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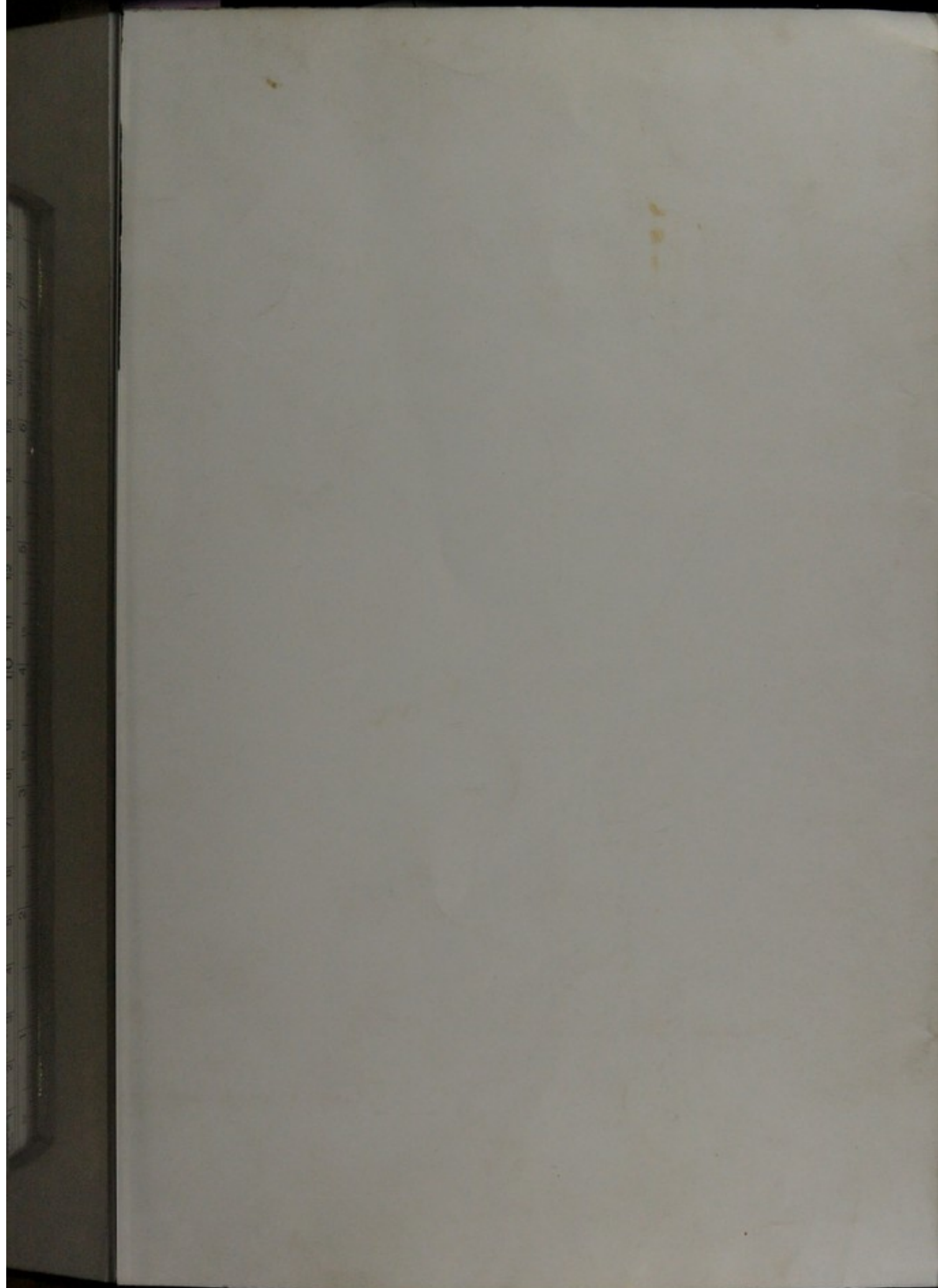
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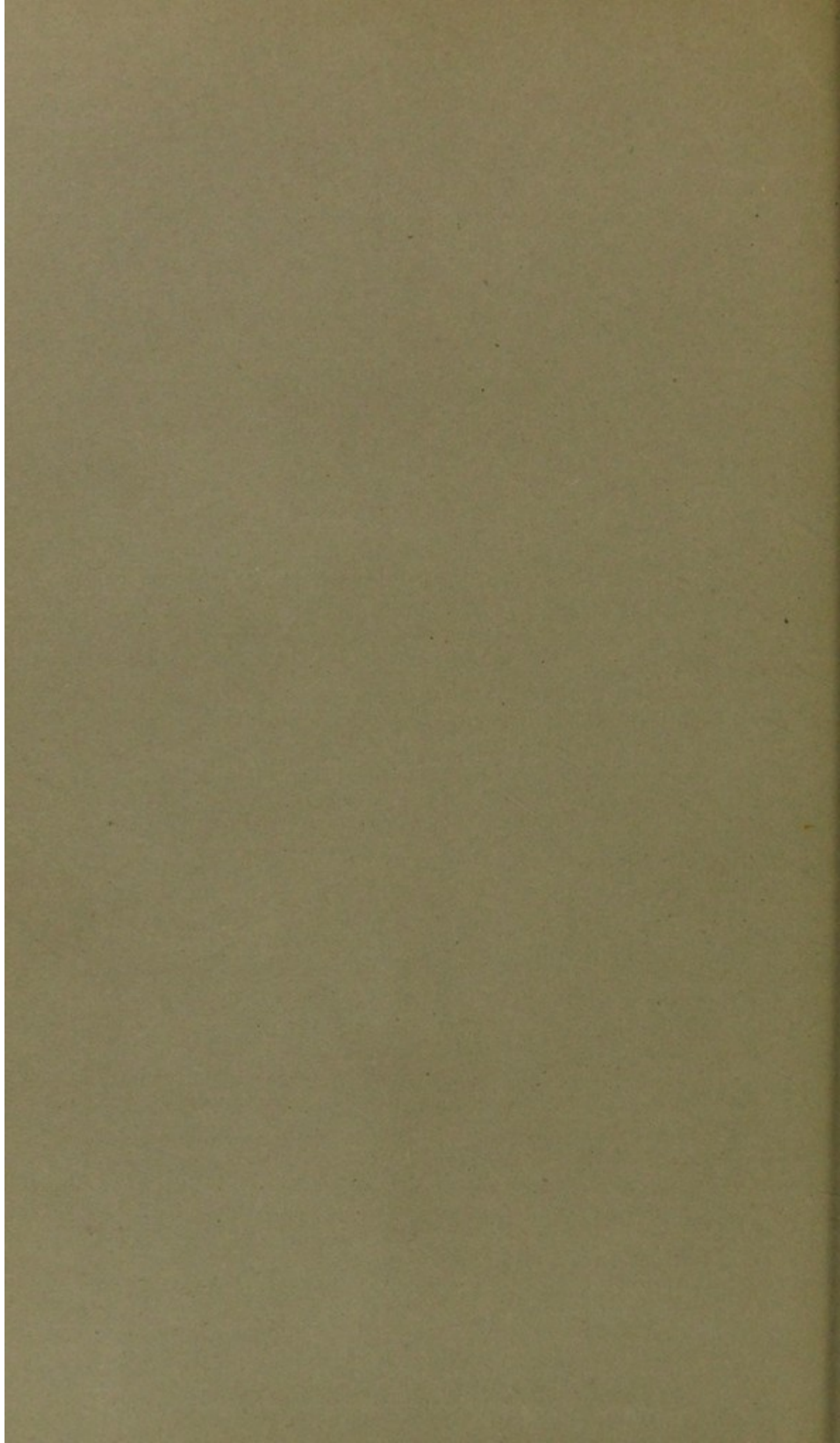
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By D'ARCY POWER, M.A., F.R.C.S (ENG.).



A COMPARISON OF THE RESULTS OBTAINED FROM THE INOCULATION OF PORTIONS OF TISSUE AFFECTED WITH PAGET'S DISEASE AND OF COCCIDIA.

By D'ARCY POWER, M.A., F.R.C.S. (Eng.).

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I PROPOSE in this paper to compare the results obtained from the inoculation of pieces of tissue from cases of Paget's disease of the breast with those produced by the introduction of coccidia to the irritated mucous surfaces of animals. My method of procedure has been to paint the genital organs of white rats and rabbits daily with acetic acid, or with liniment of iodine, so as to keep the vagina or the glans penis in a state of slight irritation for long periods of time. Certain forms of protozoa are said to grow in epithelial tissues, and I thought that the warmth and moisture of the generative organs would be a convenient place for their artificial incubation, whilst the chronic irritation of the epithelial cells might be of service in promoting their development. It is unnecessary here to detail the interesting histological results obtained from this method, as they have already been dealt with in a paper which I read before the Pathological Section of the British Medical Association.¹ Suffice it to say, that I commenced my experiments by the introduction of pieces of freshly-removed scirrhous, encephaloid, and colloid cancers and epithelioma into the generative tracts of properly prepared animals. In no case did I get the remarkable intermittent vaginal discharge, which will presently be described, as occurring after the introduction of pieces of epithelium from cases of Paget's disease of the breast, and of coccidia obtained from the rabbit's liver.

The experiments were as follows:—

I. THE INTRODUCTION OF PIECES OF PAGET'S DISEASE OF THE NIPPLE.

1. I took a portion of breast, including the skin, from a case of Paget's disease of the nipple, and being careful to avoid the immediate neighbourhood of the ulcerated part, within half an hour of its removal from the body I pushed it into the vagina of a white rat which had been kept slightly irritated

¹ *Brit. Med. Journ.* 1893, vol. ii. p. 830.

for a month by the daily application of liniment of iodine. This was done on Friday, and the animal remained apparently unaffected until the following Tuesday, when there was a free discharge from the vagina of a thin whitish fluid, which was not pus. This discharge lasted less than 24 hours, for on the next day the vulva was perfectly dry, and no discharge could be obtained even by pressing upon the abdomen. On the succeeding Friday, a week after the introduction of the tissue, pressure in the course of the vagina yielded a single drop of discharge. There was no discharge on the following Saturday or Sunday, but it reappeared to a very small extent upon the Tuesday, 11 days after the inoculation. At no time was there any thickening of the surrounding tissues, nor was there any enlargement of the lymphatic glands. During the whole of this period I was too busy to make an exhaustive examination of the discharge, but I did examine it microscopically, and I observed that the number of pus cells was extremely small, whilst the number of vaginal epithelial cells was very great. So far as could be seen, there were none of the bodies which present so remarkable a feature in the epithelium of Paget's disease.

2. On Saturday, July 25th, Mr. Jessett removed the breast from a woman, *æt.* 55, who had been suffering for 2 years from Paget's disease of the nipple, with scirrhus. Very shortly after its removal, two properly prepared rats were inoculated with pieces taken from the eczematous epithelial surface. Both animals remained unaffected for the next 4 days, but on Friday 31st a very slight discharge showed itself in one of the rats. Nothing was noticeable on the following day, but on August 2nd there was a slight discharge from the generative organs of both rats. There was no discharge on the 4th or 5th of August, but on the 6th there was a fairly profuse one from both animals. On this day I stained and carefully examined a number of microscopical preparations of the discharge. It consisted almost entirely of epithelial cells which were not materially altered in character; there were hardly any pus corpuscles, and I was unable to detect any "psorospermial" appearances.

3. Portions of Paget's disease of the breast were obtained from a woman, *æt.* 57, who was under the care of Mr. Jessett. On November 5th pieces of the tissue were introduced into the vagina (*a*) of a rat more than two years old, kept irritated since October 28th; (*b*) of a young rat similarly treated since September 22nd; (*c*) of a rabbit irritated since September 22nd; and (*d*) of a guinea-pig. The breast was removed at half-past three, the pieces were at once put into sterilised tubes, which were kept warm until the inoculations were commenced at four o'clock. In each case except (*a*) the vulva was closed by a suture of silver wire, introduced whilst the animals were under the influence of chloroform. The rats were isolated after the operation, as it frequently happens if they are kept together that one will help another to get rid of the sutures. In the old rat there was a slight purulent vaginitis on the following day, November 6th. On the 7th and 8th, however, there was no discharge. On the 9th and 10th there was a serous discharge, which was absent on the 11th and 12th, but was present again on the 14th, 15th, and 16th. There was no discharge on the two subsequent days, but on the 19th there was a slight discharge. On the following day the rat was found dead. The cause of death was the rupture of an enlarged spleen, and was not, I believe, in any way due to the experiment. The spleen weighed 16.2 grammes, and measured 3 inches in length.

In the younger rat there was no vaginal discharge from the 6th to the 12th of November. From the 14th to the 19th there was a slight serous discharge, containing large vacuolated cells and a few pus corpuscles. The discharge ceased on the 20th, and did not reappear. On November 16th I endeavoured to inoculate the discharge from this rat upon the conjunctiva of a rabbit, and

into the vagina of another rat which had been kept irritated with iodine from September 22nd to November 14th, but no result was obtained.

In the rabbit and the guinea-pig the introduction of the tissue was wholly without effect.

II. THE INTRODUCTION OF COCCIDIA FROM THE RABBIT'S LIVER.

The relation of Paget's disease of the nipple to coccidia has of late years been the subject of much controversy. I therefore determined to compare the results here detailed with those obtained from the introduction of the coccidium oviforme, obtained from the livers of rabbits, the conditions under which the two sets of experiments were performed being as nearly as possible identical. With this object in view a properly prepared male and female rat were inoculated with psorosperms taken from the liver of a recently killed rabbit.

1. A piece of the liver containing nodules of coccidia was attached by a suture to the prepuce of the male rat, whilst a small mass of coccidia, freed as far as possible from the surrounding liver substance, was inserted into the vagina of the female rat. On February 12th, 3 days after the inoculation, there was a clear discharge from the vagina of the female rat, but the male rat was unaffected, though some of the tissue was still adherent to its prepuce. There was no further discharge, however, on the next or any subsequent day.

2. On April 23rd I repeated this experiment upon a female rat whose vagina had been kept irritated in the manner described. The animal appeared to be perfectly well for 5 days, both locally and generally. On April 28th, however, a single drop of clear fluid exuded from the vagina. There was no further discharge.

3. On May 5th the experiment was repeated with coccidia obtained from the liver of a rabbit which had died the same day. There was a slight serous discharge from the vagina on the 3rd day, *i.e.* May 8th, but this did not recur.

4. On June 8th a prepared rabbit and rat were inoculated with coccidia from the liver of a wild rabbit, the vulva in each case being closed with a suture. The sutures held until the 12th, and there was no discharge from the vagina until the 15th. On that day the vagina of the rat was gaping, and on pressing in the course of the canal a sudden spurt of clear fluid came from it. Some of this fluid was allowed to dry on a glass slide, and was afterwards stained with Biondi's reagent. Microscopical examination showed that it contained numerous epithelial cells, a few pus corpuscles, and some disintegrated coccidia. On the 21st inst. there was again a discharge of fluid from the vagina. This fluid was carefully examined after it had been stained with Ehrlich's hæmatoxylin. It consisted as before of epithelium with a few pus corpuscles. There were also a number of deeply staining and oval bodies, each provided with a sharply defined capsule. These bodies were coccidia, some of them comparatively unaltered but others in a state of disintegration. There were no sickle-shaped bodies, nor any proof that the coccidia had multiplied. In the rabbit there was a slight vaginal discharge on the 20th. It consisted of pus, and did not contain coccidia. The rabbit throughout remained unaffected.

These two sets of experiments present several points of interest. In the first place it is noteworthy that the introduction, either of coccidia, or of pieces of tissue from cases of Paget's disease of the breast, produce a discharge when they are introduced into the vagina of a properly prepared animal. In each case the discharge presents almost identical characters. It is thin and white, but does not look like pus. Under the

microscope it is found to contain innumerable epithelial cells, but hardly any pus corpuscles. After the introduction of coccidia the psorosperms seen in the discharge are more or less altered, but present no sign of undergoing any multiplication. The introduction of pieces of sarcoma or carcinoma into animals similarly prepared never produces this kind of discharge. After the introduction of pieces of malignant growth, either there is no discharge at all or the discharge is simply purulent. It thus appears as if Paget's disease of the nipple and coccidia had something in common. Elsewhere I have shown that the majority of the appearances described by Wickham in cases of "psorospermiosis" are due to alterations in epithelial cells, or at any rate that similar appearances may be produced in epithelium by artificial irritation. Some of the structures described by Wickham, however, cannot be thus explained, and it is possible that these remarkable forms may be parasitic organisms differing entirely from the "cancer bodies" of Ruffer. It is not at all remarkable that after the introduction of coccidia into the vagina of a rat, coccidia in various stages of disintegration should be found even as late as 13 days afterwards in the discharges of the animal. It is rather remarkable, however, that they should set up the same kind of irritation in the vagina as is produced by the introduction of pieces of epithelium from breasts affected by Paget's disease.

The results which I have obtained may be summed up thus:—In properly prepared animals the introduction into the irritated vagina of the different forms of carcinoma may produce definite histological appearances without causing any vaginal discharge. The inoculation of epithelium from cases of Paget's disease of the breast into such animals produces a well-marked vaginitis, which is intermittent and is characterised by a non-purulent discharge. The inoculation of coccidia gives rise to a vaginitis similar in many respects to that produced by the introduction of Paget's disease of the breast, but differing from it in being much less severe and in lasting for a shorter length of time. These results point to a connection between coccidia and Paget's disease of the nipple, but they are at present insufficient to make any definite statement as to the nature of the connection. Cases of Paget's disease of the breast are of rare occurrence, and my chief object in publishing the results at which I have arrived is to obtain a further supply of material with which to continue the experiments. I would, therefore, ask every reader of this paper who may operate upon a case of Paget's disease, or of cutaneous psorospermiosis, to let me have a portion of the tissue whilst it is yet alive.



