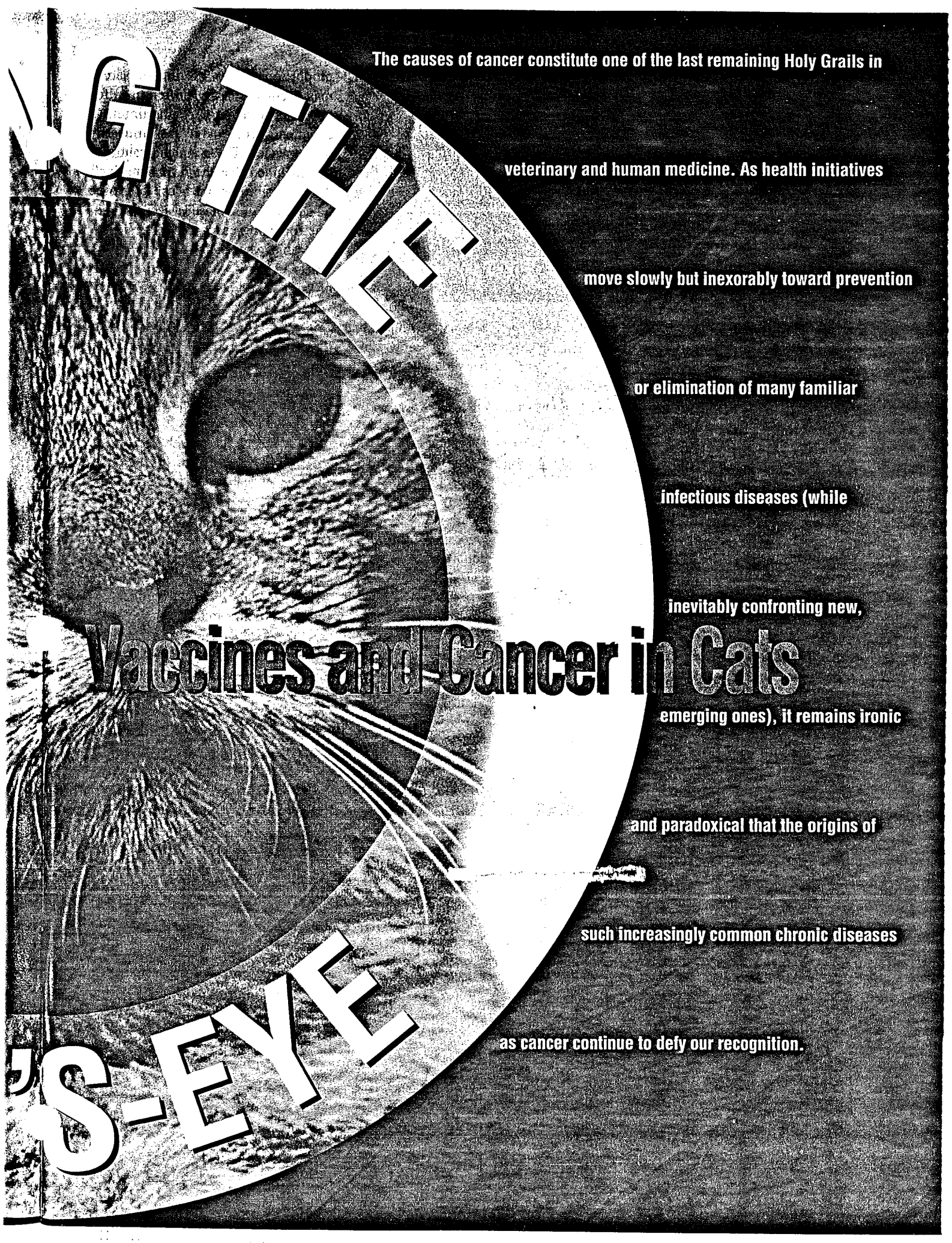
Targeting Connections Between

PHILIP H. KASS, DVM, PHD, DIPLOMATE ACVPM



THE BIG BULL'S-EYE

Vaccines and Cancer in Cats

The causes of cancer constitute one of the last remaining Holy Grails in veterinary and human medicine. As health initiatives move slowly but inexorably toward prevention or elimination of many familiar infectious diseases (while inevitably confronting new, emerging ones), it remains ironic and paradoxical that the origins of such increasingly common chronic diseases as cancer continue to defy our recognition.

Some progress undeniably has been made for various human and animal cancers (e.g., tobacco smoke and bronchial carcinoma in humans and feline leukemia virus and lymphoma in cats). Nevertheless, the causes of malignancies with the greatest impact on populations (i.e., with the highest morbidity and mortality) most likely will remain elusive until medicine moves further away from the realm of the organism and more toward that of the cell and, inevitably, to that of the genome.

A PARALLEL TO THIS STORY IN HUMAN MEDICINE WOULD BE THE DISCOVERY OF THE RELATIONSHIP BETWEEN DES ADMINISTRATION IN WOMEN AND THE LATER OCCURRENCE OF REPRODUCTIVE CANCERS IN THEIR DAUGHTERS

Veterinary medicine can look back with pride, then, on the evolution of understanding of vaccine-induced sarcoma in cats. What began as a conjecture based on circumstantial evidence quickly became, with considerable independent and cooperative initiative from researchers across the country, a strong objective basis for belief in a causal relationship. A close parallel to this event in human medicine would be the discovery of the relation between physician administration of diethylstilbestrol (DES) to women and the later occurence in their daughters of adenocarcinoma of the reproductive tract—a relation also discovered using modern epidemiologic methods.

In this article, we'll review the history and scientific support that led to this development and assess the impact it can be expected to have on veterinary practice. As with most emerging research, however, areas of controversy remain.

A QUESTION ARISES

The sentinel event in recent sarcoma research occurred in 1991, when, in a letter published in the *Journal of the American Veterinary Medical Association*, Hendrick and Goldschmidt from the University of Pennsylvania asked whether injection-site reactions induce fibrosarcoma in cats. This question arose from their observation that the number of fibrosarcomas diagnosed at their biopsy service had risen since 1987, coincidentally the same year that Pennsylvania had enacted a law mandating rabies vaccination in cats. They thought that the number of tumors identified at areas routinely used for vaccination, combined with the sequestration of foreign material within the cytoplasm of macrophages around some malignancies, was also suspicious.

Shortly thereafter, Hendrick et al presented additional findings from cases submitted to their service. They documented an absolute and proportionate increase in fibrosarcomas occurring at sites often used for vaccination and found aluminum (a common vaccine adjuvant) in nearby macrophages. These authors cautiously concluded that the increasing incidence of fibrosarcoma "appears to be related to the increased vaccination of cats following enactment of a mandatory rabies vaccination law." Also that year, Dubielzig et al published a report of a myofibroblastic sarcoma that developed in a cat 4 months after a rabies vaccination at that same site.

In 1993 and 1994, further support published for the relation between vaccines and oncogenesis in cats came from Esplin et al and McGill. In 1992, these pathologists (Animal Reference Pathology, Salt Lake City, Utah) had earlier recognized many sarcomas that appeared to resemble those described by Hendrick et al. The efforts of Esplin et al and McGill to provide a sense of the apparently limited scope of the problem, in addition to considering the role of vaccination in the mitigation of animal and human rabies, were commendable. Their conclusions, and those of Hendrick and others, were distributed to state veterinary medical associations throughout the country.

The lack of known vaccination histories in most of the cases reported up until then, however, made the evidence linking vaccinations with fibrosarcomas largely circumstantial and left the inferences drawn from it open to challenge.

Many of these legitimate concerns, however, were dispelled in 1993 when my coworkers and I at CVD, Inc., and the University of California published the results of a case-control study in which we estimated the magnitude of risk from vaccines and the actual incidence in 345 cats with fi-

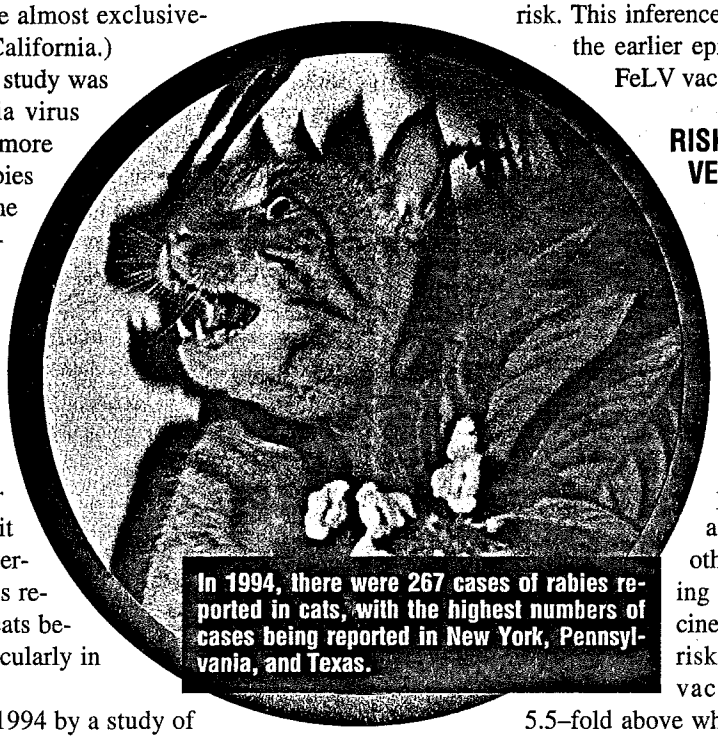
RISK OF SARCOMAS FOLLOWING VACCINATION WITH FeLV AND/OR RABIES VACCINES

Vaccine	Odds ratio	95% confidence interval	Author
FeLV	2.82	1.54–5.15	Kass et al (1993)
FeLV	2.92	1.32–6.45	Hendrick et al (1994)
Rabies (interscapular)	2.09	1.01–4.31	Kass et al (1993)
Rabies (femoral)	1.83	0.65–5.10	Kass et al (1993)
Rabies	0.31	0.01–0.92	Hendrick et al (1994)

brosarcomas. (These cats were almost exclusively from central and northern California.)

The principal finding in our study was that we found feline leukemia virus (FeLV) vaccines were much more likely to cause tumors than rabies vaccines. We also found that the *number* of vaccines simultaneously given at a site significantly increased the risk of tumorigenesis.

These intriguing results prompted several of the above investigators to pool and share their findings in the *Journal of the National Cancer Institute*. In doing so, we felt it imperative to inform our counterparts in human oncology of this reaction to vaccination in some cats because human vaccination, particularly in children, is so widespread.



In 1994, there were 267 cases of rabies reported in cats, with the highest numbers of cases being reported in New York, Pennsylvania, and Texas.

This event was followed in 1994 by a study of vaccination histories of 239 cats with sarcoma by Hendrick et al. This study supported earlier work suggesting that FeLV vaccines were associated with vaccine-site fibrosarcoma. In contrast to previous reports by themselves and others, however, they found that rabies vaccination afforded a paradoxically protective effect against sarcoma development. Although they showed that cats with tumors in probable vaccination sites survived longer than did cats with tumors in other locations, the vaccination site tumors remained aggressive and lethal. Despite the lack of evidence of metastasis in any of these cats, there is one well-documented report that a fibrosarcoma that arose in the interscapular region following FeLV vaccination in that site spread to the pericardium, mediastinum, lung, and kidney.

In our own studies at the University of California and in those by Hendrick et al, no differences in associated risk were found between brands of FeLV and rabies vaccines. In a novel experimental approach to evaluating the potential of different vaccine brands to cause sarcomas, Macy et al measured the size of vaccination-site reactions 21 days after injection. Six different vaccines were used in 36 cats (one vaccine per cat, six cats per vaccine). Areas of induration, while usually under 1 centimeter in diameter, were found to be almost uniformly larger for rabies vaccines than for FeLV vaccines. Under the hypothesis that postvaccination reactions are a precursor to tumor development, Macy et al concluded that rabies vaccines carry the highest risk. This inference, however, contradicts those of the earlier epidemiologic studies that found FeLV vaccines to carry a higher risk.

THE RELATIONSHIP BETWEEN VACCINE ADMINISTRATION AND SARCOMAS IN CATS WAS OF INTEREST TO HUMAN ONCOLOGISTS BECAUSE OF THE WIDESPREAD VACCINATION OF CHILDREN FOR VARIOUS DISEASES

RISK FROM RABIES VERSUS FeLV

Evidence to date implicates the FeLV vaccine as a cause of feline fibrosarcoma. In 1993, our group in California computed an age-adjusted odds ratio (the proportionate elevation in baseline risk from receiving the vaccine) of approximately 3 (see table on preceding page). Even when adjusting for the presence of other possible risk factors, including the cat's history of other vaccines given, we still found that the risk of a fibrosarcoma following vaccination increased 2.8– to 5.5–fold above what the risk would have been if the cat had not been vaccinated. Interestingly, no other variables (e.g., other injectable pharmaceuticals, concurrent viral infections, breed, or sex) that could explain this association were detected. Hendrick et al found a nearly identical effect, and together these two studies tracked a combined total of 584 cats with sarcoma.

Evidence implicating rabies vaccines—the originally hypothesized cause—is more controversial. Despite their earlier work that implicated the vaccine, Hendrick et al subsequently found a significantly lower risk of sarcoma in cats receiving rabies vaccine (see table). In contrast, our group computed an age-adjusted odds ratio of approximately 2 both in the interscapular and femoral regions following rabies vaccination. These odds ratios remained elevated even after adjustment for the cat's history of other vaccinations.

What Created the Disparity?

One explanation could be differences in the definition of "exposure to vaccine" between the Hendrick et al study and ours. Hendrick's group defined exposure without putting a time limit on vaccination history (although 93% of the cats "had been given vaccinations within a 3 year period before biopsy"). We defined exposure as having received a vaccination in the interscapular or femoral region within the previous 1 or 2 years.

These differences in definitions of vaccine exposure could be critical to understanding the seemingly contra-

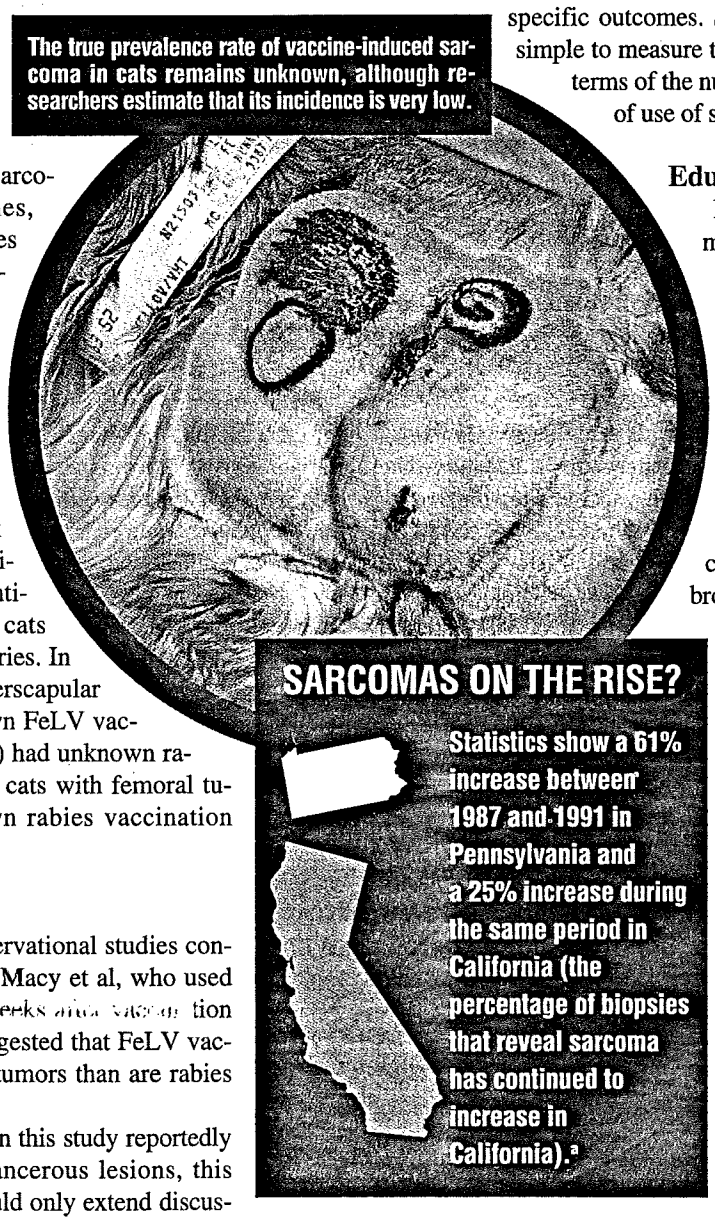
dictory study findings. In Pennsylvania, it is mandatory to vaccinate cats for rabies and it is possible that many receive the vaccine every 3 years. If nearly all of the Pennsylvania study cats had been vaccinated at some point during their lives, it would be almost impossible to detect any rabies effects because of the inability to have unvaccinated cats to compare to. Furthermore, Hendrick et al found that the age distribution of cats that had fibrosarcoma in a vaccination site was significantly ($P < 0.0001$) less than that of cats that had fibrosarcoma elsewhere. Because the cats with vaccine-induced sarcomas were therefore younger, they had, on average, less opportunity to be given a rabies vaccination at least once during their lives. And because many of the younger cats had their sarcomas caused by FeLV vaccines, this smaller frequency of rabies vaccination among these patients could make the vaccine appear to be paradoxically protective.

Differences in the response rates by veterinarians asked about vaccination histories could also alter results in either direction. In the Hendrick et al study, 181 cats with vaccination-site sarcomas were identified, but 81 (44.8%) of these cats had unknown vaccination histories. In our study of 104 cats with interscapular tumor, 22 (21.2%) had unknown FeLV vaccination history and 12 (11.5%) had unknown rabies vaccination history; of 41 cats with femoral tumors, 8 (19.5%) had unknown rabies vaccination history.

Weighing the Results

The conclusions of both observational studies conflicted with the conclusions of Macy et al, who used vaccination-site inflammation 3 weeks after vaccination as a biomarker. Macy et al suggested that FeLV vaccines are less likely to induce tumors than are rabies vaccines.

Because none of the 36 cats in this study reportedly developed precancerous or cancerous lesions, this work, although interesting, should only extend discussion of the potential of vaccines to cause inflammation, and not their potential to cause tumors. Evidence from the two epidemiologic studies of almost 600 cats with sarcoma remains the more revealing and compelling. Even studies of this size, however, haven't completely documented the role of rabies vaccines in sarcoma.



INCIDENCE OF VACCINE-INDUCED SARCOMA

A central issue in evaluating the impact of vaccine-induced sarcoma on the feline population is determining the baseline risk of sarcoma diagnosis among cats seen by veterinarians. The reason for this is obvious: an agent that is responsible for even a high percentage of cases of a rare disease has a negligible effect on population morbidity. The practical difficulty in estimating incidence is that no central feline health registry enumerates both the size of the cat population at risk and the number of cats with disease-specific outcomes. Such a registry would make it simple to measure the true incidence of sarcoma in terms of the number of cats and the frequency of use of specific vaccines.

Educated Estimates

In the absence of such information, however, some researchers have tried to estimate sarcoma incidence. Esplin et al, citing a personal communication from Hendrick, estimated a "true prevalence" of 1 to 2 cases of sarcoma per 10,000 vaccinated cats. From this estimate, we calculated an annual cumulative incidence of 2 fibrosarcoma cases per 10,000 cats seen by veterinarians in California. However, the California investigators found that only approximately half of these tumors occurred at sites where vaccines could have been given and that *at most* only half of those tumors could have been induced by vaccines. Thus, the majority of fibrosarcomas that occurred on cats as recently as 1992 were unlikely to have been caused by vaccines.

The odds ratios from the cited studies for FeLV vaccines reflected an approximate three- to five-fold increase in sarcoma risk at vaccine injection sites. We should thus expect to see a concommitant increase in the sarcoma incidence rate (e.g., the number of new cases per 100,000 cats) since the mid-1980s when feline rabies and FeLV vaccination

[a]Personal communication, Spangler WL, Director of CVD, Inc., West Sacramento, California, 1995.

became more common, although the increased incidence rate will not be on the order of three- to five–fold.

The actual increase in rate depends on the frequency of use of vaccines, which varies across the country and depends on such factors as:

- the socioeconomic status of owners,
- the existence of mandatory rabies vaccination programs, and
- the potential for exposure to infectious diseases preventable by vaccines.

Other contributory factors might include:

- the proportion of susceptible cats in the population and
- the possible synergistic effects of multiple vaccines given simultaneously or serially.

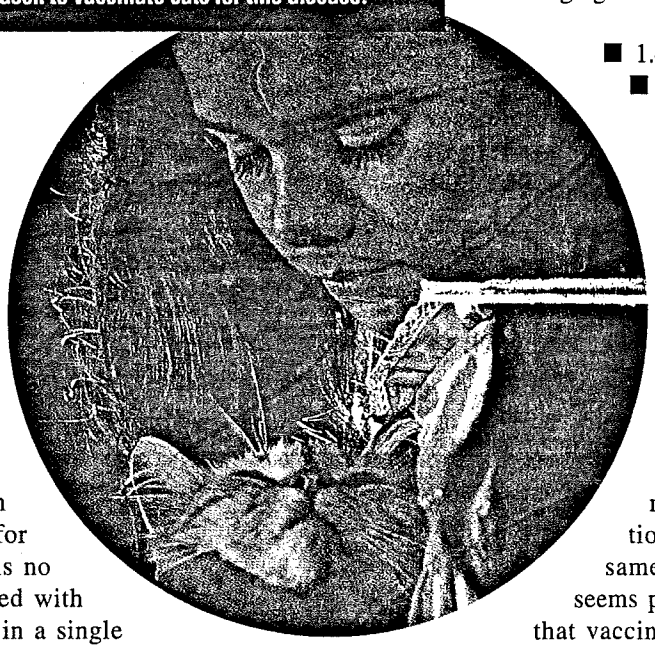
Although incidence rates remain unknown, Hendrick and coworkers and I and my associates used the percentage of biopsies that yielded a diagnosis of sarcoma. Both teams observed that the percentage of biopsies that revealed sarcoma has increased over time.

This incidence marker is biased, however, because diagnosis and biopsy rates undoubtedly changed after dissemination of information about this disease.

When considering the role of vaccination in the incidence of sarcoma, veterinarians must remember that sarcoma can occur at various locations throughout the body. Even sarcoma at a vaccination site might arise for reasons other than (or perhaps in addition to) vaccination.

NO TREATMENT OTHER THAN SURGICAL EXCISION HAS BEEN SHOWN TO IMPROVE THE GRAVE PROGNOSIS FOR CATS WITH SARCOMA

The zoonotic potential of rabies is a compelling reason to vaccinate cats for this disease.



DOES BRAND MATTER?

The evidence to date, both anecdotal and epidemiologic, fails to show systematic differences in risk between different brands of vaccine. Nor have systematic differences been found between vaccines with and without adjuvant. Although aluminum (one common adjuvant) has been found close to some sarcomas, little can be inferred about its potential for tumor induction because there is no way to isolate the risk associated with any of the vaccine constituents in a single case. Several groups of investigators have all learned of or studied cases with vaccination histories that included non-adjuvanted products.

Work examining vaccine-specific postinoculation inflammatory reactions should be interpreted cautiously. As we've pointed out, no evidence links the size of postvaccination induration to sarcoma risk. One could plausibly argue, on the other hand, that induration (an immunologic phenomenon that includes the body's processing of antigen) could be related to the ability of a particular vaccine to induce sustained, protective levels of antibody. Because the incidence of postvaccination sarcoma is so low, a randomized clinical trial to compare the ability of different vaccines to induce tumors would have to be impossibly large. Only future, large-scale epidemiologic studies could scientifically address this issue.

MONOVALENT VERSUS POLYVALENT VACCINES

No compelling scientific evidence at present suggests whether monovalent and polyvalent vaccines pose different risks for sarcoma. Studies to date have focused on whether a vaccine had been given, not on the vaccine formulation. Without knowledge of how certain vaccines can act as initiators or promoters, opposing arguments about the advisability of administering antigens of two or more viruses in the same dose versus separate doses could both have validity.

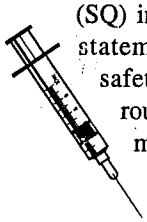
It is not yet clear whether simultaneous delivery of multiple vaccinations to the same injection site increases risk. We found a significant ($P < .02$) positive trend in risk with an increasing number of vaccines, with odds ratios ranging from:

- 1.49 with one vaccination;
- to 2.27 with two vaccinations; and
- to 2.75 for three or four vaccinations (FVRCP, FeLV, rabies, and chlamydia components of multivalent vaccines are each treated as one vaccine).

The following year, however, Hendrick et al found no difference between vaccination-site and nonvaccination-site tumors in the number of vaccinations given simultaneously at the same site. Given this ambiguity, it seems prudent, for now, to recommend that vaccines be administered at different sites.

VACCINATION ROUTE

Most popular FeLV vaccines today are administered via subcutaneous (SQ) injection. Therefore, any statement about the relative safety or hazard of the SQ route compared with intramuscular (IM) injection for FeLV vaccination would lack foundation.



In contrast, rabies vaccines continue to be administered by either the SQ or IM route. In our study, the odds ratios relating rabies vaccination and fibrosarcoma development were virtually identical for the femoral and interscapular regions. Based on this finding, there is probably no advantage of one route over the other in terms of modifying sarcoma risk. Macy, however, recommends SQ vaccination in a limb to widen treatment options (e.g., amputation) should a tumor arise.

SARCOMA IN CATS MIGHT BE RELATED TO VACCINATION BUT IS NEVERTHELESS RARE. THE DECISION TO VACCINATE CATS IS ANALOGOUS TO THE DECISION TO VACCINATE HUMANS AGAINST POLIO DESPITE THE LOW BUT NONZERO RISK OF NEUROLOGIC COMPLICATIONS

SURGERY IS BEST OPTION

Current research at the University of California is evaluating survival under various treatment protocols (e.g., radiation, chemotherapy, or surgery) administered by private practitioners. Our preliminary findings are discouraging. Median survival for cats whose sarcomas arose at potential vaccine sites was under 2 years; at this time, we are not confident that any treatments beyond surgical removal of the tumor substantially improve prognosis.

THE BOTTOM LINE

Although there is no unanimity about all issues related to vaccine-induced sarcoma, one consensus emerges from the publications of most authors on this subject: vaccination against rabies should continue. The choice to vaccinate—in essence, a risk–benefit decision—has many counterparts in human medicine. For example, should widespread vaccination against poliomyelitis have been recommended despite a small but existent risk of neurologic complications? The question of whether to vaccinate against several infectious feline diseases is analogous.

Feline leukemia virus infection remains a pervasive and frequently fatal communicable feline disease. Because of the zoonotic potential of rabies, the implications of rabies infection in pets are even more serious, particularly where epizootics in wildlife threaten nearby households.

Future research into vaccine-induced sarcoma will be redirected from verifying the reality of the problem and toward identifying high-risk individuals. That this disease is so uncommon despite extensive vaccine use underscores the inevitability of other etiologic components, perhaps including genetic predisposition. The discovery of a genetic marker could ultimately serve as a prophylactic screening device. In addition, research will be aimed at recommending appropriate treatment regimens, to improve the grave prognosis of afflicted cats. Such progress will remain dependent on and will continue to benefit from a continuing cooperative relationship between academia, private industry, and veterinarians in private practice.

About the Author

Dr. Kass, board certified in veterinary preventive medicine with a specialty in epidemiology, is an Associate Professor at the University of California, Davis, where he specializes in analytic epidemiology. Dr. Kass's current research interests include nonexperimental study design, analysis, and inference; methodologic issues in case-control study design; animal models in environmental epidemiology; and companion animal epidemiology.

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