Carcinogen-Induced Neoplasia with Metastasis in a South American Primate, *Saguinus oedipus** (33845)

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The chemical induction of neoplastic growth in primates has been rarely achieved. In 1948 Krotkina (1) reported an osteogenic sarcoma in a rhesus monkey (*Macaca mulatta*) 3.5 years after an implant of 30 mg of 3-methylcholanthrene. In 1956, Sugiura *et al.* (2) reported the induction of squamous cell carcinoma in 3 of 6 rhesus monkeys which had received skin paintings of a high boiling, catalytically-cracked oil for 3–4 years. Levy in 1963 (3) described a small fibrosarcoma in a marmoset (*Saguinus nigricollis*) which appeared 10 months after the subcutaneous injection of 2 mg of 3-methylcholanthrene. More recently, Kelly *et al.* (4) reported the production of hepatic cell carcinomas within 27 months in rhesus, capuchin (*Cebus capuchinus*) and green monkeys (*Cercopithecus aethiops*) given *N*-nitrosodiethylamine orally or intraperitoneally. Quite recently, Noyes (5) reported the induction of sarcomas in the primitive primate, *Tupaia glis* (common Asiatic tree shrew) 6–7 months after subcutaneous injection of benzo(*a*)pyrene.

The present paper reports the induction of neoplastic growths in a South American primate, *Saguinus oedipus*, or cottontop marmoset, with both benzo(a)pyrene and 7,-12-dimethylbenz(*a*)anthracene. The cottontop marmoset is a small, easily-handled primate, a member of the famliy *Hapalidae* and is included in the taxum of platyrrhine or flat-nosed monkeys. In nature these animals are limited to the tropical forest areas of Colombia, South America (6).

Materials and Methods. Adult animals, captured in the wild and maintained in the colony for 10–12 months were used in the present experiments. The experimental group consisted of 2 crested, cottontop marmosets, *Saguinus oedipus* (hereafter referred to as cottontops) and 2 white-lipped, saddle-backed, brown and black tamarins, *Saguinus fusciocollis* (hereafter referred to as tamarins). One male and 1 female of each species was used. The animals, which weighed 300–500 g, were housed as male–female pairs in galvanized wire-mesh cages measuring 18 × 24 × 36 in., similar to those described by Levy and Artecona (7). The cages were provided with 2 wooden perches near the top and a wooden nesting box measuring 8 × 8 × 12 in. with a 4-in. diameter hole in the upper half of one side. Cages were hung on a compact, castor-equipped rack constructed of galvanized piping and angle iron. The racks had an upper and lower level and accommodated 6 cages. The animals were fed once a day with approximately 50 g/animal of Rx for Primates (Agway, Inc., Syracuse, N.Y.) and a large handful of Purina high protein monkey chow biscuits. Vitamin supplements consisted of 0.25 ml of Vi-syneral multivitamin (U. S. Vitamin and Pharmaceutical Corp., N. Y.) and 7000 units of Vitamin D_3 (Nutritional Biochemicals Corp., Cleveland, Ohio) in corn oil per 8-oz can of food. This diet was found suitable for adults, including pregnant and nursing animals, and juveniles over a 3.5-year period. The food was placed in disposable 8-oz paper Lily cups, which were held in place by a spring, and water was supplied by a bottle hung on the side of the cage. In order to prevent respiratory diseases, the relative humidity of the room was maintained at 60%, and the temperature was kept at 80–85°F. The humidity was maintained with a device which employed fan-dispersed live steam, controlled by a humidistat and solenoid valve.

The animals were inoculated subcutaneous-

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ly with 10 mg of benzo(*a*)pyrene and 10 mg of 7,12-dimethylbenz(*a*)anthracene in olive oil. The injections of the 2 chemicals were made on opposite flanks of each animal and the animals were examined weekly for the development of tumors.

Results and Discussion. One week after the subcutaneous inoculation of the chemical carcinogens both tamarins became anorexic, weak, and debilitated; these animals had been in excellent health for many months prior to injection. Both tamarins died within 5 weeks. One animal hemorrhaged from the nose and mouth, and at necropsy had congested lung tissue. The other tamarin showed no gross abnormalities. Lung sections of the former animal showed pulmonary edema and acute pneumonitis, while liver sections of the animals demonstrated an acute cholangitis, with stasis and dilation of larger bile ducts, and focal necrosis of hepatic cells secondary to biliary obstruction.

Unlike the tamarins, the 2 cottontops, firm raised nodules 3–6 mm in diameter were observed at the sites of deposition of the chemicals. These nodules increased in size to 10–12 mm by the third month and several of the nodules became ulcerated. By the fifth month, the ulcers had healed and the modules became progressively smaller, but continued to persist as hard masses 3–4 mm in diameter. The male cottontop, developed progressively-growing tumors at both inoculated sites 16 months after the subcutaneous injection of the chemicals. Eighteen months postinoculation, the tumors of this animal measured 3 and 4 cm in diameter. At necropsy, the tumor induced by the inoculation of benzo(*a*)pyrene (BP) in the right flank was soft and very vascular, while the dimethylbenz(*a*)anthracene (DMBA)-induced tumor in the left flank of the marmoset was firm and not as vascular. A lymph node in the left inguinal region of the animal was greatly enlarged and measured 6 mm, presumably due to metastasis from one of the tumors. Eighteen months postinoculation, the female cottontop marmoset died without any evidence of tumor, from a septicemia following birth of progeny.

FIG. 1. Gross appearance of 7, 12-dimethylbenz (*a*) anthracene-induced tumor in *Saguinus oedipus* (cottontop marmoset) 18 months after subcutaneous inoculation of chemical; tumor measures 3 cm in diameter.

Figure 1 shows the gross appearance of the DMBA-induced tumor 18 months after introduction of the chemical. The BP-induced tumor occurred on the opposite side of the animal and was of greater mass than the DMBA-induced tumor; however, it grew into the peritoneal cavity and did not exhibit large exterior dimensions. Microscopic examination of sections of the BP-induced tumor revealed a spindle cell sarcoma. The elongated spindle cells were arranged in compact bundles and the nuclei were large and vesicular with frequent mitotic figures. The microscopic appearance of the BP-induced tumor is presented in Fig. 2. Examination of slides of the DMBA-induced tumor showed a rhabdomyosarcoma. The nuclei were highly variable in size and shape; most were large and vesicular with 2 nucleoli. Mitotic figures were very frequent in sections of this tumor. Figure 3 shows the microscopic appearance of the DMBA-induced tumor. Examination of the sections of the involved left inguinal

lymph node revealed a sarcomatous growth with morphological characteristics similar to the DMBA-induced rhabdomyosarcoma. It was concluded that the DMBA-induced tumor in the left flank had metastasized to the left inguinal lymph node of the animals.

It is interesting to note that the latent period for BP-induced sarcoma was considerably shorter in the primitive primate, *Tupaia glis* (7) than in the cottontop marmoset, as reported in the present paper. In the prosimians, spindle-cell and round-cell sarcoma developed in 6–7 months, as contrasted with 16 months before the development of sarcoma in the cottontop marmoset. These latent periods are compatible with the life spans of the animals, which are approximately 5–8 years for the tree shrew and about 10–15 years for the cottontop marmoset (6).

Summary. Sarcoma, with a latent period of 16 months, was induced in a South American primate, *Saguinus oedipus* (cottontop marmoset) by the subcutaneous inoculation of benzo(a)pyrene and also by 7,12-dimethylbenz(*a*)anthracene. Spindle-cell sarcoma was induced by benzo(*a*)pyrene, and rhabdomyosarcoma, with metastasis to an inguinal lymph node, was induced with 7,12-dimethylbenz(*a*)anthracene. These carcinogens were toxic to a related South American primate, *Saguinus fuscicollis* (white-lipped tamarin) and resulted in death within 5 weeks.

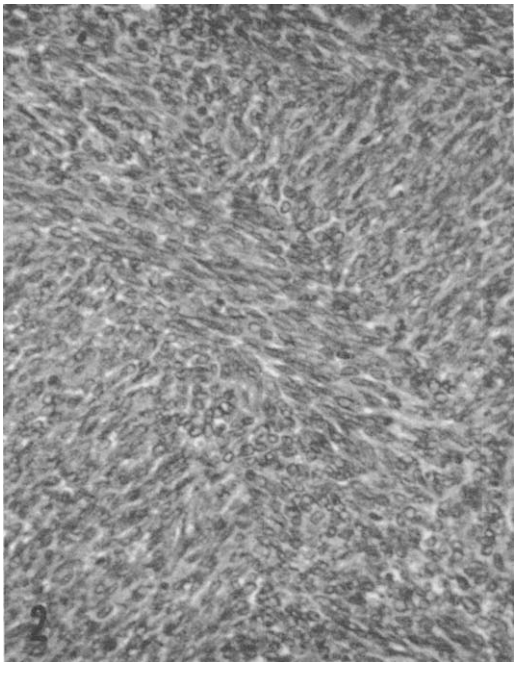

FIG. 2. Microscopic appearance of benzo (*a*)pyrene-induced spindle-cell sarcoma of cottontop marmoset; hematoxylin and eosin stain; 300×.

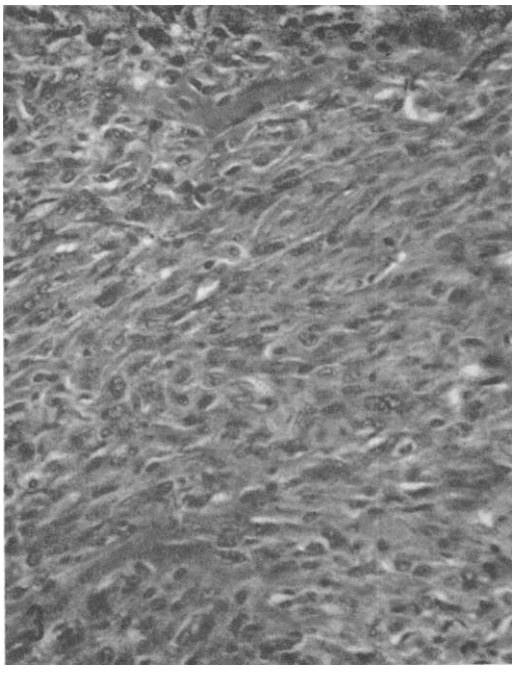

FIG. 3. Microscopic appearance of 7, 12-dimethylbenz (*a*) anthracene-induced rhabdomyosarcoma of marmoset; hematoxylin and eosin stain; 300×.

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