The characteristic distribution of uterine cancer in man with a high incidence in the cervix and a low frequency in the fundus does not obtain in the rabbit. Carcinoma of the uterine fundus is by far the most common of all neoplasms in the rabbit (1) whereas cervical cancer has not been observed in our laboratory nor has its occurrence been reported in the literature. The absence of a squamo-columnar junction in the rabbit’s cervix suggests an anatomical basis for the species variation. Unlike the situation in man where columnar and squamous epithelium meet in the region of the external os, the columnar epithelium of the rabbit’s fundus continues uninterruptedly over the cervix and down the vaginal wall to a junction with squamous epithelium at about the level of the urethral meatus. The object of the present paper is to report three cases of epidermoid cancer at this site. The occurrence of cancer at the squamocolumnar junction in both man and the rabbit despite its different location in the two species emphasizes the significance of the junction as a predisposing factor in carcinogenesis.

MATERIALS AND METHODS

The organization and management of the colony of rabbits in which the tumors occurred have been described in detail elsewhere (2). It should be noted, however, that the colony is maintained in active breeding service, the pedigrees and life histories of all animals are known and all abnormalities in behavior or general health are investigated. From September, 1931 to February, 1947, the extent of the present report, the population was made up of 14 pure breeds, including the Belgian, Beveran, Chinchilla, Dutch, English, Havana, Himalayan, Polish, Rex, Sable and Silver Marten, Siamese Sable, French Silver and Tan breeds, and numerous hybrid lines.

The animals of this colony are subjected to weekly examination with particular attention directed toward a search for neoplastic foci. When tumors are found, biopsies are performed at frequent intervals and the natural history of the growth is followed to its termination. In none of the present cases, however, was the presence of the vaginal tumor discovered during life. In all three instances, the animals bore adenocarcinomas of the uterine fundus and had been under close observation supplemented by frequent laparotomy during the year preceding death. Despite such study, no clinical signs indicative of a co-existing vaginal tumor were observed.

Two of the tumors were transplanted after death, utilizing the anterior chamber of the eye as an inoculation site. The technic employed has been described (8).

INCIDENCE

During the 16 year period covered in the present report, approximately 1,100 female rabbits more than 2 years of age came to autopsy and, in each instance, the vagina and cervices were examined. The failure to find cervical growths acquires further significance in view of the fact that the rabbit’s uterus is bicornate and contains 2 cervices. Thus, 2,200 cervices were examined without the discovery of a single tumor.

In contrast 3 tumors were found arising at the vaginal squamo-columnar junction. All were epidermoid carcinomas and, in each instance, metastasis had caused the death of the animal. It is of
interest that 3 extragenital epidermoid carcinomas were discovered in other female rabbits of this same series. One originated in the skin of the cheek (6), another in the skin of the tail and a third in a nipple. Thus, 3 out of 6 epidermoid carcinomas found in the rabbit arose at the vaginal squamo-columnar junction suggesting an increased susceptibility of this region over other bodily parts.

**Age.**—The ages of the 3 tumor-bearing animals at the time of death were 4 years, 11 months; 5 years, 2 months; and 5 years, 6 months. It should be emphasized that the given ages represent the time of death or of complete autonomous development of the tumors and that nothing is known with reference to the age at inception or the duration of the period of development. Postmortem examination was carried out on 29 females of the same age group during the period of study, indicating an incidence of the tumors in the group of approximately 13 per cent.

**Breed.**—One of the tumor-bearing animals was a purebred Havana: the others were complex hybrids. The ancestry of one hybrid involved an Havana male that had sired a parent of the purebred doe but the second hybrid bore no genetic relationship. The first hybrid contained Dutch and Polish blood as well, whereas the other was derived from a series of Belgian, Tan and Chin-chilla crosses.

**Constitution.**—All 3 animals had been bred for constitutional study and were known to carry and to transmit genetic abnormalities. The Havana doe represented a concentration in heterozygous hybrids. The ancestry of one hybrid involved an Havana male that had sired a parent of the purebred doe but the second hybrid bore no genetic relationship. The first hybrid contained Dutch and Polish blood as well, whereas the other was derived from a series of Belgian, Tan and Chin-chilla crosses.

**Fundic adenocarcinoma.**—Adenocarcinomas were present in the uterine fundi of all of the animals bearing vaginal tumors. It should be noted, however, that 23 or 79 per cent of the 29 animals in the same age group were similarly affected and the significance of the association may relate to age rather than to some other factor. Widespread endocrinological lesions comparable to those found in rabbits subjected to the long-continued administration of estrogenic substances are present in all animals bearing fundic cancers and it is assumed that the hormonal changes may be of importance in their genesis. Conceivably, the same factors may be operative in the etiology of the vaginal tumors.

**Mammary cancer.**—Two of the animals showed breast changes comparable with those found in the developmental stages of mammary cancer (2, 4). In one instance the disorder had progressed to the stage of multiple papillomas while in the other, the histological appearance of the tissue sectioned after death of the animal was indistinguishable from cancer. It seems probable that the breast changes in these cases relate to the same hormonal factor concerned in the genesis of the fundic tumors and that their association with vaginal cancers may be on the same basis.

**Toxemia of pregnancy.**—All 3 animals in this series had recovered from one or more attacks of toxemia of pregnancy. The nature of this disorder in the rabbit has been described (5) and its association with fundic adenocarcinomas noted (1).

**DESCRIPTION OF FIGURES 5 TO 10**

**Fig. 5.**—Section at edge of metastatic epidermoid carcinoma in liver of rabbit X7734-3. Mag. X 35.

**Fig. 6.**—Section of fundic adenocarcinoma in rabbit X7634-3. Mag. X 75.

**Fig. 7.**—Section of vaginal wall at squamo-columnar junction of rabbit X7634-3. Mag. X 14.

**Fig. 8.**—Higher power view of epidermoid carcinoma shown in previous photograph. Mag. X 250.

**Fig. 9.**—Section of metastatic epidermoid carcinoma in diaphragm of rabbit X7634-3. Mag. X 250.

**Fig. 10.**—Section of metastatic epidermoid carcinoma in mediastinal lymph node of rabbit X7634-3. Mag. X 250.
Figs. 5-10
It would appear to occupy an analogous position in relation to vaginal tumors. The assumption has been made that the liver damage incident to toxemia of pregnancy results in destruction of the cells normally concerned in the inactivation of estrogenic hormone, and that, as a result, the hormone piles up in the circulation to a carcinogenic level.

**Clinical History and Pathology**

The rabbit, X773-3, a Dutch-Polish hybrid, was first bred at the age of 6 months, and 13 out of the 23 matings carried out during the ensuing 3 1/2 year period proved fertile, resulting in a total of 46 living progeny. The gestation period following the 10th fertile mating was complicated by eclampsia and terminated in a dead-born litter, but no other irregularity distinguished the breeding history of the animal. Approximately a year later, a mass was detected in the uterine fundus and its identity as a developing adenocarcinoma confirmed by laparotomy and histological examination. The animal remained in good condition until a month before death and then, following a rapid weight loss, died at the age of 5 years, 2 months.

At autopsy, confluent masses of soft, necrotic tumor were found arising from the endometrium throughout both uterine horns, and in multiple areas, the growths had invaded and replaced the muscular wall. A firm mass of tumor tissue of different color and consistency was discovered in the posterior vagina opposite the urethral meatus and similar but smaller nodules were scattered irregularly throughout the upper vaginal wall. Metastatic tumor tissue with comparable gross characteristics was present in the omentum, liver, diaphragm, pleura, pericardium and almost completely replaced the lung.

The breeding history of the Belgian hybrid, X7634-3, also began at the age of 6 months and terminated with the discovery of a fundic tumor 3 years later. During this period 7 out of 20 matings were fertile and resulted in 32 living progeny. The course of 2 early pregnancies was associated with acetone breath, urine retention and fetal death but severe eclampsia with convulsions did not occur.

Three laparotomy examinations were made during the 2 year period from discovery of the uterine tumor to death. In each instance, tumor tissue was removed for microscopic study and transfer. Histologically, the tumor presented the usual picture of developing fundic adenocarcinoma. Autologous and homologous transfers were successful and the growth rates corresponded with the developmental stage of the tumor at the time of biopsy.

Several mammary biopsies were performed in this interval to investigate shotty nodules. Histological examination showed cystic disease and papillomas characteristic of the early stages of mammary cancer development in this line.

During the course of physical examination, about the middle of the fifth year of life, the animal's distended bladder was ruptured under pressure of palpation. She was killed immediately and a postmortem examination carried out. The uterus was distended by masses of confluent fungating tumor associated with widespread muscular invasion but without peritoneal extension. A mass of firm, almost cartilaginous tumor encircled the vagina at the squamo-columnar junction and extended upward to the cervix. Small nodules were present in the wall of the urethra and the bladder mucosa was diffusely thickened. In the region of rupture, a mass of tumor protruded into the bladder lumen and extended through the musculature into the peritoneum. Metastatic tumor was found in the inguinal, preaortic and mediastinal lymph nodes, in the diaphragm and in the lung. Other organs were not involved.

The Havana doe, HA550-2, was first bred at the age of 5 months and remained in breeding service for 2 1/2 years. Seven out of 19 matings proved fertile but 2 of these terminated in fetal resorption and a third in mild toxemia with fetal death. The 4 normal pregnancies resulted in 18 living young.

A laparotomy was performed, toward the middle of the third year of life, to investigate a mass noted in one uterine horn. This proved to be a retained placenta but a pronounced endometrial hyperplasia was found and it is of interest from the viewpoint of pathogenesis that a second laparotomy performed 3 months later disclosed a...
FIGS. 11-16

Greene et al.—Carcinoma of Vaginal Wall in Rabbits
small endometrial tumor. The development of this tumor was followed throughout the remaining 2 years of life by means of serial biopsies with histological study and transfer of the tissue.

Mammary changes were noted soon after discovery of the uterine tumor. These were also followed by frequent biopsy and the sequence of changes progressing from simple cystic disease through papillomas to morphological cancer was observed. Despite the presence of all of the histological alterations generally considered characteristic of cancer, transfer of the breast tumor to normal animals was never successfully affected. The rabbit died at the age of 4 years, 11 months, following a rapid weight loss over the period of several weeks. At autopsy, pelvic relations were identified with considerable difficulty. The uterus was replaced by a mass of soft necrotic tumor adherent to the abdominal wall and to the intestine. Innumerable firm nodules were scattered throughout the pelvic peritoneum and mesometrium and, on section, were discovered deep within the fundic tumor. Such nodules were comparable in all respects with the tumor mass found in the vagina. This tumor arose at the level of the urethral meatus, involved the upper two-thirds of the vagina, the urethra and bladder, and extended posteriorly to form a large mass in the pouch of Douglas. Extensions of this mass completely embedded the rectum and the abdominal aorta. The kidneys were hydropnephrotic and contained large metastases. Metastases were also present in both ovaries, the spleen, liver, diaphragm, lung, mediastinal nodes, bone marrow and spinal muscles. Secondary findings at autopsy were the mammary tumor previously mentioned and a large bile duct adenoma involving the greater part of the left half of the liver.

The histology of the tumors is illustrated in the accompanying figures (Figs. 1 to 17). The tumor found in the rabbit X773-3 was a well differentiated epidermoid carcinoma. The growth in X7634-3 was less differentiated and that in HA550-2 was the most anaplastic of the group. The metastases in all of the animals were epidermoid in type and were derived from the vaginal carcinoma. No metastases from the fundic or mammary tumors were found.

**Transplantation of the Vaginal Tumors**

Tumor tissue from the animals X7634-3 and HA550-2 was successfully transplanted to the anterior chamber of the eye in normal rabbits. Transfer of the X773-3 tumor was not attempted.

The tissue used for the transfer of the X7634-3 tumor was derived from a mediastinal lymph node. The percentage of takes increased from 50 per cent in the first generation to 80 per cent in the seventh where passage of the tumor was discontinued. The growth rate varied greatly and was not consistently increased with continued transfer. In some instances, the tumor completely filled the anterior chamber of the eye in 27 days while in others the growth had not reached a quarter of this size by the 150th day. Vascularization occurred early in both types of growth, and apparently played no part in the observed variation. Invasion of the iris was also an early occurrence but extension into the vitreous humor did not occur. The histology of the transplants is shown in Figs. 19 and 20.

Transplantation of the mammary tumor from this animal was unsuccessful. Transfer of the fundic cancer resulted in 100 per cent of takes but the growth rate was extremely slow, the tumor consistently filling one half of the chamber in 230 days.

A metastatic liver nodule was utilized in the transfer of the HA550-2 tumor. A hundred per cent of takes was obtained in the first generation and the incidence ranged from 80 to 100 per cent throughout the 14 serial passages of the tumor. The growth rate was rapid and, as a rule, the anterior chamber of the eye was filled by the 20th day. A feature of interest in the transfer of this tumor was the fact that, in many cases, growth occurred without vascularization and continued until the chamber was filled without the appearance of an independent blood supply. Apparently the cells multiplied and grew in the manner of a tissue culture, deriving their nutrient directly from the aqueous humor. Similar observations have been made in the case of other anaplastic cancers and it seems possible that the disorganized appearance of such tumors may be due to a lack of an ability of their cells to stimulate the adequate growth of stroma. The histology of the transplants of this tumor is shown in Fig. 18.

**Description of Figures 17 to 20**

![Fig. 17.—Section of metastatic epidermoid carcinoma in lung of rabbit HA550-2. Mag. X 250.](Image)

![Fig. 18.—Section of anterior chamber transplant of epidermoid carcinoma from rabbit HA550-2. Mag. X 250.](Image)

![Fig. 19 and 20.—Sections of anterior chamber transplants of epidermoid carcinoma from rabbit X7634-3. The bizarre cells seen in Fig. 20 characterized older transplants. Mag. X 250.](Image)
Transfer of the breast tumor of this animal with material obtained at autopsy was unsuccessful. Transfer of the fundic uterine tumor with material taken at autopsy gave rise to 40 per cent of takes in 3 transplanted generations and the growth rate was slow, a period of 160 days being required for the filling of the chamber. The behavior of the fundic tumor at this transfer was in marked contrast to the behavior of tissue obtained from it at a biopsy 4 months before death. At that time, 92 per cent of takes were obtained in 11 transplanted generations and the anterior chambers were consistently filled with tumor by the 45th day. The possible influence of the developing vaginal tumor on the biological behavior of the fundic growth will be considered in detail in a subsequent paper reporting transplantation experiments with a series of multiple tumors in the rabbit.

**DISCUSSION**

There is little question of the analogy between the squamo-columnar junction on the human cervix and the epithelial junction in the vaginal wall of the rabbit. It is true that both the columnar epithelium of the endocervix and the squamous epithelium of the vagina in man are coelomic in origin, while in all probability, the squamous epithelium of the vaginal wall of the rabbit represents the lining of the urogenital sinus and being derived from ectoderm is embryologically analogous to the external skin. Thus, in man the junction is one between epithelia of common embryological derivation while, in the rabbit, it is actually a meeting of mesothelium and ectodermal epithelium. This difference cannot be considered of great significance in the present connection. The junction in the two species represents the joining of epithelia of different morphological type. Both are subjected to the irritative action of vaginal secretions and the trauma of parturi- tion; neither is stable but fluctuates in location in response to inflammatory stimuli and in effect constitutes a zone of epithelial restlessness.

The occurrence of carcinoma at the squamo-columnar junction in the rabbit despite its different location in this species emphasizes the significance of the junction in the incidence of cervical carcinoma in women.

**SUMMARY**

Three epidermoid carcinomas arising at the squamocolumnar junction of the vaginal wall of the rabbit have been described. The relatively high frequency of cancer at the squamocolumnar junction in both man and the rabbit despite its different location in the two species emphasizes the significance of the junction as a predisposing factor in carcinogenesis.

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Carcinoma of the Vaginal Wall in the Rabbit

Harry S. N. Greene, B. L. Newton and Albert A. Fisk


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