PRIMARY SPONTANEOUS SQUAMOUS CELL CARCINOMAS IN MICE

STUDIES ON THE INCIDENCE AND INHERITABILITY OF SPONTANEOUS TUMORS IN MICE

FIFTEENTH COMMUNICATION

MAUD SLYE, HARRIET F. HOLMES, AND H. GIDEON WELLS

From the Otoho S. A. Sprague Memorial Institute and the Department of Pathology of the University of Chicago

Received for publication April 4, 1921

Throughout most of the animal kingdom primary carcinoma of the skin is met with but rarely, in contrast with its great frequency in man, and also with the relative frequency of other cutaneous and subcutaneous tumors in animals. The existing literature on spontaneous tumors in animals indicates that no species except dogs, horses, and fowls, show skin carcinoma except as a rare condition, and this is of particular significance in view of the fact that skin carcinomas are more certain to be recognized than those in any other location and hence their relative infrequency is even more marked than any statistical evidence would indicate. Presumably the unprotected condition of the human skin accounts for its susceptibility to cancer, as the hairy scalp rarely shows primary carcinoma, and the pigmented skin of the negro also seems insusceptible.

The classical compilation of Sticker (1), which contains records of many tumors not fully differentiated according to modern criteria, gives the following relative frequency in this material of skin tumors in different species:
The extensive compilation by Teutschlaender (2) of the distribution of tumors in animals shows that cases of squamous cell carcinoma have been described in but few species, according to his records, namely: cat, dog, mouse, rat, elephant, beef, sheep, pig, horse, mule, cockatoo, toucan, chicken, carp, and gold fish. However, in another table he mentions also a case in a stag.

Apparently birds develop cutaneous carcinoma somewhat more often than most other animals, but even here there are but few recorded. In their summary of the literature on tumors in birds, Joest and Ernesti (3) found but 4 of 37 tumors described in birds to be skin carcinomas, those being two found on the legs of chickens by Wernicke; one on the wing of a "papapeis"—reported by Guerrini, and one on the wing of a toucan reported by Herbert Fox (4), this last case exhibiting also a metastasis in the lung. In none of their own 50 cases of tumors in birds was a skin carcinoma described. This compilation, as well as all others that we have observed, omits the striking case of squamous carcinoma of the skin of the foot of a hen described by Boynton (5), in which transplantations were made without success. More recently a similar tumor arising on the thumb claw of a lark has been reported by Urra (6). Two cases of squamous cell carcinoma of the mouth in fowls have been described by Pick and Koch. The experience of Teutschlaender (7) is unique, for he reports that of 54 carcinomas in fowls observed in the cancer laboratory at Heidelberg, 28 were skin epitheliomas, of which 18 were on the foot, attributed to the irritation of parasitic infection of the epidermis (C'netidocop-
tesmilben).

<table>
<thead>
<tr>
<th>Species</th>
<th>Horse</th>
<th>Cattle</th>
<th>Dog</th>
<th>Cat</th>
<th>Swine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total carcinomas</td>
<td>332</td>
<td>78</td>
<td>706</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Skin</td>
<td>22</td>
<td>2</td>
<td>166</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Eye</td>
<td>14</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lip</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anus</td>
<td>8</td>
<td>1</td>
<td>89</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Penis</td>
<td>52</td>
<td>2</td>
<td>16</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vulva</td>
<td>11</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Apparently fish are subject to skin tumors of various structure, including carcinoma. Thus, Fiebiger (8) reports cases of epithelioma occurring on the lip of each of two “Schlei” (Tinca vulgaris Cuvier) coming from the same pond, a markedly malignant skin epithelioma in a carp, and mentions papillomatous growths in several specimens of Kletterfish (Anabus scandens). Plehn has also described numerous skin epitheliomas in cyprinoid fishes.

Bashford has reported a squamous cell carcinoma in a small fish, Gasterosteus spinachia, two cases of carcinoma of the skin in frogs, and a carcinoma of the skin glands in a Triton.

Among mammals the dog alone seems to be commonly subjected to skin carcinoma, if we except the carcinoma of the penis and prepuce occurring not infrequently in horses and oxen. It would seem to be not uncommon in cats according to the experience of Roffo (9), who found 7 tumors in 307 cats examined, of which 4 were skin carcinomas on the head and face, with lymph gland metastases, but none of 11 cases of tumors in cats collected by Bashford (10) was of this type, and but 2 of 48 tumors in dogs, although there were several squamous cell growths in the mouth and pharynx. Leo Loeb (11) reported in 1903 that from one to three carcinomas of the inner canthus of the eye were observed every week in the Chicago stock yards, but in one year no other external carcinomas were observed except two of the vulva.

Rodents seem to have skin carcinoma but rarely. The large series of wild rats autopsied in plague work and examined for tumors (McCoy, Woolley and Wherry, Beatti) have revealed no such growths except for an epithelioma of the vulva reported by Woolley and Wherry (12). It will be recalled that the early transplantation experiments of Hansau (13) were with a squamous cell carcinoma from the vulva of a white rat, and he states that there had been two previous cases of similar growths in rats in their laboratory. Roffo (14) has also observed a squamous cell carcinoma which arose in the vulva of an old white rat, which was transplanted through six generations without change in structure. In view of the great frequency of parasitic skin infection in rats,
“rat scabies,” commonly with extreme papillomatous proliferation of the epithelium \(15\), it is strange that epithelioma has not been more frequently observed. Of 123 cases of spontaneous rat tumors reported in the literature and collected by Bullock and Rohdenburg \(16\), there were but three epitheliomas, one of the tongue and two of the vulva. They reported on 48 rat tumors observed in the Crocker Laboratory, one of which was an epithelioma of the head, which was not described further. Morris \(17\) has reported a basal cell carcinoma which arose in the skin of a male rat, five months old, and which died out after two generations of transplants. He was unable to find other recorded instances of basal cell carcinomas in animals.

Several instances of squamous cell carcinoma have been described in mice, but they form an insignificant proportion of the many spontaneous tumors that have been observed in this species. Nevertheless they were looked upon as of great significance in the early days of experimental cancer research, since they established the fact that mice had other forms of tumor than the predominating mammary gland carcinoma. Haaland \(18\) reported a case of squamous cell carcinoma arising in the mouth of a mouse in Borrel’s laboratory, involving the lower jaw, showing a typical squamous cell structure. Six mice were inoculated from this, but as in six months they showed no growths they were put back into the cage with the others. Ten months after the inoculations “deux cas identiques de cette même tumeur apparurent en même temps dans cette cage,” but it was not known whether these were inoculated mice or not and Haaland does not make clear whether these later tumors were in the mouth, although this is apparently what he means. Later he observed a third case of mouth cancer in a mouse recently inoculated with a Jensen tumor. No growths developed in mice inoculated from this mouth tumor.

Murray \(19\) in 1908 described the following cases of superficial squamous cell carcinoma in mice: (1) A prickle cell growth with apparently little keratinization, arising in the skin of the neck, with metastasis into an adjacent lymph gland. (2) A carcinoma presenting both alveolar and squamous cell areas,
with keratinizing metastases in the lung. Presumably this tumor arose in the mammary gland. (3) Prickle cell growth without keratinization, interpreted as primary in the nipple; this mouse also had had a hemorrhagic adenocarcinoma of the mammary gland removed by operation. In discussing the mammary gland tumors he also describes the occurrence of areas of keratinization within tubular carcinomas, and regards them as indications of the close association of the mammary apparatus with the skin from which it develops, and points out that the ampulla which receives the terminal portions of the mammary ducts is also lined by stratified squamous epithelium. "Therefore, should the cells of the new growth have taken their origin near the nipple, variations in either direction are only to be expected."

In his later report from the London laboratories, Haaland (20) states that of 353 spontaneous tumors observed (not including those in Murray's report), 22 were squamous-celled carcinomas with marked keratinization, of which 14 arose in the mammary region and 8 outside it. Of these 8, 3 were mouth tumors similar to those observed in Borrel's laboratory, apparently arising in the mucous membrane of the inside of the cheek, there being in one metastases in the lymph nodes. One seemed to have arisen on the surface of the head, and it penetrated the skull; grafts from this were successful. (The illustrations of these tumors show the gross relations of such tumors so well that we are spared the necessity of reproducing further illustrations.) Three tumors were described as superficial verrucous growths, on the vulva, anus, and left flank. One was a typical squamous cell carcinoma of the skin of the chest, developing as a superficial ulcerating growth, "undoubtedly from the skin itself, or from the mammilla." A case of mixed squamous and sebaceous carcinoma of the vulva is also mentioned.

Several of the keratinizing mammary tumors differ from typical squamous cell carcinomas, and their cutaneous origin is doubtful. Four are described as resembling "molluscoid" tumors, characterized by long radiating cylinders of cells with a central keratinized zone, found in the mammary region and not giving successful transplants. Four tumors are described as "typical
squamous-celled alveolar carcinomata in the mammary region." Six others are called "adenocancroids," these being unquestionably mammary gland adenocarcinomas in which areas of keratinization occur. Attention is called to the occurrence of squamous-celled cysts in the normal mamma, apparently arising from mammary ducts in which the epithelium has become metaplastic, and which perhaps explains the occurrence of keratinizing carcinoma in the mammary gland. As squamous-celled growths have also been found rarely in the human breast, as well as in cats and dogs—Teutschlaender (21)—the disease in mice is not without analogy, although apparently relatively frequent among the mammary gland tumors of this species. Presumably in some stocks of mice keratinization is even more common in mammary gland carcinoma than the above reports indicate, for Woglom (30) found this change in 228 of 1000 spontaneous mammary gland carcinomas examined in the Crocker Laboratory.

Pick and Poll (22) reported as a "sweat gland carcinoma" a tubular growth arising near the scapula of a mouse, but the description published does not permit the exclusion of a mammary gland origin.

Erdheim (23) described a pedunculated tumor, which gave no evidence of malignancy, but exhibited a histological structure resembling squamous cell carcinoma. It arose from the vulva of a mouse, and after the outer part of the growth had been removed the base healed spontaneously. He was unable to classify this tumor, beyond indicating that it was a stratified epithelial neoplasm.

Tsutsui (24) has produced carcinoma on the skin of the back of mice by painting with tar, after the procedure used by Yama-

agiwa with the ears of rabbits, observing 16 carcinomas and 1 sarcoma in 17 mice surviving over 100 days. In two cases lung metastases were observed.

We find no other reports of squamous cell carcinoma arising in the skin or mouth of mice, which indicates their relative infrequency, since such tumors are most obvious when they do occur. Thus, Tyzzer (25) in his report of 83 spontaneous
tumors in mice includes no tumors of this type. In the 41 primary mouse tumors described by Jobling (26) there were no skin epitheliomas, although there was one of the molluscoid keratinizing tumors such as Murray, Haaland, and Tyzzer have described.

Squamous cell carcinomas outside the mammary gland and skin of mice are rare. Tyzzer reported that among his lung tumors “in several cases” the growth was of an epidermoid character, and Haaland described one such tumor. In our previous paper on primary carcinoma of the stomach in mice (27), we collected four cases of squamous cell gastric carcinoma reported in the literature and added three more in our own material, as well as one case of squamous carcinoma in the external surface of a chronically prolapsed rectum. Fiebiger (31) has also reported the occurrence of a few instances of squamous cell carcinoma produced experimentally in the stomach of mice by feeding cockroaches injected with Spiroptera. We have found no reports of squamous cell carcinomas arising in the esophagus or urinary tract, or in the cervix uteri, or in any other structure where they might be found in mice, except such as have been mentioned above.

OBSERVATIONS ON SKIN TUMORS AND SQUAMOUS CELL CARCINOMAS IN THE SLYE STOCK OF MICE

In 28,000 consecutive autopsies performed on mice of this stock, which had been permitted to live as long as possible without any experimental manipulations whatever, we have observed the following instances of primary neoplasms of squamous or stratified epithelial structure.

Primary squamous cell carcinoma of the skin and mouth ............ 70
Primary basal cell carcinoma of the skin ....................... 15
Primary keratinizing carcinoma of the mammary gland .......... 56
Primary squamous cell carcinoma of the stomach ............ 4
Primary keratinizing carcinoma of the lung ............. 1
Primary squamous cell carcinoma of the rectum .......... 2
Primary squamous cell carcinoma of the vagina .......... 1
Primary stratified carcinoma of the meibomian gland .......... 2
Primary sebaceous gland adenocarcinoma .................. 1

152
As we have not yet made a complete analysis of all the tumors observed in these 28,000 autopsies the proportion of stratified cell tumors to total tumors cannot be stated. Roughly there are probably about 4000 primary spontaneous tumors of all sorts, so that these squamous cell tumors constitute not far from 4 per cent of the total.

**CARCINOMA OF THE SKIN**

In our material are 85 malignant epithelial growths arising in the skin, mouth, and lips, excluding those squamous cell growths that seem to be derived from mammary gland tissue and stratified cell growths from other glands. Of these, 70 are of squamous cell type and 15 of basal cell character. Since many of the tumors which arise about the lips and mouth are, when observed, so extensive that their exact point of origin cannot be determined, we have grouped them together with the skin tumors. Roughly classifying the site of the 70 squamous cell growths, 13 were in the skin of the trunk, one on a front limb, 2 on the vulva, 15 about the lower jaw, 18 on some other portion of the face, and 23 about the ears or neck; that is, all but 16 of the 70 were on the head and neck. Presumably this is to be explained by the much greater amount of traumatism suffered by the skin in this part of the body, which is especially marked in cage mice which are always rubbing their muzzles against the rough wire meshes of the cages. The tumors of the jaw and mouth in several instances seemed to have resulted from the irritation produced by broken or protruding teeth. Nearly all of the carcinomas arising on the trunk were definitely located at the site of a healed wound, and in not a few of those of the head the same origin was observed; it is probable that less obvious wounds are responsible for many if not all of the others. A chronic dermatitis often preceded the carcinomas of the skin of the face, presumably incited by traumatism. The not uncommon fungus infections of the skin seem to be too rapid in their course to lead to carcinoma formation.
Clinically these growths are similar to corresponding forms of carcinoma in man (fig. 1). The age at which they occur is, on an average, later than with any other mouse tumors, as they rarely appear before late middle life, and usually only in old age. They arise under crusted ulcers, or develop in areas of hyperplasia from chronic irritation, spread slowly as crusting, ulcerated growths, destroying at times the eyes or other features, usually remain superficial, and most often cause death by chronic infection of the ulcerated surface, which may also lead to acute abscess formation. Occasionally death results from starvation when the cancer involves the mouth or jaw, from hemorrhage, invasion of the skull, or other coincident diseases.

The microscopic diagnosis of the skin neoplasms is often difficult, especially with the basal cell growths, since we find all stages of epithelial overgrowth from simple hyperplasia to metastasizing carcinomas. In this series no growth is included as a carcinoma unless it exhibited both the gross and clinical features of malignancy together with distinct microscopic evidence of infiltrative character. The extensive destruction of these growths by infective processes often obscures the microscopic findings. In several instances a growth that presented
**Fig. 2. Typical Squamous Cell Carcinoma of the Jaw, with Formation of Abundant Epithelial Pearls. No. 23331. × 60**

**Fig. 3. Squamous Cell Carcinoma of the Jaw Infiltrating Adjacent Tissues Extensively. Type with Little Hornification. No. 20238. × 60**
all the clinical features of carcinoma has been found at autopsy so extensively necrotized and suppurating that only examination of numerous sections from different parts of the growth has established the diagnosis of carcinoma. It is quite possible that we have lost a few genuine carcinomas through such destructive processes, to say nothing of cases in which the cannibalistic mate has selected the neoplasm for the first course.

Fig. 4. Squamous Cell Carcinoma of Skin of Chest Arising in the of an Old Wound, the Scar Tissue Being Abundant in this Field, and the Relation of the Cancer Growth to the Overlying Skin Being Shown. No. 8212. × 45

The microscopic features of the squamous cell carcinoma the skin and mouth of mice differ not at all from those that occur in man. Usually hornification is marked (fig. 2), but, as in man, growths from a similar origin may show little or no tendency to form keratin (fig. 3). Usually the amount of connective tissue formation is not large, except in some cases where the cancer has developed in scar tissue from old wounds (fig. 4). Little help in diagnosis is afforded by mitotic figures,
since these are scanty in even the most typically malignant growths, and commonly cannot be found at all. Presumably they would be much more numerous if the tumors were removed from the living animal.

The infiltrative character of growth is not usually so extensive as we are accustomed to see it in man, for the mice generally succumb to infection from the ulcerated growth while it is still small. Infiltration is usually seen best in the tumors that arise about the jaws, for here the bone is often invaded. Bone infiltration was observed in 7 of the 15 tumors that arose about the jaw. We have had one striking case (23766) in which a carcinoma of the skin of the head, beginning at the base of the right ear, infiltrated the skull and cervical vertebral canal, infiltrating the meninges about the cerebellum and compressing the spinal cord in the cervical region (fig. 5). This case resembles

![Image of a tumor](image_url)

**Fig. 5. Squamous Cell Carcinoma of the Head and Face Invading the Spinal Column in the Cervical Region, Compressing the Spinal Cord and Infiltrating the Meninges**

This tumor also invaded the skull. No. 23766. × 60
the one described and pictured by Haaland, in which the skull was invaded. In two instances we have seen infiltration of the salivary glands, and in three cases an adjacent lymph node was involved apparently by direct extension.

The absence of lymphatic metastasis is a striking feature of these tumors when compared with corresponding growths in man, which is true of all forms of carcinoma in mice. In only two cases did we find a secondary growth by metastasis into a lymph node from a skin carcinoma (7950, 15232), and it was a very common observation that lymph nodes immediately adjacent to or in contact with these squamous cell growths, were not involved. Possibly serial sections of all our mice would have revealed other instances of metastasis, but the value of the information did not seem commensurate with the labor involved. In only one case did we find visceral metastasis (12627). This mouse had a squamous cell carcinoma arising just dorsal to the rectum, and a typical secondary nodule about 1 mm. in diameter in the lung; it also had a tubular carcinoma of the mammary gland which had produced no metastasis. The infrequency of metastasis in this series of spontaneous squamous cell carcinoma is significant when compared with Yamagiwa's experimental tumors in rabbits, since the infrequency of metastasis in his material has been thought by some to speak against their being true malignant tumors. As a matter of fact the metastasis incidence obtained by him, and by Tsutsui with experimental skin tumors in mice, is distinctly higher than that observed in these spontaneous growths.

The sex incidence is strongly in favor of the female (49 to 21) in this series. As most of the growths were on the head and neck we cannot account for this on the basis of erroneous inclusion of squamous carcinomas of the mammary gland with our skin tumors. It differs from our experience with other growths of non-reproductive tissues which have shown approximate equality as to sex incidence. Even more than with other tumors we have found that age is an important factor, these squamous cell carcinomas of the skin being predominatingly in old mice, and as many male mice die early from wounds received in fighting
this may account for the relative preponderance of females in this series.

Beyond the relatively slight extent of infiltration and metastasis these carcinomas present no noteworthy differences from human skin carcinomas. Often the amount of keratin scales piled up on the surface is strikingly great, and in one case the carcinoma arose at the base of definite cutaneous horns (25785). There is often a noteworthy amount of calcification of the necrotic scales. Cyst formation is frequently observed, and benign cutaneous cysts have been observed in several mice.

The basal cell carcinomas all arose on the face, ears, and head (fig. 1), 9 of the 15 being in females. Because these growths are of relatively low malignancy, as in man, they present particular difficulty in diagnosis, and we have set aside as 'premalignant' numerous instances of basal cell hyperplasia of marked degree which did not present unqualified proof of malignancy. Quite frequently enormous hyperplasia of the cells about the hair follicles produces tumors of considerable size, and in these may be found areas highly suggestive of malignancy, in that altogether atypical plugs and masses of basal cells are formed, as shown in figure 6. Such growths, which very probably would have shown unqualified malignancy had the mouse lived longer, have not been included among the basal cell carcinomas. In general, basal cell carcinoma in the mouse corresponds entirely to the corresponding growth in man (fig. 7). To quote MacCallum (28), "In spite of the complexity of the downward growing strands all reach to about the same level. Further, it is seen that they are very sharply outlined against the stroma and show little inclination to strew their cells into the irregular crevices of that tissue." We have found the various modifications of basal cell growths commonly described, such as the formation of tubules suggestive of undeveloped hair follicles, hornifying surface areas with typical basal cell growths beneath, and the so-called adenoid epithelioma which seems intermediate between basal and squamous cell growths. Among our keratinizing carcinomas of the mammary gland was one of cells that suggested a basal cell character. No metastases were
Fig. 6. Basal Cell Hyperplasia of an Irritated Muzzle, with Areas of More Atypical Growth

There have been numerous such growths, which are probably properly designated as precancerous, but may be actually malignant. No. 16563. × 60.

Fig. 7. Basal Cell Carcinoma Which was Highly Malignant, as It Entirely Replaced the Face, Destroying Both Eyes, and Forming Tumor Masses in the Orbits. No. 9932. × 90
observed among these cases, although in one, extensive infiltration destroyed both eyes and produced large tumor masses in the eye sockets. Several of these growths arose at the site of distinct scars from wounds.

Despite the fact that these skin tumor mice were all well advanced in age the co-existence of other tumors is lower than that seen in many other forms of mouse tumor. Perhaps one factor in this is that most of the mice with skin cancer had lived beyond the age at which other tumors occur most frequently. It also seems that the heredity of these mice is responsible to some extent, but a complete analysis of this factor has not yet been made. Of the 85 cases, in which 58 were females and 27 males, but 6 showed a carcinoma of the mammary gland, 7 exhibited lung adenoma (including one that also had a mammary gland carcinoma), one had an adenoma of the ovary and one seemed to have pseudoleukemia. Despite the number of old wounds in these mice no cases of sarcoma were observed, presumably because of either old age or ancestry, but one case of carcinoma arising in the mouth and infiltrating the jawbone, showed such a flattening of the deeper cells that for some time we were in doubt whether or not it was an instance of mixed sarcoma and carcinoma. This case (8560) is described and pictured in our article on sarcoma in mice (29).

SQUAMOUS CELL CARCINOMAS OF THE MAMMARY GLAND

The keratinizing carcinomas of the mammary gland form an interesting group, and properly lie outside the scope of this paper, except for the fact that with not a few of them it is extremely difficult to tell whether we are dealing with a primary mammary gland carcinoma or a skin carcinoma arising over the mammary gland. Three types of these tumors can be distinguished.

1. Carcinomas of the mammary gland which are essentially cylindrical cell carcinomas, forming tubules and alveoli, but some areas of which undergo a transformation into stratified epithelium with the formation of keratin, often in large amounts (fig. 8). These are the "adenocanceroids" of Murray and
Fig. 8. Tubular Alveolar Carcinoma ("Adenocarcinoid") of the Mammary Gland with Areas of Keratinization

To the left is seen a band of densely keratinized tissue with no evidence of its glandular origin. No. 13336. × 60.

Fig. 9. Superficial Adenocarcinoid, Apparently Arising in the Ducts of the Mammary Gland

Shows very little evidence of origin in glandular tissue. This mouse also had three other tubular carcinomas of the mammary gland without keratinization. No. 15300 × 60.
Haaland. It is probably of some significance that the keratinization is usually most marked in the portions nearest the cutaneous surface, as if it began in the ducts. The amount of keratinization varies, sometimes appearing in only a few small spots in the tumor tissue, but often extending until little of the original columnar cell type of tissue remains.

![Image of keratinizing cysts in the mammary gland]

**Fig. 10. Keratinizing Cysts in the Mammary Gland**

Such structures are not infrequently found, and may be the precursors of some of the malignant keratinizing carcinomas of the mammary gland. No. 8271. × 40.

2. Squamous-celled keratinizing carcinomas without any evidence whatever of cylindrical cell structure, but arising subcutaneously in the mammary regions (fig. 9). Many of these present no histological evidence that they are derived from the cells of the mammary gland, but they are observed to arise within the gland substance and sometimes are still entirely subcutaneous when the mouse dies. The occasional presence
within the mammary gland of what seem to be simple benign cysts of stratified epithelium with masses of desquamated hornified material (fig. 10) indicates the probable origin of such tumors. When they ulcerate on the surface it may be impossible to differentiate them from primary carcinoma of the skin or nipple, for histologically they differ little if at all from the usual squamous cell carcinoma of the skin. When observed early their origin in the gland beneath the skin is usually the chief ground for recognizing them as mammary gland tumors; nevertheless, the fact that after differentiating, on a histological basis solely, the skin carcinomas from the mammary gland carcinomas we found that nearly all those we had selected as of cutaneous origin had

![Image](https://via.placeholder.com/150)

**Fig. 11. Molluscoid Carcinoma of the Mammary Gland**

This growth, which arose in an inguinal mammary gland, invaded the abdominal wall and protruded into the pelvis, but produced no metastases. A non-keratinizing carcinoma of the mammary gland was also present which produced pulmonary metastases. No. 15022. × 60.
arisen at the site of old skin wounds, indicates that there are usually recognizable differences.

3. Molluscoid carcinomas of the mammary gland, to adopt Borrel's designation of these striking growths with long, radiating cylinders of stratified epithelium with a large central core of keratinized material (fig. 11). These seem to grow out from the tubules near the nipple, as if they arose from the stratified portion of those ducts. They produce ulceration of the surface about the nipple, which greatly enhances their resemblance to the skin carcinomas.

We have little to add to the statements of Borrel, Murray, Tyzzer, and Haaland concerning these squamous cell growths arising within or about the mammary gland, and the excellent illustrations accompanying Haaland's article make any further illustrations by us unnecessary. A few points may be worth recording. Forty-three of the 56 squamous-celled mammary gland tumors may be best designated as of the adenocancroid type, in that they show a greater or less proportion of cylindrical cell structure. Several of these were multiple, as is often the case with primary carcinoma of the mammary gland. In three there were two adenocancroids, one mouse had three, and one had five, four arising distinctly in mammary gland tissue while the fifth arose anterior to the urethra and seemed to have originated in the skin, and this showed no glandular elements. Fourteen mice had an adenocancroid and also one or more other independent mammary gland carcinomas that showed no keratinization. Of these, one (9365) exhibited also a typical squamous cell carcinoma metastasis in the lung; one mouse with three primary adenocancroids (5738) showed a lung metastasis while three mice that had each two mammary gland tumors, one of each type, had pulmonary metastasis of the cylindrical cell type. That is, from 43 cases of adenocancroid of the mammary gland, but one metastatic nodule of adenocancroid has been seen in the lungs, and none in the lymph nodes or elsewhere. Not a few of these mice had also co-existing tumors other than those of the mammary gland, namely, one with a squamous cell carcinoma of the muzzle (9962), one with a malignant ovarian tumor
SQUAMOUS CELL CARCINOMAS IN MICE

(6801), two with uterine fibroids (14370 and 14811); one with a lung adenoma (12098); one with an adenoma of the liver and an adenoma of the lung (9544); one with an adenoma in the lung and a strange growth in a subcutaneous lymph node that might be interpreted as an endothelioma (15622) and one had an intrapelvic sarcoma with metastasis into the liver and also into an ovary which contained in addition a small adenoma (10006).

Two of the adenocancroids were examples of the not uncommon mixture of sarcoma and carcinoma in the mammary gland of the mouse (15412 and 6182).

Only four of our tumors were typical of the molluscoid cancers, although more or less of this character was shown by several of the growths diagnosed as adenocancroids. One of these four mice had also an adenoma of the ovary (496) and another had a benign lung adenoma (5581). None of these four keratinizing tumors produced metastases.

Nine squamous cell carcinomas that exhibited no glandular structure to identify them as mammary gland tumors, were believed to have this origin because they arose beneath the skin, and in most instances did not ulcerate through at any time. These growths, however, seem to be of a more malignant character than the adenocancroids; three of them produced squamous cell metastases. No. 10936, which is remarkable in being the only male with a subcutaneous stratified epithelial growth that seemed to arise in the mammary gland, exhibited squamous cell metastatic growths in the lung, in the mediastinum, and in the chest wall. Another (7950), with three subcutaneous, non-glandular squamous cell carcinomas, showed a metastatic nodule in one lymph node and direct infiltration of a second. No. 13671 with a subcutaneous squamous cell carcinoma and also a cylindrical cell mammary gland carcinoma, had three large metastatic nodules in the lungs all of squamous cell structure. As to multiplicity of tumors in this group there were three independent subcutaneous squamous cell tumors in each of two mice (2239 and 7905), two had a simple cylindrical cell carcinoma of the mammary gland in addition to the squamous cell growth (7526 and 13671), while one had adenomas of the liver and ovary
and one mouse had leukemia (8236). In this group we have included one squamous cell tumor (24858) that differs from the rest in having the non-keratinized tumor elements suggest strongly the appearance of a basal skin carcinoma, although the growth seemed to arise in the mammary gland.

SQUAMOUS CELL CARCINOMA OF STOMACH AND RECTUM

In a previous paper on primary carcinoma of the stomach in mice (27) we collected records of four reported cases of squamous cell carcinoma arising in the cardiac portion of the stomach to which we added three observed in this laboratory. Since that publication we have observed one more case (24367). This was an old female mouse that for some time before death had been isolated because suffering from tape worm infection. The stomach wall in the cardiac portion was much thickened and small white nodules were scattered over the outer surface. No metastases could be found. In the liver was an encysted cestode, and there was a prolapsed rectum showing much thickening of the wall. Microscopically the nodules in the stomach are of squamous cell carcinoma, apparently still quite early but of typical structure. One small nodule of similar structure is found in the omentum. The rectum shows a marked overgrowth of squamous epithelial plugs on the outer, ulcerated surface of the bowel, and with many of these an infiltrative character is suggested, but apparently this lesion cannot be diagnosed as carcinoma.

Another new case of carcinoma of the stomach (25911) is more difficult to classify. A female Peromyscus mouse, nearly four and a half years old, which had been isolated all her life and never bred, refused food for several days before death. At autopsy there was found a marked thickening of the entire stomach wall, particularly at the cardiac end where it seemed nearly solid from wall to wall. A thick white nodular outgrowth 6 by 4 by 4 mm. of similar tissue bound together the stomach, liver, and esophagus, while another nodule 8 by 4 by 4 mm. bound together the pancreas and intestinal mesentery posterior
to the stomach. No other metastases were found. Microscopically this growth is composed of groups of strands of infiltrating epithelial cells, which are not hornified, neither do they form tubules. They grow profusely throughout all coats of the stomach, sometimes forming sheaths about the tubules of the cardiac portion. The nodules outside the stomach are secondary growths of identically the same structure in lymph nodes. It is not possible to be sure whether this carcinoma is derived from the columnar or the stratified epithelial portions of the stomach. While the gross appearances suggested an origin in the cardia, which is the site of all but one of the recorded cases of gastric carcinoma in mice, yet all of these were frankly hornifying squamous cell carcinomas.

The full details of the three other cases of squamous cell carcinoma occurring in this series are published with illustrations in our previous communication (27) and need not be repeated here. To recapitulate them briefly they were as follows:

No. 5802, male two years old. Squamous cell carcinoma of pyloric portion of the stomach, measuring 15 by 15 by 12 mm. A secondary growth 11 by 12 mm. in the mesentery. No other metastases. Some infiltration of the pancreas.

No. 7851. Male, twenty-five months old. Cardiac portion of the stomach is ulcerated and thickened, forming a mass 16 by 12 by 8 mm. No metastasis. Structure, typical squamous carcinoma, infiltrating all coats of the stomach, and invading the adhesions between the stomach and liver.

No. 16440. Female, aged twenty-seven months. At the junction of the cardiac and pyloric portions a thickened mass from 3 to 15 mm. wide surrounds the stomach. Nodules were found in the omentum and mesentery, metastases in lymph nodes. Structure, typical squamous cell carcinoma with some hornification.

In the same paper was published with illustrations the report of a case of squamous cell carcinoma arising in the metaplastic epithelium covering a prolapsed rectum (8345). This was a male mouse, which had had a prolapsed rectum for six months before its death. The growth was not extensive but seemed to be
typically squamous cell carcinoma arising in metaplastic epithelium. Since then we have observed a second similar case.

No. 20052. Female, had a prolapsed rectum for four months before death, which was from hypertrophy of the heart and pulmonary edema. The surface of the prolapse became much ulcerated and after a time showed what seemed to be a proliferation of epithelium. The regional lymph nodes were somewhat enlarged. Microscopically the external surface of the prolapsed bowel shows, in addition to considerable ulceration, areas of definite squamous cell carcinoma, with strands of cancer cells infiltrating through a thick layer of granulation tissue down to but not into the muscularis. Apparently this has arisen from what was part of the cutaneous surface of the anus, and not from metaplastic mucosa as in the previous case. As a possible factor in the inciting irritation, a small piece of wood was found imbedded in the bowel wall, surrounded by granulation tissue and cancer cells.

Carcinoma of the Vulva and Vagina

No cases of squamous cell carcinoma of the uterus have as yet been described in mice, so far as we can learn. Although we have found a few fibromyomas and sarcomas of the uterus, we have met with but one epithelial neoplasm, which was an adenocarcinoma.

Erdheim (23) and Haaland (20) each have described a recurrent verrucous growth of the vulva, and the latter a mixed squamous and sebaceous cell carcinoma of the vulva. Two cases of squamous carcinoma of the vulva have been observed in this series and are included among the 70 squamous cell skin carcinomas. (1) No. 7950. This occurred as a condylomatous growth arising distinctly in the vulva of an old mouse, infiltrating the subcutaneous tissues, and was an unquestionably malignant squamous cell growth microscopically. There was in addition metastatic growth in two lymph nodes in the groin. (2) No. 18928. A growth of a warty character and ulcerating slightly developed on the vulva some time before the death
of the mouse, spreading about the rectum before death. At autopsy there was found in addition an enlarged lymph node attached to the right ureter. Microscopically the external growth is a typical squamous cell carcinoma with much hornification, and not very marked tendency to infiltration. The nodule attached to the ureter was a lymph node containing a cyst lined with squamous epithelium, or, to describe it better, an epithelial cyst covered with a thin layer of lymphoid tissue. The epithelial wall of the cyst is thin, shows no evidence of infiltrative or other malignant character, and hence does not at all resemble a metastatic growth, but it is difficult to explain the presence of such a structure in this location on any other basis.

In addition to these two carcinomas we have observed an excellent case of carcinoma of the vagina.

**Carcinoma of vagina** (no. 22582). This mouse was found, nearly a month before its death, with a 3 mm. pink nodule protruding from the vagina. At the time of its death from pneumonia it presented an ulcerating mass 15 by 12 by 10 mm., about one-half of which protruded from the vulva. It seemed to arise from the vaginal wall, the uterus and bladder not being involved, but it ulcerated into the rectum and was much infected and ulcerated. No enlarged glands or other evidences of metastasis could be found. Microscopically the growth is composed mostly of loose masses of keratinized scales exfoliated from the underlying growth, which infiltrates the vaginal wall as a typical squamous cell carcinoma.

**KERATINIZING TUMORS OF THE LUNG**

As mentioned in our review of the literature, Haaland has described one case of primary keratinizing growth in the lung, and Tyzzer says that he has had "several cases." The influence of heredity on the incidence of tumors of special types is suggested by the fact that of several hundred cases of primary lung tumors in the Slye stock, but one has been definitely found to show keratinization.

No. 13314. A male, age twenty months, which showed no other autopsy findings of interest, had the lower lobe of the left
lung nearly replaced by a yellowish mass, which was distinguished from the ordinary papillary adenoma of the lung chiefly by its color. This made it resemble an abscess, but it was much too hard to be an abscess, and there was no pleural exudate or adhesion. Microscopically the tumor consists chiefly of a mass of hornified scales heaped up in waving, concentric layers. Only at the very periphery are living cells found. Here is a narrow growing border of stratified epithelial cells, differing in no essentials from that seen in epitheliomas of the skin. There is no marked tendency to infiltration, the growth apparently progressing by expansion, but the presence of occasional mitotic figures is noted. About the growth there is much round and spindle cell proliferation and numerous foreign body giant cells are found. Our specimen differs from the one illustrated by Tyzzer in having a smaller proportion of living cells. We are not certain whether this growth represents a true neoplasm or a progressive metaplasia due to some persisting chronic inflammatory condition, but the former seems more probable.

Two other mice have shown somewhat related pulmonary conditions.

No. 10561. This mouse, which had also a carcinoma of the skin, had a benign adenomatous growth in the lung which showed some tendency to stratification, but without keratinization.

No. 25136. A male mouse had in the right upper lobe of the lung a mass 14 by 12 by 10 mm. resembling in appearance a malignant tumor of the lung. Microscopically this tissue resembles much more closely an unresolved organizing and necrotizing pneumonia, in which are two irregular, independent areas composed of masses of keratinized scales, with a slender border of flattened epithelial cells. It is quite impossible to decide whether this is a true tumor, or whether it is the cause or the result of the pneumatic condition, although the epithelial growth has the appearance of being much older than the pneumatic process.
TUMORS OF THE MEIBOMIAN GLAND

Two mice have presented growths arising in the eyelids, which, according to their structure, seem to be adenomas arising in the Meibomian glands.

No. 18099. A small, slowly growing mass developed beneath the left eye of a female mouse; from the eye exuded a small amount of thick white exudate. The growth had reached a diameter of 10 mm. when the mouse died from an acute lung infection, and showed no evidence of infiltration or ulceration. Microscopically the growth is composed of papillary structures covered with many layers of epithelial cells. It differs from the normal Meibomian gland in the exaggeration and lawless arrangement of the structures, and the greatly increased number of epithelial cells covering the stroma. The diagnosis of benign adenoma of the Meibomian gland seems justified, especially in view of the size of the growth and the findings in the next case.

No. 27929. An old female mouse, which died of chronic nephritis, had a soft mass, 6 mm. in diameter, beneath the left eye. The gross appearance suggested an epithelioma. Microscopically this tumor is quite the same as the one described immediately above, except for the important fact that it infiltrates down to the bone of the orbit, thus indicating that it is a malignant infiltrating adenocarcinoma.

SEBACEOUS GLAND ADENOCARCINOMA

Such tumors have been described in mice by Murray, Tyzzer, and Haaland, the last two having transplanted them successfully. We have found one case of sebaceous adenocarcinoma of the preputial gland, which closely resembles the growth described and illustrated by Haaland (20).

No. 19895. Beginning at the base of the penis is a mass 30 by 25 by 25 mm. extending well into the inguinal region. The penis was completely imbedded in the tumor, the older portions of which were softened, but about the periphery were hard nodules of newer growth. The testicles and epididymis were
not involved. Death resulted from chronic nephritis. There were no metastases. Microscopically this tumor (fig. 12) reproduces closely the normal structure of the preputial gland, but not infrequent infiltration of the stroma by strands of epithelial cells corroborates the gross evidences of malignancy. It corresponds perfectly to the illustration given by Haaland, who also comments on the close resemblance to the normal gland in spite of the definitely malignant character.

**SUMMARY**

Among 28,000 mice dying natural deaths at all ages, and carefully autopsied, have been observed 153 growths of stratified and squamous epithelium that correspond by the usual
SQUAMOUS CELL CARCINOMAS IN MICE

Standards to true neoplasms, excluding a considerable number of epithelial growths which lack positive conclusive evidence of neoplastic character, although possibly some of these are also early carcinomas. Seventy-one are examples of squamous cell carcinoma of the skin or mouth. They differ from the human skin carcinoma chiefly in a low incidence of metastasis. Fifteen others are of basal cell character, arose always about the head, and produced no metastases. In both these groups the incidence is higher in the females than in the males. Trauma and chronic irritation seem to play an important part in the production of skin carcinoma in mice, most of our cases occurring about the head and face, often recognizably at the site of wounds, and nearly all the skin carcinomas of the trunk arose in old scars. Skin cancers occur at a greater average age than other tumors in mice.

Fifty-six examples of squamous cell keratinizing growths arising in the mammary gland were observed, predominatingly adenocarcinomas with localized areas of keratinization. These also seldom produce squamous cell metastases.

Other tumors in this group were: Four squamous cell carcinomas of the stomach, two arising in the prolapsed rectum, two in the vulva, one keratinizing tumor of the lung, one sebaceous adenocarcinoma of the preputial gland, and, as hitherto undescribed mouse tumors, one squamous carcinoma of the vagina and two adenomas of the Meibomian glands, one of these being infiltrative and apparently malignant.

The literature of the comparative pathology of squamous cell carcinoma in animals is reviewed, and it is worthy of comment that as yet no cases of squamous cell carcinoma of the uterus, bladder, or esophagus seem to have been described in mice.

REFERENCES

(1) STICKER: Arch. f. klin. Chir., 1902, lxv, 616, 1023.
(4) FOX: Jour. Path. and Bacteriol., 1912, xvii, 217.
(6) URRA: Rev. de med. y cirug. práct., Madrid, 1918, exviii, 321.
(11) Loeb: Arch. f. klin. Chr., 1903, lxx, 845.
(24) Tsutsui: Gann, 1918, xii, 17.
(29) Slye, Holmes, and Wells: Jour. Cancer Res., 1917, ii, 1. Fig. 3.