ON MALIGNANT CHORIONEPITHELIOMA.

By F. MARCHAND, *Professor of Pathology in the University of Leipsic.*

(Translated from the German by T. W. EDEN, M.D.)

ALTHOUGH I have already often taken up the pen upon this subject, and have scarcely anything new to advance, yet I gladly comply with the request of the Editorial Committee of this esteemed journal to furnish a short communication upon the discussion of chorionepithelioma.

I cannot do more, in this place, than offer a brief exposition of our present views upon this remarkable new growth, which has not only awakened great interest among gynæcologists, but also possesses great theoretical importance in regard to theories of tumour formation in general. For we have here to deal with the fact that an embryonic tissue, the product of a new sexual generation, disseminates itself in the maternal organism and not infrequently destroys it. And, further, we find histological characteristics which are capable of throwing light upon other epithelial new growths. Thus we meet with the occurrence and dissemination of cell-forms of undoubted ectodermal origin, entirely resembling mesodermal cells, a peculiarity which was not understood until it was found that an entirely analogous dissemination of ectodermal cells of the developing ovum was found in the decidua in normal pregnancy, and even more in certain cases of vesicular (hydatidiform) degeneration.

It is comprehensible that authors who first recognised tumours of this nature as something unusual, above all Sänger and Pfeiffer (Chiari), should have designated them as "decidual sarcoma" (deciduoma). I may remark, historically, that to Gottschalk belongs the credit of having first rightly interpreted the masses of the so-called syncytium of the chorionic villi in a malignant tumour of this kind with metastases, but he erroneously regarded a part of the tumour as sarcoma arising from the stroma of the villi. Then L. Fraenkel, in a case described by him as carcinoma of the uterus, regarded the growth of the epithelial syncytium as the essential element, without, however, recognising the nature of the other elements of the tumour, which he regarded as quite different from the so-called "deciduoma" of Sänger. Upon my own observations the latter work had no influence, because they were completed on its appearance. By a specially fortunate circumstance it chanced that I

was able, in a case of hydatidiform mole in the uterus, to recognise the same epithelial formations as in the two layers of the chorionic mantle, and the invasion of the muscular wall of the uterus by these cells, as in malignant chorionepithelioma.

A difficulty presented itself in forming an opinion upon the origin of the tissue forms present in this growth, viz., the very diverse opinions which existed upon the two layers of the chorionic epithelium, the well-known multinucleated protoplasmic covering of the placental villi (which later was named "syncytium"), and the more recently discovered "cellular layer" of Langhans. While several embryologists (*e.g.*, Kastschenko) held both layers to be fœtal, others having in view the conditions found in animals, referred the outer layer to a maternal, the inner layer to a fœtal origin. Inasmuch as at that time I had not had the opportunity to decide this question by personal study of early human ova, I had to assent to one of these views, and I felt obliged to decide upon the latter, although I had already, both in regard to tumour formation and vesicular mole, frequently pointed out that it was often impossible to make a distinction between cells arising from the superficial layer and those arising from the deep layer. I regard as of the greatest importance, the observation that the malignant growth actually arises from the entire epithelial covering of the villi, that at least a part of the new growth, both in the primary tumour and in the metastases is of fœtal ectodermal origin, a view which later was to be strenuously opposed by a number of authorities.

It is clear that conditions found in animals cannot be directly employed in settling this question owing to the great differences between the human placenta and that of lower animals. Opinion upon single points still oscillates to and fro. In the rabbit, where the formation of abundant syncytium from the uterine epithelium can easily be made out, some embryologists refer the entire syncytium of the placenta to this source, but I have myself brought forward the observation that before the implantation of the ovum in the uterus, an undoubted syncytium or plasmodium is formed from the fœtal ectoblast.[1] And, further, it appears that these two different syncytia intermingle in parts so closely with one another, that it is often practically impossible to distinguish the one kind from the other. Why should it not be the same in the human chorion, and thus in the tumour formation both maternal and fœtal elements may participate? But inasmuch as other observations have, in my opinion, conclusively proved that the syncytial layer of the chorionic

mantle of the human ovum is of fœtal origin, this question must also be regarded as definitely settled for the tumour also.[2]

A second difficulty frequently met with consists in the fact that the new growth itself may present such different appearances that it is often truly difficult to refer it to one and the same source. While in one series of cases the same arrangement of the tumour tissues occurs as in the epithelial tissues of the young human placenta (cell-buds, cell columns), yet we find in others (the so-called "atypical" cases) almost isolated cells which spread themselves in the tissues after the manner of a sarcoma, so that they have been taken in part for decidual cells, in part for endothelial cells of the vessels, in part for muscular elements. I proved, however, that these same cells, which, in the cases referred to, were isolated, in other cases were found associated with large syncytial masses and collections of clear cells rich in glycogen. It is not right to regard these isolated elements as "syncytial cells" because their origin exclusively from the syncytium cannot be affirmed.

It has now been demonstrated in so large a number of cases that these apparently widely different epithelial formations arise from the epithelium of villi retained in the uterine vessels, that it cannot be necessary to multiply these cases. The fact that the majority of cases of malignant chorionepithelioma follow the abortion of a vesicular mole, is readily explained if we recollect that this anomaly of the ovum is characterised by the appearanc in it of abundant proliferation of the epithelium of the villi.

In many cases, though by no means in all, chorionic epithelial elements invade the decidua serotina to an unusual extent, destroy the decidual tissues, and even penetrate into the musculature. A similar process is, however, normal in the first stages of pregnancy.

And, further, there exists a series of cases of vesicular mole characterised by such progressive growth of the chorionic villi, that they have been designated "destructive (*destruirende*) vesicular moles." Following Virchow's view that vesicular mole is a kind of myxomatous degeneration of the villi, we could regard this as a variety of "malignant myxoma." This has, however, been shown to be incorrect. We now know that the development of normal villi is initiated by epithelial proliferation, and a similar relation is to be assumed here (in destructive vesicular mole). The formation of the non-vascular stroma of the villi follows that of the epithelium; the former does not grow irregularly into the tissue as in a malignant myxoma, the villi retain their typical shape, as in ordinary vesicular mole, while the epithelium penetrates into the surrounding

tissues in quite irregular fashion. It is obvious that in such cases remains of villi may become deported by the blood stream, and may preserve, to a certain extent, their proliferative activity.

While in most cases the primary localisation of the tumour is found to be in the uterus, there is yet a large series of cases in which the primary growth has not been found at all, so that we might speak of "formation of metastases without a primary growth." These cases also are readily understood when we remember that portions of villi with the chorionic epithelium deported after labour through the circulation, retain their proliferative activity and provoke malignant epithelial growths in the parts to which they have been carried, *e.g.*, the vagina, the lungs, the brain, etc.

It is natural that such tumours should have been regarded as primary sarcomata of the organs in which they were found, before there true histogenesis was understood. Very noteworthy is the fact that in some of these cases the uterine mucous membrane still possessed throughout the characters of the decidua of pregnancy (with regenerated glands), although a long time had elapsed since the labour. By some authorities the formation of the decidua in such cases was explained by the presence in the body of fœtal ectodermal elements, by others it was attributed to the continued presence of a corpus luteum.

The question whether, in those cases in which a malignant tumour is found following an abortion or a vesicular mole, a *primary malignancy* of the chorionic epithelium is to be assumed, must, I believe, be answered in the negative, but it cannot be denied that the proliferative activity of the epithelium and with it, the risk of a malignant growth varies greatly in individual cases. It is difficult to determine wherein this variability consists. Many observations, however, indicate that the increased proliferation depends upon a primary degenerative change in the ovum, and is not in the first place produced by the uterus. The remarkable fact that in many cases of vesicular mole and chorionepithelioma, cystic degeneration of the ovaries was also present, supports this view.

Although the specificity of the tumour can no longer be doubted, yet the possibility cannot, of course, be entirely excluded, that occasionally similar tissue elements may occur in other tumours. Yet, if the *typical arrangement* of the tumour tissues were preserved, any other origin than that from fœtal ectoderm would be very improbable. The question has advanced another step through observations upon tumours of the testis whose histological characteristics in part correspond with those of chorionepithelioma. Such a case

as this the late Prof. Kanthack had apparently seen, and it was in part responsible for his very decisive verdict upon the theory, at that time only recently advanced, of the specific nature of chorionepithelioma. Similar tumours, on account of the large blood spaces in the multinucleated masses, had in France been described as "angioplastic sarcoma." To Schlagenhaufer belongs the observation that tissues which completely resembled those of chorionepithelioma occurred in a testicular tumour which was proved to be a teratoma. Several similar observations were made almost at the same time by Wlassov, Schmorl, and Steinhaus. Two cases have been more recently communicated from my Pathological Institute by Dr. Risel.[3]

In these cases it is apparent that the tissue elements resembling chorionepitheloma stand in immediate continuity with epithelial tubules, so that their epithelial origin cannot be doubted, thus contradicting the view of Kanthack. Since these tumours are teratomata, the embryonic origin of the tissues resembling chorionepithelioma is undoubted, with only this difference, that we have not here to do with embryonic tissue of a younger generation as in chorionepithelioma. Schlagenhaufer has formed the opinion that the tissue arises from a true chorionic epithelium, *i.e.*, from fœtal membranes in the teratoma; he has even gone further, for he believes that the structures closely resembling chorionic villi, observed in a few cases, to have penerated the vessels, are products of the chorionic mesoderm of the teratoma.

This view appears to me to be unproved, for the reason that the structures resembling chorionepithelioma at times form only small islets of tissue, which stand among, and in intimate connection with other forms of tissue, and in the metastases they may occur quite alone. It is readily conceivable that the ectoderm of a teratoma, no matter what view of the origin of the latter we may take, may possess the power to produce tissues similar to the ectoderm of a normal ovum, without necessarily involving the formation of true fœtal membranes. Neither can I share the view of Schlagenhaufer that the growths resembling villi in certain cases of testicular teratoma, represent a true formation of vesicular mole.

I regard them rather as outgrowths from the myxomatous embryonic connective tissue of the teratoma, which, through external conditions (shape of the vessels), have assumed their characteristic form; this, we know, occurs in other tumours, especially myxosarcomata, which have nothing to do with teratomata. In any case this observation supports, if such support were needed, the view

of the similar ectodermal origin of the multinucleated syncytial masses, and the discrete clear cells.

The very remarkable observation by Pick of the occurrence of growths completely resembling hydatidiform villi in a cavity of a dermoid ovarian cyst appears strongly to support the theory of a mole formation from teratomatous fœtal membranes; but it is not quite conclusive owing to the simultaneous presence of an ectopic abortion in the Fallopian tube of the same side.

From the diagnostic standpoint it is an important question whether a "malignant growth" of progressive character should not be assumed in all cases in which after abortion or a hydatidiform mole, remains of villi and active chorionic epithelium remain in the vessels and tissues of the uterus. I cannot affirm that this is so. In my opinion, there is no such thing as "absolute malignancy," and no absolute histological indication of "malignancy." There are undoubted cases in which complete recovery has occurred after thorough curetting of the uterine musculature, even when already much infiltrated with chorionic epithelial cells, and also after extirpation of vaginal metastases. But in other cases, after prompt extirpation of the uterus, rapid dissemination of the growth throughout the body has resulted. We must, in addition to the histological characters, consider the clinical relationships. A sound organism is able, to a certain extent, to combat the further development of proliferative heterogeneous elements. It is not to be denied that in consequence of this circumstance, great difficulties may arise for the gynæcologist in deciding what to do in individual cases. On the one hand he may fall into the error of removing the uterus without sufficient reason, and on the other he may, by postponing operation too long, endanger in the highest degree the life of his patient.

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