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More Bumps on the Vaccine Road

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I. Introduction and Background

The challenge to produce effective and safe vaccines for the currently prevalent infectious diseases of humans and animals has become increasingly difficult (Bloom, 1994; Cohen, 1994; Stratton *et al.,* 1994). In veterinary medicine, evidence implicating vaccines in triggering immune-mediated and other chronic disorders (vaccinosis) is growing (Dodds, 1983, 1993, 1995a, 1997; Phillips and Schultz, 1992; Alderink *et al.,* 1995; Schultz, 1995a,b; Duval and Giger, 1996). Although some of these problems have been traced to contaminated or poorly attenuated batches of vaccine that revert to virulence, others apparently reflect the host's genetic predisposition to react adversely on receiving the monovalent or polyvalent products given routinely to animals (Dodds,

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1983, 1993, 1995a,b,c, 1997; Oehen *et al.,* 1991; Lumsden *et al.,* 1993; Wilbur *et al.,* 1994; Gloyd, 1995; Smith, 1995; Wynn and Dodds, 1995).

Determining causality for adverse effects of vaccines can be asked as three questions: Can it? (potential causality); Did it? (retrodictive causality); and Will it? (predictive causality) (Stratton *et al.,* 1994). Other factors to be weighed in considering the implications of causality include prevalence and clinical severity of the naturally occurring infectious disease, implementing more effective strategies to control infectious diseases, vaccine-related issues such as dosage in relation to body mass and age, advantages and disadvantages of modified live (attenuated) and killed (inactivated) vaccines, hormonal state during vaccination (Smith *et al.,* 1990), and periodicity of booster vaccinations in relation to duration of immunity (Dodds, 1997). Alternatives to current vaccine practices include measuring serum antibody titers; avoidance of unnecessary vaccines or overvaccinating; caution in vaccinating sick, very old, debilitated, or febrile individuals, and families known to be at high risk for immunologic reactions; and use of homeopathic nosodes either as preventive or therapeutic adjuncts. (This last option is considered an unconventional treatment that has not been proven scientifically to be efficacious. If veterinarians choose to use homeopathic nosodes, their clients should be provided with an appropriate disclaimer and written informed consent should be obtained.) A multifaceted approach is needed to further recognition of this situation, along with implementing alternative strategies to contain infectious diseases and reduce the environmental impact of conventional vaccines.

II. Overview of Adverse Effects of Vaccines

The onset of adverse effects of vaccination can be expressed as an immediate hypersensitivity or anaphylactic reaction; an acute event occurring 24–72 hours afterwards, or 10–28 days later in a delayed-type immunologic response (Dodds, 1983, 1995a, 1997; Tizard, 1990; Phillips and Schultz, 1992; Duval and Giger, 1996), or even later as seen with mortality from high-titered measles vaccine in infants (Garenne *et al.,* 1991), canine distemper antibodies in joint diseases of dogs (May *et al.,* 1994), and feline injection-site fibrosarcomas (Kahler, 1993; Kass *et al.,* 1993). The increasing antigenic load presented to the host individual by modified live virus (MLV) vaccines during the period of viremia is presumed to be responsible for the immunologic challenge that can result in a delayed hypersensitivity reaction (Tizard, 1990; Phillips and Schultz, 1992).

These adverse vaccine reactions typically include fever, stiffness,

sore joints and abdominal tenderness, susceptibility to infections, neurologic disorders and encephalitis, collapse with autoagglutinated red blood cells and icterus (autoimmune hemolytic anemia, AIHA), or generalized petechiae and ecchymotic hemorrhages (immune-mediated thrombocytopenia, ITP) (Dodds, 1983, 1993, 1995b, 1997; Jones, 1984; Phillips and Schultz, 1992; Littledike, 1993; May *et al.,* 1994; Gloyd, 1995; Duval and Giger, 1996). Liver enzymes may be markedly elevated, and liver or kidney failure may occur by itself or accompany bone marrow suppression. Furthermore, MLV vaccination has been associated with the development of transient seizures in puppies and adult dogs of breeds or cross-breeds susceptible to immune-mediated diseases especially those of hematologic or endocrine tissues (e.g., AIHA, ITP, autoimmune thyroiditis) (Dodds, 1983, 1993, 1995b). Postvaccinal polyneuropathy is a recognized entity associated occasionally with the use of distemper, parvovirus, rabies, and presumably other vaccines (Tizard, 1990; Phillips and Schultz, 1992; Dodds, 1993; Collins, 1994; Gloyd, 1995). This can result in various clinical signs including muscular atrophy, inhibition or interruption of neuronal control of tissue and organ function, muscular excitation, incoordination and weakness, as well as seizures (Dodds, 1993, 1997). Adverse reactions to vaccination also have been reported recently with increasing frequency in cats (Rosenthal and Dworkis, 1990; Kahler, 1993; Kass *et al.,* 1993). Accordingly, companion animal breeders should be advised of the potential for genetically susceptible littermates and relatives to be at increased risk for similar adverse vaccine reactions (Dodds, 1983, 1993, 1995a,b; Schultz, 1995b).

Among the most alarming adverse reactions to vaccinations are the tragic mortalities from other infections following high-titered measles vaccinations of human infants (Garenne *et al.,* 1991), development of subacute sclerosing panencephalitis in Canadian infants receiving measles vaccine at less than 12 months of age (Stratton *et al.,* 1994), and experiences with refractory injection-site fibrosarcomas in cats (Kahler, 1993; Kass *et al.,* 1993). Commercial vaccines can also be contaminated with other adventitious viral agents, presumably as a result of inadequate quality control during vaccine production (DVM Vaccine Roundtable, 1989; Tizard, 1990; Wilbur *et al.,* 1994; Ellis *et al.,* 1995a). This has been of particular concern in cattle where contamination of bovine respiratory disease and rotacoronavirus vaccines with bovine viral diarrhea virus has occurred with unacceptable frequency (DVM Vaccine Roundtable, 1988; Ellis *et al.,* 1995a; Cortese *et al.,* 1997). Another serious problem arose from a commercial canine parvovirus vaccine that was contaminated by blue tongue virus, as it produced abortion and death when given to pregnant dogs (Wilbur *et*

al., 1994). The authors linked the causality here to the ill-advised but all too common practice of vaccinating pregnant animals. The potential for side effects such as promotion of chronic disease states in male and nonpregnant female dogs receiving this lot of vaccine remains in question, although there have been anecdotal reports of reduced stamina and renal dysfunction in performance sled dogs (J. L. Olson, unpublished observations, 1995). Recently, a commercial manufacturer of distemper vaccines had to recall all of its biologic products containing a distemper component, because the vaccines were associated with a higher than normally observed rate of central nervous system postvaccinal reactions 1–2 weeks following administration (Gloyd, 1995).

Overvaccination raises other issues; the increased cost in time and dollars spent needs to be considered, despite the well-intentioned solicitation of clients to encourage annual booster vaccinations so that pets also can receive a wellness examination (Smith, 1995). Giving annual boosters when they are not necessary has the client paying for a service that is likely to be of little benefit to the pet's existing level of protection against these infectious diseases. It also increases the risk of adverse reactions from the repeated exposure to foreign substances (Smith, 1995; Alderink *et al.,* 1995). Vaccination leads to false-positive serologic test results in viral or bacterial screening assays [e.g., feline leukemia virus (FeLV), feline coronavirus, canine borreliosis]. The experts agree that certain vaccines such as canine coronavirus, Lyme disease, and the commercially available Leptospira bacterins have little justification for their widespread use (Greene, 1992), while others so rarely cause disease today (e.g., infectious canine hepatitis) that their need is questionable (Alderink *et al.,* 1995). Furthermore, only cats at high risk of exposure really need to be vaccinated for feline infectious peritonitis (FIP) or FeLV (Scott and Geissinger, 1997). A controversial canine and feline ringworm vaccine has been marketed, and a canine rotavirus vaccine is being introduced, although there is no recognized canine rotavirus disease beyond the newborn stage. An important point, raised by Dennis W. Macy in the editorial of Smith (1995), is the fallacy of assuming that recommending annual vaccination will cause a greater percentage of the pet population to be vaccinated. What actually happens is that conscientious clients come in regularly and their pets get overvaccinated with the attendant higher risk of adverse reaction.

Polyvalent MLV vaccines that multiply in the host elicit a stronger antigenic challenge to the animal and should mount a more effective and sustained immune response (Greene, 1990; Tizard, 1990; Phillips and Schultz, 1992; Schultz, 1995a,b; Hoskins, 1997). However, this can overwhelm the immunocompromised or even a healthy host that has

ongoing exposure to other environmental stimuli as well as a genetic predisposition that promotes adverse response to viral challenge (Brenner *et al.,* 1988; Garenne *et al.,* 1991, Phillips and Schultz, 1992; Dodds, 1993, 1997; Allen *et al.,* 1996). The recently weaned young puppy or kitten being placed in a new environment may be at particular risk. Furthermore, while the frequency of vaccinations is usually spaced 2–3 weeks apart, some veterinarians have advocated vaccination once a week in stressful situations (McDonald, 1992; Smith, 1995). This practice makes little sense scientifically or medically, as the relatively immature immune systems of young animals may be temporarily or more permanently harmed (Schultz, 1995a,b). One could even envision the consequences of increased susceptibility to chronic debilitating diseases in later life.

Dogs with preexisting inhalant allergies (atopy) to pollens have an augmented immune response to vaccination, as a natural example of the "allergic breakthrough phenomenon" (Frick and Brooks, 1981). The increasing current problems with allergic and immunologic diseases has been linked to the introduction of MLV vaccines more than 20 years ago (Tizard, 1990). While other environmental factors no doubt have a contributing role, the introduction of these vaccine antigens and their environmental shedding (Tizard, 1990) may provide the final insult that exceeds the immunologic tolerance threshold of some individuals in the pet population.

III. Breed Study Examples

In the early 1980s, this author began studying families of dogs with an apparent increased frequency of immune-mediated hematologic disease (AIHA and/or ITP) (Dodds, 1983, 1995b). Among the more commonly recognized predisposed breeds were the Akita, American cocker spaniel, German shepherd, golden retriever, Irish setter, Kerry blue terrier, miniature and standard dachshund, toy, miniature, and standard poodle, old English sheepdog, Scottish terrier, Shetland sheepdog, shih tzu, vizsla, and Weimaraner (Dodds, 1983, 1995b). Since then, other investigators have noted the relatively high frequency of AIHA in American cocker spaniels (Duval and Giger, 1996) and old English sheepdogs (Day and Penhale, 1992). A significant proportion of these animals had been vaccinated with monovalent or polyvalent vaccines within the 30- to 45-day period prior to the onset of their autoimmune disease (Dodds, 1983, 1995a,b; Duval and Giger, 1996).

As an example, this author's recent survey of 13 cases of vaccine-associated AIHA included the following descriptors: six males (two

neutered) and six females (four spayed) with one case of unknown sex; age at onset ranged from 1 to 10 years with a mean age of 4.9 years; time postvaccination ranged from 3 to 42 days with a mean of 19.5 days; all received polyvalent vaccines and two also received Lyme vaccine; and one was in estrus at the time, one had monthly heartworm preventive, and five had ITP concomitantly (Evan's syndrome). Findings from the author's much larger accumulated database of three susceptible breeds are summarized next.

A. Vaccine-Associated Disease in Old English Sheepdogs

The old English sheepdog apparently is predisposed to a variety of autoimmune diseases (Dodds, 1983, 1995b; Day and Penhale, 1992). Of these, the most commonly seen are AIHA, ITP, thyroiditis, and Addison's disease (Dodds, 1995b; Happ, 1995). Between 1980 and 1990, this author studied 162 cases of immune-mediated hematologic diseases in this breed. One hundred twenty-nine of these cases had AIHA and/or ITP as a feature of their disease. Recent vaccination was the only identified triggering event in seven cases, and was an apparent contributing factor in another 115 cases (Dodds, 1995b). Thyroid disease was recognized as either a primary or secondary problem in 71 cases, which is likely an underestimate of the true incidence, because thyroid function tests were not run or were inconclusive in most of the other cases.

The disease experience with a particular old English sheepdog family illustrates the relationship between autoimmune thyroiditis and the concomitant predisposition to AIHA and/or ITP (Tomer and Davies, 1993; Dodds, 1995b; Happ, 1995). Four of five littermates had severe adverse vaccine reactions between 7.5 and 12 months of age. Three of the four had elevated thyroglobulin autoantibodies, and two had thyroid biopsies, which confirmed lymphocytic thyroiditis. Von Willebrand factor antigen levels were also low (< 50%) or borderline normal (50–69%) in this litter. Other immediate family members were also affected. The sire and two litterbrothers of the dam had thyroid disease, and the dam had low von Willebrand factor antigen (31%), abnormal thyroid function tests, and elevated circulating T3 autoantibody and thyroglobulin autoantibody. The maternal grandsire also had elevated thyroglobulin autoantibodies; and the maternal great granddam produced a daughter with thyroid disease that progressed to thyroid adenocarcinoma at age 10 years. This female's paternal grandsire was the foundation sire of many dogs affected with AIHA and/or ITP and his littersister had died of AIHA. These dogs represented a closely related subset of the larger study summarized by Dodds (1995b).

Pedigrees were available from 108 of the 162 old English sheepdog cases of autoimmune disease; a close relationship was found among all but seven of the affected dogs (Dodds, 1995b). Two of three pedigrees available from the studies of Day and Penhale (1992) were also related to this large North American study group.

B. Vaccine-Associated Disease in a Family of Young Akitas

Akitas are subject to a variety of immune-mediated disorders including Vogt-Koyanagi-Harada syndrome (VKH), pemphigus, and juvenile-onset immune-mediated polyarthritis (IMPA) syndrome (Dougherty and Center, 1991; Wynn and Dodds, 1995). Juvenile-onset IMPA occurs in Akitas less than 8 months of age. This author initially studied eight affected Akitas puppies, in collaboration with Susan Wynn (Wynn and Dodds, 1995), and five of them were closely related. Affected dogs exhibit signs of profound joint pain and cyclic febrile illness lasting 24–48 hours. The mean age of onset was 14 weeks, with all dogs showing signs by 16 weeks of age. Three were male, and five were female. The dogs consistently exhibited cyclic febrile illness with signs of severe pain, usually related to the joints. Most of the dogs had elevated hepatic enzymes, creatine kinase, and blood urea nitrogen. Three of the dogs tested had low thyroid hormone levels (T4, free T4, T3). Screening for rickettsial diseases was negative. One dog was ANA positive at 1:40. Hemograms revealed mild nonregenerative anemia, neutrophilic leukocytosis, and occasional thrombocytopenia. Joint aspiration and radiography of three dogs indicated nonseptic, nonerosive arthritis. Juvenile IMPA in Akitas is a syndrome distinct from the nonerosive, noninfectious, non-neoplastic polyarthritis seen in other breeds. Affected Akitas show signs of the disease at a much earlier age, and the syndrome is heritable (Dougherty and Center, 1991). The mechanism of disease development has not been elucidated, but it shares several features with the inherited renal amyloidosis and recurrent fever of unknown origin syndrome of Chinese shar pei dogs (May *et al.,* 1992; Rivas *et al.,* 1993; Zeiss, 1994). This combination of symptoms is reminiscent of familial Mediterranean fever of humans, which has an autosomal recessive inheritance (Rivas *et al.,* 1993).

Pedigree analysis revealed that all eight dogs were linebred on one popular sire, now deceased, and that there were three sets of littermates involved (Wynn and Dodds, 1995). Treatment was unsuccessful over the long term, because all dogs had relapsing signs despite symptomatic therapy for immune-mediated disease and pyrexia. All dogs died or were euthanized by 2 years of age following progressive systemic disease and renal failure. Necropsies were performed on three dogs,

two of which had glomerular amyloidosis and multisystemic inflammatory lesions. In all dogs with known vaccination histories (seven of eight), the initial signs appeared 3–29 days following polyvalent MLV and/or killed virus vaccination with a mean reaction time of 14 days. The history, signs, and close association with immunization suggest that juvenile-onset polyarthritis and subsequent amyloidosis in Akitas may be an autoimmune response triggered by the viral antigens or other components of vaccines (Wynn and Dodds, 1995).

A ninth, related dog became affected 4 months after receiving two killed CPV vaccines. Previously the dog had received only homeopathic nosodes. This dog, a male, had a very high parvovirus HA titer (1:6250), and succumbed at 2 years of age to systemic amyloidosis that affected multiple tissues. A tenth, related male Akita became acutely febrile, and appeared paralyzed and in severe pain after receiving a killed CPV vaccine. As with the sixth, eighth, and ninth cases, only homeopathic nosodes had been given previously by the breeder, who kept meticulous records. Recurring episodes of fever continued in a cyclic fashion. The tenth dog died at 11 months after deteriorating rapidly. Necropsy showed suppurative, eosinophilic enteritis. An eleventh related male Akita began showing clinical signs of high fever and joint pain as a 4-month-old puppy. The dog was euthanized in a moribund state at 2.5 years of age, and necropsy determined the cause to be systemic amyloidosis.

The vaccine-related history of 129 puppies produced by this Akita breeder has been collected. Polyvalent MLV vaccine was given to 104 of them with 10 puppies showing adverse reactions and death (9.8%). Another 6 pups received a polyvalent all-killed vaccine product (no longer commercially available) with no reactors, and 19 pups received homeopathic nosodes initially followed by killed CPV vaccine with one reactor that died (5.6%) and one that became ill but survived.

A genetic basis for immune-mediated diseases is well recognized (Dodds, 1983, 1995b; Carson, 1992; Happ, 1995). A group of inherited immunodeficiencies characteristic of certain breeds already has been described (Felsburg and Jezyk, 1982; Felsburg, 1985; Dodds, 1992). Breed-specific disorders with suspected autoimmune etiologies are being reported with increasing frequency (Dodds, 1983, 1995b; Meric *et al.,* 1986; Scott-Moncrieff *et al.,* 1992). The mechanism for induction of immune-mediated disease in these dogs is poorly understood, but predisposing factors have been implicated. Immune-mediated disease may develop in genetically susceptible individuals when triggered by environmental agents that induce nonspecific inflammation and/or molecular mimicry (Dodds, 1983, 1992, 1995b; Barnett and Fujinami,

1992). The combination of these genetic and environmental factors overrides normal self-tolerance, and is most often mediated by T-cell imbalance or dysregulation (Sinha *et al.*, 1990).

Since Akitas are mostly inbred from a relatively small gene pool, genetic derangement of immunologic function is not unexpected. For owners of existing breeding stock, understanding the possible environmental triggers of juvenile-onset IMPA has immediate importance. Numerous agents have been implicated, including drugs, vaccines, viruses, bacteria, chemicals, and other toxins (Dodds, 1983, 1993, 1995a,c, 1997; Barnett and Fujinami, 1992; Cohen and Shoenfeld, 1996; Duval and Giger, 1996). Although littermates from affected families are usually placed in different environments, all of them undergo relatively standardized immunization procedures at a similar age. The fact that signs of the disease appeared initially during a period of concentrated vaccine exposure could provide the key triggering event, as discussed in Section II.

C. Vaccine-Associated Disease in Young Weimaraners

The Weimaraner appears to be especially prone to both immune deficiency and autoimmune disease, which have been recognized with increasing frequency in the breed during the past decade (Couto, 1988; Dodds, 1995c). Dogs of susceptible genotype are known to have transmitted these problems to some of their offspring. Autoimmune thyroiditis leading to clinically expressed hypothyroidism is probably the most common of these disorders, although an immune deficiency syndrome with low levels of circulating immune globulins (especially IgA and IgM deficiency) is being recognized more often, as is the vaccine-associated disease of young Weimaraners described previously by Couto (1988) and Dodds (1995c).

During the period between 1986 and 1988, Couto (1988) evaluated 170 Weimaraners suspected of having immune deficiency or related to suspected or confirmed cases. Fifty of these dogs were ill at the time or had been chronically ill before evaluation. The clinical signs of the affected dogs included high fevers, polyarthritis with pain, and swelling typical of hypertrophic osteodystrophy (HOD), coughing and respiratory distress from pneumonia, enlarged lymph nodes, diarrhea, pyoderma, and ulcers of the mouth. In most of these cases, clinical signs were first detected shortly after vaccination with a second dose of polyvalent MLV vaccine. Most affected puppies therefore were between 2 and 5 months of age. Laboratory assessment of these puppies showed leukocytosis, low plasma protein, neutropenia, and low levels of IgG and IgM.

A subset of dogs also had low IgA levels, but whether the plasma protein and immunoglobulin levels were below expectations for puppies of this age is unclear. A familial or genetic component was postulated because of the clustering of cases in particular kennels or litters.

In this author's series of Weimaraners with vaccine-associated disease, 24 cases were evaluated (Dodds, 1995c). The mean age of onset was 13.5 weeks with a mean reaction time of 10.5 days postvaccination. The disease syndrome predominantly affected males, although the sex was not reported in 6 of the 24 cases. All affected pups showed high spiking fevers, cyclic episodes of pain, and polyarthritis (HOD)—a group of signs identical to those of the affected young Akitas earlier. Most affected puppies also showed leukocytosis (with neutrophilia or neutropenia), diarrhea, lethargy, anorexia, and enlarged lymph nodes. Some pups also had levels of IgA and/or IgM below those expected for their age, and 1 pup had IgG deficiency as well. Other signs included coughing, pneumonia, depression, seizures or spaced out behavior, refusal to stand or move, and hyperesthesia ("walking on eggshells"). The outcome for half of these cases was good (12 of the 24 are healthy adults), although 2 died, 3 were euthanized as puppies, and 3 remained chronically ill as adults. Another 4 cases were lost to follow-up.

Management of this clinical syndrome in the author's case cohort involved use of parenteral corticosteroids followed by systemic antibiotics and a tapering course of corticosteroids over 4–6 weeks. Recurring episodes were treated by increasing the steroid dosage for a few days until the flareup had subsided. The response to initial corticosteroid treatment was always dramatic. Fever and joint pain subsided within a matter of hours. This experience is contrary to that described by Couto (1988), where corticosteroid use was reserved for refractory cases or used only with extreme caution. He also recommended vitamin C supplementation (500–1000 mg daily) and levamisole given twice weekly.

Instead of revaccination, CDV and CPV serologic titers were measured in the affected surviving puppies (19 of 24). Because all had adequate antibody titers, booster vaccinations were not given. On reaching adulthood, serum antibody titers were reevaluated and detectable CDV- and CPV-specific IgG persisted. Several of these dogs have developed hypothyroidism in the interim and are receiving thyroid replacement (Dodds, 1995c).

IV. Periodicity of Booster Vaccination

The landmark review commentary by Smith (1995) focused the attention of the veterinary research, diagnostic, and clinical commu-

nities on the advisability of current vaccine practices—that is, are we overvaccinating companion animals, and if so, what is the appropriate periodicity of booster vaccines? The answers to this provocative topic generally concur in the affirmative to the first question, but lead to another question concerning the duration of immunity conferred by the currently licensed vaccine components (Alderink *et al.,* 1995). Examples of the newly recommended protocols for cats and dogs include giving the kitten and puppy vaccine series followed by a booster at 1 year of age; further boosters to be given every 3 years until geriatric age, at which time booster vaccination may be unadvisable, especially for animals with aging or other diseases and except where vaccination is required by law. In the intervening years between adult booster vaccinations, and in the case of geriatric pets, humoral immunity can be evaluated by vaccine antibody serology as an indication of the presence of "adequate immune memory." This latter terminology is generally preferred over the term "protective immunity" because serum antibody titers may not correlate directly with protection against disease (Olson *et al.,* 1988; Sprent and Tough, 1994; Alderink *et al.,* 1995; Schultz, 1995a,b; Smith, 1995).

Relatively little published information exists about the duration of immunity following vaccination (DVM Vaccine Roundtable, 1988; Olson *et al.,* 1988; Phillips *et al.,* 1989; Tizard, 1990; McDonald, 1992; Phillips and Schultz, 1992; Dodds, 1993, 1997; Alderink *et al.,* 1995; Ellis *et al.,* 1995b; Schultz, 1995a,b; Smith, 1995). Most veterinarians recommend that annual booster vaccinations be given after completion of the initial vaccine series and continue them throughout old age. An increasing number of experts, however, advocate lengthening the interval between boosters, especially for geriatric animals (Frick and Brooks, 1981; Tizard, 1990; Alderink *et al.,* 1995; Schultz, 1995a,b), while other publications reason that the waning immune function of older animals should be boosted by giving vaccinations more frequently. It seems obvious that the latter suggestion is unwise and unnecessary, especially in light of the long-term immunologic memory elicited by earlier vaccination or exposure (Etlinger *et al.,* 1990; Sprent and Tough, 1994; Alderink *et al.,* 1995).

An in-depth study from Sweden (Olson *et al.,* 1988) examined the duration of serum antibody response to CPV, canine adenovirus 1, and CDV immunizations. Only killed CPV vaccine was used, whereas the CDV vaccine was MLV and the adenovirus 1 was either killed or MLV in origin. Several interesting conclusions arose from this work, which examined several hundred dogs. For adult dogs vaccinated with killed CPV vaccine, there was no significant difference in antibody titer between vaccinated and nonvaccinated animals. While protective levels

of immunity induced by the killed vaccine were of relatively short duration, two vaccinations with optimal spacing (21–35 days apart) adequately protected against parvovirus disease (Olson *et al.,* 1988). As expected, the MLV CDV and adenovirus 1 vaccines induced more long-lasting protective immunity. Equating the effectiveness of vaccination with humoral antibody concentration alone is fraught with problems, however, because cell-mediated immunity can fully protect against disease in the absence of circulating antibody titers (Schultz, 1995a,b). Regardless of the type of vaccine used, persistence of maternal immunity which interferes with active immunization remains the primary cause of vaccine failures (DVM Vaccine Roundtable, 1988; Greene, 1990, Garenne *et al.,* 1991; McDonald, 1992; Schultz, 1995a,b; Smith, 1995; Hoskins, 1997). Protection afforded by most MLV vaccines and by the MLV vaccines used in the Swedish study lasted at least 3 years (Olson *et al.,* 1988). In humans, once the series of childhood vaccinations is completed, protection against these diseases is generally assumed to be long-lived (Stratton *et al.,* 1994). Furthermore, Etlinger and colleagues (1990) emphasized that long after an individual is vaccinated, immunologic memory will be recalled on renewed exposure to the constituents of the vaccine. Thus, prior immunization can be successfully exploited to elicit memory responses as well as to assist in immunizing individuals against new vaccines (Etlinger *et al.,* 1990; Sprent and Tough, 1994).

In that regard, Olson *et al.* (1988, 1997) stated the protective serum neutralization (SN) titer for canine distemper virus (CDV) to be $\geq$1:16, and the protective hemagglutination inhibition (HA) titer for canine parvovirus (CPV) to be $\geq$1:80, basically in agreement with earlier published studies from Carmichael at Cornell (1997). Hoskins (1997) agrees with the Cornell group for CPV (HA $\geq$1:80), and further stated that a four-fold increase in titer from before or at vaccination as compared to 3 weeks later affords protection. McMillen *et al.* (1995) studied humoral and cellular immunity in racing greyhounds given a minimal or intensive vaccination protocol and found little difference in the outcome with respect to titers or immune protection. Both protocols afforded good protective immunity. Their titers for successful immunization were the same as those of the Cornell group for CDV and CPV. Carmichael (1997) stated the ideal protective titer for CDV SN to be $>$1:100 and for CPV HA to be $>$1:320. However, he also stated that there is no point or need to booster titers unless HA levels fall below 1:10 or 1:20. Schultz (1995a,b, unpublished observations, 1997) considered a CDV SN titer of 1:40 and a CPV HA titer of 1:160 to be "protective." Finally, for cats, the recent paper by Scott and Geissinger (1997) indicated the following protective titers for three common feline viral

diseases: feline panleukopenia virus (FPV) ≥1:8, feline herpesvirus (FHV) ≥1:2, although any titer is adequate; and feline calicivirus (FCV) ≥1:4.

V. Alternative Strategies to Conventional Vaccination

This review, which includes examples of the adverse reactions associated with conventional vaccination, illustrates the rationale and justification for seeking alternative approaches to protection against the common infectious diseases of animals. Several such approaches are discussed next.

A. Monitoring Serum Antibody Titers

Except where vaccination is required by law, animals that previously experienced an adverse reaction to vaccination or are at genetic or physiologic risk for such reactions can have serum antibody titers measured annually instead of revaccination. This approach recently has been recommended to assess the adequacy of protection during the interval between routine adult booster vaccinations, in coordination with the policy change of giving them every 3 years (Alderink *et al.,* 1995; Dodds, 1995a, 1997; Schultz, 1995a,b; Scott and Geissinger, 1997). Examples of the currently available methods are discussed in Section IV. If adequate titers are found, the animal should not need revaccination until some future date. Rechecking of antibody titers can be performed annually thereafter, and can be offered as an alternative to pet owners who object to conventional vaccination.

B. Reducing the Number of Vaccine Antigens Used or Given Simultaneously

An argument can be made for vaccinating well-nourished, healthy pet animals only against the clinically important infectious diseases of their species. For the dog, this would include CDV, CPV, and rabies virus; and for the cat, it would include FPV and rabies virus (Alderink *et al.,* 1995; Schultz, 1995a,b; Scott and Geissinger, 1997). Why, then, are we giving animals so many other antigens in polyvalent vaccines, and is this approach really necessary or safe? For example, with respect to Leptospira bacterins, the clinically important serovars are not contained in the currently licensed products, and the antibodies they elicit only last a few months. Similarly, there have been very few clinical cases of infectious canine hepatitis from adenovirus 1 infection,

although the standard polyvalent vaccines all contain adenovirus 2 to afford cross-protection. Other vaccine components such as that for Lyme disease need not be used universally, because the disease is limited to certain geographic areas. Use of FeLV vaccines could be reserved for cats that live mostly outdoors or live both indoors and outdoors, and for catteries where new animals are introduced on a regular basis, as their efficacy is only modest and they have been implicated along with rabies vaccine in producing injection-site fibrosarcomas (Kahler, 1993; Kass *et al.,* 1993). Perhaps one way to address these issues would be to offer more individual or dual vaccine components that could be given on alternating years, in between the 3-year booster vaccinations for the clinically important diseases. The overall risk–benefit ratio of using multiple antigen vaccines given simultaneously and repeatedly should be reexamined, although we have the luxury of asking such questions today only because the risk of disease has been effectively reduced by the widespread use of vaccination programs (Alderink *et al.,* 1995; Schultz, 1995a,b; Dodds, 1997).

C. Avoid Vaccinating or Overvaccinating Certain Populations

Common sense dictates that sick, very old, or debilitated animals should not be vaccinated. It also would be unwise to vaccinate immunocompromised and febrile animals until their physiologic state returns to normalcy. Animals of certain susceptible breeds or families such as old English sheepdogs, Akitas, and Weimaraners, and including those with coat color dilutions (e.g., double-dilute Shetland sheepdogs, harlequin Great Danes, albinos) appear to be at increased risk for severe and lingering adverse reaction to vaccines (Dodds, 1995a,b,c, 1997; Wynn and Dodds, 1995) (see Section III).

Another situation where needless overvaccination occurs is a consequence of the varying state regulatory policies for rabies vaccination. Because the federal U.S. Department of Agriculture has licensed rabies vaccines for 3 years now, there is no legitimate reason for some individual states to insist on annual revaccination. This is particularly worrisome because rabies vaccine is associated with significant adverse neurologic and other immune reactions, as well as producing injection-site fibrosarcomas in cats (Kahler, 1993).

D. Alternative Methodologies

In situations where an animal has experienced a severe adverse reaction to vaccination or when the owner refuses conventional vaccination, there is appropriate justification for selecting alternative

methodologies, such as homeopathic nosodes (Pitcairn, 1993; Dodds, 1995a, 1997), to protect against the common infectious diseases of animals. A word of caution is in order here, however, because a recently conducted, preliminary trial with a parvovirus nosode failed to protect puppies against challenge with a street virus strain of CPV (S. G. Wynn and R. D. Schultz, personal communication, 1997). Additional trials are obviously needed to assess the efficacy of the various nosode preparations currently in use.

These alternative techniques must be performed under the supervision of a licensed veterinarian with an established doctor/client/patient relationship, and requested by the owner of the pet after receiving appropriate informed consent. Obtaining a signed disclaimer and release form from the client is also advisable. Finally, minimizing the risk for exposure to infectious diseases should always be kept in mind, by avoiding areas where animals of unknown health status congregate or exercise.

VI. Summary and Future Directions

Veterinary clinicians are increasingly faced with patients exhibiting signs of immunologic dysfunction and disease. In a troublesome number of cases, the onset follows a recent vaccination, therapeutic or preventative drug use, infection, toxic exposure, hormonal change/imbalance, or stress event. The evidence implicating vaccines as triggering agents in genetically susceptible individuals is growing. A multifaceted approach to furthering the recognition of this situation, along with alternative strategies for containing infectious diseases and reducing the environmental impact of conventional vaccines is clearly needed. As a beginning we can increase the periodicity between adult booster vaccinations from 1 to 3 or 5 years, except as required by law, and implement monitoring of serum antibody levels for assessing protection against the clinically important infectious agents.

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