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Vaccine-Associated Feline Sarcoma Task Force: Roundtable Discussion

The current understanding and management of vaccine-associated sarcomas in cats

The **Vaccine-Associated Feline Sarcoma Task Force (VAFSTF)** has served veterinarians, cats, and cat owners for nearly nine years. Initially designed to function for only three years, the VAFSTF members found a continuing need to address this issu utmost importance. Having fulfilled its mission to stimulate research and initiate preliminary changes in vaccination protocols designed to reduce the risk of sarcoma formation in cats, the VAFSTF will conclude its official activities after a panel discussion t held during the 142nd Annual Convention of the American Veterinary Medical Association. Veterinarians participating in the following roundtable discussion will assemble during the convention and respond to questions from attendees.

Regardless of the efforts of countless individuals, the problem of vaccine-associated sarcomas in cats has not been solved. Researchers in academia and industry continue to study this singularly complex problem, but it is reasonable to assume that the definitive solution will not be identified in the immediate future. As a way of summarizing the current understanding and optimal management of vaccine-associated sarcomas, the VAFSTF members and several invited participants convened a roundtable discussion on December 6, 2004, at the headquarters of the American Animal Hospital Association. Questions asked by member the **American Association of Feline Practitioners (AAFP)** and chosen laypersons were compiled and posed to participants. The following is a condensed transcript of that discussion. Dr. James R. Richards was moderator of the panel discussion.

Several roundtable participants were strongly in favor of creating a summary statement with recommendations to accompany this transcript. Although such a statement may have merit, most of the participants believed that a summary would fail to express the complexity of vaccine-associated sarcomas and may lead to incomplete understanding or even misinterpretation. Therefore, reade are encouraged to consider the document in its entirety.

Members of the Vaccine-Associated Feline Sarcoma Task Force

James R. Richards, DVM, Cornell Feline Health Center, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, Education/Communications Chair, Roundtable moderator.

Robin M. Starr, DVM, MEd, (Chair) Freedom Service Dogs Inc, 12395 W Ohio Cir, Lakewood, CO 80228-3644.

Henry E. Childers, DVM, DABVP, 1119 Park Ave, Cranston, RI 02910, representing the AVMA.

Thomas H. Elston, DVM, DABVP, The Cat Hospital, 3069 Edinger Ave, Tustin, CA 92780, representing the American Association of Feline Practitioners.

Lyle P. Vogel, DVM, MPH, DACVPM, American Veterinary Medical Association, 1931 N Meacham Rd, Schaumburg, IL 60173, VAFSTF Staff support.

Link V. Welborn, DVM, DABVP, 4308 Hudson Ln, Tampa, FL 33618, representing the American Animal Hospital Association.

Invited Participants

Jane E. Brunt, DVM, Cat Hospital at Towson, 6701 York Rd, Baltimore, MD 21212.

Mattie J. Hendrick, VMD, DACVP, Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, Epidemiology/Pathology Chair.

Barbara E. Kitchell, DVM, PhD, DACVIM, Center for Comparative Oncology, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824, Etiology Chair.

Dennis W. Macy, DVM, MS, DACVIM, Department of Clinical Medicine, College of Veterinary Medicine, Colorado State University, Fort Collins, CO 80523, Treatment Chair.

Kent D. McClure, DVM, JD, Animal Health Institute, 1325 G Street NW, Ste 700, Washington, DC 20005-3104, representing the Animal Health Institute.

Wallace B. Morrison, DVM, MS, DACVIM, Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Purdue University, West Lafayette, IN 47907, representing the Veterinary Cancer Society.

Larry T. Glickman, VMD, DrPH, Department of Veterinary Pathobiology, School of Veterinary Medicine, Purdue University, West Lafayette, IN 47907-1243.

Philip H. Kass, DVM, MPVM, PhD, DACVPM, Department of Population Health and Reproduction, School o Veterinary Medicine, University of California, Davis, CA 95616.

Margaret C. McEntee, DVM, DACVIM, DACVR, Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853.

Lawrence D. McGill, DVM, PhD, Animal Reference Pathology, ARUP Laboratories, 500 Chipeta Way, Salt Lake City, UT 84108.

Ronald D. Schultz, PhD, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI 53706-1102.

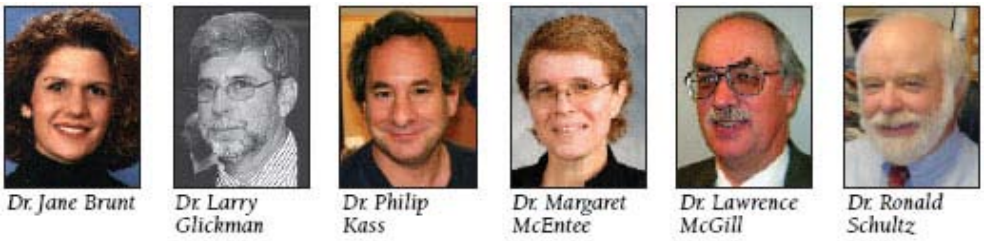
Address correspondence to Dr. Richards.

Members of the Vaccine-Associated Feline Sarcoma Task Force

Dr. Robin Starr | *Dr. Henry Childers* | *Dr. Thomas Elston* | *Dr. Mattie Hendrick* | *Dr. Barbara Kitchell* | *Dr. Dennis Macy*

Dr. Kent McClure | *Dr. Wallace Morrison* | *Dr. James Richards* | *Dr. Lyle Vogel* | *Dr. Link Welborn*

Invited Participants



Dr. Jane Brunt | *Dr. Larry Glickman* | *Dr. Philip Kass* | *Dr. Margaret McEntee* | *Dr. Lawrence McGill* | *Dr. Ronald Schultz*

Question: How is the veterinary profession responding to the problem of vaccine-associated sarcomas in cats?

DR. ROBIN STARR: A major way the profession responded was to form the VAFSTF in 1996 (Appendix 1).

Question: Has a cause-and-effect association between administration of vaccines and sarcoma formation been firmly established?

DR. LARRY GLICKMAN: A cause-and-effect association between an exposure (eg, a vaccine) and an outcome (eg, a sarcoma) can only be established with scientific certainty by use of experimental methods that control all potentially compounding factors. In such experiments, cats free of sarcomas would be randomly allocated to receive either a vaccine or a placebo injection, and then, both groups of cats would be followed over time to determine whether there was a significant difference in the incidence of sarcoma at the injection site. Such experiments, however, are unlikely to be performed because of the large number of cats that would be required to detect a significant difference between the groups with respect to a very infrequent event with an estimated incidence of one in 1,000 or one in 10,000 cats.

Observational (ie, noninterventional) epidemiologic studies have been used to identify a cause-and-effect association between an exposure and a disease when it is logistically impractical or unethical to conduct experiments. An example would be smoking and development of lung cancer in humans. Criteria established for causality and observational studies include the following: the exposure precedes the disease or outcome of interest, the association between exposure and disease is strong (ie, in epidemiologic terms, there is a large odds ratio or relative risk), there is a dose-response relationship between exposure and disease, the association between exposure and disease is fairly specific, the association between exposure and disease is biologically plausible (ie, a mechanism exists that would explain the association), and a consistent association between exposure and disease is found across several studies.

Few epidemiologic studies examining the association between vaccination and subsequent development of a sarcoma at the vaccination site have been performed. Results of a study by Kass et al[8] indicate that there is a significant association between prior vaccination for FeLV (odds ratio, 5.4) or rabies virus (odds ratio, 1.99) and the subsequent development of a fibrosarcoma at the vaccination site. Furthermore, the risk of cats developing fibrosarcomas after administration of a single vaccine in the cervical or interscapular region was approximately 50% higher than that in cats not receiving vaccines in those regions. The risk in cats that received two vaccines was approximately 127% higher than that in cats not receiving vaccines in those regions, and the risk in cats that received three or four vaccines was approximately 175% higher than that in cats not receiving vaccines in those regions. Results of a subsequent prospective case-control study by Kass et al[9] indicate that no single manufacturer or vaccine brand within an adjuvant class was found to be associated with sarcoma formation. However, certain long-acting injectable medications may have been associated with sarcoma formation.

In my opinion, results of those two studies by themselves are not sufficient to establish a cause-and-effect association between vaccine administration and sarcoma formation in cats. Rather, the results suggest an appropriate temporal sequence and indicate a dose-response association between vaccination and fibrosarcoma formation. The magnitude of this association is fairly strong, but I don't believe that enough studies have been performed to determine that there is a consistent association. Results of another study[10] reporting the presence of aluminum adjuvant in fibrosarcomas developing at vaccination sites provided some evidence for biologic plausibility.

However, I believe there is insufficient scientific evidence at this point to support a cause-and-effect association between vaccine administration and subsequent sarcoma development at the injection site. Additional epidemiologic studies are needed. Such prospective studies are now logistically feasible given the growth of large corporate practices with paperless, electronic medical records. Randomized clinical trials are unlikely to be performed because of substantial cost and time requirements.

DR. PHILIP KASS: I'm not quite as pessimistic about whether a cause-and-effect association has been established. I'm going to read an excerpt from a statement attributed to Sir Austin Bradford Hill that offers an alternative perspective. I cite him because, interestingly, he is credited with first establishing the six aforementioned criteria, although, in reality, he never actually used that word in addressing causation and claimed that none of his guidelines were even necessary for causal inference. From the 1965 proceedings of the Royal Society of Medicine,[11]

> Finally, in passing from association to causation I believe in 'real life' we shall have to consider what flows from that decision. On scientific grounds we should do no such thing but in another and more practical sense we may surely ask what is involved in our decision. All scientific work is incomplete, whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer on us a freedom to ignore the knowledge we already have or postpone the action that it appears to demand at a given time.

The point that Hill forcefully makes is that you can't always wait to have irrefutable scientific evidence before you have to take some

sort of action. I believe that through experimental work that has been performed and published, through observational and even anecdotal information that has now been generated over and over, and through the few epidemiologic studies that have been performed, although we can never truly prove anything in a scientific (and logical) sense, even through experimentation, there is a abundance of evidence to indicate that vaccine-associated feline sarcoma is a real phenomenon, and the cost of waiting and doing nothing is much greater than the cost of acting now.

DR. MATTIE HENDRICK: I agree with Dr. Glickman in that, in a totally scientific way, we have not proven that there is a cause-and-effect association between vaccination and sarcoma formation, but in every other way, I think we have. I don't think we need to spend more money to do more studies to find out whether there is a link.

DR. WALLACE MORRISON: There have been more than two studies concerning vaccine-associated feline sarcomas published by Dr. Kass.[8,9] Another study by Esplin et al[12] and numerous case reports[13-17] on vaccine-associated feline sarcomas have been published.

Another interesting aspect is what pathologists tell us about the rather unique histologic appearance of these sarcomas and the way they differ from other kinds of sarcomas. There are also two studies, one in ferrets[18] and one in dogs,[19] on the development of presumptive vaccine-associated sarcomas in other species, and the histologic appearance of sarcomas in those species was similar what has been seen in cats, including the presence of aluminum in tissues.[18,19] I believe it is a complete story, and I'm confident that there is an association between vaccine administration and sarcoma development in cats.

DR. KENT MCCLURE: I think Dr. Glickman is absolutely correct in that a cause-and-effect association has not been established w scientific certainty. We are making an inference. With time, we may realize that this inference was absolutely correct, or we may f points where the inference was not correct, and additional information will drive us in a different direction. Different people look a same data and reach different opinions. I think that is healthy for ongoing discussion and search for a solution. The uncertainty is the reasons why different veterinarians and manufacturers have taken different approaches to try to solve the issue. Manufacturers vaccines recognize that they need to be part of the solution, and manufacturers have taken different approaches because they view issue differently.

DR. JANE BRUNT: I've seen vaccine-associated sarcomas, as have my colleagues. It seems clear to me and my colleagues in AAI that results of additional studies are not needed to prove that there is an association between vaccine administration and sarcoma formation in cats. On the other hand, there are a number of others who have not seen a vaccine-associated sarcoma, and they are r inclined to continue to vaccinate as they always have. Veterinarians' belief in the association between vaccine administration and sarcoma formation depends on what their experience has been.

DR. MCCLURE: When looking at a lifetime cancer risk on a relatively rare event, it would take huge numbers of cats housed in isolation and given nothing but the vaccine you are trying to monitor. You would have to start with kittens and follow them for a l time. All would agree that is not a study that is going to be performed, and I think veterinarians, vaccine manufacturers, and researchers will look at various types of solutions. It is healthy to recognize that the association between vaccine administration an sarcoma formation is inferred; the association has not been proven with scientific certainty. Keeping that in mind will allow us to l objective in analyzing additional data.

DR. KASS: An important point is that there is a difference between scientific standards and veterinary public policy. Given the am of work that has been done on this problem during the last 10 years, it would be foolhardy to simply demand that additional scien standards be met before we elect to do something. The way we live our lives in this world, such as the need to eat healthfully, the to exercise, or the need to spay and neuter pets, is largely governed by nonexperimental studies. These issues have largely come al from small numbers of observational studies with results compelling enough to act on. We cannot demand scientific exactitude le the cost of not acting will lead to loss of health or life.

DR. GLICKMAN: The question was whether a cause-and-effect association has definitively been established. The answer is no but does not mean that we should not act on what we have found. Of course, we should act. We should have sensible responses but a admit that further research is needed. We will need to keep changing our recommendations as new evidence is analyzed. We may come back 10 years from now and determine that a cause-and-effect association still has not been proven; yet, the actions we take eliminate the problem in the meantime. Before we even knew that there was a virus that causes acquired immunodeficiency syndrome, we had identified things we could do to diminish transmission. Discovery of the virus did not come until five or six ye later. So, we must act on information we have. Our responsibility as veterinarians is to do what we think is best.

DR. DENNIS MACY: In 1999, the World Health Organization International Agency for Research on Cancer reviewed the scientific literature with regard to vaccine-associated sarcomas. They believed there was limited evidence of carcinogenicity of adjuvanted feline vaccines. That is the second-highest category out of a possible four categories that could be allocated to a potentially carcino substance.

Question: Have parenterally administered products other than vaccines been associated with

sarcoma formation?

DR. LAWRENCE MCGILL: Administration of other products has been associated with sarcoma formation. Results of early studie[8] indicate that sarcomas developed at sites in which methylprednisolone acetate sterile aqueous suspensiona was given. We have als reported on one case[20] of sarcoma formation that was associated with lufenuronb administration. Sarcoma formation has been associated with administration of long-acting penicillin.[9] In my opinion, the reason we have seen this type of tumor associated with vaccination is the fact that vaccines are consistently administered to cats, and until recently, they have been administered annually according to the manufacturer's recommendations. If other products were administered in the same location annually, then I believ those products would also be commonly associated with sarcoma formation in appropriately susceptible cats. I also believe aluminum adjuvant helped us determine the association of these sarcomas with injections. Without aluminum adjuvants, it may h taken a lot longer to confirm this disease process.

DR. JAMES RICHARDS: It is worth noting that just because a sarcoma has developed at the site of an injection that does not necessarily mean the injection caused the sarcoma. Until epidemiologic studies with parenterally administered products other than vaccines that are equivalent to studies of vaccines are completed, it is going to be difficult to determine whether administration of lufenuron or long-acting penicillins are associated with sarcoma formation.

DR. MACY: There may be different risks with different injectables. We have looked at the injection site after administration of lufenuron, and the type of reaction is different from that induced by rabies virus or FeLV vaccines. Lufenuron induces primarily a macrophage infiltrate, rather than a lymphocytic or other type of cellular infiltrate. The carcinogenic effects of various cytokines m depend on what effect is elicited by that particular product and that effect may be less with lufenuron. Otherwise, I think more cas reports would be seen for a substance that is injected twice a year (as is the case with injectable lufenuron).

We have also looked at microchip implantation sites 21 days after implantation, excised them, and looked for evidence of inflammation. No inflammation has been found with the implant itself. However, the process of implanting the microchips may c off some hair and displace it underneath the skin. Keratin induces a considerable inflammatory response. So, it may not be just th implant, but rather, some event that happens during the process of implanting the microchip.

DR. RONALD SCHULTZ: We implanted small carbon rods as controls in injection site reaction studies with vaccines, and the cellu as well as the molecular events that occur at the sites of the implants are different from those we saw with certain vaccines.[6] The difference between the vaccines themselves is tremendous as well. Adjuvanted rabies virus and FeLV vaccines induce a very diffe cellular reaction than that caused by modified live panleukopenia virus, calicivirus, or herpesvirus vaccines. We don't necessarily know what that means, but there are differences.

DR. BRUNT: Dr. Macy, you mentioned that you've seen inflammation associated with pieces of hair tracked into injection sites. W is the relative inflammation, compared with vaccines?

DR. MACY: The amount of inflammation caused by a small amount of keratin is far less than what we see with an adjuvanted rab virus vaccine. We don't know the threshold necessary to trigger a sarcoma, but the Rous sarcoma virus model in chickens[21-23] indicates that the more inflammation, the higher the potential for carcinogenesis.

DR. HENDRICK: My opinion, on the basis of what I know about basic pathology and what I have observed, is that cats have a predisposition to develop sarcomas in response to inflammation, but something changed in 1989. Suddenly, we started seeing mo sarcomas than the sporadic ones that we would have seen after administration of various injectables. In my opinion, what changed was new formulations for vaccines. In some way, they promoted a more robust, unusual, or exuberant inflammatory response an that led to an increase in the development of sarcomas. Something happened and not just because of the higher frequency of vacci administration, compared with other injectables. Cats have been receiving vaccines more often than lufenuron, fluids, or methylprednisolone acetate sterile aqueous suspension.[a]

DR. MACY: In 1985, we made a big change in the way cats are vaccinated in this country. We went from the use of a modified-liv rabies virus vaccine to an adjuvanted killed virus vaccine. In the same year, an aluminum adjuvanted FeLV vaccine was introduce Both of those events correspond temporally to the emergence of vaccine-associated sarcomas in the late 1980s.

DR. MCCLURE: I think it's important to note that the requirement to use killed rabies virus vaccines was thrust on the veterinary community as well as the vaccine manufacturers because of concern that the modified-live virus vaccines could potentially cause rabies in immunosuppressed animals.[22-24] Also, a new or novel adjuvant was not introduced during that same time. The same type adjuvants had been used for a long time in veterinary medicine, and until just a few years ago, they were the only types allowed fo in vaccines for humans.

Question: Results of epidemiologic studies[8,25] performed in the 1990s indicated an incidence rate of approximately 1 to 3 sarcomas/10,000 vaccinated cats, but some claim that results of later studies

suggest a lower incidence rate. Is there a discrepancy?

DR. KASS: Some studies measure incidence, and some measure prevalence; they're not the same thing. Simplistically speaking, incidence refers to the occurrence of new disease over a period of time. It can be measured as a cumulative proportion, or it can be measured per unit time at risk (ie, a rate). Prevalence is a reflection of the cross-sectional presence of disease in a population at a particular point in time and is, simplistically speaking, a function of the incidence rate and the duration of the disease. The early estimates were very rough approximates. Initially, when the problem was first recognized, we weren't even sure exactly what we were looking at or whether it was even a real problem. It was difficult to try to establish the incidence of something that we didn't even existed.

There are many challenges in trying to accurately measure the incidence, even in a prospective cohort study like our Web-based survey.[26] One of the single biggest problems was that the pathologists used in these studies were unable to definitively determine a sarcoma was caused by a vaccine. It's important that the results of that study are not misinterpreted. We did not say that we had determined the incidence of vaccine-associated sarcomas. Rather, the major thrust of the study was what the incidence of vaccine-associated sarcoma is not; it is not a common tumor among vaccinated cats. The results did not appear to be compatible with an incidence of more than approximately one in 5,000 cats. I don't know how many of these tumors remain undiagnosed, and that's a big impediment when performing incidence studies. But to come back to the question about discrepancies, I don't think we can compare results of various studies because the studies were performed differently.

Question: Are there any other comments on incidence studies?

DR. GLICKMAN: I think we know enough about the biology and pathology of the sarcoma to make educated guesses about which sarcomas are associated with injection sites. I think, as in any epidemiologic study, there would be confirmed cases and suspect but unconfirmed cases. Then, the incidence rate of each could be measured, and I suspect that the true incidence would be somewhere between the two. I think such an incidence study is possible. It would take tremendous resources and collaborations to conduct, but I think the challenges to doing it are not that different from those presented by other diseases that have a clinical definition but no firm diagnostic criteria. But I agree with Dr. Kass that the estimates are going to vary because the studies are extremely different. What the incidence rate is, it's going to be low.

DR. LINK WELBORN: But from a practitioner's standpoint, I think there is an incredible need to inform clients of the risk of their cat developing a sarcoma. Although I recognize the limitations associated with determining an incidence rate, I think we need to be able to give clients an educated guess.

DR. GLICKMAN: There are two ways of looking at this. First, if the risk is one in 5,000 as opposed to one in 10,000 cats, would it make a difference to the owner? How precise of an estimate is necessary for a client to make an educated decision? Second, I think what means more to the client is the relative risk; that is, if we give this vaccine, then the risk that their cat will develop a vaccine-associated sarcoma is three to four times greater than if we give another vaccine. Results of studies by Kass et al[8,9] clearly indicate that there is an increased risk of sarcoma formation after administration of rabies virus and FeLV vaccines in cats. However, that still doesn't tell the veterinarian or the owner just how likely it is that a particular vaccine will cause a problem.

DR. SCHULTZ: I think we have to be careful because there may well be a great deal of difference among vaccines. All rabies virus vaccines are not necessarily the same, nor are all FeLV vaccines.

It may be sufficient for practitioners to inform clients that there may be a potential problem but that the problem is rare. They don't have to say that the risk is one in 10,000 or one in 1,000 cats; only that it's a rare event and that if the client decides not to vaccinate cat, then here is the potential outcome. In other words, inform clients of the risk of an adverse reaction associated with vaccination compared with the risk of not vaccinating.

Question: As we have noted, one of the problems confronting epidemiologic studies is the difficulty in determining whether a particular sarcoma was indeed caused by a vaccine. Are there any histopathologic criteria that can clearly distinguish vaccine-associated sarcomas from those that develop from other causes?

DR. HENDRICK: Strictly speaking, no. When I'm looking at a sarcoma, there are no criteria that indicate to me that it was caused by a vaccine. Having said that, histologically, the sarcomas look different from other sarcomas. One study[27] compared the histopathologic findings in vaccination site and nonvaccination site sarcomas; results indicate that differences were detected. Sarcomas at the vaccination site were associated with more inflammation, necrosis, and cellular pleomorphism and increased mitotic activity and extracellular matrix. Visually, the most interesting characteristic is how much sclerosis and matrix there are in the sarcoma, and in the matrix, there are really bizarre, markedly pleomorphic tumor cells with high mitotic indices. In fact, I can pick a slide, know that the sarcoma is from a cat, look at it, and 99.9% of the time I'm correct in saying it is a sarcoma from a vaccination

DR. MCGILL: The criteria used to identify most of these sarcomas are very good. The sarcomas are just different from the typical fibrosarcomas in cats. The cells have large irregular nuclei, they are frequently pleomorphic, and the mitotic index is high. Commonly, there is a central area of necrosis containing fluid. The sarcoma will frequently have aggregates of lymphoid tissue around it and irregular aggregates of macrophages. If those macrophages have foamy cytoplasm containing bluish-gray granular material (not that the material necessarily caused the sarcoma), then this essentially locks in the diagnosis. Not all of the criteria are detected in all sarcomas. The question becomes, does a less aggressive neoplastic process related to these sarcomas exist that wou make them more difficult to identify?

We have noticed all kinds of differentiation. We have seen fibrosarcomas, malignant histiocytomas, osteosarcomas, and mixed-ce differentiation. Occasionally, we've seen hemangiosarcomas, rhabdomyosarcomas, chondrosarcomas, myofibrosarcomas, liposarcomas, and lymphosarcomas associated with this neoplastic process.

DR. MACY: A sarcoma induced by an injection of any substance may not necessarily first appear at the site of injection because antigen-processing cells can migrate away, and sarcomas can develop at some distance away from the original injection site. If the were histologic criteria that would invariably describe injection-induced sarcomas, regardless of whether they initially appeared at injection site, you could interpret the published data entirely differently in terms of incidence.

DR. HENDRICK: When I make a diagnosis, I call the sarcoma what it is: a fibrosarcoma, rhabdomyosarcoma, or whatever. Then, my comment, I will indicate that these features are most consistent with a vaccine-associated sarcoma.

DR. STARR: If the same slide was sent to different pathologists, how much agreement would there be?

DR. MCGILL: At least 70% or 80%, maybe even 90%.

DR. GLICKMAN: I agree. In a previous study,[27] we gave slides to different pathologists and there was good general agreement as to whether they were the type of sarcomas seen at vaccination sites or the type of sarcoma they had seen for years in sites that were n associated with vaccination sites.

Practitioners who might not think twice about a tumor developing at a vaccination site would read an article about vaccine-associat sarcomas and then report it or indicate that it was a tumor from a vaccination site. So, to overcome potential bias in that study,[27] we examined feline sarcomas that developed during a 20- or 30-year period and classified them as appearing either at a vaccination sit at a nonvaccination site on the basis of what was provided in the history. Then, we examined the ratio of vaccination site sarcomas nonvaccination site sarcomas with time. The ratio changed dramatically from perhaps 10% or 20% of all sarcomas developing at vaccination sites in the early 1980s to the opposite, 80% to 90% developing at vaccination sites, in the 1990s. So, something happ at vaccination sites to change that ratio. As others have pointed out, we have to try to understand what changed, but in my experien has been very difficult to determine. Specifics about vaccine formulations and manufacturing processes are proprietary informatio So, industry and veterinary scientists will have to work together to find the answer.

Question: Are there any other factors that make epidemiologic studies difficult?

DR. GLICKMAN: Retrospective studies are easy to conduct because they rely on preexisting cases of sarcomas and do not require waiting long periods for sarcomas to develop. The major drawback to retrospective studies, however, is that the incidence rate can be determined, and accurate vaccination histories are difficult to obtain. We have performed 20 or 30 studies in which we try to re vaccination history from owners, such as which vaccines were given, when, and at what site, and it's tremendously difficult. There so much inaccuracy, and veterinary records are often no better.

Prospective or cohort studies are preferable to retrospective studies because they yield incidence rates of sarcomas associated with different types of vaccines, but they generally require large sample sizes and many years to perform. However, it is now possible overcome these obstacles by use of the millions of cats vaccinated at large corporate practices with electronic records. But even the there are problems. For example, a corporate practice may use products from only one vaccine manufacturer, making it impossibl answer the question, "does this brand of rabies virus vaccine cause more reactions than that brand?" And results of those studies a easy to misinterpret if someone says, "Aha! See, that vaccine causes three reactions/10,000 cats, so let's use some other vaccine," when, in fact, we have no information on the other vaccine.

Obviously, the longer you look, the more difficult the study will be and the greater the number of external confounders (eg, other products given in the same injection site). Incidence studies may also need to be supplemented with owner questionnaires, measurement of vaccination site masses, or follow-up histopathologic examination. A single incidence study would probably cos much as all other VAFSTF-funded studies combined. I'm confident with enough resources it can be done, but I'm not sure it's wo the effort.

DR. KASS: I worry, too, that as time goes on we may be getting skewed samples of cats because veterinarians may become less inclined to submit biopsy specimens from masses for diagnosis, fearing that they may be opening themselves to litigation. I agree

with Dr. Glickman that the only realistic way to perform incidence studies is to use an enormous database from a large corporate practice. However, there would be a problem of representativeness because corporate practices tend to practice medicine in a fairly unified way, including fealty to a small number of vaccine brands.

Just for fun, I decided to perform some sample size calculations with the assumption that the incidence of vaccine-associated sarcomas in cats was one in 10,000, and I wanted to determine whether a particular vaccine doubled the risk. What sample size w be needed if I were going to perform a prospective study? I don't have the answer yet because it's so computationally difficult. The sample size was at 1.9 million cats and still going on my computer when I last looked. If complete information is contained in an electronic database, that would be great. Otherwise, I would have to go back and collect information on 2 million cats and that cou involve contacting and obtaining accurate data from perhaps millions of owners. I agree, though, that prospective studies are supe to retrospective studies for measuring incidence. This is not the case, however, for studying incidence risk factors.

I second Dr. Glickman's comments about the difficulty of getting accurate vaccination histories; owners don't remember everythir veterinarians often don't keep detailed records, and owners sometimes take their cats to more than one veterinarian for care. Performing a prospective cohort study like our Web-based survey[26] seems simple enough; here is how many cats were vaccinated, and here is how many sarcomas were diagnosed, but that doesn't necessarily translate into incidence because some cats may have vaccinated prior to the start of the study; the diagnosis in some cats may have been determined elsewhere; the diagnosis in some c may have been determined at hospitals that were contributing information, but the cats were not vaccinated there, and so on. It's m more complicated than just counting the number of cats vaccinated and the number of sarcomas diagnosed at a particular hospital.

Question: Is there any evidence that the incidence has changed as a result of newly recommended feline vaccination protocols?

DR. SCHULTZ: Because it's difficult to know the incidence, it's hard to tell whether it's changed. For the sake of argument, let's ass that rabies virus vaccines, especially adjuvanted rabies virus vaccines, are a significant risk factor. The AAFP and **the Academy of Feline Medicine's (AFM's)** recommended guidelines[28] for vaccination of cats did not really change the number of cats that is vaccinated for rabies. In fact, vaccination of cats for rabies has not decreased; if anything, it's increased because there are actually r states requiring it than was the case in the early 1990s. So, I would not expect to see any decrease in the incidence of vaccine-assoc sarcomas strictly because of a change in the number of cats receiving rabies virus vaccines. Something that has changed, though, i availability of nonadjuvanted rabies virus vaccines. Perhaps that is an area that we should investigate further.

Again, for the sake of argument, let's assume that FeLV vaccines, or at least a certain number of them, cause a problem. The curre AAFP/AFM recommended guidelines[28] are to vaccinate kittens determined to be at risk of exposure and revaccinate at a year and every year thereafter, if still at risk of exposure. So, we need to look at that recommendation again if, indeed, we believe that at lea certain FeLV vaccines are a problem (see Dr. Schultz's response to the question concerning what guidelines can be provided to veterinary practitioners)

There is at least one FeLV vaccine on the market for which the manufacturer reports no less than a three-year duration of immuni and there is a recently licensed FeLV vaccine that is quite different from other existing FeLV vaccines. All of this may impact the incidence of vaccine-associated sarcomas.

DR. THOMAS ELSTON: Regarding the AAFP/AFM's recommendations[28] on the use of FeLV vaccines, there is at least potential fo a change in the occurrence of fibrosarcomas. The AAFP/AFM guidelines[28] recommend that FeLV vaccines be used only in those cats at risk of direct exposure to FeLV-infected cats. With lifestyle changes in this country, we are seeing more and more cats beir housed totally indoors, as much as half of the cat population. With this much of the cat population at low to no risk, the use of Fel vaccine should, at least in theory, have decreased significantly. The effect of that should be a reduction in FeLV vaccine site fibrosarcomas. An example of that effect in an admittedly small sample size is that in my practice, where 90% of my patients no longer receive FeLV vaccines, during the last five years, I have not seen any fibrosarcomas associated with FeLV vaccines but continue to see as many fibrosarcomas associated with administration of rabies virus vaccines.

DR. GLICKMAN: Monitoring the ratio of vaccination site to nonvaccination site sarcomas is a good indicator of change, even if numbers of submissions of masses to laboratories vary. Results of one study[27] clearly indicate that the ratio of vaccination site sarcomas to nonvaccination site sarcomas seen in a typical diagnostic laboratory has increased dramatically. In 1989, the ratio was 0.54, meaning there were half as many vaccination site sarcomas as there were nonvaccination site sarcomas.[27] A year later, the ratio was 1.0; it more than doubled. In 1991, the ratio was 1.47; in 1992, it was 1.86; in 1993, it was 2.6; and in 1994, it was 4.3.27 W haven't followed it beyond that. This type of data can be collected from various laboratories to see if there is concordance and to ge idea of whether the problem is getting worse or getting better.

DR. BARBARA KITCHELL: How did you determine that a sarcoma was at a vaccination site versus a nonvaccination site?

DR. GLICKMAN: It depended solely on where the practitioner indicated that the sarcoma developed. If the practitioner indicated tha

was on the top of the head or the lower portion of the limb, we called it a nonvaccination site. If it was on the dorsal portion of the or interscapular space, we called it a vaccination site. The determination was somewhat arbitrary, but at least it was consistent with time. There obviously are problems with whatever criteria are used, but the data are already there, and it is worth investigating. We would have to worry about interpretation, but if the changes are consistent throughout the United States, with time, I think we would have to take notice of whether the ratio is increasing, remaining the same, or decreasing.

DR. ELSTON: There is no reliable data on how many veterinarians actually have changed the way they vaccinate cats, but I think manufacturers might know if the number of vaccines sold now is different than it was several years ago.

DR. MCCLURE: I don't have data on vaccine sales, but regarding the entire vaccination issue, I believe manufacturers have tried to navigate a path to work with the profession. Yet, we must realize that the veterinary biologics industry is highly regulated by the USDA. We have not seen many vaccine label changes, for example, because manufacturers are not free to change them. Label wording is negotiated, sentence-by-sentence, with the government; if a manufacturer wants to change it, they must generate solid data acceptable to the USDA Center for Veterinary Biologics. Many questions remain, and right now, there is more opinion than data. Manufacturers are trying to support practitioners who have decided that the data are sufficient to change their vaccination practices while at the same time supporting those who have decided that it's not.

Question: Early on, FeLV and rabies virus vaccines were more frequently implicated with sarcoma development than were other vaccines. Do we still believe this is the case?

DR. KASS: I think that is probably still the case. I have not seen anything to cause me to change my opinion.

DR. HENDRICK: In my pathology service, rabies virus vaccine has always been more commonly associated with sarcoma formation.

Question: What evidence do we have that inflammation induced by injectable products plays a role in sarcoma development?

DR. KITCHELL: It has long been recognized that chronic inflammation and wound healing can contribute to oncogenesis in many mammalian species. Unstable fracture repairs with metal implants are associated with tumor development, as are chronic nonhealing ulcers and burn wounds. In cats with ocular injuries and leakage of lens material, an inflammatory response results because the lens is an immunologically privileged site, and by some unknown mechanism, a sarcoma develops.[29] There is a great deal of evidence supporting the contribution of inflammatory cytokines and wound-healing mediators to carcinogenesis. During the process of wound healing, cells listen to their external environment and decide whether it is appropriate for them to replicate. Whenever there is tissue wounding or inflammation, wound-healing factors and cytokines are released within the tissue bed. Potentially, in the right individual with the right predisposing genetic elements, cell replication can lose control and become a neoplastic process. Dr. Hendrick can speak about results of her platelet-derived growth factor immunohistochemistry study. Under normal circumstances, fibroblasts in any tissue have platelet-derived growth factor receptors. But in vaccine-associated sarcomas, apparently an autocrine signaling process is taking place; the tumor cells themselves start to produce platelet-derived growth factor, which they then listen to or inflammatory cells present in the wound release platelet-derived growth factor, which fuels the replication of these fibroblasts.[d]

DR. HENDRICK: Those findings are not unique to my laboratory. Investigators in the laboratory of the late Greg MacEwen had cultured vaccine-associated sarcoma cell lines and, in molecular experiments, found that there was overexpression of platelet-derived growth factor and its receptor in those cells as well. Later, results of studies by Carew et al[30] and Katayama et al[31] indicate that a chemical that could block the interaction between platelet-derived growth factor and its receptor caused decreased growth of cultured sarcoma cells and increased their sensitivity to chemotherapeutic agents.

DR. KITCHELL: Beyond that, we have the whole issue of angiogenesis. A tumor cannot grow without a blood supply. What is it about these tumors that makes them particularly angiogenic and allows them to generate a blood supply? Specific immunologic players likely to trigger the response. Lymphocytes and macrophages infiltrating a tumor are probably not innocent bystanders but may, in fact, be biologically contributing to driving tumor development forward. We don't see the same types of tumors in areas with, say, neutrophilic inflammation, as in abscesses. Dr. Schultz, what about the cytokine profiling your group has performed in cats with vaccine-associated sarcomas? Is there something specific in the way these cats handle an inflammatory reaction that may predispose them to sarcoma development?

DR. SCHULTZ: We had hoped that we would be able to determine some unique sequence of events with regard to the cytokine profile and although we had some interesting findings, we were not able to demonstrate with certainty that a specific cytokine profile was more likely to lead to a neoplastic event. We hope to actually monitor the transition from inflammation at a vaccination site to neoplasia in the same cat, but that will be virtually impossible because we can't study enough cats. We need to evaluate cats that have a history of developing vaccine-associated sarcomas and compare events that develop after vaccination in those cats with events in clinically normal cats. Presently, we have a large amount of information on clinically normal cats, and hopefully, we can identify some key

signal.

DR. KITCHELL: Is there anything to suggest that macrophage cytokines are more predominant there?

DR. SCHULTZ: In certain reaction sites, yes, but we can't say that that would more likely lead to a neoplastic event. In fact, there is some evidence from other studies[32,33] in which the macrophage was the predominant cell type that the reaction was less likely to be associated with sarcoma development, possibly because of the suppressive effects of transforming growth factor-β.

DR. MACY: In our study,[e] 90% of the inflammatory cells detected at lufenuron injection sites were macrophages; there were very f lymphocytes and neutrophils. Yet, this has not led to a multitude of lufenuron-associated sarcomas. Plasma cells and lymphocyte have been the major players in other forms of carcinogenesis at implantation sites in humans and other animals, and I think that is more characteristic of sites in which rabies virus and FeLV vaccines have been administered. What is puzzling is that the magnitu the inflammatory response (ie, the size of the mass) was much greater after administration of the rabies virus vaccines we tested tl was after administration of FeLV vaccines. But the incidence of sarcoma development was similar for both or perhaps even highe FeLV vaccines. The difference between the response to FeLV and rabies virus vaccines may be a key in helping us understand a l bit more.

DR. HENDRICK: In many of the foreign body carcinogenesis studies[34-36] in other species, the fibroblast had to be a component of th inflammatory response. The mass had to form a capsule or have a proliferation of fibroblasts. In my opinion, the key has to be tha some component of the vaccine-induced inflammation turns on fibroblasts.

Question: Do vaccines with adjuvant consistently create more inflammation at the injection site than nonadjuvanted vaccines?

DR. MACY: Results of our studies[37,38] evaluating the histologic appearance of vaccination sites for a number of vaccines 21 days a administration, indicate that administration of nonadjuvanted vaccines induced no more reaction than does administration of saline (0.9% NaCl) solution in control cats. For adjuvanted products, the type of reaction didn't necessarily depend on the antigen class b rather on the composition of the adjuvant in the product. The amount of inflammation induced by products containing aluminum directly correlated to the aluminum content; more aluminum caused more inflammation. When adjuvant classes are compared (eg comparison between products containing aluminum adjuvant with products containing carbopol adjuvant), there is a difference in terms of the quality of the reaction. There may be more necrosis with products containing aluminum adjuvant than with carpobol-based products, but there is more edema 21 days after administration with carpobol-based products than there is with products containing aluminum adjuvant.

In all cases, the inflammation associated with administration of a three-year rabies virus vaccine was greater than that with adjuva FeLV vaccines. There was no histologic difference among the canarypox-vector rabies virus vaccine,[f] nonadjuvanted products, and control (saline solution) injection sites 21 days after administration.[39] So, adjuvanted products are doing what they were designed to do, stimulate antigen-processing cells and induce granulomas. It just may be detrimental to the cat in some cases. Our results suggested that aluminum induced inflammation more consistently and other adjuvants induced inflammation less consistently.

DR. MCGILL: Dr. Macy, in my laboratory, we find aluminum in only approximately half of the sarcomas that we see. I'm not rea say that aluminum adjuvants are the only ones involved with sarcomas.

DR. MACY: I agree. The point I'm trying to make is that not all adjuvanted products elicit the same type of response. The key, in t of relative risk among products, may be that the repertoire of cytokines from the cells at the injection site may be different depend on the vaccine or other injectable used.

Question: Building on that point, do we have evidence that injectable products that induce inflammation are more likely to be associated with sarcoma development? Can we say that the more inflammation a vaccine induces, the more likely a sarcoma will form?

DR. HENDRICK: We don't have enough scientific evidence to unequivocally say that, but on the basis of our theory of pathogenes one would predict that injectable products that induce inflammation would be more likely to be associated with sarcoma developm I don't think we can say that the more inflammation a vaccine induces, the more likely a sarcoma will form.

DR. MCCLURE: It is very important to note that the statement, "inflammation secondary to injection is a necessary precedent to sarcoma formation," is a hypothesis. We recognize that anything stimulating the immune system causes some degree of inflammation, and all vaccines cause some degree of inflammation. But is there some particular threshold, some combination of chemicals or molecules associated with the inflammation that triggers a neoplastic transformation? We have talked about different aspects of inflammation, and clearly, not all inflammatory processes are identical. As a result, manufacturers are adopting differer

approaches to vaccine formulation. Perhaps each manufacturer may look differently at the evidence, and they will each deal with a particular factor they see worthy of addressing. If a single factor was found to be causing the problem, they would all say "Aha, th it!" and then develop vaccines to alleviate the problem. But we are not there yet and that is why we will see different approaches.

Question: We now have a rabies virus vaccine[f] that, according to studies performed by Macy and Chretin[39] and Carroll,[c] induces less inflammation than other rabies virus vaccines, but it must be given annually as opposed to every three years. A frequently asked question concerning sarcoma formation is would it be better to administer a less inflammatory vaccine annually or a more inflammatory vaccine every three years?

DR. SCHULTZ: This is just my opinion. There is virtually no cellular infiltrate at the site of injection with the canarypox-vectored recombinant feline rabies virus vaccine[f] so there is virtually no cytokine response either; histologically, the site of injection looked much like the injection site in control cats receiving saline (0.9% NaCl) solution.[5] With the understanding that there is the potential for simply the trauma of injection to elicit a reaction, we can't say that there is no risk. But my opinion and my recommendation at this is that it is better to use the less inflammatory product more often than to risk the insult potentially triggered by the more inflamma product. That's what I recommend, but there's no information whatsoever on the likely outcome.

DR. HENDRICK: My understanding is that the depot of substance inducing inflammation remains at the injection site and serves a nidus to which the body responds. If that's the case, I would agree that you would want a less inflammatory substance given more frequently rather than a highly inflammatory substance given less frequently.

DR. KITCHELL: But it is a big leap of faith to say that it is solely the inflammatory reaction that induces a sarcoma. That leap has n been filled in with any kind of concrete structure. It takes the right kind of triggering event in the right individual cat to lead to neoplastic transformation. One could argue that we need fewer numbers of vaccinations to lower the risk that an individual cat will the trigger because we haven't identified the trigger. So as Dr. Schultz says, "we can accept more frequent vaccination with less inflammatory products." But I might counter by saying perhaps it would be better not to vaccinate as often because that may reduc overall risk. It may seem like common sense to say that there is an inflammatory reaction and that the reaction may lead to cancer, we don't know that for certain.

DR. MACY: But prior to 1985, we used modified-live virus vaccines every year and we did not observe the development of high-g sarcomas. Modified-live virus vaccines do not induce the inflammation. I agree that it's a leap of faith, but I would rather give a noninflammatory vaccine every year than give a more inflammatory vaccine every three years.

DR. RICHARDS: Clearly, we are not going to reach total agreement on this, at least on the basis of firm scientific evidence, but wh can do is lay out what the scientific evidence supports. If we believe that less inflammatory products are superior in terms of reduc the risk of sarcoma formation, let's list the evidence that supports that belief; then, let's separately list the caveats that prevent us fr taking an absolutely firm stance (Appendix 2).

Question: Some veterinarians diagnose vaccine-associated sarcomas with far greater frequency than others. Do certain geographic regions have a higher rate of occurrence?

DR. KASS: We have seen cases from all over North America, but it's impossible to tell whether the incidence is uniformly the sam The difference from practice to practice is really an issue of probability. For the sake of argument, suppose that the incidence is on 10,000 cats/y and suppose that the typical veterinarian vaccinates 10 cats/d, works 5.5 d/wk, and works 52 wk/y. The probability t veterinarian will not see a sarcoma in 10 years is approximately 5.7%. So, of 50,000 small animal practitioners who vaccinate cats almost 3,000 will not see a sarcoma in 10 years.

Question: Are vaccine-associated sarcomas a problem outside of North America?

DR. MORRISON: Papers published from Italy[19] and the Czech Republic[40] report them. In fact, they are seen throughout Europe.[41,g]

DR. MCGILL: In my personal experience in pathology, I've seen cases from Japan.

DR. HENDRICK: ...and Australia.[42]

DR. GLICKMAN: It's a worldwide problem.

Question: The AAFP and VAFSTF recommend that vaccines be given as distally as possible in different limbs, depending on the vaccine. Does this alter the likelihood of sarcoma development?

Would it improve treatment success should a sarcoma develop?

DR. MORRISON: I don't think it has any effect on the development of a sarcoma.

DR. KITCHELL: The most reliable method of curing these sarcomas is by complete surgical excision. If the sarcoma is located in t distal portion of the limb, amputation may allow complete excision. However, some sarcomas are so aggressive that they recur at amputation site.

DR. HENDRICK: Results of a study by Hershey et al[43] indicate that cats with sarcomas in the distal portion of the limb treated by amputation had longer median times to first recurrence than did cats with sarcomas excised from other sites.

DR. MARGARET MCENTEE: It is important to make sure that vaccines are given as distally as possible on the limb. For example, when vaccines are given high up on the hind limb, a sarcoma can extend into the pelvic area. Then, surgery is extremely invasive, complete excision is not possible. Additionally, when sarcomas are distally located on a limb, I think we find them earlier. We ca detect small sarcomas located on the distal portions of limbs.

DR. MACY: Along that same line, a misconception exists that sarcomas are less likely to form if the vaccine is given IM as oppos SC. All this does is make a mass more difficult to detect; you can't feel a granuloma, and you're not going to feel a sarcoma until i large. It delays treatment and worsens the prognosis.

Question: There have been reports of sarcomas that appear to be vaccine associated in other species, for example, ferrets[18] and dogs.[19] Will this become as large a problem in other species as it is in cats?

DR. MCGILL: We have seen vaccine-associated sarcomas in other species, but it's never going to be a problem in the other species it is in cats. We see maybe one a year in other species in our laboratory but as many as five a day in cats.

DR. SCHULTZ: We published a study[44] comparing the cytokine response to the same vaccine in cats, ferrets, and mink, and the responses were phenomenally different. The response in dogs is even more different.

DR. MACY: If the same vaccine is given to a mouse, a rat, and a cat and the excised vaccination site is examined histologically 21 after vaccination, there is a lot more vascularity in the vaccination site from the cat, compared with the mouse or rat. The granulom the site may be the same size in the cat as it is in the rat, but it's much more vascular. So, the same vaccine induces greater angiog in cats than it does in rats. One other thing that is unique about the cat is its sensitivity to oxidative injury. I'm speculating here, but may be part of the mechanism involved in cats' susceptibility to vaccine-associated sarcomas.

Question: Is there evidence to support the contention that the genetics of cats plays a role in the development of vaccine-associated sarcomas?

DR. HENDRICK: In my opinion, there is little evidence to support that genetics plays a role, other than the fact that genetics plays a in everything the body does. In an individual cat, genetics will be a part of the pie, of course, but I don't believe there is adequate evidence to support there being a genetic component that predisposes cats to vaccine-associated sarcoma formation.

DR. GLICKMAN: A difference in the incidence of vaccine-associated sarcomas in cats in different communities may suggest a genetic predisposition.

DR. RICHARDS: Investigators of one of the studies supported by the task force were seeking to find a genetic marker that could predict susceptibility to vaccine-associated sarcoma development.

DR. KITCHELL: The investigators were looking for derangements of the sarcoma suppressor gene p53. They evaluated biopsy specimens obtained from a sarcoma and from normal tissue at measured intervals away from the sarcoma. They hypothesized tha cats with vaccine-associated sarcomas were, in some way, more vulnerable to neoplastic transformation because they had a partic allelic difference in the p53 gene. To my knowledge, no published reports of this study have yet appeared. But humans with p53 defects develop multiple types of cancer, with many of them appearing early in life. This is clearly not the case with vaccine-assoc sarcomas in cats.

In addition, there is evidence that humans with tumors overexpress p53. Overexpression of p53 has sometimes been associated w a mutation that results in prolonged p53 activity or increased production of a nonactive form of the protein encoded by the gene. T problem is, we don't know if that's the cause of a tumor or a response to a tumor. All of this is still really unclear.

DR. MACY: In my personal experience, I know of a situation in which cats from the same litter developed sarcomas at injection si

even though they went to separate veterinarians and received various substances. But these reports have not been rigorously evalu for information such as type of sarcoma or feline sarcoma virus infection status.

DR. GLICKMAN: The real payoff would be if a family of cats that had a higher than expected rate of vaccine-associated sarcoma development could be identified, and a sexually intact male or female could be selectively bred. Presently, I'm not convinced that t is a strong genetic component. In my experience, when there is a strong genetic component, breed risks are different. Clearly, we not seen that.

DR. SCHULTZ: One reason I suggest that genetics plays a role is that many of the studies[45,46] on genetics of tumor development have been performed in certain inbred strains of mice in which a genetic component has been clearly detected. In a particular mouse str inflammatory events will lead to development of sarcomas, whereas in most other inbred strains, the same events have no effect. is not to suggest that this is true in cats, but at least in certain models, there is a genetic component.

Question: Should a cat that has had a vaccine-associated sarcoma be vaccinated in the future?

DR. SCHULTZ: What is to be achieved by vaccinating the cat? The most important vaccine, at least as it relates to the health of the for feline parvovirus. In this case, there is a good correlation between antibody titer and immunity. So, measure the cat's antibody if the titer is indicative of protection, then don't vaccinate the cat.

From a regulatory aspect, we have a dilemma with rabies virus vaccines. This is, of course, a regional issue that we may not be ab get around. But my recommendation would be to not vaccinate a cat that has had a vaccine-associated sarcoma.

DR. RICHARDS: Would that be with any vaccine or specifically with the vaccine associated with the sarcoma?

DR. SCHULTZ: Any vaccine.

DR. ELSTON: Including intranasal vaccines?

DR. SCHULTZ: We do not have any evidence to suggest that topical application of a vaccine can lead to a sarcoma, but is revaccina really required? Not from the standpoint of feline parvovirus; immunity is probably lifelong, but if in doubt, measure antibody. A that cat is probably going to be restricted to the indoors, and considering the effectiveness or ineffectiveness of herpesvirus and calicivirus vaccines (and also figuring that the cat has already been exposed to herpesvirus and calicivirus sometime during its life wouldn't even use the intranasal herpesvirus-calicivirus vaccine. Additionally, that cat may be in a compromised state of health as result of cancer and treatment.

DR. MCGILL: How many cats actually recover from vaccine-associated sarcomas, and why put the cat through another injection?

DR. MCENTEE: We have seen cats live long enough to get another vaccine-associated sarcoma from subsequent vaccine administration at another site.

DR. HENDRICK: We have anecdotal evidence that a cat that has had a vaccine-associated sarcoma is more likely to get a second or it's revaccinated. Why take the risk?

DR. GLICKMAN: My comment is to obtain DNA from those cats. We may not be able to do anything with it now, but this is clea unusual, highly susceptible cat. I would also ask practitioners to contact veterinary epidemiologists if they see multiple cats from a pedigree cattery with sarcomas.

DR. RICHARDS: Should we avoid any injectable products in these cats?

DR. SCHULTZ: If there is an alternative route, I recommend its use. If you have a choice between an injectable form and an oral fo of an antimicrobial, for example, pick the oral form. At least that's my recommendation.

DR. HENDRICK: Yet, an association with other injectable agents has not been proven.

DR. GLICKMAN: But I think it would be judicious, even though there is no evidence to support it.

Question: A few years ago, the VAFSTF created guidelines,[47] what I call the 3-2-1 guidelines, for handling postvaccination masses. We recommended biopsy of a postvaccination mass if it continues to be present three months after vaccination, if it is larger than 2 cm in diameter, or if it is increasing in size one month after vaccination. We recommended biopsy rather than removal of the mass because if the mass turns out to be a sarcoma, then excision of the mass is clearly not sufficient, and the opportunity

for an aggressive first surgery has been missed (survival is highly associated with the completeness of the first attempt at surgical excision). Quoting from the guidelines,

> A tru-cut needle biopsy or incisional wedge biopsy is preferred for diagnosing lesions. Tru-cut biopsy should be done in such a way that subsequent surgical removal can readily include the entire needle tract. Wedge biopsy should be performed so that subsequent surgery can remove all tissue affected by the biopsy. Fine needle aspiration cytology is considered unreliable for the diagnosis of vaccine-associated feline sarcomas and is not recommended.

Are we still comfortable with these biopsy methods?

DR. MCGILL: We have seen cases of vaccine-associated sarcomas in which some parts of the lesion are granulomatous, but in another place, a sarcoma is forming. We are missing the diagnosis if inadequate tissue is submitted; a single tru-cut biopsy core specimen may be insufficient.

DR. KITCHELL: We perform incisional (wedge) biopsies of those lesions because I'm concerned that a tru-cut biopsy specimen w be nondiagnostic.

DR. HENRY CHILDERS: Even if a wedge biopsy is performed, the diagnosis could still be missed if no cancerous tissue is includ in the biopsy specimen. These are heterogeneous masses.

DR. GLICKMAN: That's possible. Instead of handling the mass according to the 3-2-1 protocol, why not just widely excise it?

DR. RICHARDS: Then, we are talking about major, perhaps disfiguring, surgery for every cat with a mass that meets the criteria. I believe that's excessive for the vast majority of cats in which the mass is probably only a granuloma.

DR. MACY: Client compliance sometimes determines the success of a program. If you recommend a tru-cut biopsy with local anesthesia, you will have higher client compliance than if you recommend an incisional biopsy during general anesthesia, if for nc other reason than cost. Yes, we may miss a few cases, but what is the trade-off for the number of clients who will deny incisional biopsy?

DR. MCGILL: It is important to mention that tru-cut biopsy specimens obtained from at least three to five different sites of the mas will increase the likelihood of getting sufficient material for accurate diagnosis. Again, a single core specimen just isn't sufficient.

Question: Suppose I have submitted biopsy specimens from a mass that meets our 3-2-1 criteria, and the pathology report indicates that the tissue is a granuloma; no neoplastic tissue was seen. Should the mass be excised, or should it just be monitored?

DR. MORRISON: I think you have to look at it as a suspect lesion with the potential for malignant transformation. I recommend excising the mass, applying the same surgical principles as if dealing with tumor tissue. Masses that meet any of the 3-2-1 criteria atypical; most postvaccination masses won't meet these criteria. You have to be more aggressive with these because persistent inflammation increases the probability of sarcoma development.

DR. HENDRICK: But atypical does not necessarily mean neoplastic. Even masses that persist and match the 3-2-1 criteria may not proceed to sarcoma, just because of the low incidence rate of vaccine-associated sarcomas. I wouldn't necessarily be worried if the histopathologic diagnosis was an inflammatory granuloma, but areas of fibroplasia would raise my level of suspicion.

DR. KASS: In our Web-based study[26] we followed cats that had postvaccinal masses, and virtually all of the masses were gone by approximately four months. They simply went away on their own without any intervention.

DR. MACY: I would still remove the mass, but I would not take wide margins (3 to 5 cm). I use the histologic diagnosis to determ my dose of surgery (ie, whether to shell out the mass or take wide vs [3- to -5-cm] surgical margins).

DR. RICHARDS: So, regardless of the diagnosis, you are automatically recommending at least two procedures, first biopsy then removal of the mass, and that the size of the surgical margins is determined by the histologic diagnosis of the biopsy specimen?

DR. BRUNT: If so, I think communication with clients is critical. We need to inform them that they are looking at two or more procedures, depending on the histologic diagnosis. That has to be clear from the beginning.

DR. HENDRICK: I suggest that if the histopathologic diagnosis is an inflammatory granuloma, wait one month before doing anything.

DR. GLICKMAN: Given this amount of uncertainty, which is not unexpected because of the lack of data, we need to encourage stu of cats with postvaccination masses on which to base our recommendations. There are probably thousands of cats that could be followed, but it's easier said than done.

As an aside, how many of us instruct owners of vaccinated cats to palpate the sites weekly? In terms of early cancer detection, I th veterinarians can gain a lot by telling owners what to look for. Veterinarians, in general, have not done an adequate job of educatin owners about the early signs of cancer, and in this case, we have a very specific cancer; we know where it's going to develop, and know what it's going to feel like. Veterinarians need to emphasize the importance of owners checking injection sites, which may s many cats' lives.

DR. RICHARDS: On the basis of our current level of understanding, do we agree that Dr. Macy's "dose of surgery" (shell out vs 3 5-cm surgical margins) approach is reasonable? If histologic examination of the biopsy specimen reveals only inflammatory tissu simple lumpectomy should suffice. If neoplastic tissue is detected, then a much more aggressive surgery with wide surgical marg as described in the VAFSTF guidelines[47] will be required. Are we going to miss some cats with sarcomas that were not detected v histologic examination of the biopsy specimen? Perhaps. If so, we will have lost our best chance at completely removing the sarc because we weren't aggressive enough from the outset, but I suspect this will be a rare situation.

Question: The next questions involve survival time of cats with vaccine-associated sarcomas. First, what is the survival time of cats with vaccine-associated sarcomas without any treatment?

DR. MCENTEE: The mean survival time in cats that do not receive any treatment has not been documented, but it would range fro zero days to potentially six or more months from diagnosis and would depend on a number of factors including the stage of disea (ie, extent of the primary tumor and whether there is any evidence of metastasis) and if there is any negative impact on quality of l with discomfort because of ulceration of the tumor. Pet owners will at times choose euthanasia at the time of diagnosis, whereas others may decide to allow their cats to die naturally from the disease.

Question: What is the survival time of cats with vaccine-associated sarcomas after treatment with aggressive surgery alone?

DR. MCENTEE: Median survival time of cats that have undergone an aggressive first surgery has been reported to be 807 days (2. years)[43] and > 16 months (1.3 years).[48] Because there is so much difference in how information is reported (whether mean or median) and how survival time is measured (whether it is from the time of the original diagnosis or from the start or completion therapy), it's hard to compare some of the study results. I think it's more appropriate if we look at median time to first recurrence. Results of one study[43] indicate that cats tend to have a shorter time to sarcoma recurrence with each successive surgery and that median time to first recurrence is significantly longer after radical first excision (325 days) than after marginal first excision (79 d Results of another study[48] indicate that cats with complete excision had significantly longer median survival times (> 16 months) t cats with incomplete excision (nine months).

DR. MORRISON: In the data you are citing, the authors define aggressive surgery as that performed by a diplomate of the America College of Veterinary Surgeons at a referral institution and nonaggressive surgery as that performed by a private practitioner.

DR. MCENTEE: Right, but even the term aggressive is variably defined at different institutions. There are veterinary surgeons train in the techniques of oncologic surgery who consider an aggressive first surgery to require 5-cm margins in all directions; when th not possible because of anatomic limitations, they recommend that at least two muscle planes are resected. Of 82 cats that underw aggressive surgery alone, only seven (8.5%) have had local recurrence.[49] This is in comparison to information obtained from a survey[50] of cats with vaccine-associated sarcomas in which 36 of 58 (62%) cats had sarcoma recurrence on the basis of informati from cats with fibrosarcomas in 1991 to 1992. The low recurrence rate documented in 2001[49] indicates the impact that knowledge of the aggressive nature of vaccine-associated sarcomas has had on the surgical approach to treatment. Vaccine-associated sarcomas an extremity are often treated by amputation, although surgery alone may not be effective for more proximally located sarcomas. Maybe we are going to see a shift in what is considered as aggressive surgery and a decline in the rate of local sarcoma recurrence that sarcomas are recognized as being locally aggressive.

Question: What about with treatments in addition to excision, such as chemotherapy, radiation therapy, or both?

DR. MCENTEE: Unfortunately, many of the studies involve only small numbers of patients. Results of a study[51] in 12 cats treated with a combination of doxorubicin and cyclophosphamide indicate that six cats had a partial response with a decrease in sarcoma of > 50%, although the median response duration was only 125 days. In that study, four of those cats initially had nonresectable sarcomas, and the remaining cats had been treated surgically and metastatic disease or nonresectable sarcomas had subsequently b

detected. The median survival time was significantly longer in cats that responded to chemotherapy (242 days) versus those cats tl did not have a response (83 days). So, we can see some response in cats with large sarcomas, but it is fairly short-lived. This is in agreement with results of other reports[52] of chemotherapy used in the macroscopic disease setting. Macroscopic disease setting refers either to patients that have not had surgery and have gross disease or to patients that have recurrence after surgery. Chemotherapy alone is not particularly effective, but hopefully, it will be more effective when used in combination with other treatments.

In one randomized study,[53] liposome-encapsulated doxorubicin and doxorubicin were evaluated in cats with vaccine-associated sarcomas (both in cats that had macroscopic or gross disease and in cats that had undergone surgical resection but had residual microscopic disease). Results of that study indicate that there was no significant difference in response rates between the two drug Of the 33 cats with macroscopic disease that received chemotherapy, the overall response rate was 39% (five complete responses eight partial responses), again with a short response duration (median time to progression, 84 days). Seventy-five cats with microscopic disease received chemotherapy; cats treated with chemotherapy after cytoreductive surgery had a prolonged median disease-free interval of 388 days, compared with a historical control group treated with surgery alone that had a median disease-fr interval of only 93 days.

Ifosfamide has been evaluated in cats with measurable tumors or gross disease with complete and partial responses observed.[h] Further evaluation will be necessary to determine the efficacy of ifosfamide in cats that have undergone surgical resection but have residual microscopic disease and in combination chemotherapy protocols[h].

From my personal experience, we have found that if there is any efficacy from treatment with a drug alone, it's short-lived. Of mu more promise is combination therapy. The combination of radiation therapy and surgery has resulted in improved response rates survival times. The timing of surgery relative to radiation therapy and whether chemotherapy has been administered varies among studies, and the way in which outcome is measured and reported has not been consistent between studies. Results of one study[54] indicate that the median survival time of 33 cats preoperatively treated with radiation therapy was 600 days (1.6 years). In that stu the only prognostic factor impacting outcome was the presence of tumor cells at the surgical margins. The median disease-free interval in five cats with tumor cells at the surgical margins was 112 days (3.7 months) versus 700 days (1.9 years) for 26 cats tha not have tumor cells at the surgical margins. Results of a subsequent study[55] of 92 cats preoperatively treated with radiation therapy (including the original 33 cats) indicate that the median time to first recurrence (measured from the first day of radiation treatment was 584 days (1.6 years), with only completeness of excision significantly related to time to first recurrence. Median time to first recurrence in cats with complete excision was 986 days (2.7 years) versus 292 days (9.6 months) in cats with incomplete excisior that study, time to first recurrence was determined from the first day of treatment until local sarcoma recurrence, metastasis, or da death or euthanasia. Although not significant, the clinical outcome for cats was improved with the addition of carboplatin chemotherapy; cats had a time to first recurrence > 986 days (2.7 years). Local recurrence was documented in 42% of cats with complete excision; this brings into question the ability to accurately assess surgical margins. It is important to recognize that a pathologist typically determines surgical margins on the basis of a small portion of a submitted tumor specimen that has been trimmed to fit into a cassette for automatic processing. The final assessment is based on viewing one 5- to 6-µm-thick cut from th trimmed specimen. Assurance that the margins viewed by the pathologist are totally representative of the excised tumor mass is n possible.

Radiation therapy administered postoperatively has been evaluated alone and in combination with chemotherapy.[56,57] In a small group of 25 cats, the median time to first recurrence (time from completion of radiation to recurrence) was 661 days (1.8 years) fo cats treated with doxorubicin, surgery, and radiation, but the median time to first occurrence had not been reached in cats treated w surgery and radiation alone.[56] The median survival time (from completion of radiation therapy to death) was 674 days (1.8 years) i cats treated with doxorubicin, surgery, and radiation and 842 days (2.3 years) in cats treated with surgery and radiation alone. Ther was no significant difference in median survival time between the two treatment groups.[56] The response to electron beam irradiation administered postoperatively with or without chemotherapy was assessed in a group of 78 cats, and the median disease-free interv (from start of radiation therapy) was 405 days (1.1 years), with a median survival time from onset of disease (measured from wh the owner had first noticed the mass) of 730 days (two years).[57] In that study, chemotherapy was not significantly associated with recurrence, metastasis, or survival. These results suggest no advantage in survival time is gained in cats treated with doxorubicin chemotherapy in conjunction with surgery and radiation therapy versus cats treated with surgery and radiation therapy without chemotherapy. It is very difficult to compare the results of these studies because they were looking at different time points, the dat were analyzed differently, and the treatments were different. But certainly, we are seeing prolonged survival times and improved l tumor control rates with a combination approach.

The emergence of vaccine-associated sarcomas has provided the impetus to further define dosing strategies for chemotherapy dru already being used in cats, such as carboplatin,[58] and explore the use of new chemotherapeutic agents, such as liposome-encapsulate doxorubicin[53] and ifosfamide.[h] Carboplatin is associated with severe and prolonged neutropenia in cats, which can lead to treatmer delays as well as potentially life-threatening infections. A dosing strategy was developed for carboplatin in cats on the basis of a targeted area under the concentration-versus-time curve and an individual cat's glomerular filtration rate.[58] This method of individualizing the carboplatin dose allows for more accurate prediction of bone marrow suppression. In the process of addressing

problem of vaccine-associated sarcomas, in vitro studies have evaluated chemosensitivity of vaccine-associated sarcoma cell lines doxorubicin and mitoxantrone[59] and vincristine and paclitaxel.[60] Another area of investigation is the use of hyperthermia to increase the local accumulation of liposomes in feline sarcomas; this has the potential for targeting the delivery of liposomes and drug relea from thermosensitive liposomes.[61]

Question: If there were no limitations, what would be the optimal diagnostic regimen?

DR. MCENTEE: From a clinical standpoint, the importance of a thoughtful, preplanned, and coordinated approach to the diagnosis treatment of vaccine-associated sarcomas cannot be overemphasized. The optimal approach requires consideration of each cat on a case-by-case basis with the involvement of surgeons, medical and radiation oncologists, radiologists, and pathologists. Baseline laboratory diagnostic tests should include, but may not be limited to, a CBC, serum biochemical panel, and urinalysis. The FIV ar FeLV status of cats should be determined if not performed previously. Three radiographic views of the thorax should be obtained determine if there is any evidence of pulmonary metastasis, although there usually is no evidence of metastasis at the initial evalua On the basis of tumor location as well as to identify any other underlying disease processes, abdominal ultrasonography may be indicated.

As we discussed earlier, histologic examination of an incisional biopsy specimen is recommended to confirm a diagnosis of vaccine-associated sarcoma. A well-planned biopsy should be appropriately placed, the incision should be short in length, and meticulous attention should be paid to hemostasis. If there is evidence of ecchymosis around the biopsy site or if liquid from the r is allowed to track along tissue planes, this can potentially make planning of surgery, radiation therapy, or both more difficult by seeding tumor from the primary tumor mass. As in human oncology, it may be important to consider performing a core needle biopsy in lieu of open biopsy to decrease the rate of complications from the biopsy procedure itself.[62] Cross-sectional imaging of the tumor via computed tomography or magnetic resonance imaging will delineate the extent of disease and provide valuable informa to aid development of a therapeutic plan. Imaging even prior to performing a biopsy is the optimal approach because there will no any alteration of the site and tissue planes by the biopsy.

Sarcomas that are small (< 3 cm) and do not have marked infiltration of the surrounding normal tissues may be effectively contro with surgery alone. However, a combination of surgery and radiation therapy is usually indicated to affect local tumor control. The are advantages and disadvantages of performing radiation therapy preoperatively and postoperatively.[63] In humans with soft tissue sarcomas, there is not a significant difference in outcome on the basis of the timing of radiation therapy relative to surgery; howev there are more wound-healing complications when radiation therapy is performed preoperatively and increased adverse effects wh radiation therapy is performed postoperatively.[64,65]

The question that still remains is the role of chemotherapy and selection of patients that will benefit from it. In a study[55] of 92 cats with vaccine-associated sarcomas, 21.7% (20/92) had metastasis, most commonly to the lung (n = 18), but also to a regional lymph no (2), kidney (2), spleen (1), intestine (1), and skin (1). The metastatic rate was likely higher because full follow-up with necropsy v not available for all cats. In that study, the addition of chemotherapy did not have a significant impact on response, although the us carboplatin chemotherapy was associated with a better outcome. Currently, it is not possible to identify the subset of cats that will develop metastasis and that might benefit from the addition of chemotherapy to the treatment regimen. The recommendation for treatment should be aggressive surgical resection when feasible or a combination of radiation therapy (preoperatively vs postoperatively), aggressive surgical resection, and chemotherapy when indicated.

DR. HENDRICK: One could come to the conclusion, both from results of this study[55] and a few other studies,[48,54] that the rate of metastasis increases after radiation therapy. Many tumors change their biological behavior and metastatic rate secondary to radiatic therapy, and I think there are some cats with vaccine-associated sarcomas in which it may increase metastatic rate.

DR. MCENTEE: A change in tumor behavior can be seen with any intervention, even surgical intervention. From my experience, t clinical impression is that sarcomas will tend to grow back more rapidly each time they are resected. On the other hand, when we intervene with treatment, presumably our patients are living longer. So, is the development of metastatic disease a result of our intervention or could it be that the patient has now lived long enough to develop metastatic disease? I don't think we have the answ

DR. KITCHELL: It's a very difficult question to tease out biologically. Did the therapy result in this change, or has the primary tum evolved a clone of cells that has different biological properties? Regardless, I'm still a strong advocate of multimodality therapies because vaccine-associated sarcomas in cats are often not amenable to surgery alone.

Question: If the optimal diagnostic and treatment regimen is not possible, what is the most important?

DR. MCENTEE: An incisional rather than an excisional biopsy specimen should be obtained prior to administration of definitive treatment. This is perhaps the most important step. A marginal first excision can have a negative impact on the ultimate outcome a should be avoided. A computed tomography scan before and after administration of contrast agent, or magnetic resonance imagin

will facilitate identification of the regional anatomic structures (muscles and bone) that should be resected to obtain complete excis Referral to a diplomate of the American College of Veterinary Surgeons with experience in resection of vaccine-associated sarcon is the most important component of the therapeutic approach. Particularly for pet owners who cannot afford a multimodality regir all attempts should be made to provide an aggressive surgical resection.

Question: How have vaccine manufacturers responded to the problem?

DR. MCCLURE: Manufacturers are very concerned about injection site sarcomas and have made huge investments of time, effort, and money for research development and education. They have partnered with the profession to create and fund the VAFSTF, providing the bulk of the funding for research and other activities. They have also invested heavily in research and development of novel vaccines, formulations, and delivery systems for feline vaccines, most of which have not yet made it to market. Once a vacc candidate has been identified, it typically takes four or more years of development and scrutiny by the USDA Center for Veterinar Biologics before a manufacturer can gain approval to market the product. That means we are just now beginning to see new and different types of products. Because a widely accepted product-specific factor involved with sarcoma development has not yet bee identified, veterinarians may anticipate manufacturers to take different approaches. Manufacturers will continue to evaluate their o internal research and any external research they support from groups like this task force. If and when an accepted specific compor of vaccines has been identified, I think the profession can rest assured that manufacturers will move expeditiously.

Question: Is there any source of funding that will help clients cover the expense of treatment?

DR. MCCLURE: Along with veterinarians and cat owners, manufacturers are very concerned about injection site sarcomas. Despit the fact that sarcomas are rare events, they are very real to owners of affected cats. However, it is important to note that feline vacc approved by the Center for Veterinary Biologics have been determined to be safe; thus, there is no legal liability on the part of manufacturers. That said, some manufacturers have established programs that provide some funds if the conditions of the progra are met, and others will work with their customers on a case-by-case basis.

Question: Are you aware of anything that the USDA has done with regard to this issue?

DR. MCCLURE: The Animal Health Institute has been in dialogue with the AVMA Council on Biologic and Therapeutic Agents a the USDA for over two years on what should be included on vaccine labels for all species, not just cats. They have gathered all interested parties at the table: the people who manufacture the products, the people who regulate them, and the people who use the The impetus was not only the issue of injection site sarcomas but also data on duration of immunity and other information that veterinarians and vaccine producers wanted on product inserts. A draft of the new rules for product inserts has been created, and i moved onward from the USDA to other sections of the federal government. This is a lengthy and complex process, and no one ca tell exactly when we will see results; they may be published tomorrow or a year from tomorrow.

Question: As we draw near to the conclusion of this session, is there any guidance this group can provide to vaccine manufacturers?

DR. MCGILL: I recommend that manufacturers continue to work toward creating products that induce less inflammation at the injection site. Although there is not enough data to prove it, at this point, it looks like inflammation has a causative effect on sarco (Appendix 2).

DR. RICHARDS: If we believe that inflammation plays a role in sarcoma formation, fully realizing that we lack absolute scientific certainty, we then have consensus in encouraging manufacturers to develop products that are less inflammatory. Unfortunately, th only way we are going to know whether this solves the problem is after widespread use of these products; it is impossible for the studies required for licensure to detect events that occur this rarely.

Question: What guidance can we provide to veterinary practitioners?

DR. SCHULTZ: Because adjuvanted FeLV vaccines have been implicated in vaccine-associated sarcoma development, I suggest limiting FeLV vaccination even beyond the current AAFP/AFM recommendations.[28] There is a strict age-related susceptibility to FeLV. Approximately 90% of kittens younger than three weeks old will become persistently infected when sufficiently challenge Between three weeks and three months of age, approximately 50% will become infected when similarly challenged. Between thre months and approximately nine months of age, the number decreases to approximately 30%, and over a year of age, the number i 15%. Results of an independent study 66 indicates this, as do results of every manufacturer of an FeLV vaccine.

For FeLV, my current recommendation is to vaccinate the kitten that is at risk, and virtually all kittens are at risk. You can rarely determine what a kitten's lifestyle is going to be, and kittens are at the greatest risk of infection because of the age-related resistanc FeLV infection that develops in cats as they mature. If the cat is still at risk of exposure at a year of age, then revaccinate at that tin

Thereafter, I recommend never revaccinating the cat. I don't know the incidence of vaccine-associated sarcomas associated with Fe vaccines, nor do I know the risk of a nonvaccinated cat developing FeLV-associated disease, but I would suggest that the risks are probably about the same. In fact, it's possible that the risk of developing a vaccine-associated sarcoma may even be greater than th of developing FeLV-associated disease. With the prevalence of FeLV viremia between 1% to 3% nationwide, the fact that FeLV i highly contagious, and the fact that adult cats have extraordinary innate resistance to persistent infection, the risk of FeLV infectio cats vaccinated according to this recommendation is probably 0.001% to 0.0001%. Ironically, I believe that cats at greatest risk of developing persistent infection (ie, cats younger than four months old) actually receive little or no benefit from the vaccine. Effecti immunity requires two or more weeks to develop after administration of the second dose of vaccine, by which time those cats are least 12 weeks of age and are developing innate resistance.

If we believe that the extent or type of inflammation at the vaccination site plays a prominent role in the subsequent formation of a sarcoma, then one of the new products on the market may create an even greater risk than either rabies virus or FeLV vaccines. Th new product is the *Giardia* vaccine for cats. Results of our study[5] indicate that the inflammatory response to that product at injection sites was phenomenal, surpassing that of the most reactive adjuvanted rabies virus product. Unfortunately, we cannot really determine what it is within an inflammatory response that has the potential to lead to oncogenesis. The inflammation from that particular vaccine may not be as important as that from an adjuvanted rabies virus vaccine, but it clearly was much more inflamm in terms of the types of cells and cytokines produced.

However, rabies virus vaccination is more complex. As we discussed earlier, we don't know the exact role that the type or quantit inflammation plays in sarcoma formation, and we don't know what the situation is with regard to the canarypox-vectored recombi rabies virus vaccine[f] for cats. We have administered this vaccine in our veterinary medical teaching hospital since it became commercially available, but it must be boosted every year. However, many believe that client compliance will decrease if vaccinat for rabies virus must be repeated annually; from a public health standpoint, we might then have a much larger problem on our ha than injection site sarcomas. Our hospital recommends administration of a three-year adjuvanted rabies virus vaccine given only every three years or the recombinant product given annually. This recommendation should not compromise the public health statu associated with rabies virus and may help reduce the incidence of injection site sarcomas. We present these two options to clients being roughly equivalent, but my personal preference is to give the recombinant product that induces little or no inflammation onc yearly.

DR. CHILDERS: Use of a three-year adjuvanted rabies virus vaccine given only every three years is not possible in all states. For example, Rhode Island requires that a three-year rabies virus vaccine be given every other year. Maine had a similar requirement, has just been changed. A recommendation from this group should be that rabies vaccination laws reflect the duration of immunity indicated on the vaccine label.

DR. MACY: We were successful in changing Colorado state law approximately five years ago. The law now requires that rabies vaccination be repeated no more frequently than is indicated on the label. This gives veterinarians the option of choosing what they believe is the safest approach, a nonadjuvanted recombinant product given annually or a three-year adjuvanted product given triennially.

DR. RICHARDS: We are in agreement, then, that our order of preference would be first to use less inflammatory products and sec if a more inflammatory product is chosen, it should be given no more frequently than the label permits.

I think it's important to affirm a statement from the AAFP/AFM vaccine advisory panel report[28] for vaccination of cats:

> The overall objectives of vaccination are to vaccinate the largest possible number of individuals in the population at risk, vaccinate each individual no more frequently than necessary, and vaccinate only against infectious agents to which individuals have a realistic risk of exposure and subsequent development of disease.

This way we are maximizing the benefits of vaccination while minimizing the risks.

I also think we should reaffirm the VAFSTF recommendation for vaccine placement as distally as possible on a limb (eg, administration of rabies virus vaccines in the right rear limb and FeLV vaccines in the left rear limb).[7]

Additionally, the AAFP will be updating its feline vaccination guidelines in the near future, and I'm sure the issues raised during t roundtable discussion will be strongly taken into consideration.

DR. KITCHELL: When the VAFSTF first made its recommendations, we were trying to sort out some of the epidemiologic considerations by standardizing what vaccines had been given in which sites. We also hoped it would facilitate treatment, and fro my perspective as an oncologist, I believe it is the best thing we can do. It's potentially life saving for the rare cat that develops a vaccine-associated sarcoma.

DR. SCHULTZ: Not meaning to introduce another caveat, but I doubt that anyone has looked at the effect on the immune response when rabies virus or FeLV vaccines are given distally in the rear limbs of cats. Those vaccines were not tested or licensed if given those sites. In mice, antigens located in the rear limbs are some of the poorest at inducing an immune response. Granted, mice are cats, but I think it is something that should be investigated.

Question: Can the less inflammatory products be safely given anywhere on the body?

DR. KASS: On the basis of results of our last study[8], I was not able to discern that one group of antigen-specific vaccines was safer o riskier than another. Nonadjuvanted vaccines were far less commonly used than the others, so it could have simply been an issue statistical power. I wish it was a clear picture, but it's not. In addition to the studies cited, there have been anecdotal reports on the Wide Web of sarcomas developing at sites in which nonadjuvanted vaccines have been given.

DR RICHARDS: So, we are still somewhat concerned about nonadjuvanted products; therefore, we agree that they should be given distally as possible on an extremity. If given proximally on a limb and a sarcoma develops, then complete excision of the tumor w be difficult or impossible.

Question: What problems remain and what questions remain unanswered? Where do we go from here?

DR. CHILDERS: First, I think we should encourage development of tests for cell-mediated immunity, as we have done for humora immunity (ie, antibody tests). I know this is a big order, but it would help veterinarians make science-based recommendations on frequency of revaccination. Second, I think infectious disease surveys in different regions of the country would help veterinarians decide which vaccines should be given.

DR. KITCHELL: Prospective randomized control trials are desperately needed to try to resolve the question of how best to treat cats with vaccine-associated sarcomas. These studies are very costly and time-consuming to perform. They will have to be performed multicenter settings to have sufficient numbers of cats to draw meaningful conclusions. I think a better understanding of what the molecular targets are is needed, so we can use molecularly targeted therapeutics. Examples would be receptor tyrosine kinase inhibitors or inhibitors of the platelet-derived growth factor signaling pathway. These types of studies would potentially be useful animal models as well as helping develop therapeutic strategies for cats.

DR. MCENTEE: I think there are ways we can optimize what we already have available to us. An example would be delivering chemotherapeutic drugs on the basis of the agents' pharmacokinetics in individual cats. Carboplatin clearance is currently being investigated.

DR. MACY: Products that reduce local inflammation might potentially reduce the risk of vaccine-associated sarcomas. For exampl the effects of nonsteroidal anti-inflammatory drugs on the immune response have not been explored, and there are a variety of thi such as blocking platelet-derived growth factor receptors and reducing inflammation, that could be pursued to perhaps provide so short-term solutions.

DR. KASS: As an epidemiologist, first and foremost, I would like a way to differentiate vaccine-associated sarcomas from non-vaccine-associated sarcomas. In a previous study[9], I tried a number of different ways to analyze the problem including use of time windows methods and other methods. If pathologists could clearly distinguish cases from noncases, then I would not have t through these statistical convolutions, and the epidemiologic studies would be much more meaningful.

Second, I would like to focus far more on nonadjuvanted vaccines, particularly canarypox-vectored recombinant rabies virus vacc However, the problem confronting investigators performing epidemiologic studies is that this particular vaccine is not used nearly much as the other rabies virus vaccines, so the sample size is too small. Given the results of the previous study[9], I do no longer think it's fruitful, and it's certainly not cost-effective, to ask whether vaccine-associated sarcomas in cats are a real phenomenon; I think they I also think results of that study indicate that all the other things that have been hypothesized to be potential problems (eg, needle g or the role of autoclaved syringes) cannot possibly be an explanation for these sarcomas. Our results indicate that there are likely o products besides vaccines that have the potential to cause sarcomas, but they play only a minor role.

DR. SCHULTZ: I would like to better define the population of high-risk cats by establishing colonies of predisposed cats (eg, cats t have developed sarcomas as a result of vaccination or other injection). It would be possible to breed such cats, and if there is a gen predisposition, hopefully, we could define markers that would predict susceptibility.

DR. MCCLURE: Vaccine-associated sarcomas in cats are a very complex issue, and there is ongoing concerted effort by manufacturers to develop new and different approaches. However, without knowing the etiology, it is impossible to know exactly how to change vaccine formulations. We are looking at a complex problem that occurs rarely in a large population, and we may n have definitive answers. It may be that we have to evaluate these different approaches over time to see an effect.

DR. BRUNT: In closing, I would like to note that we may never eliminate the problem completely. But we are increasing our understanding of the disease, and veterinarians and cat owners are becoming more informed about optimum standards of care, including vaccination protocols that are tailored to each individual cat. Perhaps most importantly, each day we are striving to offer best care possible for each cat, while respecting the owner's needs and wishes, as we seek to maximize protection and minimize r to our patients and the public.

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Appendix 1
Summary of the history, goals, and achievements of the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF).

There is considerable concern about vaccine-associated sarcomas. As a result, the VAFSTF was organized by the AVMA, the American Animal Hospital Association (AAHA), the American Association of Feline Practitioners (AAFP), and the Veterinary Cancer Society (VCS) to fund research into the epidemiology, etiology, and treatment of vaccine-associated sarcomas and to provide valid current information to veterinarians and the public.

- The task force originated when AAHA and the AAHA Foundation hosted a meeting during the 14th Annual Forum of the American College of Veterinary Internal Medicine, San Antonio, Tex, June 1996.
- During that summer, AAHA, AVMA, VCS, and AAFP created a steering committee.
- The steering committee invited academicians in the areas of epidemiology, pathology, and oncology as well as representatives of the Animal Health Institute and the USDA Animal and Plant Health Inspection Service Center for Veterinary Biologics.
- The VAFSTF first met in November 1996.

Among its achievements, the VAFSTF has accomplished the following:

- Raised over $903,000 to fund 26 research studies on vaccine-associated feline sarcomas.
- Developed initial feline vaccination recommendations and guidelines for diagnosis and treatment of suspected sarcomas in cats.
- Developed informative Web resources on the AVMA Web site.[1]
- Developed a client education brochure.[2]
- Responded to numerous inquiries from cat owners and the media.
- Developed a list of selected bibliographic references.[3]
- Presented at the 135th AVMA Annual Convention, Baltimore, July 19984; the 138th AVMA Annual Convention, Boston, July 20015; and the Veterinary Cancer Society Mini-Conference, Bodega Bay, Calif, February 1999.[6]
- Published the VAFSTF Report.[7]
- Conducted roundtable discussion on vaccine-associated sarcomas.

Appendix 2
Evidence supporting the role of inflammation in the induction of vaccine-associated sarcomas in cats.

Evidence	Caveats
Historical evidence of change from live to killed adjuvanted rabies virus vaccine and increased number of antigens available (FeLV vaccine) coincide with increase in sarcomas.	Precise molecular mechanisms not fully elucidated.
Results of a study by Kass et al[8] indicate an association between adjuvanted rabies virus and FeLV vaccines with sarcoma formation.	Other sources of inflammation (nonvaccine injections, nonadjuvanted vaccine injections, and trauma) have been infrequently associated with tumorigenesis.

Aluminum adjuvant detected in sarcomas by microscopy.	Various adjuvants (some not detectable by microscopy) can cause substantial inflammatory reactions that may lead to transformation.
Known link between inflammation and tumorigenesis: * Historical cancer biology. * Specifically in sarcomas.	Not proven that inflammation causes vaccine-associated feline sarcomas or obviates tumorigenesis.

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