

an explanation of their formation. The function of the ovary is one of cyst-formation from its earliest existence to its latest, and in its pathology we need not go far away from its physiology. It seems to me, therefore, *à priori*, very unnecessary to resort to the ingenious explanations of cyst-formation advanced by Dr. Wilson Fox, though they may be fitted to exceptional cases. Experience in the examination of the growths themselves has strengthened this view; for my wonder is greater, the more I see of them, that they do not occur more commonly and with more complexity than they do, considering the apparently reckless amount of ovarian cyst-production that goes on throughout life.

The aim and object of this cyst-formation is the production, maturation, and discharge of the ovum. But, if the ovum be not formed, or if it be produced only to a rudimental extent, may it not happen that the cyst will not be ruptured, but go on aimlessly expanding? Whatever be the source of the change, we know that it does not affect one ovisac alone, but may influence them in great numbers, whether it be in a tumor where the ova have been matured and subsequently prevented from escaping by sclerosis of the coat of the ovisac, or in a growth where the ova are not to be found. There is a great clinical difference between these two kinds of tumor; for in the one the growth is very limited and slow, and in the other it may be, and often is, extremely rapid, and is practically unlimited in extent. In fact, the growth of these cysts without ova partakes somewhat of the character of malignancy assigned to them originally by Bright for clinical reasons. Malignancy, apart from any association with cancerous structure, is always indicated histologically by a tendency to the production of a form of tissue which is young and immature, and this is certainly the condition of these ovaless ovisacs.

As a matter of fact, ovarian cystomata are a great deal oftener malignant than has yet been admitted. The recovery from an ovariectomy is generally so rapid and easy that at the end of a month we say "cured," and discharge the patient. But a number of these "cures" die speedily of cancer of the peritoneum or of other organs, and the more our primary mortality from the operation has diminished, the more numerous have become these secondary deaths from cancer, occurring between three and thirty months after the operation.

A few months ago I removed an ovarian tumor from a child aged twelve, and did not see, either in the tumor or in the abdomen, a single trace of malignant disease. She recovered from the operation, but died within the month with cancer in all the large organs. This singular sequence requires explanation, and

I believe that has now been arrived at, the last link being supplied by the work of De Sinéty and Melassez; and if the observations be correct, then a bright light is shed by them on the whole question of cancer. Elsewhere ("Diseases of Women," 1877) I have said: "Histologically, the characters of cancer are essentially those of immature and reckless cell-proliferation, the presence of numerous nuclei, both in the cells and free, suggesting the idea that they have had no time to become full-grown; and I have never failed to find evidence that the primary changes take place in the epithelium." The bearing of this will be seen more fully later on, when I speak of cancer of the ovary, but at present it leads up to the remarkable discovery of De Sinéty and Melassez, to which I have alluded.

"If, then," say these authors, "we cannot absolutely deny the possibility of the formation of a large cyst of the ovary at the expense of a follicle, it may be seen that this formation does not appear to result from a simple dilatation of these follicles, as many have said, and that we must admit a destruction of the ovules and a transformation of the epithelium when the follicles exceed a certain volume." It will afterwards be seen that there is probably an error in the last clause of this quotation, in that the cause is put for the effect; but it is in the establishment of the fact of the change in the epithelium, or rather in the interpretation of it, that the merit lies. I had long been quite familiar with the fact that between the epithelium of a healthy Graafian follicle and that of a large ovarian cyst there was a great difference. I had also ascertained the fact that, in an ovarian cystoma where ovules were to be found (Rokitansky's tumor, or the multiple cystoma), the epithelium remains as it is in the Graafian follicle. I had concluded, therefore, that the cyst in the latter case was merely the result of follicular dropsy, and that therefore probably all ovarian cysts were the same; but I had not seen, in the alteration of the epithelium, the explanation of the marvellous difference in the two kinds of tumors, nor that here we might find an explanation of the growth of ovarian cystomata. Such, however, I now believe to be the case.

Among other facts which lead me to the conclusions which I propose now to discuss were the absolute resemblance between the arrangements of the blood-vessels of a Graafian follicle and those of an ovarian cystoma which has not been altered by rupture, tapping, inflammation, or malignant degeneration. If such a cyst be carefully injected, cut into sections, and compared, in the matter of its vascular arrangements, with a Graafian follicle either before or after its rupture, no difference can be seen. The description of these will be seen in the first chapter. Roki-

tansky, Cruveilhier, Schroeder, Arthur Farre, and De Sinéty all record observations—to which I might add several—of cysts which had clearly been produced in the follicle after its rupture by a continuation and recurrence of the hemorrhage, and which have been called hæmatic cysts.

The theory, therefore, of this method of growths of cystomata, is that there is a reversion to the premoliminal condition of the ovary, so far as the ova of the affected ovisacs are concerned. The whole ovary does not, of course, become simultaneously implicated, and matured ova may still be given off by some ovisacs still unaffected and within reach of the Fallopian fimbriæ. Impregnation may thus occur from a degenerated ovary, though it is much more likely to occur from the one which remains healthy.

We have in these facts the reason that these adenoid tumors occur with greatest frequency during menstrual life, if indeed a future experience may not yet show that they do so exclusively. The menstrual congestion and excitement induces a dropsical distention and growth of a cell which would not be so perverted during childhood or senility, when its blood-supply would be sufficient only for passive nutrition.

The growth of cysts in the walls of the major sacs, appearing sometimes outside and sometimes within in great numbers, depends wholly on the relation of the original adenoid tissue to the cyst-wall; and, as that wall grew primarily in that tissue and surrounded by it, it would be indeed surprising if it did not carry along with it in its expansion some of the cells of the *couche ovigène* from which it sprang. These displaced cells have in their turn a stimulus for development, prematurely perhaps, on account of the increased hæmic activity of their abnormal surroundings, due to the growth of the sac. They also go through the process of dropsical distention, developing no ova, not rupturing, but becoming secondary cysts—perhaps ultimately to rival, or even to excel that which has preceded them, on which they grew, and of which they have been supposed to be the offspring.

Sometimes these intracystic growths line the cavity of the major cyst like an eruption of small-pox. In the case of a tumor which was removed by my colleague, Mr. C. J. Bracey, hundreds of little separate cysts lined the major sac of the tumor, as if the whole adenoid tissue had been spread on the inner surface of the cyst grew, and as if it were degenerating; and I have no doubt that this was really the case, for these little cysts were all Graafian follicles beyond a doubt.

The great change effected within the Graafian follicles, which

is doubtless that to which they owe their subsequent development as cysts, lies in the epithelium. To quote the words of the French writers: "The epithelium in these new formations shows every possible variety; but in none, not even those which simulate the Graafian follicles, have we found any epithelium similar to that of the follicles, neither have we ever found any ovules in their interior." But they very carefully point out that this change is by no means effected suddenly, nor is it extended uniformly over the whole surface of the cyst.

Speaking of the pathogenia of follicular dropsy, they say:

"In all the cases we have just stated the follicular epithelium was normal in its form as in its dispositions, although it must have been the seat of a certain degree of proliferation, since it covered a larger surface, the volume of the follicle being augmented. The ovule could be detected in a tolerably large number of follicles, even in the largest, and it did not appear altered. The lesion appears then to consist in an augmentation of the follicles, and in a greater quantity of follicular liquid. We cannot say whether this liquid is or is not modified in composition, if the secretion is or is not altered."

In those cavities which they regard as pseudo-follicles, that is, resembling in every particular save that of their epithelial lining the follicles they have just left, De Sinéty and Melassez note that "the differences are still more considerable. The epithelium which lines these cavities resembles in nothing that of the follicles. There are found in it cylindrical epithelial cells more or less voluminous, cells with *cilia vibratilia*, sometimes even caliciform cells. The different kinds of epithelium may be observed in the same cavity. In general these cells are disposed in a single row.

"In no cavity did we find anything that in any way resembled an ovule or a proligerous disc. The contents are a transparent liquid, more or less fluid, coagulating and becoming opaque at the contact of alcohol, reassuming its fluidity and transparency in water, and showing in its interior granulations and degenerated cells, proceeding no doubt from the epithelial investment of the walls. In one of these cavities there existed large, radiated cells disseminated in the contents, which gave it the aspect of mucous tissue."

The only points concerning the epithelium in which my own observations do not entirely concur with those of the writers I am quoting are, first, the frequency with which they appear to have met with cells furnished with vibratile cilia. I have found these in only one of the tumors I examined, and that was a dermoid cyst, having abundant indications of immature nerve-

structure; these cells I regarded as probably representing the lining membrane of a cerebral ventricle. Beneke speaks of having found them once or twice, but I do not know that any other observers have seen them frequently. De Sinéty and Melassez speak even of having seen them in a very fresh specimen with the cilia in motion. From the general accuracy of the observations of these gentlemen I am bound to accept these remarkable statements, but I do not see that the occurrence of these cells can be looked upon as having any importance or significance. The second point of difference between us is that in the dropsical follicles containing ova I have found the epithelium quite normal in arrangement and appearance.

We have, however, from them a complete establishment of the facts that I have so often seen, that we may have in the same ovary—indeed, we may have in the same cyst—indications of a reversion of type in epithelial growth; that is, we may have the normally cylindrical cells at one part of the lining membrane of a large ovarian cyst, while at another part we may have round, immature, rapidly growing cells, presenting all the appearances they would possess upon a mucous surface. Such cells as these, however, are not seen in a Rokitansky's tumor. In columnar cells the arrangement is, of course, in a layer single, or nearly single, and the first change from the type is seen when we have cells increasing largely in size, becoming somewhat irregular in shape, and having underneath another layer polyhedral and polymorphous. We may, I think, accept the following description as perfectly accurate:

"Sometimes these are flat cells, with sinuous borders, and occasionally of considerable dimensions. Seen in front, in silver preparations, they simulate a pavement with irregular designs, quite different from the very regular mosaic formed by the cylindrical epithelium. Seen in profile, on sections, their thickness is found to be somewhat variable; it is generally larger on a level with the nucleus. It possesses one and sometimes several nuclei.

"Sometimes, instead of flat cells, we have thick, voluminous ones, of the most varied and fantastic forms. Some are seen presenting a broad base of implantation, and terminating in a narrow, tapering extremity, which causes them to resemble cones. Others, on the contrary, are only attached to the wall by a thin pedicle, more or less long, while their extremity is distended, which gives them the appearance of clubs. There are some that are broad at the base, broad at their free extremity, and of which the two voluminous extremities are united by a more or less narrow neck. We have seen some which presented

successively two constricted portions, and consequently three distended portions; others which were carried, like grapes, upon a ramified pedicle. The free extremities have a tendency to approach the spherical form, while the others are polyhedral through reciprocal pressure.

"The protoplasm of these singular cells is in general granulous, with large grains. It takes a brownish yellow color under the action of picrocarminate, except in the portions constricted or in the form of pedicles, which portions are more homogeneous and more refractive. These generally possess large nuclei, with one or several voluminous nucleoles. Those that present several distended portions have nuclei in each of these portions. It will be perceived that they are elements that proliferate and bud with very great activity."

The epithelium of a cyst-cavity, after having undergone the changes of type already described, takes on a further growth, and, departing from an arrangement in a single layer, as seen in the normal follicle (Fig. 12), or in the cyst still containing an ovum, it increases in thickness, adding layer upon layer of the immature cells. As these layers grow, the cells alter more and more from the normal and adult forms, and finally cease to have any resemblance to them. Waldeyer, as well as De Sinéty

and Melassez, have fully confirmed my observations on this point. The new layers are not uniformly distributed over the interior of the same cyst, and they are often so localized as to form elevated patches, or even tubercles, on the inside of the cyst. To the naked eye these often look very like cancer, and on microscopic examination they have all the appearances which I have already described as belonging to that tendency. The French authorities I have so often quoted say of these masses: "They have the aspect of carcinomatous fungosities, and they appear also to have their malignity." Boettcher and Waldeyer, besides other authorities, fully support my conclusions.

In some tumors we find velvety-looking tufts hanging from the walls into the interior; and these are found, on examination, to consist of a basis of nucleated fibrous tissue—in fact, ovarian stroma—lined on each side of their many branches by regular



FIG. 26.—Altered Epithelium from Walls of Ovarian Cysts. (After De Sinéty and Melassez.)

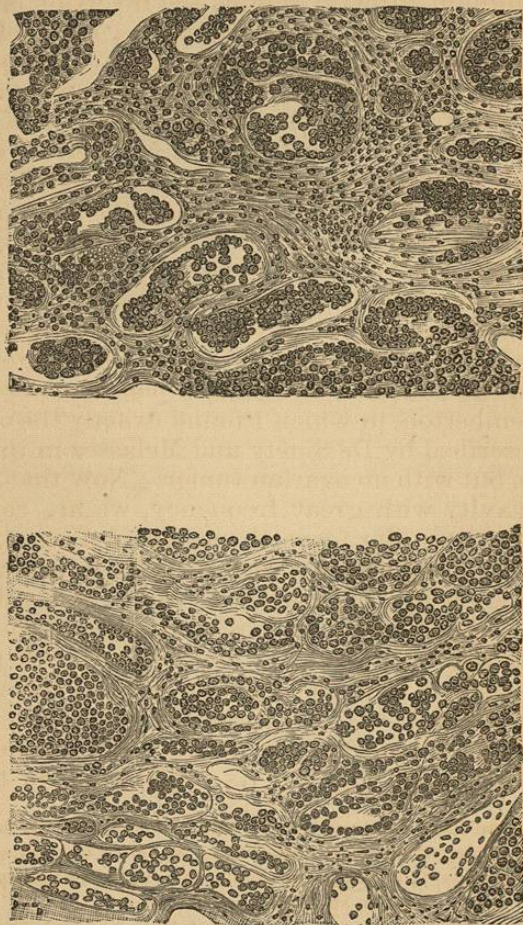
columnar epithelium, or by epithelium of the immature forms. They are sometimes, in fact, transformed into pediculated masses of villous cancer.

As these structures divide and redivide into branches, they very much resemble trees, and therefore have had conferred upon them, among other names, that of intracystic dendritic growth. If a cyst in which they exist be injected and the sections stained, they will be found to consist merely of the remains of follicles which have burst in their efforts to become cystic, the skeleton branches retaining the epithelium of the cysts which formerly were on each side of it. By the growth of subsequent cysts these papillary remains are often forced into irregular and very complex folds, the apparent complexity of which may be greatly increased by the accidents of the section.

We have here, therefore, among other things, an explanation of the extraordinary differences of opinion which have been expressed regarding the results of microscopic examination of the contents of ovarian tumors. Many years ago Professor John Hughes Bennet described what he termed an "ovarian cell." Dr. Drysdale, Mr. Thornton, and several others, have all fallen into a similar error in believing that any one form of cell could be made diagnostic of these curious growths.

In the second edition (1868) of his book on "Ovarian Dropsy" Mr. Baker Brown discusses the views of Professor Bennet, of Edinburgh, who believed that it was possible, by microscopic investigation, to decide as to whether the fluid was ovarian or peritoneal. Mr. Brown, in conjunction with Mr. Nunn, seems to have gone very fully into this matter, and, in the words of the latter, it seems to have been decided as follows:

"I am inclined to say, as the result of many examinations of different specimens of ovarian fluid, that the most constant characteristic of such fluid is its containing, in greater or less abundance, cells gorged with granules, and, in addition, circumambient granules having the same measurements as those encompassed by the cell-wall. At one time I considered the size of these granules was constant, but subsequent observations have convinced me of the incorrectness of this conclusion. The size of the gorged cells and of the granules varies greatly, even in the fluids from different cysts of the same ovary." "In the present state of our knowledge I do not think we are justified in asserting that the nature of the fluid would be diagnostic of the disease which gives rise to its production. What I believe to be the value of a microscopical examination of the fluid is that it may serve to strengthen an opinion, but alone it ought not to decide one."



a, section of fetal ovary; b, section of rapidly growing cancer of the ovary. Comparison of the two sections show that cancer is a reversion to the fetal type of growth.

We may also find, from the observations of De Sinéty and Melassez, a confirmation of what I advanced many years ago in a discussion upon this subject: that there was no kind of cell of epithelial origin that it was not possible to obtain from the cyst-cavities of an ovarian tumor.¹

In the last paragraph quoted from the French authors there is a most concise description of what must also be regarded as a tendency to malignant growth; that is, the reversion of type in the production of these cells toward immature, incomplete, and rapidly growing elements which are practically cancerous.

This of course at once explains the clinical fact which all ovariologists are quite familiar with, and to which Dr. Keith has especially drawn attention—that the rupture of certain cysts, on the escape of their fluid into the peritoneal cavity, is followed by, or at least is associated with, the infection of the general peritoneal surface with papillary cancer, this accident having a uniformly fatal result. On the other hand, I have seen over and over again the same cells and the same expressions of immature growth in the peritoneum, without the presence of any ovarian tumor; and only on the morning in which this sentence was written I opened the abdomen of a patient placed under my care by Mr. Oliver Pemberton, in which I found exactly the condition so accurately described by De Sinéty and Melassez in the above-quoted sentence, but with no ovarian tumor. Now that we open the abdominal cavity with great frequency, we are constantly coming across this peculiar form of malignant disease, and we find it is by no means confined to the inside of ovarian tumors or to the peritoneal cavity, even when no tumor exists there, for I have had occasion to examine pieces of the pleura and of the pericardium where exactly the same appearances were found.²

The conclusion from all this is that to which I have already pointed, that the growth of ovarian tumors is associated with a tendency toward malignant disease, which finds constant clinical expression, and which receives its explanation in the mar-

¹ Dr. Mathews Duncan speaks of this question with his usual force in these words: "In fact, we have, in all departments of ovarian diagnosis, more to admire in the zeal and diligence of histologists, in regard to the fluids, than in the exactness and reliability of the practical results they can show."

² But my most recent experience tends to show that there are two forms of papilloma associated with ovarian tumors, one malignant, and one not so. The latter speedily disappears after the removal of the tumor and the patient gets quite well, though its naked-eye appearances are quite indistinguishable from those of the malignant kind. I have had two cases within the last year, aged 57 and 38 respectively, where I have left large masses of papilloma, fixing the uterus in both cases. Since the operations these masses have entirely disappeared, and the patients are both in perfect health.

vellous changes we find produced in the epithelial linings of its cysts. Much more requires to be done in the study of this most interesting question, and doubtless, when the method of its progress is made clear, we may find some indications for a more sure prevention of it. One thing I am certain it clearly establishes, and that is the absolute propriety of removing ovarian tumors at a very much earlier stage of their existence than has been, till recently, the accepted rule in practice. If these epithelial changes are progressive—as doubtless they are, and if they are malignant—as I certainly believe them generally to be, then, acting upon the principles which guide us in the treatment of all tumors, we ought to remove an ovarian cystoma early in its history, before these changes have been effected, and certainly before there is any risk of cyst-rupture. Finally, we ought to regard the operation of tapping as one which ought to be discarded, save under very exceptional circumstances, because not only is it fraught with considerable immediate danger, but it seems to possess a still more important secondary risk, which has until lately been almost overlooked. I may say that in my own practice it is an operation never performed, unless I am certain the tumors cannot be removed.

There is one fact which may be quoted in support of the views advanced by De Sinéty and Melassez, to which they have not drawn attention, but the significance of which becomes apparent; that is, that while, in the cysts of the tumors which I shall afterward describe as possessing ova, the contents are always limpid, whereas in the cysts where the changes have occurred the contents are mucous, viscous, highly albuminous, and often bloody; in fact, they present all the characteristics which the contents of mucous cysts would possess. It might not be inappropriate also to point out here that the arguments I have given above also point in the direction of establishing for cancer a local origin. We have, then, ovarian tumors with well-pronounced and distinctive characters, possessing the power of infecting the system generally with cancer, as they most undoubtedly do when their removal is too long delayed, or when they have ruptured or been frequently tapped; and, on the other hand, we have tumors with the same characters, but which have never been tapped and have not ruptured, but have been removed early in their history. By the early removal of these latter tumors we remove the source of the systemic infection, and prove, it seems to me, a local origin for cancer—as far as the ovary is concerned, at least.

There comes then the question—if we should see any of these altered and sprouting cells in fluid removed from a cyst or from

a serous cavity—Should we set the case down as being hopelessly malignant, and, in the case of an ovarian cyst, refuse on that account to operate? I certainly could not answer these questions in the affirmative. I believe that such appearances indicate the high road to cancer, but it is possible that the goal may never be reached. I think it perfectly certain that removal of the tumor may arrest the progress of the change before a general infection is reached. Dr. Mathews Duncan very well points out that the ovary is in every way the most isolated organ in the body. Removal of a cystoma in which such changes are being effected, at an early stage, may avert a systemic affection; and, as a matter of fact, I have observed all these changes in tumors which I removed many years ago, and the patients from whom they were cut out are alive and well at this date. In one case the period which has elapsed is eleven years.

Upon the question of the origin and diagnosis of this condition a good deal has been written, especially by Dr. Foulis, of Edinburgh, and Mr. Thornton, of London. They both claim the credit of having discovered masses of sprouting epithelium, both in the cystic fluid and in that of the peritoneum, which will enable us to diagnose cases of cancer. After a very large experience, both of microscopic manipulation and of cases of this character, I must absolutely dissent from the views they express. Dr. Foulis goes so far as to say that the absence of these sprouting masses from ascitic fluid is an almost certain sign of the absence of malignant peritonitis and malignant ovarian tumor. But I have had, in at least two cases, reason to suspect malignant tumors, when I found none of these cells in the fluid, and yet I found abundant reason afterward to know that my suspicions were correct. In fact, I place no reliance on the presence or absence of these cells in fluid removed by tapping, and as I never tap removable tumors at all now, I never have any occasion to look for them, or any opportunity. The changes to which their presence is due certainly lead to a malignant condition in their later stages, but their presence is no guide for a prediction that the patient will die of cancer, and it is the best of all arguments for the speedy removal of the tumor.

It is also quite certain that this form of papillary cancer frequently arises long after the removal of an ovarian tumor under circumstances which make it extremely unlikely that the tumor should be regarded as its cause. They are both probably the result of the same condition, whatever that may be. Thus, in the *Lancet* of October 25, 1875, I published a brief note of a case of ovariectomy in a young girl, in which the operation was made to cure a complete protrusion of the uterus. The operation was