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HORMONE SECRETING TUMORS OF THE TESTIS

by

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HISTORICAL

The nature of testicular tumors was not known until 1696 when Saint Donat (1) identified a skull and optic cups in, and established the fetal character of, one of these growths. In 1803 Prochaska (2) found fetal limbs and in 1833 Andre de Perrone (3) described a tumor in the testis containing hair, teeth and bones. Curling (1853) (4) classified these tumors as benign cystic and solid malignant. In 1854, Johnson pointed out their tridermal origin. Astly Cooper (5) gave testicular tumors the name, hydatid disease.

Langhan, (6) (7) in 1887, with the aid of the microscope, classified these tumors of the testis according to structure. He classed the simple tumors with the teratomas and observed the carcinomatous nature of the "alveolar sarcomas". He observed that a large proportion of all testicular tumors were of teratoid origin.

In 1902 Wilms (8) stated that all the complex tumors of the testis were tridermal and divided them into (a) adult cystic embryomas and (b) solid embryoid teratomas.

Although chorionepithelioma was described in the male as early as 1878 by Monad and Malassez (9), it was not recognized as embryonal until Wlassow (10) reported four cases in 1902.

Chevassu (1906) (11) wrote that while two-thirds are tridermal, one-third have their origin in another source, i.e. spermatoblasts. He called these "seminomas".

In 1911 Ewing (12) refused to accept this extra-teratogenous origin but insisted that when only one type of cell was seen it was due to a predominance of one germ layer over the others. Ewing, Bell and Stevens (13) have separately cited six cases that were exceptions to this idea. In 1930 Brinnes (14) reported that, after going back and studying additional sections in each of thirty-two cases of teratoma of the testis, he was able to transpose six cases from the homologous tumor group to the mixed tumor group. "This is valuable proof", he wrote, "of the correctness of Ewing's position". "However, Ewing's explanation (that the almost pure epithelial nature of these tumors is due to a one sided development of a teratoma) does not appear as reasonable as to say that these tumors arise from very young sex cells which are still totipotent and are capable of giving rise to heterologous elements". Brinnes, in this statement, is not wholly in agreement with Ewing. In 1935 Dean (15) wrote, "Ewing's theory as regards the origin of testicular tumors is the most widely accepted".

In 1938 Aschheim and Zondek (16) published what is now known as the Aschheim-Zondek test for pregnancy. In 1930 Zondek (17) found that out of thirty cases of carcinoma in men, two reacted positive to the A-Z test. These two were "sarcomas".

In July 1930, Zondek (18) reported fifty-five cases of genital carcinoma in women and found eighty-one per cent of them positive. Five of a group of fourteen women with extr^o-genital carcinomata were positive.

In March 1930, Zondek (19) found four positives out of thirty extra-genital carcinomata in men. In two "sarcomas" of the testis the reaction was positive.

Heidrich and Fets (1930) (20) reported the excretion of hormone in the urine of a case of chorion-epithelioma.

Ferguson (1931) (21) studied twelve cases and found excretion of prolan A in all. He observed a decrease in prolan after irradiation. He also noted its absence in benign lesions. Ferguson wrote, "We find that certain neoplasms of the testis cause the excretion of hormone whose presence in the urine can readily be detected by biological means". This author studied fifty-one cases of teratoma testis and found all to be positive. He grants that there is nothing conclusive as yet but feels that the findings are consistent enough to warrant this preliminary report.

CLASSIFICATION

The best classification of testicular neoplasms like nioplasms elsewhere in the body is probably histological. Due to the great variability in the structure of these tumors attempts at histological classification have been some what complex. Further, the attempt by some to base the classification on pathogenesis has lead to considerable controversy, since the exact origin of some of them is a matter for conjecture. As a result of many different classifications, numerous terms have come into the literature which make a clear understanding of the nature of the tumors difficult.

In order to avoid further confussion in this matter the classification which I feel to be the most widely accepted at present, will be given here first, along with a brief description of each type.

Presented here is a simple, widely accepted classification of tumors of the testis taken from Herger and Thibaudeau (1934) (22):

1. Malignant teratoma with adult features:

These tumors contain portions of adult organs such as cartilage, fat, bone etc. They may contain only a few of these elements or many. They may be typical

dermoid cysts and contain hair, skin, fatty material, teeth etc.

2. Embryonal Carcinoma (Seminoma): These are described as consisting of large round polyhedral cells with vesicular hyperchromatic nuclei separated by fibrous bands. There are seen areas of central necrosis in the large tumors.
3. Embryonal Carcinoma with lymphoid stroma: These are similar to the Embryonal Carcinomata (above). They differ in that the stroma is more prominent than in the seminoma. The stroma contains many lymphocytes which divide the tumor into many islands.
4. Embryonal Adenocarcinomata have definite characteristics. The alveoli are lined with hyperchromatic nuclei. Papillary structure is often seen and hemorrhage is not uncommon.
5. Chorionepithelioma in the testis is identical with the same tumor in the uterus. There is seen a syncytium which resembles squamous epithelial cells, some being multinucleated, and arranged in a more or less disorderly manner. Close to these syncytial cells are

seen cells of Langhans layer growing in sheets.

Attempts (23) (24) (25) (26) have been made to classify tumors of the testis according to the amount of prolan excreted in the urine. This has many practical advantages over histological classifications. An idea of the degree of malignancy and the prognosis can be obtained from such a method.

Townsend (1935) (27) described a case of lymphadenoma (Hodgkins disease) in the testis. He stated that Sicard, Pavil, Gulland, Murray and Ziegler had cited cases but that it was otherwise quite rare.

The term teratoma testis has from common usage come to be synonymous with the term tumor of the testis. Actually the work derivation of teratoma means monster or fetal maldevelopment. Since it has been shown by Wilms (28), Ewing (29) (30) and others (that all the common tumors of the testis arise from totipotent sex cells, that monodermal growths are "one sided developments" from tridermal teratomas and that malignant tumors developing from mature rete, epididymus or testis cells are rare or non-existent) this term is not so much a misnomer as it might seem at first. However, Brinnes (31), while agreeing with Ewing's (32) position does not agree with the term teratoma for the reason that so

many of these tumors do not have the characteristics of teratomas. He suggests embryonal carcinoma. This term has actually come more into general use since Brinne's paper was written.

Ferguson (1933) (33) studied 120 cases of teratoma testis and listed them according to their bio-assay reaction. As the amount of prolan increases, the predominating type of cell is seen to become more embryonal:

adult teratoma ----- 5 - 500 mouse units per liter

seminoma ----- 400 - 500 mouse units per liter

embryonal carcinoma with

lymphoid stroma - 1000 - 10000 mouse units per liter

embryonal adeno-

carcinoma ----- 10000 - 50000 mouse units per liter

chorionepithelioma - 50000 - 100000 mouse units per liter

INCIDENCE

Teratoma testis is rare. Stelle (34) has reported fifteen cases in 14,381 general admissions in twenty-eight months. In this series, out of 620 cancers, only 0.024% were teratomas. The incidence of teratoma however varies considerably in different series. Ferguson, (35) in a study of 292 patients with teratoma testis found them to be 2.09% of malignant tumors. Teratomata comprise over half of all tumors of the testis (36).

It has been shown that tumors of the testis occur most frequently during the years of greatest sexual activity. Due to the rarity of these tumors there is considerable variation between the statistics of various writers. Ferguson (37) found in his series that the average age at which the first symptom was noticed was thirty-one years. Herger and Thibaudeau (38), in a small series of fifty-five cases found the average age to be thirty-three years. Dean (39) found that fifty-two per cent occur on the right and forty-seven per cent on the left.

Chorionepithelioma is one of the rarer of testicular neoplasms. Belt (1937) (40) stated that they were about one per cent of testicular tumors. Fortner (41) found three chorionepitheliomata in one hundred cases of teratoma testis. In a review of the literature, Heaney

(42) found 131 cases of chorionepithelioma in the male, ninety per cent of which arose primarily in the testis; seven cases were definitely of extra-genital origin. Heaney reports another case of extra-genital chorionepithelioma.

Pierson (1932) (43) found forty-six cases of bilateral malignant testicular tumors in the literature and added one of his own.

ETIOLOGY

Trauma has long been considered as a very important factor in the cause of testicular tumors. In many instances the first symptom is noticed after some minor injury to the testis. Dean (44) found trauma to be a factor in ten per cent. Entwisle and Hepp (45) cited cases in which injury to the testis preceded the onset of symptoms. The occurrence of testicular tumors during the time of greatest sexual activity may in some way be related to the etiology.

Dean (46) found fifty-two per cent on the right and forty-seven per cent on the left. This, according to some, is due to the fact that cryptorchidism occurs more frequently on the right than on the left. Bulkley's (47) statistics showed that tumor was more apt to develop in undescended testis probably due to the greater possibility of trauma.

In a series of 39,359 male patients collected by Hinman and Benteen (1936) (48), 155 were cryptorchids. In this series tumors of the testis occurred twenty times more frequently than in normally placed testes.

Dean (1935) (49) found that operations for hernia had been performed on twelve per cent before enlargement was noticed.

Mac Kenzie (1834) (50) reported two cases of

malignancy in cryptorchids. He summarized by stating that there were no facts supporting the view that cryptorchidism predisposes to malignancy. He gave no reasons for not supporting this view. Statistics (51) (52) (53) published before and since this paper show that cryptorchidism is a definite etiological factor. Whether the one predisposes to the other, or cryptorchidism and testicular tumors have common etiological factors, is not known.

Lepshutz, (54) in a review of the literature on this subject cited Dean as finding 13.5% of all tumors of the testis in cryptorchids, Hinman twelve per cent, and Rubaschow eleven per cent; and on the other side of the question Eccles reported 859 cases of undescended testis without any cases of malignancy. This author makes no mention of the ages of these patients. Coley has reported 1,357 cases of cryptorchidism without any malignancy; Kocher found one case of malignancy in one thousand cryptorchids; and Hinman one in sixty thousand. Christofferson (55) found that in two of his five patients the teratoma became noticeable some time after the testicles had been drawn into the scrotum. Belt wrote, "Since the spermatogenic cells in all cryptorchids are abnormal, it is generally felt that some factor other than trauma is involved in the production of testicular

tumors in these individuals".

Bell (56) has offered a rather unique theory on the etiology of chorionepitheliomata in women. He states that early in pregnancy chorionic tissue is like somatic malignant tissue. It shows a pH below 7.4. He suggests that chorionic epithelium is malignant until the fetus becomes large enough to make the chorion "subservient" to the fetus.

In support of this idea Fraenkel (57) has demonstrated a substance lytic to the chorionic epithelium, in the serum of normal pregnancies, while the serum of a chorionepithelioma patient lacks this. These ideas may be applied to chorionepitheliomata in women but not in men.

CLINICAL COURSE

One of the earliest symptoms is a painless swelling of one testis frequently following injury (58). The testis loses its elasticity and becomes firm and hard. In ninety per cent of a series of 124 cases, Dean found the first symptom to be "increase in size". In forty-one per cent of Young's (59) cases and fifty-seven per cent of those of Dean, (60) loss of weight was present on first examination. The first sign in three-fourths of the cases is painless swelling (61). A large proportion of patients with testicular swelling, due to the absence of pain do not seek medical advise right away. Belt, (62) says that seventy per cent have not sought medical advise until the elapse of four or more months. Two-thirds of the patients referred to the Memorial Hospital, New York (63) had lost about six months because of incorrect diagnoses.

Belt (64) stresses the point that every intra-scrotal swelling should be examined to rule out teratoma.

A brief review of a typical case history will serve to show the symptoms, course, and prognosis in this condition. This case is taken from a paper by Owen (1935) (65). In September 1929 the patient, a white male, age thirty, entered complaining of a mass in his right testicle of three months duration. The mass was seen to enlarge

for two weeks and on September 24, 1929 an orchidectomy was done. In November 1931 (after two years feeling well) the patient reentered complaining of pain in the back. A mass was palpated in the right abdomen. On November 25, 1931 X-ray treatment was started at two to three day intervals giving doses of two hundred kilovolts at fifty centimeter distance with a nine by nine centimeter port and filtered through fifty millimeters of copper and one millimeter of aluminum. Thirty-five by five milliamperere minutes were given, one thousand R (French) units into right and left hemi-abdomen alternating anterior and posterior. On December 22, 1931 the tumor had decreased from six by six centimeters to two centimeters in diameter. July 1934 the patient returned again after having felt quite well for two and a half years complaining of increasing shortness of breath. Chest plates showed an opacity in the left lung. He was given daily doses of X-ray for fourteen doses as follows: Fifteen hundred international (r) units to each of four ports thru 3.5 millimeters of copper and two millimeters of aluminum at sixty centimeters distance and with a kilovoltage peak of 250. The patient again resumed work. In September 1934 (two months later) X-ray plates showed a diminution in size of the mass but the patient was having considerable shortness of breath. This

was at the height of the radiation reaction and there was probably considerable congestion and mediastinitis. The patient died October 29, 1934.

The story is by no means always as favorable as this one. In the case of more malignant types and especially chorionepitheliomata the primary may not be discovered until an autopsy is done. Craver (66) cites a case of a boy of fifteen years who came to him with the complaint of dyspnea and pain in the right shoulder. A chest plate showed a mediastinal mass. The patient died soon after this of intra-cranial metastases. Before death the testes had been found to be atrophic. A possible connection between the atrophied testis and the mediastinal mass was suggested and the Aschheim-Zondek was found to be 10,000 mouse units per liter. This high A-Z suggested chorionepithelioma. This diagnosis was verified at autopsy, chorionic tissue being found in the lung, mediastinum and brain. By very careful serial sections of the atrophied testes two, one millimeter masses were seen in the left testis. One was seen to be a mucous gland and the other a cyst lined by sloughing stratified squamous epithelium. Blood obtained at autopsy was found to contain 250,000 mouse units per liter. This case is significant in that the primary was in such an accessible organ and yet was found only after careful

histological examination of both testes. Similar cases have been cited by den Hartog (1933) and Prym (1927) (67).

In order to properly treat teratoma testis an early diagnosis is essential. The usual story is that of a man between the ages of twenty-five and fifty who presents himself with painless swelling in one testis with or without a history of trauma or infection. The testis usually retains its proportions which point is important in differential diagnosis.

In examining these tumors the lightest touch should be used as malignant cells may be dislodged (68). Scrotal skin is seldom involved. When it is it occurs late. The inguinal glands are involved only when the tumor has invaded the scrotal skin. Any fluid which may surround the testis should be aspirated taking care not to puncture the tunica albuginea. "All ages are effected including infancy" (69).

According to Belt (70), Dean (71) and Henline (72) the following conditions should be considered in the differential diagnosis:

- (a) Gumma is slow growing. Normal testicular substance can be felt to one side and does not give the impression of having atrophied. A positive Wassermann practically rules out teratoma and a weeks

administration of antiluetics should diminish the size of a gumma.

- (b) Tuberculosis is usually associated with fever and some pain. "Confusion is brought about by the fact that the combination of tuberculosis and teratoma is not uncommon". In tuberculosis, nodules may be palpated in the epididymus, vas, seminal vesicles and prostate.
- (c) Hydrocoele is a translucent tumor and is usually located near the base of the penis. Tapping of the hydrocoele renders the testis more easily palpated.
- (d) Old scars are seen in some cases where extensive trauma has occurred.

According to Belt microscopic sections were necessary to rule out new growth. Metastatic tumors are sometimes seen in the testis having been conveyed there by the blood stream.

As metastasis takes place later, abdominal cramps, back ache, and indigestion appear (73).

Dean (74) states that metastases may occur from a very small tumor. There is first seen an abdominal mass due to involvement of the lumbar glands on the same side as the lesion. Then there follows

involvement of the mediastinal and supraclavicular glands. The lungs usually are next, due to venous metastasis. The average time from the first symptom to death in fatal cases under treatment is twenty-four months. Ferguson (75) quotes Cunio as saying that from the lumbar glands which extend up to the renal artery, lymphatic channels extend on up above the kidney in ninety per cent of normal individuals and connect with the mediastinal lymph nodes.

The clinical course also varies with the type of teratoma, i.e. the degree of malignancy. This depends on the proportion of embryonal tissue present. The most common type, as was seen in the section on classification, is the embryonal teratoma. This type is very malignant. It contains partly adult tissues and partly malignant embryonal tissues.

It is interesting to note that, due to the anterior pituitary hormone found in the blood of these patients, an undescended testicle may sometimes come down - Dean (1935) (76). The same result is seen in the therapeutic administration of pituitrin.

In a certain percentage of chorionepitheliomata there is seen a gynecomastia. This is, according to Warthin (1909) (77), an index of the progress of the disease. Entwisle and Hepp (1935) (78)

report a case of an injury to the testis followed in a few months by general pains and loss of weight. Only a very small innocent appearing tumor was found in the testis while there were seen to be enormous metastatic growths elsewhere in the body. The breasts were lactating, the Aschheim-Zondek was positive, there were found histologic changes in the pituitary identical with those occurring in pregnant women.

In discussing the diagnosis mention should be made here of a very valuable laboratory procedure. Belt, (79) in his recent paper states, "The discovery, that hormones are produced by a large majority of testicular tumors and that these hormones appear in abundance in the urine of many individuals afflicted with these growths, has been of the utmost diagnostic value". "The test serves three purposes: (a) The amount of hormone present gives some idea of the type of tumor and the degree of malignancy, (b) The bio-assay after treatment is started gives an indication of the radiosensitivity, and (c) Repeated tests after treatment is finished gives an index of recurrences and metastases".

PATHOLOGY

The following is the pathological outline of testicular neoplasms as put forth by Belt (1937) (80).

I Embryonal tumors 90-95%

A. Embryonal carcinoma

1. Gross: Firm with cartilaginous consistency
Cut surface: homogeneous, cream colored, firm and fleshy. They may be fibrous septa.

2. Microscopic

- a. Small cells with well marked lymphoid stroma forming distinct bands.
- b. Majority have larger pale staining cells with varying amounts of lymphoid stroma. These are usually called seminomata.
- c. Typical seminoma with large vesicular, oval or round cells resembling spermato-cytes that form structures resembling a rete. The nuclei are reticular. The cells are not closely packed and a section reveals a uniform areolar like net of similar cells. Lymphocytes commonly infiltrate in several areas. These tumors elaborate much less hormone than

(a) and (b), averaging about two-hundred mouse units per liter.

- d. Included in this group is the occasional tumor with large primitive cells which are pale staining and reticular. The hormone output equals that of chorionepithelioma, but the syncitial cells which characterize the chorioepitheliomata are not present.

B. Mixed embryonal teratomata:- Contain a much higher proportion of the three germ layers.

1. Gross: Firm, hard, possible soft cystic areas. Cut surface: Irregular growth of fibrous tissue, separating glandular and cystic areas. Color is pale, creamy in some areas and dark and vascular in others.

2. Microscopic:

a. Marked teratoid type: Mostly differentiated layers with some primitive cells and areas of adenocarcinoma scattered through irregular strand of fibrous tissue. Most of the cells will be hyperchromatic and dark staining.

b. Adenocarcinoma: closely packed, hyper-

chromatic dark staining cells with the appearance of acini separated by fine connective tissue fibres. It is common to see complete necrosis in parts. "a" and "b" are not separate entities, but merely express the varying degree of differentiation of the cellular structure. The anaplastic darkly staining cell predominates in both types, and a higher proportion of radio-sensitive cells occur in "b".

c. Chorionepithelioma: One per cent. Very irregular growth of tumor with lobulated outline, typical syncytial cells and villi similar to those occurring in women.

II Adult teratomata: Five per cent of testicular tumors.

- A. Gross: Hard firm tumors, frequently with soft areas due to cysts. Cut surface: variegated heavy connective tissue septa with pale cellular areas interrupted with many cysts of various sizes.
- B. Microscopic: Fully differentiated adult type of active glands, squamous epithelium, and possibly bone or hair. Malignant cells scattered between the adult structures. They do not respond well to

irradiation.

III Miscellaneous tumors

Form one to two per cent of testicular tumors.

Except for the rare sarcoma, they are usually benign and clinically unimportant, except as a diagnostic hazard".

In further discussion of the pathology, the classification put forth by Herger and Thibaudeau (81) under the section on classification will be used wherever possible.

As has been stated previously there is some difference of opinion among the various writers as to the origin or pathogenesis of the so called seminomata. Chevassu (1906) (82) (83) used the latter name while Ewing (84) (85) (86) (87), gives these tumors the name embryonal carcinomata, believing them to be one sided developements of true embryomata. He believes that these sex cells, being totipotent, may produce any tissue derived from these three primary germ layers. Ewing (88) reviewed three hundred sections and stated that he was certain that the embryonal carcinoma with lymphoid stroma was derived from three layers. He believes that by careful serial sections of the entire tumor, all three germ layers can be demonstrated. Boyd (89) using the term of Chevassu described seminomata as resembling sarcomata in

that they are fleshy and homogeneous on cut surface. Microscopically the cells may be large and clear or dark and small like a lympho sarcoma. They may be tubular and slow growing or diffuse and rapid growing. Thus by describing the variations in these tumors Boyd has included the "embryonal carcinoma", "embryonal carcinoma with lymphoid stroma" and the "embryonal adenocarcinoma" of Herger and Thibaudeau (90) under one term: "embryonal carcinoma" or "seminoma". Boyd's (91) embryoma or teratoma is described as a tumor containing all three germ layers. His third type is chorion-epithelioma.

In 1930 Brinnes (92) was able, by going back and studying additional sections, to transpose six cases out of thirty-two tumors of the testis from the homologous group to the mixed tumor group. This is valuable proof of the correctness of Ewing's position - Ewing (1911) (93).

Strangely enough the first case of chorion-epithelioma that was described was a testicular tumor (1878) (94). Its embryonal nature was not realized at this time however. In 1889 Sanger (95) described the first case in women. In 1906, Frank (96) wrote, "In the typical group the characteristics of the chorionic epithelium, which appears in the first stage of gesta-

tion, are represented with few or no variations. They show well developed continuous syncytial masses of irregular, multinucleated strands, and branching, protoplasmic buds, and with a more or less well developed ground work of numerous transparent polyhedral cells of the nature of 'Zellschecht' (viz. Langhan's cells)". His summary of the elements found is: (a) Syncytium. (b) Langhans cells. (c) Chorionic wandering cells. (d) Masses of blood and fibrin. In 1925 Handfield-Jones (97) wrote a classical description of each of the above elements and illustrated them with colored plates.

In 1907, Bonney (98) collected only twenty cases and in 1925 Handfield-Jones (99) collected 109 cases of chorionepithelioma of the testis. Thus it is not a common tumor. "The occurrence of extra-genital chorionepithelioma has been doubted" - Prym (100). When found extra-genital, it is practically always metastatic - Obendorfer (1931) (101). In 1933 Heaney (102) found eight extra-genital chorionepitheliomas out of a total of 131 cases.

Ross (103) described the appearance of a primary chorionepithelioma of the testis as being grossly necrotic and showing the remains of old blood channels in the necrotic mass. The metastatic lesions she described as identical with the primary. Where well pre-

served the tumor tissue consisted of typically malignant polyhedral cells closely packed, and forming broad sheets or narrower columns.

A rather unique explanation for the occurrence of chorionepithelioma in women is presented by Blaire Bell (104). His idea is that in normal gestation, the chorionic epithelium is malignant until the fetus becomes large enough to make the chorion "subservient" to it. Fraenkel (105) has demonstrated in the serum of normal pregnancy, a lytic substance to chorionic epithelium while the serum of a patient with chorionepithelioma lacks this. On the basis of this Fraenkel has attempted to treat cancers and more particularly chorionepitheliomata with the serum from pregnant women. The above theories with a history of pregnancy and retained placental tissue afford a possible explanation for the occurrence of these tumors in women but not in the male.

Chorionepitheliomata of the testis are, according to Warthin (106), Cooke (107), and Gaborini (108), associated with a gynecomastia.

Greulich and Burford (1936) (109) have reported the study of gynecomastia in three male dogs. In one, seminoma was proven histologically. All three attracted other normal male dogs. In one of these dogs surgical removal of the enlarged testis resulted in the

loss of the mammary prominence and the attraction for other male dogs.

Craver's (110) case of a boy of fifteen with extensive metastases and atrophic testes illustrates the treacherousness of as well as the diagnostic problem presented in this condition. Diagnosis could be proven only by biopsy or the biological test. Krantrowitz (111) has reported a similar case.

It has been shown by Ferguson (112) (113) and verified by Entwisle and Hepp (114) that structural changes occur in the pituitary in cases of teratoma, similar to those occurring in normal pregnancy, chorion-epithelioma in the female, and certain neoplastic diseases accompanied by high prolactin A output. Hyperplasia of the basophilic cells of the anterior lobe is always seen in these conditions. Ferguson offers this as an explanation for the presence of prolactin in the urine, i.e. increased secretion of prolactin by the pituitary.

Stelle (115) expresses the opinion that every malignant tumor of the testis is either embryonal carcinoma or embryonal adeno-carcinoma of teratomatous origin. Stevens, Bell and Ewing include one other type i.e. adult teratoma. Why, chorionepithelioma is not mentioned here is not clear. It would seem that this

writer does not consider this tumor a teratoma. Jean Calleus (116) in February 1935, pointed out that the occurrence of chorionepithelioma in the testis and its response to the pregnancy test is proof of the tumors identity as an embryonal tumor.

Kirwin (1937) (117) presented a case of chorionepithelioma with metastases to the lungs, liver, spleen, brain, kidneys, thyroid, jejunum, ilium, colon and mediastinal and retro-peritoneal lymph nodes. Striking similarity was seen between metastases and original testicular lesion: 1. Sheets of cells were separated by the syncitial masses from large pools of blood, some of which were lined with epithelium. 2. There was a conspicuous absence of fibrous tissue. The cells were classified as the Langhans type i.e. syncitial cells of chorionic villi.

As regards metastases Ferguson (118) states that in ninety per cent of normal individuals at least one chain of lymphatics from the lumbar glands extends up above the renal artery and into the mediastinal nodes.

Of seventy-seven of his cases, seventy-two were classified as embryonal carcinomata. Forty-five of the seventy-two had metastases which were beyond radical surgery i.e. above the renal pelvis.

"Sufficient evidence has been adduced to show

that the natural history of the embryonal forms of teratoma consists in a progressive involvement of the normal lymphatic apparatus of the testis, which on anatomical, pathological, and clinical grounds includes the spermatic, lumbar, epigastric, mediastinal and supra-clavicular lymph nodes; and further, that the disease extends through venous channels to the parenchyma of the lung in a formidable number of cases".

On examination of metastases there is usually seen only one germ layer. Ewing (119) described a case of teratoma testis with several metastases, each containing a different element. Steinert (120) reported a case with metastases containing more than one element. Smadel (121) presented a case in which individual metastatic nodules contained all three germ layers.

An interesting case cited by Lelienthal (1932) (122) pointed out the high degree of malignancy of chorion-epitheliomata and the early metastases. His case entered with symptoms referable to the chest. X-ray revealed a lesion in one of the lungs giving the appearance of a benign sarcoma. The patient showed enlargement of the breasts. At operation the entire lung was found to be infiltrated and a biopsy was taken before closing the incision. Dr. Ewing found what he thought was chorionepitheliomatous tissue, in these sections, and

BIO-ASSAY

Ferguson (1931) (127) reported the first use of the Aschheim-Zondek test in the diagnosis of testicular neoplasms. However, to Aschheim and Zondek (1928) (128) goes the credit for the discovery of Prelan A in the urine of pregnant women. In July 1930 Zondek (129) reported fifty-five cases of genital carcinoma in women and found eighty-one per cent of them positive. A group of fourteen women with extra-genital carcinomata gave five positives. Zondek (1930) (130) found four positive A-Z reactions out of thirty extra-genital carcinomata in men. In two cancers of the prostate the reaction was negative. In two "sarcomas" of the testis the test was positive. With this work as a lead Ferguson, (1931) (131) studied fifty-one cases and found all teratomas positive. In the summary of this report, Ferguson wrote that it is granted that there is nothing conclusive in these results but it is felt that the findings are consistent enough to warrant this preliminary report.

Zondek's original technique was a qualitative procedure and is not suited for the more accurate quantitative requirements of a study of the course of a new growth. Thus there developed the necessity for a method

of concentrating the hormone before undertaking its quantitative estimation. Zondek's method was one of alcoholic extraction, however Owen and Cutler (132) have outlined the Katzman-Doisy benzoic acid concentration method and recommend it in preference to that of Zondek. One hundred cubic centimeters of urine are first acidified with acetic acid to give a final pH of 4.5 or 5.0. This is chilled over night and filtered. To the filtrate is added ten cubic centimeters of chilled acetone, previously saturated with benzoic acid. The specimen is constantly agitated while the acetone-benzoic acid solution is added drop by drop. The precipitate is then spread out to dry after which it is placed in twenty cubic centimeters of chilled acetone. The remaining residue is washed twice with ten cubic centimeter portions of chilled acetone, after which it is allowed to dry. This residue contains the hormones as well as some water insoluble material. Add five to one hundred cubic centimeters of water and discard the water insoluble portion.

The animal of choice in carrying out the biological assay is the mouse. For each assay, six immature virgin mice eight to ten grams in weight are required. Mice one to three receive 0.1, 0.2, and 0.4 cubic centimeters of urine. Mice four to six receive

0.1, 0.2, and 0.4 cubic centimeters of a five fold extract. Injections are spaced during a forty-eight hour period, and ninety to one hundred hours after the first injection both gross and histological examinations are made. For this purpose hemotoxylin-eosin is the dye of choice.

In the interpretation of the results of the test, three things are looked for: (a) Hyperemia of the graafian follicle, (b) Corpora hemorrhagica within the ripened follicle space and (c) Corpora lutea. The unit used in tabulating the results is based on the following reactions: (A) Reaction (a) (above) with or without (b) in mice one to six inclusive indicate respectively two thousand, one thousand, five hundred, four hundred, two hundred, and one hundred mouse units of hormone per liter of urine assayed. (B) The presence of (c) with or without (a) and (b) in mice one to six indicate ten thousand, five thousand, twenty-five hundred, two thousand, one thousand, and five hundred mouse units of hormone, respectively, per liter of urine assayed. The lowest figure supplied by the test (one hundred mouse units) is well above the normal output of man.

As a result of the test malignant tumors can be differentiated from non-malignant, and the various

types can be classified according to their hormone output. The ranges of hormone output of the various types of tumor were found by Owen and Cutler (132) to be as follows:

Type of Histology	Mouse units per liter
Chorionepithelioma	10000 - 125000
Embryonal adenocarcinoma	
Embryonal carcinoma with lymphoid stroma	200 - 500
Seminoma	100 - 200
Mixed or adult type	0 - 400

In 1933 Ferguson (133) revealed, after a study of a large number of cases that (a) excretion of anterior hypophysis sex hormone in the urine of a man with a testicular tumor indicates teratoma; (b) irradiation produces a marked decrease in the amount of hormone eliminated, (c) recurrence after treatment is seen in the increase in the excretion of prolactin A; (d) this anterior hypophysis hormone, when excreted in large amounts causes a soft swelling of the prostate and seminal vesicles and the pituitary is indistinguishable from that of pregnancy; and (e) there is a hyperplasia in the interstitial cells of the testis. Stelle found the Aschheim-Zondek test positive in all cases of teratoma studied (134).

According to Ferguson's (135) statistics the biological estimation of prolan A, in the diagnosis and prognostication of testicular neoplasms, greatly improves the results of treatment when used routinely. The presence of prolan in the urine has come to be considered by some (136) as presumptive evidence of testicular malignancy and its absence, strong evidence against it.

There is a large group, according to Dean (137), who, having had orchidectomy or irradiation, and a negative test for a number of months or years, show an irregular variation in the test from zero to two thousand mouse units per liter. Therefore the test is not recommended for diagnosis or prognosis later than approximately eight months after irradiation or surgical removal. Dean emphasizes, however, that the "test, when performed and correlated with the physical observations, is of considerable diagnostic and prognostic value." Numerous papers have been published expounding the value of the Aschheim-Zondek test in diagnosis, and prognosis (138) (139) (140) (141). The following chart taken from Hinman (142) serves to correlate the prognosis with the A-Z test, the histology, and conditions:

"Patients without metastases and in good condition

(a) Gonadotropic hormone disappears within two weeks after castration.

(1) Structure indicates radiosensitivity
(prognosis good).

- (2) Structure indicates radioresistance
(prognosis fair).
- (b) Gonadotropic hormone present after two weeks after castration. The therapeutic test by irradiation:
- (1) Causes diminution or disappearance of the hormone (prognosis fair).
 - (2) Little affect on hormone (prognosis poor).

Treatment: Choice of radical surgery in a-2 and b-2.

Patients with clinical evidence of metastases

- (a) In good physical condition
 - (1) Radio sensitivity shown by diminution in or disappearance of size of metastases and amount of hormone under irradiation (prognosis fair).
 - (2) Radioresistent (prognosis poor)

Treatment: Irradiation."

In further support of the biological assay of prolan in the urine of patients with teratoma testis, Zondek (143) reported the bio-assay of forty normal men and of thirteen normal men with benign lesions of the testis. Prolan A was below fifty mouse units per liter in every case.

Since the discovery of prolan in the urine of patients with testicular neoplasms an explanation for its

presence has been sought. There are three possibilities (144) (145) (146): (a) An increase in prolactin A in the body may stimulate the growth. (b) The tumor may produce prolactin A in such excess that it appears in the urine. In support of this idea is the fact that more prolactin A can be obtained per gram of tumor tissue than per cubic centimeter of blood in a given case. Zondek has shown that fresh teratoid transplants in immature mice produce the typical ovarian response. (c) The more likely possibility, according to this writer is that the origin and growth of the embryonal tumor produces a hormone which stimulates the anterior lobe of the pituitary to secrete more prolactin A. Zondek (147) had previously put forth this theory. In support of this theory the point is made that the same structural changes are seen in the anterior pituitary in cases of normal pregnancy, chorionepithelioma in the female, and teratoid tumors in the male. This change is a hyperplasia of the basophilic cells of the anterior lobe. Further proof of this theory is in the observation that X-irradiation of the pituitary in teratoma testis causes a temporary decrease in the prolactin A in the urine. In opposition to this idea of the part played by the pituitary, Mussie-Fournier (1937) (148) found both prolactin A and B in the urine of a patient in whom the pituitary body had been completely destroyed by metastases from the testicular tumor.

At the time that Zondek demonstrated the excretion of gonadotropic hormone in the urine in 1931 he pointed out that since it was primarily a stimulant to follicles it was identical with prolan A in contra distinction to prolan B (the leutinizing hormone of pregnancy. Freed and Coppock (149) found that the hormone was similar to prolan B (or the hormone of pregnancy) in that it produced corpora lutea. However, they pointed out that the corpora produced by the hormone of teratomata are avascular and more numerous and the uterine appearance is distinctly different. It was observed that the gross appearance might be mistaken for a prolan A reaction. This possible error might explain the divergence of opinion in the findings of Evans (150), Zondek (151) and others who have described the reaction as being purely follicular and thus unlike that of pregnancy.

In a further attempt to identify the hormone and differentiate it from other closely allied hormones, Hinman and Powell (152) wrote that the stimulation of the growth of the gonads and genitals of infantile animals depends on the origin of the hormone, the amount present, and the animal used. They distinguished four types of gonadotropic hormone: (a) anterior pituitary hormone, (b) prolan or anterior pituitary like hormone of pregnancy, (c) the hormone of castrates and (d) testicular neoplastic hormone. Evans et al (153) believe that the prolan of testicular tumors may have the characteristics of both the anterior pituitary sex hormone and the factor

suggested an A-Z test be done on the basis of a possible testicular primary. The test was strongly positive although there was nothing palpable in the testis.

Townsend (123) described a case of lymphadenoma (Hodgkins disease) of the testicle. Similar cases have been described by Sicard and Pavil (124). Simmond (125) cited cases of Gulland, Murray and Ziegler.

Moore (126) in a review of the subject of the testicular hormone pointed out that it is chemically a ketone alcohol and its secretion is under the control of the pituitary gland. Its primary function is the control of the secondary sex glands. It is not a testicular stimulant.

occurring in the urine of pregnant women. Hamburger (154) in a study of five men with teratoma testis and one woman with an ovarian teratoma found the same histological picture in the ovaries of immature mice as that resulting from the injection of urine from pregnant women. Fuhlman (155) also believes that the hormone is more like that of pregnancy in that it causes an increase in weight of the ovary and leutinization.

There is some evidence that the testis has two internal secretions (156). Moore, (157) however wrote that "the facts available indicate a similarity so close that both are extracted by the same means and react alike to purification". It has been shown many times that the interstitial cells produce the testis hormone (158). "The male hormone influences the primitive cells and the body as a whole" (159). Experimental injection of the pituitary gonadotropic hormone produces, through the testis, prostatic enlargement in rats; whereas castration is followed by atrophy of the prostate and seminal vesicles, and by enlargement of the pituitary and the adrenal cortex" (160). "The fat soluble hormone, regarded as derived from the interstitial cells has been called androsterone. It corresponds to the oestron in the female. It was isolated in crystalline form in 1931 by Butenandt from male urine and has been prepared

synthetically" (Ruzicka et al 161).

Although it has been stated by various authors that the finding of prolan in the urine of a man is presumptive evidence of teratoma testis, yet the more recent literature reveals an occasional positive in other conditions as well as an occasional unexplained negative. Owen (162) found that in 125 proven cases of teratoma, the urine contained more than one hundred mouse units per liter in every case, and that false negatives and false positives occurred in less than ten per cent. Hirsch and Hoffman (163) have reported three cases of cerebral tumor and a case of acromegaly in females with positive bio-assays. Biedl and Morgetay-Becht (164) have reported positive prolan reactions in two-thirds of acromegalies. Hyperthyroidism has been listed (165) as likely to produce false positives. Castrates may occasionally show false negatives (166). Rapidly proliferating tumors such as myomata, carcinomata and genital hypoplasia may give false positive reactions (167). Malisoff (168) has reported a case in which the bio-assay was repeatedly negative both before and after removal of a histologically proven embryonal carcinoma.

Lindsay (1937) (169) wrote that "the pituitary is the master gland of the endocrine chain". Prolan, a pituitary like substance, is known to be associated

with a product of actively functioning chorionic tissue. Since the presence of hyperplastic tissue(chorionic tissue) can be diagnosed by testing biologically, the unconcentrated urine, and since the presence of small tumors (teratoma testis) can be ascertained by injection of concentrated urine or blood into laboratory animals perhaps an "antihormone" can be found with which malignancy can be treated. Cancer patients have been injected with blood of delivered mothers on the theory that the termination of labor is based on the presence of some "antihormone". In conclusion Lindsay wrote that the Achheim-Zondek is worthy of more frequent use in the study of tumors, and that it is not a substitute for but a stimulus to a careful clinical study.

A case is reported by Malisoff (1936) (170) in which the Biological test was repeatedly negative both before and after removal of a histologically proven embryonal carcinoma.

TREATMENT

As in neoplasms elsewhere in the body an early diagnosis is essential to a favorable prognosis.

The type of treatment is dependent upon the presence of metastases, radio sensitivity, duration and the degree of malignancy as shown by bio-assay.

After six months without treatment it is shown (171) that metastases have always occurred. In these cases intensive X-irradiation from the chin to the scrotum is mandatory. If the case is seen early (within the first five or six months), orchidectomy is followed by X-irradiation of the abdominal lymphatics. Dejarins and Smith (172) report fifty per cent cures when treated by simple orchidectomy before the elapse of six months. "The physician using simple orchidectomy is ignoring the presence of silent and unknown metastases which later develop and cause speedy death". "Bio-assay is readily obtained and should always be done before and after operation as a verification of the diagnosis and as a means of searching for possible metastases". In removal of a teratomatous testis the cord should be clamped and severed with cautery before the testis is touched (173).

The variation in the response of different tumors to radium was noted early (61). The markedly

"embryonal" type responded well to radium while the teratoid or adult types did not.

According to some writers (174) simple castration cures less than six per cent and castration plus radical excision of the primary abdominal lymphatic drainage, cures ~~seventeen~~ percent. This is done only when there are no metastases.

Dean (175) has suggested radium pack or high voltage X-ray both before and after removal. He claims 29.2% five year cures. Young (176), Lowsley (177), and MacKenzie (178) also advocate radical surgery plus irradiation.

"The radical operation of Hinman and Chevassu has simultaneously" with the swing toward the general use of X-ray, "undergone a sharp decline as the method of choice".

Radical surgery is indicated only when there are no evidences of metastases. The prognosis after the radical operation is determined by the effect of castration on the hormone and on the histological structure (179).

Treatment by irradiation in 154 cases was found to be superior to radical surgery in 29.2% (180).

Ferguson wrote, (181) "Sufficient evidence has been adduced to show that the natural history of the

embryonal forms of teratoma consists in a progressive involvement of the normal lymphatic apparatus of the testis, which on anatomical, pathological, and clinical grounds includes the spermatic, lumbar, epigastric, mediastinal, and supra-clavicular lymph nodes; and further that the disease extends through venous channels to the parenchyma of the lung in a formidable number of cases. It is demonstrated that nine patients with metastatic involvement beyond the scope of radical surgery were cured with irradiation and that no patient in Hinman's series with metastases above the level of the renal pedicle is cured. It is obvious that the radical operation disregards the normal pathogenesis of the disease and is based on false premises. It should be entirely discarded".

Many surgeons on first suspicion do an orchidectomy without the diagnosis being certain. This leads to local recurrence (38).

Belt (182) has recommended the following treatment when there is no clinical evidence of metastasis:

1. Diagnostic bio-assay is completed.
2. The abdomen including the epigastrium and pelvic region and the testis, is irradiated.
3. The testis is irradiated more intensely

than the other areas.

4. Orchidectomy is then to be done.

5. Bio-assays of hormone are done at three to six months intervals to detect metastases.

6. Repeated treatments with irradiation should become positive.

"The choice of radical surgery is governed by the following factors:

1. The patient must be in good physical condition.

2. There must be no clinical evidence of metastases or the duration must be less than four months.

3. Therapeutic irradiation must have had but little effect on hormone excretion.

4. Histological structure preferably after irradiation must indicate radio-resistance.

CONCLUSION

It has been the purpose of this paper to show, by means of a review of the literature and selected quotations, that:

1. The term teratoma testis applies to a heterologous group of tumors of the testis which may be of varying degrees of malignancy and cellular consistency. They are probably all derived from the three primary germ layers.

2. Due to the many possible variations in the histological structure, no very good structural classification is available, the most practical being based on the degree of malignancy as determined by the Aschheim-Zondek.

3. Teratoma testis is rare, being between 0.024% and two per cent of all malignancy.

4. The only etiological factor of any prominence is trauma but this is doubted by some. The literature is very controversial on the place of cryptorchidism as a factor.

5. The course is characterized by an insidious onset of painless swelling in one testis, and usually terminates in extensive metastasis through the lumbar, epigastric, mediastinal, and supra-clavicular lymphatics

and to the lungs through venous channels.

6. The pathological description of various types of teratoma has been given.

7. The procedure for the concentration and bio-assay of urine is given as outlined by Katzman-Doisy.

8. X-irradiation has in recent years gained much favor as the treatment of teratoma testis. Radical surgery has lost favor.

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