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Introduction

Since 1994, wildlife biologists and wildlife health specialists have worked to determine the cause of avian vacuolar myelinopathy (AVM), a neurologic disease of bald eagles (*Haliaeetus leucocephalus*) and other birds. The causes of morbidity and mortality in wildlife typically are determined through both antemortem and postmortem examinations, combined with ancillary tests for microbiological organisms, toxicants and other etiologies. However, the etiology of AVM has not been determined yet, despite extensive diagnostic investigations, including examinations for common disease agents, as well as infrequent or unusual causes of mortality. With the failure of standard diagnostic testing to determine the cause of AVM, investigations have evolved to include an ecosystem-oriented approach, conducted through the collaborative efforts of numerous state and federal wildlife resource agencies, universities, private foundations and other institutions. Projects that have been conducted or are underway to determine the cause of AVM include behavioral

studies of affected species, aquatic plant inventories, water quality and sediment analyses, epidemiological studies of AVM in wild birds, sentinel studies, and feeding trials. In addition to scientific research and extensive interagency cooperation, it is expected that persistence and serendipity will be key components of a successful search for the cause of AVM, its source and possible methods to reduce its impact on wildlife resources.

Recognition of AVM as a Cause of Eagle Mortality in Arkansas

During the winter of 1994 to 1995, unprecedented bald eagle mortality occurred at DeGray Lake, in southwestern Arkansas. A total of 29 dead or dying bald eagles were found at this location from November 23, 1994 through January 15, 1995 (Thomas et al. 1998). Most of the eagles were found dead, however those observed alive had difficulty with flight and crashed into trees, embankments or other objects. Birds captured alive died shortly thereafter, despite supportive care. All eagle carcasses were submitted to the National Wildlife Health Center (NWHC) of the US Geological Survey for diagnostic evaluation. Microscopic examinations revealed consistent lesions in the central nervous systems of the eagles, but further testing failed to identify other consistently abnormal findings or a causative agent.

The microscopic lesion observed in the brains of eagles consisted of widespread, bilateral and symmetrical vacuolization of the white matter of the brain, spinal cord and optic nerve (Thomas et al. 1998). The lesion was distinctly different from the transmissible spongiform encephalopathies, such as chronic wasting disease, scrapie and bovine spongiform encephalopathy, that predominantly affect the gray matter of the brain. The NWHC previously had not encountered vacuolar myelinopathy in wild birds during 20 years of mortality investigations.

Vacuoles were found in white matter at all levels of the brain, but they were particularly severe in the optic lobes. Affected tissues did not contain significant infiltrates of inflammatory cells, as occurs in many infectious disease processes. When viewed with a transmission electron microscope, it was apparent that the vacuoles were formed by separation of the myelin sheaths surrounding axons. Normal myelin sheaths have a laminar or onionskin appearance in cross section. Vacuole formation, due to splitting of these laminations, is characteristic of intramyelinic edema, which can be due to a

variety of causes, including acute toxicosis. A point-source exposure to a toxicant was regarded as the most likely cause of the eagle mortality in view of the lesions, the absence of apparent infectious disease agents and inflammation, and the epizootiology of the mortality event. However, significant toxicants were not found in any of the carcasses, despite extensive testing for a variety of agents known to cause wild bird mortality as well as those known to cause intramyelinic edema.

Toxicants that previously have been associated with intramyelinic edema in domestic animals and human beings include a wide variety of natural and manmade compounds. For example, exposure to triethyltin is one cause of intramyelinic edema (Fleming et al. 1991) that was initially considered as a possible cause because it is used in marine paints to protect boat hulls, and there was a history of it in a paint factory in the DeGray Lake vicinity. However, significant amounts of triethyltin were not detected in the eagle carcasses (Thomas et al. 1998). Additional compounds associated with intramyelinic edema, such as the rodenticide bromethalin (Dorman et al. 1992) and the antituberculosis therapeutic isonicotinic acid hydrochloride (Blakemore et al. 1972) seemed implausible because they were unlikely to be available in quantities sufficient to produce such eagle mortality. Nonetheless, tests were run for these substances, and results were negative. In addition to the above manmade compounds, intramyelinic edema has been associated with two plants, *Stypandra imbricata* (Huxtable et al. 1980) and *Heliochrysum argyrosphaerum* (Van der Legt et al. 1996). However, these plants do not occur naturally in North America. Although the list of substances known to cause intramyelinic edema is relatively short, it represents a broad variety of types of compounds ranging from pharmaceuticals to organic metals to plant toxins.

Eagle mortality was not observed at DeGray Lake during the following winter of 1995 to 1996, although a single dead eagle with AVM was found at nearby Lake Ouchita. However, during the winter of 1996 to 1997, another 26 dead bald eagles were recovered: 14 at DeGray Lake, 11 at Lake Ouchita and one at Hamilton Lake, (Thomas et al. 1998). Eagle mortality began in mid-November and continued until late January. Of great significance during this period was the recognition that American coots (*Fulica americana*) at DeGray Lake were suffering from the identical neurological disease. Beginning on November 6, 1996 (approximately one week prior to the first eagle mortality), an estimated five percent of wintering coots at the lake were reluctant to fly,

wobbled in flight, had difficulty swimming or had a drunken or staggering gait on land. Low numbers of coots were found dead. Captured coots ate readily, but showed no improvement in neurological signs in 72 hours (Thomas et al. 1998). Dead coots generally were not found at DeGray Lake, despite frequent surveillance. By early December, much of the coot population at DeGray Lake had migrated further south and by mid-December, observations of affected coots declined greatly.

Diagnostic evaluation of affected coots from DeGray Lake yielded microscopic lesions identical to those in affected eagles (Thomas et al. 1998). Furthermore, white matter vacuolization of varying severity also was found in coots not displaying signs of neurologic disease (J. R. Fischer, personal files). Again, extensive diagnostic testing of eagles, as well as numerous coots, failed to identify the cause of the neurologic lesions and mortality. At this point, it was hypothesized that eagles acquired AVM by ingesting affected coots, however it could not be ruled out that each species was independently exposed to the causative agent. Coots can be a major food item, especially of immature bald eagles (Sobkowiak et al. 1989), and eagles are considered opportunistic feeders (Johnsgard 1990) with a hunting strategy that may focus on sick or injured prey, potentially including neurologically impaired coots. Additionally, bald eagles feed on carrion (Griffin et al. 1982), and coot carcasses may be available during AVM outbreaks.

Recognition of AVM in Additional States and Additional Species

During the 1997 to 1998 migratory and wintering season, American coots with clinical signs and brain lesions of AVM were identified at Lake Juliette, Georgia and Woodlake, North Carolina. In one case, a wildlife biologist recognized affected coots after returning home from a bald eagle recovery meeting at which AVM was discussed, thus emphasizing the value of education of wildlife personnel regarding the newly recognized disease. Although low numbers of bald eagles were present near the Georgia and North Carolina sites, eagle mortality was not observed. However, two additional bald eagle deaths were attributed to AVM at Lake Ouchita, during the winter. With the discovery of affected coots in two additional states, AVM was recognized as a regional issue, rather than a situation unique to Arkansas. Furthermore, epidemiologic investigations at Woodlake indicated that neurologic disease

and brain lesions similar to those of AVM were found in coots there as early as 1990 (Augspurger 1997).

During the winter of 1998 to 1999, severe AVM morbidity and mortality occurred in coots at Lake Juliette and Woodlake, and affected coots were identified at Lake Ouchita, as well as at Lake Murray, Lake J. Strom Thurmond (also known as Clarks Hill Lake) and a Savannah River Site reservoir in South Carolina. At the North Carolina site, AVM was diagnosed for the first time in low numbers of ducks, including mallards (*Anas platyrhynchous*), ring-necked ducks (*Aythya collaris*), and buffleheads (*Bucephala albeola*). Additionally, AVM was documented outside of Arkansas for the first time by bald eagle mortality; single dead bald eagles with AVM were found at Lake Juliette, Woodlake, the Savannah River Site and Lake J. Strom Thurmond (T. Augspurger er, personal files).

In subsequent years, AVM generally continued to occur in coots at the previously affected locations, and it has been documented in the deaths of low numbers of bald eagles in Arkansas, Georgia, North Carolina and South Carolina. However, AVM killed at least 16 bald eagles at Lake J. Strom Thurmond during the winter of 2000 to 2001 and was suspected or confirmed in seven more dead eagles at this site during the 2001 to 2002 migratory season. Two eagle deaths at Lake Ouchita were attributed to AVM in early 2002. During the severe eagle mortality events at Lake J. Strom Thurmond during the winters of 2000 to 2001 and 2001 to 2002, AVM also was documented in a large number of coots. Additionally, clinical disease and brain lesions were found in other species, including Canada goose (*Branta canadensis*), great horned owl (*Bubo virginianus*) and killdeer (*Charadrius vociferus*) (Fischer et al. 2002).

Through the spring of 2002, AVM has been confirmed or is suspected in deaths of at least 90 bald eagles at eight reservoirs in four southeastern states, with the majority of eagle deaths (55) occurring in southwestern Arkansas during the winters of 1994 to 1995 and 1996 to 1997. The impact of this newly recognized disease on the country's recovering bald eagle population is uncertain, but it is clear that the disease can devastate local populations. In southwestern Arkansas, where large numbers of eagles spend the winter, it was estimated that 30 to 65 percent of wintering eagles were killed by AVM from 1994 to 1997 (Thomas et al. 1998).

Avian vacuolar myelinopathy has been diagnosed in several other wild bird species in four other avian taxonomic orders, including ducks and geese.

One of the original questions regarding AVM concerned the apparent absence of this disease in birds other than bald eagles and coots at affected sites, despite the presence of numerous other species associated with water, predation and scavenging. The expanding list of affected species indicates that the species susceptibility range is much broader than originally suspected. Lesions of AVM have not been confirmed in mammalian species, and it remains unknown whether the cause of AVM will affect mammals, including human beings. However, the confirmation of AVM in ducks and geese, combined with the knowledge that ingestion is the apparent mode of transmission for eagles, has prompted public health and wildlife management agencies to advise hunters not to consume ducks, geese or other wildlife displaying signs of AVM or other disease.

Cooperative Efforts to Determine the Cause of AVM

There has been extensive collaboration to identify the cause of AVM by an ever-expanding group of wildlife resource, public land and water management agencies, universities, and other institutions, including private foundations such as the Ross Foundation and the Arcadia Wildlife Preserve, Inc. Each organization has contributed assistance, ranging from labor, materials, local expertise or financial support to aid in the investigations. It is impossible to identify every agency that has contributed to this effort, so the following list must be regarded as partial.

During the first mortality event involving only bald eagles, efforts were led by the Arkansas Game and Fish Commission, the US Army Corps of Engineers, and the NWHC, along with assistance from other agencies. The Southeastern Cooperative Wildlife Disease Study (SCWDS), which is contracted annually by 15 southeastern states and Puerto Rico to assist with the management of healthy wildlife populations, became involved as AVM was recognized in additional species and at additional sites. Furthermore, the Georgia Department of Natural Resources, the North Carolina Wildlife Resources Commission, the South Carolina Department of Natural Resources, the US Fish and Wildlife Service, universities and others assisted with investigations. Much of this work has been done with the existing finances of the organizations with a relatively low amount of supplemental support for AVM investigations. The following are selected examples of efforts of many of the collaborators to determine the cause of AVM and its source.

With the failure of standard diagnostic testing to identify the cause of AVM, investigations have been modified to include an ecosystem-oriented approach. Although the ultimate objective is to identify the cause of AVM, many of the projects have been conducted with the goal of better defining the problem. The first investigations centered on DeGray Lake and included thorough epidemiologic studies, including field investigations of the lake and region, determination of current and former land use in the area, and aquatic plant inventories. Subsequent projects at DeGray Lake included food habit studies of bald eagles and coots in the area, behavioral and movement pattern studies of these species, and analysis of water quality, sediment and algal communities.

Several additional investigations arose as AVM was found in more species and at more sites. Reservoirs at which AVM occurred were compared in order to identify commonalties between the sites that might suggest an etiology or its source. To date, wildlife morbidity and mortality due to AVM has been identified only at man-made reservoirs in Arkansas, Georgia, North Carolina and South Carolina. The reservoirs range from just over 1,000 to more than 70,000 acres in surface area. Most of the reservoirs are on publicly owned land; some are used for production of hydroelectric power and one has a coal-fired power plant on its banks. In many cases the land is managed by an agency, such as the US Army Corp of Engineers, and is accessible to the public. Woodlake is a private residential community with gated access. Two affected reservoirs at the Savannah River Site are within a high security area with no public access. The primary common feature among all of the sites is that the water is relatively clear with abundant submergent vegetation that serves as a food source for migrating and wintering coots. The predominant vegetation varies from site to site with *Hydrilla* or *Egeria* spp. being the most common. These plants are not known to be poisonous.

Recognition of AVM lesions in coots that appeared clinically normal, combined with information suggesting AVM occurred as early as 1990, indicated that the problem may be more widespread than originally suspected and that active surveillance would be necessary to document affected sites. Detection of affected reservoirs would identify sites that should be studied to determine the cause of AVM. With Section 6 funds provided through the Arkansas Game and Fish Commission, SCWDS conducted a multi-state epidemiological study of AVM in coots from autumn 1998 through spring

2001. Sampling of wintering coots at more than 40 lakes in 15 states throughout the Southeast, Northeast, Midwest and Southwest detected AVM at nine sites, including Sam Rayburn Reservoir, in Texas, where birds clinically affected with AVM never have been observed (Fischer et al. 2001). Additionally, it was determined that coots developed lesions after arriving at wintering sites free of lesions, the peak of clinical disease occurred from late November through mid-December, and there was poor correlation between brain lesions and clinical signs of AVM.

Information from this study strongly suggested that exposure to the cause of AVM occurred at sites where the affected birds were found. This was confirmed through a sentinel bird study conducted by the NWHC and the US Fish and Wildlife Service. Healthy domestic mallards and wild-trapped coots from a remote site developed brain lesions shortly after release at a site during an AVM outbreak (Rocke et al. 2000). Additional studies at this site, conducted in cooperation with North Carolina State University, suggested that exposure to the site is necessary because healthy mallards did not become affected when co-housed with sick coots removed from a lake during an AVM outbreak (Larsen, personal communication 2002). Furthermore, information obtained in these trials indicated that clinical signs of AVM resolved in some affected coots (Larsen et al. 2002). This is consistent with resolution of intramyelinic edema due to hexachlorophene toxicosis (Towfighi 1980).

Feeding trials also have been used in attempts to identify the source of the AVM agent and its mode of transmission, as well as to develop animal models for AVM investigations. In 2001, SCWDS experimentally reproduced AVM for the first time by feeding tissues from affected coots to rehabilitated but unreleasable red-railed hawks (*Buteo jamaicensis*) (Fischer et al., unpublished data: 2001). Feeding trials are continuing at SCWDS to determine potential mammalian susceptibility to the cause of AVM and to develop animal models for future AVM trials. Feeding trials also have been conducted by other organizations, including NWHC and North Carolina State University. Materials, including water, sediment and vegetation collected from lakes during AVM outbreaks, have been fed to laboratory mice, mallards and bobwhites; results have been negative to date (Rocke et al. 2002).

Investigations of AVM continue to be conducted by a number of organizations. In addition to those listed above, the South Carolina Department of Natural Resources, Clemson University and the Savannah River Ecology

Laboratory have collaborated to investigate potentially toxic algae that are one possible cause of AVM. The NWHC and SCWDS continue to conduct diagnostic examinations of eagles and other birds with AVM, as well as field investigations during AVM outbreaks, to identify additional species, particularly mammals, that may be susceptible to this recently recognized disease.

The wildlife biologists and health specialists that have been investigating AVM since 1994 frequently have called upon scientists in other disciplines for consultation. University of Arkansas Medical Center neurologists have conducted examinations and radiologists have performed diagnostic imaging of affected bald eagles found alive. Researchers of myelin disorders at the Mayo Clinic in Rochester, Minnesota have reviewed diagnostic materials and provided consultation regarding birds with AVM. Human neurologists, state and federal public health authorities, and toxicologists have met with AVM investigators to assess the efforts and to offer suggestions for future diagnostic and research projects.

Summary

Wildlife biologists and health specialists have been frustrated by a long list of negative findings in their AVM investigations, however studies continue to provide pieces of information to aid the determination of the cause and its source. Available data indicate that AVM may have been present at least since 1990, occurs in at least five states, has been documented during October through April at sites of wintering populations of birds where the exposure apparently occurs, and has killed at least 90 bald eagles. Birds with AVM have difficulty or inability to fly, swim, walk or perch, but there has been resolution of clinical signs in some affected coots. The list of affected species continues to grow, but remains confined to wild avians, including bald eagle, American coot, great horned owl, killdeer, Canada goose, mallard, ring-necked duck and bufflehead. The effects of the AVM agent on mammals, including human beings, are unknown. A neurotoxicant of manmade or natural origin is the suspected cause of AVM because no infectious disease agents, such as viruses, bacteria, parasites and prions, have been found, and the lesion and epizootiology of AVM resemble those of toxicoses. Additionally it is documented, experimentally, that exposure to raptors can occur through ingestion of affected coots.

Collaborative studies will continue in the effort to identify the cause of AVM, its geographic distribution and the range of species susceptibility. Hopefully, this information can be used to identify measures that might be taken to reduce the impact of AVM on the wildlife resource. Multiple agencies, institutions and individuals must rely on each other's expertise in the multidisciplinary approach to this problem, persevere in their efforts and take advantage of serendipity that presents itself during investigations of this newly recognized cause of wild bird mortality.

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