Steroid Hormone-Producing Tumors in Man

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Introduction

Tumors derived from the steroid hormone-producing cells of the adrenal, ovary, and testes are uncommon but quite interesting neoplasia. Patients with such tumors usually come to the attention of a physician because of clinical symptoms caused by the biosynthesis and release of biologically potent steroid hormones by the tumor.

Although tumors of steroidogenic tissue cause specific clinical syndromes the site of the tumor cannot be localized by the syndrome. Tumors anatomically located in the adrenal (1-9) or testes (10) may cause clinical Cushing's syndrome. Likewise virilization or feminization may be caused by adrenal (11,12), testicular (13-19) or ovarian (20-36) tumors. A proportion of tumors localized at any site may fail to produce any clinical endocrine syndrome (37). This occurs in some cases because these tumors are deficient in one or more enzymes required for the biosynthesis of potent steroid hormones. Nonfunctioning adrenal tumors are presumably tumors of this sort. In other cases the tumor may synthesize potent steroid hormones, but the effect is not apparent because the biological function is already maximally expressed. An example of this type of tumor is an androgen-synthesizing tumor in an adult man.

A cardinal characteristic of steroid hormone-producing tumors is autonomous steroidogenesis. These tumors may produce massive quantities of steroid hormones without pituitary trophic hormone stimulation (9,19,27-30). Although tumor steroidogenesis is largely, or in some cases entirely, constitutive, some tumors may respond to trophic hormone stimulation, either to the appropriate trophic hormone (9,19,23,25,34) or to other trophic hormones (11,23). Tumors located in the adrenal have been shown to respond to gonadotrophin stimulation (11) while tumors of the gonad may be responsive to ACTH (23,38).

No precise histological definition of malignancy exists for tumors of steroidogenic tissue (2-8,16,20,22). No single characteristic of the tumor such as size or location completely defines the malignant potential of the tumor. Patient characteristics are useful in assigning a general prognosis for certain tumors but are too poorly defined to be very useful in establishing an individual prognosis. Differentiation of benign from malignant tumors is probably only known with certainty in retrospect.

In this review steroidogenic tumors will be considered from two perspectives: the gland of origin and from the orientation of the clinical syndrome produced by the tumor. Placental tumors and adrenal tumors causing hyperaldosteronism will not be discussed. To understand the wide range of clinical syndromes produced by the tumors, it is useful to review the basic steroid biosynthetic pathways as well as some features of steroidogenic cell morphology and histology.

Table I. Characterization of Steroid Hormone-Producing Tumors by Gland of Origin

Adrenal Cortex

-Adrenal Cortical Adenoma
-Adrenal Cortical Carcinoma
-Aldosterone-Producing Adenoma
-Very Rare Tumors: Capsular Granulosa Cell Tumor
Leydig Cell Containing Ganglioneuroma

Ovary

-Sertoli-Leydig-Cell tumors: Arrhenoblastoma
Hilus-Cell Tumor
-Feminizing Mesenchymomas: Granulosa-Cell Tumor
Theca-Cell Tumor
Granulosa/Theca-Cell Tumor
-Lipoid-Cell Tumors
-Adrenal Rest Tumors?
-Stomal Luteoma
-Hamartomas: Hyperthecosis
Luteoma of Pregnancy

Testes

-Leydig-Cell Adenoma
-Leydig-Cell Carcinoma
-Sertoli-Cell Tumor
-Adrenal Rest Tumor

Table II. Characterization of Steroid Hormone-Producing Tumors by Functional Endocrine Syndromes

Cushing's Syndrome

Adrenal Cortical Adenoma/Carcinoma
Testicular Adrenal Rest Tumor

Virilization

Adrenal Cortical Adenoma/Carcinoma
Most Ovarian Tumors

Feminization

Adrenal Cortical Adenoma/Carcinoma
Feminizing Mesenchymomas
Leydig Cell Tumors
Sertoli Cell Tumors

No Recognizable Endocrine Syndrome

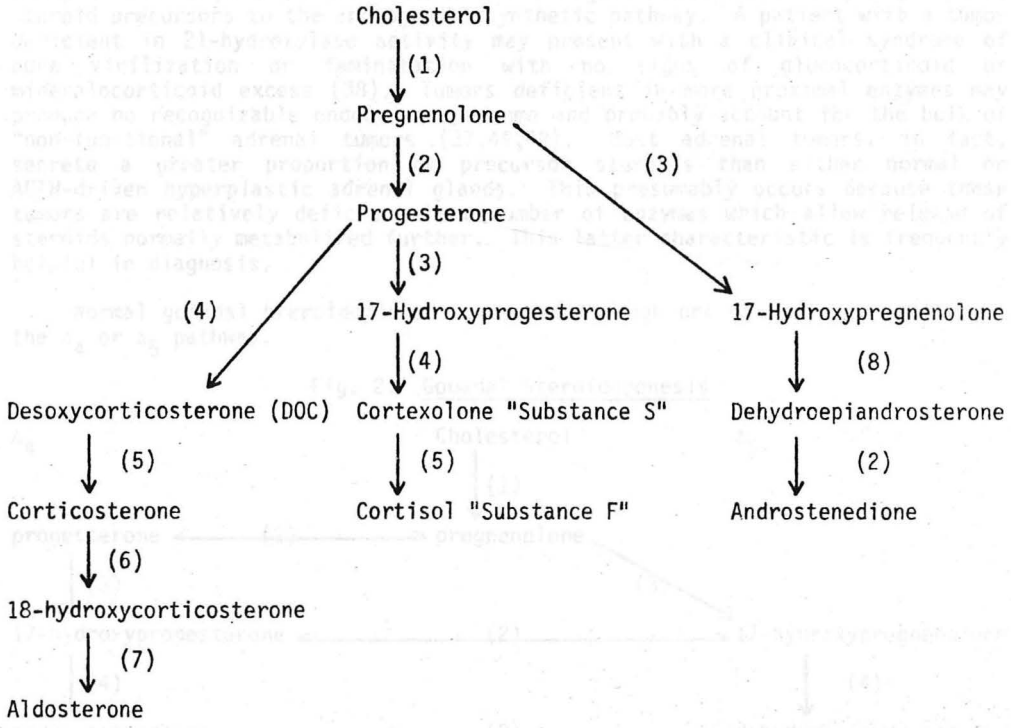
Adrenal Cortical Adenoma/Carcinoma
Most Leydig-Cell and Sertoli-Cell Tumors in Men
Some Feminizing Ovarian Tumors in Women

Steroid Hormone Biosynthesis in the Human

The adrenal synthesizes all classes of biologically active steroid hormones. Its major role is maintenance of adequate glucocorticoid and mineralocorticoid levels. In postmenopausal women the adrenal also supplies the bulk of substrate for estrogen biosynthesis (39). Primary control of adrenal glucocorticoid, and probably adrenal androgen synthesis, is mediated through

pituitary secretion of ACTH. Mineralocorticoid biosynthesis is stimulated by ACTH but is primarily controlled through the renin-angiotension system (40).

Fig. 1. Adrenal Steroid Biosynthesis



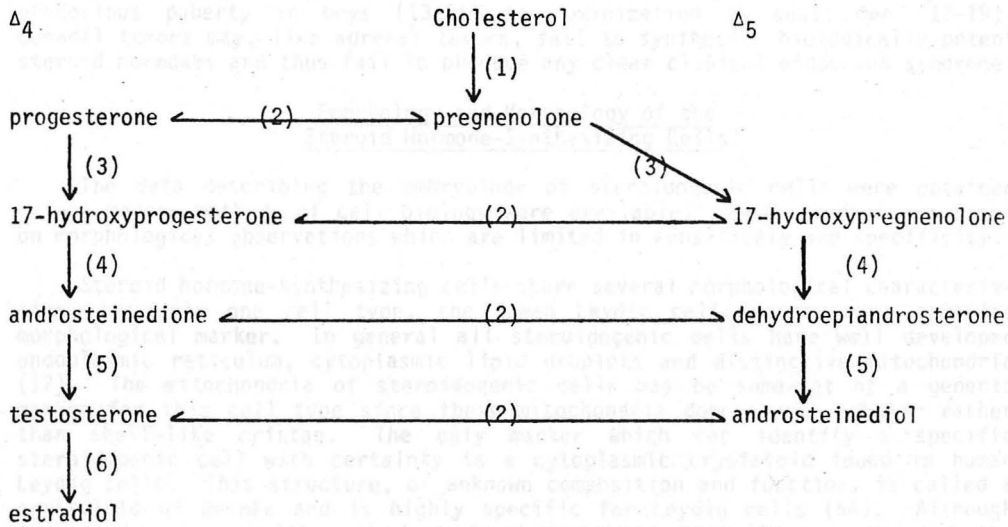
1 Cholesterol Side Chain Cleavage Enzyme
2 3-β-Hydroxysteroid Dehydrogenase/Δ_5, Δ_4 Isomerase
3 17α-Hydroxylase
4 21-Hydroxylase
5 11 β-hydoxylase
6 18-Hydroxylase
7 18ol-Dehydrogenase
8 17,20-Desmolase

Tumors anatomically located within the adrenal may constitutively synthesize either excessive quantities of the steroid hormones normally synthesized by the adrenal or steroid hormones which are not generally thought to be major adrenal products. In the simplest case, synthesis of steroid hormones by the tumor results in dexamethasone-nonsuppressible Cushing's syndrome. Often however, these tumors are relatively or absolutely deficient in one or more enzymes of the steroid biosynthetic pathway and produce unusual clinical syndromes, many of which are remininsent of the congenital adrenal hyperplasia

syndromes. A patient with a tumor deficient in 11 β-hydroxylase activity may present with hypertension and signs of androgen or estrogen excess, but no specific stigmata of Cushing's Syndrome, such as metabolic bone disease, muscle weakness, diabetes mellitus or centrifugal fat distribution (3). This occurs because the tumor cannot synthesize cortisol or other potent glucocorticoids but instead makes a potent mineralocorticoid desoxycorticosterone (DOC) and diverts steroid precursors to the androgen biosynthetic pathway. A patient with a tumor deficient in 21-hydroxylase activity may present with a clinical syndrome of pure virilization or feminization with no signs of glucocorticoid or mineralocorticoid excess (38). Tumors deficient in more proximal enzymes may produce no recognizable endocrine syndrome and probably account for the bulk of "non-functional" adrenal tumors (37,41,42). Most adrenal tumors, in fact, secrete a greater proportion of precursor steroids than either normal or ACTH-driven hyperplastic adrenal glands. This presumably occurs because these tumors are relatively deficient in a number of enzymes which allow release of steroids normally metabolized further. This latter characteristic is frequently helpful in diagnosis.

Normal gonadal steroidogenesis procedes through one of two major pathways, the Δ_4 or Δ_5 pathway.

Fig. 2. Gonadal Steroidogenesis



1 Cholesterol Side Chain Cleavage Enzyme
2 3-β-Hydroxysteroid Dehydrogenase/$\Delta_5 \rightarrow \Delta_4$ Isomerase
3 17α-Hydroxylase
4 17,20 Desmolase
5 17 β-Hydroxysteroid Dehydrogenase
6 Aromatase

In the female gonad, steroidogenesis is believed to be divided between different cell types within the ovary (43-46). The luteal cells are believed to synthesize only progesterone; theca cells synthesize androgens while granulosa cells utilize androgen substrate supplied by the theca cells for synthesis of

ovarian estrogen. Under certain in vitro conditions any of the cells of the ovary may be capable of estrogen synthesis (47,48). The primary control of ovarian progesterone and androgen synthesis is mediated through pituitary Luteinizing hormone (LH). Aromatization of androgens appears to be controlled by Follicle stimulating hormone (FSH) (49,50).

Steroidogenesis in the testes occurs mainly within the Leydig cell. Leydig cells possess the requisite enzymes for synthesis of androgens and estrogens from cholesterol (51). Leydig cells stimulated by LH synthesize all testicular testosterone and are responsible either directly or indirectly for the synthesis of testicular estradiol. Both Leydig cells and Sertoli cells express aromatase activity. Leydig cell aromatase activity is quantitatively small and is not clearly under trophic hormone control (52). Although Sertoli cells do not express the enzymes required for androgen synthesis, these cells are believed to contain the bulk of testicular aromatase activity. Aromatase activity is at least partially under the control of FSH (53).

Tumors of the male or female gonad function autonomously as do the adrenal tumors. These tumors may synthesize excessive quantities of androgen or estrogen, which in turn usually suppress pituitary gonadotrophin release. Steroidogenesis in gonadal tumors is frequently aberrant. Leydig cell tumors for example, may produce a variety of clinical syndromes, each syndrome dependent on the enzymes expressed by the tumor. These syndromes may range from precocious puberty in boys (13,16) to feminization in adult men (17-19). Gonadal tumors may, like adrenal tumors, fail to synthesize biologically potent steroid hormones and thus fail to produce any clear clinical endocrine syndrome.

Embryology and Morphology of the Steroid Hormone-Synthesizing Cells.

The data describing the embryology of steroidogenic cells were obtained before modern methods of cell biology were available. These studies are based on morphological observations which are limited in sensitively and specificity.

Steroid hormone-synthesizing cells share several morphological characteristics, but only one cell type, the human Leydig cell, possesses a specific morphological marker. In general all steroidogenic cells have well developed endoplasmic reticulum, cytoplasmic lipid droplets and distinctive mitochondria (17). The mitochondria of steroidogenic cells may be somewhat of a generic marker for this cell type since these mitochondria demonstrate tubular rather than shelf-like cristae. The only marker which can identify a specific steroidogenic cell with certainty is a cytoplasmic crystaloid found in human Leydig cells. This structure, of unknown composition and function, is called a crystaloid of Reinke and is highly specific for Leydig cells (54). Although this marker is specific, it is only detected in a small percentage of the testicular Leydig cells. No unique marker exists for ovarian or adrenal cells and identification is dependent on architectural features of the gland.

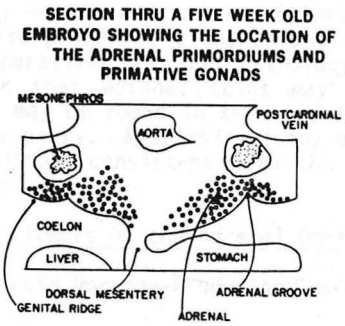


Fig. 3. Section through a five week human embryo

Embryologically, all cells destined to synthesize steroid hormones share a common mesenchymal origin. By the fourth or fifth week of human fetal development cells destined to become adrenal or gonadal steroidogenic cells are all located on the gonadal ridge (55). By the fifth week of human development the adrenal groove begins to separate the adrenal primordium from the primitive gonad. The adrenal primordium remains associated with the mesonephros while the primitive gonad moves caudally. Adrenal gland differentiation diverges from the gonad at this point and soon becomes recognizable by histological criteria as adrenal. Gonadal cells remain undifferentiated until the later formation of the gonad. No data are available which define the gestational age at which specific enzyme activities are expressed in human fetuses. It is also not known at which gestational age steroidogenic cells first express receptors for pituitary trophic hormones. In the rabbit, both gonadotrophin binding and 3 β-hydrosteroid dehydrogenase/$\Delta^5,\rightarrow\Delta^4$ isomerase activity increase shortly before formation of the phenotypically male gonad (56,57). It is not known if these changes are occurring in undifferentiated "generic" steroidogenic stem cells or cells already committed to gonadal differentiation.

Some clinical observations may be explained by the limited data available concerning the embryology of steroidogenic cells: 1) clusters of cells morphologically similar to normal adrenal cortical tissue may be found along the line of gonadal descent or in the gonads (55); 2) some patients, most notably those with congenital adrenal hyperplasia syndromes, may develop ACTH-responsive testicular tumors which regress with dexamethasone treatment (86); 3) a patient has been described with Cushing's syndrome and a primary tumor of the testes (10); 4) adrenal tumors have been described which respond to gonadotrophin stimulatation (103,104); 5) typical Leydig cells with crystaloids of Reinke have been detected in the adrenal (106,109); and 6) a number of ovarian tumors may contain cells with typical crystaloids of Reinke (20). Such observations may be

explained by either of two hypotheses. The first and most commonly invoked hypothesis states that cells committed to expression of either adrenal or gonadal function migrate aberrantly. A second and equally plausible hypothesis states that undifferentiated cells from the gonadal ridge are present in normal adrenal and gonad and may manifest the characteristics of any steroidogenic cell when neoplastic. Definite proof for either hypothesis is not presently available and both may be operative in human pathology. Regardless of the exact mechanisms, it is clear that adrenal cells may be found in the gonad and phenotypic gonadal cells may be found in the adrenal. Moreover, typical Leydig cells may be found in the ovary. Neoplasia of any of the cells would be expected to cause clinical symptoms consistent with the cell type but inappropriate for the site of the tumor.

Tumors of the Adrenal Cortex

Table III. Steroid Hormone-Producing Tumors of the Adrenal

Adrenal Cortical Adenoma	
Adrenal Cortical Carcinoma	
Aldosterone-producing adenoma	
Very rare tumors:	Capsular Granulosa Cell Tumor
	Leydig Cell Containing
	Ganglioneuroma

Adrenal cortical neoplasia are rare. The estimated incidence of adrenal carcinoma is approximately two cases per million patients per year (8). About an equal number of patients will present with benign adrenal adenoma each year. As with any disease of such a low incidence, information must be pooled over many years and frequently from many medical centers. Even so, adrenal neoplasia are the most frequent and most studied neoplasia of steroidogenic tissue. From this larger base, generalizations can be made which may be useful in dealing with the more rare testicular or ovarian tumors. One form of benign adrenal adenoma, the mineralocorticoid-synthesizing adenoma, will not be included in this discussion.

Adrenal cortical tumors may produce any endocrine syndrome or no endocrine syndrome at all. The most common clinical presentation of an adrenal cortical tumor is that of Cushing's syndrome either with or without associated virilism or feminization. More rarely these tumors will cause syndromes of pure virilization or feminization.

Differentiation of Benign from Malignant Adrenocortical Neoplasia

The differentiation of adrenal adenoma from carcinoma is critical if any prognosis is to be made. A number of gross morphological characteristics, histologic characteristics, and biochemical tests have been used for this purpose. No single test or finding except for obvious distant metastasis can absolutely resolve this issue. Several findings, however, may be useful in defining a prognosis.

The large size of malignant adrenal tumors has been noted by a number of authors. In 1961 Soffer and coworkers reviewed tumors causing Cushing's syndrome (58). They found that benign adenomas ranged in weight from 6 to 24 g., while carcinomas weighed from 30 to 910 g. Gabrilove and coworkers specifically

reviewed feminizing adrenal tumors and did not find such a clear separation on the basis of size (12). Only seven of the 52 patients which they reviewed had an adenoma and these tumors ranged from olive sized to grapefruit sized. The largest, grapefruit sized, tumor could not be called an adenoma with certainty since the patient died of other causes soon after surgery. The largest tumor which could unequivocally be called an adenoma was 200 g. The size of carcinomas is not clearly defined but most often was described as large or enormous. In no case where a tumor weight is recorded was any carcinoma found to weigh less than 200 g. Schteingart and coworkers reviewed twelve patients seen at the University of Michigan medical center (5). All of these patients presented with Cushing's syndrome. In this series five of the twelve patients proved to have an adenoma with weights ranging form 16 to 27 g. The remaining seven patients had carcinomas which weighed from 100 to 2390 g. Lewinsky and coworkers reviewed a very selected population of patients with "non-functional" adrenal tumors and found all to be carcinomas (37). The carcinomas in their series weighed 700-4500 g. Tang and Gray reviewed the features of 39 adrenal tumors seen at the Cornell medical center (7). These authors worked from histological records and found that tumors classified originally as adenomas ranged from 0.7 g. to 2460 g. These authors made two other observations of interest. Twelve of the twenty-three patients with adenoma had apparently "nonfunctioning" tumors discovered incidently at autopsy. They also list four patients which had demonstrated prolonged survival after operation for a tumor which was histologically called a carcinoma. These patients tumors were all small, ranging in weight from 0.7 g. to 4 g., with a mean weight of 2.7 g. The patients who died as a result of their carcinoma had tumors ranging in weight from 96 g. to 2460 g. Most recently Bertagna and Orth reviewed 58 patients who presented to the Vanderbilt medical center between 1951 and 1978 (9). These authors report adenomas ranging in weight from 12.5 g. to 126 g. with mean and medium weights of 36 g. and 20 g., respectively. Only two adenomas weighed more than 70 g. Carcinomas ranged in weight from 39 g. to 1800 g. with a mean weight of 508 g. and a medium weight of 240 g. The findings of these studies are summarized in Table IV below.

Table IV. Differentiation of Adrenal Tumors by Size

Authors	Tumor weight (g), range, mean, medium	
	Adenoma	Carcinoma
Soffer L.J. et al.	6-20, --, --	30-910, --, --
Gabrilove, J.L. et al.	olive-grapefruit, --, --	200-2650, --, --
(4 false adenomas)		175-244, --, --
Schteingart, D.E. et al.	16-27, --, --	100-2390, --, --
Lewinsky, B.S. et al.	--, --, --	700-4500, --, --
Tang, C.K. and Gray, G.F.	7-40, --, --	0.7-2460, --, --
incidental autopsy finding	12-35, --, --	
surgically cured Ca.	0.7-4, --, --	
Ca resulting in death		96-2460, --, --
Bertagna, C. Orth, D.N.	12.5-126, 36, 20	39-1300, 508, 240

A number of histologic features of adrenal tumors have proven to be useful but not infallible indicators of malignancy. These features include: increased mitotic activity, nuclear or cellular pleomorphism, gross or microscopic hemorrhage and necrosis, and capsular or blood vessel invasion. The frequency of these findings in adenomas and carcinomas is shown in Table V. Probably the best way to check the adequacy of these histologic tests for malignancy is to analyze the patients who were diagnosed as adenoma and subsequently developed metastasis or those diagnosed as carcinoma who subsequently survived long term. Tang and Gray described three patients who were diagnosed as having carcinoma on histologic grounds but who were subsequently found to survive for many years (7). These cured carcinomas (adenomas?) differed from the ultimately fatal carcinomas in two respects. The tumors were smaller, 0.7 g. to 4 g. for carcinomas cured by surgical excision, versus 96 g. to 2460 g. for carcinomas which ultimately proved fatal. The carcinomas cured surgically also showed no evidence of capsular invasion on pathological study. The tumors from three patients in Gabrilove and co-workers' series were originally diagnosed as adenomas but subsequently metastasized (12). The authors state that these tumors showed more pleomorphism and mitotic figures than other adenomas. One patient reviewed in their series, a five year old boy with precocious puberty and a 26 g. tumor, was originally diagnosed as having a carcinoma but went on to survive 10 years without evidence of recurrence. Bertagna and Orth also report cases of misdiagnosis (9). One patient underwent resection of a histologically benign, 39 g. adenoma with no evidence of capsular invasion. The patient later presented with metastatic disease. Three patients presented with large tumors diagnosed as carcinoma yet survived for long periods free of disease. One patient presented with Cushings syndrome, was found to have a 3.4 cm. tumor, and was still free of disease 16.7 years later. A second patient presented with virilism, was found to have a 340 g. tumor, and is free of disease 18 yrs later. A third patient presented with a mass lesion but no endocrine syndrome, was found to have an 1802 g. tumor, and is free of disease after 28 yrs. One other patient presented with Cushings syndrome, was found to have a 384 g. tumor which was resected but developed metastasis 11.7 years later.

The biochemical test most often cited as a good biochemical marker of carcinoma is the urinary 17-ketosteroid determination. This test is generally available and in some series has given good discrimination between adenoma and carcinoma. The highest levels of 17-ketosteroids are aways encountered in patients with carcinoma. Low to moderately elevated 17-ketosteroid values may be found in the urine of patients with either adenoma or carcinoma. Hence, the 17-ketosteroid determination is only useful when very elevated and in this circumstance always indicates the presence of a carcinoma. The reported values for 17-ketosteroid determinations in several series are listed in Table VI.

Table V. Histologic Findings in Adrenal Neoplasia

Series		Calcification, Hemorrhage, Necrosis (Gross)/(Microscopic)	Pleomorphism (Nuclear)/(Cell)	Mitotic Figures	Capsular Invasion	Giant Cells
Lipsett et al.	adenoma	_____	(+)/(+)	(+)	(-)	_____
	carcinoma	_____	(+)/(+)	(+)	(+)	_____
Tang and Gray	adenoma	$(-)/_{1/23}$, $(-)/_{1/23}$, $(-)/_{1/23}$	3/23	4/23	(-)	3/23
	carcinoma	$(-)/_{4/13}$, $7/13/_{12/13}$, $4/13/_{11/13}$	11/13	12/13	6/13	(+)
Gabrilove et al.	adenoma	_____	(+)	few	(-)	(+)
	carcinoma	_____	(+)	many	3/7	(+)
Bertagna and Orth.	adenoma	$(-)/_{(-)}$, $(-)/_{5/26}$, $(-)/_{5/26}$	?	?	(-)	2/26
	carcinoma	?, ?, ?	?	?	?	?

Table VI. 17-Ketosteroid (KS) Excretion in Patients with Adrenal Neoplasia

Series		17-ketosteroid (Range)	(Mean ± SEM)	Comment
Lipsett et al. (1963)	Adenoma	(3-15)	(---------)	
	Carcinoma	(25-800)	(---------)	
Gabrilove et al. (1965)	Adenoma	(4-61.1)	(15.56±6.87)	only a single patient >24mg/24hr
	Carcinoma low KS	(<20)	(10.13±1.25)	9/25 patients
	moderate KS	(20-50)	(33.25±2.11)	10/25 patients
	high KS	(>50)	(297±59.45)	8/25 patients
	Carcinoma misdiagnosed as adenoma	(12.4,30,35.6)		
	Benign carcinoma	(5.1)		
Schteingart et al. (1968)	Adenoma	(6.5-20.2)		
	Carcinoma	(19.5-213)		
Bertagna and Orth (1981)	Adenoma	(2-71)	(15.1±2.3)	
	Carcinoma	(8-354)	(56.2±13.9)	

One other biochemical test may have some use in differentiating adenoma from carcinoma. A two-fold increase in urinary 17-hydroxysteroids in response to an eight hour infusion of 50 U of ACTH is a good indicator of a benign lesion. Although Lipsett and coworkers state that this test is not very useful (3), Bertagna and Orth reported that 10 of 18 patients with adenoma tested responded appropriately to ACTH infusion (9). In contrast, only one of 13 patients with carcinoma responded to ACTH. This patient had a tumor which caused virilism only. No patient with a carcinoma causing Cushings syndrome responsed to ACTH infusion.

Adrenal Adenoma; Prognosis and Treatment

Adrenal adenoma should be cured by surgical removal of the tumor. Since it is not possible to define with certainty the malignant potential of an adrenal neoplasm, prognosis should be guarded. A patient with a small, histologically benign tumor which responds to ACTH infusion and which does not synthesize excessive quantities of steroids detected as 17-ketosteroids will probably be cured by surgery. Any endocrine syndrome should regress or disappear after surgery, but some residual problems caused by the adenoma may require additional therapy. Osteopenia seen in patients with Cushing's syndrome may not be cured by correcting the hypercortisolism. Virilism or feminization may not fully regress and may require cosmetic treatment.

Adrenal Carcinoma; Prognosis and Treatment

Adrenal carcinoma is only rarely cured by surgery. The prognosis for this disease is generally poor; however, survival of patients with adrenal carcinoma ranges from days to many years. Survival times from a number of series are listed in Table VII.

Table VII. Survival After Diagnosis of Adrenal Carcinoma

	Category	Deaths			patients not followed to death-number; years of follow up
		<1 yr	1-5 yr	5-10 yr	
*Lipsett et al. (1963)	Nonoperable	11/17	4/6	1/1	3;1,3,5 yrs
	Curative resection	1/14	9/13	4/4	4;5,8,8,9 yrs
Gabrilove (1965)		23/34	10/11	1/1	18 patients
Hutter and Kayhoe (1966)	Male	13/43	27/43		4 yr follow-up
	Female	23/92	46/92		4 yr follow-up
Lewinsky et al. (1974)		9/14	1/5	2/4	6;1/12,5/12,6/12,3.5, 4,18 yrs.
Hajjar et al. (1975)		8/32	14/24	7/10	---
Greenberg and Marks (1978)					
Nonoperable - average survival		5 mo.			
Extensive - average survival			21 mo.		
Radiation and curative - resection		1/10		5/10	
Bertagna and Orth (1981)		11/26	6/15	8/9	5;3,6.5,16.7, 17.9,28 years

* All series included patients who had been followed for various lengths of time and were still alive at the time of each report. The follow-up time was sometimes short so it is possible that these patients may have eventually died as a result of their disease.

Features which correlated with long-term survival are difficult to identify. Patients who are children tend to survive longer than adults and patients with smaller tumors tend to survive longer. Candidates for "curative" resection also tend to survive longer; however, this finding may simply reflect less extensive disease. The series with the lowest short-term death rate, Hutter and Kayhoe (4,59) and Hajjar et al. (60), employed chemotherapy with o,p'-DDD or other agents. In all series survival after 10 years is rare and patients initially diagnosed with extensive or metastatic disease survive the shortest time. The variability in prognosis for patients with adrenal carcinoma is graphically demonstrated by the survival data reported by Bertagna and Orth (9). Survival varies radically from days to years and the usefulness of different therapeutic modalities appears to vary equally markedly.

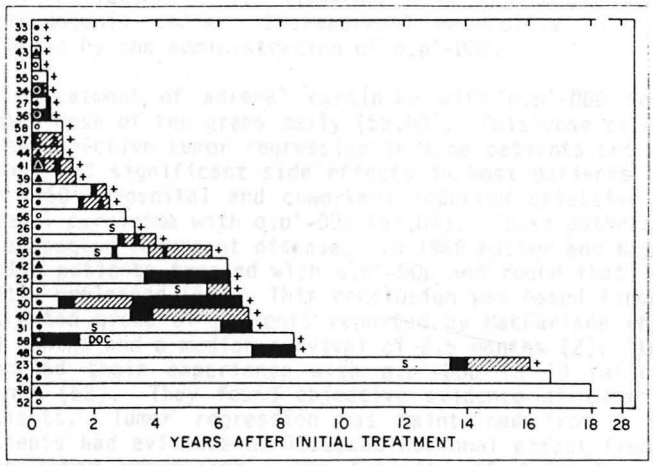


Figure 8. *Survival after initial treatment for adrenal carcinoma. Patients are identified by number at left. All patients except Patients 36, 41, 43 and 53 had surgery as their initial therapy. Patient 54 was not treated, and died one month later. ● = Cushing's syndrome; ▲ = virilization only; ○ = no clinical endocrine syndrome or hypertension only; DOC = primarily deoxycorticosterone-secreting tumor; □ = no evidence of recurrent or metastatic tumor; ▨ = recurrent or metastatic tumor; ■ = treatment with o,p'DDD; S = subsequent surgery; + = deceased.*

Fig. 4, from ref. 9

The presumptive diagnosis of adrenal carcinoma is usually made at surgery. The surgical approach to a hormonally-functioning adrenal mass is adrenalectomy in grossly benign-appearing lesions and radical surgery in obviously-invasive lesions. Radical surgery may include nephrectomy, retroperitoneal dissection and exploratory laporatomy and dissection (8). Before any surgical exploration is attempted a thorough search for metastatic disease should be conducted. Adrenal carcinoma may locally invade the kidney, great vessels or peritoneum, and may metatasize to lung (60%), liver (53%), lymph nodes (43%) or bone (10%)(60). In the event that preoperative evaluation reveals metastatic disease, surgery should probably be limited to biopsy. If preoperative evaluation reveals restricted disease, resection of all tumor should be attempted. Although it should be appreciated that radical surgery will not usually cure this disease, surgery may help control hormonally mediated symptoms, may cause a long term remission or occasionally may affect a surgical cure. Although chemotherapy has not been dramatically effective in ablating this tumor, prophylactic chemotherapy possibly should be employed when surgical resection is thought to be incomplete.

A substantial proportion of patients will have metastatic disease when first diagnosed, and most other patients will develop metastatic disease sometime after initial surgical therapy. Chemotherapy has a role both in controlling hormonal effects of the tumor and may have some effect on the rate of progression of the tumor.

The insecticide derivative, o,p'-DDD (1, 1, dichloro-2-o-chlorophenyl) -2-(p-chlorophenyl) - ethane, has been the drug most extensively used in the treatment of metastatic adrenal carcinoma (9,59,60). Initial toxicological studies of this drug in dogs showed that it caused adrenal cortical necrosis and atrophy (61). The effects of o,p'-DDD on the adrenal are two-fold and not specific for the adrenal (62). This chemical inhibits steroidogenesis by

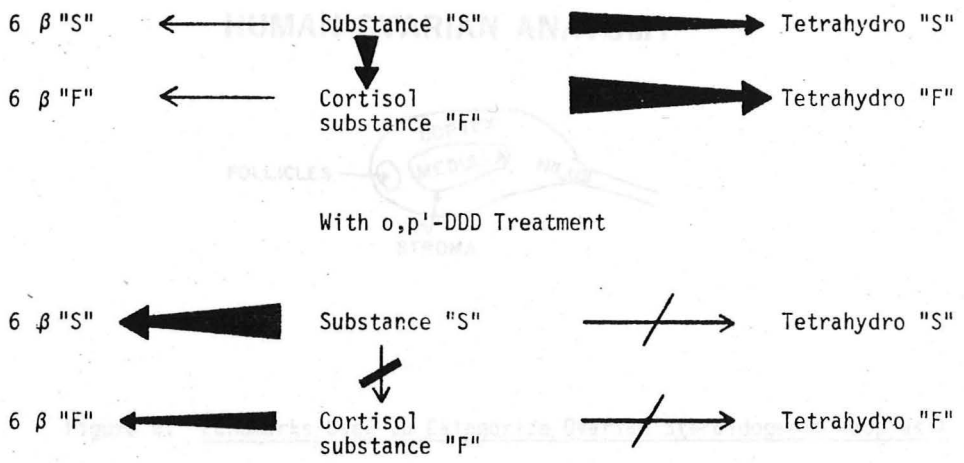
interfering with mitochondrial cholesterol side-chain cleavage and 11-hydroxylation. This compound also has a pronounced cytotoxic effect on steroidogenic cells. Extraadrenal metabolism of cortisol is significantly affected by the administration of o,p'-DDD.

Treatment of adrenal carcinoma with o,p'-DDD has usually been attempted with a dose of ten grams daily (59,60). This dose of o,p'-DDD has been shown to cause objective tumor regression in some patients but will cause adrenal sufficiency and significant side effects in most patients so treated (62). In 1959 and 1960 Bergenstal and coworkers reported objective regression of metastatic adrenal carcinoma with o,p'-DDD (63,64). These authors advocate early treatment of suspected recurrent disease. In 1966 Hutter and Kayhoe reviewed the findings of 138 patients treated with o,p'-DDD and found that life was probably significantly prolonged (59). This conclusion was based largely on comparison with an untreated group of patients reported by MacFarlane who had a mean survival of 2.9 months and a median survival of 2.5 months (2). In 1972 Hoffman and Mattox reported their experience with o,p'-DDD in 19 patients treated at the Mayo clinic (62). They found objective evidence of tumor regression in only four patients. Tumor regression was maintained from 3 to 24 months. Two more patients had evidence of lessened hormonal effect from the tumor but no objective tumor regression. The toxicity of this drug greatly impressed these investigators. In 1973 Lubitz and coworkers reported that the mean survival of patients treated at the National Institutes of Health was 8.4 months with a median survival of 5 months (65). In 1975 Hajjar and coworkers reported their experience with 32 patients treated at M.D. Anderson Hospital (60). These workers report a mean survival of 27.86 months for their patients. They state, as have other authors, that radiation therapy provides no objective benefit. They tested several other chemotherapeutic agents, all of which appeared inactive. These included vinblastine, L-arcolysine, methotrexate, 5-arcolysine fluorouracil, Provera, hydroxyurea, Daunomycin, cyclophosphamide, MCCNU and Adriamycin. In this same year Becker and Schumacher reported two patients who presented with metastatic adrenal carcinoma and subsequently survived for 4.5 and 7.75 years respectively, without tumor recurrence (66). In 1981 Bertagna and Orth reported 32 patients with adrenal carcinoma treated at Vanderbilt (9). These authors state that o,p'-DDD offered "objective temporary improvement". Reviewing the studies which utilized o,p'-DDD leaves the reader with the impression that o,p'-DDD is an agent which was initially thought to have great potential but which subsequently has proved to be only marginally efficacious and quite toxic.

Since o,p'-DDD is effective to some degree in most patients and since this agent may occasionally cause a long term remission or cure, it might seem reasonable to use the drug prophylactically for all patients. This agent should not be used in this manner for three reasons. First, o,p'-DDD used at the usually prescribed dose of 10 g/day is extremely toxic (62). The drug almost universally causes nausea, vomiting, diarrhea and mood changes ranging from malaise to psychotic depression. The drug may induce peripheral neuropathies and has been reported to cause a syndrome similar to subacute combined degeneration of the spinal cord. The toxicity is to some degree dose-related and has been reported to be minimal at doses below three grams per day (67)(many patients will spontaneously reduce their drug dose). It is not clear if o,p'-DDD is always effective at low doses although one patient presumably cured of adrenal carcinoma took only about 1 g o,p'-DDD/dy (66). Secondly, at any

effective drug dose, o,p'-DDD will probably induce eventual adrenal and gonadal insufficiency necessitating hormonal replacement therapy (62). A third reason for not employing o,p'-DDD on a routine basis is that this drug substantially alters steroid secretory patterns and metabolism, making detection of tumor recurrence difficult (62,67,68). Since this agent inhibits the 11 ß-hydroxylase enzyme to a greater extent than it does other steroidogenic enzymes it becomes impossible to follow a patient with serial cortisol values or serial urinary free cortisol determinations. If only 11ß-hydroxylase inhibition in turn caused false positive diminution of steroid valves, patients could be followed by serial urinary 17-hydroxysteroid determinations. Unfortunately o,p'-DDD also causes an induction of 6 ß-hydroxylase activity which causes most glucocorticoid metabolities to be excreted as 6 ß-steroids. These steroids are not quantitatively detected in 17-hydroxysteroid assays. Thus, early or prophylactic treatment with o,p'-DDD has the combined disadvantages of extreme toxicity, inhibition of normal steroid hormone producing cells, and of removal of the most sensitive and available markers for recurrent disease.

Fig. 5 Alterations in Usual Biochemical Tests of Adrenal Function induced by o,p'-DDD



Steroid Hormone-Producing Tumors of the Ovary

Ovarian neoplasia capable of synthesizing steroid hormones are rare. These tumors most commonly synthesize and release androgens and/or estrogens and have on occasion been reported to synthesize glucocorticoids as well. Unlike adrenal steroidogenic tumors, the ovarian steroidogenic tumors are less often malignant and thus less frequently cause death.

To understand the categorization of ovarian steroidogenic tumors, some knowledge of ovarian anatomy and histology is required. The human ovary is about 4 cm long, 2 cm wide, and 1 cm thick. The ovary is anchored to the broad ligament at the ovarian hilum by the ovarian ligament and the mesovarium. The hilum of the ovary is an important anatomical landmark used for naming ovarian steroidogenic tumors. This region of the ovary contains cells which microscopically resemble normal testicular Leydig cells. Tumors arising near the ovarian

hilum and/or which contain cells which demonstrate typical crystals of Reinke make up a group of ovarian tumors capable of androgen biosynthesis. The blood vessels of the ovarian hilus penetrate into the medulla of the ovary and then branch into the cortex of the ovary which contains the ovarian follicles. The follicles are the site of a second class of ovarian steroidogenic neoplasia. Ovarian follicular steroidogenic cells are usually designated theca cells, granulosa cells or luteal cells. These cells are histologically distinct and are believed to have somewhat separate functions. All originate from the cortical stroma, and tumors which histologically resemble a specific cell type have been described (22). A third point of reference used in the categorization of ovarian steroidogenic neoplasia is the capsule of the ovary. This is the site at which tumors of nonovarian functional identity would be expected to arise. Tumors such as adrenal rest tumors would be expected to arise from this area of the ovary.

HUMAN OVARIAN ANATOMY

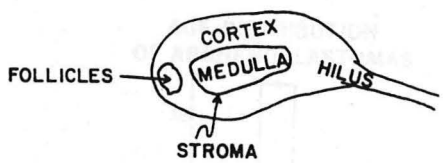


Figure 6. Landmarks Used to Categorize Ovarian Steroidogenic Neoplasia

Table VIII. Categorization of Ovarian Steroidogenic Neoplasia

Sertoli-Leydig-Cell Tumors:	Arrhenoblastoma
	Hilus Cell Tumor
Feminizing Mesenchymomas:	Granulosa-Cell Tumor
	Theca-Cell Tumor
	Granulosa/Theca-Cell Tumor
Lipoid-Cell Tumor	
Adrenal Rest Tumors?	
Stromal Luteoma	
Hamartomas:	Hyperthecosis
	Luteoma of Pregnancy

The largest class of androgenic ovarian steroidogenic tumors are generically described as Sertoli-Leydig-cell tumors. The normal ovary contains cells which microscopically and possibly functionally resemble Leydig cells of the testes (69). These cells are usually found near the ovarian hilus. Any tumor arising near the hilum and containing cells with crystals of Reinke would be classed as a Sertoli-Leydig-cell tumor. The arrhenoblastoma and hilus cell tumor are similar tumors, both having a generally good prognosis, but they arise in women at different ages. The Sertoli-Leydig cell tumors may be further subdivided on the basis of tumor differentiation characteristics. Well differentiated tumors are usually benign, while poorly differentiated lesions, especially those with heterologous elements, may be malignant (70).

The arrhenoblastoma is the most common tumor of the Sertoli-Leydig cell group (20,34,36). This tumor has been reported in patients as young as four years of age and in women as late as the sixth decade of life. The age distribution of this tumor in 240 patients reviewed by Pedowitz and O'Brien is shown below (20). About twenty percent of arrhenoblastomas from this series

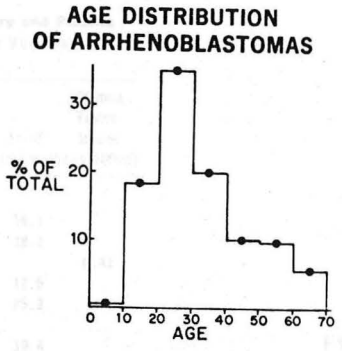


Fig. 7. Age Distribution of Patients with Arrhenoblastoma

were less than 5 cm in diameter and more than seventy-three percent were less than 15 cm in diameter. The presenting symptoms of patients with these tumors are usually related to defeminization or to virilism. Of the 240 patients reviewed by Pedowitz and O'Brien only 5 percent were asymptomatic. The commonest symptoms reported in their review are tabulated in Table IX.

Table IX. Common Symptoms of Arrhenoblastoma

Hirsutism	76%
Amenorrhea	68%
Male voice	50%
Enlarged clitoris	44%
Abdominal Pain and enlargement	32%
Breast Atrophy	33%

Hormonal findings in patients with arrhenoblastoma are variable. Typical patients with arrhenoblastoma will have normal to slightly elevated 17-ketosteroid excretion in the urine but elevated plasma testosterone values (20). Thus, a typical arrhenoblastoma synthesizes potent androgens which cause virilization without appreciably elevating urinary 17-ketosteroid levels. Exceptions to these typical findings have been rare. Two patients with metastatic arrhenoblastoma excreted large quantities of 17-ketosteroids (71,72). Stimulation or suppression testing yields no consistent result in patients with arrhenoblastoma. Tucci, Zah and Kalderon studied a 19-year old woman with an arrhenoblastoma (23). In this patient urinary 17-ketosteroids and plasma testosterone values were suppressed by the administration of dexamethasone and stimulated by the administration of ACTH or hCG. These authors results are summarized in Figure 8.

TABLE I Pre- and Postoperative Urinary and Plasma Steroid Data Before and After Various Manipulations

	Day	17-OHCS (mg/day)	17-KS (mg/day)	Plasma Testosterone (μg/100ml)
Preoperative				
Control	1	7.93	16.1	
	2	5.32	18.2	
				0.41
Metyrapone	1	14.87	12.5	
	2	26.18	25.3	
				...
Dexamethasone	1	6.66	19.4	
	2	2.23	10.5	
				0.25
Dexamethasone, HCG	1	2.10	26.4	
	2	1.77	17.5	
	3	1.35	25.8	
				2.30
ACTH	1	17.68	73.0	
	2	33.98	66.0	
				2.10
Postoperative				
Control*	1	3.55	3.2	
	2	5.75	4.5	
				0.03
Dexamethasone	1	3.63	8.7	
	2	2.15	8.1	
				...
Dexamethasone, HCG	1	1.04	5.3	
	2	1.01	7.7	
	3	1.25	4.6	
				0.23
ACTH	1	16.59	11.3	
	2	39.76	16.6	
				0.07

Fig. 8. Response of an Arrhenoblastoma to Dexamethasone and to ACTH., from ref. 23.

Lamberts and coworkers carefully studied a 53-year old women with an arrhenoblastoma and found similar paradoxical results (34). Plasma testosterone and urinary 17-ketosteroid concentrations were suppressed by dexamethasone and simulated by hCG. In general, no suppression or stimulation test will adequately differentiate an ovarian arrhenoblastoma from a testosterone synthesizing adrenal tumor.

The prognosis of patients with arrhenoblastoma varies depending on the histologic grade of the tumor. The histology of the tumor does not however,

Table X. Malignant Potential of Arrhenoblastoma

Tumor Grade	Description	% malignant
I	well differentiated "adenoma tubulare testiculare ovarii"	12.8
II	intermediate	13.9
III	Undifferentiated "Sarcomatus"	42

accurately predict prognosis. Arrhenoblastomas are unpredictable and the true malignant potential of a tumor will only be known with certainty by following the clinical course of the patient (20). Survival times after discovery of malignant arrhenoblastoma are variable and are summarized in Figure 9. As in the case of adrenal carcinoma more than one half of the patients die within one year, although occasional patients may survive as long as sixteen years.

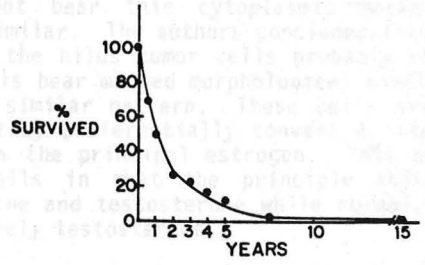


Fig. 9. Survival with Malignant Arrhenoblastoma

Treatment of arrhenoblastoma is primarily surgical. In women above childbearing age hysterectomy and bilateral salpingo-oophorectomy are usually performed. For women of childbearing age with well encapsulated lesions unilateral salpingo-oophorecotomy is usually performed. No adequate treatment is available for metastatic arrhenoblastoma. Presumably steroidogenesis could be blocked with aminoglutethimide or possibly with analogues of luteinizing releasing hormone (LRF)(34). Treatment with o,p'-DDD might be of some benefit in these patients, although I am unaware of a study which employed this drug for this tumor.

Hilus cell tumors are rare androgen-synthesizing ovarian tumors (24,26,31-33,35). By 1983 about sixty case reports of women with this tumor had appeared (35). Hilus cell tumors usually occur in postmenopausal women and all of the cases reported but one were benign. Typically these tumors are less than 6 cm in diameter and thus may be difficult to detect. Two of the reported cases were bilateral (35).

Despite the few published cases, steroid secretory patterns of hilus cell tumors have been studied. Urinary 17-ketosteroid excretion may be normal or elevated in patients with hilus cell tumors. Plasma testosterone levels are elevated in all patients and may be substantially elevated. At least one tumor appeared to express 5α-reductone activity, since ovarian venous blood contained 10.6-fold more dihydrotestosterase than peripheral venous blood (33). This patient also demonstrated a 13.5-fold and a 71.5-fold ovarian peripheral gradients for testosterone and androstenedione respectively. One particularly interesting patient has been studied: a 62 year old woman with a hilus tumor, bilateral hyperplasia of hilus cells and hyperthecosis (32). Serum hormone levels before operation showed marked elevations in pregnenolone, 17-hydroxypregnenolone, progesterone, 17-hydroxyprogesterone, androstenedione, testosterone, estrone and estradiol. All elevated hormone levels except for estrone could be further increased with hCG administration. Steroids of the Δ_5 but not the Δ_4 pathway could be suppressed with dexamethasone. At surgery catheterization of the right and left ovarian veins was performed. Both ovaries demonstrated marked gradients of steroid hormones relative to peripheral blood. The pattern of steroids measured in both ovaries was qualitatively similar but quantitatively greater in the ovary with the tumor. Microscopic examination of the tumor showed cells with crystals of Reinke. The hyperplastic hilus of each ovary also showed occasional crystals of Reinke. The hyperplastic stroma (hyperthecosis) did not bear this cytoplasmic marker but contained cells morphologically very similar. The authors concluded that the hyperplastic hilus and stromal cells and the hilus tumor cells probably share a common precursor cell since all the cells bear marked morphological similarities and all produce steroid hormones in a similar pattern. These cells are similar to testicular Leydig cells in that they preferentially convert Δ_5 steroids to androgens and synthesize estradiol as the principal estrogen. This patient's cells differed from normal Leydig cells in that the principle androgens synthesized were dehydroepiandrostenedione and testosterone while normal testicular Leydig cells synthesize almost entirely testosterone.

The prognosis of patients with hilus cell tumors is excellent. Almost all patients should be cured by surgical excision of the tumor.

Lipoid cell tumors of the ovary are rare tumors which usually cause virilization (28-30). It is estimated that 73 percent of lipoid tumors are virilizing, 23 percent produce estrogens and about 10 percent cause Cushing's

syndrome (28). These estimations are based on clinical findings and are not supported by specific hormone measurements. The lipoid tumor is histologically nondiscrete and is usually diagnosed when a more specific diagnosis cannot be made. Some authors argue that the lipoid tumor is actually a number of heterologous and functionally dissimilar tumors which have been grouped together because the tumors lack more specific histological markers (73). Approximately 20-25 percent of patients with lipoid tumors will develop metastases.

Classically, patients with lipoid cell tumors excrete large amounts of 17-ketosteroids into their urine and demonstrate markedly elevated plasma concentrations of androstenedione; they have only moderately elevated concentrations of testosterone. Bonaventura and coworkers compared hormonal studies of four patients with lipoid tumors and two patients with hilus tumors (28). Both tumors produced androgens; however, the pattern of androgen production was quite different. The four lipoid tumors produced more androstenedione than testosterone while the two hilus cell tumors produced much more testosterone than andostenedione. The next year Farber and coworkers carefully studied a patient with a lipoid cell tumor and found normal 17-ketosteroid excretion, slightly elevated plasma androstenedione concentrations, and markedly elevated plasma testosterone concentrations (30). Testosterone was not suppressed by dexamethasone but was stimulated by the administration of hCG. Check and coworkers studied a 15-year old patient with a lipoid-cell tumor which also responded to hCG administration (29). Administration of estrogens caused the serum testosterone to fall and markedly reduced urinary 17-ketosteroid excretion. Thus, it would appear that lipoid tumors may demonstrate a wide range of hormonal secretory patterns and that the pattern of urinary or plasma steroids is of no use in identifying this specific tumor.

The treatment of lipoid tumors is surgical. Removal of the tumor and immediately surrounding tissues should result in cure in 75 to 80 percent of cases. One reported patient with metastatic lipoid-cell tumor responded to o,p'-DDD with a dramatic reduction in plasma steroid concentrations (74). This report suggests that this agent may be useful in treating patients with metastases or incomplete resections of primary tumor.

Stromal luteoma is a very rare and poorly characterized ovarian tumor (73,75). This tumor is morphologically distinct and is characterized by small size and benign behavior. The description of this tumor in 1964 by Scully, preceded most modern hormonal assays. He reported six cases in which he had examined the pathology and five cases from the literature which showed similar pathology. Biochemical studies revealed elevated urinary estrogen levels in one patient and elevated urinary testosterone levels in one more. No definite biochemical data was collected from the other patients. All the patients reviewed were either perimenopausal or postmenopausal. Five of Scully's six patients were virilized and one of the patients with a histologically similar tumor reported in the literature was virilized and demonstrated increased urinary testosterone excretion. More recently Givens and coworkers studied one patient with a stromal luteoma (75). This 17-year old patient was virilized and was found to have elevated plasma concentrations of androstenedione and testosterone which increased further with hCG administration.

Tumors which histologically resemble normal ovarian follicular cells are classed as feminizing mesenchymomas (22,76,77). These tumors are the most common ovarian steroidogenic tumors. Feminizing mesenchymomas are classified as either granulosa-cell tumors, granulosa-theca-cell tumors or as thecomas. As a

group feminizing mesenchymomas constitute about 14-17 percent of all solid ovarian neoplasia (22). Estimations of malignancy vary between the groups of tumors and from study to study.

Pure granulosa-cell tumors are estimated to make up from 23 to 70 percent of feminizing mesenchymomas (20,76). Between 32.2 and 38.7 percent of these tumors occur below the age of forty; however, granulosa-cell tumors may occur at any age.

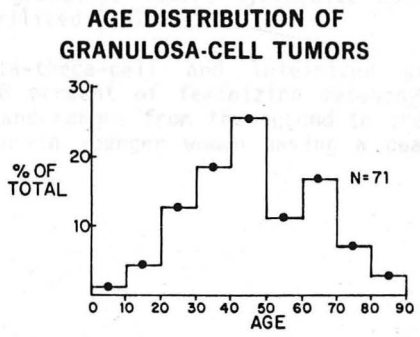


Fig. 10. Age Distribution of Granulosa-Cell Tumors

Granulosa-cell tumors are said to account for 10 percent of all cases of isosexual precocious puberty in girls. The incidence of malignancy for this tumor has been estimated to range from 5 to 58 percent (76). The largest series, reported by Novak and coworkers using data from the Ovarian Tumor Registry, estimates survival at five years to be 78.5 percent, indicating a rate of malignancy of 21.5 percent (20). In this series metastases were detected in some patients as late as 18 years after initial surgery. Although an earlier series derived from Ovarian Tumor Registry patients noted a correlation between survival and tumor histology, this large series found no such correlation. There is however a correlation between granulosa-cell tumors and adenocarcinoma of the endometrium.

Although granulosa-cell tumors are relatively common, little is known about the synthesis of steroids by this tumor. Children with granulosa tumors develop isosexual precocious puberty. This has prompted some investigators to suggest that these tumors directly synthesize estrogens. Aromatase activity has been found in granulosa cell tumors in vitro (78,79). This issue has been investigated in at least one child with isosexual precocious puberty. Madden and McDonald studied a 3½ year old girl with breast development and uterine bleeding

(27). Despite these signs of feminization this patient had no pubic or axillary hair. These investigators measured plasma concentrations of steroids and did isotope studies to determine steroid conversion rates. The patient demonstrated strikingly elevated levels of estradiol, with low levels of androstenedione and testosterone. Although the tumor could extensively utilize androstenedione to form estradiol the metabolic studies indicated that the tumor was directly synthesizing estradiol. One possible source of error was cited by the authors. At the time they initially investigated the child they did not anticipate such extensive utilization of plasma precursor steroids. Thus, levels of dehydroisoandrosterone and dehydroisoandrosterone sulfate were not determined. Although poor substrates for peripheral conversion to estradiol, these steroids can readily be converted to estradiol by trophoblastic tissue and could conceivably have been converted to estradiol by the tumor. Although it seems probable that most granulosa tumors synthesize estrogens, patients have been reported who are virilized (20).

Mixed granulosa-theca-cell and luteinized granulosa-theca-cell tumors constitute 15 to 48 percent of feminizing mesenchymomas (76). The peak age incidence is broad and ranges from the second to the fifth decade. Luteinized tumors tend to occur in younger women having a peak incidence in the second decade (20).

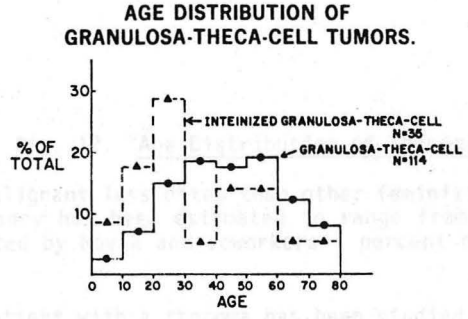


Fig. 11. Age Distribution of Granulosa-Theca-Cell Tumors

Isosexual precocious puberty may be caused by this tumor as well. Estimates of the incidence of malignancy in granulosa-theca-cell tumors range between 7.6 and 27 percent (76). Luteinized tumors have not been reported to metatasize (20).

Information on steroid synthesis by these tumors is also scarce. These tumors characteristically cause uterine endometrial hyperplasia and probably synthesize estrogens. Virilism is occasionally found in patients presenting with these neoplasia.

Pure thecomas are the least common of the feminizing mesenchymomas, constituting 12 to 29 percent of this class of tumor (76). This tumor is found at all ages with an approximately equal incidence between ages 20 and age 70 (20).

AGE DISTRIBUTION OF THECOMAS

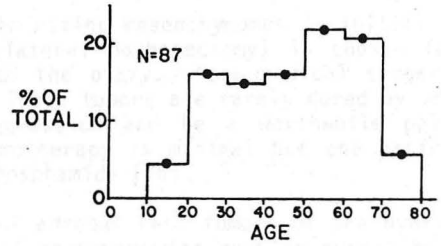


Fig. 12. Age Distribution of Thecomas

Thecomas are malignant less often than other feminizing mesenchymomas. The incidence of malignancy has been estimated to range from 0 to 12 percent (76). In the series reported by Novak and coworkers 7 percent of thecomas were malignant (20).

At least one patient with a thecoma has been studied in detail. Givens and coworkers investigated a 31-year old women with a 4 cm thecoma (25). This patient had presented because of amenorrhea, progressive hirsutism and deepening voice. This patient demonstrated elevated basal levels of a number of plasma steroids. Plasma androstenedione ranged from slightly above the upper limit of normal to more than two-fold greater than normal. Plasma values of testosterone were four- to six-fold above normal levels and testosterone-binding globin values were suppressed. Plasma 17 α-hydroxyprogesterone levels were elevated about three-fold. Plasma estradiol and estrone values were normal. Administration of hCG after dexamethosone treatment resulted in dramatic

increases in all plasma steroids measured. Plasma 17 α-hydroxypregnenolone, which had not been elevated in the basal state, increased to supernormal values with hCG. Ovarian catheterization was performed at surgery and the tumorous right ovary demonstrated a marked gradient in testosterone concentration relative to peripheral blood. Interestingly, other steroids were not so dramatically increased in the right ovary, probably because the patient had coexisting polycystic ovarian disease. This patient may have been unusual in that plasma LH values were elevated, and it seems possible that her LH/hCG responsive tumor was not truly autonomous.

Follicular cell tumors could provide evidence favoring the two-cell theory of ovarian steroidogenesis for humans. This theory states that ovarian androgens are produced by theca cells and are in turn aromatized by granulosa cells. This theory has experimental support in the rat but not in the human. Studies of humans with hyperthecosis (83) and at least one patient with a "pure" thecoma (25) suggest that human theca cells produce androgens and very little estrogen. Patients with feminizing mesenchymomas and high urinary estrogen excretion are usually found to have a tumor which contains granulosa cells (110). Systematic study of patients with pure thecomas and thecomas containing granulosa cells could provide evidence for extending the two-cell theory of ovarian steroidogenesis to humans.

Treatment of feminizing mesenchymomas is initially surgical (76). Conservative surgery (unilateral oophorectomy) is chosen for patients in which the tumor is confined to the ovary. More radical surgery is chosen for patients with local spread. These tumors are rarely cured by irradiation but irradiation may cause tumor regression and be a worthwhile palliative measure (20,76). Experience with chemotherapy is minimal but one patient has been reported who responded to cyclophosphamide (76).

The existence of adrenal rest tumors of the ovary is a subject of controversy. Many patients reported with ovarian tumors have some clinical stigmata which could be associated with Cushing's syndrome. Obesity, hypertension and acne are common findings in women with ovarian tumors and may have led early investigators to believe these patients had "adrenal-like tumors". No ovarian tumor has been unequivocally shown to both synthesize cortisol and demonstrate typical adrenal cellular associations (80). A few women with ovarian tumors have been shown to excrete increased amounts of 11-hydroxylated ketosteroids (73). The capacity to 11-hydroxylate is exclusively found in normal adrenal cells or neoplastic cells. It seems that the large number of early cases of ovarian "adrenal-like tumor" were probably not glucocorticoid synthesizing at all. Some very minute fraction of ovarian tumors may in fact be of adrenal rest origin, as indicated by patients with ovarian tumors and increased excretion of 11-hydroxylated steroids.

A final class of ovarian steroidogenic tumor should be mentioned. This class of tumor includes the luteomas of pregnancy and hyperthecosis. These hypertrophic lesions are probably not true neoplasias but hamartomas.

The luteoma of pregnancy is always a lesion incidently discovered either at Caesarean section or at postpartum sterilization (81). The reported cases are all of women with histories of numerous childbirths. This tumor may be quite large, up to 12 cm, but is benign and will regress after pregnancy. The tumor probably synthesizes the steroid hormones normally elevated in pregnancy; however, this has not been established with certainty. One patient with a

luteoma of pregnancy, and the child of another patient with this tumor, became virilized (81). The microscopic appearance of this tumor is specific enough to allow unequivocal diagnosis even in frozen sections. The major point to emphasize is that patients with this tumor do not need surgical treatment.

Hyperthecosis is an uncommon finding in the ovaries of hirsute women (82). Theca cell hyperplasia is associated with elevated ovarian androgen production (83). The hyperplastic theca cells are most often found in polycystic ovaries and are under the control of the high LH values characteristic of this disorder (25). Some theca-cell tumors probably are derived from ovaries in which hyperthecosis has been long-standing. Treatment of the hirsutism associated with hyperthecosis consists of estrogen therapy to reduce the plasma LH concentrations.

Hyperthecosis occurs in one other clinically important situation. Epithelial tumors of the ovary which do not synthesize steroid hormones may cause virilization (84,85). This phenomenon has been studied by MacDonald and coworkers here. Aimen and coworkers studied a postmenopausal woman with bilateral cystic teratomas and found that the ovaries were synthesizing excessive quantities of androstenedione and testosterone (84). Plasma estrogen levels could be largely accounted for by extraglandular conversion of androgen substrate. Pathological examination of the patient's ovaries revealed nests of cells which resembled luteinized stromal cells. The tumors themselves contained no endocrine tissue. MacDonald and coworkers also studied another postmenopausal patient who had signs of estrogen excess (85). Isotope studies indicated that this patient's production rate of androstenedione was increased five-fold, as was her conversion of androstenedione to estrone. The patient was found to have a mucinous cystadenocarcinoma and ovarian stromal hyperplasia of the involved ovary. The cause of ovarian stromal hyperplastia and/or hyperthecosis in these patients is unknown. Possible explanations include increased ovarian blood flow or promotion of growth factor like substances from the tumor. The latter theory is at present most favored.

Testicular Steroidogenic Neoplasia

Testicular neoplasia which synthesize steroid hormones are the rarest steroidogenic neoplasia. Testicular tumors may cause isosexual precocious puberty, feminization or sexual dysfunction (16). Adrenal rest tumors of the testes are well documented (86). Testicular tumors may be classified into four groups.

Table XI. Testicular Steroidogenic Neoplasia

Leydig-Cell Adenoma
Leydig-Cell Carcinoma
Sertoli-Cell Tumor
Adrenal Rest Tumor

Of steroid hormone-synthesizing testicular tumors, Leydig-cell tumors are most common (16). Leydig-cell tumors made up 1.2 percent of one large series of

testicular tumors (87), 1.9 percent of a second smaller series (88) and 1.4 percent of a third large series (89) of testicular tumors. In 1957 Dalgaard and Hesselberg collected 94 instances of Leydig-cell tumors and were able propose a bimodal age distribution for this lesion (16). They found that 23 cases occurred in boys under the age of 15. Peak incidence in boys was between the ages of five and ten years old. Seventy-one patients were adults and peak incidence occurred between the ages of 30 and 35. In this series, about 10 percent of the tumors were malignant. Only one case of a malignant Leydig cell tumor has been reported in a child.

Leydig-cell tumors are generally small. Many tumors may be too small to palpate and almost all of the patients collected by Dalgaard and Hesselberg had tumors less than five centimeters in diameter. Malignant lesions tend to be the largest Leydig cell tumors.

Symptoms from Leydig-cell tumors are more pronounced in young patients (16,18). Boys are almost always virilized by these tumors but may also develop gynecomastia. Almost 82 percent of adults will not have endocrine symptoms and will present to a physician for other reasons, most commonly a testicular mass (18). Adults who do develop endocrine symptoms may manifest gynecomastia, impotence or loss of libido. The more pronounced clinical symptoms in children may explain why only one child has been reported with a metastatic Leydig cell tumor.

The histologic appearance of Leydig-cell tumors varies and can not be utilized to differentiate benign from malignant lesions (16,18). All Leydig-cell tumors contain cells with typical ultrastructural features of Leydig cells (17). The cells have abundant smooth endoplasmic reticulum, large numbers of mitochondria with vesicular cristae and cytoplasmic lipid droplets. These tumors probably contain fewer Reinke crystals than do normal Leydig cells. A histologically well-differentiated Leydig-cell tumor may metastasize while a very anaplastic tumor may be cured by unilateral orchidectomy.

Some information is available on steroid secretory patterns in patients with Leydig-cell tumors. Children with Leydig-cell tumors generally excrete large quantities of 17-ketosteroids while adults rarely do (16,18). An exception to this rule is found in metastatic Leydig cell tumors which may cause the urinary excretion of 17-ketosteroids to be increased markedly (18,90,91). Patients with feminizing Leydig cell tumors generally demonstrate elevated urinary and plasma estrogen levels (18,19). Three early studies investigated spermatic vein concentrations of testosterone, estrone and estradiol (18,92,93). The spermatic vein of the involved tumorous testes in all cases secreted subnormal amounts of testosterone, normal amounts of estrone and elevated levels of estradiol. The estradiol concentrations in the spermatic vein of the tumorous testes were about two- to five-fold above the levels detected in spermatic blood of normal patients, but were 85- to 260-fold greater than plasma estradiol concentrations. In each of these cases, testicular tumor-draining blood demonstrated markedly reduced ratios of testosterone to estradiol. The reduced ratios of these steroid hormones was cited as the probable cause of gynecomastia in these patients (18). Altered balance between androgen and estrogen levels could explain the gynecomastia sometimes detected in patients with normal or elevated plasma testosterone concentrations. In a recent study Bercovici and coworkers investigated a 36-year old man with gynecomastia and a testicular Leydig-cell tumor (19). This patient, like most other patients with Leydig-cell tumors, had low plasma gonadotrophin values. Urinary 17-ketosteroid levels were

low, as were plasma testosterone and androstenedione levels. Plasma estradiol levels were elevated about two-fold. Administration of hCG caused plasma androstenedione, testosterone, estrone and estradiol levels to rise. Testicular catheterization demonstrated an 18-fold gradient for estrone and a 334-fold gradient for estradiol from the tumor bearing testes. All four studies are in agreement and suggest that Leydig cells or at least neoplastic Leydig cells may synthesize estrogens directly. Bercovici and co-workers extended these observations somewhat further and showed that minces of their patient's tumor could more efficiently convert testosterone to estradiol than either peritumoral tissue or the tissue from the contralateral testes.

Steroid hormone synthesis by malignant Leydig-cell tumors has been less studied. Most patients with malignant Leydig-cell tumors demonstrate suppressed plasma gonadotrophin concentrations and elevated excretion of 17-ketosteroids (17-19,90,91). Gynecomastia may be seen in these patients, although it has not been shown that these tumors produce estrogen directly. It is equally possible that the tumor supplies substrate for peripheral aromatization.

Treatment of all localized Leydig-cell tumors is surgical. Since benign lesions can not be differentiated from malignant lesions by histologic criteria, prognosis should be guarded. Metastases from presumably completely resected Leydig-cell tumors have been documented as late as 10 years after orchidectomy. In general, if no sign of distant metastases is present on initial surgery the prognosis for prolonged survival is good. The shortest recorded survival of a patient with such a tumor is four years and one patient survived 17 years (18). If evidence of lymphatic, hepatic or boney metastases is found at initial evaluation or surgery, survival will be generally be less than 20 months (18,90,91).

Metastatic Leydig-cell cancer is not radiosensitive but may respond to treatment with o,p'-DDD. One patient treated with o,p'-DDD showed objective reduction in metastatic deposits in a supraclavicular lymph node but died soon after (90). An autopsy demonstrated extensive deposits of tumor at other sites. Azer and Braunstein reported a patient with pulmonary metastases which regressed with o,p'-DDD therapy (94). Their patient was unusual in that he demonstrated o,p'-DDD sensitive hypokalemia, hypertension and desoxycorticosterone values. Both hypertension and hypokalemia normalized with o,p'-DDD therapy. Insufficient testing was performed to clearly define if this patients primary testicular tumor and subsequent metastases were of Leydig cell or adrenal rest derivation. The testicular tumor was similar histologically to a Leydig-cell tumor but lacked crystals of Reinke.

Sertoli-cell tumors are rare testicular neoplasia (95). The prototype for the human Sertoli-cell tumor is the canine tubular adenoma, a feminizing tumor of dogs which is believed to be derived from Sertoli cells (96). Study of the canine tumor led to the hypothesis that Sertoli cells synthesize estrogens and remains the best evidence for this hypothesis. Derivation of the canine tumor from Sertoli cells is not, however, proven. The canine neoplasm may resemble testes tubules or it may more closely resemble interstitial (Leydig) cells. The human Sertoli-cell tumors have an even more varied histological appearance (95). These tumors may histologically resemble testes tubules, Leydig cells, granulosa cells, arrhenoblastoma cells, theca cells or non-descript spindle-shaped cells. Several different cell types may be present in the same tumor. The human tumors do not invariably feminize patients. Possibly Sertoli-cell-tumors should be

considered tumors of mesenchymal precursor cells, which may differentiate into several different cell types.

Gabrilove and co-workers recently reviewed 72 published cases of Sertoli-cell tumors in man (95). They found that feminization occurred in only a minority of patients (24 percent). The histologic descriptions of the tumors they reviewed were incredibly variable. These tumors were designated as either adenomas or carcinomas. Adenomas were most prevalent in the first year of life (17/56 patients) but were described in patients as old as 84 years. Carcinomas generally were found in patients older than 25 years, but one patient with a carcinoma was seven years old. Gynecomastia was present in only 16 percent of patients with adenomas but in 60 percent of patients with carcinomas.

The time from onset of symptoms to diagnosis ranged from one month to 30 years. Insufficient information was given in most of the reviewed case reports to allow much more generalization. Survival data were reported for six of the twelve patients with carcinoma. After diagnosis, four patients lived one year or less, one patient survived three years and one patient survived five years. Four of five patients with carcinoma died within two years of the onset of symptoms, while one patient survived 8.5 years.

Hormonal data for these tumors are meager. Of the 72 patients reviewed, hormonal studies were only available for a few. Urinary estrogen levels were elevated in two patients. The authors' patient, a five-year old boy, demonstrated elevated plasma estradiol levels. A fourth patient had normal total estrogens but slightly elevated estriol levels. Gonadotrophin levels were reported as elevated in two patients and were normal in seven patients. Urinary excretion of 17-ketosteroids was reported for ten patients and was normal in nine and elevated in one. Plasma androgen levels were only reported for the authors' patient and were increased in that patient.

On the basis of the variable histology and uncertain hormonal function of these Sertoli-cell-tumors, Gabrilove and associates suggest that these tumors should more appropriately be considered tumors of undifferentiated precursor cells. This view is consistent with the available data and might explain why some tumors resemble normal testicular cells, while some closely resemble ovarian cells. This issue can not be completely resolved until more hormonal data are available.

The testes are the site of occurrence of another rare and interesting neoplasm, the adrenal rest tumor (86). As discussed in an earlier section, groups of cells morphologically identical to adrenal cortical cells are found in the capsule of the testes and along the line of testicular descent (55). These "adrenal rests" appear to be more common in children who are below the age of one year. The presence of bilateral testicular tumors in children with congenital adrenal hyperplasia has been known since 1940 (86). These tumors have been investigated both in patients and in vitro. Kirkland and co-workers showed that infusion of ACTH into the spermatic artery of a patient with an adrenal rest tumor caused increased spermatic vein testosterone concentrations (97). At least three groups of workers have been able to demonstrate 11 β-hydroxylation of steroids by tumor tissue in vitro (97-99). A recent study by Franco-Saenz and co-workers has expanded past work (100). The authors did tissue culture studies of an adrenal rest tumor removed from a patient with 21-hydroxylase deficiency. This patient's tumor avidly converted ^{3}H-desoxycorticosterone to ^{3}H-aldosterone, indicating that the tumor contained

11 β hydroxylase activity. These workers grew tumor tissue or normal testicular tissue in tissue culture. They found that ACTH stimulated 21-deoxycortisone and cortisone synthesis by the tumor and by the normal testes tissue. Testosterone synthesis was also stimulated in the tumor incubations after ACTH treatment, but this tissue contained adrenal-like cells. Testosterone synthesis by the tumor cultures could be stimulated by ACTH or by hCG. Addition of both hormones did not cause an additive effect. The authors concluded that the tumor was made up of a precursor cell which responded to ACTH and hCG. The experimental approach these authors chose may have answered the important question they asked; however, they did not make the necessary measurements. As shown below, their Table 4 contains serious deletions. They did not conduct hCG stimulation on normal testes cultures. More importantly they do not provide values for 21-deoxycortisol or cortisol in the incubations with hCG or with hCG and ACTH. These determinations are all critical if the authors contentions are to be believed. Until such time as a clear experiment is conducted, the cellular origin of adrenal rest tumors will remain uncertain.

TABLE 4. Steroid studies in tissue cultures: 24-hr incubations

	21DF (pg/ml)	F (pg/ml)	Testosterone (pg/ml)
Fresh medium	ND	35	ND
Normal testis	ND	37	
Normal testis + ACTH	250	77	
Tumor"	159	48	ND
Tumor + ACTH"	315	162	180
Tumor + hCG			80
Tumor + ACTH + hCG			197

ND, Nondetectable
" Mean value of two tissue culture flasks.

Table XII. from ref. 100.

Treatment of adrenal rest tumors of patients with congenital adrenal hyperplasia is medical. Adequate suppression of pituitary ACTH by glucocorticoids should cause regression of the tumors. The tumors will recur if glucocorticoid therapy is discontinued. It is possible that tumors present for long periods of time might become autonomous. Unresponsiveness to glucocorticoid suppression or the appearance of a tumor in a patient without a congenital adrenal hyperplasia syndrome is an indication for surgical removal.

Only one malignant neoplasia of adrenal rest tissue has been reported (10). Morimoto and co-workers reported a 57-year old man who presented with florid clinical and biochemical evidence of Cushing's syndrome. The patient was found to have several large retroperitoneal tumors (these were felt to be lymphatic metastases) and a large left testicular tumor which appeared identical to the retroperitoneal tumors. The testicular mass had preceded any clinical symptoms of Cushing's syndrome. In vitro incubation of tumor tissue with precursor steroids demonstrated that the tumor could synthesize cortisol, corticosterone, progesterone and dehydroepiandrosterone. It thus seems doubtful that this patient had the most common forms of congenital adrenal hyperplasia since tumor tissue expressed both 21-hydroxylase and 11β-hydroxylase activities. This

patient died soon after surgery, so no assessment of tumor chemotheropetic sensitivity was available.

Consideration of Steroidogenic Neoplasia by Clinical Syndrome

General Considerations

Tumors of the steroidogenic glands generally function independently of trophic hormone control. This characteristic is clinically useful in differentiating syndromes caused by other mechanisms. Probably the best known test which exploits tumor autonomy is the dexamethasone suppression test (1). Pituatary ACTH-dependent hypercortisolism, but not the hypercortisolism associated with steroidogenic neoplasia, can be suppressed by pharmacologic quantities of glucocorticoids. This principle is also applied to the diagnosis of causes of isosexual precocious puberty. Patients with precocious puberty caused by steroidogenic tumors will have low concentrations of plasma gonadotrophins and elevated plasma steroid hormone concentrations. Hirsutism or virilism associated with polycystic ovarian disease or ovarian hyperthecosis is characteristically seen in women with elevated plasma gonadotrophin levels. Virilization caused by a thecoma, hilus-cell tumor or arrhenoblastoma is usually associated with low plasma gonadotrophin concentrations. An important exception to this rule should be pointed out. Pituitary trophic hormones may be suppressed by a few steroid hormones at most. If a steroidogenic neoplasm does not either directly or indirectly synthesize a steroid inhibitor of trophic hormone release, the general rules described above do not apply. Adrenal tumors deficient in 11 β-hydroxylase activity are examples of this sort of tumor. Since these tumors do not produce potent glucocorticoids, pituatary ACTH may not be suppressed.

Occassionally, patients are reported with androgen- or estrogen-synthesizing tumors and normal or even high serum gonadotrophin concentrations. This finding has always been puzzling. A recent study by Veldhuis and co-workers may offer a possible solution (101). They studied a man with an estrogen-synthesizing adrenal tumor. These authors measured serum LH by radioimmunoassay and by bioassay both before and after surgical removal of the tumor. They found that preoperative bioactive LH values were more suppressed than immunoreactive LH values. After surgery bioactive LH increased two to five fold more than immunoreactive LH. Thus, a patient could have "normal" immunoreactive LH values and actually have subnormal circulating LH bioactivity. The nature of the apparently biologically inactive LH which was detected preoperatively was not elucidated in this report.

Specific Syndromes

Cushing's syndrome. - Cushing's syndrome may be caused by the ectopic production of ACTH or by direct steroid hormone synthesis by adrenal or, rarely, testicular neoplasia. In general, the differential diagnosis of Cushing's syndrome is not difficult. Ectopic ACTH secretion most commonly occurs in patients with lung tumors which are detectable on chest radiographs (102). Other tumors, even clinically inapparent tumors such as small carcinoids, may secrete ACTH and cause Cushing's syndrome (102). Any of these tumors should cause bilateral adrenal hyperplasia. Adrenal tumors large enough to cause Cushing's syndrome should be easily visible on computerized tomograms of the adrenal and are easily differentiated from bilateral adrenal hyperplasia. Testicular tumors of adrenal rest origin which are large enough to cause

Cushing's syndrome should be obvious on physical exam (10). No well documented case of biochemical Cushing's syndrome has been caused by an ovarian tumor.

Virilization. - The presence of frank virilization in contrast to hirsutism should always make the physician suspect a tumor of steroidogenic tissue. Virilism associated with suppressed pituatary gonadotrophin levels and undetectable hCG levels is almost always diagnostic of a tumor. Ingestion of androgens, usually by female athletes, would be another rare cause for these findings.

Differentiating virilism caused by adrenal or ovarian neoplasia may be difficult. Stimulus or suppression testing is interesting but not clinically useful. Tumors anatomically located in the adrenal may be stimulated by hCG (103,104), and tumors of the ovary may respond to ACTH (23). Plasma or urinary steroids are not diagnostic for tumors of either anatomic site. Generally, virilism associated with high plasma testosterone levels and normal urinary 17-ketosteroid excretion would suggest an ovarian site for the tumor. Small adrenal adenomas may cause identical steroid hormone levels to result and may in addition respond to hCG stimulation (103-106).

Careful anatomic localization procedures coupled with judicious biochemical testing probably provides the greatest chance for successful localization. Ovarian ultrasonography can frequently detect a unilateral ovarian mass. This technique is rather insensitive; however, and may miss a small hilus-cell tumor or a larger tumor in enlarged polycystic ovaries. Examination of the adrenals by computerized tomography should detect adrenal nodules as small as 1 cm in diameter (107,108). In 1981 Gabrilove and coworkers reviewed all reported cases of virilizing adrenal adenoma and found no tumor smaller than 1 cm in diameter or 5 g in weight (11). Probably about 1.7% of the population harbors clinically silent adrenal nodules which may be picked up on CT scanning (107). Thus, the finding of an adrenal nodule in a virilized patient is not in and of itself diagnostic of an androgen-synthesizing adrenal neoplasm. Urinary 17-ketosteroid excretion and plasma dehydroepiandrosterone and dehydroepiandrosterone sulfate values are often increased in patients with functioning adrenal nodules. In Gabrilove and coworkers' series of adrenal adenomas causing virilization, 71 percent of adults and 87 percent of children demonstrated urinary 17-ketosteroid excretion above 20 mg/24 hours (11). Plasma determinations of DHEA and DHEA sulfate were only performed on six patients but were elevated in one half (11). Although urinary 17-ketosteroid excretion and plasma concentration of DHEA may be elevated in women with ovarian tumors, these findings coupled with evidence of a mass on CT scan would be sufficient indication for unilateral adrenalectomy.

Table XII. Responses of Steroid Hormone-Producing Tumors to Trophic Hormone or Suppression Testing

-Virilizing tumors of the adrenal or ovary may respond to LH/hCG or ACTH

-Dexamethasone or estrogens may suppress tumors of adrenal, ovary, or testes

-Plasma or urinary steroid hormone or metabolite levels will not consistently differentiate tumors localized in adrenals, ovaries, or testes

Feminization. - Male feminization, manifested by gynecomastia, loss of beard and impotence may occur association with either adrenal or testicular neoplasia (12,18). Elevated estrogen levels or decreased testosterone to estrogen ratios are required for these symptoms to occur (18). If these symptoms are associated with suppressed plasma gonadotrophin concentrations and no evidence of estrogen exposure, Kallman's syndrome or systemic illness exists, then a tumor must be suspected. Testicular tumors which cause feminization, either Leydig-cell tumors or Sertoli-cell tumors should be palpable on physical examination or detectable by testicular ultrasonography. Almost all feminizing adrenal tumors are large and should be detected by computerized tomography of the adrenals (12).

Estrogen-synthesizing tumors in girls result in isosexual precocious puberty. The critical determination in this case involves defining whether elevated estrogen levels in an affected child are gonadotrophin-dependent or independent. Evaluation of a child with elevated estrogen levels and suppressed gonadotrophin levels requires a careful search for environmental estrogen exposure. The most common source of estrogen ingested by children is their mother's oral contraceptives.

Most ovarian, and probably all adrenal, neoplasia occurring in adult women synthesize sufficient androgen to cause hirsutism and/or virilism. Granulosa-cell or granulosa-theca cell tumors occurring in adult women may cause only menstral disturbances in premenapausal women and postmenapausal bleeding in older women. These tumors are then usually detected on physical examination or during evaluation of the other much more common causes of these symptoms.

Conclusions

Tumors derived from the steroid hormone-synthesizing cells of the adrenal, ovary and testes are rare causes of certain clinical syndromes. The control of steroidogenesis in these neoplasia is different than that of normal tissues and provides the major clue which allows differentiation of symptoms caused by neoplasia from symptoms caused by benign processes. Localization of tumors causing a specific syndrome is usually not difficult unless the presenting clinical complaints are of virilism. Primary treatment of almost all steroidogenic neoplasia is surgical. Postoperatively, it is usually not possible to formulate an accurate prognosis for an individual patient although characteristics of the patient and tumor may allow formation of a general prognosis. Treatment of metastatic steroidogenic neoplasia is rarely curative but may provide reasonable short term palliation.

It seems probable that careful study of these rare neoplasia may significantly increase the present understanding of steroidogenic tissue differentiation and function.

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