

Vaccine-associated feline sarcomas

Wallace B. Morrison, DVM, MS, DACVIM; Robin M. Starr, DVM, MEd;
and the Vaccine-Associated Feline Sarcoma Task Force

A letter to the editor published in the *Journal of the American Veterinary Medical Association* in October 1991 first raised the issue of a potential association between vaccination of cats for rabies and development of sarcomas.¹ At about this same time, the vaccine industry had shifted from production of modified-live virus vaccines for rabies prophylaxis to killed-virus vaccines. This change had been encouraged by the USDA-Animal Plant Health Inspection Service (APHIS) primarily because of concerns about vaccine-induced disease with the use of modified-live rabies virus vaccines. Most killed-virus vaccines contain adjuvants to enhance the immune response, and injection of some killed-virus vaccines has been shown to result in inflammatory granulomas in cats.² Some of these inflammatory granulomas to progress to sarcomas.³

Additional reports, including individual case reports and retrospective epidemiological studies, that supported concerns voiced in the initial letter quickly followed.^{4-20a} The weight of these cumulative reports resulted in alarm and controversy in the veterinary medical profession, which continues today. As the evidence for a causal relationship between vaccination for rabies and development of sarcomas grew, it became apparent that a causal relationship between vaccination for FeLV and development of sarcomas also existed.^{4,7,14} In addition, there appeared to be much smaller, but nonetheless real, associations between development of sarcomas and vaccination for other infectious diseases in cats and between development of sarcomas and injection of nonvaccine products.^{4,16,21}

In response to concerns about this emerging health issue of cats, the American Veterinary Medical

Association (AVMA), American Animal Hospital Association (AAHA), American Association of Feline Practitioners (AAFP), and Veterinary Cancer Society (VCS) jointly formed the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) in November 1996. The mission of the VAFSTF was to plan and execute a coordinated response of research and education to what had become a substantial problem for cats, cat owners, and the veterinary medical profession. The task force was authorized by the sponsoring organizations to address the problem during a 3-year period. Because most sarcomas that developed at injection sites were associated with injection of vaccines, the VAFSTF focused on the issue of sarcoma formation associated with vaccination in cats.

The VAFSTF has brought substantial financial and scientific resources to bear on this problem. The task force has provided educational information to veterinarians and the public and funded research to understand the fundamental nature of postvaccinal sarcoma development and how best to treat affected cats. By providing accurate scientific information and funding research, the VAFSTF has kept this problem before the veterinary medical profession and the producers of vaccines and other products meant for parenteral use in cats. The VAFSTF has responded to media and public inquiries, has demonstrated that the profession is addressing the issue, and, thereby, has helped defuse potential adverse publicity. In addition, the VAFSTF, along with other veterinary organizations, has recommended standardized sites for vaccination of cats in the United States and has offered guidelines for the management of injection site masses and sarcomas. The purposes of the present white paper are to present a summary of the current understanding of vaccine-associated feline sarcomas (VAFS) and to describe the activities of the VAFSTF since its inception.

Definition of the Problem

Vaccination against serious infectious diseases is a necessary component of delivering state-of-the-art health care to cats. The diseases that can be prevented by vaccination can be devastating and life threatening. In addition, vaccination against rabies is an important part of the public health responsibilities of practicing veterinarians and is required by law in many states.

For most vaccines used in cats,

From the Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Purdue University, West Lafayette, IN 47907 (Morrison); and Starr and Company LLC, 31575 Griffin Drive Conifer, CO 80433 (Starr).

Address correspondence to Dr. Starr.

Members of the Vaccine-Associated Feline Sarcoma Task Force

Steering Committee

American Animal Hospital Association Dr. Michael Paul
American Association of Feline Practitioners Dr. Thomas Elston
Dr. James Richards
American Veterinary Medical Association Dr. Leonard Tinney
Veterinary Cancer Society Dr. Wallace B. Morrison

Subgroup Chairs

Molecular Biology/Etiology Dr. Barbara Kitchell
Treatment Dr. Dennis Macy
Epidemiology/Pathology Dr. Mattie Hendrick
Education/Communication Dr. James Richards

Allied Group Representation

Animal Health Institute (1996-1998) Dr. Kent McClure
Dr. Mark Woods
USDA-APHIS (1996-1999) Dr. Donna Gatewood
Dr. Ted Williams

Administrative

AVMA Staff Support Dr. Lyle Vogel
Task Force Chair Dr. Robin Starr

annual booster vaccination has been the standard of practice. However, for most vaccines other than rabies vaccine, studies of the **duration of immunity (DOI)** induced by vaccination are not required for licensing by the USDA-APHIS, the federal entity responsible for licensing of vaccines. Unless a DOI study had been done that proved efficacy beyond 1 year, the USDA-APHIS required that the vaccine label contain a recommendation for annual revaccination. The **Council on Biologic and Therapeutic Agents (COBTA)** of the AVMA and most colleges and schools of veterinary medicine adopted these label recommendations as part of their vaccination guidelines. In the case of rabies vaccines, even when vaccine manufacturers marketed vaccines shown to induce immunity for 3 years, local and state requirements would often mandate annual revaccination. The USDA-APHIS now requires manufacturers of vaccines containing novel antigens (antigens not contained in previously licensed products) to provide data to support the DOI claim stated on the product label.

Recently, the profession has begun to question some previously held beliefs regarding vaccination practices and the DOI induced by vaccination. Studies^{22,23} of a single commercially available inactivated, adjuvanted, feline panleukopenia, herpesvirus, and calicivirus combination vaccine found evidence that vaccinated cats were completely protected from challenge exposure to virulent panleukopenia virus and partially protected from exposure to herpesvirus and calicivirus for substantially longer than 1 year. The authors concluded that DOI following administration of this product was in excess of 7 years and that persistence of antibody titers against all 3 viruses for more than 3 years supports recommendations that cats may be revaccinated against these viruses at 3-year intervals.

It is estimated that 22 million cats were vaccinated during 1991.⁵ However, because many cats received multiple vaccines, the number of vaccines administered to cats that year was much higher than 22 million. In addition, there has been a proliferation of new vaccines for cats in the marketplace since the late 1980s, including vaccines for FeLV, feline infectious peritonitis virus, *Bordetella bronchiseptica*, *Giardia* spp, and dermatophytes. The need to prevent infectious diseases should now be balanced against the risk of VAFS and other adverse events. Vaccination should be viewed as a medical, rather than a routine, procedure. However, the profession lacks sufficient data to accurately assess the relative risk of administering a particular vaccine or antigen to an individual cat.

Incidence of VAFS—The true incidence of vaccine-associated sarcomas in cats is unknown. Sarcomas develop at vaccination sites at rates ranging from 1 case/10,000 cats to 10 cases/10,000 cats and develop primarily after administration of rabies virus and FeLV vaccines.^{3,4,16} These estimates are based on retrospective epidemiologic studies and surveys of biopsy specimens submitted to diagnostic laboratories and, in conjunction with current estimates of the US cat population and the number of annual visits to veterinarians, suggest that between 2,200 and 22,000 cats will develop vaccine-associated sarcomas each year.

In a retrospective study⁴ of 345 cats with vaccine-associated sarcomas, the risk that a cat would develop a sarcoma after administration of a single vaccine in the cervical-interscapular region (a site not recommended by the VAFSTF or AAFP guidelines) was 50% higher than the risk that a cat not receiving any vaccines at this site would. In the same study, the risk for a cat given 2 vaccines at the same site was approximately 127% higher, and the risk for a cat given 3 or 4 vaccines was 175% higher than the risk for a cat not receiving vaccines at that site. Time to tumor development in cats following vaccination was as short as 3 months and as long as 3 years or longer.⁴

Pathologic abnormalities—Vaccine-associated sarcomas in cats are most often fibrosarcomas, but many other types of sarcomas have also been reported.^{6,12,14} These sarcomas in cats are usually characterized by marked nuclear and cellular pleomorphism, high mitotic activity, and large central zones of necrosis, features consistent with an aggressive biological behavior. Often a peripheral inflammatory infiltrate consisting of lymphocytes and macrophages is seen. Macrophages in these sarcomas often contain a bluish-gray foreign material identified by electron probe x-ray microanalysis to be aluminum and oxygen. Aluminum hydroxide is 1 of several adjuvants used in currently available feline vaccines. Similar inflammatory responses and foreign material have been described for inflammatory vaccination-site reactions in cats, dogs, and humans.^{3,24}

Vaccine-associated sarcomas consist of cells that are morphologically and immunohistochemically compatible with fibroblasts and myofibroblasts. The precise pathogenesis of vaccine-associated sarcomas is unknown but may involve stimulation of these cells by highly immunogenic and persistent adjuvants or other vaccine components resulting in inflammation that alone or in association with unidentified carcinogens or oncogenes leads to neoplastic transformation and tumor development. Transition zones from inflammatory granuloma to sarcoma have been identified and strongly suggest that the inflammatory response to vaccination is antecedent to sarcoma development in cats.²⁵ Inflammation is known to precede development of other types of cancers in cats and other species.²⁶

A study published in 1996²⁷ reported that FeLV and feline immunodeficiency virus did not appear to play any role in the pathogenesis of vaccine-associated sarcomas.

Treatment—Vaccine-associated feline sarcomas are highly invasive and, often, rapidly growing neoplasms that require aggressive treatment, which may include a combination of surgery, radiation therapy, and chemotherapy.^{28,29,b,c} Metastases may develop, and the metastatic rate increases with survival time. Because vaccine-associated sarcomas often mimic benign postvaccinal injection site granulomas, differentiating these lesions is critical.

Current task force guidelines recommend that masses at vaccine sites that are still evident ≥ 3 months after vaccination, are > 2 cm in diameter, or are growing in size 4 weeks after vaccine administration be treated aggressively (**Appendix 1**).

Task force-funded studies have shown the value of computed tomography and magnetic resonance imaging in determining the extent of these tumors before surgery or radiation therapy. These types of diagnostic imaging studies have improved the effectiveness of treatments and the overall outcome. The control rate is higher for lesions located on limbs, presumably because wide surgical margins can be obtained with limb amputation. The best treatment results are associated with aggressive resection at the first surgery; there appears to be minimal opportunity for tumor control if the patient has undergone previous surgeries for the tumor.²⁸

Radiation therapy when combined with surgery increases tumor control. Radiation therapy has been shown to be beneficial if given before or after definitive surgery. Despite the combination of aggressive surgery and radiation therapy, however, treatment will fail in many patients.^{29,b,c} Vaccine-associated feline sarcomas are somewhat sensitive to a variety of chemotherapeutic agents such as doxorubicin, carboplatin, mitoxantrone, and cyclophosphamide. However, the addition of chemotherapy to radiation therapy and surgery has only modestly prolonged disease-free intervals. The unfortunate truth is that there are no good treatment options for cats with these tumors, further emphasizing the importance of tumor prevention.

Summary of the problem—The essence of the problem is that cats need to be vaccinated for several important diseases. In the case of rabies, vaccination of cats is also important to controlling the disease in humans and is required by law in most states. Intramuscular or subcutaneous injection of some vaccines may result in inflammatory granulomas in some cats, and some of these inflammatory reactions progress to sarcomas. Once a sarcoma is established in a cat, there are no good treatment options, and the prognosis is poor.

The Vaccine-Associated Feline Sarcoma Task Force

After the initial recognition of the association between vaccination and sarcoma development, several groups, including the AAFP, the Academy of Feline Medicine, and the California Veterinary Medical Association, developed preliminary recommendations for vaccination of cats. However, the breadth and complexity of the issue needed a unified response by the profession that would bring the combined financial, communication, and human resources of major national veterinary medical organizations to bear on this health threat to cats.

The first meeting of the VAFSTF was held Nov 11, 1996. A combined effort of the AVMA, AAHA, AAFP, and VCS, the task force has representatives from each of the sponsoring organizations and from the USDA-APHIS and the Animal Health Institute. The 10-member task force was assembled to address the issue of development of sarcomas at injection sites of commonly used vaccines in cats.

The objectives of the VAFSTF have been to define the scope and incidence of the problem, determine causal and prognostic factors relating to this disorder,

evaluate treatment options, and educate and inform veterinarians and the public. The task force established 4 subgroups. Three of these were developed to assist in meeting research objectives in the general areas of epidemiology and pathology, molecular biology and etiology, and treatment. A fourth was established to develop and disseminate educational information to veterinarians and the public.

Raising funds to support the research and educational missions of the VAFSTF was an early priority, with initial efforts funded largely by the sponsoring veterinary organizations themselves. To date, \$708,378 in contributions has been raised in support of the VAFSTF goals, and \$549,863 has been distributed to support 16 research studies.

Research—The initial mandate for the 3 research subgroups was to identify research priorities in each area. The task force established criteria for the awarding of research funds and developed and distributed requests for proposals for the years 1997–1998, 1998–1999, 1999–2000, and 2000–2001. Research funds were awarded on the basis of criteria proposed by the subgroups and approved by the task force. Submitted proposals were independently reviewed by committees consisting of members representing the AAHA Scientific Review Committee, the AVMA Council on Research, researchers and clinicians in academia, and scientists in research and development in industry.

The objective of the Epidemiology and Pathology subgroup was to promote multicenter prospective and retrospective studies to determine the incidence and prevalence of vaccine-associated sarcomas and identify the vaccines involved. The objectives of the Molecular Biology and Etiology subgroup were to explore prognostic and predictive factors, identify causative components of implicated vaccines, and identify markers of susceptibility in affected cats. The objective of the Treatment subgroup was to explore treatment protocols and investigate the efficacy of various therapeutic regimens.

Education and communication—The objective of the Education and Communication subgroup was to develop and disseminate information to the veterinary profession as soon as it became available from the other subgroups. The chair of the Education and Communication subgroup was designated as the official spokesperson for the VAFSTF, with responsibility for all public communication. The VAFSTF recognized that the immediate need of the profession and cat-owning public was reliable information. In 1996, little was known about this problem except that there was an apparent causal relationship between vaccination and tumor development. The initial action of the VAFSTF was to summarize and distribute information regarding vaccine-associated sarcomas as they were then understood. This included development of a recommended protocol for vaccine administration and a client information brochure (*Vaccines and Sarcomas: A Concern for Cat Owners*) to assist veterinarians in addressing client concerns about vaccine-associated sarcomas (Appendix 2). In 1999, the VAFSTF developed a protocol for diagnosis and treatment of VAFS (Appendix 1) that was distributed by vaccine manufacturers.

Copies of the client brochure are available by contacting the AAHA, AVMA, or Cornell Feline Health Center. All of the task force guidelines and updates of task force activities, along with a complete list of references relating to vaccine-associated sarcomas in cats, are available at the VAFSTF Web site at www.avma.org/vafstf.

Key events—On Jul 25, 1998, a symposium on vaccine-associated sarcomas in cats was held during the 135th Annual Convention of the AVMA in Baltimore. The symposium was cosponsored by the VAFSTF and the Arm & Hammer Division of Church & Dwight Co, Inc. Symposium topics included a historical review of the problem; risk factors, pathogenesis, etiology, and treatment of the disease; formation of the task force and its funding of studies; and education and communication with the public and veterinarians regarding the disease. Another symposium is planned for the AVMA Annual Convention in 2001.

On Feb 4–7, 1999, a special midyear meeting of the Veterinary Cancer Society in Bodega Bay, California, was devoted to the topic of vaccine-associated sarcomas in cats. Topics included results of various treatment protocols and interim reports from investigators funded by the VAFSTF and other sources.

The future of the task force—The original intent of the veterinary organizations that established the VAFSTF was that the task force would coordinate and promote awareness, education, and research relating to vaccine-associated sarcomas in cats for 3 years. It was expected that after 3 years the issue would have enough momentum of its own to continue on to resolution without the direct involvement of the task force. However, the veterinary organizations that established the task force have requested that the VAFSTF continue to fund research on the epidemiology and pathology, molecular biology and etiology, and treatment of VAFS and continue to interpret and disseminate information from research already funded. In addition to studies funded during 2000, final reports from several earlier studies are not yet available, and none are yet published. The problem of vaccine-associated sarcomas in cats remains undiminished, and vaccine formulations that are not associated with any risk of sarcoma development are not yet standard. The task force believes it has an ongoing responsibility to continue updating vaccination and treatment recommendations and publicizing factors that put cats at risk for developing sarcomas as research findings and new vaccines become available.

Sponsors of the VAFSTF—As of Dec 7, 2000, a total of \$708,378 had been contributed or pledged to the task force to fund research into the prevalence, causes, and treatment of VAFS. Sponsors include Pfizer Animal Health (\$225,000), the AAHA Foundation (\$100,000), Fort Dodge Animal Health (\$75,000), AVMA (\$50,000), AAEP (\$45,000), Novartis Animal Health (\$45,000), Cornell Feline Health Center (\$30,000), Intervet America Inc (\$30,000), Merial (\$30,000), Schering-Plough (\$30,000), the VCS (\$15,000), Biocor Animal Health (\$15,000), Bayer Corporation (\$10,000), the Ohio Ani-

mal Health Foundation (\$5,000), Synbiotics (\$2,500), and individual contributors.

Research funded by the VAFSTF—Research rarely reveals secrets to difficult problems with bold announcements but rather unmasks the truth in multiple modest steps that conflict and support and then eventually coalesce to create an accurate understanding of the problem. Vaccine-associated sarcomas are complex biological problems without simple solutions. Nevertheless, research is beginning to characterize them and to delineate potential preventative and therapeutic strategies. Preliminary findings from studies funded by the VAFSTF represent a foundation for a process of discovery that is ongoing.

One of the most important studies funded by the VAFSTF is a nationwide prospective multicenter epidemiologic study of the determinants of vaccine-associated sarcoma development in cats. This study is nearing completion, and its results will be important in shaping future decisions of the task force.

Another study^d demonstrated that vaccine-associated sarcomas have lost heterozygosity of the critical cell cycle regulating gene p53. This represents an important finding, because p53 dysregulation is common to most cancers in humans. Normal p53 gene function mediates normal programmed cell death or apoptosis, and an absence or inhibition of programmed cell death can contribute to unrestricted growth and survival of cells. Thus, it is possible that alterations in p53 gene function may mediate the final pathway of oncogenesis in vaccine-associated sarcomas.

Many oncogenes cause cancer through overexpression of growth factors or their receptors.³⁰ Platelet-derived growth factor and platelet-derived growth factor receptor are inappropriately expressed in vaccine-associated sarcomas.^e Platelet-derived growth factor is normally released by disintegrating platelets and stimulates the division of fibroblasts as part of the normal wound healing process. Fibroblasts respond to platelet-derived growth factor but do not normally produce it. When platelet-derived growth factor is present in inappropriate amounts, normal fibroblasts can be transformed into sarcoma cells.³¹

Preliminary results of a study using an *in vitro* assay system indicate that some feline vaccines are directly mutagenic.^f The responsible components and cellular mechanisms of the mutagenic damage have yet to be elucidated.

Other preliminary results indicate that papillomavirus, herpesvirus, and polyomavirus do not play any role in the pathogenesis of vaccine-associated sarcomas.

Treatment of VAFS is expensive, associated with considerable morbidity, and frequently unsuccessful. A promising chemotherapeutic agent, liposome-encapsulated doxorubicin, was found in 1 study to induce unacceptable rates of delayed toxicoses, necessitating a reduction of the dosage used during the clinical trial.

Contrast-enhanced computed tomography has demonstrated early extensive cancer invasion into normal tissues surrounding a grossly visible mass. New treatment strategies need to be developed to successfully manage this aggressive tumor.

Clinical Recommendations

Vaccination should be viewed as a medical procedure to be performed only after careful assessment of the needs of the patient, rather than as an automatic act dictated by the calendar. Each veterinarian and cat owner must determine the relative risk of disease for individual cats and make appropriate decisions regarding vaccination. Rabies vaccination recommendations should follow state and local regulations.

The AAFCP and Academy of Feline Medicine Advisory Panel on Feline Vaccines has stressed the importance of vaccinating the largest number of cats possible within a population, vaccinating each individual cat no more frequently than necessary, and vaccinating only against infectious disease agents to which individuals have a realistic risk of exposure and subsequent disease. The panel concluded that annual revaccination is not always needed and may increase the risk that sarcomas will develop at vaccination sites.³²

The VAFSTF and AAFCP guidelines for vaccination of cats stress standardization of vaccination sites. These guidelines for vaccination sites have been adopted by many of the schools and colleges of veterinary medicine in North America and by the US Army.

Conclusions

Vaccination is a medical procedure that should be undertaken with the same thoughtful consideration as any other medical procedure in veterinary practice. As with most aspects of medical practice, there are benefits and risks to vaccination. Accordingly, vaccination protocols should be individualized to the patient, with consideration given to the medical importance and zoonotic potential of the infectious agent, the patient's risk of exposure, and germane legal requirements.

Vaccine-associated feline sarcomas are a conundrum for the veterinary medical profession. We do not understand the attributes of the feline immune system and genome that make cats susceptible to VAFS, yet we must continue to vaccinate cats against key infectious diseases. Vaccination was once considered an essential routine medical procedure with minimal risk. In the past decade, we have recognized that vaccination protocols must include assessment of the risk of sarcoma development. Until more is known about the epidemiology and pathogenesis of VAFS, we can only limit vaccination to the minimum required for optimal health. As new vaccines and technologies are developed, their potential advantages and limitations should be evaluated. The VAFSTF recommends that previously issued guidelines on standardization of vaccination and injection sites, diagnosis and management of VAFS, and reporting of adverse events be followed.

Billions of dollars have been spent to understand the causes of and find cures for cancers in humans. In comparison, our efforts to understand and cure vaccine-associated sarcomas in cats are just beginning. There is still much to be done. Further research into the epidemiology, causes, treatment, and prevention of vaccine-associated sarcomas is essential to solving this problem.

^aMeyer KE. Vaccine-associated feline sarcomas: a summary of USP data (abstr), in *Proceedings. Vet Cancer Soc* 1998;18:47.

^bKobayashi T, Hauck ML, Price GS, et al. A retrospective analysis of 189 cats evaluated for feline vaccine site sarcoma from 1985 to 1998 (abstr), in *Proceedings. Vet Cancer Soc* 1999;19:23.

^cBurke JK, Sorenmo K, Duda L, et al. The effect of adjuvant orthovoltage radiation therapy on feline vaccine-associated fibrosarcomas: a retrospective study of 15 cases (abstr), in *Proceedings. Vet Cancer Soc* 1999;19:20.

^dKanjilal S, Banerji N, Fifer A, et al. p53 tumor suppressor gene alterations in vaccine-associated feline sarcoma (abstr), in *Proceedings. Vet Cancer Soc* 1999;19:48.

^eCarew JS, Schmidt JA, Humphrey SA, et al. Growth factor expression and vaccine-associated sarcoma tumorigenicity (abstr), in *Proceedings. Vet Cancer Soc* 1999;19:25.

^fMcNiel EA, LaRue S, Vannais D, et al. Evaluation of feline rabies vaccines for mutagenicity using the A_L assay (abstr), in *Proceedings. Vet Cancer Soc* 1998;18:48.

Appendix 1

Protocol for diagnosis and treatment of suspected vaccine-associated sarcomas in cats

The following recommendations from the Vaccine-Associated Feline Sarcoma Task Force are based on information available as of April 1999 and are subject to revision as new information becomes available.

Diagnosis

1. Record anatomic location, shape, and size (measured by caliper in 3 dimensions) of all masses that develop at the site of an injection.
2. Treat any mass that develops at an injection site as if it were malignant until proven otherwise. A mass should be fully assessed and aggressively treated if it
 - ▶ Persists > 3 months after injection,
 - ▶ Is > 2 cm in diameter, or
 - ▶ Is increasing in size 1 month after injection.

If a mass meets 1 or more of these criteria, a diagnostic biopsy should be performed prior to surgical excision. A cutting needle biopsy or incisional wedge biopsy is preferred. Cutting needle biopsy should be done in such a way that any subsequent surgical procedure to remove the mass can readily include the entire needle tract. Incisional wedge biopsy should be performed in such a way that any subsequent surgical procedure to remove the mass can also remove all tissue affected by the biopsy. Cytologic evaluation of fine-needle aspirates is considered unreliable for the diagnosis of vaccine-associated feline sarcomas and is not recommended.

Management

If a mass that develops at a vaccination site is confirmed to be malignant, the following procedures should be followed:

1. Routine thoracic radiography and preoperative laboratory analyses should be performed.
2. When feasible, computed tomography or magnetic resonance imaging should be performed. Soft-tissue sarcomas often spread along fascial planes, and these local extensions of the tumor may be undetectable visually during the early stages of tumor growth. Results of advanced diagnostic imaging may be useful in determining the extent of surgery and the size of the radiation field that will be needed to maximize the chances for successful treatment.
3. Prior to initiating any treatment, consult a veterinary oncologist for current treatment options, which may include radiation therapy, chemotherapy, surgery, and other modalities.
4. Never "shell out" a sarcoma. Incomplete surgical removal of a sarcoma is the most common cause of treatment failure. Use standard oncologic surgical techniques to avoid seeding malignant cells. Remove at least a 2-cm margin of normal-appearing tissue around all sides of the mass, including the deep side. In some instances, reconstruction of the body wall, removal of bone, and other advanced surgical techniques will be required.
5. Submit the entire excised specimen for histologic evaluation. Mark the excised mass with India ink or suture tags to provide anatomic references to facilitate subsequent treatment.
6. Report all histologically confirmed vaccine-associated feline sarcomas to the vaccine manufacturer and the United States Pharmacopeia Veterinary Practitioners' Reporting Program. To make a report or request reporting forms, call 800-4-USP-PRN (800-487-7776) or visit the United States Pharmacopeia Web site at www.usp.org.

After a vaccine-associated sarcoma has been removed, the patient should be rechecked and a physical examination performed monthly for the first 3 months after surgery, then at least every 3 months for 1 year. Additional diagnostic procedures should be performed as appropriate for the abnormalities detected.

Appendix 2

Protocol for administration of vaccines to cats

The issue of vaccine-associated sarcomas is clearly complex, and complete answers are expected only after the expenditure of considerable effort. In the interim, veterinarians and cat owners alike can make decisions that may reduce the possibility of sarcoma development and improve the chances of successful treatment. More complete recommendations will be made as information from the task force is generated, but, on the basis of material from the American Association of Feline Practitioners, the Academy of Feline Medicine, and the California Veterinary Medical Association, the task force presents the following guidelines:

1. The manufacturer's label recommendation is the only official item veterinarians currently have to demonstrate the basis for vaccination.
2. Alternative vaccination routes (eg, nasal or topical) should be considered if and when feasible.
3. Use of vaccines packaged in single-dose vials should be encouraged.
4. Vaccination is a medical procedure, and customized vaccination protocols should be developed for individual patients. No vaccine should be administered until the medical importance and zoonotic potential of the infectious agent, the patient's risk of exposure, and the germane legal requirements have been considered.
5. Any vaccine-associated sarcomas and other adverse reactions should be reported to the vaccine manufacturer and the United States Pharmacopeia. Information about the United States Pharmacopeia's Veterinary Practitioners' Reporting Program can be obtained by calling 1-800-4-USP-PRN. Submission of forms by diagnostic laboratories will be facilitated if the laboratories include a report form for each instance of a vaccine-associated sarcoma. The report form should include vaccine type, serial number, and vaccination site; this information should also be incorporated in the patient's permanent medical record.
6. To further characterize the causal link between vaccination and development of sarcomas and to facilitate treatment of vaccine-associated sarcomas, the following general guidelines for administration of vaccines and other injectable products are suggested:
 - a. Veterinarians should standardize the sites for administration of vaccines and other injectable products in their practices and document the location of each injection, the type of vaccine or other injectable product administered, and the manufacturer and serial number of any vaccine given in the patient's medical record.
 - b. The following sites for administration of vaccines are recommended*:
 - i. Vaccines containing antigens limited to panleukopenia virus, feline herpesvirus type-1, and feline calicivirus, without or without *Chlamydia* antigens, should be administered on the right shoulder, according to the manufacturer's recommendations.
 - ii. Vaccines containing rabies virus antigen, with or without any other antigen, should be administered on the right hind limb, as distally as possible, according to the manufacturer's recommendations.
 - iii. Vaccines containing FeLV antigen, with or without any other antigen except rabies virus antigen, should be administered on the left hind limb, as distally as possible, according to the manufacturer's recommendations.

*Initial recommendations of the Vaccine-Associated Feline Sarcoma Task Force distributed in November 1996. These recommendations vary slightly from the 2000 American Association of Feline Practitioners and Academy of Feline Medicine guidelines.

References

1. Hendrick MJ, Goldschmidt MH. Do injection site reactions induce fibrosarcomas in cats? (lett) *J Am Vet Med Assoc* 1991;199:968.
2. Macy DW. Vaccine associated sarcomas in cats, in *Proceedings*. Am Coll Vet Internal Med 1995;13:842-843.
3. Hendrick MJ, Goldschmidt MH, Shofer FS, et al. Postvaccinal sarcomas in the cat: epidemiology and electron probe microanalytical identification of aluminum. *Cancer Res* 1992;52:5391-5394.
4. Kass PH, Barnes WG Jr, Spangler WL, et al. Epidemiologic evidence for a causal relation between vaccination and fibrosarcoma tumorigenesis in cats. *J Am Vet Med Assoc* 1993;201:396-405.
5. Esplin DG, McGill LD, Meininger AC, et al. Postvaccination sarcomas in cats. *J Am Vet Med Assoc* 1993;202:1245-1247.
6. Hendrick MJ, Brooks JJ. Postvaccinal sarcomas in the cat: histology and immunohistochemistry. *Vet Pathol* 1994;31:126-129.
7. Hendrick MJ, Schofer FS, Goldschmidt MH, et al. Comparison of fibrosarcomas that developed at vaccination sites and at non-vaccination sites in cats: 239 cases (1991-1992). *J Am Vet Med Assoc* 1994;205:1425-1429.

8. Roark MJ. Practitioners' exchange. *J Am Vet Med Assoc* 1996;208:1382.

9. Gemmill LT. Practitioners' exchange. *J Am Vet Med Assoc* 1996;208:1382-1383.

10. Manderino DM. Practitioners' exchange. *J Am Vet Med Assoc* 1996;208:1383.

11. Macy DW, Bergman PJ. Vaccine-associated sarcomas in cats. *Feline Pract* 1995;23:24-27.

12. Doddy FD, Glickman LT, Glickman NW, et al. Feline fibrosarcomas at vaccination sites and non-vaccination sites. *J Comp Pathol* 1996;114:165-174.

13. Lester S, Clemett T, Burt A. Vaccine site-associated sarcomas in cats: clinical experience and a laboratory review (1982-1993). *J Am Anim Hosp Assoc* 1996;32:91-95.

14. Esplin DG, Jaffe MH, McGill LD. Metastasizing liposarcoma associated with a vaccination site in a cat. *Feline Pract* 1996;24:20-23.

15. Weigand CM, Brewer WG Jr. Vaccination-site sarcomas in cats. *Compend Contin Educ Pract Vet* 1996;18:869-875.

16. Coyne MJ, Reeves NCP, Rosen DK. Estimated prevalence of injection-site sarcomas in cats during 1992. *J Am Vet Med Assoc* 1997;210:249-251.

17. Hendrick MJ. Historical review and current knowledge of risk factors involved in feline vaccine-associated sarcomas. *J Am Vet Med Assoc* 1998;213:1422-1423.

18. Sandler I, Teeger M, Best S. Metastatic vaccine associated fibrosarcoma in a 10-year-old cat. *Can Vet J* 1997;38:374.

19. Rudmann DG, Van Alstine WG, Doddy F, et al. Pulmonary and mediastinal metastases of a vaccination-site sarcoma in a cat. *Vet Pathol* 1996;33:466-469.

20. Esplin DG, Campbell R. Widespread metastasis of a fibrosarcoma associated with a vaccination site in a cat. *Feline Pract* 1995;23:13-16.

21. Esplin DG, Bigelow M, McGill LD, et al. Fibrosarcoma at the site of a lufenuron injection in a cat. *Vet Cancer Soc Newsletter* 1999;23(2):8-9.

22. Scott FW, Geissinger C. Duration of immunity in cats vaccinated with an inactivated feline panleukopenia, herpesvirus, and calicivirus vaccine. *Feline Pract* 1997;25:12-19.

23. Scott FW, Geissinger CM. Long-term immunity in cats vaccinated with an inactivated trivalent vaccine. *Am J Vet Res* 1999;60:652-658.

24. Hendrick MJ, Dunagan CA. Focal necrotizing granulomatous panniculitis associated with subcutaneous injection of rabies vaccine in cats and dogs: 10 cases (1988-1989). *J Am Vet Med Assoc* 1991;198:304-305.

25. Hendrick MJ, Kass PH, McGill LD, et al. Postvaccinal sarcomas in cats. *J Natl Cancer Inst* 1994;86:341-343.

26. Morrison WB. Environmental causes of naturally occurring cancers in dogs and cats. In: Morrison WB, ed. *Cancer in dogs and cats: medical and surgical management*. Philadelphia: The Williams & Wilkins Co, 1998;31-41.

27. Ellis JA, Jackson ML, Bartsch RC, et al. Use of immunohistochemistry and polymerase chain-reaction for detection of oncornaviruses in formalin-fixed, paraffin-embedded fibrosarcomas from cats. *J Am Vet Med Assoc* 1996;209:767-771.

28. Hershey AE, Sorenmo KU, Hendrick MJ, et al. Prognosis for presumed feline vaccine-associated sarcoma after excision: 61 cases (1986-1996). *J Am Vet Med Assoc* 2000;216:58-61.

29. Cronin K, Page RL, Spodnick G, et al. Radiation therapy and surgery for fibrosarcoma in 33 cats. *Vet Radiol Ultrasound* 1998;39:51-56.

30. Hendrick MJ. Feline vaccine-associated sarcomas: current studies on pathogenesis. *J Am Vet Med Assoc* 1998;213:1425-1426.

31. Klein G. Oncogenes. In: Holland JF, Frei E, Bast RC, et al, eds. *Cancer medicine*. 3rd ed. Philadelphia: Lea & Febiger, 1993:65-77.

32. Elston T, Rodan I, Flemming D, et al. 1998 report of the American Association of Feline Practitioners and Academy of Feline Medicine Advisory Panel on Feline Vaccines. *J Am Vet Med Assoc* 1998;212:227-241.