

TISSUE REACTIONS TO MICROCHIP IMPLANTATION IN LABORATORY ANIMALS AND PETS

INTRODUCTION

Implantable microchips have become a well-accepted means of pet identification in the global veterinary community. Over the last 15 years, millions of dogs and cats throughout the world have safely received an implantable microchip that can quickly and reliably document the identity of a pet. As a result of this life-saving technology, some 8,000 dogs and cats are successfully reunited with their owners every month.

While the ability of microchips to drastically improve pet safety is unarguable, a recent veterinary case report associated microchip implantation with sarcoma development in 1 dog.¹ Furthermore, in the context of microchip use in humans, sporadic reports of sarcoma development in implanted laboratory mice and rats have received recent publicity in the popular media.

Unquestionably, veterinarians would not continue to implant microchips if they believed the devices presented significant, scientific risk of causing malignant tumors in dogs and cats. However, because recent publicity has raised awareness and concern about this topic, a review of the relevant database of research regarding both laboratory animals and pets follows.

MICROCHIP SAFETY IN LABORATORY RODENTS

Laboratory mice and rats are routinely used for the detection and classification of toxic or cancer-causing materials as part of product-safety studies required for most any type of chemical agent used in humans or animals (e.g., drugs, sanitizers, cosmetics, etc.). Because the identification of laboratory animals is a critical element of long-term toxicity and carcinogenicity studies, test subjects are usually implanted with microchip identification devices to help ensure accurate collection of research data. Implantable microchips are recommended as an easy, secure, and durable method of identification, in contrast to conventional but unreliable or painful means of identification such as ear notches/tags, toe-clipping, and tattooing.²

Historically, neoplasms have been documented as occasionally occurring in areas of chronic fibrotic tissue reaction in response to injury due to asbestosis, schistosomiasis, and foreign bodies.³ Mice, rats, and to some extent, dogs were found to be more susceptible to foreign body tumorigenesis compared to pigs, chickens, and hamsters. Early 1970's research demonstrated that most any foreign body (solid inert material) implanted in the subcutaneous regions of a mouse or rat could potentially cause a sarcoma, including plain glass (mild Class 2 sarcoma)^{4,5} but only microchips have tended to receive on-going scrutiny beyond the other substances/objects implicated in earlier research efforts. Examination of tissue reactions to microchip implants in various zoo animals,⁶ rabbits, guinea pigs, woodchucks, and amphibians⁷ produced connective tissue capsules, but not sarcomas. Over the years, several studies have reported observations regarding tissue reactions of laboratory mice and rats implanted with microchips. The incidence of microchip-associated sarcoma development in laboratory rodents is very low, and researchers acknowledge that direct extrapolation of laboratory rodent sarcomas to dogs, cats, food animals, or humans is inappropriate.

MICROCHIP STUDIES WITH NO HISTOPATHOLOGY

A 2-year study was conducted in 1990 to assess tissue reactions to microchip devices implanted in subcutaneous tissues of mice.⁸ The study involved 70 male and 70 female B6C3F1 mice that were implanted with a microchip. No histopathological or neoplastic effects were observed for up to 24 months in any tissues around the implanted microchips. The devices were found to be highly reliable (> 95%) and more dependable than other methods for the unique identification of mice in long-term studies.

Similar results were reported in a year-long 1991 study involving 40 Sprague-Dawley rats.⁹ No adverse clinical or

histopathological effects associated with the microchips were observed, and no evidence of persistent inflammatory reaction.

MICROCHIP STUDIES WITH HISTOPATHOLOGY

A 1997 study involving 4,279 laboratory mice found lesions at the site of microchip implantation in 36 of the CBA/J mice (only 0.8%), primarily in female mice about a year after implantation.² The majority of the tumors were benign fibrosarcomas (collagen, connective tissue, etc.), but a few were histologically malignant. None of the animals experienced metastases of the described tumors. Overall, the study found the incidence of tumor formation, whether benign or malignant, was extremely low.

A much higher incidence of histopathology was found in a 1999 study involving 177 genetically engineered mice.¹⁰ Strains of specially devised tumor-prone mice have been developed in recent years for the use in carcinogenicity product-safety studies. These bioengineered animals, lacking a particular tumor-suppressor gene, were created in an effort to reduce the amount of time needed for carcinogenicity studies compared to similar investigations involving normal, genetically intact mice. Using these animals (heterozygous *P53*^{+/-} transgenic mice), investigators noticed the development of sarcomas in some mice in the area of the implanted microchip device. Eighteen of 177 mice (10%) were diagnosed with an undifferentiated histologically malignant sarcoma arising at the transponders site, the earliest at 15 weeks after implantation.

The researchers published their observations to alert the research community that a relatively high rate of sarcoma development appeared to occur as a result of a foreign body (i.e., microchip) in these specific types of tumor-prone, genetically modified laboratory mice. Since the tumor-prone animals are being used for carcinogen detection, researchers wanted to understand all the characteristics of these bioengineered animals so results from various product-safety studies could be reliably assessed.

The authors concluded that their observations regarding foreign body carcinogenesis in a particular strain of tumor-prone mice reinforce the importance of evaluating and integrating the sum total of understanding about experimental models. They remind readers that blind leaps from the detection of tumors to the prediction of health risks in other species should be avoided, and that carcinogenesis data solely from experimental animals alone should never be used for the generation of regulatory policy.

A paper published in 2006 reported a retrospective evaluation of subcutaneous microchip-associated tumors collected from 3 carcinogenicity studies involving a total

of 1,260 mice (strain B6C3F1).¹¹ The overall occurrence of tumors was 4.1% (52 mice). Almost all tumors appeared during the second year of the studies (1 exception at week 51). The authors concluded that, in the context of other published data, their research supports the hypothesis that a difference in tumor susceptibility exists between various strains of laboratory mice.

MICROCHIP SAFETY IN DOGS

As mentioned earlier, the safety record for use of microchips in dogs and cats is extraordinary. Because millions of implantations have been performed in pets throughout the world over the past 15 years, any major underlying health issue associated with the use of microchips in dogs and cats should have become evident. Still, additional research has been conducted to further quantify the safety of microchips in pets.

HISTOLOGICAL EVALUATION STUDY

The histologic effects of microchip implantation were the subject of a long-term 2003 study where dogs were evaluated for up to 6 years after implantation.¹² The study involved 9 dogs implanted with the Destron Fearing® LifeChip®. Subsequently, 8-cm³ of cutaneous tissue containing the microchip were surgically removed from 2 dogs each at 3 days, 3 months, 1 year, and 3 years after implantation, and from 1 dog at 6 years post-implantation. The histology of the tissue samples was described for each sample date.

Insertion of the microchip with the injection needle produced an inconsequential wound approximately 1 mm in diameter that completely disappeared after 7 to 10 days. At 3 days post-implantation, foreign body reactions to the subcutaneously implanted microchips were observed in the form of inflammatory cell infiltration, fibroblast proliferation, and granulation tissue formation; this inflammatory reaction disappeared by 3 months after implantation. At 12 months, a firm capsule of connective tissue 10 to 50 μ thick around the microchip was complete. Samples collected at 3 years and 6 years after implantation appeared similar to those at 1 year post-implantation. The researchers concluded that implanted microchips were likely to function safely throughout a dog's lifetime, without causing further histological changes.

LIPOSARCOMA CASE-REPORT

Even though extensive global use of microchips over many years has firmly documented the safety of the technology, and the negligible tissue effects associated with microchips have been studied, some practitioners have expressed concern about a recent singular adverse event involving a canine microchip. A case report published in 2004 described a liposarcoma at the site of a

microchip implant in a dog¹. (A "case report" is not a controlled scientific study; rather, it is a preliminary and singular observation reported to veterinary colleagues).

The case report involved a single 11-year-old male mixed-breed dog examined for a subcutaneous mass located in the lateral region of the neck above the left shoulder blade. The owner had noticed a small nodule at this site 19 months after implantation of a microchip. The mass was eventually excised 2 years post-implantation and diagnosed as a low-grade liposarcoma. The mass was well circumscribed, the surrounding tissues were not infiltrated, and no metastases were found. The dog showed no signs of recurrence at 3 months post-surgery.

The authors chose to publish their experience in a brief veterinary journal article because tumors arising at the site of microchip implantation had never been reported in dogs. (As discussed earlier, tumors had only been reported in mice and rats, with the mechanism of carcinogenicity ascribed to a foreign body-induced tumorigenesis.) However, as noted, this report was not a controlled scientific study; in the absence of further research, any inference that the microchip was the cause of the tumor would be premature. The authors point out that microchips provide a safe, painless, and durable identification technique for dogs and cats, and that thousands of microchips are implanted into dogs, cats, and horses each year. They concluded the report by simply encouraging veterinarians to annually check the microchips in implanted pets (e.g., when animals are brought in for vaccination), and to report any adverse reactions.

The same authors subsequently published an additional case report in 2006 regarding a 9-year-old French bulldog.¹³ However, in this case a fibrosarcoma developed at a vaccination site and the microchip was adjacent to it, outside the tumor. The location of the microchip beyond the tumor margin, therefore, casts doubt on whether the microchip had any involvement with the resulting histological abnormality, especially since post-injection fibrosarcoma is a well-known pathologic entity, particularly for cats. Though rare, feline sarcomas have been associated with vaccine administration,¹⁴⁻¹⁷ while no evidence of reaction to microchips or subsequent sarcoma development has been offered.¹² Still, prudence may suggest that vaccinations should not be administered in the same area as implanted microchips, so common inflammatory responses associated with vaccinations are not attributed to the presence of a microchip.

ONGOING EVALUATION/SURVEILLANCE

Though the global database potentially associating sarcoma development in dogs with microchip implantation is extremely limited (1 dog), Destron Fearing is proactively

examining the subject and has involved prominent veterinary pathologist researcher Lawrence McGill (DVM, PhD, Diplomate American College of Veterinary Pathologists) in the process. Dr. McGill is a 30-year industry veteran and noted expert in the study of sarcomas in companion animals. Notably, he was a key contributor in recent epidemiology studies involving injection site sarcomas in felines.^{14,15} Dr. McGill was founding Chair of the American College of Veterinary Pathologists Oncology Committee (currently Chair of the Mammary Oncology Subcommittee), former Chair of the Council of Communications of the American Veterinary Medical Association, former President of the Utah Veterinary Medical Association, and currently Technical Vice President and Veterinary Pathologist at Animal Reference Pathology, a division of Associated Regional and University Pathologists (ARUP) located in Salt Lake City.

With Dr. McGill's assistance, Destron Fearing intends to continue reviewing all publications in the scientific literature and determine the potential causes of any such adverse events that might arise in the future. Furthermore, as always, Destron Fearing encourages practitioners to monitor implanted pets and report any concerns.

CONCLUSIONS

The use of microchips in pets is a safe, effective, and durable means of identification that has been used globally in millions of animals for nearly 2 decades. To date, the entire global database of sarcoma development in microchipped dogs is limited to a single case report involving 1 animal. Furthermore, though low incidences of vaccine-related sarcoma development have been documented in cats (even more rare in dogs), microchip-associated sarcoma development has never been reported in felines. In the context of millions of microchip implantations spread over many years, this near absence of adverse event documentation comprises an impressive and expansive safety record. Therefore, the benefits of microchip implantation with regard to the safety and welfare of pets should they become lost or separated from their owner have proven to be infinitely greater than the remote and unsubstantiated risk of tumor development associated with microchip implantation.

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