Three Carcinomas of the Tongue in Two Monkeys
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The factors predisposing to carcinoma of the tongue in man are stated to be: (a) trauma from broken teeth or poorly fitting dentures, (b) the use of tobacco, especially pipe-smoking, (c) the ingestion of excessively hot foods, (d) syphilis, (e) vitamin deficiency, and (f) heredity. The simultaneous occurrence of 3 carcinomas of the tongue in 2 monkeys which apparently had none of these factors is of interest. In its clinical course and its gross and microscopic pathology the disease resembled that seen in man. Furthermore, as is usual in man, the victims were elderly males.

Among primates carcinoma of the tongue appears to be a disease of man exclusively. It is not mentioned in the reports on tumors in the lower primates by Fox (5) and by Ratcliffe (12) from the Philadelphia Zoo, in that of Zuckerman (14) from the London Zoological Society, or in those of Kennard (8) and Kennard and Willner (9). In the upper alimentary tract, Zuckerman (14) reported a case of carcinoma of the floor of the mouth in a rhesus monkey, and Fox (6) described a squamous cell carcinoma of the esophagus in a Japanese macaque.

Carcinoma of the tongue is not mentioned in the book on neoplasms of domesticated animals by Feldman (3) or in the review by Wells, Slye, and Holmes (13) of the comparative pathology of cancer of the alimentary canal, including more than 142,000 necropsies in the Slye mice. Cadot (2) collected 7 cases of carcinoma of the tongue in domesticated animals from the older literature, including 3 in horses, 2 in cats, and 1 each in a cow and a dog. To these Hartig (7) added 2 cases in horses, 3 in cows, and 1 in a dog all collected from the literature, together with various types of connective tissue tumors. There appears to be no case in animals recorded in the American literature. The extreme rarity of this tumor among American meat-producing animals is shown by Bengston (1) who writes "... our records show that only one such case has been encountered since 1906. This occurred in a ten year old cow in 1922. It was reported that there was a large well-organized growth at the base of the tongue and that the submaxillary, atlantal and parotid lymph glands contained tumor growths. Microscopic examination showed squamous cell carcinoma in the lesions on the tongue and in the involved lymph glands." His experience covers the large autopsy service at the stockyards in Chicago.

CASE REPORTS

These 2 monkeys were members of a colony of Old World and New World primates kept by one of us (H.K.) for long range neurophysiological and behavior studies (10, 11).

Monkey No. 1.—A male rhesus monkey (Macaca mulatta), approximately 16 years old, under study in the laboratory since February, 1934, first developed difficulty in swallowing solid food on Jan. 22, 1942. Weight 154 pounds. Examination 2 days later revealed a deep ulcer along the right lateral border of the tongue, at the junction of the middle and posterior third. It had a rolled, hard, white margin and a clean floor. Biopsy on Jan. 27, 1942, disclosed a squamous cell carcinoma. Under nembutal anesthesia, on Feb. 4, 1942, the anterior three fourths of the tongue was surgically amputated. The post operative course at first was uneventful but eating was not resumed. On one occasion when a stomach tube was being passed the trachea was inadvertently entered and food was poured into the lungs. Death occurred on the 8th postoperative day.

![Fig. 1.](image1.png)

**Fig. 1.**—The ulcerated tumor on the lateral margin of the tongue in monkey No. 1.

![Fig. 2.](image2.png)

**Fig. 2.**—The tumor on the under surface of the tongue adjacent to the frenulum in monkey No. 1.

Operative specimen: The tongue in general was soft and pliable and had a thin epithelium. On its right lateral border beginning 4.2 cm. from the tip and extending back, was a large ulcer which measured about 23 mm. wide. Its margins were rolled and hard and about 5 mm. wide (Fig. 1). On the cut surface the pearly gray white tumor was seen to extend into the tongue to a depth of 4 mm. beneath the floor of the ulcer and up to 7 mm. a its margins.
On the ventral surface of the amputated tongue to the left of the frenulum was a second tumor. It was a white, firm, slightly mammillated papilloma which measured 9 X 7 mm. in diameter and was elevated to a maximum of 2 mm. (Fig. 2). On cutting through this tumor no appreciable gross extension into the muscle of the tongue was seen.

Microscopic examination of the larger tumor showed an infiltrating squamous cell carcinoma. It was not highly undifferentiated although there was little keratinization. Groups of tumor cells penetrated into the muscle up to 6 mm. beneath the surface at the levels studied (Fig. 5). The smaller, papillary tumor was also a squamous cell carcinoma. It, too, was a fairly well differentiated tumor but with only slight keratinization. In cells penetrated deeply into the muscle. They were seen up to 6.5 mm. beneath the surface (Figs. 3 and 4).

Autopsy: The postmortem examination disclosed no residual cancer in the tongue and no metastases. The principal abnormality was much food material in the bronchial system with some pulmonary edema and focal congestion. Evisceration was moderate; the weight was now 11½ pounds.

Monkey No. 2.—A male Java monkey (Macaca irus), about 14 years old, under observation in the laboratory since July, 1933, developed lassitude and difficulty in swallowing solid food in November, 1941. Examination disclosed an ulcer on the left margin of the tongue. This did not heal when gentian violet and other local medication was applied but enlarged progressively so that eventually a deep, transverse ulcer, which covered its posterior third (Fig. 6). This extended posteriorly to the epiglottis, and laterally over the pharyngeal margins of this ulcer were hard and showed grayish-white lesions, although they were in different locations. The tongue was shortened, which had been unusually unhealthy in appearance, lost weight rapidly, although some liquids were taken. A biopsy made from the margin of the tongue ulcer on Jan. 27, 1942, disclosed squamous cell carcinoma. The monkey died on Feb. 4, 1942.

Autopsy: Autopsy disclosed definite emaciation (weight 6½ pounds), extensive bilateral aspiration pneumonia with multiple lung abscesses, and left empyema. The tongue was shortened, fixed in position, and partly amputated by a large, deep ulcer which covered its posterior third (Fig. 6). This extended posteriorly to the epiglottis, and laterally over the pharyngeal walls and the adjacent hard and soft palates. The floor and margins of this ulcer were hard and showed grayish-white tumor tissue. The floor of the mouth was rigid and the tongue was firmly adherent by tumor tissue to the right ramus of the mandible over an area about 2 cm. in length.

Microscopic examination showed that the tumor was an undifferentiated, widely infiltrating, squamous cell carcinoma with some areas of keratinization (Fig. 7). It involved much of the tongue and infiltrated the floor of the mouth, the upper end of the esophagus, the larynx, the lateral and posterior pharyngeal walls, the upper trachea, the capsule of the thyroid gland, and the submaxillary salivary glands. One submaxillary lymph node showed metastatic carcinoma. There were no metastases below the neck. One section taken through the lower lip showed an area of leukoplakia (Fig. 8). This had not been noticed upon gross examination.

**ETIOLOGICAL STUDIES**

The almost simultaneous appearance of 3 cancers of the tongue in 2 monkeys led to a search for possible etiological factors. Although these studies yielded no positive information they are placed on record.

**Hereditary factor.**—A common hereditary factor seems very remote for the following reasons: The monkeys were of different species of the genus *Macaca*. They were purchased from different dealers in New York City at different times—one in July, 1933, and the other in February, 1934. They probably originated in different countries. Thus while members of these species can interbreed successfully it is highly improbable that these 2 monkeys were born of interspecific crosses.

**Brain lesions.**—One factor which these monkeys had in common was experimental bilateral cerebral lesions, although they were in different locations. Monkey No. 1 had a left occipital lobectomy in June, 1937, and a right occipital lobectomy in September, 1937. Monkey No. 2 had bilateral removal of the prefrontal lobes in August, 1935. The removals were made with a knife under pentobarbital sodium anesthesia supplemented by ether. Other members of the colony having had similar operations at about the same time are in good health.

**Hormonal and sex factors.**—Both monkeys were males. Monkey No. 1 was the father of a female baby born in April, 1935, and still living. He showed repeatedly a pronounced reddening of the scrotum and skin of the face, especially between the eyes, in 1939. This occurred again in 1940 and 1941. A similar reddening has not been observed in other male rhesus monkeys and other macaques in this colony. Gross and microscopic examinations of the genital tracts of both monkeys at autopsy showed that they were not sexually senile.

**Age factor.**—The approximate ages at death were 16 and 14 years respectively. In view of what is known about the duration of life of members of the genus *Macaca*, both must be considered aged (4).

**Diet factor.**—The diet fed this colony has apparently been adequate as judged by longevity, freedom from disease, general condition, learning ability, and reproduction. Births have frequently occurred and even South American monkeys have thrived. For example, 3 births have occurred during the past 2 years in night monkeys (*Aotes*), to our knowledge the only such births in captivity.

The monkeys are fed one main meal a day consisting of fruits and vegetables, white bread, milk, and water. This is supplemented by peanuts, sunflower seeds, cod liver oil, sugar, wheat germ, and chinchickers at other times of the day. Depending on seasonal availability the fruits and vegetables fed were: bananas, apples, pears, oranges, tangerines, grapefruit, grapes, watermelons, honeydew melons, carrots, pineapples, cantaloupes, peaches, tomatoes, potatoes, lettuce, spinach, cabbages, squash, sweet potatoes, green beans, yellow corn, green peas, peppers, plums, pumpkins, cucumbers, onions, rutabagas, lemons, cauliflower, asparagus, celery, rhubarb, and eggplant.
Fig. 3.—The tumor of Fig. 2, showing penetration of groups of abnormal epithelial cells deep into the muscle. Mag. X17.

Fig. 4.—Higher power of the field marked in Fig. Mag. X120.

Fig. 5.—The tumor shown in Fig. 1. Mag. X25.
Fig. 6.—A sagittal section through the tongue and floor of the mouth from the tip to the larynx in monkey No. 2. Ulceration of the tumor with deep penetration is shown. Mag.×44.

Fig. 7.—The structure of the tumor in Fig. 6. Mag.×100.

Fig. 8.—The margin of an area of leukoplakia in the mouth of monkey No. 2. Mag.×150.
Cancer Research

Chimcracker formula:

- 40.8 per cent and clear wheat flour
- 16.5 per cent soybean meal
- 8.7 per cent corn meal
- 4.85 per cent ground wheat
- 4.85 per cent milk powder
- 4.85 per cent ground raisins
- 4.85 per cent bone meal
- 4.85 per cent salad oil
- 3.9 per cent molasses (blackstrap)
- 0.6 per cent salt
- 4.3 per cent wheat germ
- 1.0 per cent irradiated yeast

Except for the leukoplakia of the lip in monkey No. 2, discovered incidentally and illustrated in Fig. 8, no evidence for any vitamin deficiency was found. In this animal the poor nutrition for 3 months consequent to the inability to swallow may well account for this change.

Infectious and contagious factors.—These 2 monkeys were housed on different floors of the same building, during the past 6 years, with other monkeys which have remained well. They had, however, the same caretakers and the same experimental staff who used no aseptic precautions. There have been occasional colds and a few single cases of amebic dysentery. Tuberculosis was last seen 8 years ago and that among newly purchased animals. Monkey No. 1 was the cleanest and most fastidious animal seen in the colony in the last 10 years.

Filtration experiment.—The 2 portions of the papillary carcinoma (illustrated in Figs. 2, 3, and 4) which remained after a block of tissue was taken entirely through its center for the microscopical examination, were dissected from the tongue. This tumor tissue weighed about 200 mgm. It was minced with scissors in 5 cc. of physiological salt solution, after which it was ground in a mortar. Half of the saline was then passed through a Seitz filter. Small portions of this filtrate were injected into the mucous membrane at the lateral margin of the tongue of another monkey (Macaca mulatta). Examination of the tongue of the latter 3½ months later revealed no abnormality.

Other environmental factors.—These animals were used for behavior studies before and after the brain operations. Monkey No. 1, for example, was tested daily except on week ends from April, 1936, to December, 1941. Thus they were under constant close observation.

The temperature in the laboratory is kept at 75-80°F. during the winter. The rooms receive daylight but sunlight hardly ever reaches the animals and that through windowpanes. Artificial radiation is never employed.

The cages are of metal and chemically untreated wood. Wooden shavings, also untreated by chemicals according to the dealer, are used on the floor. The food pans are aluminum or enamel. Other metals with which the animals have had contact are iron, brass, tinned copper braid, and galvanized iron. The cages and food pans are cleaned with hot water, no chemicals being used. No drugs other than the anesthetics mentioned were ever given. No injuries of the tongue were ever noted. Other animals, at times, in the laboratory were: cat, mice, rats in cages, cockroaches, men.

These monkeys showed no gross or microscopical evidence of vascular or central nervous system syphilis. They were not addicted to the use of tobacco. They were never given hot or boiled food or drink. Dental plates or other dentures were not worn. Their teeth were in good alignment and there were no palpable rough spots or visible caries.

SUMMARY

Three squamous cell carcinomas of the tongue occurred simultaneously in 2 macaque monkeys (Macaca mulatta and Macaca irus) in a primate colony. One monkey died of aspiration pneumonia with local tumor metastases, and the other died postoperatively without metastases. Attempts at transmission were made and remain negative after 3½ months. None of the commonly quoted etiological factors for cancer of the tongue in man were present except that both were elderly males. Both had experimental brain lesions of long standing. This is the first report of cancer of the tongue in subhuman primates, and also the first in nondomesticated animals.

ADDENDUM

The case of carcinoma of the tongue in a horse reported by Henson (J. Am. Vet. M. A., 94:122, 1939) has come to our attention since the above was written. Also, we have seen microscopic sections from a third instance of carcinoma of the tongue in a macaque. This was discovered in a newly purchased animal in 1940 by Dr. Elizabeth Hemmens of the Department of Bacteriology, The University of Chicago.

REFERENCES

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