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Tumors in long-term rat studies associated with microchip animal identification devices

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Abbreviations: RFID: radio frequency identification technology; **HIER:** heat-induced epitope retrieval; **PBS:** phosphate buffered saline; **F344:** Fischer 344.

Summary

Tumors surrounding implanted microchip animal identification devices were noted in two separate chronic toxicity/oncogenicity studies using F344 rats. The tumors occurred at a low incidence rate (approximately 1 percent), but did result in the early sacrifice of most affected animals, due to tumor size and occasional metastases. No sex-related trends were noted. All tumors occurred during the second year of the studies, were located in the subcutaneous dorsal thoracic area (the site of microchip implantation) and contained embedded microchip devices. All were mesenchymal in origin and consisted of the following types, listed in order of frequency: malignant schwannoma, fibrosarcoma, anaplastic sarcoma, and histiocytic sarcoma. The following diagnostic techniques were employed: light microscopy, scanning electron microscopy, and immunohistochemistry. The mechanism of carcinogenicity appeared to be that of foreign-body induced tumorigenesis.

Introduction

Animal identification methods have been used historically for a variety of reasons and in a diverse array of species. Animal industries where identification plays an important role include: companion animals, equine, fish, wildlife, birds, reptiles, laboratory animals, meat-producing animals, and amphibians. Uses of animal identification include: animal control and recovery, disease control and eradication, theft prevention, animal production programs, and in biomedical and industrial research settings [1, 10–13, 16, 17].

In the laboratory animal research environment, many of the traditional means of animal identification are no longer considered ideal by today's criteria: 1) easily and quickly read, 2) durable, 3) unalterable, 4) simple to apply, 5) humane, and 6) reasonably priced [17, 21]. Ear notching/punching is a time-consuming procedure to perform, has inherent human-error possibilities, is considered inhumane, and may become unreadable due to fighting or cage-associated trauma [21, 22, 24]. Ear tags may be lost, and have also been cited to produce deleterious tissue reactions including inflammation, hyperplasia, metaplasia and even neoplasia at the tag site [2, 22–24]. Toe clipping is one of the oldest forms of laboratory animal identification, however it is considered a painful procedure and may also interfere with the animal's ability to hold material [21, 22, 24]. And lastly, tattoo identification may not be feasible in pigmented animals or in animals with total body fur [17, 21, 22, 24].

A new means of laboratory animal identification was introduced in the late 1980's, based on radio frequency identification technology (RFID) [24]. Unlike traditional bar code technology that requires either line-of-sight or physical contact with a scanning device, RFID technology, also known as electronic microchip technology, can identify an object remotely through the use of radio frequencies [10]. The materials consist of a microchip (transponder) which is implanted subcutaneously into

the animal, a scanner (transceiver) which reads the microchip's unique identification number, and an optional digital display unit which acts as a computer interface for automated downloading of data [2, 10].

The implantable microchip consists of a miniature, battery-free, passive cylindrical device that is sealed in a biocompatible glass receptacle and partially enclosed in a porous polypropylene polymer sheath [20, 21]. It is activated by a low-power radio frequency signal emitted by the scanner, which supplies the power to the microchip for transmission of its unique identification number [10, 14, 21]. The microchip is preprogrammed with a permanent, unalterable, unique 10 to 15 digit alphanumeric identification code. An additional advantage of some microchips is the dual use for collection of body temperature data, a procedure which is less stressful and time-consuming than traditional techniques [15].

By today's standards, electronic animal identification has been considered one of the most promising methods available; it is quickly and easily read, decreases human error by computer interfacing, is permanent and unalterable, moderately easy to apply (comparable to a subcutaneous injection), and is relatively humane [2, 10, 17].

A few of the disadvantages include high set-up and recurrent costs [24], occasional microchip failure and/or migration from the original implantation site [7, 8, 10, 20], and intentional incompatibility between different manufacturers' implants [1, 9, 13, 18, 20]. The latter has been especially problematic for companion animal control and recovery programs. However in 1996, a "universal" scanning device was developed for all technology marketed in the United States, which has encouraged more widespread acceptance of this form of animal identification [18, 20].

The present paper deals with one of the more serious potential disadvantages of electronic animal identification from the standpoint of long-term carcinogenicity rodent studies; that of foreign-body induced tumorigenesis as a result of microchip implantation. There have been several recent reports of microchip-associated tumors in the laboratory mouse used in long-term studies [3,14,19,22]. The purpose of this paper is to document, for the first time, the occurrence of microchip-associated tumors in the Fischer 344 laboratory rat used in two-year chronic toxicity/oncogenicity feeding studies. Although the resulting tumor rate was observed to be low, the overall health of the affected rats was compromised due to tumor size and the occurrence of metastases, leading to early sacrifice. Researchers need to be aware of the possible association of subcutaneous tumors with microchip implantation when interpreting oncogenicity data from these studies.

Material and methods

Animals: 1200 Fischer 344 rats (F344/N or F344/SAS; derived from NIH stock) were procured from Sasco, Inc. (Madison, WI). Rats were approximately 6 weeks old, nulliparous and non-pregnant, and were placed on two separate chronic/toxicity oncogenicity studies (600 rats/study at study start). During the two-week acclimation period, animals were examined for general appearance and/or behavior, and were checked for serological evidence of common rodent infections. Rats were housed individually throughout the acclimation and exposure periods in suspended stainless steel wire-mesh cages with deotized cage board in the bedding tray. The test facility was accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International), and constant environmental control (temperature, humidity, airflow, and light) was monitored throughout the study.

Animal identification: All rats deemed adequate after the acclimation period were placed on study at eight weeks of age. Rats were implanted subcutaneously with animal electronic identification microchips (BioMedic Data Systems, Inc., Maywood, NJ) several days prior to study start. Each microchip was encoded with a unique number, specifying the animal's sex, dose group, cage number, and study affiliation. The microchip measured 2 × 12 mm, was prepackaged in a sterile 12 gauge injection needle, and was attached to an implantation device supplied by the manufacturer. It was inserted subcutaneously into the animal's dorsal region between the scapulae.

Diet: Food (Purina Mills Rodent Lab Chow 5001-4 in "etts" form, St. Louis, MO) and municipal tap water (dispensed by an automatic watering system) were provided continuously for ad libitum consumption. Cage racks were rotated weekly, and replaced with clean racks every two weeks. Feed (control and test diet) as well as feeders were replaced/changed weekly. Feed, water, and corn oil (used in the diet to facilitate mixing of the test substance in the feed) were periodically sampled and analyzed for a variety of potential impurities. The results of these analyses were unremarkable.

Experimental design: Both chronic toxicity/oncogenicity studies, from which the affected animals originated, were conducted in accordance with the following guidelines: FIFRA (no. 83.5), OECD (no. 453), TSCA (no. 798.3320), and MAFF (guideline 59, no. 4200). Prior to study initiation, all rats were randomly assigned to control or treatment groups using a body weight stratification-based computer program (INSTEM Computer Systems, Sone, Staffordshire, UK). Each chronic toxicity/oncogenicity study contained one control group (supplied with a feed/corn oil mixture only), as well as a low-, mid-, and high-dose group which was fed a combination of test substance and corn oil mixed homogeneously into the feed. There was an interim 1-year sacrifice group consisting of 20 rats/sex in the control and high-dose groups, and 10 rats/sex in the low- and mid-dose groups; and a 2-year sacrifice group consisting of 50 rats/sex/group. Additionally, there was a replacement group of 5 additional rats/sex/group placed on study as part of the 1- and 2-year sacrifice groups, which was maintained for approximately the first month of the study. The purpose of these animals was to serve as potential "replacements" for any animals that died unexpectedly or developed non-compound-related problems at a very early stage in the study. When replacement

occurred, the animal retained its original microchip and identification number, and all data collected previously and in the future on the replacement animal were incorporated into the database of the dose group in which the replaced animal was a member. At the end of the replacement period (month 1 of 24) all remaining replacement animals which were not utilized for replacement purposes were removed from the study room and/or sacrificed in a timely manner. Thus the final animal count for each chronic study was 520 rats (260/sex).

In-life animal observations and procedures: Examination for clinical signs of toxicity, which included evaluation of external surface areas, orifices, posture, general behavior, respiration, and excretory products, was performed once each week on all animals. Individual body weight and food consumption determinations were performed weekly for the first 8 months, and once a month thereafter on all animals. Ophthalmic examinations and standard clinical pathology evaluations were performed according to the afore-mentioned guidelines.

Table 1. Incidence of microchip-induced tumors from two chronic toxicity/oncogenicity rat studies.

Tumor type	Study 1*		Study 2*	
	males	females	males	females
Malignant schwannoma	1	0	1	1
Fibrosarcoma	1	1	0	0
Anaplastic sarcoma	0	1	1	0
Histiocytic sarcoma	0	1	0	0

*n = 260 rats/sex

Post mortem evaluation: Complete necropsies were performed on all study rats, regardless of fate (found dead, sacrificed in extremis, or sacrificed at termination). Rats that were moribund during the study as well as those surviving to study termination were euthanized by CO_2 asphyxiation. Necropsies were performed according to agency guidelines, and included: documenting and saving all gross lesions, weighing designated organs, and collecting standard protocol tissues for histopathologic evaluation. Tissues were preserved in 10 percent buffered formalin. All microchip animal identification devices were removed at the time of necropsy and placed in the collection bottle for identification of tissue specimens. Unless a gross lesion was present surrounding or adjacent to the microchip, microchip-associated tissues were not collected or evaluated microscopically.

Micropathology: Tissues were trimmed and processed routinely, then embedded in paraffin, sectioned at 5 microns, stained with hematoxylin and eosin (H & E), and evaluated via light microscopy by a veterinary pathologist. An in-depth peer-review process was performed by an independent pathologist, including the examination of all microchip-induced tumors.

Immunohistochemistry was performed using the labeled avidin-biotin technique, on the formalin-fixed and

Table 2. Chronology and description of microchip-induced tumors from two chronic toxicity/oncogenicity rat studies.

Animal #	Dose level	In-life appearance (days)	Animal fate (days)	Cause of death	Gross description of microchip masses*	Microscopic diagnosis	Metastases
Study 1							
2006 (male)	mid	693	ST (727)	study's end	"4.0 cm diameter, firm, white, necrotic"	Fibrosarcoma	no
2018 (male)	mid	658	SE (706)	microchip	"7.0×5.5×5.0 cm, hard, white/pink"	Malignant schwannoma	no
1111 (female)	low	441	SE (511)	microchip	"7.0×6.5 cm, hard, white/tan, nodular"	Anaplastic sarcoma	yes
2123 (female)	mid	665	SE (705)	leukemia	"1.5 cm diameter, firm, tan/red"	Histiocytic sarcoma	no
3102 (female)	high	567	SE (670)	microchip	"8.0×6.5×5.0 cm tan, nodular"	Fibrosarcoma	yes
Study 2							
2010 (male)	mid	558	SE (653)	nephropathy	"4.5×3.5 cm, hard, pink/white"	Malignant schwannoma	no
2038 (male)	mid	609	SE (645)	microchip	"6.0×6.0×4.0 cm, firm, tan"	Anaplastic sarcoma	yes
3139 (female)	high	490	SE (588)	microchip	"8.0×7.0×6.0 cm, ulcerated, white/tan"	Malignant schwannoma	no

*All masses were located in the dorsal thoracic subcutaneous area and contained embedded microchips.
ST = sacrificed at study termination; SE = sacrificed in extremis

paraffin-embedded microchip-associated tumors. Sections were cut at 5 μm and placed on charged slides, which were dried at 56 °C for 85 minutes. After deparaffinizing, and rehydrating, the slides were treated with 3% hydrogen peroxide in methanol. Heat-Induced Epitope Retrieval (HIER) was performed with citric acid-sodium citrate buffer, pH6, for 1 hour in a 90 °C water bath. Slides stained for desmin and alpha-sarcomeric actin did not undergo HIER. Slides were then treated with either normal goat serum (Vector # S-1000) or normal donkey serum (Sigma # D9663), followed by avidin and biotin blocking solutions at room temperature. They were incubated with primary antibody overnight at 4 °C. The following primary antibodies were used: vimentin (Santa Crux Biotechnology #SC-6260), desmin (Zymed #18-0016), alpha-sarcomeric actin (Zymed #18-0177), S-100 ((Sigma #S-2644), and neuron-specific enolase (The Binding Site #PH508). Appropriate biotinylated secondary antibody was applied at room temperature: Goat anti-Mouse IgG (Vector #BA-9200), Goat anti-Mouse IgM (Vector #BA-2020), Goat anti-Rabbit IgG (Vector #BA-1000), or Donkey anti-Sheep/Goat IgG (The Binding Site # AB360). HRP-avidin D (Vector cat# A-2004) was applied at room temperature. Slides were developed using DAB (3,3'-Diaminobenzidine Tetrahydorchloride-Plus Kit from Zymed, cat # 00-2020), followed by a hematoxylin counterstain (Gill's #2 from Fisher, #CS401-1D).

Tissue sections from female 3102 were also prepared for examination using scanning electron microscopy by post-fixation for 30 minutes with 1 percent osmium tetroxide buffered in PBS. Tissues were dehydrated in a graded ethanol series, dried, and mounted onto a 15 mm aluminum stub using an adhesive. A layer of gold was sputter-coated onto the tissue to render it conductive. Evaluation was performed with an Hitachi S-2700 scanning electron microscope.

Results

Microchip-associated tumors occurred at a low incidence in both chronic toxicity/oncogenicity rat studies

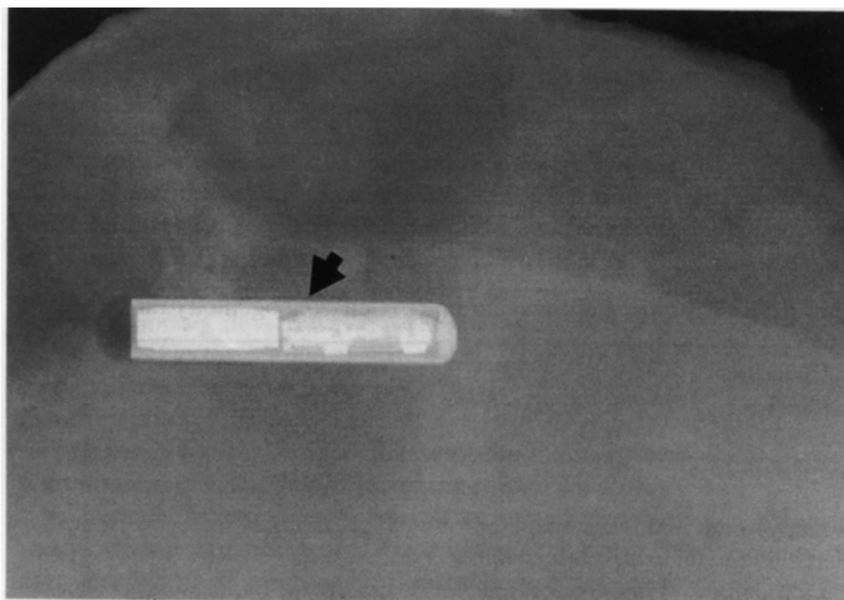


Fig. 1. Radiograph of an in-situ microchip device (arrow) surrounded by a semi-radiopaque mass (female #1111).

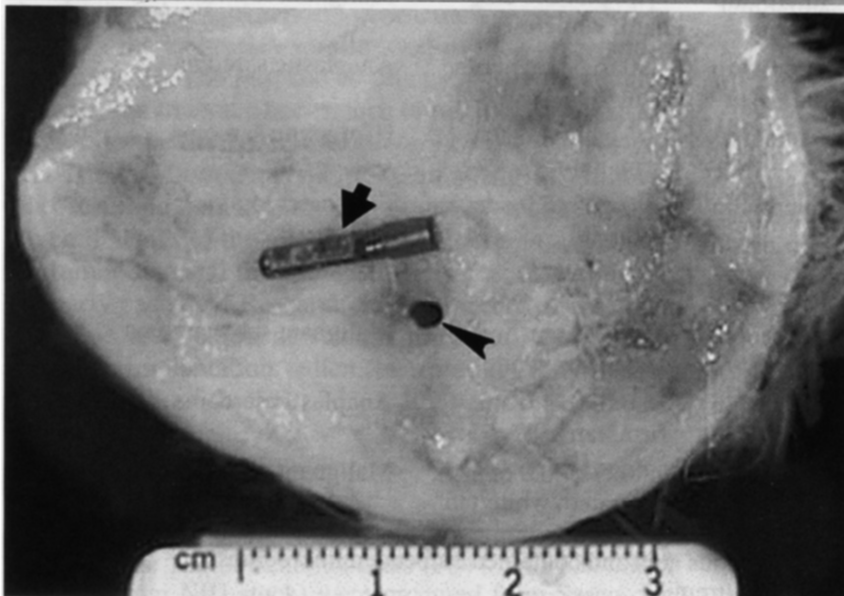
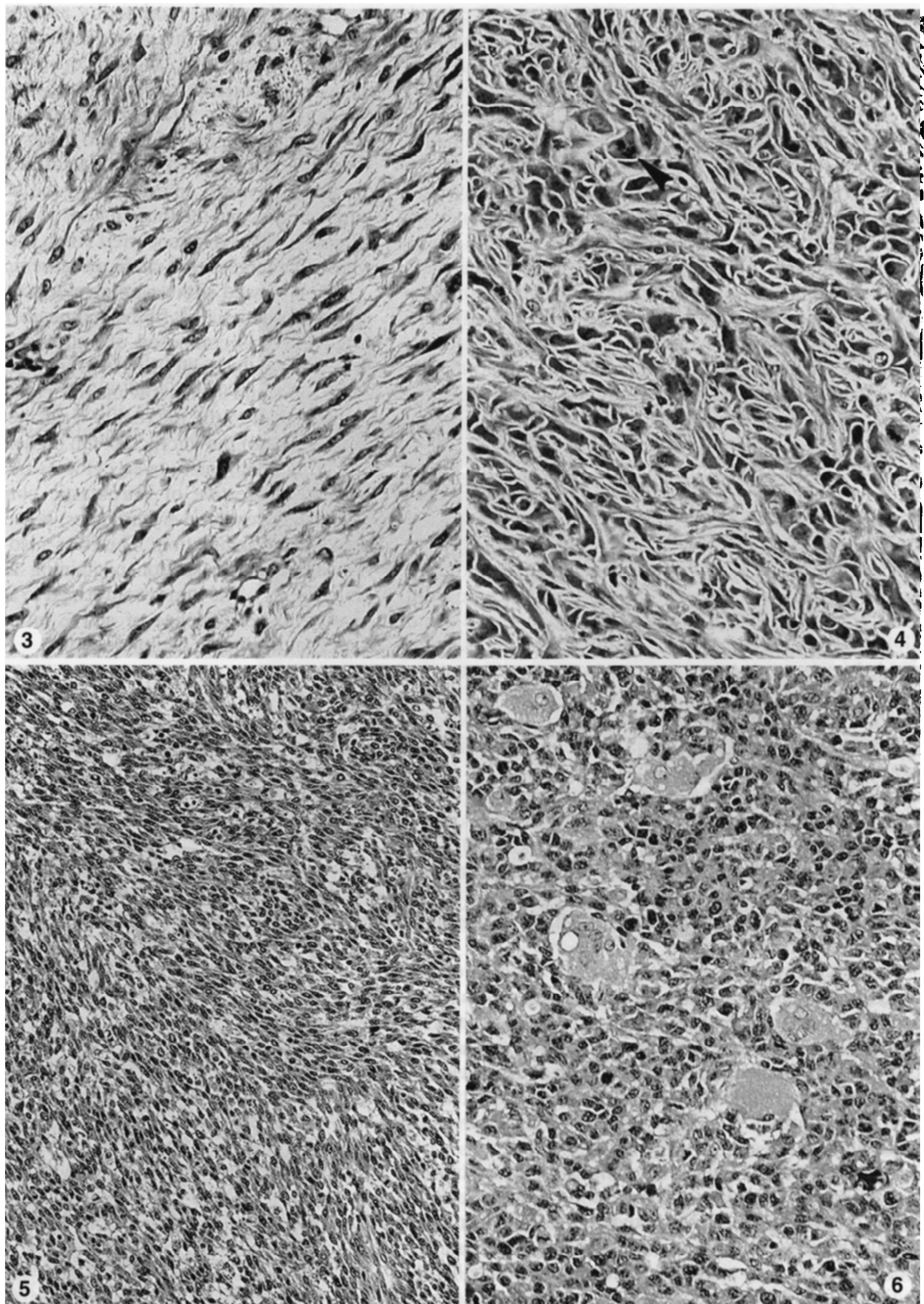


Fig. 2. Gross appearance of a microchip-associated tumor. The microchip (arrow) has been removed from the cavity where it resided in-situ (arrow-head) (female #3102).



Histological appearance of a microchip-induced tumors:

Fig. 3. Malignant schwannoma, characterized by loosely-arranged spindle-shaped cells with scant cytoplasm, widely separated by a poorly-staining matrix (female #3139) (H&E, ×100).

Fig. 4. Anaplastic sarcoma, characterized by highly pleomorphic, anaplastic cells and bizaare mitotic figures (arrow-head) (female #1111) (H&E, ×100).

Fig. 5. Fibrosarcoma, characterized by spindle-shaped cells densely packed in interlacing bundles (male #2006) (H&E, ×50).

Fig. 6. Histiocytic sarcoma, characterized by sheets of round histiocyte-like cells with interspersed multinucleated giant cells (female #2123) (H&E, ×100).

reported in this paper, with no apparent sex-related trends (table 1). In Study 1, there were two males (0.77 percent) and three females (1.15 percent) with microchip-associated tumors out of 260 rats/sex. The overall microchip-related tumor incidence for Study 1 was just under 1 percent (0.96 percent). Study 2 contained a lower incidence of microchip-associated tumors; there were two males (0.77 percent) and 1 female (0.39 percent) out of 260 rats/sex, with an overall incidence of 0.58 percent. It should be noted, however, that these tumor incidences only approximated the potential incidence of microchip-induced tumors for these studies. The original intent of the studies was to characterize the toxicological profile of the chemical test substance in question, therefore tissue surrounding the animal-identification microchips was not examined microscopically unless there was a gross lesion. Thus, small pre-neoplastic or neoplastic lesions may have been missed.

None of the microchip-induced tumors from either study occurred in control animals, however the tumor incidence was distributed across dose groups and showed no test-substance related trends (table 2). In Study 1, both affected males resided in the mid-dose group, and each of the three affected females came from a different dose group (one from the low-, mid-, and high-dose groups). In Study 2, both affected males again resided in the mid-dose group, and the one affected female came from the high-dose group.

All microchip-associated tumors were observed during the second year of the studies. The initial in-life appearance ranged from days 441-693 for Study 1 and days 490–609 for Study 2. Some masses were extremely fast-growing, enlarging as much as 1 cm per week. As a result, the size of the masses often necessitated early sacrifice of the animal. Five of the eight total animals with microchip-associated tumors from Studies 1 and 2 had masses equal to or greater than 6.0 cm in measurement at the time of sacrifice.

Grossly, all masses were confined to the area of microchip implantation (subcutaneous dorsal thoracic area) and contained embedded microchips (fig. 1 and 2). The tumor consistency ranged from firm to hard, and occasionally had a nodular appearance . In some instances, the masses were difficult to differentiate macroscopically from mammary gland fibroadenomas which are seen commonly in the aging F344 rat [4].

Microscopically, all microchip-associated tumors were mesenchymal in origin (figs. 3–6). Out of the combined tumor incidence from Studies 1 and 2 (8 animals total), there were three malignant schwannomas, two fibrosarcomas, two anaplastic sarcomas, and one histiocytic sarcoma. All diagnoses were confirmed with immunohistochemistry. All tumors exhibited immunoreactivity with vimentin, indicating mesenchymal origin, and were negative for desmin and alpha-sarcomeric actin, indicating no muscular components.. The malignant schwannomas also stained positively for S-100 and neuron-specific enolase.

Although animal morbundity and mortality were attributed partially to tumor size in several animals, an additional contributing factor consisted of occasional metastases which occurred in two out of the three females from Study 1 (a fibrosarcoma and an anaplastic sarcoma), and in one of the two males from Study 2 (an anaplastic sarcoma) (fig. 7). Metastatic sites included: the lungs, thymus, epicardium of the heart, mediastinal lymph nodes, and the musculature of the right foreleg. In all cases, metastases occurred when the primary tumors were quite large (≥ 6.0 cm in measurement).

When viewed with scanning electron microscopy, the microchip-associated fibrosarcoma in female rat 3102 (Study 1) was composed of extremely compact tissue surrounding the cavity originally containing the microchip (fig. 8 and 9). On low magnification, the tissue surface adjacent to the microchip was smooth, conforming to the shape of the microchip. On higher power (fig. 10), numerous long, interwoven cytoplasmic processes were evident, suggestive of fibroblastic components. There were a few scattered erythrocytes, however no evidence of active inflammation. This was also confirmed in a light-microscopic section containing an in-situ microchip (fig. 11). The tumor conformed to the microchip device, with no evidence of active inflammation immediately surrounding the microchip.

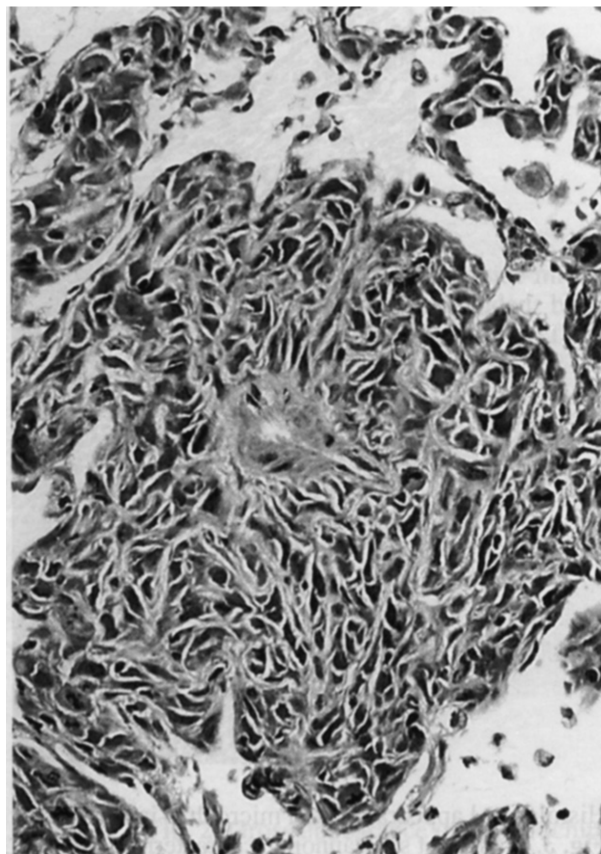


Fig. 7. Metastatic anaplastic sarcoma to the lungs (female #1111) (H&E, ×100).

Scanning electron micrographs of the cavity created by the microchip device:

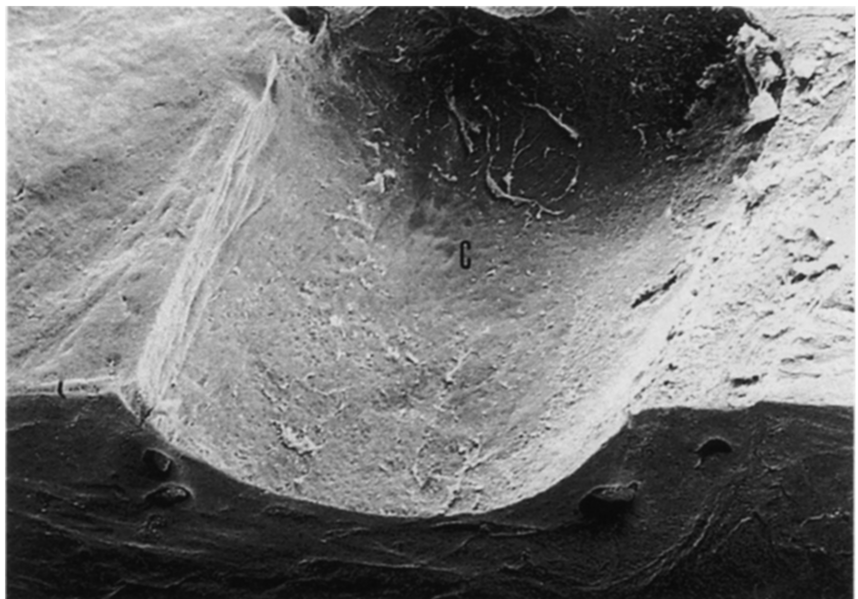


Fig. 8. The cavity (C) is surrounded by a densely-packed tumor (fibrosarcoma), which conforms tightly to the shape of the microchip device (female #3102) (×35).

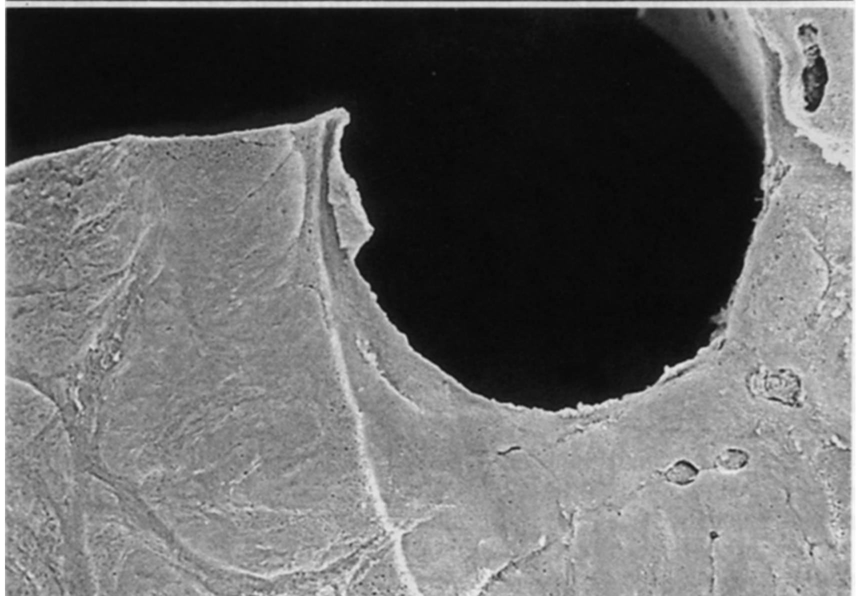


Fig. 9. Appearance of the cavity's cut-surface (female #3102) (×50).

Discussion

This paper, for the first time, describes the occurrence of microchip-induced tumorigenesis in the F344 rat used in long-term chronic toxicity/oncogenicity studies. Prior to this, a one-year study using Sprague-Dawley rats reported no adverse clinical or histopathological side effects; only very thin rims of mature fibrous connective tissue were present surrounding the microchip implant sites [2]. Several other papers confirmed this minimal tissue reaction in rats, mice, and a variety of other animal species [12, 13, 17, 20, 21].

Tumors associated with microchip implants have been described previously in various laboratory mouse strains, including the $B_6C_3F_1$ [19], CBA/J [22], and in heterozygous *p*53+/- transgenic mice [3]. As per the literature, there appear to be strain-related differences in the mouse; there have been no citings of microchip-induced tumors in the CD-1 mouse [19]. The same observations were noted in two historical oncogenicity CD-1 mouse studies conducted at this laboratory (800 mice total); no evidence of microchip-induced tumorigenesis was observed in any of the mice. However due to the original intent of these studies, the site around the microchips was not examined routinely unless a gross lesion was noted. Therefore, small pre-neoplastic or neoplastic lesions may have been missed.

The occurrence of tumors due to microchip implantation is not an entirely unexpected finding. According to the literature on foreign-body tumorigenesis, any inert substance inserted into the body for long time periods can produce neoplasia [5, 6]. Citings have been noted in various species, including humans, mice, rats, dogs, and hamsters, and with a variety of materials, such as asbestos, prosthetics made of different materials, and relatively non-degradable infectious agents such as schistosomal eggs [5]. The commonality among all of these citings is the physical characteristic of the foreign body.

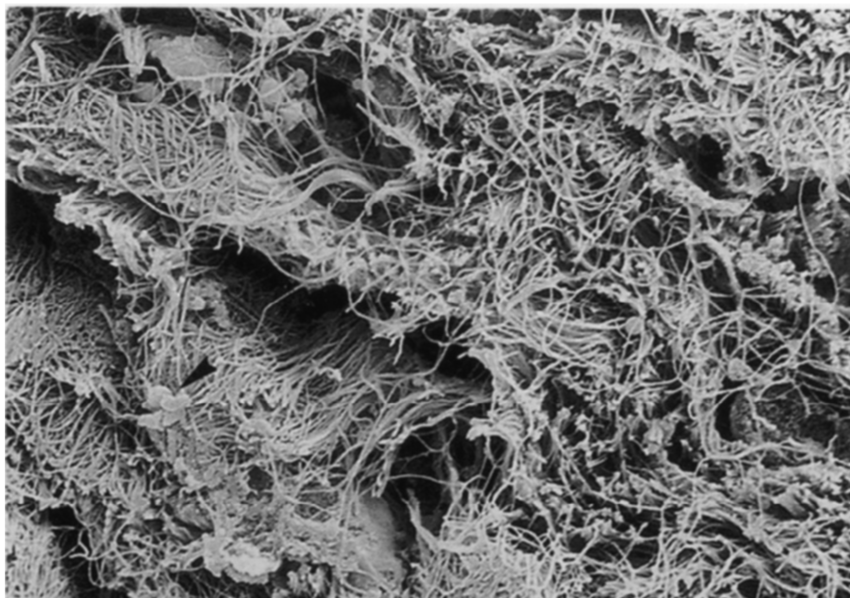


Fig. 10. High-power view of the cavity's surface. Although there are occasional erthrocytes (arrowhead), the surface is composed predominately of densely-packed cells suggestive of fibroblasts, with long, interwoven cytoplasmic processes (female #3102) (×5000).

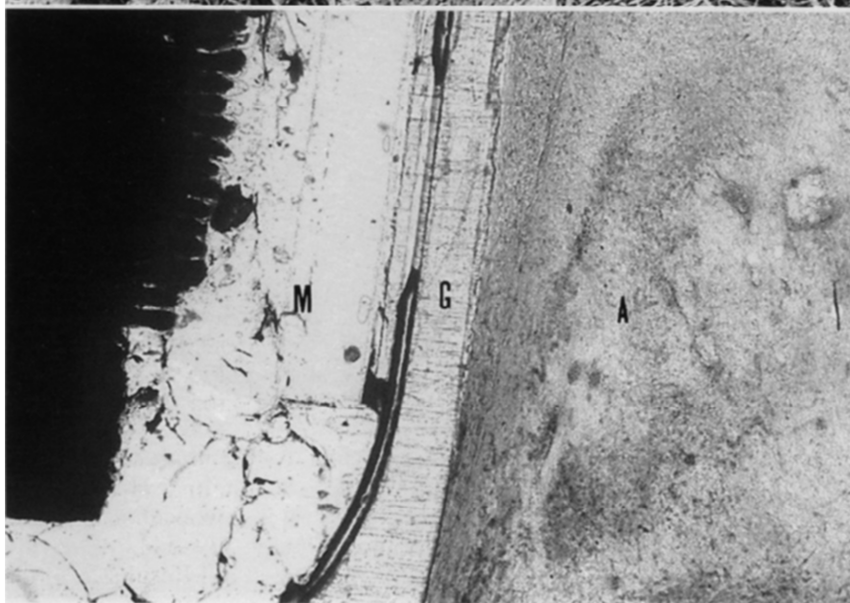


Fig. 11. Histological appearance of an anaplastic sarcoma (A) surrounding a microchip device (M) in-situ. Note the inflammatory quiescence surrounding the implant's glass capsule (G) (female #1111) (H&E, ×25).

The size and surface texture of the foreign body are the most important overall criteria determining potential carcinogenesis. It is reported that foreign bodies with smooth, continuous surfaces are more carcinogenic than those with rough, scratched, or porous surfaces. Additionally, the larger the surface area, the more likelihood for neoplastic transformation due to the increased number of reactive cells [5, 6].

The tumorigenic foreign body reaction consists of two basic morphologic phases: (1) an acute cellular reaction with phagocytically active macrophages, and (2) dormancy of macrophages and fibrotic encapsulation of the foreign body. There is a direct correlation between the foreign-body reactive tissue response and tumorigenicity. The formation of a fibrous tissue capsule around the foreign body appears to be the important factor in carcinogenesis; foreign-body surfaces that prolong the active inflammatory process (phase 1) and delay inflammatory cell quiescence with fibrous tissue encapsulation (phase 2) result in reduced tumorigenicity. Thus, the occurrence of tissue fibrosis is linked to neoplastic development. A chronic foreign body such as the electronic microchip, surrounded by a rim of mature fibrous connective tissue with little or no active inflammation, may therefore be more tumorigenic than one with ongoing active inflammation [5, 6]. And, as depicted in the scanning electron micrographs (figs. 8–10) and the light microscopic photograph with an in-situ microchip (fig. 11), the tissue immediately surrounding the microchip cavity was in a state of inflammatory quiescence.

Differences in species susceptibility to foreign-body tumorigenesis have been noted in the literature, and appear to stem from the magnitude of the chronic fibrotic tissue reaction. In humans, fibrotic scar formation proceeds at a much slower rate than in rodents. Chickens produce only very thin capsules around implants. In guinea pigs, fibrotic encapsulation of foreign bodies regresses after a few months. Thus, these species appear to

be more resistant to foreign-body induced tumors than rats and mice [6].

The types of tumors described in this paper concur with those depicted in other papers describing foreign-body tumorigenesis [3, 5, 6, 19, 22]. Most tumors arising from foreign bodies are malignant mesenchymal neoplasms and have a rapid growth rate, killing the animal in a matter of weeks [6]. A wide variety of mesenchymal neoplasms have been reported to arise from foreign bodies in rodents, but the most commonly reported tumor was variably identified as a fibrosarcoma, spindle-cell sarcoma, or anaplastic sarcoma [5, 6]. Likewise, fibrosarcomas and anaplastic sarcomas were noted in four out of the eight cases documented in this paper. The single most common tumor noted in these rats, however, was the malignant schwannoma.

For the first time, tumors due to microchip implantation have been documented in long-term rat studies, and may be a complicating factor in the interpretation of carcinogenicity data.

Electronic microchip technology as a means of animal identification may affect animal moribundity and mortality, due to the large size and rapid growth rate of microchip-induced tumors as well as the occurrence of metastases. Fortunately, the tumor incidence was low (approximately 1 percent). The process of differentiating microchip-induced tumors from suspected compound-related tumors was fairly easy in the cases described here, for all contained the embedded microchip device. Additionally, there were no problems in identifying the tumor of origin in instances where metastases occurred. This may be a potential source of difficulty, however, if the animal contains more than one tumor with metastases. Thus, the researcher must be aware of this phenomenon of inducible carcinogenesis due to microchip animal identification when interpreting data from long-term rodent studies.

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