A NEOPLASTIC DISEASE OF THE KIDNEY OF THE FROG, RANA PIPiens

II. ON THE OCCURRENCE OF METASTASIS

BALDUIN LUCKE

(From the Laboratory of Pathology, School of Medicine, University of Pennsylvania, Philadelphia)

Tumors of the kidney having the histologic structure of adenocarcinoma have been observed in about 2 per cent of several thousand leopard frogs (1). Like human carcinoma, these frog tumors are non-encapsulated, they invade and destroy the adjacent renal tissue, and

![Figs. 1 and 2. Dorsal and Ventral Views of Frog 127 F 15](image)

The vertebral column has been removed. The dorsal view (left) shows the huge renal tumor which has destroyed all but the tip of the lower pole of the right kidney (this appears as a small triangular body contrasting by its darker color with the ivory white tumor). The ventral view (right) shows several small tumor nodules in the liver and a large round tumor which occupies the site of the urinary bladder. The white tissue lying between this tumor and the stomach is part of the renal growth. The small mass at the side of the bladder tumor is part of the oviduct.

many exhibit evidence of rapid growth as indicated by the presence of numerous mitotic figures, but unlike human carcinoma the tumors rarely metastasize. In the series of 158 cases previously reported no instance of metastasis was observed. This apparent absence of metastasis seemed, therefore, to be a fundamental difference between this neoplastic disease of frogs and histologically similar tumors of man.

1 This investigation has been aided by grants from the International Cancer Foundation and from the Faculty Research Committee of the University of Pennsylvania.
However, in examining 118 additional cases of frog tumors, three examples of metastasis have been encountered. In the present communication these three cases are reported, and the occurrence of metastasis in cold-blooded animals in general is discussed.

**REPORT OF METASTATIC TUMORS**

1. **Adenocarcinoma of Both Kidneys and of Urinary Bladder; Multiple Metastases to Liver:** In a female frog of average size there was a large tumor which had replaced the entire left kidney and all but the lower pole of the right kidney (Fig. 1). The mass measured $38 \times 27 \times 15$ mm.; it was ivory-white, solid, and coarsely lobular. The cut surface had the same color, and appeared nearly homogeneous; no grossly visible blood vessels were present. A separate and somewhat smaller tumor, $17 \times 14 \times 8$ mm. in its greatest dimensions, occupied the site of the urinary bladder; no trace of the latter could be found. The tumor was solid, had a smooth surface, and closely resembled the larger growth (Fig. 2).

![FIG. 3. REPRESENTATIVE AREA FROM TUMOR OF THE KIDNEYS FROM CASE I (X 125)
Contrast with Fig. 5.](image)

In the liver there were a number of circumscribed whitish nodules 1 to 2 mm. in diameter (Fig. 2). Four of these tumors extended to the anterior surface of the liver; others were confined to the interior. Histologically the tumors of the kidney, bladder, and liver were of similar structure, namely, irregular gland-like tubules usually composed of several layers of cells (Figs. 3, 4, and 5). The stroma, while definite, was scanty; there were few blood vessels. Mitotic figures were fairly abundant. Nuclear inclusions were not observed in any of the tumors in this frog. The renal tumor had a somewhat more compact appearance than did the tumors of the bladder and liver; in many areas of the latter the glandular spaces were dilated, and into many of them projected papillary processes.

2. **Adenocarcinoma of Both Kidneys; Metastasis to Liver and to Orbit:** In this specimen, also a female of average size, which, however, had not previously been used

---

2 This frog (127 F 15) is one of a series which had received an intracranial inoculation of tumor cell suspension; it died 176 days later. While in a considerable proportion of frogs inoculated by various routes tumors were subsequently found in the kidneys, this and frog II are the only inoculated animals in which tumors were found outside the urinary tract. For reasons stated below, these tumors are regarded as metastatic.

A further discussion of the results of transmission experiments must be deferred until the series is completed.
Fig. 4. Low-power View of Two of the Hepatic Tumors in Case I

Note that they are well circumscribed. The black markings in the liver tissue are due to chromatophores normally present in this species.

Fig. 5. Edge of One of the Liver Nodules Shown in Fig. 4, at Higher Magnification (× 125)

The tumor is seen to have the same general structure as the principal growth in the kidney. Contrast with Fig. 3.
for experimental purposes, the upper half of the left kidney was replaced by a solitary ivory-white tumor of roughly globular shape and measuring about 10 mm. The right kidney was the seat of two separate tumors each about 4 mm. in diameter.

![Image](image_url)

**Fig. 6. Section through Tumor of Left Orbit in Case II**

The tumor is the dark mass to the right. The cornea is seen at the top of the photograph with the lens beneath. Note the lateral compression of the eye and the displacement of the crystalline lens.

![Image](image_url)

**Fig. 7. Another Section through Tumor of Left Orbit in Case II, to Show Its Relation to Harder's Gland, Which Is the Mass Occupying the Greater Part of the Right Half of the Photograph**

To either side of the gland are portions of the tumor.

A tumor of similar color and about 1.5 mm. in diameter was found just below the surface near the anterior border of the liver. Another and much larger occupied the greater part of the left orbital cavity. It was located chiefly on the nasal side of the eye. In shape it was oval and it measured 7 × 4 × 4 mm. Its anterior portion extended to
the inner canthus; the posterior portion was in contact with the optic nerve. Above and below the tumor was approximately bounded by the recti muscles. In sections the growth was seen to be firmly united to the adjacent sclera without, however, infiltrating the latter.

The general relation of the tumor to the eye is shown in Fig. 6. It is seen that the eye is greatly deformed by lateral pressure from the neoplasm. The crystalline lens is

![Fig. 6. Representative Area from One of the Renal Tumors of Case II (x 125)](image)

...dislocated, the various layers of the eye exhibit degenerative changes (edema of retina, separation of pigment epithelium, hyperemia and detachment of choroid, etc.).

Serial sections disclosed no infiltration of the eye proper, but the tumor was found to involve Harder's gland (which corresponds to the lacrimal gland of man). It appears that the tumor either grew out from this gland or else freely infiltrated it (Fig. 7).

The structure of the tumors in the kidney, liver, and orbit are remarkably similar (Figs. 8, 9, and 10). As in the preceding case, the general appearance is that of adeno-
carcinoma. There are many mitotic figures. Intranuclear inclusions, such as have been
described as characteristic of this disease, are present in considerable numbers in the renal
and orbital tumors, but they are not clearly defined in the hepatic tumor.

III. Adenocarcinoma of Both Kidneys; Metastasis to Liver: The third specimen
(B 126 F 7) was again an average-sized female. Like frog I it belonged to a series

which had received an injection of tumor material, in this case intraperitoneally. It
died 129 days later. (For further comments see footnote on page 327.)

The right kidney was nearly replaced by an ivory-white solid tumor which measured
13 × 8 × 7 mm. The lower half of the left kidney was the seat of a smaller and other-
wise similar new growth measuring 8 × 7 × 5 mm. The liver was externally normal, but
two circumscribed white nodules, each about 1.5 mm. in diameter, were seen on the cut
surface. Microscopically the renal and hepatic tumors were identical in structure and
closely resembled those described in the two preceding cases, i.e. the growths had the
appearance of adenocarcinoma. Many mitotic figures were present; typical nuclear
inclusions were not observed.

DISCUSSION

Three questions arise concerning the nature of the tumors described:

(1) Are they true metastatic growths originating by dissemination
of cell emboli from primary tumors?

(2) Are they due to dissemination of a tumor-producing agent which
has excited to neoplastic growth cells in several organs?

(3) Are they multiple primary growths which have arisen inde-
pendently?

While at present it may not be possible to give a decisive answer to
these questions, the evidence at hand indicates metastasis from primary
tumors of the kidneys. In all but one of 276 frogs in which this neo-
plastic disease has been observed, the tumors were located in the
kidneys,8 which may therefore be regarded as the characteristic primary
site. The histologic structure of these tumors is, in the great majority,

8 The exception is a case of bilateral massive retroperitoneal tumors without involvement
of the kidneys (1).
very similar. In the three cases reported the structural type of the renal neoplasm is so accurately preserved in the tumors of the other organs involved that the origin of all of the tumors from the same kind of cells appears to be most probable. The close histologic resemblance of tumors in several organs having dissimilar structure makes unlikely the second or third of the suppositions mentioned above.

Another point in favor of the view that the renal tumors are primary and those of the other organs metastatic is the fact that the latter are less infiltrating than are the renal tumors.

**FIG. 11. EDGE OF ONE OF THE HEPATIC TUMORS IN CASE III (× 80)**

The growth is well circumscribed but not encapsulated. The liver tissue adjacent to the tumor is normal, the black markings representing chromatophores. The insert shows a field at higher magnification (× 650) with two mitotic figures, only one of which is in focus.

**TUMOR METASTASIS IN COLD-BLOODED ANIMALS GENERALLY**

It has repeatedly been stated in the literature that tumors of cold-blooded animals show less tendency to metastasis than do human neoplasms (2-7). Such statements are based largely upon study of neoplasms in fish, the only class of cold-blooded animals in which a considerable number of tumors have been observed. Thus Thomas (4) in a recent review collected 270 cases of tumors (exclusive of osteomas); of these, 40 were regarded as malignant epithelial growths and 106 as sarcomas of various kinds. Among them he found about

4 This does not necessarily mean that neoplastic diseases in fish are more common than in amphibia or reptiles. Probably the great economic importance of fish has led to a more systematic investigation of their diseases.
A NEOPLASTIC DISEASE OF THE KIDNEY OF THE FROG

10 cases of metastasis. The sole investigator who questions the alleged rarity of metastasis of malignant tumors in fish is Takahashi (3), who reports the finding of three examples among (approximately) 20 tumors that are probably malignant.

The literature on tumors of frogs has been reviewed in the first paper of this series (1). To the 15 more or less complete records, two others (8, 9), previously overlooked, must be added: a carcinoma of the skin glands in a bull-frog and a fibroma of the mouth cavity in a European edible frog. Including these, the group contains 10 tumors probably malignant: 5 adenocarcinomas of skin, 2 adenocarcinomas of the kidney, 1 of the ovary, 1 hypernephroma, and 1 sarcoma of the foot with multiple metastases to liver. This last appears to be the only example of metastasis to a distant organ. Several of the multiple skin cancers may represent either multiple primary growths or secondary tumors by direct extension from a single primary growth.

There are in the literature 4 reports of tumors in amphibia other than frogs, namely, two cases of fibroma of the foot in Japanese giant salamanders (11, 12), one of carcinoma of the testis in the same species, with alleged metastasis to another portion of this organ (7), and one of carcinoma of the skin glands in a triton (13).

Of tumors in reptiles I have been able to find 10 records. Two of these occurred in snakes: a fibroma in a python (9) and a medullary carcinoma of the ovary with multiple metastasis to the liver, lung, and kidneys, also in a python (14). Of tumors in lizards there are 3 reports of multiple papillomas of the skin, said to be common in several European species (6, 15, 16). In addition there have been described multiple enchondromas in an Indian monitor (14), and a non-metastasizing carcinoma of the foot in a South American teju (12). There are 3 cases of tumors in turtles: an adenoma of the thyroid of a Brazilian species (7), an adenocarcinoma of the stomach of an elephantine turtle (17), and a sarcoma of the heart of a sternothere turtle (17). Lastly in a crocodile there has been found a sarcoma of the liver with metastasis to the heart and brain (17).

Analysis of these reports discloses that a total of 29 cases of amphibian and reptilian tumors are now on record. Of these, 15 may be considered malignant. Two of this group unquestionably metastasized to distant organs (sarcoma of a frog; carcinoma in a python);

Because these reports are somewhat inaccessible, brief abstracts are given here.

**Adenocarcinoma of skin glands (Duany, 8):** In a bull-frog brought to Havana some years before from the United States there were found two cutaneous tumors. The smaller, about the size of the frog's eye, was situated between and slightly posterior to the eyes. A larger tumor, about the size of the frog's head, was situated directly back of the smaller growth. The tumors were not adherent to the underlying structures. Histologically they consisted of atypical glands which bore some resemblance to the skin glands; there was a definite supporting stroma. No metastasis to internal organs was present. The author discusses whether the smaller may be a metastasis (or extension) from the larger neoplasm. He considers his case similar to those reported by Murray and by Mason and Schwartz. An abstract of these papers will be found in the previous communication (1).

**Fibroma of mouth cavity** (Vaillant and Pettit, 9): In connection with a report on a tumor in a python the authors briefly mention a fibroma of a frog, *Rana esculenta*. The tumor originated in the buccal cavity and projected outwards, presumably forcing the mouth open.

See also a more recent paper of Plehn (10) wherein she describes a similar tumor in a fish.
in two others there was dissemination in the same organ, which the authors believed to be metastatic (carcinoma in giant salamander; carcinoma in a triton).

Metastasis of histologically malignant tumors has, therefore, been shown to occur in all classes of cold-blooded vertebrates. As in the neoplastic disease of frogs which I have described, the incidence of tumor metastasis appears to be small.  

**Summary**

Among 276 cases of neoplastic disease of the kidney of the leopard frog, tumors were found in distant organs in 3 animals, namely in the liver and bladder of one, in the liver and left orbit of another, and in the liver of a third. These are believed to represent true metastases.

The occurrence of tumor metastasis in cold-blooded vertebrates generally has been discussed.

**References**


*For possible explanations for the scarcity of metastasis in cold-blooded vertebrates the reader is referred to the papers by Teutschläender (2), Takahashi (3), Thomas (4), Haddon and Blake (5), Plehn (6), Pick and Poll (7).*