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## Chorionepithelioma of the uterus

Richard S. Heath  
*University of Nebraska Medical Center*

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CHORIONEPITHELIOMA OF THE UTERUS

BY

RICHARD S. HEATH

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## CHORIONEPITHELIOMA UTERI

In the review of literature on chorionepithelioma of the uterus the big question throughout the period of the knowledge of the condition as a disease entity, has been that of etiology. With the understanding of the etiological factors a better knowledge as to diagnosis and treatment arises,

As illustrated in this paper little is as yet known concerning the etiology other than the association of chorionepithelioma with the pregnant state, normal or abnormal. Coupled with the advancement made in the field of obstetrics, a diagnostic biological reaction has been perfected. This reaction is reliable in all cases of chorionepitheliomata, suspected or unsuspected.

With the advent of this diagnostic aid treatment, although little changed since Marchand's time, has been considerably aided. As with the early diagnosis treatment may be instituted early with a more favorable prognosis offered than in those cases to which treatment is resorted late in the process.

The purpose of this paper is to present in an orderly fashion the views of the outstanding men concerning chorionepithelioma. There is an attempt to correlate the accepted findings with suggestions as to problems which have arisen and not sufficiently investigated.

Definition:

Chorionepithelioma of pregnancy is a malignant tumor originating in connection with pregnancy. It is foetal in origin; arises at the site of placental implantation, and develops following hydatidiform mole, abortion, term or near term, and ectopic pregnant states. Clinically it is characterised by recurring uncontrollable hemorrhage, progressive anemia, early metastases, and cachexia - very often the first sign is that arising from metastatic lesions. Morphologically it is characterised by a friable, hemorrhagic, invasive, and destructive tumor usually situated at the site of placental implantation. Histologically it is characterised by the presence of chorionic tissue showing malignant tendencies. The disease is rare.

History:

The earliest description of chorionepithelioma with consideration of it as a disease entity is found in Saengers work of 1889.

Saenger (62) reports a case of a young woman, four months married, who aborted at the eighth week of pregnancy. Within seven months the woman died. Histopathological study revealed large decidual like cells with malignant characteristics. The decidual cells being known as maternal tissue led him to state that the condition was sarcomatous. The decidua being associated only with pregnancy forced him to make the statement that the tumor was not sarcoma coinciding with pregnancy, but sarcoma arising from the decidua of a

pregnant uterus; hence he designated this disease entity as deciduoma malignum.

Just one year later, 1890, Pfeiffer (70), not knowing of Saengers work, reported similar cases and designated the disease as deciduoma malignum associated with pregnancy.

Previous to Saenger there had been similar clinical reports but with no definite connection with pregnancy. R. Volkmann in 1867 clearly described the placental polyp, Other men reported cases designated as carcinoma and sarcoma (12) which cases were later reviewed and shown to be the same pathology as Saenger's report. Although these men had given accurate descriptions no association with pregnancy was given. These cases were reported by Metzel, 1872, Mayer, 1876, and Chiari, 1878. Saenger is rightly credited as being the first to point the way in developing the histopathology of chorinepithelioma.

After Pfeiffer came Pestazolla (22). In 1891 he reported three cases of sarcoma haemorrhagica sen infectiosum and recognised the importance of pregnancy. Pestazolla regarded it as sarcomatous but not of decidual origin. However he did state that the uterine musculature contributed to the tumor, and recognised placental tissue noticing the capability of local and general manifestations

Schmorl, (70) in 1893, reported a case and stated that foetal tissue was absolutely necessary for the tumor to develop but did not agree with Saenger entirely.

At this time Saenger, after collecting and studying a series of cases from a histopathological standpoint, reported a histological classification(63):

- a. sarcoma decidua with chorionic villi, recognising that the placenta played some part in the tumor.
- b. sarcoma deciduoma malignum.
- c. Malignant interstitial hydatidiform mole and placental polyp which was parasitic but not malignant.

With the advancement of these histological studies Saenger changed from his original name to that of sarcoma uteri deciduo-cellulare. With this first classification added impetus was added to the study of chorionepithelioma.

Gottschalk, 1894, (31) was the first man to point to the entire foetal origin. His case showed Langhans cell proliferation. He designated this as sarcoma chorio cellulare as he stated that Langhans cells arose from foetal mesoderm; hence sarcoma.

In 1895 considerable advancement was made in the classification and histogenesis. It was during this year that Fränkel reported a case entirely of syncytial cells. Pick called the tumor chorio-epithelioma; and Marchand's work was reported.

Marchand (42), after much studying of the normal placenta and chorioepithelioma, showed that the tumor was neither carcinoma nor sarcoma. He reported that the tumor arose from the two layers of the chorion and <sup>was</sup> ~~were~~ foetal and maternal in origin. As Peters work on the histogenesis of the placenta had not been developed, it was commonly accepted that the chorion was both foetal and maternal. Marchand designated the disease as chorionepithelioma sui generis and stated that the important factor in malignant changes was the excessive proliferation of syncytial and Langhans cells. He also recognised the close relationship between hydatidiform mole and chorionepithelioma. He also noted the great difficulty in differentiation of the simple mole and the mole undergoing malignant changes. Therefore he considered it one disease condition with many variations and a progressive degree of malignancy. This gave rise to his classification which was very widely accepted. His classification appeared in 1898 (43)

- I. Simple mole, nonperforating type
- II. Malignant mole, perforating mole.
- III. Chorionepithelioma, showing no visible villic core
- IV. Indifferent stage, with many variations.

During this period German and Americans accepted Marchand's work. However the English maintained that it was sarcoma and followed Saenger's lead with the exception of



Teacher who studied extensively under Continental European men and was very strong in his acceptance of Marchand's work.

Shortly after the report of Marchand J. Whittbridge Williams (73), of Johns Hopkins, published his American series. He recognised foetal and maternal origin in his cases and called the disease deciduoma malignum.

In 1896 Appelstedt, Aschoff, and Neumann (12) readily traced the origin to chorionic villi and illustrated villi in the general tumor. Aschoff openly stated that syncytium and Langhans cells were definitely and entirely foetal in origin with no maternal components. It was about this time that Peter's work on the placenta came out and clearly demonstrated that such was the case.

Marchand (43) again appeared in print in 1898; at which time he advanced his classification, previously recorded, and came out strongly behind Aschoff. No doubt Peter's (22) most extensive work was responsible for the strong declarations of the Germans at this time. Again in 1903 Marchand, to support Teachers reports in England, wrote a brief article in an English journal at the same time that Teacher gave his report before the Obstetrical and Gynecological Society of England. In this report Marchand specifically stated that the tumor was entirely ectodermal and foetal in origin and that it may show

metastases with no definite primary tumor.

Teacher's (71) work in 1903 was statistical in scope; presenting facts and features with the intention of routing the then accepted sarcoma theory of Saenger from the British mind. He did stir up considerable comment within the membership of his society and was censored by many for stating that the British were backward. His statistics were outstanding just as those that Ladenski had brought out in this country the year previous. There was little left to approach from a statistical standpoint after the work of these two men.

During this entire period investigators were dissatisfied with the clinical and histopathological correlation and much work was done toward alleviating this condition. Considerable reports began to appear in the next five years. Caturani, Stone, Pierce, Brothers, and Ewing published papers; the latter arriving at a classification which he thought was the most workable.

In 1910 Ewing (22) felt the need of a classification that would have more significance than Marchand's. He reviewed the literature and with personal contacts and arrived at his classification which is excepted today with exception that Novak would prefer the inclusion of the mole in the classification.

Ewing's classification is a modification of Marchand's with a more basic study of the histopathological picture and a correlation of diagnosis, prognosis, and course. Ewing ~~discussed~~ discussed chorionepithelioma from three viewpoints: Choriadenoma, Choriocarcinoma, and Syncytioma with syncytial endometritis, the Choriocarcinoma being the most malignant and syncytial involvement the least malignant. Larrier as does Novak believes that the classification should include mole. He states that hydatidiform mole is the first stage, not necessarily followed by the second stage, chorionepithelioma(52).

The methods of approach upon the general problem varied little in the next ten years other than the recognition of the difficulty of early diagnosis and adequate treatment. It was with the advent of the Aschheim-Zondeck (1) pregnancy test reported in 1928 that the next important issue arose in the consideration of chorionepithelioma.

Aschheim and Zondeck promulgated a test in which the anterior pituitary like substance (prolan B) secreted in the urine of pregnant women could be biologically assayed with the determination of whether or not the pregnant state exists. In this test mice are used as the experimental animal, in the Friedman modification rabbits are used.

It was but a short period after this report that investigators knowing the close association of chorionepithelioma with pregnancy, used this test in an attempt to evaluate and arrive at a method of diagnosis and prognosis. Numerous reports were published, all of which arrived at the same conclusions of the specificity of the reaction for chorionepithelioma and hydatidiform mole as well as for pregnancy. The outstanding contributions in this light were those offered by Aschheim, Zondeck, Fels, and Roessler in 1929 (76). Since that time the question of quantitative as well as qualitative methods in the evaluation of the reaction has arisen. At present quantitative methods are those most accepted (76).

Coincidental with the development of the general problem associated findings have been reported since the time of Marchand. Marchand (42) noticed the occurrence of bilateral cystic changes in the ovaries. Throughout the history of the disease men have confirmed this finding. This finding has been so consistent that cases have been diagnosed (14) solely on the finding of bilateral cystic ovaries without the symptoms of chorionepithelioma being present. This finding has been closely related to possible etiological factors since the first report of its consistency constancy.

### Etiology:

What factors bring about malignant changes in the chorion. This question has been asked since the discovery of the condition as a disease entity. As in all tumors the etiological factors are vague and open to conjecture. Chorionepithelioma is no exception. The rarity of the disease is undoubtedly one of the outstanding factors in inhibiting the complete study of this phase. Considerable work has been done from a statistical view by Ladenski and Teacher; Pierce, Spencer, Frank and others have made worthy contributions to this field. These men have been somewhat limited in their scope due to the inability to personally study the numerous cases reported. Teacher, however, was able to contact personally the physician in charge and to study the histopathology in most of the cases that he reported.

Chorionepitheliomata show many characteristics of malignancy in general. It has invasive and destructive power as seen in sarcoma and carcinoma. Tissue analysis shows a similarity with carcinoma in that of a high lecithin content. The condition shows the ability to metastasise. It is probable that, with the advent of greater understanding of the factors causing sarcoma and carcinoma, a better understanding of the etiological factors in chorionepithelioma will develop.

Since Saenger's first report, the disease has been definitely associated with pregnancy (with the exception of chorionic tissue, foetal arrests, found in teratoma). This relationship is the primary factor in all cases and is deemed necessary that the hemochorionic union of ovum and maternal tissue must take place before there is a possibility of the tumor developing (66). In some cases it is difficult to demonstrate the association with pregnancy, as is seen in so called latent cases in which the tumor has developed four to eighteen years after the last known pregnancy and some after the menopause (60). There is a possibility that the latter may be explained upon the same basis as teratoma; namely: foetal arrests in which incarceration of placental tissue in the uterine wall has taken place at the last pregnancy and has waited for a more favorable opportunity to develop malignant changes.

There is no doubt that in the normal development of the placenta chorionic tissue shows marked ability to invade and destroy maternal tissue. What the trigger is that sets off the malignant invasion is the big question. Could it be some lowering of maternal resistance in that Nitabuch's membrane is some factor in retaining the placental tissue in its place. This membrane is found

and noted in normal pregnancy as demarkating maternal and foetal tissue, but it is not always present and never so definite in chorionepithelioma.

Is there some substance in the maternal blood stream which should inhibit this anaplasia and metaplasia. Veit, Fränkel, and others have demonstrated that serum of normal pregnant women shows lytic action upon placental tissue which it does not show in women suffering from chorionepitheliom(39). Also it has been demonstrated that there are pulmonic emboli of syncytial wandering cells in the majority of pregnant women which seldom give rise to symptoms, undergo no malignant changes, and are absorbed by endothelial and wandering cells(25).

Why is it that Prolan B is found in such high concentration in the urine, blood, and spinal fluid of these patients. This fact was unknown until after the establishment of the Aschheim-Zondeck reaction in 1928. However in considering this factor it must be considered as the effect and not the cause as it is found only after the chorion undergoes hyperplastic and anaplastic changes (76).

The question, in regards to etiology, of degree of malignancy arises. Why do some metastatic lesions show regression after removal of the primary tumor,

some tumors show regression without treatment. Is there some reaction in the host - an immunity developing - or does the tumor kill itself. Kelley and Teacher (32) try to explain this by connective tissue overgrowth and organization of blood clots in and around the tumor. with a choking off of the tumor. Just what controls the malignant changes is unknown. In the consideration of the problem in this same light, metastases have been the cause of death with no apparent primary site demonstrable. Undoubtedly the degree of malignancy is a story of both the host and the tumor and if revealed could offer much in the study of the etiology.

With the many reports of of cystic changes of the ovaries, 91% of the cases showing this (55), arising in connection with chorionepithelioma many men have been led to attribute some ovarian factor as the cause of malignant changes. Fräkel in 1895 (730) stated that he thought that the cysts were the cause and that the wandering cells were most apt to go wild. Williams as did Beard believed much the same (7). Bandler felt that some alteration in ovarian secretion was a prominent feature. Durante in his explanation of cystic degeneration of hydatidiform mole said that end arteritis in the chorionic vessels was the probable etiological factor. In this respect he stated it permitted degeneration and



that this was proven in syphiletics who did not show mole formation due to too marked a process of syncytial destruction. Caturani (13) however retaliated by reporting his case of secondary syphilis which had developed a chorionepithelioma. The men who were strong on ovarian factors in the etiology propugated their theories before adequate endocrine study had been made. As Murati and Aachi (40) have produced these same multilocular corpus luteal cystic changes experimentally by injections of placental, molar, and chorionepitheliomatous tissue and have fairly conclusively demonstrated that chorionepithelioma was the cause and not the effect of the cystic changes.

So many questions arise that to bring some semblance of order we must resort to statistics. to form some conception of the etiological background. However it is only by weighing and investigating every problem as it arises that we will be able to arrive at any specific conclusions.

The incidence of the condition is a debated question. Authorities vary considerably in their reports ranging in frequency from 1: 10,000 to 1: 50,000. Szollsman (66) reports in a study of 53,000 cases of pregnancy: thirty-nine cases of mole, and eleven cases of chorionepithelioma, five of which developed subsequent

to the extrusion of mole. This gives a ratio of 1: 10,000. Yet with this frequency, though rare, chorionepithelioma should be found more frequently in the literature; to, the present day there have been but 600-700 reports since 1889. This lack of data may be due to inadequate vital statistics, failure to report, or failure to recognise the disease.

Age and frequency of chorionepithelioma (35)

Age	Frequency (cases)
17-20	3
20-25	19
25-30	35
30-35	24
35-40	14
40-45	17
45-55	11

Frequency of occurrence in respect to gravida

Beaugard's 178 cases (22)	Ladinski's (35)
Multip. grav. 5 plus. 37%	With first preg. 4.77%
Nullip.....12%	After " " 15.37%
	After 2 & 3 " 28.24%
	After fifth " 37.86%

Occurrence after extrusion of mole is 44.5%, after abortion 25%, after term or near term 24.5%, and following ectopic 4%, these figures were arrived at with a consideration of available reports and represent the frequency in respect to

the immediate precursory pregnant state (72, 56, 22, & 35).

There is no doubt that this condition does fall into the fertility period and does show association with pregnancy. The most numerous in relation to age falls well within the period of most marked fertility, 25-30 years; however there is also noted that the average age, 32, is slightly higher than the period of most marked fertility. Were this a small series little significance could be attributed, however such is not the case so there must be some explanation.

The explanation may in multiparity as the statistics would lead one to believe, however Ladenski did not believe this to be so. If such is the accepted fact, could there not be some such a thing as uterine trauma and repeated pregnancy lower the resistance to later pregnancy with the possibility of chorionepithelioma developing. This should not be lightly cast aside just because one man believes that multiparity has not much influence in the background. If numerous pregnancies were related to the etiology, possibly some uterine changes might be demonstrable. It would be interesting to study an adequate series of uteri histopathologically with an attempt to correlate gravida with the histological picture. I have used the term trauma in pregnancy believing that the pregnant state is a normal physiological process, but which as most processes, can be overdone and trauma result. In this

it is of interest to note that chorion degeneration as seen in hydatidiform mole, cystic, has been produced experimentally by trauma to the uterus of pregnant animals.

The accepted factor in multiparity is that after thirty years of age <sup>hydatidiform mole</sup> chorionepithelioma, most frequent precursor of chorionepithelioma, occurs more frequently and markedly so after the forty-fifth year. It is difficult to arrive at an average for multiparity, but one could easily say that the fifth child occurs more after thirty than before. As statistics show 39% of chorionepithelioma are found after the fifth pregnancy, that mole is more frequent in these ages, and that from 1% - 10% of mole become malignant, then with this in mind we can say that it is not multiparity but the age at which the pregnancy exists is the main factor.

In reviewing the statistics on immediate precursors we find term and and abortions account for 25% each and ectopic only 4%(59). Possibly the latter can be explained upon the fact that surgical intervention is the practise in ectopic pregnancies and that either the entire products of conception are entirely removed or that the blood supply is so altered that the remaining tissue is unable to progress and is resolved. Also there may be some endocrine hookup which is disturbed with surgical intervention.

Permit me to recapitulate. The etiology of chorion-epithelioma is unknown. The disease is associated with pregnancy, normal or abnormal ( 80% of the pregnancies developing chorionepithelioma are abnormal: hydatidiform mole, abortion, and ectopic states). The frequency is debateable, 1: 10,000 being a low ratio, occurring more after mole. There is no evidence that ovarian disorder is the cause the evidence points to it as being the effect. Future study as regards blood serum reactions and the role of multiparity is indicated.

#### Pathology:

Ewing (22) in 1910 recognised the need of a classification with a closer relationship to the histopathological and clinical picture and with this in mind he developed his classification which is accepted today. Ewing believed that three distinct groups could be established, it being easy to distinguish between malignant and nonmalignant states but transitional stages might be more difficult. Novak (52) and others have questioned this so called clear cut picture; he believes as does Larrier (6) that the mole should be included in the classification . Larrier states that mole is the first stage not necessarily followed by the second, chorionepithelioma. Many men have recognised the difficulty to

classify histologically or clinically chorionepithelioma. Nevertheless Ewing's picture is the most widely accepted and clear cut classification of today.

There will be no attempt in this paper to acquaint the reader with the normal histology of the placenta; suffice to say that Peters et al demonstrated (58) conclusively that it was entirely foetal in origin. The three cell layers have been described by various men and an adequate description may be found in any embryological book of today.

In Ewing's classification there are three types of chorionepithelioma (22&23) distinguishable by microscopic and gross structure, the Chorioadenoma destruens, malignant mole of Marchand; the Choriocarcinoma, choriionepithelioma malignum of Marchand; and the Syncytioma and syncytial endometritis.

#### Chorioadenoma:

This consists of a mild type of neoplastic change, consisting of elongated hypertrophic villi infiltrating uterine sinuses over a large area. It shows a tendency to remain long confined to the uterine cavity. Rarely are there general metastases, more often a retrograde vaginal metastasis is the first sign. The tumor produces in an orderly fashion all the parts of a normal villus, namely: the connective tissue core, Langhans cells, and syncytium. The

destructive power of the choriadenoma is not so great as indicated by the need of the connective tissue core to carry the blood supply. The characteristic is metaplasia of Langhan's cells with budding vacuolated syncytium usually entire villi may be demonstrated.

The uterus is grossly enlarged, more so than in choriocarcinoma. The uterine wall is thickened, honeycombed, and may show vacuolation. The serous surface presents nodular elevations, soft and dull red in color which is due to invasion of the tumor mass into the subserous veins. The tumor mass is decidedly hemorrhagic and often shows marked necrosis with tissue resembling a massive blood clot adhering to the implantation site.

Microscopically the sections <sup>show</sup> overgrowth of all elements. The connective tissue core is not markedly vascular, but a compact cellular core often showing edematous changes. Langhan's cells, the inner layer lying between syncytium and connective tissue core, are greatly increased in numbers. These cells form multiple layers at the base of the villi and also long broad sheets scattered throughout the section and not directly connected with the villi. The size and shape of the cells vary from the normal, the nuclei are hyperchromatic, and are most often separated from the overlying syncytium by the appearance of a clear cytoplasm with glycogen granules present.

But few mitotic figures may be present and Langhan's cells very seldom undergo necrosis. The syncytial portion is represented in the early stages show sprouting buds of markedly acidophilic cytoplasm with abundant hyperchromic nuclei. The buds may be very numerous and make up most of the tumor mass. Later stages show budding with elongated sheaths. Syncytial wandering cells, giant polyhedral cells, may be demonstrated single or in groups lying in villi, blood lakes, or infiltrating veins and musculature, which, although present in normal pregnancy, is much more marked than in the uterus of a normal pregnancy.

#### Choriocarcinoma:

This is characterised by the absence of villi and shows a marked metaplasia of the Langhan's cells. Early, blood borne metastases is the usual picture. The metastases show marked loss of differentiation. Metaplasia and marked infiltration and destruction is the big picture presented in choriocarcinoma.

Grossly the uterus is but moderately enlarged, less so than in adenoma. The tumor mass is compact and shows little or no vacuolation or honeycombing. Although quite compact, it is friable and necrotic and hence it is impossible to remove completely by curettage. The tumor is usually situated at the site of placental implantation,



although in some cases the primary tumor is not demonstrable in the uterus. There is extensive invasion of uterine sinuses and veins, extension is so rapid that there is little distention of the subserous veins. It rapidly perforates the musculature and perforates the uterus either through extension along sinuses or directly through the musculature of the uterus.

Microscopically the sections show uniformity and are highly characteristic. There are no villi present. Bands and masses of acidophilic syncytium are mingled in a disorderly fashion with islands of rapidly growing Langhan's cells. There is no connective tissue stroma. Syncytial and Langhan's cells are always present but the proportion varies. The syncytium may show isolated elongated buds or diffuse sheets with large vesicular nuclei. Wandering cells are quite numerous. Langhan's cells may be found as isolated islands or as compact masses sheathed with syncytium. These cells are markedly anaplastic in type, show considerable hypertrophy and hyperchromatic nuclei. Mitotic figures are for the most part limited to the Langhan's cells.

#### Syncytioma and syncytial endometritis:

As the name indicates this condition may present a true tumorous picture or a generalised proliferation. This type probably shows many gradations between

Choriocarcinoma and syncytial endometritis with considerable variation from many to less Langhan's cells and with a progressive increases in syncytial cells.

Grossly, as a rule the uterus presents no well defined tumor process. Portions of the uterine wall are infiltrated with large or giant acidophilic cells of the general syncytial wandering cell type. The uterus is greatly enlarged. The vessels of the uterus show their walls thickened and invaded by large cells.

Microscopically the infiltration of the uterine vessels is easily demonstrable. Stroma containing lymphocytes and fibrin is ~~was~~ usually demonstrated in the general infiltrating mass. There is a reactive growth of the endothelial cells, and fibroblasts may be present. Muscle cells may develop multiple nuclei and split into acidophilic fragments resembling the syncytial wandering cells. The decidua may participate in the general reaction to, invasion and quite often shows extensive degenerative changes. The entire picture is that of marked syncytial metaplasia.

In Ewing's attempt to correlate the histopathology with the clinical picture he states that it is not difficult to differentiate the malignant from the benign. However cases have been reported in which the picture has been that of a malignant chorioneplithelioma

the Aschheim-Zondeck reaction has been negative(11) and watchful waiting has proven the absence of malignancy. Mazer (47) reports cases in which the diagnostic D.&C. revealed a benign state while the Aschheim-Zondeck was positive and surgery disclosed the presence of a malignant chorionepithelioma; so one cannot depend upon the histopathological picture with material obtained solely for diagnostic purposes. Ewing further states that chorioadenoma more frequently follows mole and is seen most often in the multipara (22). Chorionic carcinoma, the most malignant phase may follow any pregnant state as does syncytioma. Ewing has made a very worthy contribution to the histopathological study but his correlation with the clinical picture is questioned by most investigators.

#### Symptomatology:

Common symptoms of chorionepithelioma have been known since the time of Saenger; the difficulty encountered is the interpretation. Symptoms encountered are hemorrhage, sepsis, anemia, symptoms of embolic phenomenon, and cachexia. Chorionepithelioma is so infrequent that it is not always considered, but it should never be relegated to a rare and uncommon disease and should always be considered when unexplainable symptoms are encountered.

Hemorrhage is the most persistent and prominent

feature. It is present in all cases. However syncytial endometritis may present a picture of profuse and slightly irregular menstruation (61) while a more persistent type is found in adenoma and carcinoma of the chorion. Hemorrhage may be profuse and exanguinating or a persistent (3) uncontrollable lochial like discharge often simulating sepsis and subinvolution. Usual methods of control are for the most part of no avail. Dilatation and curettage may aggravate the condition but will not show any marked effect in stopping the hemorrhage.

Shortly after hemorrhage has made its appearance a foul, offensive discharge, usually watery in character, appears. This marks the onset of sepsis. With blood being the ideal culture medium and knowing that it is next to impossible to have a sterile birth canal, it is easily seen why sepsis develops so early in the process. Sepsis may be the outstanding feature and as such is the most misleading factor in establishing a true diagnosis. Septicemia and marked rigors may develop.

Regardless of sepsis a temperature and leukocytosis develop, as with necrosis there is absorption of broken down tissues with the resulting foreign protein and chemotaxic response.

Pain (72) , although early reports considered it a prominent feature (3), is very often not present or

Or only in a mild degree. The pain, when present, is crampy in character and most often associated with the passage of blood clots.

Anemia, a constant and progressive condition, soon makes its appearance (#37). As stated previously hemorrhage may be exanguinating and the loss of blood is a fatal manner. However the usual picture is that of persistent bleeding in which cases the anemia is out of all proportion to the amount of blood lost. Most of these patients are dehydrated and the true blood picture is often concealed by a smaller volume of blood in circulation, however a haemoglobin percent of 30-40, Sahli, is not uncommon.

Concurrent with anemia marked weakness and loss of weight rapidly develop. The patient may show gastro-intestinal symptoms with nausea, vomiting, and marked anorexia. Cachexia appears early and the patient starts to fade from the picture. Cachexia, due to the rapidity of the disease process, is not as marked as in carcinoma as death supervenes before there is much opportunity for other findings to develop.

Metastases can give practically any symptom complex. Metastases are blood borne early in the disease, and any organ of the body may be involved. The most frequent symptom is that of hemoptysis from pulmonary

metastases. Urinary findings are not uncommon. Hemiplegia and other brain signs have been reported(17).

Clemmer (14) has reported an asymptomatic diagnosis based upon the finding of a positive Aschheim-Zondeck reaction and bilateral cystic ovaries. This latter is the exception and Clemmer must be given credit for the earliest reported diagnosis in the literature with the hope that other men will show the same judgement in the future.

Diagnosis:

Any unexplainable hemorrhage, not controlled by the usual methods, developing in a woman after expulsion of hydatidiform mole, following abortion, ectopic or term pregnancy should be considered chorionepithelioma until proven otherwise.

Since the first report of chorionepithelioma, Saenger as his cases as reviewed by Schmorl showed the histopathology of chorionepithelioma (70), diagnosis has been recognised as a difficult problem. Ewing felt that history of the pregnant state followed by uncontrollable hemorrhage and with tissue study following dilatation and curettage would be sufficient to establish a diagnosis. This has been proven to be grossly inaccurate in many cases. Every man reporting on this subject has regretted the fact that he could add no more to the diagnostic approach. With

the advent of the Aschheim-Zondeck pregnancy reaction the missing link, in diagnosis has been reached. It is now that the clinician must become acquainted with the use of this biological reaction and its applications.

Laboratory methods in aids to the diagnosis have been used since Saenger's time. Diagnostic dilatation and curettage has been on the mat for the past fifty years. There is no doubt that this method has its place. However there are dangers. Inadequate curettment is misleading, there is always the factor of introducing sepsis, and the facilities for microscopic technique is not in the hands of every physician. It is a well known fact that unless one does considerable histopathological work, accurate study is not always the picture. Another danger is perforation due to the friability of the infiltrating tumor, and then severe exanguinating hemorrhage may result.

e The microscopic picture to be accurate demands skill in preparation of the sections. Adequate technique in fixation, sectioning, mounting, staining, and dehydrating is not in the makeup of everyone as nowhere in the medical course is microscopic technique taught. Some men have been fortunate to take up special work in this line or in pre-medical studies to bolster the weakness in this respect. The human equation is another factor that

must be taken in to consideration, adequate knowledge of tissues . D.&C. has not proven to be the diagnostic aid that it has been accredited.

Roentgenographs have proven of considerable help in demonstrating metastases to the lung and brain. Radiographs are indicated in the early process of the disease to give one basis to determine extent and in some cases the degree of malignancy of chorionepithelioma(29). It must be noted that 71% of the cases show metastases (35).

The most outstanding diagnostic aid in the history of chorionepithelioma is the biological pregnancy test developed in 1928 by Aschheim and Zondeck(1). This test consists of injections of urine from pregnant women into female mice with a resulting ovarian changes in the virgin mice. This test involves some anterior pituitary like substance which is found in the placenta, ovaries, foetus, blood, and spinal fluid of pregnant (76). Aschheim himself states that the test is positive in 98% of the cases (1). The reaction is measured on the minimal amount of fresh, morning (preferably) sample of urine which will cause follicular or corpus luteal changes in the ovaries of infatible mice. It is not the purpose of this paper to give the accepted techniques; suffice to say that there are three reactions noted: 1. Formation of follicles,



ll. Blutepunkte, and lll. Lutinization.

In normal pregnancy the amount or concentration of the anterior pituitary substance increases up until the third or fourth month and then decreases (ll&76). In this respect it closely follows the life history of the placenta and it is safe to say that the placenta plays an important part in the production of this substance. Knowing the close association of chorionepithelioma with the placenta it needed but for the opportunity to be offered for it to be tried for the possible effects in chorionepithelioma. Zondeck reported a case of mole which showed a great increase concentration in the urine and also the contents of the cystic fluid of the mole(76). Meyer reported an increased concentration in chorionepithelioma of teratomatous origin and Fels and Roesler reported the same findings in case of chorionepithelioma of the uterus(11). Numerous reports were forthcoming to confirm this finding, Edeiken reported that the pregnant woman showed a concentration of five mouse units per cubic centimeter of urine (47) while Erhardt(10) as others reports a concentration of 70- 100 mouse units per c.c. in the urine of those women suffering from chorionepithelioma.

Recognising the marked results in this reaction, Falbusch (15) in 1930 refused to operate in a case with positive curettage findings but negative Assheim-Zondeck reaction and clinical follow up proved him to be right. Dietrich reported a case which a D. & C. had shown malignant

chorionepithelioma but eight days later the Aschheim-Zondeck test was negative (76) and remained negative with the results that surgery was postponed and the patient remained healthy. Another case was reported by Balkow (41) in which the D. & C. was confusing but the Aschheim-Zondeck reaction was positive with surgery histopathological study of the removed specimen showed malignant chorionic changes. Kimbrough (34) diagnosed a case of chorionepithelioma in the absence of uterine hemorrhage but with bilateral cystic ovaries and a positive Aschheim-Zondeck test. However it must be remembered that cases of mole (76) have been reported with a negative pregnancy test.

Undoubtedly the Aschheim-Zondeck test is the most accurate means of diagnosing chorionepithelioma. However there are certain qualifications which must be known before this can be fully evaluated. The positive reaction should be determined by two changes only, the blutpunkte or the hemorrhage into the follicular and the formation of corpus luteal cysts (76). The reaction remains positive 2-15 days after normal pregnancy (37) has been terminated. It may be present 8-15 days after foetal death and 1-3 months after discharge of a mole, however in all these cases the concentration as expressed

in mouse units, is decreasing.

Other factors qualifying the test are that false positive reactions may be elicited in hypoovarian states, hyperthyroidism, and carcinoma. However the concentration is never as marked as that in chorionepithelioma (75). Toxemias of pregnancy show a very high concentration of prolan B in the urine and spinal fluid and may be confusing as this develops before all the signs of a toxemia are present, therefore toxemia of pregnancy must be ruled out in cases of chorionepithelioma developing during the last trimester of pregnancy (69).

The question of use of blood or urine in running the test has been asked by many men. Biological assay shows that the concentration is higher in urine and spinal fluid than in blood (76) although all show higher concentration in chorioepithelioma than in normal pregnancy.

The laboratory animal of choice has proven to be the infantile female mouse. Friedman's modification uses the rabbit, however the consensus of opinion is that the mouse can more easily be standardized. Smith(69) reports in his work that the mouse use gives more accurate results and strongly recommends the use of the mouse in all future tests.

With the knowledge that chorionepithelioma produces a higher concentration of prolan B, then is it

justifiable to run quantitative tests only. It is my belief that quantitative tests is the one of choice. First, more data would be forthcoming as to the range in concentration in normal pregnancy, and more data on concentration in chorionepithelioma, second, it would give a better opportunity to check false positives.

In reviewing the diagnostic aids we find that the Aschheim-Zondeck pregnancy is reliable, that dilatation and curettage is not reliable. Roentgenographs are of aid in demonstrating metastases. With these aids the clinical judgement as to their use is paramount. What then must be considered as the diagnostic approach to a patient with the of hemorrhage following the pregnant state.

In the differential diagnosis sepsis, endometritis, polyps, sarcoma, carcinoma, and submucous fibroids should be considered.

History is the prominent feature in these cases. Sepsis and chorionepithelioma present a common history, that of the pregnant state or its complications, and may present a difficult problem. However, sepsis so often is an early complication of chorionepithelioma, that the latter should be ruled out first. The cost of an Aschheim-Zondeck is so trifling when the severity of the disease is so marked. An Aschheim-Zondeck test is indicated.

Submucous fibroids very often, 50%, give a history of sterility; the symptoms are of longer duration with menorrhagia as the rule. A pelvic examination with a diagnostic dilatation and curettage should serve to differentiate the two.

Uterine polyps give a longer history, quite often the tumor may be presenting at the external os. A diagnostic D. & C. should serve to indicate the condition.

Endometritis may present the same history as that of chorionepithelioma and the possibility of syncytial endometritis should not be overlooked. An Aschheim-Zondeck test is indicated in such a case. In case of negative history curettment will aid.

Chorionepithelioma, as a rule, presents a clear cut history of a pre-existing or present pregnant state. Latent cases are the exception especially those developing after the menopause and four to eighteen years after the last known pregnancy. Physical signs in chorioepithelioma are a soft cervix, in contradiction to carcinoma, Hegar's sign is often present (17). There may be vaginal metastases, soft round dark masses. The uterus is usually soft and moveable, somewhat increased in size, and upon D. & C. the musculature is soft and a tumor mass may be felt at the site of placental implantation.

Carcinoma of the fundus and sarcoma may be confusing in some of these respects. Carcinoma is more frequent after 45 years, sarcoma 35-50 years. Hemorrhage is late in carcinoma, both chorionepithelioma and carcinoma show a watery discharge. Metastases are lymphatic borne and slower to manifest themselves in carcinoma; while in chori nepithelioma they are blood borne and occur early in the disease process. Sarcoma in this respect is between the two and is blood borne. Carcinoma presents itself as hard and indurated, sarcoma firm but friable, and chorionepithelioma is soft and sluffing. The microscopic picture is significant in all three cases. Diagnostic D. & C. has more to offer in carcinoma and sarcoma as tumor particles are more easily obtained than in chorionepithelioma by this means. Again the quantitative Aschheim-Zondeck test will clarify the diagnosis where doubt exists.

Smith (69) has noticed another constituent in the urine of patients suffering from mole and chorionepitheliom, and that is the lowering of the oestrin concentration simultaneously with the increase in prolan B concentration. Testing for this principal is not practical at present and until it is, it will have little or no clinical value.

### Complications:

Associated changes have been noted in other organs of those suffering from chorionepithelioma. These changes are closely related in the endocrine hookup of pregnancy. The most consistent finding has been that of bilateral cystic formation in the ovaries (71). Novack believes that the hypophysis cerebri (55) has shown some changes.

91 % of the ovaries in these cases show bilateral corpus luteal cysts. This fact has been known since Marchand's and Fräkel's work in 1895 (22) and has been used as a diagnostic aid. It has been accepted that these multilocular cysts are the effect and not the cause of chorionepithelioma.

Novack (53) has been interested in pituitary changes in this respect. He has no definite findings to offer, primarily from lack of tissue to study, but he has reported that there is an increase in the acidophilic cells consistent with normal pregnancy. Zondeck (76) has been unable to produce any biological reaction with the use of pituitary tissue in his pregnancy, while he has with placental and ovarian tissue. At present there are no definite findings in the pituitary which could be associated with chorionepithelioma.

Complications in chorionepithelioma are most common. Sepsis, intra and extra uterine hemorrhage, peritonitis, and metastatic complications are the most frequent.

Sepsis is invariably a complication and very often conceals the true identity of the underlying pathology. Sepsis is probably most often introduced at the time of diagnostic dilatation and curettage. However, autoinoculation, both vaginal and blood borne, is not unusual. It may be introduced in radium and x-ray therapy. The persistent hemorrhage and necrosis of tissue offers a most excellent culture medium. Sepsis is marked by fever of spiked character, foul smelling lochia, toxic symptoms, and a more marked chemotaxic response than in chorionepithelioma alone.

Hemorrhage as a complication is of the exanguinating type and rapid death is the usual picture. Hemorrhage may be intra or extra uterine, may be visible or not, and should always be suspected when the patient shows signs of severe shock. The cause is due to invasion and erosion of a large blood vessel, usually a vein. There is marked congestion of the pelvic vessels and exanguination is rapid. The fragility of the tissue makes it next to impossible to ligate or impinge upon the bleeding vessel,



packing increases uterine pressure and often leads to perforation. The treatment for excessive hemorrhage is most difficult and is usually of no avail. General supportive measures may be resorted to with the hope that the hemorrhage ceases.

Peritonitis is quite often seen in the terminal stages of chorionepithelioma (8). It may be chemical from intra peritoneal hemorrhage or septic from frank perforation of the uterus either by the invasion and destruction of the tumor proper or by the operator during curettment. Peritonitis is always a sign of poor prognosis, and little if any hope can be offered the patient.

Metastatic lesions, occurring early, offer the widest variety of complications. As previously stated 70% show metastases. In Ladanski's report of ninety cases showing metastases the following figures are reported(35):

Lung ..... 47

Vagina..... 40

Liver..... 13

Spleen.....13

Kidney .... 13

Ovary ..... 10

Gut ..... 8

Brain ..... 7

Lymph glands, heart, stomach, and pancreas 1 each

Lung metastases show hemoptysis, and this sign may be the

first sign of the disease. Quite often these emboli of chorionic tissue are considered to be from thrombosed pelvic veins. Hemoptysis is the usual first sign of pulmonary involvement, however pain from pleural involvement, pulmonary shock, and death may occur. Radiographs demonstrate the presence of metastases. Lung abscesses and bronchopneumonia may develop. There have been cases reported in which recovery has been noted after pulmonary involvement.

Vaginal metastases are next in frequency. They, as pulmonary, may be the first indication of malignant changes. A case seen in the University of Nebraska, College of Medicine Hospital in 1935 showed this finding. The lesions appear as small hematomas, soft and dark red; They may be multiple or single and are due to retrograde venous involvement or true retrograde venous metastases. Quite often the picture is of marked necrosis and profound hemorrhage. The hemorrhage is most difficult to control.

Liver, spleen, and kidney metastases are next frequent in occurrence. The liver and spleen involvement may give little or no symptoms. Stretching of the capsule in either organ will give referred pain. Organ enlargement may be demonstrable. Splenic veins may be eroded and result in fatal hemorrhage. Kidney metastases, however, may give profound symptoms. Hematuria, gross, is the common

finding. Although hematuria and albuminuria is quite marked, casts do not appear in pathological numbers to until late in the process. Infection, is quite often superimposed.

Ovarian metastases may give rise to symptoms of cystic changes, and as cysts are the common finding in chorionepithelioma little attention is paid and the malignant changes are demonstrable only at autopsy or during a laparotomy. Gut metastases on the other hand may give a variety of symptoms. Blood in the stool is a frequent observation, this may be either bright red or the dark red of reduced hemoglobin. Obstructive symptoms appear late. With evidence of gastro-intestinal involvement the prognosis is grave.

Brain metastases, occurring seven times in Ladanski's series, gives an opportunity for various syndromes to manifest themselves. Hemiplegia, cranial nerve involvement, and cerebellar signs may point to the focus. General symptoms of intra cranial pathology are not as frequent as the focal signs (17). Needless to say that with the development of these signs the life span is but little; however Cushing (17) had a case in which multiple brain metastases had developed and the patient lived for eight months.

**Prognosis:**

Prognosis is always to be guarded. There is usually little that can be accomplished. The course is rapid. Ladinski gives the average duration as seven months following mole, six months following abortion, and five months following chorionepithelioma developing at or near term (35). However his figures showed the range of from one week to three years. It must be remembered that there are exceptions as in all malignancy. Diagnosed chorionepithelioma has regressed without treatment, metastases have disappeared after the removal of the primary tumor, while metastases have been responsible for death without the presence of a primary tumor being demonstrable. With such variation prognosis must be guarded. Ewing attempted to give some idea of the course of chorionepithelioma in his classification of 1910 (22).

Syncytial endometritis and syncytioma (61&22) probably shows the least degree of malignancy and responds best to conservative measures of treatment. With the difficulty of establishing a definite diagnosis from a histopathological study it is best not to rely upon this fact unless, with no room for doubt, the diagnosis is made of syncytial involvement.

Chorioadenoma is a condition that is most apt to

follow hydatidiform mole and hence is found more frequently in the fourth decade. Metastases are for the most part not generalised until late in the course. It has responded to curettment but this is not the procedure advocated by most men. Vaginal metastases are the most frequent finding and due to the marked tendency to hemorrhage the course may be considerably shortened. (74)

Choriocarcinoma is the most malignant type. Metastases are early and generalised. The course is very rapid.

It is fairly easy to discuss chorionepithelioma as showing these various types, but the great difficulty is in the inability to classify that makes the problem complex. Ewing (22) believed that it was simple to differentiate the benign from the malignant, however this has not proven to be the case. Also the great variety of transitional types gives added hindrance. It is best not to rely upon a diagnosis as to type, but to consider chorionepithelioma, in the light of prognosis and course, as a most malignant disease and to combat it with all the resources that therapy can offer with the hope that one is dealing with a less malignant form and that the course may prove more favorable than would be expected.

Prognosis must be guarded as the majority of cases terminate fatally.

Course varies somewhat depending upon the immediate precursor(35). Chorionepithelioma, as an average, develops eight weeks after molar pregnancy, seven weeks after abortion, and six weeks after full term. The duration shows much the same relationship as previously recorded. Little has been said concerning chorionepithelioma developing following ectopics; the rarity of this condition gives no adequate number of cases upon which any statistical value can be placed. However, chorionepithelioma developing after ectopic pregnancy does give the gravest prognosis, 90% being fatal with a very rapid course (26).

In Ladinski's series of 124 cases (35) there was a 59% mortality of which metastases accounted for 64%, hemorrhage 27%, perforation of uterus 6%, and sepsis and shock 3%. Operative therapy gave the best results. Greater mortality was seen in those cases developing chorionepithelioma after full term. However as stated before those following ectopic pregnancy give the most grave prognosis.

There is one aid to prognosis which has developed concurrently with the Aschheim-Zondeck reaction. Should this reaction become negative or show a regression in the concentration of prolactin B in the urine of these patients after treatment has been instituted the prognosis is more favorable. However, should this positive Aschheim-

Zondeck test persist and shows no decrease in the concentration of prolan B in the urine, the prognosis is grave and the test indicates that the tumor has not been destroyed or removed. Also should the test become negative after treatment then later become positive with increasing concentration, there is indication that either the tumor is reoccurring or that metastases are present, and as such a favorable prognosis can not be offered (50).

**Treatment:**

What can be offered in the way of treatment? As with all cases of malignancy complete removal of the tumor mass is the most favorable procedure. Since Saenger's time radical hysterectomy has been recommended as the best measure. It is still the most frequent procedure used today.

Today we have other means of tumor destruction. Radiation therapy has developed to the extent that it is the accepted treatment in many forms of malignancy (20&50) Radiation therapy may be either radium implantation or deep x-ray therapy. Reports in respect to both have been most favorable. However there is a tendency toward sepsis especially in radium implantation.

Therapeutic curettage has been used with favorable results. Complications are more apt to follow this than any

other form of therapy (52). Syncytial involvement is supposed to be taken care of in this respect better than other types of chorionepithelioma (61). The reason that curettage is used in some cases is that in young women desiring children, the less radical procedure is the one first used.

Fleurent (26) believes that in all ectopics the tube involvee should be completely removed at time of surgery as a prophylactic measure.

Surgery with radical hysterectomy undoubtedly gives the best results (38). The entire tumor mass with its extensions into, the broad ligament and other structures may be removed and radiation therapy to metastases and to the primary site be instituted. Whenever in doubt as to the measure to use, surgery should be the choice; also in those cases with a persistent Aschheim-Zondeck reaction after other therapeutic measures have been used, surgery is indicated.

Prophylaxis should be stressed. Following the expulsion of a mole repeated Aschheim-Zondeck tests should be run. It must be remembered that after the expulsion the test remains positive from one to three months but that there is a decrease in the concentration of prolan B in the urine. The test should be run on a quantitative basis. Should there be a persistent positive reaction, early intervention is indicated.



Since Fräkels report that serum from pregnant women shows lytic action on chorionic tissue and that the serum from women suffering from chorionepithelioma does not show this action (21), then a therapeutic tests should be tried. There is no report in the literature of this measure being tried, but in those cases not responding to the accepted measures, it would only be justifiable to use this with the hope that it will prove of some value.

Along this same line experiments have shown that with the injection of Theelin (69) there is a reduction in the concentration of prolan B in the urine and spinal fluid of women suffering from chorionepithelioma. It would be justifiable to use theelin in the treatment of chorionepithelioma as a test of its possibilities in the general treatment. This and the use of sera from pregnant women should be an object for further study.

Metastases have responded to radiation therapy and is indicated.

General supportive measures are important. Transfusion is the best supportive measure. The loss of blood from hemorrhage is tremendous; it is not uncommon to find a hemoglobin of 20-40%, Sahli, and operative treatment may be more easily used in those cases having sufficient blood to better withstand shock and post operative complications.

Other supportive measures are those advocated for any serious illness. A light high carbohydrate diet is indicated. Intravenous saline, glucose and acacia have their place in the treatment of these cases.

Early treatment is indicated in all diagnosed cases. It is the duty of every physician to know the principals of the Aschheim-Zondeck reaction and to use the test whenever indicated. It is only with early diagnosis that any therapy is reliable, and the Aschheim-Zondeck reaction offers the only aid to an early diagnosis.

Summary:

Chorionepithelioma of the uterus is a malignant disease of the chorion. The etiology is unknown; it may occur after any pregnant state or its complications.

Chorionepithelioma was first described by Saenger in 1889; since that time Marchand, Gottschalk, Teacher, Ladinski, Ewing, Novack and many men prominent in the field of gynecology and malignancy have added considerable to the knowledge of the problem of chorionepithelioma.

Persistent hemorrhage following the expulsion of a hydatidiform mole, term, or abortion should raise the question of chorionepithelioma. Diagnosis is aided by a quantitative Aschheim-Zondeck reaction in which the concentration of prolactin B in the urine, blood, or spinal

fluid is far greater than in the normal pregnant woman.

Metastases are blood borne and occur early; the first sign of developing malignancy may be a metastatic lesion.

Prognosis is always to be guarded. The course is rapid on the average of a duration of six to eight months.

Therapeutic measures are not specific. Surgery and radiation therapy offer the best results at the present time. The use of serum from pregnant women and the use of theelin should be further investigated in respect to possibilities in therapy.

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