ON "CHORIONEPITHELIOMA."

A DISEASE

of

PREGNANCY.

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I N T R O D U C T I O N.

Very few diseases of a correspondingly brief history, have gathered around them, such a voluminous literature as has Chorionepithelioma.

Although it is only some twenty years since Sanger first discovered this "Sarcomatous-like Tumour of the Uterus found in association with Pregnancy," yet the problems suggested by the more intimate study of the disease, have been so numerous and so varied that it has fascinated investigators in almost every country.

Probably one of the greatest barriers in the progress of scientific investigation in so far as the Profession of Medicine is concerned, is our deeply rooted prejudice in favour of accepted views: we so often look upon what we have been taught, and as it were, inherited from our Forefathers as if it meant finality in one subject after another, that it is only on rare occasions that our knowledge gets a shock or jar, shaking us up to a fresh effort of investigation.

Thus owing to our prejudiced notions regarding the Placenta and early Embryonic life, this disease of Chorionepithelioma, remained undiscovered until Sanger happened to observe it in the year 1899.

This discovery of a Uterine growth that in many respects failed to conform to the characteristics of other malignant tumours, sent the workers back to a fresh study of the physiological process, with the result that many of the old ideas were found to be fallacious, and that from the new standpoint, a restatement of the case had to be made.

The recent views have been well summarised by Clarence Webster in his book on "Human Placentation."

There are three important dates that stand out as landmarks in the historical evolution of this disease, viz:

In 1893, Sanger published the earliest views as to the origin of this disease, and believing that it arose from the maternal Decidua applied to it the name of "Deciduoma Malignum."

In 1898 Marchand published his famous work on the histological characteristics of the disease, and clearly demonstrated, the origin of the Tumour to be Foetal and thus that its correct name should be Chorionepithelioma.

In 1902 Schlagenhaufer startled the Pathologists by his describing two cases of Chorionepithelioma occurring, not in the Uterus, but in the Testicle; for hitherto the presence or history of pregnancy, had never been doubted as being an essential to the origin of the disease; but here were two cases occurring in the Male.

This latest question of whether Pregnancy is essential for the origin of this tumour or not, is one that is at present arousing much interest and discussion. It is somewhat remarkable to note the great persistence by which the Sarcoma-theory of origin has been upheld, especially by Veit and later by Winkler,

and previous to Teacher's publication in 1903, it was the generally accepted Aetiology in the English School.

Much as has been the discussion and greatly elucidating as Marchand's work has proved to be, yet at present, there are still many subjects connected with Chorionepithelioma, which are matters in dispute and are being eagerly investigated.

Such subjects in dispute are:

1. The varying degrees of Malignancy.
2. The Aetiology and Diagnosis of the Malignant element.
3. Spontaneous Involution or Natural Healing.
4. Ectopic or Primary Chorionepithelioma occurring outside of the Uterus.
5. The relationship between Cystic Mole and Chorionepithelioma.
6. The value of Lutein tissue and Lutein Cysts as an Aetiological factor in Cystic Mole and Chorionepithelioma.
7. The presence of Chorionepithelioma in Teratoid tumours especially in the Male.
8. The presence of Chorionepithelioma in woman apart from any Pregnancy or Teratoma.

My interest in the study of Chorionepithelioma has been much stimulated by the occurrence in my own practice of the following interesting case.

A woman aged 24 was three months gone in her first pregnancy, when she suffered from an attack of

Abdominal pains and accompanied by haemorrhagic discharge from the Vagina. Her private Medical Attendant found on examination that she was aborting of a Cystic Mole, and this he cleared out with his fingers in the usual manner.

Her recovery was uneventful until three weeks after the Abortion when she had a 'flooding' and one or two black looking clots came away in the discharge. Thinking some placental tissue might have been overlooked her doctor asked me to see her, and then I learned her history. I curetted the Uterus and got a large amount of placental-like tissue away, but the most striking feature and the one that impressed my mind most was the unusually free bleeding.

This bleeding of itself, along with the history aroused my suspicions of the presence of Chorionepithelioma. There seemed to be no end to the placental-like tissue within the Uterus, and latterly I could feel that I was excavating in some sort of cavity situated in the Fundus. Microscopically the scrapings from the Uterus showed unmistakable evidence of Chorionepithelioma, containing both Langhans cells and Syncytial masses, but there was no evidence of villi.

I watched the patient carefully for some weeks to note the therapentic effect of the curetting; but at the end of a fortnight she again had a 'flooding' and without further delay I decided on Operation - removing Uterus, Tubes and Ovaries.

I have had the patient under Observation for twelve months and up to the present she remains well, without any evidence of vaginal nodules or of Pulmonary Metastases.

Just after the operation, on cutting into fundus of the Uterus for about 1/6th in. I came upon growth;

the specimen was immediately photographed and I herewith append the two pictures: the one showing the great thinning out of the musculature at one part of the fundus, x in contrast with the normal thickness of the adjoining Uterine Wall; a the other picture shows the anterior wall of the fundus removed showing the extent of the tumour formation.

The microscopic slides showed the arrangement of cells, so well known as being characteristic of the disease.

From the microscopic appearances a I was at first inclined to regard the specimen as one of destructive Cystic Mole, but the short history of the case, the rapid growth, the presence of Tumour tissue showing the characteristic cells of Langhans and Syncytium and the notable absence of Villi, led me to the diagnosis of Typical Chorionepithelioma Malignum treated by operative interference at an unusually early stage.

In the following pages I have sought to study some of the aspects of Chorionepithelioma that are still subjects of discussion.

In my first Chapter I have set forth some of the recent ideas on Human Placentation, especially dealing with the question as to the Origin of the Syncytium or Covering layer of the Chorionic Villi - a subject that has often been raised in dispute, and even still, by some authorities, accepted very reluctantly as being of Foetal origin.

In the Second Chapter I have endeavoured to trace the connection existing between those two diseases of Pregnancy, viz: Cystic Mole and Chorionepithelioma; seeking especially to trace the Aetiology of first the one and then of the other disease.

In Section C of the same chapter I have carefully studied the reports of several workers on the subject of "The Co-relationship of the Ovarian and Uterine functions"; for it presents itself to me as an important line of study that must be thoroughly investigated, if we would lessen the degree of our ignorance of this disease - Chorionepithelioma; for surely it is only by a thorough knowledge of the Physiological, that we may hope to be able to deal with the Pathological.

In the concluding section of Chapter II, I have critically examined the various views at present held regarding the Ovarial changes found associated with Cystic Mole and Chorionepithelioma, dealing especially with the Lutein theory of Aetiology of these diseases.

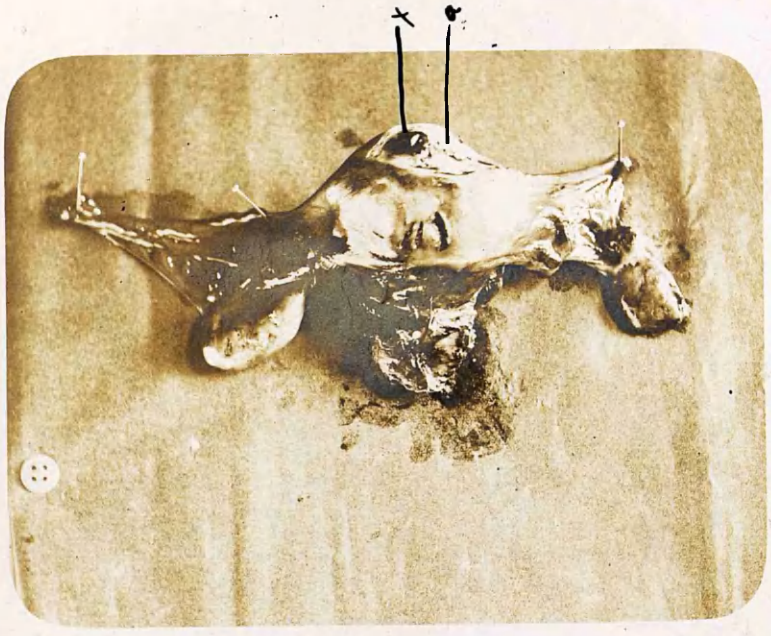
To many it seemed a most feasible hypothesis and it was generally accepted by several of the Continental Schools, and was not without its supporters in this country; but after reviewing the able researches of such authorities as Wallart, Seitz and Risel, I can see no option but that we must abandon this view of Aetiology and look upon the Lutein tissue as a Consequence and not the Cause of Chorionepithelioma.

The question of Chorionepithelioma in the Male and that found in Teratomata I have not discussed, confining myself to the Obstetrical standpoint of investigating the disease in relationship to Pregnancy.

In Chapter III, there is discussed that very interesting group of cases of Ectopic Chorionepithelioma, especially dealing with the genesis of such cases: and in the concluding chapter are discussed such aspects of the disease as, the varying degrees

of Malignancy, especially dealing with the difficulties in diagnosis and Prognosis, and also with that most elusive of all the attributes of Chorionepithelioma, namely its occasional Spontaneous Involution.

The disease of Chorionepithelioma is not merely of supreme interest to the Obstetric practitioner and to the Gynaecologist, but from the obscure problems that it raises, it is from the Pathologist's point of view one of the most interesting of all the abnormal tissues.



I

II

CHAPTER I.

NORMAL PLACENTATION & EMBEDDING of the YOUNG OVUM.

Up to the year 1889, Intra Uterine Attachment of the human ovum was believed to be effected by a surface interlocking of foetal and maternal tissues and the folding around the attached ovum of the adjoining endometrium to form the Decidua Reflexa.

This view was largely the result of investigations on comparative placentation especially in such animals as the sheep: a very early example of the human ovum never having been investigated.

But in 1889 several investigators, stimulated by the discussions in connection with the pathology of Cystic Mole and Chorionepithelioma, turned their attention afresh to the study of early placentation.

Among these workers were Duval, who studied the Bat, Von Spee (a) who worked on the guinea pig: Hubrecht (b) on the hedge hog and later Selenka (c) and Strahl (d) who worked on the Anthropoid Apes.

All these authorities demonstrated a new phase of Intra-Uterine Placentation namely that it was not a Passive process, but that the ovum became embedded in the Uterine Mucosa by means of an Active destruction of the Maternal tissues at the site of attachment.

(a) Spee: "Die Implantation des Murschwveinchen-eies in die Uterus wand" Zeitoch f. Morphologie u Anthropologie No.3 1901

(b) Hubrecht: "Placenta Von Tarsius u Tupaya" Inter Congress of Zoology, Cambridge 1896.

(c) Selenka: "Studien ueber Enturchelungs geschechte" 10th part 1903.

(d) Strahl: "Die Embryonelkullen der Sauger" Hertwigs Handbook 1902.

To Hubrecht, more especially belongs the honour of being the first to supply us with the minute description of the Ectodermal cells of the Ovum and in demonstrating the function of those cells to be Trophoblastic i.e., a corroding the surface epithelium of the Uterine Mucosa and opening up of maternal capillaries, thus permitting the escape of blood for the young ovum to lie in and to yield its nourishment.

In 1899 Hubert Peters (e) epoch making discovery was announced, based on the examination of a very young human ovum, from five to seven days old.

He found the human blastocyst was completely buried in the Uterine Mucosa. The wall of the blastocyst was at its outer part composed of a many-layered cell mass, constituting the Trophic Ectoderm or Trophoblast, which was irregularly excavated by blood extravasations from the maternal vessels, while the maternal tissues lying in contact with it appeared to be undergoing degeneration.

The site of the Ovum appeared as a slightly raised convexity, projecting into the uterine cavity. This ridged or furrowed condition of the Endometrium has been confirmed by more recent observers and would appear to be indicative of early pregnancy.

At one part of the ridge Peters found the epithelium to be absent, being replaced by a mass of fibrin, marking the spot where the Ovum had apparently penetrated the maternal tissue.

The trophoblast consisted of two kinds of cells - large mononuclear cells and multinuclear syncytial masses, and between these two distinct types were to be seen all manner of transition forms.

(e) Peters: "Die Embettung des Menschlichen Eies" 1899 Vienna.

Jutting into the trophoblast were to be seen commencing outgrowths of the Chorionic Mesoblast, but no Villi were to be found.

The Embryo itself resembled that of the hedgehog at a corresponding period of development.

Hubrecht in his description of Placentation of the hedgehog says that at an early stage of segmentation, the ovum comes to rest in a hollow or furrow in the Uterine Mucosa. Around it, the mucous membrane swells up forming a cleft for the ovum to lie in.

The Uterine tissues in the immediate vicinity degenerate and disappear: the blood vessels are opened up and the ovum becomes surrounded by blood and is shut off from the Uterine cavity by means of a plug of blood clot. One of the most striking characteristics of the trophoblastic function of the Ectodermal cells is the change effected on the blood vessels.

These cells attack the maternal vessels, either directly invading the vessel from without while still maintaining their connection with a similar mass of cells outside: or these cells may appear in the vessel wall without any apparent connection with cells outside.

They entirely replace the vessel wall, except the endothelium, around which they appear as a circular band or tube, Occasionally they invade the lumen and form thrombi but this is very exceptional.

From the resemblance to and close proximity, often without any apparent connection with structures outside the vessels, it is little to be wondered at that the pathologist has not infrequently mistaken them for commencing Endothelial tumours.

While the maternal tissues immediately surrounding the newly embedded Ovum continue to degenerate, there developes outside of this destructive zone, a <u>reaction</u> on the part of the maternal tissues, which proliferate to form what is known as the Decidua - the

hypertrophied endometrium of pregnancy.

An equilibrium or truce becomes established between the destroying trophoblastic cells on the one hand and the proliferating or reacting maternal tissues on the other.

The spongy network filled with blood, the result of the trophoblastic excavation awaits the development of the foetal mesoblast, which soon buds out, every here and there as outgrowths of connective tissue with blood vessels: these outgrowths later on becoming covered by the trophoblastic cells, arranged as a double layer of epithelium.

The innermost of these two layers consists of small cubical cells, mononucleated and afterwards known as Langhans layer.

External to this and continuous with it are masses of protoplasm or plasmodium, showing much larger nuclei, and between these and the blood in the trophoblastic spaces is a complete layer of syncytium, acting as if it were an endothelial lining to the blood spaces.

Quite recently Peters conclusions have received striking confirmation from Prof. Leopold's description of another very young human ovum.(a) The ovum was obtained from a young woman who died of phosphorus poisoning. Pregnancy was suspected, although there was no menstrual history. The uterus was removed and carefully opened by Prof. Schmorl. The Ovum, after a very careful search over the deeply congested and charseteristically furrowed endometrium

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(a) Prof. Leopold: "A very young human ovum in situ"
Arbeiten aus der konighlichen
Frauen Klinch in Dresden.
VOL. IV, 1906.

was discovered as a minute spot, which was somewhat clearer than the deeply injected surrounding tissues, and was situated on a ridge of mucous membrane.

Of this piece of tissue after hardening, some 160 sections were cut and in the middle sections was found a very small ovum, measuring 1.4 m.m. in its greatest diameter: 0.9 m.m. in height and 0.8 m.m. in breadth.

From its smaller size, the absence of any villus projections into the trophoblast and the thinness of the trophoblastic processes themselves, Leopold believes it to be at least a day younger than Peters Ovum.

Leopold describes the endometrium as showing the characteristic signs of decidual formation viz: it is swollen and oedematous, with dilated and engorged capillaries, some of which are here and there ruptured.

The glands are hypertrophied and their mouths widened and in the region of the Ovum they are flattened and elongated as if being crushed by the growing ovum. Some of these are filled with blood and their epithelium separated: none of the glands opened into the Ovum chamber and no epithelial lining to the chamber was found.

The Ovum chamber was filled with blood, but no trace of the forming embryo was to be seen.

Leopold believes the Ovum becomes embedded as described by Von Spee in the case of the guinea pig - by boring its way through the endometrium. The roof of the chamber is of decidual tissue and immediately beneath this thin tissue is a mass of fibrin.

The Ectoblast consisted of two rows of cells - the inner made up of round or oval, mononucleated cells with large well stained nuclei - the Langhans cells: the outer row was made up of large cells, multinucleated and with granular protoplasm - the syncytium.

The Syncytium was to be seen wandering in to the maternal tissues and at places it was found lying beneath the endothelium of the capillaries. A similar process of the embedding of the Ovum takes place in Tubal pregnancy. This was first shown by Furth in 1898, but in his case it was believed to be exceptional: soon afterwards however, the accuracy of his description was verified and proved to be normal in Tubal cases just as in the Intra-Uterine Pregnancies.

Tubal placentation has been well described by Aschoff (10a), Lockyer (54) and Berkley and Bonney (130) and an admirable summary of the condition is to be found in a paper by Russell Andrews (a)

In the Tubal condition, surrounding the gestation sac. are usually to be found several layers of fibrin with foetal cells intermixed. This admixture is known as the "cell-sheet", and it appears to reach its maximum development in the early weeks of pregnancy, for when the Villi appear the cell sheet appears to atrophy.

In early abortions, either intra-or extra-uterine, the cell-sheet remains in the maternal tissues after the embryo with its membranes and villi have been cast off, whereas at full time labour, the cell sheet accompanies the membranes and placenta; here is probably an explanation as suggested by Bonney, of the persistent bleeding in Abortion cases, which occasionally requires the curette to obtain a cure.

(a) RUSSELL ANDREWS: "The Anatomy of the Pregnant Tube" Jour. Obstet & Gynaec, Vol IV, Page 208.

HISTOGENESIS of the TROPHOBLASTIC CELLS.

There has been much dispute and prolonged discussion as to the origin of the various cells composing the Trophoblast: All are now agreed as to the Foetal origin of the Primary or Langhans layer of cells, but there is still considerable diversity of opinion as to the origin of the syncytium or Covering layer, for instance Strahl believes it to be of maternal origin, while Pfannensteil (x) goes further in believing it to be formed from the endothelium of maternal vessels: there is something to be said for this view, for the microscopic appearance, not infrequently shows the syncythium lying under the endothelium and occasionally within the lumen of the vessels.

Sternberg (h) agrees with Pfannensteil as to the Endothelial origin; he arrives at this conclusion from his study of Chorionepithelioma in Testicle teratomata.

Seigenbeck and Langhans (22) believe the origin of the syncythium to be still an open question.

Duckworth in "The proceedings of Cambridge Phil. Soc., Vol. XIV, part III, 1907" reports the histological conditions present in an early stage of placental formation in the macacus nemustrinus. The decidual portion was the Compacta Basalis: no reflexa was present.

A series of 520 sections were cut through this part of the Uterus and stained.

(x) Pfannensteil: "Die Bildung der Placenta" Winkel's Handbook of Obstetries, 1903.

(h) Sternberg: "Zur Kenntius der chorionepitheliomartigen, Uricherungen in Malignen Hoderterotomen" 1904.

The Uterine tissues immediately below the area of attachment of the Blastocyst and for some distance on either side of this, were aedematous.

Immediately beneath the Blastocyst was an accumulation of fibrinous exudation, by which the degenerated uterine epithelial cells had been thrust off to be destroyed either by the ectodermal cells or by the leucocytes or by both.

There was no evidence of the transformation of of cells of the Uterine epithelium or of the glandular lining into syncytial masses as described by Selenka and Langhans.

Further the intervillous spaces were not lined by any derivatives of maternal cells: the epithelial cells of the Uterine glands play no part in placental formation: these gland cells may be destroyed by haemorrhage or by the embryonic cells.

Two varieties of Embryonic Ectodermal cells are recognised.

" (1) The outer and more deeply stained, irregular masses - the so called syncytial tissue (plasmodi-trophoblast), does not seem to play a permanent part in placental formation, although it may invade capillary vessels and uterine glands and seems to determine the opening up of communications between maternal capillary vessels and the intervillous spaces

(2) A polyhedral cell tissue (the cyto-trophoblast) which has permanent relations to the placenta as ultimately formed.

Such conclusions of Duckworth are in agreement with those of Peters, Marchand, Leopold, Spee, Bonnet and Robert Meyer, in short , with all who have worked with very young ova - they are all agreed as to the Foetal

origin of the Syncytium.

Peters concludes that the individual cells adjacent to the chorionic mesoblast are the primitive type, out of which all other forms arise. His view of the origin of the syncytium is by a flowing together of the outer layers of individual cells.

Teacher (12) holds that the development of the Syncytium of the human placenta is a proliferative process and not as Peters says by a process of fusion of originally distinct cells.

Teacher sums up the relationship of the different cell forms found in Chorionepithelioniatous tumours and their physiological prototypes, thus:

(1) The primitive type from which they all originate is of course a mono-nucleated cell - the undifferentiated Blastomere.

In the differentiated trophoblast or chorionic epithelium, it is represented by the individual or Langhans-layer cell.

The Syncytium develops out of these by growth of the cell and division of the nucleus, without division of the cell body i.e., a proliferative process.

(2) Both the Langhans layer element and the Syncytium have each an extensive power of growth into cells of their own type: they are thus capable of independent development although they usually grow in intimate association.

This is shown by the continuance of the Syncytium after the disappearance of Langhans layer in the later months of pregnancy.

Also the Syncytium gives off buds which may be mono - or multinucleated but otherwise preserve the characters of the parent tissue - the Syncytial Wandering cells."

Leopold is firmly convinced that the Syncytium is as much a part of the Ovum as are Langhans or the true trophoblastic cells.

C H A P T E R II.

CYSTIC MOLE in its RELATION to and BEARING UPON CHORIONEPITHELIOMA.

The history of the Cystic Mole extends over a long period. R. Kossman of Berlin in his historical review of the disease, mentions (2) that it was a pathological entity quite well known at the beginning of the 16th century.

Ruysch and Morgagni, in describing the condition, saw the resemblance to the cysts of the Echinococcus and thus named the condition as Hydatid disease of the Uterus. Even up to the beginning of the 19th century pregnancy was not believed to be essential to the production of Hydatidiform mole.

Velpeau and Madame Bovin in 1827 were the first authorities to recognise the condition as being a disease of the Chorion.

Then in 1847 Gierse described the cysts as a "hypertrophy of the natural (1) structures of the chorionic Villi with secondary aedema," - thus linking the disease definitely with pregnancy.

In 1865 Braxton Hicks insisted that the disease was a transformation of the (3) normal villi.

Virchow (Collected works - Frankfort 1856) in 1853 was the first to advocate the modern view of the degeneration process, but described it as being a mucoid or myxomatous change.

Storch disagreed with Virchow as to the nature of the process and for a time the disease was known as the "cystoid degeneration of Storch."

Such was the unsatisfactory condition of affairs until 1895 when Marchand(5) published his exhaustive work

on "Bau der Blasenmole". This was followed by the investigations of L. Pick (6) and L. Frankel (7) - definitely placing the pathology of Cystic Mole on a scientific footing.

The more recent works, especially that of Kermauner (8) on the "Anatomy and Aetiology of Cystic Mole" and the chapter on Cystic Mole by L. Seitz (9) in Winkel's Handbook of Obstetrics - have confirmed the earlier work of Marchand.

In Cystic Mole the appearances are exactly the same as seen in the normal Placenta, but in a much more exaggerated condition and accompanied by destruction of the Decidua and underlying maternal structures.

The <u>essential characteristic of Cystic Mole is the unusual proliferation of the epithelium along with necrosis and swelling of the Villus Stroma</u>

Much of the confusion to be found in the descriptions by various writers on this disease, such as some failing to find any evidences of epithelial proliferation, others finding no evidence of invasion or destruction of maternal tissue, such confusion appears to be due to the investigation of solitary cases, Dunger (10 has done much to clear the air of this confusion by showing that in the investigation of a series of cystic moles, he has found considerable variations in the histological condition, but his conclusions strongly support Marchand's views.

He disagrees with Aschoff (10a) and Franque (10x) who believe that the condition present in Cystic Mole, to be already Malignant and showing all transition forms from the simple cystic mole up to Malignant Chorionepithelioma, and insists on the distinct separation of destructive cystic mole from malignant

Chorionepithelioma; in support of his statement, Dunger points to the fact that in destructive Mole, there is no tumour formation to be found in the deeper areas of destruction; as is to be found in the case of malignant chorionepithelioma.

Whether we agree with Dunger or not, there is no getting away from the fact, that there exists a very close association between Cystic Mole and Chorionepithelioma.

Formerly one half the number of Cystic Mole cases were believed to be followed by Chorionepithalioma, but more extended observation has shown this estimate to be much too high

	Chorionepithelioma Cases.	Cystic Moles	Percentage of Mole Cases followed by Chorionepith--elioma
Ladinsky (14)	128	51	39%
Teacher (12)	188	73	36.6%
Briguil (13)	217	90	41.5%

The most recent statistics are those of Kroemer (15) in a paper on "The Aetiology and treatment of Chorionepithelioma especially on the treatment of Cystic Mole."

He reviews the cases at the Geissener clinic from 1899 to 1906.

During that period there were 3856 pregnancies observed, including 299 Abortions and 17 cases of Cystic Mole.

Of the 17 moles, the majority occurred in Multipara; 9 of the 17 cases were complicated by severe renal disturbance, one going on to Eclampsia and afterwards developing Chorionepithelioma.

Ovarial tumours were present in 10 of the 17 cases, and in three of those ten cases they were of such size as to call for operation.

Seven of the 17 cases developed Chorionepithelioma. Five of the seven resulted in cure by repeated curetting.

Two cases of Chorionepithelioma followed full time pregnancies, developed lung metastasis and ended fatally.

The histological nature of the scrapings obtained by the curette gave no indication whether the disease was benign or malignant, and Kroemer states that the clinical picture indicated the nature of the cases and the treatment to be employed.

De Senarcleus (11) in 1902 from an enquiry of the Physicians of the Kanton Waadt found that in 35 out of the 49 cases where a Cystic Mole had existed there was complete recovery.

Of the remaining 14, seven cases could not be traced to ascertain the result and of the remaining seven, one developed Chorionepithelioma with fatal termination sixteen months after removal of the cystic mole.

Two others died in three months: the others were diagnosed as cases of Chorionepithelioma, in three to four weeks after the Cystic Mole, but the termination is not stated.

Bauer (16) reports the case of a woman aet 45 in her 9th month of Pregnancy who had characteristic symptoms of Chorionepithelioma, and obtaining no benefit from curetting, the Uterus was removed. This case resembled the series of nine reported by Kroemer, in having very marked renal lesion, but in the Ovaries no lutein cysts were present.

Personally from the number of cases of Cystic Mole that I have observed in practice, and carefully followed up their after histories, I am inclined to believe that even these later statistics, still show a too high per centage of Cystic Mole followed by Chorionepithelioma.

In Palmer Findley's series of 210 cases of Cystic Mole, the malignancy tendency is well brought out by the death of 32 cases from Chorionepithelioma and although there is no report given of any operative treatment, being employed he thus shows a percentage of 16. (4)

In Teacher's 73 cases of Cystic Mole, 39 died of Chorionepithelioma and of these 73 cases, 42 were operated on with thirty three recoveries.

It is a notable fact, that almost with every fresh series of statistics dealing with the relative frequency of Cystic Mole as a disease of pregnancy, there is a tendency to show the disease to be much more frequent than had hitherto been believed.

This, I am convinced, is a correct tendency, for there is a large number of cystic molar cases that are never reported, for instance in one neighbourhood during the past two years, I have known of four such cases none of which were reported; so that the statistics of Cystic Mole are not to be much relied upon.

Madame Bovin put the frequency at 1 in 20,000
Williamson " " " " 1 in 2,400
Jellett (Rotunda Hospital) (17) " " 1 in 1,500
Berry Hart " " 1 in 1,000

Neuman in a paper he published in 1897 on the diagnosis of the benign from the malignant cystic mole, points out as suspicious of malignancy, the invasion of the epithelial cells into the stroma of the Villus but Marchand failed to find this inva- (18)

sion in a Malignant Mole and Ruge found the stroma invaded in a case of undoubted benign Cystic Mole.

S E C T I O N A.

AETIOLOGY of CYSTIC MOLE.

Considerable as was the advance made in our knowledge of Cystic Mole during the 19th century, yet notwithstanding all the work that has been done in connection with this disease, we still have no real knowledge of its causation. The various theories put forward may be classified into two main divisions.

I. The cause lies in some diseased condition of the Egg. = Ovular Causation.

II. The cause lies in some diseased condition of the Uterus, especially the Decidua = Maternal Causation.

I. Marchand (5) believes Cystic Mole to be due to a primary disturbance of the egg while it is yet in the Graafian Follicle and that this disturbance is occasioned by some influence on the part of the Mother; so that the epithelial elements at a very early age assume proliferating powers, akin to those of a Malignant tumour. But he is willing to admit of other causes occasionally being at work in such cases as partial cystic mole e.g., in some disturbance of the Uterus or altered nutrition consequent on the death of the Embryo.

Virchow was the first to suggest the possible causal relationship of Endometritis and hydatid mole.

But many observers find it extremely difficult to determine whether the changes in the Endometrium are primary or secondary; and further those changes in the Endometrium that have been described by many are by no means constant. Cases of twin pregnancy,

where one ovum becomes cystic, while the other proceeds to full development, have been quoted in favour of the primary disease being in the Ovum; and so also the great frequency of Ovarian cysts found in association with Cystic Mole and Chorionepithelioma, suggests a similar origin.

The death of the Embryo in cases of Cystic Mole has been the subject of much controversy.

Barnes (19) in his paper published about the middle of last century, adhered to the idea of the death of the Foetus, being the result of the Chorionic disease While Graily Hewitt (20) firmly maintained the opposite view, namely, that the death of the embryo occurred first and the chorionic disease was secondary. Quite recently this view of Hewitt's has been advanced by Eva Chaletsky (21) who believes that the proliferation of the Villus Epithelium is the result of the cessation of the foetal circulation - thus causing an enforced alimentation of the villi, Langhans (22) also is inclined to support this view.

But if death of the Embryo be the cause, how are we to account for the rarity of the lesion in cases of missed labour and abortion with the dead foetus remaining in Utero for weeks or months?

Whereas on the other hand, cases of partial cystic disease of the Chorion with the foetus remaining healthy are in favour of Barnes' idea, viz: that the complete cystic disease would result in the death of the foetus .

II. In support of the opposite view - that the cause of Cystic Mole is to be found in some diseased condition of the Uterine tissues, many reasons are put forward, e.g.

(1) Repeated appearance of cystic mole, in the same woman, even in the impregnation

of different men.

(2) The relatively frequent appearance of Cystic Mole in elderly women - especially near the menopause, or in those who have been for a long time sterile (Findley in his series of 210 cases, disputes this relative frequency in elderly women; he found the average age to be 27 years.)

(3) Endometritis and some general diseases of the mother e g., nephritis, anaemia etc., are found in frequent association with Cystic Mole. But in opposition to such a view of causation, is the experience of every Gynaecologist - that normal pregnancy frequently occurs in women suffering from such diseases.

(4) Seitz (9) speaks of the decidua as being thickened and showing degenerative and inflammatory evidences - especially a small round cell invasion, while later on as the cystic disease grows, the decidua becomes attenuated, and he further believes that the dropsical swelling of the villi to be due to the altered nutrition of the pathological endometrium and the increase of the wandering ectodermal cells in the serotina.

(5) Gottschalk (23) in his recent work has adopted the old theory of an obstructed umbilical vein - this obstruction being due to a kinking of the cord or stenosis of its tissues, or to Thrombosis occurring in its vessels - thus setting up an

oedema of the villi and a consequent proliferation of the villus epithelium.

He believes that the villi lying in maternal blood, remain active by their epithelium continuing to take up nourishment from the Maternal blood and there being no demand for this nourishment on the part of the foetus, it becomes stored up in the epithelial cells, which being thus over-nourished commence to proliferate. In this theory he sees an explanation of the predisposition to Malignancy. He found the epithelial proliferations present only at those places where the Villi were bathed in maternal blood.

S E C T I O N B.

THE AETIOLOGY OF MALIGNANT CHORIONEPITHELIOMA

(excluding the lutein tissue theory.)

In several of his writings Marchand (24-25) discusses the aetiology of malignant chorionepithelioma including his latest views.

He sees the actual cause of the malignancy "in the proliferating powers of the cells of the chorionic epithelium, - increased through the altered nutritive conditions, - in connection with the chemiotaxic stimulus."

So long as the Ovum develops in a normal manner, the proliferating powers of the chorionic epithelium, keep within bounds, but if the normal course is interrupted as in partial or total cessation of the foetal circulation, such as might result from (a) the decay of the embryo or (b) the transportation of isolated normal villi, the normal and regulated development of the villus epithelium ceases.

The epithelium continues to absorb abundant nourishment from the surrounding maternal blood and the individual cells develop and multiply in increased masses, although here and there showing degenerative processes, both in their cell bodies and their nuclei. These cells whose normal function (trophoblastic) at the embedding of the ovum, was closely akin to malignancy, develop destructive qualities - invading and destroying the maternal tissues.

Lending some assistance to this destructive power is the somewhat lowered resistance of the basal layer upon which the new formation is growing. Another factor which Marchand believes to be conducive to the penetration of the Uterine tissues is the serous infiltration and consequent loosening of puerperal uterine structures, and also the hypertrophy of the blood and lymph spaces - conditions manifesting much less resisting powers than do the non-puerperal uterine tissues. These conditions may in some measure, explain the greater destructive power and increased mortality, that is found to be so characteristic of Chorionepithelioma following full time pregnancy.

But the actual work of destruction is due to the chemical and mechanical influences of the tumour cells.

While the ectodermal cells by their chemical and mechanical changes are causing dissolution by necrosis and coagulation, the uterine tissues set up reactive changes which offer a certain degree of resistance to the invading tumour elements and may even lead to a degree of cure (See remarks on spontaneous healing. Chapter IV, Sub-section I.)

R. W. Mackenna (26) suggests the cause of the malignant proliferation of Chorionic epithelium to be the stimulus of some toxin, the nature and composition of which remains unknown, which develops in the Ovum

or in the Uterine tissue during pregnancy. This toxin may be the cause of the commencement of Cystic Mole and a large dose or more prolonged operation of it may stimulate the cells to assume malignant tendencies.

Schmauch (27) seeks for the aetiology of malignant Chorionepithelioma in the application of Ehrlich's side chain theory. He traces the disease to a deficiency of Sycytiolysm - a substance which Veit believes is to be found in the body of every pregnant woman. This substance has the physiological power of loosening and displacing the cells of the chorionic villi; but these cells have less proliferative power when an entire villus is displaced.

The displaced cells or villi will remain local, surrounded by fibrin and quantities of blood and thus be buried or expelled, so long as the maternal organism produces anti bodies. Local tumours are made possible only by the reducing of the protective power, as after great loss of blood, and can be removed by operation A return of this protective power, with the strengthening of the body prevents dissemination of the cells. But general metastasis is possible only in complete deficiency of the immune bodies, and the prognosis of the tumour formation depends less upon the quantity of displaced cells than upon the circumstance, whether the affected body is able to form a sufficient number of receptors to cope with the final extermination.

He believes that it is the Anti-body formed in the Maternal Organism that keeps the trophoblastic function in check.

He further believes that this same deficiency explains the frequent appearance of Chorionepithelioma after Cystic Mole; and again, that the Chorionepithelioma tumours can be overcome by means of immunisation

or the replacing of the lost protective power. He looks upon the Ovum in Utero as biologically similar to a parasite and the act of parturition as a kind of spontaneous help of nature.

Reeb (28) criticises Schmauch's views and puts forward as an objection the case of Multiparae who according to the theory of Eclampsia have, stored up in their organs an excess of the Antibody-syncytiolysm; and yet after eclampsia are known to have developed Chorionepithelioma malignum.

Fleischmann (29) supports Schmauch's theory and believes it possible that through a mobilisation of the protective material - perhaps syncytiolysm, the non-malignant course of many cases of Chorionepithelioma is to be explained.

Schmidt (31) believes the course to be not only over-activity on the part of the epithelial cells, but also a deficient coagulability of the Uterine blood.

Kworostansky (32) believes the cause to be due to a deficient blood quality and suggests, that under the influence of Cardiac disease, Kidney disease, Tumours of the Uterus, or deficiency of mucosa - in short any bad nourishing condition for the placenta, the exuberant chorionic elements assume their penetrating powers.

Schmorl (33) in two of his cases of Chorionepithelioma, reports the presence of a high degree of Anaemia, and in two other cases there was present a pelvic infection; accordingly he supports the theory that Chorionepithelioma is due to a lowered resistance of the maternal tissues.

Robert Meyer (34) believes the cause to be due not only to an increased nutritive condition of the chorionic cells, but also in part to some cessation of the normal tissue resistance. He holds that these cells originally derive a certain 'momentum' from the Ovum

to function as Trophoblasts but to account for their self depen dence afterwards, they require the existence of some special stimulus, the nature of which is unknown.

Schlagenhaufer (34x) looks for the explanation of the different clinical conditions of histologically similar chorionepithelial proliferations, in a temporarily differing releasing faculty of the constituent elements of the tumour formation; and that the earlier the stage of commencing proliferation i.e., the younger the stage of malignancy the more capable are the cells of proliferating.

Ribbert (35) by his hypothesis explains the malignant proliferation of these chorionepithelial cells, as being due to their reaching a greater degree of self dependence, resulting from their severance from their natural bond. When they separate plus the Villus, they remain normal, as the severance is largely a passive or mechanical process.

He thinks this releasing from their natural bond, must take place very early - as soon as the foetal membranes develop and before the villi have assumed their normal shape and size; he doubts whether the epithelium that has separated from already formed Villi, is able to produce Chorionepithelioma after its severance.

In the case of Cystic Mole he assumes that from the very outset the villi have not been normal, but have been injured during formation or never clothed properly with epithelium.

Marchand in criticism of this hypothesis, mentions the fact that the epithelium already proliferates, while yet it clothes the villi and that at the normal embedding of the Ovum, the Ectodermal cells can be seen migrating into the Uterine Mucosa.

THE PARASITIC THEORY OF AETIOLOGY.

La Torre[36] in 1900 sought to prove that the disease was due to a localisation of Blastomycetes, the existence of which he claimed to have proved in the placenta from a case of Deciduoma Malignum

So also Franque[37] in 1903 sought to demonstrate a similar causation. More recently, in 1905 Rossi Doria[38] has traced the origin of malignant Chorionepithelioma to an inner Embryonal and an outer parasitic stimulus, which was eliminated by Blastomycetes, which penetrate between the foetal elements which have remained in the Uterus.

Many experiments have been performed to test this parasitic theory, e.g., subcutaneous and intraperitoneal implantation of Chorionepithelioma tissue in the Rabbit (Vassmer[38x]) and by Schmauch[38a] but without any definite result.

A similar fate has followed the injection of placental tissue into animals.

Halban[39] puts forward the most suggestive theory of the causation of Malignant Chorionepithelioma, namely, that the stimulating substance - syncytiolysm or whatever we may call it, has its origin in the placenta, and that it is most likely the internal secretion of the chorionic epithelium. This epithelium is the product of union between spermatozoon and Ovum, both specific products of organs which are believed to possess internal secretions: this view I'll refer to again, more fully, in the following section.

In October 1907 before the Obstetrical Section of the Royal Society of Medicine, Prof. W. E. Dixon and Dr. Frank Taylor[40] gave an account of their ex-

periments, showing the physiological action of the Placenta

They made alcoholic extracts of fresh normal human placentae and injected them intravenously into cats, rabbits and dogs.

The results on the Uterus differed in the pregnant and non-pregnant condition. In the Pregnant Uterus there resulted an increased tonus of the Uterine Musculature, plus a well marked increase in its rhythmic contractility.

They concluded that the placenta produces a chemical substance which develops with the ripening of the placenta, and which by contracting the Uterus and its vessels, may induce the onset of normal labour; and that a perverted metabolism might produce an antointoxication resulting in Albuminurin, Acute Yellow Atrophy, Eclampsia, or even Hyperemesis Gravidarum.

Acconci (41) in 1906 published a lengthy paper on "Researches on the formation of plastein from placental extracts." The conclusions he arrives at are somewhat similar to those of Dixon and Taylor - that there is an internal secretion of a substance to be called 'Plastein.'

S E C T I O N C.

THE CO-RELATIONSHIP of OVARIAN AND UTERINE FUNCTIONS:

Halban (39) has published the details of his investigations on Pregnancy Reactions in the organs of the Foetus and their puerperal involution.

There are certain substances, circulating in the maternal blood, which excite reactive changes in the maternal tissue; these substances also circulate in the foetal blood, and his researches had the object of ascertaining the reactions excited in the foetal

tissues.

He examined the organs of female foetuses and those of the newly born, and also of children from a few weeks up to two years old.

He found the Uteri of newly born infants in a remarkable state of Hyperaemia especially the Endometrium, the histological appearances of which corresponded exactly to those of an adult menstruating Uterus.

He found that those changes begin in the foetal Uterus about the eighth or ninth month and believes them to be due to some substance circulating in the foetal blood; and not to any Ovarian influence - for he invariably found the Ovaries in an unripe condition.

From this he deduces the conclusion in opposition to Frawkel, - that the pregnancy reaction of the Maternal Organism is not due to the influence of the Ovary.

Further that the corpus luteum has no influence in the production of the pregnancy reaction in the foetal organs, because this reaction is only seen in the later months, when the corpus luteum is atrophied.

Bayer's observations confirm those of Halban, in showing that there is a puerperal involution of foetal organs - the Uterus of the newly born is usually much larger than that of an older child and that the involution is usually complete in about three weeks after birth.

The foetal breasts also are seen to undergo remarkable changes in the later stages of pregnancy - a proliferation of the glandular epithelium, a dilatation of the lumen and the appearance of colostrum. A few days after birth, there is the well known clinical observation that the breasts of the newly born

female fill with milk just as in the case of the mother and that these mammary glands gradually involute, in the first few weeks after birth. Similar changes he observed, were present in the breasts and prostates of male children.

Halban in the same paper discusses the subject of Eclampsia, and points out that the condition has frequently been observed in both mother and foetus, and that in the nephritis of pregnancy Albumen has also been found in the urine of the foetus. In these toxic conditions Halban sees an exaggerated degree of the pregnancy reaction, the effect of the internal secretion of the chorionic epithelium. Further this work of Halban's gathers confirmation somewhat from the frequency of kidney lesions as observed by Kroemer and Bauer in their cases of Malignant Chorionepithelioma.

Frans Daels (42) details his experiments, showing the relationship between the Ovaries and the Uterus, He criticises the experiments of Strassman, who maintains that by raising the intra ovarial pressure, as by the injection of fluid into the ovaries, that he induced changes in the pelvic organs, resembling those of 'rut' and concluded that menstruation is due to reflex hyperaemia excited by pressure of the growing follicle on the nerve terminals in the ovary.

Daels objects to such a conclusion and from his experiments on bitches both by the injection of iodine into pelvic tissues and by Yokimbinum by the month, he produced intense hyperaemia of the pelvic organs but no 'rut'; he therefore maintains that hyperaemia is not the starting point of 'rut' or menstruation, but only one of its symptoms.

He quotes Halban's experiments, as proving that menstruation is dependent on an internal ovarian secretion with a specific influence on the Uterine Mucosa.

Again, he adversely criticises Fraenkel's theory of the relationship of the corpora lutea to menstruation and the embedding and development of ova; he believes such a theory is not in accordance with clinical and experimental observation, Hyperplasia of the lutein tissue in cases of Chorionepithelioma and Cystic Mole, is neither the cause, nor consequence of those diseases but the synchronous expression of some general pathological condition at present unexplained.

Regarding the influence of Oophorectomy on the continuance of pregnancy he concludes from his control experiments, that the meretrauma of exterpating both Ovaries, may probably be sufficient to account for the interruption of pregnancy; and further that feeding the animals on lutein extract and oophorin, did not exercise the slightest influence in the preservation of pregnancy.

Marshall & Jolly (43) from their experiments on the transplantation of the ovaries of rats by peritoneal grafting, found that the uterine degeneration which follows simple removal of the ovaries did not occur in the cases in which the transplantation of the ovaries was successfully effected: they therefore conclude that the influence of the ovaries on the Uterus is chemical rather than nervous and probably due to an internal secretion, elaborated not merely at periods of heat and during pregnancy, when the ovaries show their greatest activity, but throughout the whole of the aestruous cycle.

Carmichael & Marshall (44) from their experiments on rabbits, especially the removal of ovaries at different ages conclude that

(1) the removal of the ovaries in young animals prevents the development of the uterus and Fallopian tubes, which remain in an infantile condition

(2) In Adult Animals, removal of the ovaries leads to fibrous degeneration of the Uterus and tubes, most marked in the Mucosa;
The subsequent health and nutrition of the animals remain good.

In five other animals the Uterus was removed and they found that

(1) Removal of the Uterus in a young animal has no influence in preventing the further development of the ovaries which in adult life are still capable of ovulating and forming Corpora lutea.

(2) Removal of Uterus in Adult Animals does not give rise to any degenerative change in the Ovaries.

Kleinhaus & Schenk (45) of Prague describe their results of an experimental enquiry into the function of the Corpus Luteum

They attribute the priority to Born, of the hypothesis, that the Corpus luteum is a gland with an internal secretion presiding over the embedding and development of the Ovum within the Uterus and that Fraenkel confirmed, by experimental research Born's views and added his belief that the corpus luteum also presided over menstruation.

In their present paper, their object is more especially to ascertain the connection between the corpus luteum and the continuance of pregnancy; rabbits were the animals used, and the series of 25 experiments was divided into two groups.

In the first group the abdomen was opened by median incision and the corpus luteum destroyed by the thermo-cautery; In the other group, to minimise the traumatiom, the ovaries were exposed by lateral incisions and the corpus luteum scooped out, instead of being burned.

They conclude especially from their control experiments that:

(1) the pregnant rabbit is especially sensitive to trauma

(2) In rabbits, if after the embedding of the Ovum, the corpora lutea be removed with all possible precautions and not earlier than the ninth day pregnancy is not necessarily interfered with

(3) That it is not a function of the Corpus Luteum to preside over the development of the Ovum after its fertilisation.

S E C T I O N D.

THE OVARIAL CHANGES FOUND ASSOCIATED WITH CYSTIC MOLE AND CHORIONEPITHELIOMA.

Of recent years considerable attention has been paid by many observers to the Ovarial changes especially the presence of Lutein cysts and Lutein tissue more particularly to their bearing on the Aetiology of Cystic Mole and Chorionepithelioma.

It has long been noted by such observers as Barnes [46] in 1866, Waldeyer [47] in 1868, Runge [48] in 1880, Haberlein in 1895 and others; all merely recording the fact, but [49] placing no interpretation upon it.

Marchand [5] in his historic work on Cystic Mole, published in 1895, drew attention to the remarkable coincidence of cystic degeneration of the ovaries with

Cystic Mole. This work was the means of attracting other observers to devote special attention to those cases, cystic, among whom may be specially mentioned Schaller and Pforringer (50) in 1899 and W. Stockel (51) in 1902.

These observers were the first to point out that here we had not to deal with ordinary follicular cysts as had hitherto been believed, but with cysts with walls formed of lutein cells.

The work of these last mentioned observers must be regarded as the standard on the subject, for all the more recent workers have merely confirmed the accuracy of the first published details.

In 1903 Runge (52) published his Analysis of a series of 144 cases of sycytial tumours. In 24 only did he find any statement of the co-existence of ovarial cysts. Eleven others reported Ovarian cysts absent on palpation.

28 others reported Ovarian cysts absent on inspection during abdominal section. In 63 cases there was no mention made of the Ovarian condition

He collected 28 cases of Cystic Mole and in 16 of these, there was no mention made of the ovaries, whilst in the other 12 cases cystic degeneration was present.

In 1905 Patellani (53) collected the statistics of all observations in which ovarian changes were published as being associated with Cystic Mole and Chorionepithelioma. These changes were found 44 times in Cystic Mole and 18 times in Chorionepithelioma following Cystic Mole and 32 times in Chorionepithelioma following full time labour or Abortion.

This series includes some cases which were published without any histological details.

In this country Cuthbert Lockyer (54) first published his investigations on the Lutein reaction in con-

nection with Chorionepithelioma in "The Practitioner" December 1904, and again more fully in the Jour. Obsetet and Gynace of British Empire, Vols. 1 and 2 1905.

MICROSCOPIC DESCRIPTION.

The cysts may be unilateral or bilateral and of varying size - from that of a pea to that of a foetal head. Many of them contained blood, in others the contents were yellowish white to brownish red.

The number of cysts in one ovary may be very large, and the cysts are seldom in communication with each other. After evacuating the contents, most of the cysts show a smooth inner wall, while the outer wall is often rough, nodular or even villous in appearance.

Microscopically. The lutein cysts were composed of two layers - an outer one consisting of connective tissue, rich in nuclei and with numerous blood vessels; the inner layer is made up of many rows of epithelium, some cubical, some round, and others flat with large well stained nuclei, and small nucleoli and diffusely stained protoplasm. These cells are arranged in rows between which run capillaries, branching off from the vessels of the outer layer. The innermost layer of cells showed signs of degeneration (deficient staining capabilities) and gradually passing into amorphous detritus; or they were separated from the cystic contents by a thin layer of fine fibred connective tissue which springs evidently from the adjoining delicate capillaries.

In this fine membranous layer, were found occasionally, brown pigment corpuscles giving the iron reaction.

Lutein Cells. In addition to these cysts were found, scattered throughout the ovarial stroma, but especially in the vicinity of the cysts, large fatty cells, filled with yellowish pigment granules and well

defined cell outline - these are the typical lutein cells.

In the centre of some of these masses of lutein cells was to be found an attempt at mucoid softening. Stochel describes his case of Lutein cysts thus "The inner wall was slightly undulating and at times distinctly folded, only exceptionally quite smooth. The contents appeared reddish white to dark brown."

Then he goes on to give a minute description of the cyst wall into four layers:

" (1) An outer layer of thick coarse connective tissue forming a sort of capsule and which separate the cyst from the ovarian stroma - this is the Theca Externa.

(2) Next comes a layer of loose connective tissue - the Theca Interna, very rich in cells and blood vessels.

(3) The third layer is formed of many cells in rows of palisade-like arrangement, lying perpendicularly to the cyst wall; these cells are large, vesicular and frequently showed mitosis. Between the rows is a framework of fine connective tissue fibrils and numerous capillaries - offshoots from the Theca Interna which force their way in between the cells of the first row to be gradually lost amongst them.

(4) Lying on the inside of the cyst wall, separating the inner layer of epithelial cells from the cyst contents is the fourth layer of membranous connective tissue derived from blood or fibrin deposit, - this layer is frequently deficient at intervals."

Stockel further observed outside the vessel layer of the theca interna, whole lines and accumulations of cells running far into the Ovarian stroma and these could be recognised as Lutein cells.

Much discussion has arisen from the confusion of corpus luteum cysts and lutein cysts. Most authors allow, that the large lutein cysts in cases of Cystic Mole are developed from the corpora lutea graviditatis or menstrationes, but Stockel believes that they may possibly arise from Atretic follicles.

Schallar and Pforringer interpret the cysts as corpus luteum cysts and the scattered lutein cell masses, to arise from the cyst wall and to represent these individual wandering cells as possessing greater proliferating power - so much so that they describe them as a Carcinomatous stage of the lutein cells; whilst Stockel believes that the lutein cells of the cyst wall, originate from the connective tissue of the Theca Interna and are to be distinguished from the true theca cells only by their considerable size and weaker staining powers.

He also takes a different view from Schaller and Pforringer as to the origin of the isolated masses of lutein cells, scattered throughout the Ovarian Stroma and instead of believing them to be a malignant overgrowth penetrating into the Stroma, looks upon them rather as a passive development due to the increase in size of the vessels of the lutein cell layer and partly to the aedematous condition of the stroma.

Jaffe (55) attaches no significance to these displaced lutein cells found in cases of Cystic Mole as he found a similar disposition or arrangement in other conditions and believes it to be a physiological breaking away from their attachments, owing to the

rapid and abundant proliferation of lutein tissue.

CONSIDER THE INTERPRETATIONS PUT ON THESE OVARIAL CHANGES BY THE VARIOUS AUTHORITIES.

Kattenback (56) entertains no doubt as to the meaning of these ovarial changes; he sums up his opinion thus: "The Cystic Mole is based upon a primary disease of the Embryo, that is furnished by the fertilised Ovum of a diseased Graafian follicle"

Scholler & Pforringer take the same view as Kattenback.

Stockel & Marchand are much more cautious in their interpretation, and speak merely of the casual connection existing between Cystic Mole and lutein cysts.

The Born-Frankel (58) hypothesis is expressed thus: "the corpus luteum may be a gland with an internal secretion which may possess the function of making possible the insertion of the fertilised ovum in the Uterus and of securing its further development."

Runge interprets this hypothesis by stating that the development of the Ovum in the Uterus depends upon the integrity of the Corpus luteum pertaining thereto, and therefore an inner connection exists between them. In consequence of this it may be possible, that when under special circumstances a heightened proliferating power is inherent in the corpus luteum, that this power may transmit itself to the Ovum and thus produce the peculiar changes which are so characteristic of Cystic Mole and Chorionepithelioma.

L. Frankel after deducing from his experimental researches, that the normal trophoblastic action is due to the production of lutein tissue within the

ovary, arrives at the inexplicable conclusion that the exaggerated trophoblastic function, so characteristic of Cystic Mole and Chorionepithelioma is the result of a minus quantity of lutein tissue and suggests as treatment for these diseases the giving of lutein tissue tablets.

Lockyer in his work above quoted points out the inconsistency of such reasoning.

L. Pick (59) speaks of what he calls the Chorionepitheliomatous reaction in the Uterus in Cystic Mole and Chorionepithelioma, as being due, not to a minus quantity, but to an Overproduction of the Lutein substance and that this substance is not merely formed from lutein cysts, but also from the isolated masses of lutein cells.

In complete opposition to these various interpretations above mentioned we have the observations of Dunger (60) who maintains that these ovarial changes are not the causes but the consequences of Cystic Mole and Chorionepithelioma: he agrees with the previous observers in describing the presence of a plus production of lutein substance, but interprets it as being not a primary, but a reflex condition due to the chorionepithelial overgrowth in the Uterus; and that this lutein production is only one of the many secondary changes which are taking place throughout the maternal tissues during pregnancy: such other changes being (1) the decidual transformation of the Uterine Mucosa (2) the enlargement of the whole uterus as in Tubal pregnancy and (3) the decidual proliferations in different places in the connective tissue, especially subserous and also on the surface of the ovary.

Birnbaum (61) also takes exception to this lutein tissue in the Ovary being solely the cause of Cystic

Mole and Chorionepithelioma and in illustration quotes his own case of Twins, one Ovum developed Cystic Mole, while the other went on to full time pregnancy, so that if lutein tissue had been the sole cause of Cystic Mole, it would have affected both pregnancies. The latest pronouncement on the value of this aetiological factor is an important communication by Risel (62) in Lubarsch-Ostertags, Ergebn, Dec. 1907.

An investigation was undertaken by the following authorities:

Boshagen (62a) working under Aschoff's guidance; J. Wallart (62x); C. Pinto (62b); L. Seitz (62c) and W. Risel; each undertook separately to inquire into the different processes of Involution in the Normal Ovary. Risel says "They all came to the same conclusion, independently that the changes above described, represent nothing specific for Cystic Mole and Chorionepithelioma; that much rather similar changes are found even in normal conditions in both Intra and Extra Uterine Pregnancies.

Boshagens investigations relate to the Ovaries of Women at different ages. In the ovaries examined during pregnancy, he saw in the follicles that were commencing to involute a specially strong proliferation of the Theca Interna, so that even small follicles were surrounded by a belt of young lutein cells.

Even in the midst of hyaline degeneration of the Theca Interna, specific cells of a lutein nature were preserved for a long time.

Further he found that the nearer the corpora atretica and Fibrosa - through the absence of hyaline degeneration - approach in structure to the old ovarian tissue, the more it gains the appearance as if lutein cells separately or in clumps were deposited in the normal ovarian stroma.

From such 'findings' the author no longer doubts that the changes in Cystic Mole and Chorionepithelioma are caused by excessive proliferations of lutein cells at the places where they or their young forms were normally found. To decide the question whether there is an actual pathological proliferation of lutein masses, through vessel proliferation, or even from active development of lutein tissue already present in normal but highly aedematous ovaries, he thinks that a still larger number of ovaries of pregnancy will have to be examined. He is inclined to believe that there may be some truth in the suggestion of Stockel and Runge, that the source of lutein proliferations may be the normal theca cells of the small follicules, or the lutein masses of involuted follicles - as supplying an explanation of the lutein cell proliferation of Cystic Mole.

Wallart concludes from his investigations that in the pregnant, a transformation takes place of the Theca Interna of many non-ruptured Atretic follicles into an Epithelioid tissue - which seems similar to the lutein tissue of the true corpus luteum. This follicle can transform itself into cysts or solid masses of epithelioid tissue. These same changes - a massive production of lutein tissue and the formation of large and small cysts with walls partly composed of lutein cells - he found in a case of Cystic Mole and Chorionepithelioma. In his second case (63) similar appearances were found: he says: "The changes, contrary to those in ordinary pregnancy, show by no means essential differences, but solely (when present at all) slight ones"

Any special or diagnostic feature of the ovaries of Cystic Mole and Chorionepithelioma he holds not to be proved at the present state of our knowledge.

In his latest work he comes to the conclusion that he frequently observed 'lutein cell proliferation' which appears in Cystic Mole and Chorionepithelioma are for the greater part to be regarded as Interstitial Gland Tissue.

This interstitial gland tissue is developed most strongly from the early years up to puherty, and later, recedes against the other structures of the Ovary, no longer taking up a prominent position and that its highest development is reached during pregnancy and especially so in pathological pregnancy

This interstitial gland tissue occasionally attains enormous enlargement - at other times it may hot be greater than in normal pregnancy. But these ovarial changes have no causative influence on Cystic Mole.

L. Seitz arrives at practically the same conclusion as Wallart just quoted. He studied a large number of pregnancy ovaries of varying ages from 2 to 10 months and also in the early puerperium & compared them with those found in a case of Cystic Mole.

He specially observed the Atretic follicles and found that during pregnancy they manifested an unusually strong development of the Theca Interna cells - this he found as early as the second and third months of pregnancy and that it progressed, reaching its height at the end of pregnancy.

This lutein cell development appears not only on the follicles of a spherical shape, but also on the compressed or collapsed follicles - and showed a thickness never seen apart from pregnancy. He found difficulty at times in determining whether the Theca Externa played any part in this epithelioid transformation.

In his case of Cystic Mole he found the changes exactly coinciding with those recorded by earlier workers, viz:

(1) Formation of large lutein cysts

(2) Lutein cell proliferation of the Theca Interna in Atretic follicles

(3) The lutein cell complexus from the compressed or collapsed follicles

(4) Isolated lutein cell groups scattered throughout the Ovarian Stroma.

But these changes he recognised to be identical with those occurring in normal pregnancy. He recognised that in all these Ovarial changes whether in normal pregnancy or in Cystic Mole, that the increase of the lutein cells of the follicle is a pre-existing one.

Seitz holds this lutein cell increase in the Atretic follicles to be of connective tissue origin and as its great increase is always associated with pregnancy, whether normal or pathological, that therefore the presence of foetal elements has something to do with it. In short that it is a change specific to pregnancy just as the decidual cells are - this conclusion will be seen to closely coincide with Dunger's hypothesis quoted above.

Seitz proceeds to point out, that so long as foetal elements are present in the mother, ovum maturing and ovulation cease and the further developed follicles degenerate.

Under the influence of pelvic congestion and possibly under the direct influence of the foetal elements, the Theca Interna of the imperforated follicle is transformed into the typical lutein layer. He holds therefore as being more probable than the Born Franhel theory, the assumption that it is a question of a

specific inner secretion of the ovary during pregnancy which does not secure the development of the Ovum, but transmits to the Mother, substances which possibly effect the characteristic changes, or part of them, that manifest themselves in the pregnant woman. The inner secretion of the ovary which he assumes as certain would be modified during pregnancy by the secretion of lutein cells of the Atretic follicles. It is probable that in this modification lies the causation of the lowered maternal resistance during the trophoblastic invasion. He attaches no importance to the varying sizes of the cysts found in Cystic Mole and Chorionepithelioma, but believes the differences to be purely accidental, and more than likely influenced by the pelvic hyperaemia, causing an increased aedema of the Ovarian Stroma.

FOR THE ORIGIN OF THE LUTEIN CELLS, HE DISCUSSES THREE POSSIBLE CAUSES

I. The actual breaking away of a piece from the Corpus luteum - but this is rare and merely a question of deposits close in the neighbourhood, inside or just outside the Theca Interna.

II. The second possibility is that the dispersed lutein cells, proceed from the Atretic follicles, which have collapsed with the disappearance of their cavity, being pressed flat by an adjoining cyst and thus the lutein tissue appears in close relationship to the cyst wall.

III. Lutein cells could also proceed, here and there from the stroma cells.

In favour of this view are the direct transitions of Stroma cells into lutein cells; and the circumstance that in these dispersed lutein cells no connection has been found with the Atretic follicles.

In his summing up he discusses the aetiological connection, between the ovarial changes and Cystic Mole and Chorionepithelioma and concludes by accepting that these two diseases (the causes of which are still unknown) lead to cyst formation and aedematous infiltration of the Ovarial stroma and that largely, through circulatory disturbances of a mechanical nature and probably also through chemical substances more or less dependent on the proliferation of the villus epithelium.

His conclusion thus lends support, somewhat to Halbans hypothesis - that there is an internal secretion of the Chorionepitheliomatous tissue.

Pinto's investigations closely coincide with Seitz's work, but he questions the transformation of stroma cells into Lutein cells during pregnancy.

His conclusion is that between the Ovarial changes in Cystic Mole and in ordinary pregnancy there exist only gradual differences.

In ordinary pregnancy it is a question of the over production of epithelioid tissue: in Cystic Mole, of over production of lutein tissue, with aedema and an intense serous transudation into the follicle cavities. The Ovarial changes in Cystic Mole are of a secondary nature, chiefly the result of disturbed circulation; while the primary cause is to be found in the degeneration of the Villi.

Risel (62) from a very extended series of examina-

tions based on 12 cases of Chorionepithelioma, 5 cases of Cystic Mole, and a large number of Ovaries of different ages, from both intra and extra uterine pregnancies, altogether confirms the statements made by Wallart and Seitz and comes to the following conclusion. "I can therefore not consider the described Ovarial changes as specific for Cystic Mole or Chorionepithelioma."

C H A P T E R III.

PRIMARY CHORIONEPITHELIOMA OUTSIDE THE UTERUS.

(Ectopic Chorionepithelioma.)

These ectopic tumours are closely akin morphologically to the Chorionepithelioma tumours found in Utero.

Schmorl (63) was the first to demonstrate a Primary Chorionepithelioma of the Vagina in association with a healthy uterus.

About the same time Pick (64) published a similar case found in conjunction with a Cystic Mole in the Uterus.

Altogether some 40 cases have been recorded; such a series has been published by Risel and in this country the report of an interesting case of this kind was read by Hicks before the Obstet Soc. of London in June 1907.

The whole class is divisible into two groups:

A. Where the Uterus was found perfectly healthy

B. Where in the Uterine substance, tumour nodules were found, but showing no connection with the Uterine Mucosa which was found in tact.

Of Risel's series of 36 cases of Ectopic Chorionepithelioma in 27 of them the disease appeared as nodules in the Vaginal walls. These vaginal nodules or growths were usually first discovered or diagnosed by the repeated severe bleedings.

HISTOLOGY.

In structure these tumours show no difference from the Intra-uterine growths: occasionally they conform to the Typical structure of Marchand, while at other times they are of the Atypical arrangement. Frequently there is seen a direct connection between the tumour tissue and the transported cystic villus

epithelium.

Occasionally these vaginal tumours follow on a normally concluded pregnancy, but in all such cases the patient died except in Findley's case.

These tumours possess a peculiar interest because of the nature of their genesis.

ORIGIN:

All authorities are agreed that they spring from the transplantation of chorionepithelial elements, via the blood channels. The point in dispute is whether (1) the transported elements were originally malignant and came from a malignant placenta or (2) the transported elements were originally innocent and came from a healthy placenta, and later on assumed malignant characteristics in their new resting place. In describing his first case Schmorl believed it to arise from Malignant Emboli, transported into the Vaginal veins from a malignant placenta; but that the uterus owing to a shallow embedding of the growth was able to throw off the tumour along with the foetus.

Schlagenhaufer (65) expressed a similar opinion, believing that the Malignant Emboli came from the malignant Chorionepithelioma in Utero which had either been spontaneously ejected, or removed by curetting or undergone spontaneous Involution.

The observations of Krewer (83) and Hammerschlag (84) prove that we may yet have a metastatic tumour development in spite of a spontaneous cure of the Uterine growth.

Krewer's case was that of a woman who died of diffuse Chorionepithelioma nodules in many organs, and yet no distinct tumour could be found in the Uterus, only a scarry place and a few small areas of cells akin to those of Langhans layer and Syncytium.

Hammerschlag's patient died 2¼ years after expelling a Cystic Mole and in the broad ligament was found Chorionepithelioma tumour; the endometrium being quite free of disease.

Seven weeks after removing the Cystic Mole, Uterine scrapings suggested the presence of an Atypical Chorionepithelioma; but three months later nothing of this could be found.

Krewer's case suggests no doubt of the disease having actually healed in Utero, while in Hammerschlag's case the growth may have been removed by the curette.

In opposition to Schmorl's hypothesis, Marchand and Pick have shown that the existence of a Malignant placental tumour is not at all requisite to explain the genesis of these vaginal cases, for as these observers have pointed out, it is no uncommon thing for chorionepithelial cells and even villi to be transported to different parts of the body during the existence of a normal pregnancy; this fact has been well described and demonstrated by Schmorl himself to be especially characteristic of Eclampsia cases.

Of course by far the greater number of such cases of transported placental elements remain normal, with no untoward development - the villus epithelium so transported dying and being absorbed.

But according to Marchand it is quite possible for these transported emboli, occasionally to remain preserved in distant organs e.g., the lungs or Vagina, and there at some future date, start proliferating and form the origin of a malignant new growth. He maintains that such a view is possible, especially when the epithelial cells come from a case of Cystic Mole or from a very early stage of Ovum development - as in such cases the epithelium is known to possess unusually active properties.

Walthard (85) has published a very remarkable case belonging to this class;at the Post Mortem examination were found multiple Chorionepithelioma tumours, in the Vagnia, Liver, Lungs, Kidneys and Brain, the foetus being perfectly normal and the uterus quite in tact.

This case went far to establish Marchand's view of the genesis of these so called Ectopic Chorionepithelioma - with the result that most authorities have now accepted his views and even Schmorl himself accepted this hypothesis in explanation of his second case..

Why the transported chorionepithelial cells in cases of Cystic Mole should develop into Chorionepithelial tumours in some cases while in others these elements die and are absorbed, is unknown.

Dunger (86) who has made a special study of such transported Villus epithelium, has found in the majority of cases that the embolic cells stimulate a strong reaction of the surrounding tissues, and has found all transitions of the reactive process up to completely cicatrised tissue. In the case of true chorionepithelioma, a final healing of lung metastasis was also believed, but histologically has only been supported by proof in one case, namely that of Risel.

A further striking peculiarity of some of these Ectopic Chorionepitheliomata is the accompanying formation of Decidual tissue within the Uterus. Even in such cases where the Uterine Mucosa was found in tact and showing no evidence of growth, the mucous membrane was changed into a delicate layer of grayish pink appearance and microscopically showing decidual cells.

Schmorl was the first to suggest that the origin of this decidua was exactly the same as the Uterine decidua found in cases of Tubal Pregnancy: namely: a reflex action of the tumour growth. Dunger, March-

and and Risel all support this hypothesis of Schmorl.

The case recorded by Hicks (81) conforms to the usual type and in all the important points it follows the description above quoted from Dunger and Schmorl.

The patient was 28 years of age, when admitted into Guy's Hospital in July 1906 complaining of Dyspnoea and pain in the left chest.

She had had three children, but no miscarriages and always enjoyed good health up to her present illness.

Menstruation had been regular and of normal quantity until seven months before admission, since which time she had Amenorrhoea. Her present illness dated from June 21st, when she was seized with a rigor and left basal pneumonia was diagnosis.

She had also a free uterine haemorrhage when she was admitted to Hospital. On Pelvic examination, the Cervix was found to be dilated; the Uterine contents were cleared out and found to consist of a five months dead foetus and a large hydatid mole. The periphery of the placenta showed marked cystic changes; the interior of the uterus was found to be smooth and no evidence of twin pregnancy.

Her chest condition developed into an Empyema which was opened and drained. A fortnight after her admission her pelvis was again examined, when the uterus was found to be subinvoluted. There was still a hemorrhagic discharge from the uterus, but no evidence of pelvic inflammation. High up on the left vaginal fornix was found a soft single cyst about the size of a big tangerine orange: it felt to be a superficial vaginal cyst and the mucosa over it was normal. At the lower margin of the posterior vaginal wall was found a small nut like tumour, covered by

purplish mucous membrane: this latter tumour was removed and found to be very vascular and microscopically showed the structure of a Typical Chorionepithelioma, with large quantities of both Langhans and Syncytial cells but no evidence of Chorionic Villi was found.

The pelvis was again examined, some months after the operation, when it was found that the uterus had involuted, to nearly its normal size and the vagnial cyst had disappeared: her general appearance was greatly improved and menstruation had returned and was normal.

The uterus unfortunately was not curetted, but there was no evidence of any intra uterine growth.

In January 1907, seven months after her Chest illness, she again returned to Hospital for examination, and another small bluish nodule was found on the Anterior Vaginal wall: this grew very rapidly and seemed to spread down towards the Clitoris and on removal it was found to be of similar structure to the first nodule.

Within three weeks still another vaginal nodule appeared and the cystic swelling again returned. There was now free hemorrhage and evidences of Bronchopneumonia but no haemoptysis. She died in May 1907, some eleven months after removal of the cystic mole.

At the autopsy the Uterus was found to be normal, showing no evidence of growth. The Ovaries were small and contained a few small blood cysts with characteristic lutein cells in their walls, but no evidence of lutein cells in the Ovarian stroma. Large fungating masses of Typical Chorionepithelial structure were found permeating the vaginal tissues. In the right lung there were numerous small metastatic growths of similar structure to those in the vagnia.

A noteworthy point of the case is that these vaginal nodules were only diagnosed by repeated and regular vaginal examinations, and before any bleeding appeared, or in fact any complaint on the part of the patient. The question of the Prognosis and degrees of Malignancy of these Ectopic growths will be considered more fully in the following chapter.

C H A P T E R IV.

THE QUESTION OF THE VARYING DEGREES OF MALIGNANCY, BASED ON THE DIAGNOSIS AND INFLUENCING PROGNOSIS. ALSO SPONTANEOUS INVOLUTION OR NATURAL CURE OF CHORIONEPITHELIOMA.

Chorionepithelioma has been described by some authorities as "The most rapidly fatal malignant growth with which we are acquainted" (Williams) The severity of this indictment was largely the result of the treatment adopted in the early recorded cases namely repeated curettings, nearly always with a fatal issue. But the more ripe experience of recent years goes to prove that Chorionepithelioma is not altogether worthy of this bad name, for quite a large number of cases resulting in cure, have now been recorded as the result of a more drastic treatment.

Of recent years from the large amount of interest which the disease has attracted and from the fact that the clinical history of nearly every case has been published, it has come to be believed that there are widely varying degrees of Malignancy to be found associated with this tumour.

Then it is fitting that we should consider briefly the grounds on which the diagnosis of Chorionepithelioma is based.

S E C T I O N A.

Subsection I. Histologically.

Subsection II. Clinically.

Virchow's classification of new growths, into those of Epithelial and of Connective tissue origin, although it has been much criticised, still remains our accept-

ed standard to-day.

To declare a tumour malignant the pathologist must recognise certain signs of cell arrangement and proliferation, which from long experience have come to be recognised as characteristic of an actively operating growth. This implies experience gathered from careful study of the clinical histories and terminations of such cases.

Thus we see how convergent these two lines of investigation run towards the terminus of Diagnosis.

Considering then the foundations upon which the Histological features of Malignancy rest, it will readily be seen how fallacious our conclusions may be, when arrived at by means of the histological highway alone.

Both routes - the histological and the clinical must be traversed if we are to reduce the possibility of error. A well known illustration may here be given in the villous Papilloma of the Bladder, which although histologically innocent, yet clinically it is considered to be malignant, whereas histologically all chorionepithelial proliferations are malignant, but clinically, the fact is well established that many of them are benign.

In 1898 Ruge in discussing a paper by Veit on "Deciduoma Malignum" was probably the first to put forward the statement, that from the clinical standpoint there was both a benign and a malignant form of Syncytioma.

SUBSECTION I. HISTOLOGICAL DIAGNOSIS.

This aspect I will discuss very briefly as the subject has been exhaustively dealt with by many of the authorities, but especially by Teacher.

We are indebted to Marchand who from his masterly

study of series of cases both of Cystic Mole and of Chorionepithelioma, supplied us with the earliest classification of our disease.

He divided Chorionepithelial growths into:

I. Typical Chorionepithelioma -

made up of Langhan's cells and Syncytium.

II. Atypical Chorionepithelioma -

composed chiefly of large syncytial cells and syncytial or plasmodial masses.

This classification was a considerable advance on that of Sanger who divided his cases into:

(1) Sarcoma deciduo-cellulare

(2) Sarcoma deciduo-cellulare with Chorionic Villi

(3) Malignant Hydatid Moles and Placental Polypes.

But to further elucidate the histology I would suggest a still broader classification of Chorion epithelial tissues, viz:

I. PLACENTARY POLYPES:

where there has been a deep embedding of the villi: this class would include certain cases of adherent Placenta, and of persistent hemorrhage after cases of abortion.

We may tabulate them thus:

PLACENTARY POLYPES: two forms

A Simple (adherent Placenta) as after abortion or full time labour: hemorrhage may persist.

B Destructive: Invades or permeates Uterine wall, but the epithelial coverings remain intact on the Villi (local malignancy.)

II. CYSTIC MOLE SIMPLEX

where there is found a proliferation of the Chorionic epithelium with cystic degeneration of the Villus stroma, but where the villi do not burrow deeply

into the Uterine tissues, and thus may be thrown off by the Uterus itself, or be removed by the Physician, leaving healthy tissues behind.

III. CYSTIC MOLE MALIGNUM:

a localised malignancy. In these cases the Chorionic epithelium and the Villi, are found at varying depths in the Uterine Musculature, and may even penetrate the fundus on to the peritoreal surface.

This class of case usually confines itself to a limited site of the fundus Uteri and has to be separated from malignant Chorionepithelioma, by the fact, that at its deeper parts, where the destructive powers are most active, there is to be found no evidence of tumour formation as we have in cases of Chorionepithelioma proper.

IV. TYPICAL CHORIONEPITHELIOMA: (Marchand)

composed chiefly of proliferating Langhans cells and masses of Plasmodia , together with some wandering Syncytial cells. This tumour contains no connective tissue stroma or bloodvessels of its own: it is virtually a parasite akin to its physiological proto-type - the Trophoblast, - destroying maternal tissues and nourishing itself from the maternal blood. Unlike other malignant growths such as the scirrhous cancer, which attains its destructive qualities in large measure, in a mechanical manner,

i.e., from the overgrowth and proliferating powers of its cells, the malignancy of Chorionepithelioma is mainly due to a Chemical Action rather than to any mechanical pressure. This chemical action is typically exhibited in the action of the tumour on the maternal blood vessels - replacing the elastic and muscle structures in the vessel walls and converting them into flaccid tubes, thus permitting of the severe hemorrhages, which are amongst the chief clinical characteristics of the growth This group is equivalent to a persistence of the earliest stages of pregnancy.

V. ATYPICAL CHORIONEPITHELIOMA: (Marchand.)

composed chiefly of Plasmodial masses and resembling more the picture found in the puerperal Uterus of later pregnancy. This group is recognised clinically to be less harmful than the Typical class.

VI. TRANSITIONAL CASES OF CHORIONEPITHELIOMA:

here we would place those cases of not infrequent occurrence that have present in large measure the Syncytial Wandering cells as well as some syncytial masses.

Schmauck epitomises the difficulty from the Histologists point of view thus: he says: "The difficulty is to decide between excessive physiological and excessive pathological proliferation."

Excessive invasion of the Uterine tissue by Villi and the persistence of chorionic epithelium, for some time after labour or abortion, have frequently been

the means of deciding on a harsh and unjustifiable form of treatment. The Pathologist is not infrequently misled by such a condition: the following case from my own practice illustrates this difficulty.

A patient aet, 26 years, aborted of her first pregnancy at the 3½ months; for nearly a month afterwards slight hemorrhage persisted. The usual treatment having failed I decided to curette the Uterus: this operation was done some six weeks after the abortion and the Uterine scrapings were sent to a reliable pathologist for examination and report. His report was "Malignant disease of the Endometrium showing proliferating epithelial cells."

From the clinical observations of the case, I refused to act on the Pathologist's diagnosis: for since the day following the operation the patient had remained perfectly free of symptoms and in twelve months afterwards, she was delivered of a full time healthy child and has never shown the slightest evidence of disease either local or general.

This experience well illustrates the liability of error in the histological examination and the seriousness of basing the treatment without any consideration of the clinical condition.

Here I would refer to a number of cases published during the past few years - all dealing with one of the most remarkable features of Chorionepithelioma, namely:

SPONTANEOUS INVOLUTION OR NATURAL CURE.

Some of these cases were diagnosed histologically to be malignant

I. Marchand-Evereke's case (66) : Five months after labour at term, Chorionepithelioma was diagnosed and hysterectomy performed. The Uterus could not be removed within sound tissue: part of the growth extending into the broad ligament and attacking the pelvic wall was left behind. The tumour was diagnosed as an Atypical Chorionepithelioma: the patient was found well one year after the operation.

II. Kolomenkin (67) : Ten months after labour at term, the Uterus was removed and the growth found perforating the fundus and adherent to Intestine. The Bowel was not resected: the histological diagnosis was atypical Chorionepithelioma. Patient well six months afterwards.

III. Noble (68) : Chorionepithelioma following Abortion, The growth was found involving the Bladder. SupraVaginal Hysterectomy was performed, but the Bladder growth left behind.

HISTOLOGY: No Langhans cells and no Plasmodium, only large syncytial cells. Patient well sixteen months after the operation.

IV. Buerger's case (69) : Showed after Abortion, a Vaginal nodular tumour in the region of the Bladder; operation was not attempted and yet the patient was well six months later.

V. Fleischmann's case[70] : is one of the most remarkable in the history of the disease. The patient had a Cystic Mole and 2¼ years afterwards a small bluish nodule about the size of a chestnut was found at the Vaginal entrance. During the act of curetting the Uterus, the Curette perforated the wall, going through into the broad ligament. Histologically, the Vaginal nodule showed large syncytial wandering cells - an atypical Chorionepithelioma; the characteristic invasion of the vessel walls was well marked. From the histology and the incompleteness of the operation, an unfavourable prognosis was given. But the patient recovered and menstruated regularly and later was delivered of a full-time child.

VI. Hoermann's[71] case was somewhat similar: the patient was 3 years old and 5½ and 7½ months after an abortion, bulky tumour masses were removed from the Uterus by the curette. Hysterectomy was not performed on account of the serious condition of the patient: but she completely recovered and a year later passed through a normal parturition and some two years after the diagnosis of Chorionepithelioma, the patient was quite well. Microscopically the tumour showed Langhans cells and Syncytium.

VII. LANGHAN'S CASE[72] was a patient in whom he discovered a Chorionepitheliomatous nodule in the Vaginal wall, showing itself after a full time pregnancy: the growth entirely disappeared, undergoing spontaneous healing.

VIII. Dunger[73] reported a case occurring after an Abortion. Four weeks later hysterectomy was performed; there were two foci in the Uterus and an ulceration of the posterior lip of the Cervix, but no villi were found. Nine weeks later, there was a recurrence in the form of a vagnial nodule; removal of this was not permitted and yet recovery followed. Microscopically the Uterine tumour was recognised as a Typical Chorionepithelioma.

A large number of cases have been reported at various times pointing out the spontaneous healing of Pulmonary Metastases- i.e., haemoptysis without any evidence of inflammatory mischief, - after removal of the central growth. In Risel's first case, he showed definite histological proof of the existence of a Pulmonary metastatic deposit which ultimately disappeared.

The hypotheses put forward in explanation of this remarkable process of spontaneous healing, are numerous and varied, none of them so far are capable of direct proof, but a consideration of them may help to bring us somewhat nearer the truth.

FLEISCHMANN'S theory is that the maternal organism, under certain conditions at present unknown, mobilises the protective materials (syncytiolysm, or Plastein etc.) which are able to cause the Chorionepithelial proliferations to cease, and to decay or to become absorbed

MARCHAND[74] believes that a sound organism is able to combat the proliferating elements up to a certain degree.

KISSEL (75) and BUTZ (76) consider the most important 'momentum' to be a different resisting power of the maternal organism.

SCHLAGENHAUFER (65) believes that the earlier the metastases occur, the more energy they possess and that the transported complete villus with its epithelium, possesses only a small energy of growth. The question here arises, whether these cases, showing all the typical symptoms of metastases, and histologically showing malignancy, are not really benign forms of the disease.

L. PICK (64) some ten years ago, suggested that there were two forms of Metastases - a Benign and a Malignant type: and that not infrequently after Cystic Mole, the Vaginal metastases, did not represent an embolism from a primary malignant growth, but was merely a deported villus, manifesting some activity within a varicose vein.

VEIT: also laid stress on this necessity of distinguishing between real metastatic deposits and mere Villi deportation; he says that these latter are not true metastases, but rather Infarcts.

SCHAUTA & SCHMIDT (77) in discussing the spontaneous healing in their cases of vaginal nodules, point to the fact that these nodules were usually surrounded by masses of blood clot, which seemed to impede the progress of the proliferating cells: this suggestion will be further referred to under Teacher's Views (see below).

NEUMANN'S theory of the certain evidence of malignancy, being found in the presence of the large syncytial cells penetrating the stroma of the villi, has already been referred to as untrustworthy.

VOIGT (78) suggests as a sign of malignancy, the great increase of Chromatin in the nuclei of the syncytial cells. Gottschalk (23) also supports this view

VELITS (79) who was probably the first to undertake histologically to differentiate the benign from the malignant chorionepithelioma offers the latest suggestion, namely, that the cause of the spontaneous healing of Chorionepithelioma is due to the Necrobiosis, which in many cases, with favourable termination, was found to be extensive. In advanced cases he says that the condition can be seen with the naked eye. "The microscopic picture of spontaneous healing, reveals itself in the reduced vitality of Langhan's cells, (lacking in Mitosis) and in the appearance of the migratory cells, indicating the dissolution of the syncytium, which are degenerative products of the decaying Chorionepithelioma and Cystic Mole."

It is very difficult to accept this explanation of Velits, for Necrobiosis is a well known process in other types of epithelial growth: and further these migratory syncytial cells, are certainly not degenerative products of the syncytium, for they alone have been found to be the chief component in tumour nodules that have caused death. (Krebs).

VELITS further believes that the presence of Sepsis plays an important part in destroying the Uterine tissues and that the destruction is not always due to Malignancy.

There is, I think, much more to be said for this view, for it is well known that in any variety of Malignancy, the presence of Sepsis, by setting up a toxaemia of the system, lowers the resisting powers and thus aids the progress of the disease. The proof of this is well established in the treatment of inoperable carcinoma of the Uterus; for by remov-

ing the septic element and keeping the parts antiseptic, the progress of the disease is comparatively slow

FRANQUE: (80) in his latest publication expresses the view that in the doubtful cases, the question is one of the Atypical Chorionepithelioma and goes on to say "if the curette, some time after a pregnancy, brings away masses of tumour tissue, having the Typical structure of Chorionepithelioma and only that, then there will be no need to doubt the presence of Malignancy". But in Hoermann's case above quoted, there was this typical structure found and yet the case ended favourably. Surely this proves conclusively, the impotence of the histological examination of Uterine scrapings as a basis of diagnosis, All the more is this the case when we remember, that soon after a full time pregnancy and after Abortions and cases of Retained Placenta, there may be found proliferations of chorionic epithelium, without their having any pathognomonic significance whatever, beyond the fact of Pregnancy. No matter, then, what the various 'findings' may be - invasion of the uterine musculature or even the characteristic invasion of the maternal blood vessels, - if found in the presence of Villi, are not to be regarded as diagnostic of the malignant disease.

TEACHER who has done more than anyone else in this country in the investigation of Chorionepithelioma has been engaged in the study of the healing process of the metastatic deposits, and quite recently he demonstrated some of his results before the Pathological Society; the full details being published in the current number of the Transactions of the Pathological Society of Great Britain and Ireland.

He describes the deposit of the Embolus and its formation into the secondary nodule in the lung, by its cells attacking the neighbouring vessels, embryonising their walls, which dilate, forming an aneurysmal swelling ultimately bursting, and giving rise to hemorrhage; while this process is taking place an inflammatory reaction is set up, in the form of pneumonic consolidation and proliferations of the connective tissue and blood vessels of the alveolar walls; this reactive process, virtually comes to form a capsule around the tumour nodule and enclosing the effused blood.

He describes the healing process as taking two forms:

(1) the hemorrhage within the inflammatory capsule, through pressure and clotting is able to destroy all the tumour tissue

(2) the healing is brought about by a process of encapsulation within a zone of actively growing connective tissue; and the blood clot being under pressure within the capsule tends to destroy the tumour tissue. But the ultimate process of healing is due to the process of repair in the surrounding tissues, outstripping the growth of the tumour and enclosing it in a capsule of connective tissue; thus wrapping it up like some foreign body.

The relatively favourable outcome of all those cases described as Chorionepithelioma, in which villi were present, is readily understood, because the Langhans cells and Syncytium are still adherent to their natural anchorage, while the wandering cells may keep up the bleeding by preventing coagulation.

But Malignancy is threatened when we find these Langhans cells and Syncytium becoming emancipated from their bondage (or Villus attachment) and assuming an autonomous proliferation. This I think is the full extent to which a histological examination will carry us.

The Langhans cells are always to be looked upon as the chief proliferating part of a Chorionepithelioma, just as they are to be regarded as the most active tissue at the embedding of the Ovum.

Schmauch even gets the length of saying that the prognosis depends on the richness of the tissue in Langhan's cells - the more numerous they are, the worse the prognosis.

But finally, in criticism of these various views, it would seem that there is only one conclusion possible, namely, that from a histological standpoint the differential diagnosis between Malignant and Non-Malignant Chorionepithelioma is not possible.

SUBSECTION II. THE CLINICAL PICTURE.

Here is probably our final court of appeal in the estimation of Diagnosis. The early symptoms and signs of Chorionepithelioma, closely resemble those of Retained Pregnancy Products, or Subinvolution, following either Abortion or Full-time labour, with this important difference, that the symptoms persist in spite of treatment.

The nature of the hemorrhage is usually suggestive, being specially severe during the act of curetting.

There may be some degree of Pyrexia, even [illegible] one or more rigors. The uterus is enlarged and may feel nodular: From the amount of blood clot lying about the genital tract, Sepsis is early invited, At an early stage the patient shows a marked Anaemia,

but from the blood examination I have failed to find anything diagnostic beyond the evidences of a secondary anaemia.

I would summarise the following conditions as being suspicious of Chorionepithelioma, should they persist in spite of the usual treatment:

(1) Irregular hemorrhages following a case of Adherent Placenta.

(2) Hemorrhage persistent or recurring after an Abortion.

(3) Hemorrhage recurring after a Cystic Mole.

(4) Hemorrhage recurring after a Full-time labour.

(5) Haemoptysis and Cough, without any evidence of Pulmonary Tuberculous or Inflammatory disturbance occurring during or following a Pregnancy.

(6) Unusually severe hemorrhage with very early rupture of Tubal Pregnancy.

(7) Bluish nodules in the Vaginal wall, in association with a history of Pregnancy.

(8) Persistence of hemorrhage from and Sepsis in the Uterus following a Pregnancy.

Odd cases of Amenorrhoea have been recorded by Croom (82) and Griffiths (87) and also by Krebs and Fluschmann, but these are extremely rare.

In Croom's case, the tumour cells may have obtruded into the lumen of the vessels setting up Thrombosis. While in Griffith's case there was haemotometra from blocking of the Internal Os by blood clot.

But even the clinical phenomena may fail us in making a Diagnosis for in the case reported by Butz, nothing suspicious was found by the curette after the

birth of a Cystic Mole: the hemorrhages ceased and Menstruation became regular and normal, and yet about a year later, there was an attach of Haemoptysis and only shortly before death was there any genital bleeding; the Autopsy showed a Syncytial tumour of the Uterus with Pulmonary Metastasis. A difficulty that seriously detracts from the diagnostic value of the clinical picture is the varying dates of the appearance of Malignancy. For example in MacCann's case (31) nothing appeared until some nine years after pregnancy. In Hollman's case it was four and a half years. In Fleischmann's case 2¼ years: in Dunger's case it was 3 years, while Schlagenhaufer's case died about 32 days after a full time labour. In making a diagnosis of Chorionepithelioma Malignum, we have seen how the histological examination may deceive us and although much more helpful, yet even the clinical picture may lead us into error by the delay of its full completion.

Such indefiniteness in Diagnosis, must at all times place heavy responsibility on the Physician who would decide the Prognosis and the Treatment: for in some cases a healthy uterus may needlessly be removed and yet in other cases we may postpone operative interference until the case has gone beyond our reach. In all doubtful cases then, surely the course indicated by Wisdom would be to regard the process as malignant and act accordingly - namely: hysterectomy, rather than by longer observation to lose the favourable opportunity for the operation.

SECTION B.

PROGNOSIS.

From what has been said in the foregoing section on Diagnosis, the difficulties that present themselves in forming a Prognosis will readily be understood.

Although formerly looked upon as a very Malignant and fatal disease, Chorionepithelioma, in the light of recent statistics and more intimate study has now come

to be regarded with less dread. The outlook of a large percentage of such cases is distinctly hopeful.

Upon what grounds then are we justified in basing our Prognosis of any of any given case?

From the Clinician we may receive some assistance:-

(1) As to the nature of Pregnancy:

Most authorities are agreed that cases of Chorionepithelioma, that follow on a Cystic Molar pregnancy, show a less degree of Malignancy than those following a normal pregnancy.

(2) The majority of cases of Chorionepithelioma, that accompany or follow a Full-time pregnancy, show a very high degree of Malignancy.

This would seem rather opposed to Schlagenhaufer's hypothesis, that the earlier in pregnancy, the emancipation of the chorion epithelial elements takes place, the greater the degree of Malignancy.

(3) Those cases of Chorionepithelioma that have been found in association with Tubal pregnancy and of which Risel has collected a series, have to be regarded in a serious light. In fact every case of unusually early rupture of Tubal pregnancy accompanied by severe bleeding ought to be carefully examined for evidences of Chorionepithelioma.

(4) Cases of Chorionepithelioma tumour of the Uterus even accompanied by Pulmonary metastases causing Haemoptysis etc., are by no means hopeless, i.e., that the

evidence of Pulmonary metastases is not as in the case of other Malignant Tumours, a contra-indication for treatment: for after removal of the genital focus the Metastases frequently disappear.

From the Histologist also we may receive some help:-

(1) The most important fact which we gather from this source would appear to be, that a distinctly hopeful outlook belongs to these cases where Chorionic Villi are demonstrated in the presence of the tumour tissue - whether that tumour be Primarily in the Uterus, or Primarily in the Vaginal tissues.

(2) If the tumour tissue shows the structure of the so called Typical Chorionepithelioma, i.e., containing all three types of cells, but especially Langhans cells in quantity, then the prognosis must be very guarded.

But, if the structure corresponds more to the Atypical or Transitional types, then more hope of the case may be entertained.

(3) The presence in the Ovary of Lutein cysts of any size or of Lutein tissue in excess, has no bearing on the prognosis whatever; if anything it may probably come to be regarded, that the more Lutein tissue, the more favourable the case; that is if the lutein tissue is a manifestation of Maternal reaction.

(4) The recurrence of growth nodules in the vaginal walls after repeated removal is not a favourable sign.

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