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On the Microscopical Diagnosis of
Benign and Malignant Growths
of the Cervix Uteri

BY

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On the Microscopical Diagnosis of Benign and Malignant Growths of the Cervix Uteri.

By H. G. PLIMMER, F.L.S., F.R.M.S.

THE time has come when the older signs, by which it was thought practicable to distinguish between benign and malignant tumours of the cervix uteri, are no longer regarded as conclusive, and the microscope is now alone relied upon to determine the exact nature of doubtful growths.

Schröder says that the therapeutics of cancer of the uterus consist in the total extirpation of the organ; and as this operation is a very grave one in any case, and a mutilation if not required, it behoves us to be extremely careful as to the accuracy of our diagnosis before deciding upon operative treatment. The difficulties of exact diagnosis are often very great, even when modern microscopical methods are added to clinical acumen and experience; so that, in the early stages of the disease at any rate, mistakes not infrequently occur. There is, unfortunately, no *one* method of diagnosis, either clinical or histological, it being only by an exact adjustment of the two that a right interpretation of the symptoms and physical signs of any new growth in its early stage can be arrived at. Of the clinical aspect of these cases I shall not speak. The various clinical signs are much better known and classified than the corresponding histological changes in the tissues, but a microscopic examination ought always to be made in any case which is not quite certainly clear. I shall try to indicate the characteristics of the various new growths, and the difficulties and possibilities of error in diagnosing them one from the other; and to point out those ways by which such errors may be avoided. To show that

these difficulties of diagnosis are real and dangerous elements in the decision as to what the treatment of this class of uterine disease should be, I will mention my own experience with regard to them. I have, during the last three years, had occasion to examine 92 cases of uterine tumours, 72 of them tumours of the cervix, which were diagnosed as cancer, of which they possessed many of the physical signs; but on close and careful examination 12 were found to be benign in nature. The experience of others is much the same, all pointing to the fact that the exact diagnosis of the early stages of tumours of the cervix is not always easy or certain, so that all the modern means and methods of microscopical examination at our disposal should be brought to bear on these cases.

The first point of importance is, that everyone who examines tumours of the uterus should be perfectly acquainted with the normal histology of the uterus, not only of one part, but of the various parts—os, cervix, internal os, and body; and not only at one period, but at all ages, before, during, and after the period of menstrual life, and especially during the various intermediate periods of the latter, *i.e.*, just before, and just after, and during menstruation, during pregnancy, and after childbirth. For what, for instance, would be normal in a woman over the menopause, would be pathological in a woman of 30; so that the exact knowledge of the histological differences of these various periods is most important, as many mistakes have been made through inexact knowledge of them.

Then, also, it is best that those who undertake such work should use one method of fixation of the tissues, so as to be able to compare accurately, in their own minds, the various and changing appearances of the manifold uterine conditions. Many errors have been made by the indiscriminate use of different methods, since those workers, who are not experienced histologists, get no one standard appearance under any given condition.

Where time is not of great consequence the following

method gives the best results, and it is easy enough to be generally applicable.

A piece of the tissue to be examined should be placed at once after removal in the following solution for twenty-four hours :—

| | | | |
|---------------------|-----|-----|----------------|
| Sodium chloride | ... | ... | 7.5 gr. |
| Glacial acetic acid | ... | ... | 10 c.c. |
| Distilled water | ... | ... | 1 litre |
| Mercuric chloride | ... | ... | To saturation. |

It should then be washed in running water for 2 or 3 hours, and placed in 50 per cent. alcohol for twenty-four hours, then in 90 per cent. alcohol for twenty-four hours, then in absolute alcohol for twenty-four hours. It should then be either cut with a freezing microtome or passed through cedar-oil into paraffin, and cut with a rocking, or other paraffin microtome. This latter method gives the best results; and in the case of scrapings, which are often very soft and friable, it is the only method which gives anything like a certain result; moreover, with the paraffin method it is possible to get an exact orientation of the piece you have to cut, and, as will be shown later, this is sometimes of great consequence.

The best stain for such sections is hæmatoxylin, and the best form in which to use it is in the so-called hæmalum of Mayer. This can be used either alone or, better still, with a counter stain of Congo-red (in 1 per cent. solution in water) which, besides being an excellent ground stain, has, in one condition at least, which I shall mention further on, a selective action. The sections are then dehydrated in the usual way, and mounted in balsam.

By this method uniformly good results are obtained, both as regards normal and pathological conditions, and the various elements—cells and nuclei, vessels, muscular and fibrous tissues—come out with a distinctness and certainty obtainable by no other method. But sometimes there are cases in which the few days this method takes are too long, and some quicker way has to be made use of. The following method I have often used, and find that the fixation is good, and the

staining quite easy, so that it may be used when there is any urgent hurry.

Place the piece of tissue—it must be in this case the smallest possible piece in order to get the best results—in a 30 per cent. solution of formalin for from three to twelve hours, then dry it on filter paper, and place it in absolute alcohol for at least an hour, and then into aniseed oil till it sinks.

These last two stages are more effectually and quickly done if the bottle is placed in an incubator at 37°C . The piece is then taken out of the oil, and frozen and cut on a freezing microtome (oil of aniseed freezing quite firmly enough, as has been pointed out by Kühne). The sections are taken from the razor and placed at once into spirit, then into fresh spirit to get rid of the oil; and then they can be stained as before described, by hæmatoxylin alone, or by it and Congo-red. With care, this quick method—which can be got through the same day as the piece is removed—gives very good and clear sections, with very little alteration of the cellular elements.

With regard to the pieces to be examined, it is of course quite easy, when a supra-vaginal amputation has been done or a good-sized piece removed, to cut out a piece or pieces from different parts, which shall include both the mucous membrane and a small portion of the underlying muscular layer. These ought always to be included if possible in the section, in order to be quite sure of the nature of certain growths. When bits are scraped out for examination, they ought to be taken from more than one part of the cervix, and to be scraped or curetted deeply enough to include the surface of the muscular layer. Fewer mistakes would be made, and certain diagnosis would be much easier, were these precautions always taken.

The sections, in cases of suspected cancer, should be made very thin—some as thin as possible—for in early cases of cancer, where the growth is rapid, and there is much round-celled infiltration, unless the section is very thin the round cells hide the cancer cells, which are thus apt to be over-

looked ; but if the sections are very thin the epithelial cancer cells will stand out quite clearly from the round-celled growth.

With regard to the making of the sections, workers should get accustomed to the various appearances in the normal cervix caused by cutting the sections more or less obliquely or transversely to the surface. In pathological specimens the most misleading appearances will be seen and misinterpreted, unless the direction of the section be very carefully adjusted ; the best direction being as near as can be got to that of a right angle to the surface. In dealing with the somewhat complex and often misleading histological appearances of the mucous membrane of the cervix, we must always remember one or two points connected with the normal histology of the part. These points are, firstly, the fact of there being two different kinds of epithelium in the cervix, whose boundaries are not constant, but variable, or apparently so, as in the slight ectropion of the cervix of a uterus which has borne children ; each of which two kinds is subject to important changes of form upon slight irritation, especially to rapid proliferation ; secondly, the fact that the glands do not go vertically downwards, but often bend when just under the surface of the mucous membrane and so, at the junction of the columnar with the squamous epithelium, they may run underneath and parallel to the surface of this squamous part, giving rise to appearances sometimes mistaken for pathological. They are, of course, not pathological, but as mistakes have occurred by misinterpretation of them, the fact should be always borne in mind. In doubtful cases serial sections should be made, by which the glands may be followed to their openings.

The principal points to keep before you when deciding whether you are dealing with a new growth, or an obliquely or transversely cut section of normal tissue are these : firstly, the regular arrangement of the epithelial cells and the condition of the connective tissue stroma. For, in the case of a new growth, this latter is infiltrated with a greater or lesser number of round cells, gathered together for the purpose of resisting and destroying the new growth. But this round-

celled infiltration also occurs in simple inflammation, which can be distinguished by the regular arrangement of the epithelial cells. For a malignant growth does not contain regularly arranged cells of the same size and shape, but of many shapes and sizes. This is important to remember. In oblique or transverse sections through the glands, you may get the columnar gland cells to look very like squamous epithelium, with or without a nucleus according to the point in the cell through which the section is made. So that when a gland is cut obliquely, appearances very like proliferating epithelium are seen, which are sometimes very misleading; and if the fundus of a gland be also included in the oblique section, it may look very like a cancer alveolus. This is one of the most deceptive appearances to remember, and as it is common, it may often mislead unless care be taken. The great point of difference here also to be remembered, for diagnostic purposes, is the regular arrangement and likeness of the cells, which at once differentiate them from cancer cells. To avoid these errors in some cases we must make serial sections, by which we can follow the course of the glands; and we must also pay especial attention to the amount of karyokinesis in the specimen. In rapidly growing cancers, in every field, many nuclei undergoing mitosis may be seen in various stages, which are but rarely seen, in this condition, in the obliquely cut but normal gland cells.

Now I will examine a little more closely the conditions of the cervix which we have to differentiate one from the other. First of all with regard to simple inflammation. In this there is, of course, a considerable small-celled infiltration. The vessels, especially the capillaries, are enlarged and filled with blood, and new capillaries will be seen in process of formation, about which the round-celled infiltration will be most marked. The inflammatory process, as a rule, diminishes as you go deeper into the tissues, until at the muscular layer, or just within it, the round-celled infiltration ceases. Often you can see the formation of granulation tissue just beneath the epithelium, and you can trace the round cells into

spindle and even epithelioid forms. But since we know that primary inflammation of this part of the uterus is very rare, it is very important that we should find what it is secondary to, and therefore the patient in whom such conditions as the above alone are found, ought to be kept under observation, and a small piece ought to be removed for further examination if the symptoms do not quickly disappear. In ectropion with inflammation, much the same appearances are seen as in simple inflammation of the cervix. In the early stages the glands are unchanged, and only a few leucocytes are to be seen between the epithelial cells. But of this acute stage we very rarely get a specimen to examine, nor does it come in as an alternative diagnosis to cancer; but we often see it in the chronic form, in which the characteristics are much more marked. Then the glands become enlarged, or even increased in number, and there is a hyperplasia of the glandular epithelium. But in mere inflammation these changes are confined entirely to the superficial part of the mucous membrane. In this condition we get sometimes so much round-celled infiltration that the gland canal becomes compressed, and perhaps stopped up, so that you may find small cystic spaces. But sometimes the inflammatory process causes only a hyperplasia of the gland epithelium. Then the gland, instead of having one single layer of columnar epithelium, is filled up with several layers one on the other, so that they lose their original columnar form and get flattened. Then if the section happens to be oblique or transverse, these columnar epithelium cells look just like squamous epithelium, and give you the impression that you are dealing with an early stage of carcinoma. But in such a case as this we cannot be too careful; and we must not, on any account, diagnose this as a cancer without further evidence, such as is to be got from serial sections, the state of the surrounding tissue, and the quantity of mitoses, &c. As a help in the differential diagnosis of this condition from cancer, I may here mention the selective action to be obtained by counterstaining the section with Congo-red, which I mentioned before. This differentiates the

gland epithelium from the atypical epithelium, which, in some cases of cancer, grows into the glands and fills them up, destroying thereby, little by little, the gland epithelium, and it does so in this way, as has been pointed out by Amann. The gland epithelium is stained strongly red; the protoplasm of the cancer cells, on the contrary, remains almost uncoloured, so that by the difference in the colour we can easily see in a gland whether we are dealing with a hyperplasia of its epithelium, or with an ingrowth of atypical cancer cells.

This is a condition, also, which should be watched, and in which pieces should be examined from time to time according to the clinical symptoms. We must never forget also, that with every inflammation hyperplasia of epithelium may occur.

As regards the so-called "erosions," they are characterised by the vaginal surface of the cervix, which is normally covered by squamous epithelium, getting covered by more or less cylindrical epithelium, which may sometimes even dip a little into the tissues. This condition is really so like ectropion that it is only in a virgin uterus that it can be easily differentiated. A real erosion in the pathological sense it is not, but rather the covering of a surface with columnar epithelium, which normally would be covered with squamous epithelium. There is here not much change in the connective tissue stroma, and only a small quantity of round-celled infiltration. The dipping in of the columnar epithelium into the tissues forms gland-like formations, which, however, are much shorter than the ordinary cervical glands. This is the condition usually called "*erosio simplex*." When this columnar epithelium sinks deeper into the connective tissue stroma, and is raised to the original level of the surface, small pseudo-papillæ are formed; this is the so-called "*erosio papillaris*." Again, if the surface is flatter, and more columnar epithelium is cut off in the deeper parts, it is called "*erosio follicularis*." But these old distinctions are not clear, nor are they ever separated in a typical case, so the characteristics of erosion mentioned before are better; namely, the covering of a part of the cervix

normally covered with squamous epithelium, with columnar epithelium which dips more or less deeply into the connective tissue stroma; and characteristic also of "erosion" is that this part of the connective tissue stroma, which is normally free from glands, has a number of gland-like bodies produced in it, concurrently with the covering of its surface with cylindrical epithelium.

There are also, no doubt, cancerous erosions, but in the opinion of many continental writers the relations of erosions to cancer have been much overrated. Usually in the cases in which the "erosion" appearances described above are seen, there will be no cancer found.

Now let me turn to what are more strictly new formations. These are of two kinds—benign and malignant. To the former belong hypertrophies and hyperplasias of the epithelium or connective tissue stroma, to the latter cancer and sarcoma. Certain is it that all the apparently harmless polypi should be carefully examined, because we may find destructive and malignant processes going on in them, although in my experience they are, as a rule, benign. With regard to hypertrophy of the epithelium from prolapse, it is very seldom, according to the clinical authorities, that this hypertrophy becomes cancerous. In the *condyloma acuminata*, which sometimes, but rarely, appears in the portio vaginalis after gonorrhœa, there is a well-marked appearance, viz., the whole growth is covered with many layers of squamous epithelium which do *not* dip down into the tissue. Here, again, the regular arrangement of the epithelium, and the appearances before described as likely to mislead, should be thought of, so as to prevent errors from being made.

In hypertrophy of the cervix—*elongatio colli*—we get, of course, only the normal appearances, with the addition of an increase in the fibrous connective tissue, and an enlargement of the vessels.

With regard to cervical polypi, Williams says they have a tendency to become malignant; they should therefore always be very carefully examined.

These cervical polypi may be either covered with squamous or columnar epithelium. If with the latter, carcinoma supervenes very rarely. But when they are covered with the former, the danger of their developing into a carcinoma is much greater; this squamous epithelium, under the influence of irritation—perhaps of specific parasitic irritation—sends down processes into the deeper lying tissues, which processes, careless of the landmarks of the various tissues, grow into the glands, break through the walls of the vessels, and become carcinomatous. The exact diagnosis here is very difficult, as there is a general hypertrophy of all the tissues in this kind of polypus itself, and also in the neighbourhood of its origin. In diagnosing the so-called “cancerous degeneration” of these polypi we cannot be careful enough; and we must remember that three or four layers of columnar epithelium in a gland are not *alone* sufficient to enable us to diagnose the growth containing them as cancer, and we should always keep the exact appearances of cancer and its immediate neighbourhood in our minds.

Here the use of Congo-red, as before described, will be found of great service in differentiating, in doubtful or oblique sections, the kinds of epithelium which may be in the gland.

Now we come to the most important question—that of the diagnosis and recognition of cancer. When we diagnose a uterine tumour to be “cancer” we must always bear in mind that it means the removal of the whole organ; so that all our experience and technical skill should be brought to bear upon the examination of specimens supposed to be of this disease. That mistakes in gross diagnosis do occur is known to all of us, so that I think we ought to have one rule, viz., that no uterus should ever be excised on the supposition of its being cancerous, without a confirmatory microscopic examination having first been made.

With regard to the kinds of cancer of the cervix, there are two different forms—either it arises from the squamous surface epithelium, or from the glands in the cervical mucous membrane, which glands it destroys before it gets to the surface.

The squamous variety of cancer has a great tendency to ulcerate; and if watched from an early stage, in which one lip only is affected, we shall soon see the other lip becoming infected. But contrary to ordinary ulceration, which is depressed below the normal level, this is raised above the normal level of the mucous membrane; this is of course in the early stages, before excavation has begun, at the time when pathologists are most often asked to diagnose the disease in specimens sent to them.

The glandular variety shows, at the same period, no ulceration, the surface of the cervical mucous membrane looking pretty normal. But the nodules can be felt with the finger, and one should be deeply excised for examination—deeply, because of the surface being normal, so that no mere scraping will give us certain evidence; it is even better to remove a piece with the knife, afterwards closing the wound with sutures.

On examining a specimen of cancer, we see that the cells are irregular, atypical in form, and are not confined to the tissue in which they arise, but that they spread in any direction, destroying the glands and the walls of the vessels, and penetrating into the muscular layers, till eventually little or nothing is left of the original tissues. But the tissues react, too, against this invading growth, by an enormous infiltration of small round cells, much greater in quantity than in any other disease of this part. So the principal characteristics of cancer may be summed up into (*a*) the atypical proliferation of the epithelium of the mucous membrane or gland; and (*b*) an intense small round-celled infiltration, by which the boundaries of the various parts of the tissue are obscured, altered or destroyed. Then, again, let me mention as of great importance, the irregularity in the shape and size of the cells; the nuclei, too, are usually larger than in the normal epithelial cells, and are very variable in form, and there are often from two to five or more in a single cell. The protoplasm of the cells differs very much

in quantity, sometimes forming quite a large zone round the nucleus, sometimes quite a small one.

This is the place to say a word with regard to another sign of cancer—namely, the presence, in the cancer cells of bodies regarded by others as well as myself as parasitic protozoa. I have not failed to find them in every case of cancer of the cervix which I have examined, but they are somewhat difficult to find in some cases, and require patience, as well as special methods of staining for their demonstration. They are not to be found in the older or degenerated parts of a growth, but must be looked for in the growing part, especially at its extreme edges.¹ In doubtful cases their presence is, I think, a complete proof that the growth is cancerous; moreover, they are best found in the early period of a case, just when we sometimes want every confirmatory sign to enable us to be quite sure of our diagnosis. They occur as round or ovoid bodies, with a nucleus, most often in the protoplasm of the cell, but sometimes in the nucleus and they have quite distinct staining reactions from the rest of the cell, for a description of which I must refer readers to the papers before mentioned.

As well as the irregularity in the size of the cells in the cancerous parts, we can often demonstrate the presence between them of single capillary vessels, and leucocytes, which are not seen in normal epithelium.

With regard to the ingrowing of the epithelium into the glands, we must be careful, so long as the gland boundaries have not been disturbed or encroached upon, not to diagnose cancer from this appearance alone. This point in the diagnosis of glandular cancer is of the greatest importance; there can never be any doubt as to the malignancy of a growth if it *has* destroyed or broken through the gland wall or border.

In the case of epithelium growing into the glands I would

¹ Should anyone wish to look for them he will find an account of them, and of the methods by which they can be demonstrated, in papers by Dr. Ruffer and myself in the *Journal of Pathology and Bacteriology*, 1893.

again recommend the use of Congo-red as a differential test of the nature of the epithelium.

In cases where there is nothing to be seen but an enormous over-growth of the gland tissue—*adenoma*—we must be guided as to its malignancy by the relation of this over-growth of gland tissue to the muscular layer. If this latter is at all destroyed there can, of course, be no doubt that the growth is malignant—the so-called malignant adenoma. But if the glandular overgrowth is confined to the mucous membrane it need not be malignant. But when the gland type is not well adhered to, and when columns of cylindrical cells get into and destroy the tissues, then we must look on this kind of adenoma as malignant. This malignant kind is not common in the cervix, in fact is very rare, which is another point to remember. The appearances which make for a benign adenoma are the regular typical growth, just like healthy glands, and the limitation of this growth to the mucous membrane: those which make for a malignant adenoma are the atypical form of the growth, which never has an accurate resemblance to the original cervical glands, and the arrangement of the cells, which lie in disorder one against or over the other, and invade the muscular tissue to varying depths.

There is another very rare new growth of the cervix, namely, tuberculosis, which we must remember, if a piece of tissue supposed to be cancerous does not give the appearances associated with cancer, and does not fit in with any of the other growths described above: it can generally be recognised by the characteristic tubercles with giant cells, &c., and further confirmation can be obtained by staining in the usual way for tubercle bacilli.

Before bringing this paper to a conclusion I should like to express my great indebtedness to the following books; principally to Dr. Karl Abel's *Die Mikroskopische Technik und Diagnostik in der Gynäkologischen Praxis*, which was reviewed in the last number of the Journal, and to Ruge and Veit's *Die Krebs der Gebärmutter*, and to Dr. Amann's *Ueber*

Neubildungen der Cervicalportion des Uterus, which have been very suggestive in many of the points I have mentioned; all of which also I have been able to confirm from my own observations.

In conclusion, I have tried to give such practical facts with regard to the preparation and interpretation of sections made from the various cervical new growths, as may, I trust, be useful in helping towards a more exact and certain diagnosis of them, before operative treatment is resorted to. When we see how easy it is to make mistakes in the differential diagnosis of these growths, it is surely well that all the light possible to be obtained from modern methods and observations should be thrown on this subject, which, besides being pathologically interesting, is humanly of such importance.



