Comparative Medicine
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Vol 52, No 2
April 2002
Pages 171-175

Outbreak of Hind Limb Paralysis in Young CFW Swiss Webster Mice

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An outbreak of paralysis among 16- to 20-week-old CFW Swiss Webster sentinel mice developed in one of our barrier facilities. Two months after arrival and over a period of four weeks, six of 400 mice purchased from an approved vendor, developed progressive hind limb paralysis without other clinical signs of disease. On the basis of the histopathologic changes and negative serologic test results, lymphoblastic lymphoma causing compression of the spinal cord was diagnosed. There were two leading features to this outbreak: its unusual epidemiologic presentation, and the localization of the lesions principally in the lumbar muscles. A presumptive diagnosis of retroviral infection with Abelson's murine leukemia virus (A-MuLV) was established on the basis of histopathologic and immunohistochemical findings. Little is known about retroviral status in many commercial colonies, and few users report presence of spontaneous lymphomas. This report points out complications derived from commercially available animals that carry endogenous retroviruses. It also emphasizes the need of diagnosing and reporting clusters of hind limb paralysis or lymphomas in mice to assess the prevalence and relevance of retroviral infections in commercial colonies.

Hind limb paralysis in laboratory mice is an unusual clinical sign of disease that has been associated with dysfunction of the musculoskeletal and nervous systems, as well as infections caused by specific viruses and bacteria, including Theiler's virus, lactate dehydrogenase-elevating virus, polyoma virus, and *Streptobacillus moniliformis* (1, 2). Natural infection with these agents can surface as outbreaks, with multiple cases of hind limb paralysis in colonies of immunodeficient animals (3, 4). However they rarely cause overt disease in immunocompetent mice, and only sporadic cases of hind limb paralysis may develop in endemically infected colonies, while most mice remain free of clinical signs of disease. These infections also have low prevalence in contemporary colonies of laboratory mice (1).

Non-infectious causes of paralysis include inherited neurologic diseases, such as myelin disorders or neuronal degeneration. These conditions usually become clinically apparent in juveniles carrying certain recessive mutations (i.e., *jp/Y, shi, mnd, wst*) (5). Neoplasms and non-neoplastic diseases, such as osteoarthritis, bone fractures, or peripheral neuropathies, usually cause sporadic cases and mostly affect older mice (6).

We describe an unusual outbreak of paralysis associated with lymphoma that developed among four- to five-month-old sentinel mice housed in one of our specific-pathogen-free (SPF) facilities. All animals in these areas, including sentinels, are housed in static microisolator cages. Cage bottoms are changed once weekly, and the whole setup (cage bottoms, wire lids, bottles, and filter tops) is changed every other week. Handling of animals is performed under a laminar flow hood, and personnel must wear protective garments (gown, shoe cover, face mask, head cap, and gloves) at all times. Mice in these areas are free from at least the following: Sendai virus, mouse hepatitis virus (MHV), *Mycoplasma pulmonis*, minute virus of mice (MVM), Theiler's virus (GD VII), pneumonia virus of mice (PVM), reovirus 3 (REO-3), ectromelia virus, lymphocytic choriomeningitis virus (LCMV), and mouse parvovirus (MPV) infections, and epizootic diarrhea of infant mice (EDIM).

Case History

As part of the health surveillance of the mouse colony, we run a sentinel program using outbred, immunocompetent, SPF female mice, purchased at the age of six to 10 weeks. Sentinel mice are obtained from commercial vendors chosen on the basis of the evidence they provide to guarantee an outstanding and reliable health status. One sentinel cage is placed in every rack housing experimental animals. Cage bottoms are changed weekly, receiving soiled bedding from all experimental mouse cages in the corresponding rack. Sentinels are euthanized quarterly. Screening tests performed are: necropsy, tape test (for *Syphacia* sp.), parasitologic examination (fecal flotation, processed in house), and serologic screening for antibodies against a panel of the 11 aforementioned murine pathogens.

Four-hundred Crl:CFW (SW) BR, eight- to10-week-old, SPF female mice were acquired from an approved vendor to be used as sentinels in one of our barrier SPF facilities. After five days of acclimation, mice were randomly separated, housed four mice per microisolator cage, and distributed at a rate of one cage per rack throughout the facility.

Two months after arrival, one mouse was examined because of hind limb paralysis, but it did not manifest other clinical signs of disease and was euthanized. Blood collection and necropsy were carried out. Over the following four weeks, five more mice were examined because of similar clinical signs of disease. At inspection, three of these animals were seen to move around the cage by dragging their hind limbs. They appeared bright, alert, responsive, able to eat and drink, and did not manifest any other

Received: 11/19/01. Revision requested: 1/09/02. Accepted: 2/14/02.
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Figure 1. Clinical presentation: two months after arrival, the main clinical sign of disease was hind limb paralysis. Most of the affected mice were bright, alert, and responsive.

clinical signs of disease (Fig. 1). The other two paraplegic mice had signs of depression, and were able to move only in circles. The perineum was wet, suggesting urinary incontinence. As soon as the cases were reported, all five animals were euthanized by use of CO_2 inhalation. Complete necropsy was performed, and blood samples were collected. The sick animals were from four rooms and six cages. None of their cagemates was affected.

Materials and Methods

Animals. Crl:CFW (SW) BR, eight to 10 weeks old, SPF female mice were purchased from an approved vendor (Charles River Laboratories, Hollister, Calif.). To ensure humane care and use of animals, all procedures, including husbandry practices and euthanasia method, followed the recommendations of the ILAR "Guide for the Care and Use of Laboratory Animals." Room temperature was maintained at 21 ± 2°C, with relative humidity between 40 and 70%. The light/dark cycle was 12/12 h. Animals had ad libitum access to pelleted commercial rodent chow (NIH-31 Sterilizable diet 7013, Harlan Teklad, Madison, Wis.) and tap water.

Histologic examination. Tissues obtained from necropsy were fixed in buffered 4% formaldehyde, processed in routine manner, embedded in paraffin, sectioned at four- to six-micron thickness, and stained with hematoxylin and eosin (H&E). Sections of the thoracic and lumbar parts of the vertebral column were decalcified overnight in Cal-Ex decalcifying solution (Cat No. CS510-1D, Fisher Diagnostics, Fair Lawn, N.J.). Sections of brain and spinal cord were stained with the Kluver and Barrera stain for myelin (7).

Immunohistochemical analysis. Formalin-fixed paraffin-embedded sections were immunostained, using the peroxidase-antiperoxidase (PAP) indirect method (8). Briefly, four-micron-thick sections were cut and deparaffinized. Unmasking was carried out by steaming the sections for 20 min. After inhibition of endogenous peroxidase by addition of hydrogen peroxide and incubation with normal goat serum, the primary antibodies were applied at the recommended dilution. After washing, the secondary antibody was applied and the sections were then incubated with avidin/biotin horseradish peroxidase (Vector Laboratories, Burlingame, Calif.). Development was done, using DAB Substrate Kits for Peroxidase (SK 4100 and SK 4200, Vector Laboratories). Sections were then counter-stained with hematoxylin and mounted in routine manner.

Purified CD45R/B220 monoclonal antibody (BD PharMingen, San Diego, Calif.) and purified CD3-12 monoclonal antibody (Serotec Inc, Raleigh, N.C.) were used as B- and T-cell markers, respectively. The secondary antibody was purified rabbit anti-rat IgG (Serotec Inc.).

Blood analysis. Blood samples were centrifuged at 2,500 ×g for 15 min, and the serum was recovered for testing. Serum samples from two mice were sent out for routine screening for pathogens including: Sendai virus, MHV, *M. pulmonis*, MVM, Theiler's virus (GD VII), PVM, REO-3, LCMV, ectromelia virus, EDIM agent, and MPV. Two more serum samples were sent to the vendor for review by their laboratory and included all of the aforementioned agents plus K virus, polyoma virus, mouse adenovirus (MAD), mouse cytomegalovirus (MCMV), Hantavirus, *Encephalitozoon cuniculi*, mouse thymic virus (MTV), and cilia-associated respiratory (CAR) bacillus. All pathogens were tested, using an ELISA method, except for MTV, which was assayed by use of an indirect fluorescent antibody (IFA) test.

Results

Necropsy. Generalized, mild to moderate enlargement of lymph nodes, including cervical, axillary, renal, mesenteric, and lumbar, was seen in all animals. Four mice had moderate splenomegaly. The paravertebral muscles of three of the mice were swollen, with gray discoloration and shiny, gelatinous appearance. Grossly, these lesions extended from the last two thoracic to the first two sacral vertebral segments. Findings for other organs were unremarkable.

Histopathologic findings. The outstanding pathologic finding in all of the affected mice was massive infiltration of the lumbar muscles with mononuclear cells and a few neutrophils. Mononuclear cells were predominantly intermediate-sized, and large lymphoblasts, many of which had round nuclei and prominent nucleoli. All lesions had moderate to high numbers of mitoses. This lymphoid infiltration had virtually replaced all of the muscle fibers surrounding the spine and invaded the vertebral canal, meninges, and epidural space (Fig. 2). Meningeal lymphocytic infiltration extended along the spinal cord and into the brain. Peripheral nerves within the tumor masses were not infiltrated. A hemorrhagic infarct, with necrosis at the lumbar level of the spinal cord, was found in one of the mice. The vertebral canal of this animal also contained a large mass of neoplastic tissue surrounding the cord, which strongly suggests that it

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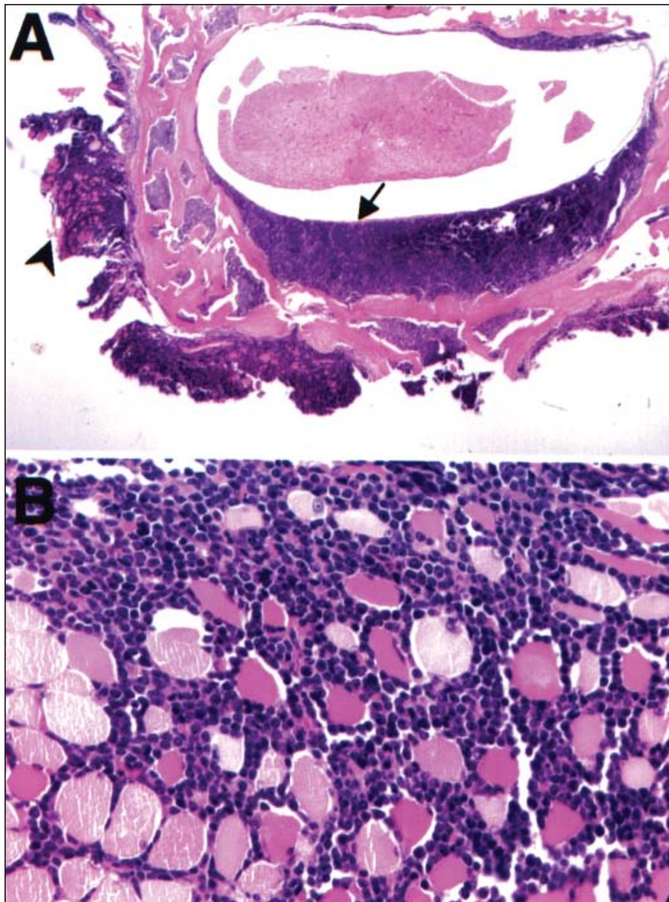

Figure 2. Photomicrograph of a section of the lumbar muscles and vertebral canal. (A) Notice mononuclear cells have virtually replaced all the muscle fibers (arrowhead) and invaded the epidural space (arrow). H&E stain; magnification, 4×. (B) Higher magnification showing infiltration due mostly to small and medium lymphocytes and fewer large lymphocytes and neutrophils. H&E stain; magnification, 40×.

may have caused the vascular lesion.

Mesenteric, pancreatic, internal ileac, renal, mediastinal, and cervical lymph nodes had remnants of a normal cortex with a few germinal centers. The remaining cortex, paracortex, and medulla were invariably infiltrated with uniform sheets of densely packed medium and large lymphocytes, a few pale cells with abundant cytoplasm (starry sky appearance), and many mitotic figures. Neoplastic lymphocytes often extended beyond the capsule into the adventitia. The bone marrow of some, but not all bones also had diffuse infiltration with large lymphocytes.

The spleen of the affected mice had variable degrees of hyperplasia of the white pulp and marked cellular heterogeneity within some follicles, which suggested early follicular lymphoma. However, normal splenic architecture was preserved in all cases.

In addition, moderate to severe infiltration of cells similar to those described previously was found in several organs, including but not limited to liver, lung, kidney, pancreas, mediastinum, peritoneum, mesentery, mesovarium, mesosalpynx, and salivary glands.

Immunohistochemical findings. Use of the B-cell marker, CD45R/B220, revealed staining of neoplastic cells in muscle, pancreas, and lymph nodes. Stronger staining of lymphocyte aggregates was observed in kidney, liver, and lungs. Staining was not seen in the tumors when the T-cell antibody, CD3-12 (Fig. 3), was used. Spleen and thymus from unaffected mice were used as positive controls of B- and T-cell markers, respectively.

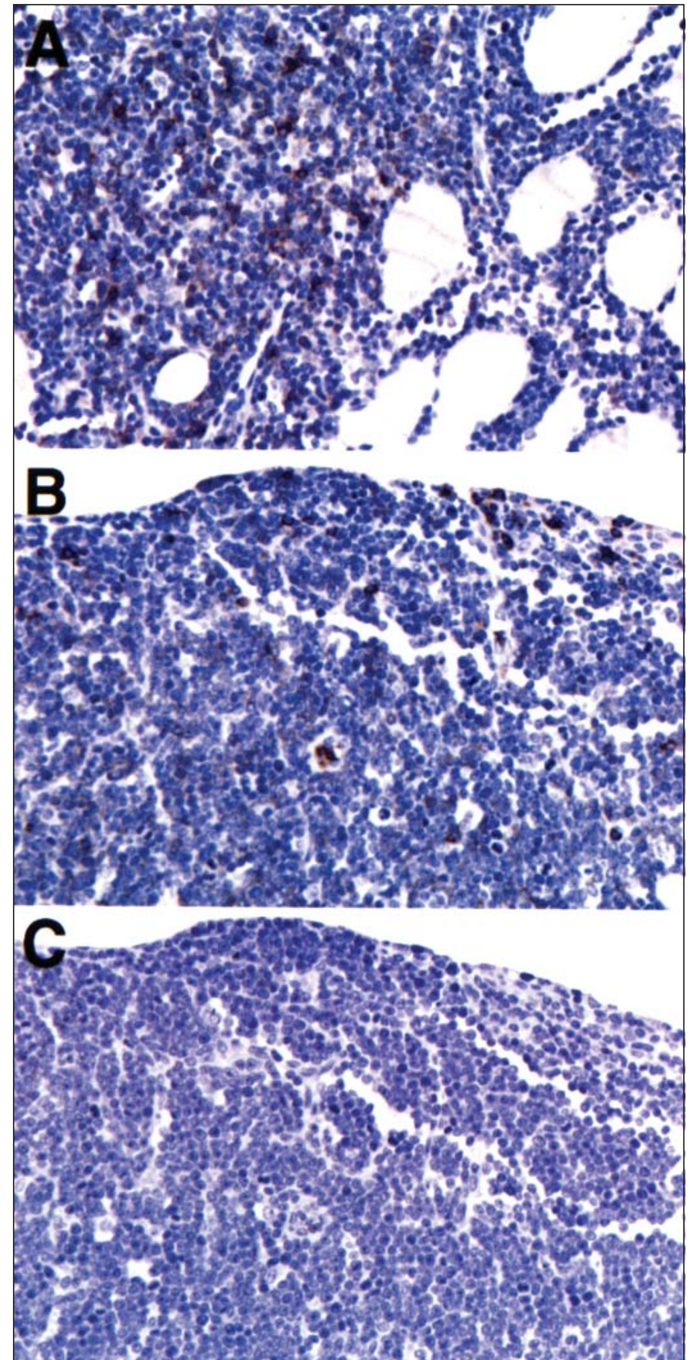

Figure 3. Photomicrographs of a section of lumbar muscle after immunohistochemical analysis with B-cell marker CD45R/B220 and T-cell antibody CD3-12. The B-cell marker stains tumor cells infiltrating lumbar muscle (A) and solid tumor masses (B). Staining reaction to the T-cell antibody was negative in the subsequent section of the tumor (C). Magnification, 40×.

Serologic test results. All results were negative for the murine pathogens tested: Sendai virus, MHV, *M. pulmonis,* MVM, Theiler's virus (GD VII), PVM, REO-3, LCMV, ectromelia virus, EDIM agent, MPV, K virus, polyoma virus, MAD, MCMV, Hantavirus, *E. cuniculi,* MTV, and CAR bacillus.

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Discussion

The two outstanding features of this outbreak were localization of the lesions with their consequent clinical signs of disease, and the unusual epidemiologic presentation. A diagnosis of lymphoma of the lymphoblastic type (9) was made on the basis of results of histologic examination. The brain, spinal cord, and peripheral nerves had no lesions that would explain the clinical signs of disease in terms of neuronal degeneration. Thus, the paralysis was most likely due to infiltration of the tumor into the meninges, causing compression of the spinal cord and the spinal nerve roots. Only three animals had gross changes in the lumbar muscles, but histologic examination revealed massive lymphocytic infiltration of the lumbar muscles in all affected mice. It is likely that this lesion, if not causal, may have at least substantially contributed to the clinical signs of disease. The question of which were the primary organ site(s) of lymphoma in these mice remains. The spleen often is the primary tumor site of B-cell lymphoma in mice. However, only four animals had splenomegaly, and histologic lesions were mild to moderate in all affected mice. This suggests that the spleen may not have been the primary organ site in these mice. Moreover, the severity of lymph node lesions and infiltration in other organs was mild to moderate in all the animals.

Thus, one of the unusual features of this outbreak remains the massively predominant localization of lymphoma in the lumbar muscles. Three researchers specifically reported lymphoma cells that preferentially invaded dorsal muscles and spinal cord (10-12). All three were found in the course of studies of transmissibility of murine lymphoma virus. To the best of our knowledge, this is the first report of naturally acquired lymphoma in the lumbar muscles that led to hind limb paralysis of mice.

A second unusual feature of this outbreak was the clustering of cases over a four-week period, which a priori suggests an infectious origin. However, the absence of pathognomonic lesions, and the negative serologic results militates against infection with those pathogens known to cause hind limb paralysis, such as Theiler's and polyoma virus. In addition, the remaining sentinel animals that came in the same batch, and were euthanized at the end of the quarter, tested negative for all pathogens included in the routine serologic screening (Sendai virus, MHV, *M. pulmonis*, MVM, Theiler's virus (GD VII), PVM, REO- 3, LCMV, ectromelia virus, EDIM agent, and MPV) as well as for gastrointestinal parasites.

Another possible explanation for this clustering of cases is that the sick animals were in a group of closely related mice that inherit the same genetic condition. Susceptibility to develop spontaneous lymphomas can be transmitted congenitally within a mouse strain, and has been described in wild and laboratory mice (13-15). This possibility, however, does not fully explain why all affected mice shared the unusual localization of the lesions in the lumbar region.

Lymphomas can result from exposure to chemical or physical carcinogens, or from specific mutations (e.g., phosphatase [PTEN] or *p53* deletions). In addition, development of spontaneous lymphomas in mice can result from vertically transmitted retroviral infection with a murine leukemia virus (MuLV). The retroviruses comprise a large group of genetically related viruses that have different tissue tropism and diverse host preferences, which may result in different expression in development of lymphomas. These viruses can be integrated in the germ line, and transmitted genetically as a Mendelian dominant trait (endogenous route), or may be acquired after birth via ingestion of contaminated milk (exogenous route) (1, 13, 16-18). One of these oncogenic retroviruses, Abelson's murine leukemia virus (A-MuLV), has been reported to induce solid lymphomas in mice (12), and is suspected to be the cause of parosteal lymphoma reported in man (19). Mice inoculated experimentally with MuLV had invasion of the vertebral bone marrow and the paravertebral muscles, resulting in progressive hind limb paralysis and death within five to 15 days after the onset of clinical signs of disease. Lymphadenopathy and splenomegaly also were present, and the histologic examination revealed uniform populations of immature lymphocytes (12).

It is apparent from literature that, in the mouse, experimental infection with Abelson's virus can cause mainly B-cell lymphomas, although it can also induce T-cell lymphomas depending on several factors, such as route, time of infection, and virus interactions (20, 21). In the study reported here, the clinical signs of disease and the lesions resembled those of experimentally induced A-MuLV infection, and many cells stained with the CD45 antibody in a pattern similar to that found in B-cell tumors (22).

Taken together, the negative results obtained by use of the T-cell marker, and the presence of cells stained with the B-cell marker, suggest that the tumor originated from the latter cell lineage. A definitive diagnosis to confirm retrovirus infection would have required the use of electron microscopy (EM), or tests such as the XC plaque or extended mink cell focus assays. Unfortunately, these could not be done because tissues were not adequately preserved. For EM, one-cubic millimeter-thick sections must be cut and fixed in glutaraldehyde. This is not routinely done during every necropsy in the facility. For XC plaque and extended mink focus assays, tissues must be fresh or frozen. By the time the results were analyzed, and the desirability of further studies was apparent, there no longer was any fresh tissue available. The rest of the sentinels from that batch had already been euthanized.

After consulting with the vendor and performing a literature search, we found that little is known about retroviral status in many commercial colonies, and the last report of spontaneous lymphomas in CFW control mice not exposed to any chemical or physical carcinogen was dated 1974 (23). However, recently, a surprisingly high incidence of lymphomas was reported in control CFW Swiss Webster mice that were being kept at the Centers for Disease Control and Prevention (CDC) (24). That study indicated high-level expression of ecotropic and mink cell focus-inducing (MCF) MuLVs, with a high frequency of hematopoietic neoplasms that developed as early as five months of age. Coincidentally, the strain, age, and source of the mice in that study were the same as those reported here, as were the lesions, with the exception that the mice at the CDC did not develop hind limb paralysis and lymphocyt infiltration into lumbar muscles. Although we could not establish an etiologic diagnosis, both reports taken together have strong similarities that suggest a link between both outbreaks and the probability of a common cause.

The importance of acquiring and maintaining animals with a good, well known health status can never be overstated; thus, purchasing animals that are free from endogenous retroviruses would be desirable. However, screening for retrovirus is not presently a routine practice in commercial colonies. Doing this would substantially increase the cost of animals. This addi-

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tional cost may also appear unwarranted since only a few reports of complications due to retrovirus infections or lymphomas have been reported from the users to the vendors. In addition, given the fact that MuLV fragments have been identified in the mouse genome (16, 24), the chances of clearing colonies of these infections are virtually nil at present.

Notwithstanding the present difficulties of controlling retroviral infections, it is also certain that these viruses can insidiously infect a colony through breeding and eventually affect many mice, causing suppression of humoral and cellular immunity (25, 26). They could pose a problem in interpretation of results from studies involving exposure to carcinogens using "control" and "exposed" animals (27). They could also interfere with research that requires long-term studies due to the presence of unexpected lymphomas (24), or in the case presented here, complicate the normal course of the sentinel program. In the present outbreak, detection of the disease was possible because of the unusual clinical presentation with hind limb paralysis, and because the animals had been purchased for the sentinel program and were carefully monitored. If these same animals had been used for breeding or other experiments, the possibility of an infection of this nature would have never been detected since routine screening techniques would not detect the condition.

It is, therefore, evident that more information is needed to establish the real prevalence and impact on research that could derive from retrovirus infections in commercial colonies. Our present inability to eliminate these infections should not preclude us from attempting to gather the information we need to understand its magnitude and extension. The case reported here emphasizes the importance of diagnosing, recording, and reporting clusters of unusual cases, whether they be rare, such as hind limb paralysis, or fairly common findings, such as sporadic cases of lymphomas in mice colonies. In addition, it is highly recommended, whenever possible, to preserve tissues from unusual cases in proper manner to be used for further analysis (i.e., frozen, glutaraldehyde fixation). This will enable use of better techniques to reach a definitive diagnosis.

Acknowledgments

We thank Timothy Lawson, DVM, Director, Division of Laboratory Animal Medicine, UCLA for his support of this study. We thank Long Sheng Hong for technical support. The Division of Laboratory Animal Medicine and the Department of Pathology of the University of California Los Angeles supported this paper. A portion of this work was presented at the 51st AALAS National Meeting, San Diego, Calif., November 2000.

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