That the uterus is the most frequent primary site of tumours in the rabbit was shown by Polson (1927) and subsequently confirmed by Fardeau (1931). In Polson’s collected series of 67 tumours, including one which was added while the paper was in proof, 31, or 46 per cent, were primary in the uterus. In Fardeau’s series of 73 tumours, 32, or 44 per cent, were uterine. Fardeau omitted 2 of Polson’s series, but included 3 new instances, namely that of Rusk and Epstein (1927) and two unpublished tumours of Paine and Peyron. We now add 3 more reported cases (Watrin and Florentin 1930, Cutler 1934, and Twort 1937), together with an account of 5 new tumours from our own animals, bringing the number of recorded primary uterine tumours in the rabbit to 42. These are briefly as follows:

1. Lack (1900) Adenocarcinoma with widespread metastases, believed by the author to be the result of an experiment, but regarded by Shattock and subsequent writers as a spontaneous tumour.
2. Shattock (1900) Papilliferous adenocarcinoma. No metastases.
9. Leitch (1911-12) Adenocarcinoma. No metastases. Grafted into other rabbits, but “takes” were only temporary.
12-24. Stilling and Beitzke (1913) Thirty tumour nodules in 13 rabbits, including 4 myomata, 1 adenomyoma, and 25 adenomata or adenocarcinomata. The authors do not draw a sharp distinction between the last two terms, and this appears to have led to differences of opinion between Polson and Fardeau in their interpretation of the histological descriptions. An adenoma or adenocarcinoma was present in every one of the 13 animals. Metastases in 2 cases.
27. Dible (1921) Adenocarcinoma. Widespread metastases.
34. Rusk and Epstein (1927) Papillary adenocarcinoma. Widespread metastases.
35. Watrin and Florentin (1930) Decidual tumour of uterus accompanied by active lactation.
38–42. Orr and Polson ......... Carcinoma (?carcinosarcoma). Widespread metastases.
   Adenocarcinoma with metastases, associated with a melanoma of the skin. Active lactation.
   Two adenocarcinomata. No metastases. Active lactation in one.
   Papillary adenocarcinoma. No metastases.

Forty of the tumors were carcinomata, one was a myosarcoma, and the remaining one, recorded by Watrin and Florentin, consisted of decidual tissue. Although this last belongs to a different category from ordinary neoplasms, it is included in the list for completeness. Metastasis was unusual in this series; it was associated with 9 carcinomata and the myosarcoma.

The particular interest of the present communication centers in the first of the 5 new tumors to be reported, which appears to be unique in the range of morphological variation in the histologic picture. Our second case is also unusual, in that a metastasizing uterine carcinoma was associated with a melanoma. The remaining 38 tumours, including our other 3 cases, appear to have been more or less straightforward adenocarcinomata, sometimes containing areas of papillary structure or of solid growth without lumina.

It is possible that some of these tumours were not malignant. Stilling and Beitzke (1913), for example, in their 13 cases frequently leave the diagnosis as between adenoma and adenocarcinoma in doubt. Though this is justified, since the purely histological diagnosis of malignancy is always open to criticism, it has had the result that some of these tumours which were classified as adenomata by Polson were regarded as adenocarcinomata by Fardeau. We have here grouped together all the epithelial tumours of the German authors, who themselves adopted a similar course. In none of the published tumours was dedifferentiation sufficient to give rise to doubt about the parent tissue of the growth, as in our first case.

**Case 1: Uterine Carcinoma, with Metastases; Unusual Dedifferentiation Suggesting Carcinosarcoma:** A fully grown rabbit received (June 19, 1933) an injection, under ether anesthesia, of 0.5 c.c. of 0.4 per cent solution of 1:2:5:6-dibenzanthracene in lard into the left lobe of the thyroid. It received no further experimental treatment, and periodic examination of the thyroid region gave negative results. The animal eventually refused food and lost weight (Jan. 18, 1937) and was killed, being at this time at least four years old.

Necropsy showed a dissemination of growth quite exceptional in the rabbit. The apparent primary tumour was situated in the uterus, the largest mass (4.5 × 3.0 × 1.8 cm.) being in about the middle of the left cornu; smaller foci were also present in both left and right cornua. There was a large secondary mass in each mesometrium; the ovaries were not involved. The growth was firm and cohesive, though easily cut, and was very pale, almost white. The individual deposits had an irregularly lobulated surface.

Numerous peritoneal metastases, mostly of miliary size, but occasionally larger, were scattered throughout the mesentery and omentum, and over the serous surfaces of the stomach and intestines. There was a large secondary nodule in the left kidney and a smaller deposit in the right. Two large isolated metastases were present in the liver. The spleen was free from growth except at the hilum. The left adrenal was involved, but the right was free. The lungs were riddled with metastases. In the posterior mediastinum was a large
mass with necrotic haemorrhagic centre, adherent to the left lung and investing the lower end of the trachea and both bronchi completely, and the oesophagus and aorta partially.

The thyroid and parathyroid glands were normal. The bone marrow was hyperplastic, and the medullary cavities were widened and filled with soft pultaceous marrow of greyish yellow colour and high specific gravity. The tumour was grafted into normal rabbits subcutaneously and intratesticularly, but without success.
Histology: Blocks from the various tumours were fixed in 4 per cent formaldehyde-saline, embedded in paraffin, and stained by Harris' haematoxylin and eosin, Weigert's haematoxylin and van Gieson, Mayer's mucicarmine, Callego's modification of Mallory's aniline blue connective-tissue method, Masson's haematoxylin-acid fuchsia-light green method, and Laidlaw's silver reticulum stain.
The primary tumour in the uterus displays much variation in morphology (Fig. 1). While in some areas it is frank carcinoma, in others its structure recalls that of spindle-cell sarcoma. The "carcinomatous" parts are composed partly of solid acini of polyhedral cells, but more frequently the structure is that of tubular cuboidal-cell or low columnar-cell carcinoma. In these latter parts there is great variation in the size of the lumina, some being quite small, while others are cystic and contain material which gives the staining reactions of mucin. In some places there is intratubular papillary formation. There is little stroma except where the "carcinomatous" and "sarcomatous" parts encroach upon each other; here the latter might give the impression of a cellular stroma. The "sarcomatous" parts consist of loosely arranged spindle cells embedded in a hyaline matrix, which gives the staining reactions of mucin. Silver impregnation of the reticulum fibres shows them dividing the cells of the "carcinomatous" parts into well marked acini and alveoli (Fig. 2), while in the "sarcomatous" parts the reticulin bears no such definite relationship to the cellular arrangement. All the layers of the uterine wall are extensively invaded by the tumour, and the mucosa is ulcerated over it.

The metastases in the mesometrium are "sarcomatous" in structure, the spindle cells in many places being widely separated in a mucinous matrix, while in other places they are more compactly arranged (Fig. 3). Their cytoplasm is acidophile, but not so much so as that of smooth muscle cells; most of them have long, irregular cytoplasmic processes. The nuclei are vesicular, with two or three nucleoli and numerous fine chromatin nodes; mitoses and multinucleated forms are present in moderate number. Collagen is found only in small amounts. The reticulum fibres have the "sarcomatous" arrangement (Fig. 4).

The intestinal metastases examined also have a "sarcomatous" structure, the bulk of the neoplastic deposits being in the subserosa, but occasionally spreading through to give rise to ulceration of the mucosa. A similar type of growth is found in the kidney, in which there is also evidence of a mild degree of the characteristic nephritis of rabbits.

"Carcinomatous" morphology is found in the deposits examined from the mesentery, omentum, and liver. The mesenteric metastasis is mostly solid acinar, polyhedral-cell carcinoma, but occasional tubular areas are present, the lumina containing mucinous material;
collagenous stroma is rather more marked than in the lesions previously mentioned. The omental deposit, from which the unsuccessful transplants were taken, was similar to the mesenteric except that its stroma was more cellular, these cells being typical fibroblasts and different in appearance from the spindle cells of the tumour foci.

In the liver, the structure is mostly solid, lumina are never very prominent, and when present are small; necrosis is a prominent feature, mitoses are unusually numerous, and stroma is scanty (Fig. 5).

In the lung and mediastinum, metastases of both "carcinoma" and "sarcoma" are found, but the deposits of each are separate (Fig. 6), never mingled together. The "carcinomatous" parts are mostly tubular cuboidal-cell carcinoma, with some tendency to papillary ingrowth, but there is also much solid growth without lumina; stroma is scanty, necrosis marked, and mitoses are numerous. The "sarcomatous" foci resemble those found elsewhere.

The adrenals were histologically free from growth, and showed no abnormality; the bone marrow was hyperplastic with a relative predominance of granulocytes, a condition which appears to be constant in rabbits with disseminated neoplasms (Orr 1937).

CASE 2: Adenocarcinoma of the Uterus; Subcutaneous Metastasis; Melanoma of the Skin: A "hare" doe rabbit of about 2 kg. was received into stock during the summer of 1931 and reserved for breeding purposes. Between Sept. 25, 1931, and July 7, 1937, she had seventeen pregnancies, all of which were apparently completed at term, and without complications; no abortions were recorded. The dates of mating and delivery were known, and the period of gestation was usually twenty-eight to thirty days. There are records of 62 young, usually in litters of from four to seven, with seven deaths. The last four litters (November 1934–July 1935) were of only one to three rabbits, and included 4 of the 7 which died. Although the animal was mated four times in the latter half of 1935, no young were produced, and she was then deemed sterile and discarded for breeding purposes.

During 1937 the animal appeared thin, and in May a lump was noticed beneath the skin, on the left side, in the line of the breasts, near the uppermost nipples. The overlying skin
had broken down, and suppuration was present. A second lump was felt beneath the skin over the right shoulder. These tumours were excised under ether anaesthesia in June 1937, at which time a third tumour was found beneath the skin immediately above the pubes. The "breast" tumour measured $3.5 \times 2.0 \times 2.0$ cm. and appeared to be an abscess, being composed of stout strands of connective tissue enclosing creamy material resembling pus. The shoulder tumour was greyish and translucent, $1.5 \times 1.0 \times 1.0$ cm., adherent to the skin, but not to the deeper tissues. The lower abdominal tumour was explored and found to be cystic. No solid tumour tissue was seen on this occasion, and the lesion was thought to be a parasitic cyst, and left in situ. The three wounds healed by first intention, and, although the rabbit appeared to improve, she remained thin. In August the lower abdominal tumour was again large, and on August 10 it was excised. It measured $6.0 \times 2.5 \times 2.0$ cm. and weighed 32 gm. Much of it was cystic, but at the upper end was a cap of solid, cream-coloured tissue. Two small deposits of tumour, each $1.0 \times 0.5$ cm., were found above this large deposit. [One of the small deposits was grafted into a healthy rabbit but failed to "take."] The wound became septic, and on Aug. 17 the animal was sacrificed.

Necropsy showed that there were four tumours in the uterus (Fig. 7), the horns of which, between the tumours, were 1.5 cm. in diameter. The largest tumour, believed to be the primary growth, occupied the outer third of the right horn. Externally, the uterus here resembled one containing a foetus almost at term. The growth was attached to the mesometric border, and measured $6.0 \times 3.0 \times 2.5$ cm. It was solid and varied in color from fawn to dark brown in different areas. A second tumour was situated at the bend of the horn, 3.5 cm. above the external os, and 4.0 cm. from the primary growth. It was approximately spherical, 1.5 cm. in diameter, and from each side a finger-like process of growth passed along and occluded the lumen of the horn. A similar growth, in point of size and position, was present in the left horn. This third growth had also grown in a similar manner to occlude the lumen of the horn. A fourth growth, spherical and approximately 1.5 cm. in diameter, was present at the free end of the left horn. Secondary deposits were confined to the subcutaneous tissues of the anterior abdominal wall. The breasts on the right side were active, and lactation was observed. Except for superficial focal scarring of the kidneys, all the other organs appeared healthy.

Histologically, the uterine growths (Figs. 8 and 9), and the subcutaneous deposits were essentially of like structure, namely, frank adenocarcinoma of columnar-cell type. In some areas papillary arrangement was present; elsewhere there were areas of solid acini without lumina. The lower abdominal deposit (Fig. 10), in addition, was distinctly cystic, some of
the spaces, notably that which was explored, measured several centimetres in diameter. The breast deposit was also affected by widespread necrosis and secondary inflammation.

The tumour over the right shoulder was of entirely different structure; and obviously not a secondary uterine deposit (Fig. 11). It was of lepidic type, consisting of solid masses of polyhedral cells which extended into elongated club-like processes without lumina. A
proportion of the tumour cells contained melanin pigment, which was also present in occasional macrophages. The assessment of the malignancy of melanomata by histological examination is always difficult. In view of the biological behaviour of this nodule, which did not recur after biopsy, and the absence of like deposits elsewhere, we regard it as a benign melanoma.

**CASE 3**: *Adenocarcinoma of the Uterus*: Nothing is known as to the age or previous history of this rabbit, which died Dec. 12, 1932, eleven days after thyroidectomy. At necropsy there was nothing noteworthy, apart from the uterus, which was distended into a sausage-shaped mass, $7.0 \times 3.0 \times 2.0$ cm.; on opening, the interior was found to be lined over fully three-quarters of its extent by papilliferous growth. None of the individual papillae was of any great size, but they were very numerous and closely packed together. The right cornu showed a smaller lump, consisting of a solitary solid spheroidal tumour. There were no metastases.

Histologically, the growth is a columnar-cell papillary adenocarcinoma (Fig. 12). Infiltration of the muscle is slight, and present only in places, and the malignancy of the tumour is by no means indubitable (cf. cases of Stilling and Beitzke).

**CASE 4**: *Adenocarcinoma of the Uterus*: A rabbit known to have been at least 4½ years old at death. Over four years previously, 2.5 c.c. of 0.4 per cent dibenzanthracene in lard was injected into the left kidney, but this was without effect on the kidney, and is almost certainly without significance in relation to the uterine tumour.

At necropsy, the changes of interest were confined to the uterus and breasts. In the uterus a soft fleshy tumour, $3.0 \times 2.0 \times 2.0$ cm., had its centre at the junction of the left and right cornua, and spread to an approximately equal extent into each. There were no metastases. Active lactation was present in all the mammae.

Histologically, the uterine tumour was a tubular cuboidal-cell carcinoma, with occasional areas of solid growth (Fig. 13). Intratubular papillary formation was rarely seen. The stroma was oedematous, containing a moderate number of widely separated histiocytes, but very little collagen. Penetration of muscle was slight.

The mammary glands showed the typical picture of physiological activity, with numerous, closely packed, distended acini containing milk, and lined by cells a large proportion of which showed cytoplasmic vacuolation.

**CASE 5**: *Adenocarcinoma of the Uterus*: A Dutch doe of 1620 gm. was received in May 1935. It was given 5 c.c. of an oily suspension of 3:4-benzpyrene, a dose of 50 mg. per
kilo, intraperitoneally, on June 3, and was killed on June 7. At necropsy there was no trace of the benzpyrene in the peritoneal sac. The liver contained three coccidial cysts, each 3 mm. in diameter, presenting at its surface. The uterus was abnormal in that its left horn was swollen, 1.5 cm. in diameter; the right horn was only 0.5 cm. in diameter, and appeared healthy. When the left horn was laid open in the midline of its free border, a series of

![Figure 12: Case 3: Papillary Carcinoma. X 22](image)

fleshy tumours, superficially resembling placentae in size and appearance, were situated at intervals of approximately 1.5 cm. on the mesometric border of the horn. The intervening mucosa was congested and hyperplastic. The tumours measured $1.0 \times 0.5 \times 0.5$ cm. and the intervening mucosa was as much as 0.5 cm. thick at most points. An attempt to transplant one of the tumours into two healthy rabbits failed.

![Figure 13: Adenocarcinoma with Areas of More Solid Growth. X 22](image)
Histologically, the growths were columnar-cell papillary adenocarcinomata. The endometrial hyperplasia between them was essentially benign.

**COMMENT**

The diagnosis of the unusual tumour in Case 1 is by no means certain. Four possible diagnoses require consideration: (1) carcinoma with great anaplasia, (2) carcinosarcoma, (3) carcinoma with aberrant stroma reaction, (4) teratoblastoma.

The diagnosis of carcinoma with great anaplasia, implying that all the tumour cells were derived from epithelial cells, is the most probable. It appears more reasonable to assume that a malignant epithelial tumour should in part lose its lepidic characteristics rather than that a contemporaneous malignant change should occur in both the epithelium and the connective tissue of the same organ. It is significant, also, that the “sarcomatous” portions appeared to have produced material which yielded the staining reactions for mucin, although it must be remembered that these are by no means strictly specific. Another feature of the tumour, suggesting its wholly epithelial origin, was its wide variation in structure in different lepidic areas.

The possibility that the tumour was a carcinosarcoma, originating from two cell types, is supported by the wide dissimilarity between the lepidic and the hylic cells, most particularly in their nuclear structure. At the same time, the hylic cells all have a strong generic resemblance to one another. The tendency to separate metastases of the two types of growth, and the scanty intermingling in the primary growth, also suggest a carcinosarcoma. It must be remembered, however, that this is equally explicable on the ground that the “sarcomatous” masses resulted from vegetative proliferation from a single group of cells previously dedifferentiated, or, for that matter, even from a single cell; such a tumour would be properly regarded as an anaplastic carcinoma.

It is difficult to accept this tumour as one in which the “sarcomatous” tissue represents aberrant stroma reaction, mainly on the ground of lack of intimate relationship between the “abnormal stroma” and the frankly carcinomatosus portions of the tumour.

The diagnosis of teratoblastoma is rejected because it is difficult to reconcile it with the tendency of the lepidic and hylic parts of the tumour to grow in almost pure strains in individual tumour foci. Had the cells been truly pluripotential, a more intimate mingling of the various cell forms might have been expected.

Of these four diagnoses, we favour that of carcinoma with great anaplasia, although others might well term the growth a carcinosarcoma.

Our second case is the only instance on record of the coexistence of unrelated tumours originating in different regions in the same rabbit. Stilling and Beitzke (1913) found fibromyomata in association with uterine carcinosmata, but in our case the uterine carcinoma was accompanied by a melanoma. It is an unusual case, also, in that melanomata are rare in the rabbit; the only other recorded instance being a melanoma of the eye, probably arising from the ciliary body or iris (Brown and Pearce, 1926).

The tumours in the fifth case, in particular, were associated with notable
hyperplasia of the endometrium, a coincidence to which Leitch (1911-12) and Polson (1927) drew attention. Although it is easy to construct a theory to explain the development of these growths as the result of malignant transition of this abnormal endometrium, it cannot yet be denied that the hyperplasia may equally well be the result, and not the cause, of a malignant neoplasm in the uterus. The relationship of pregnancy as a precipitating cause, or of repeated pregnancies as a direct cause, is another attractive theory. Although the rabbit in Case 2 was known to have been prolific over a period of four years, the evidence that she developed uterine cancer for this reason requires amplification before it can be accepted. Uterine cancers in the rabbit are frequently multiple, and many grow from the mesometric border. This suggests that they arise from placental sites and that there is a relationship with pregnancy, but proof is lacking.

Two of our rabbits with uterine cancer had distinct mammary activity, for not only did a milk-like fluid exude from the breasts (Cases 2 and 4), but in Case 4 there was also histological evidence of typical physiological activity. This was also noted by Watrin and Florentin (1930) in their rabbit, but since its tumour consisted of decidual tissue lactation is more comprehensible. Neither of our rabbits had been pregnant for a considerable time. The rabbit in Case 2 had been segregated for over eighteen months, and that in Case 4 for four years. This coexistence of lactation and uterine carcinoma may or may not be of significance.

Although the rabbits of Cases 1, 4 and 5 had received doses of a carcinogenic hydrocarbon, it is improbable that this was in any way related to the development of uterine cancer. In Case 5, for example, the interval between dosage and death was but four days.

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