the production of the clinical syndrome accompanying the tumor, but also in initiating the changes in growth of these foetal remnants, the medullary cords and the rete ovarii.

This mode of origin cannot be proven, nor can the theory of Pick be disproven, but the line of differentiation cannot be sharply drawn because as Novak and Gray (25) point out, "the distinctly female characteristics are developed over the fossil remains of a male apparatus." In this case, these cells are probably not so "fossil", as we might be led to think.

In an article by Novak and Long (26), we find
the following statement, "every woman shelters within the medulla of the ovary a potential testis."

Another viewpoint which has been presented, but is not as generally accepted, is that these tumors are teratomatous in nature, basing this on the fact that tissue has been found in some of them which normally is not found in the ovary or testis, as was discussed under the classification.

The etiology of teratomas is not yet definitely decided but Mueller (22) gives the following three theories; (1) the earliest theory was that they were "mixed tumors", arising from foetal rests of already differentiated cells in the ovary. (2) the theory of Marchand-Bonnet that a blastomere became displaced in early foetal life and later developed, having the potentialities for all three germ layers. (3) the parthenogenetic theory of Wilms holds that a primitive sex cell, perhaps a cell from a medullary cord or Pfluger's cord is retained and begins to divide without being fertilized.

If we consider the first theory, we see that there is also no definite line of demarcation as the medullary cords and rete testis can be considered as "foetal rests" of already differentiated cells.

Likewise in the parthenogenetic theory of
Wilms, the primitive sex cell would be found in the medullary cords, the supposed point of origin according to Meyer.

In considering the blastomere theory of Marchand-Bonnet, if this were the mode of development, we would probably find more consistently, evidence of other histologic structures.
PATHOLOGICAL PHYSIOLOGY

The pathological physiology in this syndrome is almost entirely in the realm of hormones and while it is interesting to speculate and theorize, it is rather difficult to prove all of our points, as our knowledge of this part of medicine is still incomplete, not only for the pathological, but also the normal physiology as well. We do, however, have some quite well proven points that help us.

Novak, in discussing a paper presented by R. Meyer (20), quotes the dictum of Virchow, laid down many years ago, "Propter ovarium mulier est quod est", (Because of her ovaries, woman is what she is). This was later modified by Blair Bell by saying "Propter secretiones tolas mulier est quod est", (Because of her internal secretions woman is what she is). While this later statement is quite true we cannot disregard the facts of sex determination according to the genetic theory of chromosomes and genes, and the fact that the tissues are primarily determined in a female direction.

According to Wolf (35), the primary determiners of the secondary sexual characteristics are the gonads, ovary and testis, with the secondary influence from the pituitary and adrenals.
Crew (9) states that the ovarian and testicular hormones are "sex specific", and act only upon those structures with which each is normally associated, that is, genetically female tissues such as the uterus, vagina, mammae etc., respond preferentially to ovarian hormones, and genetically male tissues such as the prostate, seminal vesicles, the penis and its homologue the clitoris, respond preferentially to the testicular hormone. He believes that there is an "agonadic" full grown type of individual, which resembles more the female sex characterization than the male. Following removal of the gonads of either type, there is a tendency to swing toward the agonadic type, which might be interpreted by some as a swing towards the opposite sex, while it actually is not.

However, if gonadectomy is followed by implantation of the gonad of the opposite sex, there is a definite development of the secondary characteristics of that sex. This has been shown experimentally many times as by Appel (9), in which testis grafts were made in hens, in some cases of which there was a distinct male type of plumage developed with increase in size of spurs, comb and wattles. This was also noted in a case reported by Crew and referred to by Meyer (20) in which a hen, the mother of many chickens, began to assume the appearance and behavior of a rooster and became the father of a number of chickens.
Upon examination it was found that the left ovary had been completely destroyed by tuberculosis and that the undifferentiated gonad of the opposite side had then developed as a testis.

Thus we see that the testis has a direct stimulating effect upon the secondary sex characteristics of the male. In addition to this we have a more or less specific effect, produced indirectly by the pituitary and adrenal glands.

From the pituitary gland there are two main hormones, or fractions, or they may be the same hormone which produces different effects at different times in the menstrual cycle. These are Prolan A which causes maturation of the Graffian follicle, but this does not occur until the follicles are ready to ripen, after puberty. The other is Prolan B which causes luteinization of the ruptured follicle. The follicle and corpus luteum, especially the former, elaborate oestrin, which is important in the maintenance of sex characteristics, along with other effects.

In addition to this there is supposedly a reciprocity between an ovarian stimulating hormone of the pituitary and a pituitary stimulating hormone of the ovary, a disturbance of which would cause an upset in maintenance of the characteristics.
The pituitary hormone is however, not sex specific and acts as a stimulator to growth of the testes as well as the ovary, and an increase in size of the testes, prostate, seminal vesicles and Cowper's glands results from its administration to males, according to Wolf (35).

The role of the adrenals in the determination of secondary sex characteristics is not as yet clearly defined. The fact that they and the gonads have a common origin from the urogenital ridge makes it quite probable that it does have a quite definite role, according to Novak and Gray (25), but they do not believe that it is necessary to assume that there is any inclusion of adrenal tissue within the ovary to explain their action.

Saphis and Parker (31) state that the function of a sex hormone from the adrenal is clear and unique, judging from the clinical evidence at hand. They claim that it does not stimulate the sex characteristics of the same sex, but those of the opposite sex. In women an excess gives a male hair distribution, deep voice, amenorrhea, atrophic breasts and genitalia, with elongated penis like clitoris, all of which are similar to those found in the clinical picture accompanying arrhenoblastoma. In males are seen a female type of
obesity, breast hypertrophy with milk secretion, atrophy of the testes and absence of libido.

In the case presented by Saphis and Parker (31), there was a marked increase in the estrogenic content of the blood and urine, determined by the Frank-Goldberger test. They classified their case as "adrenal virilism", produced by cortical tissue in the ovary. They believe that the cells of the adrenal cortex might retain the faculty of producing gonadal hormones under pathological conditions, due to their close embryological origin to the gonads. We wonder, however, if closer examination might not bring out the fact that this was an arrhenoblastoma and not adrenal cortical tissue which was found in the ovary.

In a paper presented by Wolfe and Kaminester (36), they described a number of cases of females which exhibited virilism or pseudohermaphroditism in which tests were done to determine an abnormal amount of "male hormone", in the urine. This was done by injecting the urine into castrated rats and then measuring and weighing the prostates, and also into capons and measuring the comb growth. Many of their cases showed an abnormal amount of this male hormone, but they were at a loss to explain its occurrence, whether it was the cause of the virilism, or merely one of its manifestations.
The secretion of the adrenal is also influenced by a so-called "adrenotropic", hormone from the anterior pituitary, an insufficiency of which results in an atrophy of the adrenal cortex and an excess of which causes an hypertrophy of the cortex with an increase in the amount of adrenalin content of the blood, according to Wolf (35). Cushing (10) supports this and further states that nothing comparable to this occurs in the reverse direction.

In connection with the adrenals we must also consider the fact that its hormone, adrenalin, along with the thyroxin from the thyroid are classed as sympathetic stimulators and stimulators of the ovary, with the ovary as their inhibitor, according to Robinson (30). Sympathetic stimulation promotes luteinization and inhibits follicle formation, thus acting the same as Prolan B, but antagonistic to Prolan A. With this there would be a persistence of the corpus luteum and amenorrhea.

Most authors, Geist (12), Spielman (33), Novak and Gray (25), McLester (19), Novak and Long (26), Taylor, Wolferman and Krock (34), Meyer (20), Maxwell (23), Crew (9), Appel (1), Chynoweth (7) and Wolfe and Kaminester (36), agree that masculuation can come directly from the action of the male sex hormones, probably secreted by the interstitial cells of Leydig in
the normal testis and elaborated by the fusiform type of cell found in the arrhenoblastoma.

This cell type is, in this stage, undifferentiated and possesses unexhausted masculine potentialities and probably the ability to secrete the male sex hormone. According to McLester (19), the Leydig cells in the testis are thought to be holocrine in nature, that is, one which liberates its hormone upon disintegration and the fact that the mitotic figures are more prominent in the fusiform type cell, he points out as only such as was necessary to provide for the replacement of the functioning cells.

It is quite evident that this cell type is the one which liberates the hormone, as virilism very seldom accompanies the typical type while it practically always accompanies the atypical type. Just why this should be, since the typical type most closely resembles the normal testis, is still a question. Taylor, Wolfermann and Krock (34), believe that the tubular formation is merely another form of expression of tumor function and the underlying tendency toward masculinity. Schiller, quoted by Maxwell (23), attributes the absence of hormonal effects of the typical type to the fact that this form does not resemble the canicular
substance of the testis but rather the rete testicu-
lar, which possesses no incretory function.

With this excess of male hormone there must also be an insufficiency of female hormone which is shown by the defeminization and also by the atrophy and lack of function of the opposite uninvolved ovary. In a case of hirsutes, reported by Peters (27), the simple administration of ovarian follicular hormone caused a falling out of the hair. This lack may be caused by neutralization by the male hormone, because after removal of the tumor, the ovary resumes its normal function, thus indicating that it is not primarily due to an insufficiency of ovarian function or of Prolan from the pituitary. The resumption of normal sex characteristics after removal of the tumor also indicates that there is no disturbance in adrenal cortical hormone output. However, instead of a direct neutralization of the ovarian hormone it is also likely that the male hormone reacts either directly upon the anterior pituitary or with its hormone to make them inactive as far as ovarian changes are concerned, as was stated by Baldwin and Gafford (3).

The male hormone may also act either directly upon the adrenal or indirectly through the pituitary by causing an excess of adrenotropic hormone to be produced, thus assisting in promoting the masculinizing process.
Dr. J. E. Davis, in discussing the article presented by Novak and Gray (25), raises the question, "does the estrogenic substance, when excessive and combined with hereditary factors, dispose to malignancy in Mueller's tracts and the mammary glands or is it tumor function that causes the estrogenic excess?" Likewise, Wolfe and Kaminester (36), in reporting their cases of virilism and pseudohermaphroditism, with an excess of male hormone in the urine, do not know whether this is the cause of the virilism or only one of its manifestations.

Thus in discussing the etiology of the tumor, we are at a loss to explain whether or not an excess of male hormone is a definite etiological factor, present before the tumor made its appearance, or whether it is merely one of its manifestations. Likewise it may be due to a primary lack of female hormone which permits some basic male principle found in the remnants of the primarily bisexual anlagen to develop and thus produce the tumor. Also a disturbance in pituitary function or an excess or adrenal cortex hormone may be definite etiological factors as well as manifestations accompanying the clinical syndrome.
BIBLIOGRAPHY


