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SOME EFFECTS OF CHRONIC IRRITATION UPON LIVING TISSUES, BEING FIRST STEPS IN A RATIONAL STUDY OF CANCER.

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WE may say of epithelium as Aristotle tells us that the men of old were accustomed to say of Africa *'Αεί τι καινόν φέρει ἡ Λιβύη* ("Africa always produces something new"). The more closely epithelium is studied the more complex it appears to be. The discussions upon the organisms found in cancer which have formed so marked a feature in the pathological work of the last year have demonstrated to us our ignorance of the appearances met with in carcinomatous tissues examined under high powers of the microscope after the use of special methods of preparation. If we are ignorant of the appearances seen in carcinomatous cells, we are still more ignorant of the changes occurring in normal epithelium as a result of simple but chronic irritation. The great advance recently made in histology consists in the application of biological methods to morbid anatomy. In biology the tissues are of necessity preserved whilst they are physiologically living, for they are often so delicate that death is synonymous with disintegration. The reagents employed, therefore, are those which simultaneously kill, fix, and harden. In morbid anatomy, on the other hand, it has too long been customary to take tissues from the deadhouse, and to subject them to reagents by which they are slowly and imperfectly hardened, thereby allowing changes to take place in the more delicate structures, which renders impossible any minute microscopical examination. This alteration in *technique* is revolutionising our knowledge of the structure and life-history of cells in the different parts of the body. It has presented us with a number of facts which as yet we are hardly capable of using, so imperfect is our present knowledge.

I propose in this paper to deal with a few of the facts obtained by a series of experimental researches into the cause of cancer carried out at the Conjoint Laboratories in London.

At the beginning of my investigation I found that it would be necessary to distinguish appearances due to simple irritation from those produced by the specific action of cancer, for it seemed that many of the histological appearances in carcinoma are the consequence of simple irritation. My plan of investigation required that animals should be kept for long periods of time with some of their tissues in a mild but efficient state of irritation. I have, therefore, been able to study the effect of chronic irritation upon such extravascular tissues as epithelium and cartilage. The results are interest-

ing, and the generosity of the BRITISH MEDICAL JOURNAL enables me to represent some of the more striking appearances by figures reproduced directly from photographic negatives, prepared by Mr. Doudney, the very able assistant in the laboratories of the Conjoint Colleges. The sections in each case were photographed under an enlargement of 400 diameters.

It is well to remember that the appearances here depicted were, with the single exception of the last preparation, the result of simple irritation of normal tissues, and have nothing to do with carcinoma. The interest of the preparations lies in the resemblance they bear to the appearances seen in can-

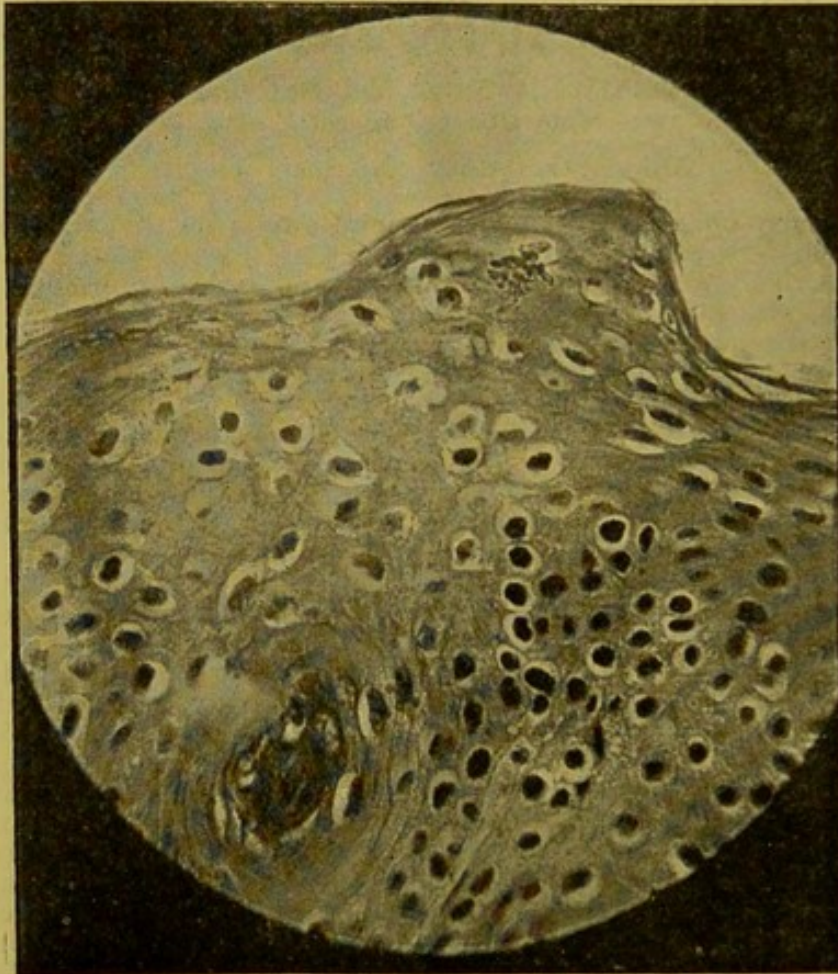


Fig. 1.—Epithelium of the ear of a rabbit, showing the vacuolation of cells due to chronic irritation $\times 400$.

cerous growths, a resemblance which has led some observers into the realms of mysticism and others into the depths of error.

1. *The Vacuolation of Cells* is the most constant phenomenon met with in tissues which have been kept in a state of chronic irritation. It is, as everyone knows, a prominent appearance in some sections of rodent ulcer and in Paget's disease of the nipple, as well as in many papillomatous conditions. The photograph reproduced in Fig. 1 represents a section through the skin of a rabbit's ear, which had been irritated by the application of iodine liniment from October 29th to November 21st, 1892. The stratum corneum remains unaltered. The cells of the stratum granulosum are nearly

all vacuolated, that is to say there is a transparent zone round the nucleus of each cell. This zone appears to be due to the conversion of the cell substance into eleidin, or some allied body which shrinks. The nucleus in some cases remains loosely attached within the cell, and readily drops out unless special precautions are taken to maintain it in position. The nucleus appears in other cases to become entangled in the shrinking and degenerate cell substance, and thus becomes distorted.

Another form of vacuolation is well seen in these cartilage cells—Figs. 2 and 3—from the ear of a rabbit, kept

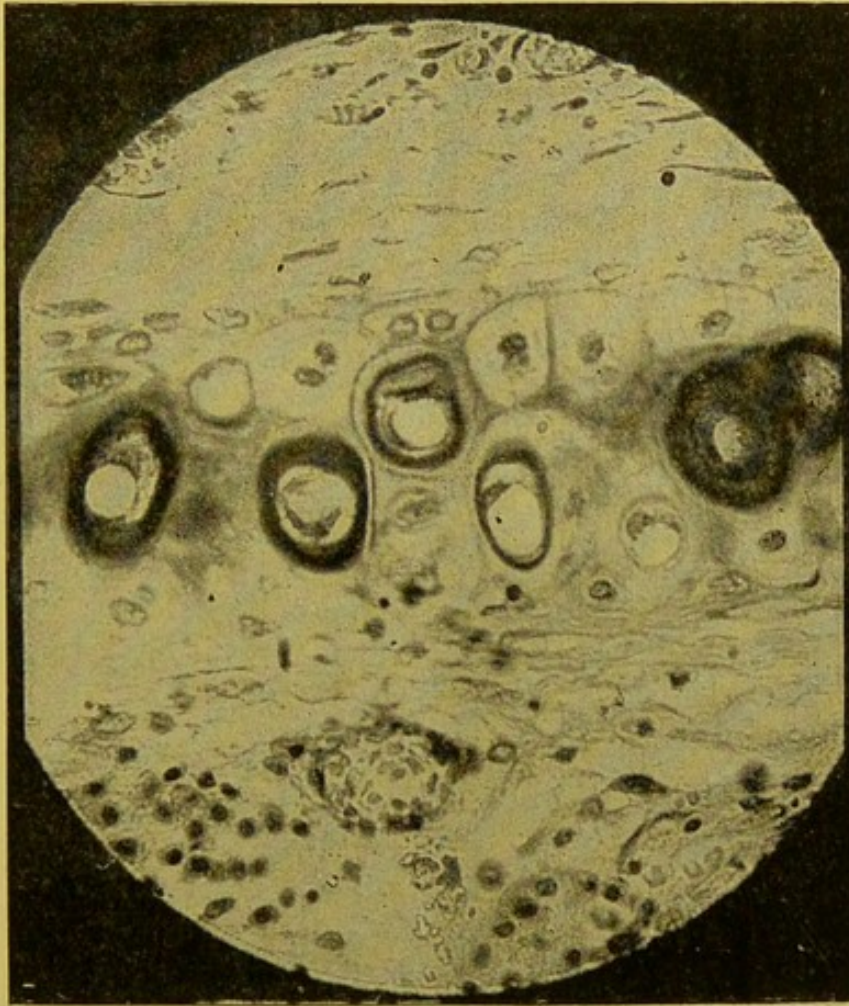


Fig. 2.—Cartilage from the ear of a rabbit. The cell substance has undergone degeneration. Some of the nuclei have slipped aside, others have become pressed out of shape $\times 400$.

irritated from November 7th, 1892, to February 28th, 1893. The majority of the cartilage capsules contain two nuclei, though the cell substance shows no trace of subdivision. The degeneration of the cell often commences between the two nuclei, which are thus pushed aside and squeezed until they become triangular or are even flattened. The outline of the degenerate portion is sharply defined, and is usually circular. In the larger number of cells the space is quite empty—no doubt because in the course of preparation the tissue had been soaked in ether—but it occasionally contains a little granular *débris*. In some cases the circumscribed in-

tracellular space appears to be produced by the nuclei slipping aside, for the nuclei may often be seen lying on one side of the space, and in a different plane to the rest of the cell. This form of degeneration, so far as I have been able to observe, is never intranuclear.

2. *Edematous Cells*.—Another result of irritation is that epithelial and other cells often become cedematous and present obvious signs of degeneration, as is seen in Fig 4. The appearances are quite distinct from the vacuolation just described, though they are no doubt akin to it. The spaces in these dropsical cells appear to be due to a fluid produced within the cell in droplets, which subsequently coalesce to

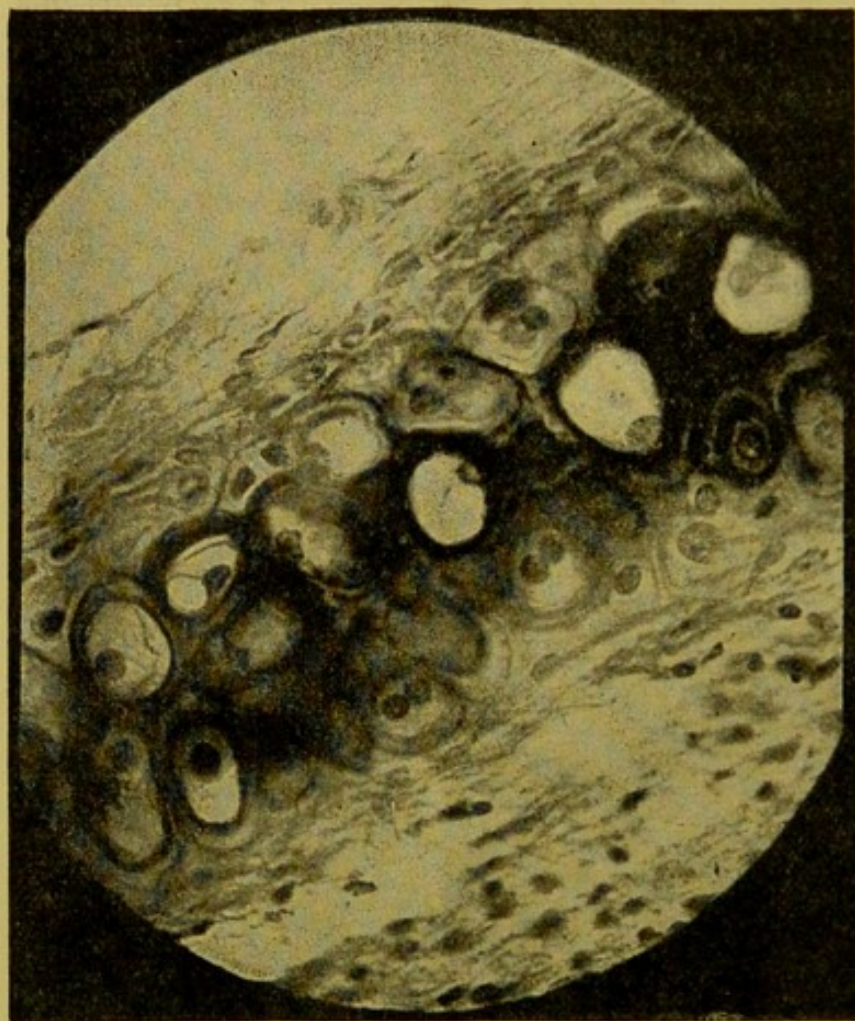


Fig. 3.—Cartilage cells from the ear of a rabbit showing degeneration. Many of the nuclei have slipped aside. The spaces are very sharply defined $\times 400$.

form larger drops, whilst the cell itself becomes enlarged and swollen. The process is, therefore, analogous to that by which fat is normally formed in connective tissue cells, or to the manner in which cells degenerate in colloid change. The degenerate cell is plump and contains a central nucleus surrounded by a remarkable and sharply defined zone. The cell and its nucleus stain deeply, the transparent zone does not stain. This process of cedematous cell formation has been carefully studied by Boyce, who showed some excellent examples of the process as it occurs in carcinomata at a recent meeting of the Pathological Society in London.

The œdematous cell can be easily produced experimentally in a rabbit. It happens from time to time that the discharge from the vagina of a rabbit which is being kept irritated be-

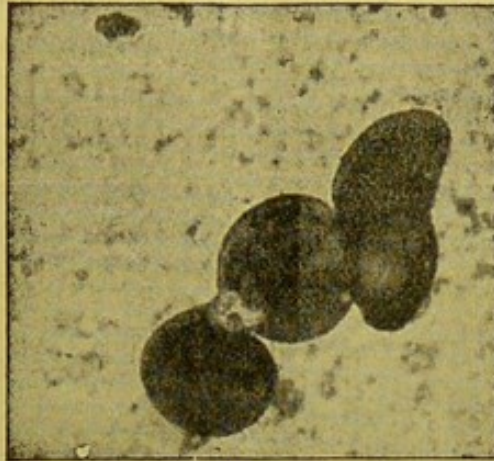


Fig. 4.—œdematous cells contained in the purulent vaginal discharge of a rabbit $\times 400$. In the large cell the vacuole is at the lower part and the nucleus can be dimly seen above it.

comes purulent instead of remaining serous. Two days after the appearance of the pus the epithelial cells which it contains are large and regular in outline, the cell substance stains



Fig. 5.—Cell nest from the vaginal epithelium of a guinea-pig, irritated from January to April, 1893 $\times 400$.

pink with Biondi's reagent and the nucleus green. There is no trace at this time of droplets either in the cell substance or in the nuclei. The vacuoles usually appear on the third

or fourth day and become more and more sharply defined on the succeeding days, and it is then easy to see one or two in each cell either in the nucleus or in the cell substance. Some of the cells occasionally contain bodies which seem to be partially digested pus corpuscles. The vacuoles eventually coalesce to form a well-defined zone surrounding the nucleus, and the nuclei themselves undergo granular degeneration. These changes are of common occurrence in rabbits, but I have failed to observe them in rats or guinea-pigs.

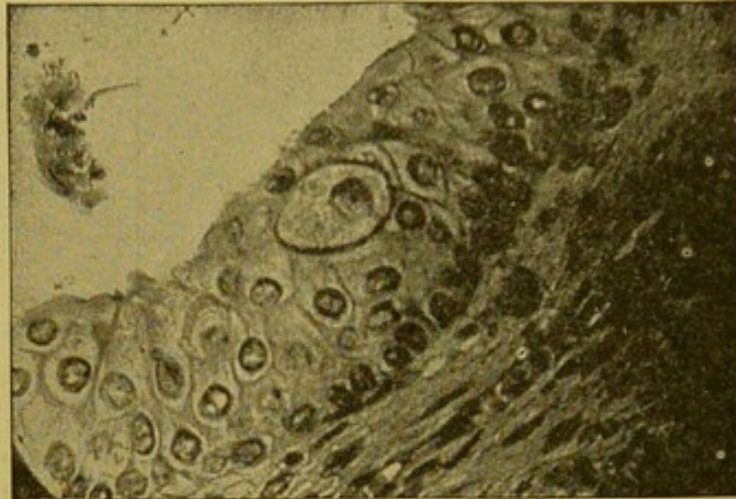


Fig. 6.—Vaginal epithelium of a rabbit showing one cell very much larger than the rest $\times 400$.

3. *Modified Cell Growth*.—The commonest, and, at the same time, the best known type of modified cell formation resulting from irritation is the cell nest. Cell nests appear to be one of the few changes in the vaginal epithelium of guinea-

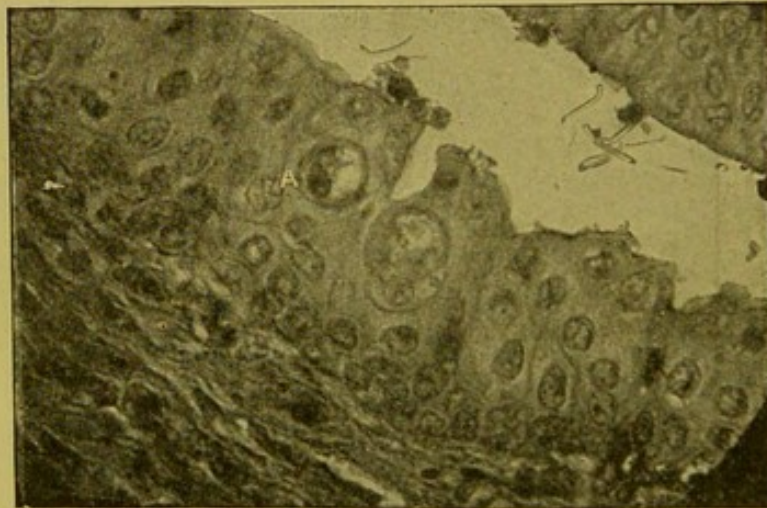


Fig. 7.—Degenerating cells from the vaginal epithelium of a rabbit. The large cell to the left, marked A, is very similar to that drawn by Wickham (Plate II, Fig. 5), and described by him as a psorperm $\times 400$.

pigs which are produced by chronic irritation. Cell nests have been so fully described and so often discussed that no further notice need be taken of them than to show a photograph of this one, which was artificially produced (Fig. 5). Another point which has struck me in examining preparations of irritated epithelium is the strange diversity in the

size of the constituent cells. In normal epithelium the cells are tolerably uniform in size; in irritated vaginal epithelium the cells are often strikingly dissimilar in size, as is seen in Fig. 6. These cells are so remarkable that I have very considerable doubt whether they are not in reality parasitic amœbæ, as it is known that some forms inhabit the vagina of the rabbit.¹

4. *Circumscribed Collections of Leucocytes.*—Irritated epithelium which has been in contact with pus often presents the appearances shown in Figs. 8 and 9. These are minute cir-

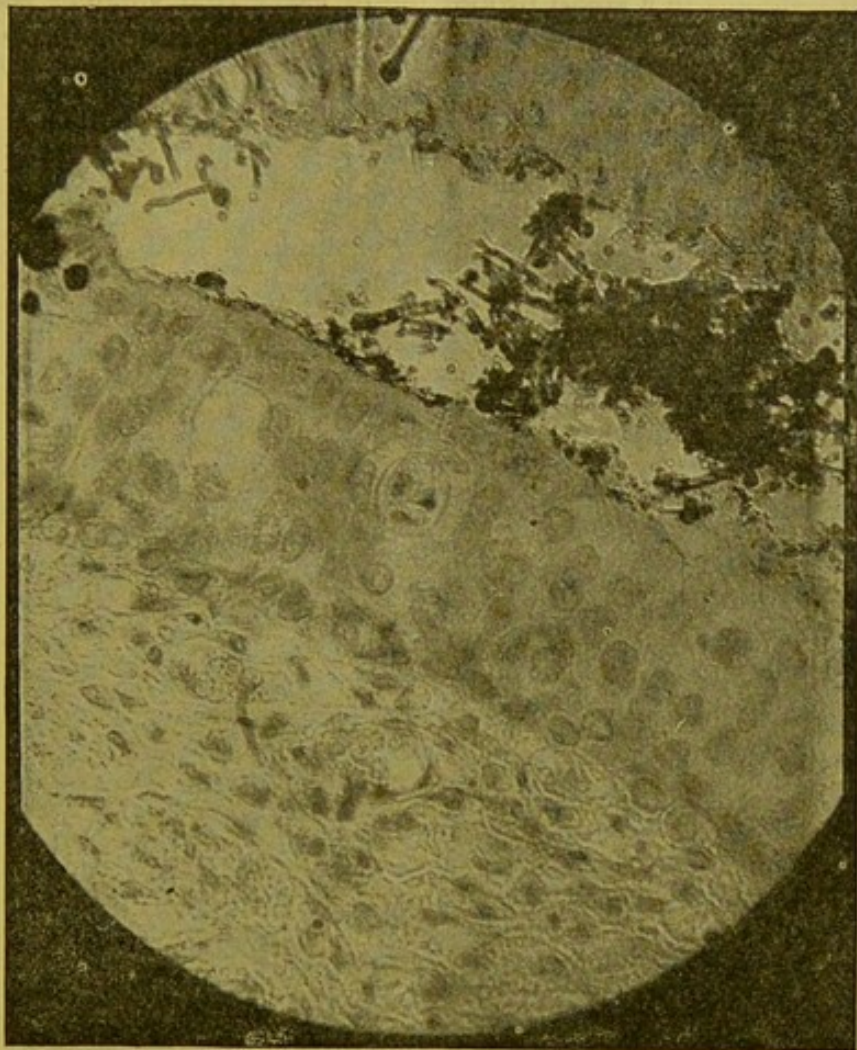


Fig. 8.—A small collection of leucocytes in the vaginal epithelium of a rabbit $\times 400$. Cf. Wickham, *l. c.*, Pl. II, Fig. 8.

cumscribed collections of leucocytes. In some cases they are very minute (Fig. 8), and only consist of two or three corpuscles; in other cases they are larger and resemble large oval cells (Fig. 9), which in growing have flattened their neighbours on every side. These masses are usually well defined, and appear to be enclosed by a definite capsule. The cells are often collected at one point in the capsule, and it is remarkable how little injury these minute collections of white corpuscles do to the surrounding cells,

¹ Fig. 7 shows two other forms of degenerating epithelial cells. The cell on the left, marked A, is of special interest, as it is almost identical in appearance with that described as a psorosperm by Wickham, and drawn by him in Plate II, Fig. 5, of his thesis on *Psorospermiosis*.

though it is obvious from the amount of chromatin present that a certain number of epithelial cells must have undergone complete disintegration. The collections of corpuscles have given rise to a variety of interpretations, some observers describing them as cells undergoing endogenous gemmation, others as parasites. There is no doubt, however, as to their true nature; they are minute masses of leucocytes and nothing more, and the constituent cells are identical with the cells which are so widely scattered in the inflamed sub-mucous tissue.

It happens in a small proportion of cases that some of the epithelial cells completely disappear after irritation and leave nothing but a space behind. The spaces formed in

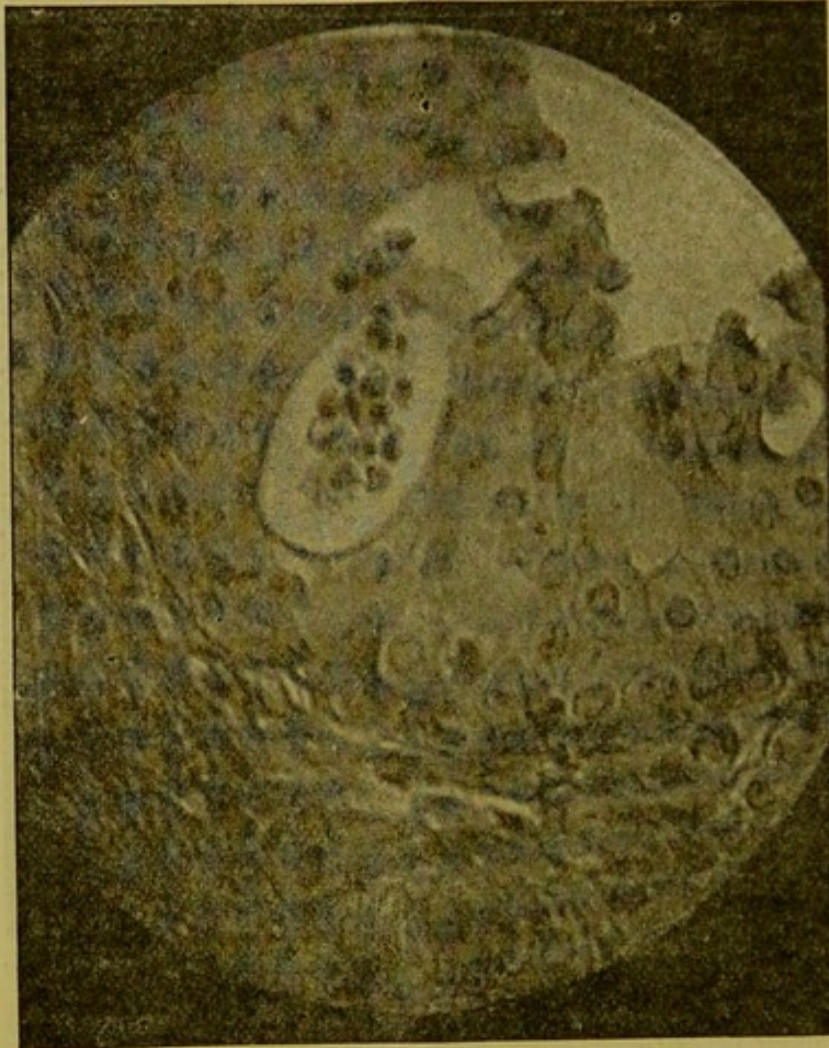


Fig. 9.—The vaginal epithelium of a rabbit showing a larger collection of white corpuscles lying amongst the cells in a well-defined capsule $\times 400$.

this manner are not due to the cells dropping out, but appear to be the result of advanced degenerative changes affecting the entire cell, or in some cases, perhaps, to still further changes occurring in connection with the minute masses of leucocytes just described. These spaces are shown in Figs. 11 and 12. Similar appearances are frequently seen in cases of Paget's disease of the nipple.

5. Noteworthy changes sometimes occur in the lymphatic glands in connection with irritated epithelial surfaces. Fig. 13 represents a section from the enlarged lumbar glands of a white rat, whose vagina had been kept irritated from November 26th, 1892, until March 23rd, 1893, when it was killed. The section presents many of the appearances of an endothelioma. I am sure, however, that the changes are merely the result of the chronic irritation of the neighbouring mucous surface.

I have thought it right to bring forward these few observations at the present time when there is some danger of allow-

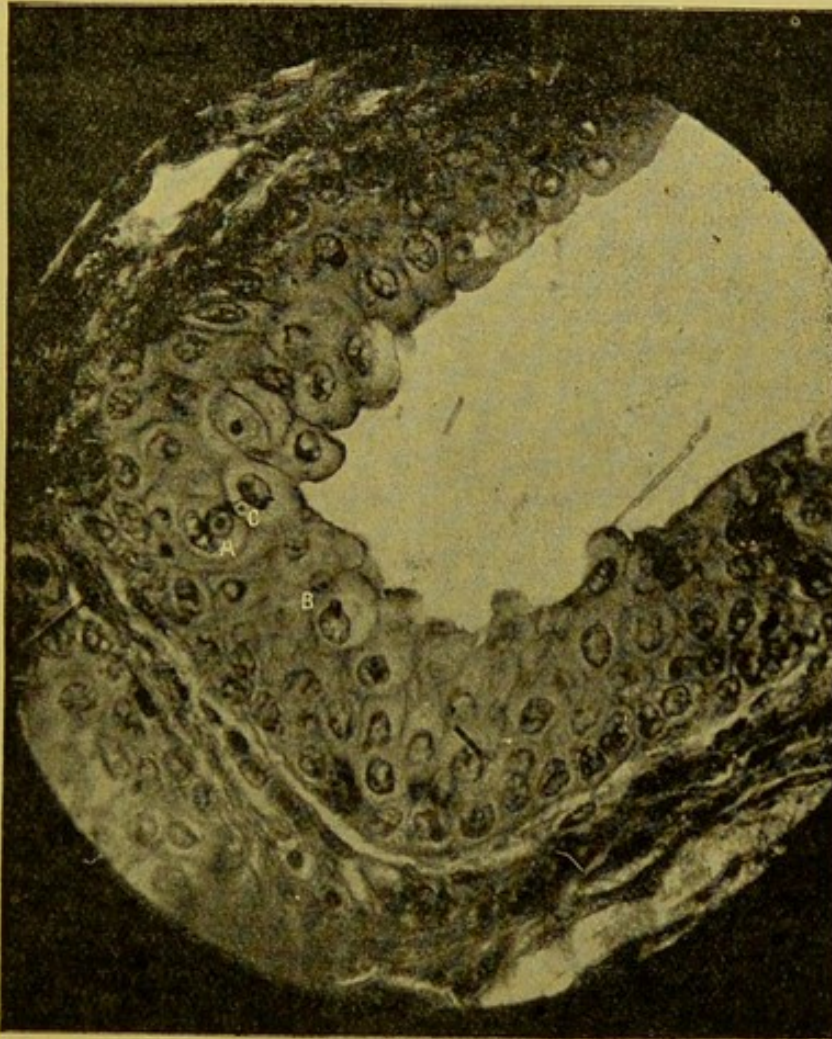


Fig. 10.—Section of the vagina of a rabbit, showing two "cancer bodies" distinctly, and one dimly. The body marked A is intracellular, whilst that marked B is situated above the junction of two cells, and C is very minute, and lies on a slightly different level from A. $\times 400$.

ing a fascinating theory, which is an excellent working hypothesis, to ride roughshod over us. Unless we know what appearances are due to simple irritation, it is impossible to get very far in a histological examination of cancerous tissues from a parasitic standpoint without falling into very serious error. Much steady, continuous, and careful observation of the changes occurring in epithelial cells is still required before we can arrive at any definite conclusion about the ap-

pearances seen in cancer. I hope to have brought into prominence a few of the pitfalls into which we are liable to fall in our search for the cancer organism, if organism there be. I feel very strongly that in all cancer investigations these points connected with cell degeneration should be borne in mind, and I have therefore chosen to entitle my paper "First Steps in a Rational Study of Cancer."

Effects of Inoculating Cancerous Tissues upon Irritated Mucous Surfaces.—I wish now to draw attention to certain results obtained by the introduction of cancerous tissues into the irritated vaginae of rabbits. A piece of a secondary epitheliomatous nodule, obtained from the *post-mortem* room on a very cold day was introduced on February 16th into the vagina of a



Fig. 11.—Vaginal epithelium of a rabbit showing spaces resulting from cell degeneration. The lumen of the vagina contains crystals of the corrosive sublimate used to harden the tissue intermixed with the *débris* of epithelial cells $\times 400$.

rabbit which had been kept sore by the daily application of iodine. The animal was killed during the night of February 18th-19th, by another rabbit who lived with it in the same cage. The generative organs were preserved in Foa's solution, and a subsequent examination revealed the appearances seen in Fig. 10, where it is obvious that the epithelial cells contain those well defined, and circular bodies, described by Ruffer and others, about which there has lately been so much discussion. In the particular piece of epithelium which is here photographed two of the bodies are intracellular (one large and well defined at A, the other c, much smaller) whilst another (B) lies between the cells exactly in the same way as occurs in carcinoma.

I repeated this experiment to make sure that the result was not an accident. On June 23rd a piece of absolutely fresh scirrhus was introduced into the irritated vagina of a rabbit, a wire suture being passed through the vulva to prevent the escape of the tissue. The animal was killed late in the day on June 26th, and its generative tract was also preserved in Foà's solution. Similar bodies were found in some of the epithelial cells.

I do not wish to dogmatise on the results of two experiments, for I may state frankly that I do not yet know how to interpret the appearances which these sections present, nor can I esti-

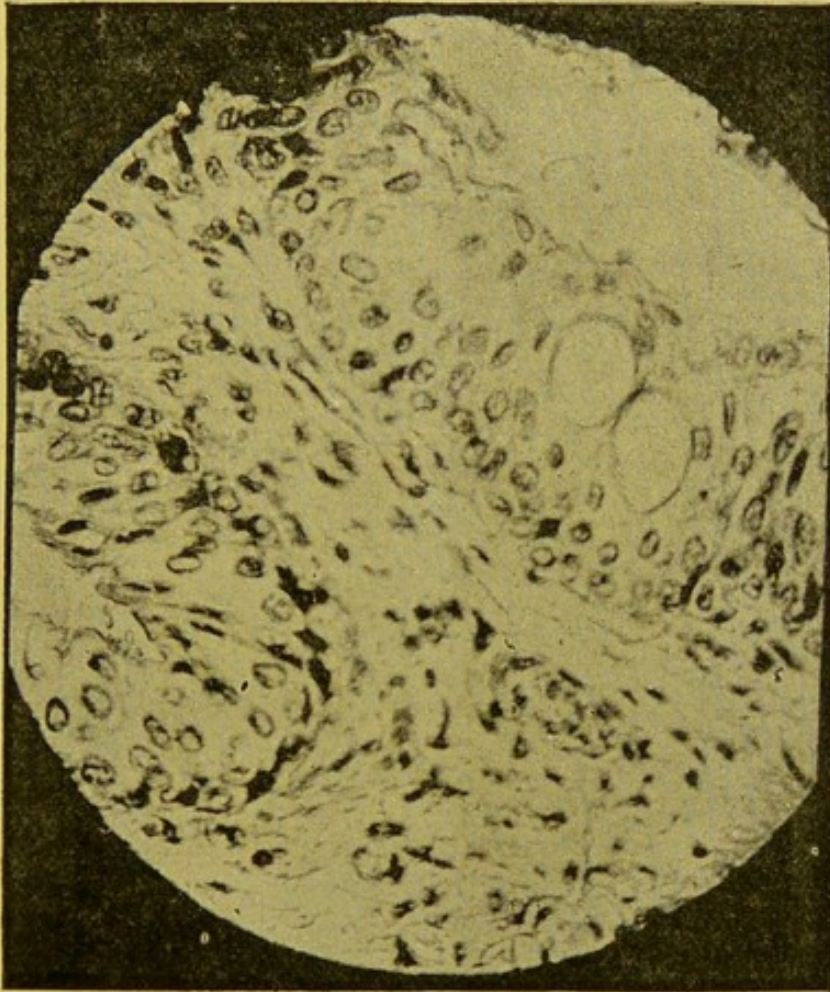


Fig. 12.—Spaces, resulting from cell degeneration, in the vaginal epithelium of a rabbit $\times 400$.

mate the value to be attached to "cancer bodies" in general. I may say, however, that, so far as I have been able to observe, these bodies are entirely different from any epithelial appearances met with as a result of simple irritation, and that personally I have only seen them in cases where cancerous tissues have been brought into contact with mucous membranes kept in a state of chronic irritation. This is suggestive of some relation between cancer and the bodies; and the fact that they are localised to one or two places in the mucous membrane of each animal, and are not scattered

broadcast, is to my mind still more suggestive. It is interesting to notice, on the other hand, that, although the cells containing the bodies are healthy, their nuclei and the nuclei of the cells in their immediate neighbourhood are undergoing very active changes. Supposing, however, that these bodies were merely detached nuclei, it would be hard to explain how they came to lie free amongst the cells, and why they are not much more numerous. However, as one of the bodies is safely ensconced in an epithelial cell, I propose to leave it there without further remark, until abler hands than mine

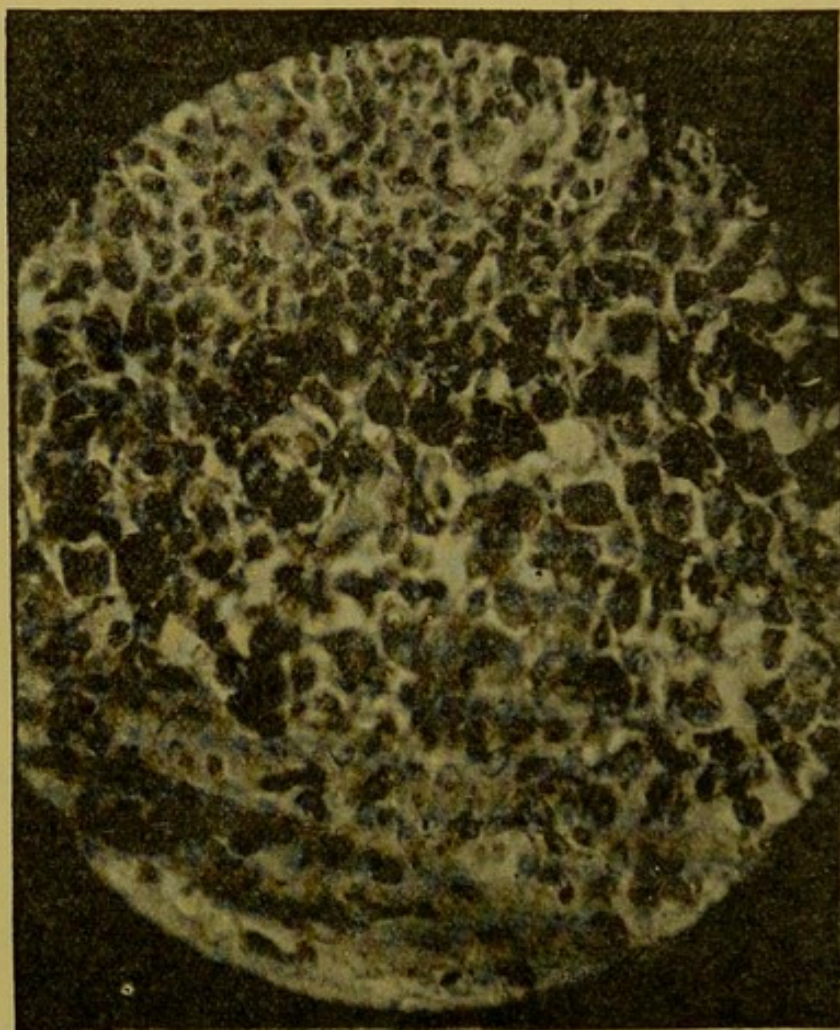


Fig. 13.—Lumbar lymphatic gland of rat whose vagina had been irritated for four months. The section presents many of the appearances of an endothelioma $\times 400$.

have placed others in a similar position. I would merely add for the benefit of those who desire to repeat the experiment, that I have always been careful to select the oldest animal it was possible to obtain, and to have the mucous membrane thoroughly irritated before making any attempt to inoculate diseased tissues upon it.

Finally, it is a pleasure as well as a duty to express to the Laboratories Committee of the Conjoint Colleges in England my very best thanks for the permission they have accorded me to work under their director, Dr. Sims Woodhead.