seven tandemly arrayed guide snoRNAs. A total of 19 singlets occur outside of known protein-coding genes, presumably as independent transcription units. All tandemly arrayed snoRNAs within the same cluster are oriented on the same strand, and recent results indicate that these genes are polycistronic (*26*). Six yeast snoRNAs occur within the introns of host protein genes, all on the pre-mRNA coding strand. The mixture of snoRNAs in yeast occurring within introns and tandem arrays and as singlets is in contrast to vertebrates, where all currently known guide snoRNAs are within host gene introns. Polycistronic arrays of snoRNAs have also been reported in plants (*27*). Some plant polycistrons contain a mix of snoRNAs from both major families of guide snoRNAs (C/D box and H/ACA box snoRNAs), whereas none of the yeast tandem arrays contain members outside of the C/D box family.

It is possible that a large number of noncoding RNAs remain to be discovered. Both computational screens and experimental screens tend to be biased against RNAs. Many functional RNAs are not polyadenylated, so they are not well represented in oligo(dT) primed cDNA libraries or in expressed sequence tag sequencing projects. Often the genes for RNAs are small and may occur in multiple copies. RNAs are of course not affected by stop codons or frameshifts, so they are probably somewhat refractory to genetic screens. Most functional RNAs known today have been identified by biochemical means, but these approaches are best suited to abundant RNAs. Using probabilistic modeling methods, we are beginning to gather the tools necessary to computationally screen genome sequences for noncoding RNAs.

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Novel Endotheliotropic Herpesviruses Fatal for Asian and African Elephants

Laura K. Richman,[1,2]* Richard J. Montali,[1] Richard L. Garber,[3] Melissa A. Kennedy,[4] John Lehnhardt,[1] Thomas Hildebrandt,[5] Dennis Schmitt,[6] Douglas Hardy,[7] Donald J. Alcendor,[2] Gary S. Hayward[2]

A highly fatal hemorrhagic disease has been identified in 10 young Asian and African elephants at North American zoos. In the affected animals there was ultrastructural evidence for herpesvirus-like particles in endothelial cells of the heart, liver, and tongue. Consensus primer polymerase chain reaction combined with sequencing yielded molecular evidence that confirmed the presence of two novel but related herpesviruses associated with the disease, one in Asian elephants and another in African elephants. Otherwise healthy African elephants with external herpetic lesions yielded herpesvirus sequences identical to that found in Asian elephants with endothelial disease. This finding suggests that the Asian elephant deaths were caused by cross-species infection with a herpesvirus that is naturally latent in, but normally not lethal to, African elephants. A reciprocal relationship may exist for the African elephant disease.

In 1997, there were an estimated 291 Asian elephants and 193 African elephants in North America. About 115 elephant births have occurred, mostly since 1960, but perinatal deaths and stillbirths have been and remain exceedingly high. Because elephants from the wild are no longer accessible for import, captive breeding populations could be repro-

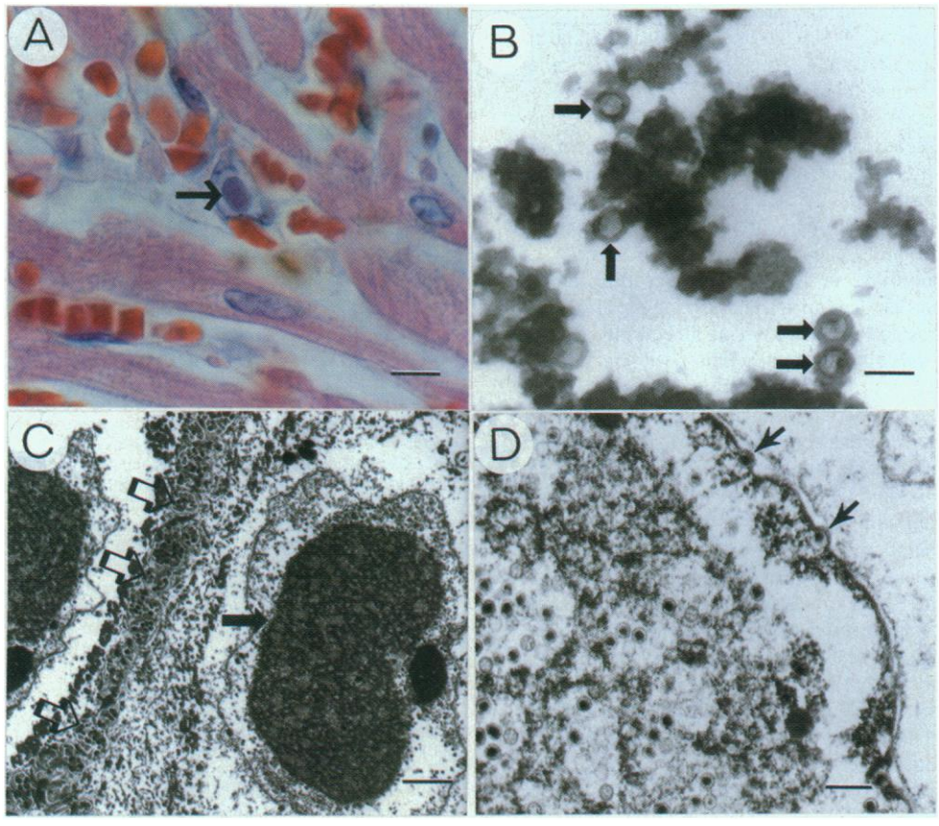

Fig. 1. Microscopic appearance of diseased heart tissue from an Asian elephant with endotheliotropic herpesvirus compared to a localized skin papilloma from an African elephant. (**A**) Tissue from the index case (Asian elephant case 1), demonstrating diffuse myocardial hemorrhage and a basophilic intranuclear viral inclusion body within a capillary endothelial cell (arrow). Hematoxylin and eosin stain; scale bar, 20 μm. (**B**) Transmission electron microscopy (TEM) of heart, showing details of an intranuclear inclusion body within an endothelial cell. Herpesvirus capsids (diameter 80 to 92 nm) are evident within the intranuclear inclusion body (arrows). Scale bar, 150 nm. These viral inclusions are histologic hallmarks of the disease and were present in all nine of the elephants dying with the endotheliotropic herpesvirus disease. Such inclusions did not occur at any sites in normal Asian elephants nor those dying of unrelated conditions. Herpesvirus particles were present in all of the cases examined by electron microscopy (cases 1, 2, 4, 7, 9, and 10). (**C**) TEM of a skin papilloma from an adult African elephant showing an epidermal cell containing an intranuclear inclusion body (solid arrow) and intercellular enveloped herpesviruses (open arrows). Scale bar, 4.0 μm. (**D**) Higher magnification of (C), showing detail of intranuclear nucleocapsids. Arrows show viruses undergoing envelopment at the nuclear membrane. Scale bar, 250 nm.

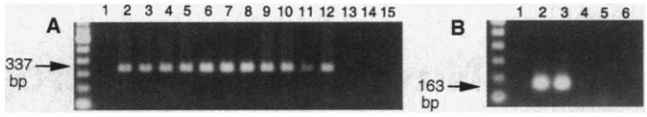

Fig. 2. Agarose gel electrophoresis of the ethidium bromide–stained products of PCR reactions testing DNA extracted from elephant tissue samples. (**A**) PCR using elephant herpesvirus terminase gene primers on samples from Asian elephants that were diagnosed with endotheliotropic herpesvirus disease (lanes 2 to 9). Lanes 2 to 8 represent deceased animals (cases 1, 4, 5, 6, 7, 9, and 10); lane 9, peripheral blood from the one surviving Asian elephant (case 3). DNA from skin papillomas of two asymptomatic (one wild, one captive) African elephants (lanes 10 and 11), and a vaginal lymphoid patch biopsy from one healthy African elephant (lane 12) were also tested. A 337–base pair (bp) reaction product was present in all of these elephants, but not in heart tissue from two Asian elephants without endothelial disease (lanes 13 and 14). M, 100-bp DNA ladder markers; lane 1, no DNA control; lane 15, human placental DNA control. (**B**) PCR reactions using elephant herpesvirus DNA polymerase primers and DNA from heart tissue of two captive African elephants (cases 2 and 8) that died with endotheliotropic herpesvirus infections (lanes 2 and 3) resulted in a 163-bp product. No product arose in reactions using DNA from two African elephants that died of unrelated causes (lanes 4 and 5). M, 100-bp DNA ladder markers; lane 1, no DNA control; lane 6, human placental DNA control.

ductively unfit in 20 to 30 years if not sustained by younger generations (*1*). We report here a new, highly fatal endotheliotropic herpesvirus disease of elephants that is responsible for a substantial proportion of perinatal deaths and which, if left unchecked, may imperil the successful propagation of elephants for the future.

The pathological aspects of this rapidly progressive hemorrhagic disease of young elephants in North America have recently been described (*2*). The disease had a sudden onset and was characterized by edema (fluid retention) in the skin of the head and proboscis, cyanosis of the tongue, decreased white blood cell and platelet counts, and internal hemorrhages. Histological abnormalities were predominantly localized to the heart, liver, and tongue and included the appearance of basophilic intranuclear viral inclusion bodies in the microvasculature of these organs (Fig. 1A). Electron microscopy showed that the inclusion bodies contained viral capsids (diameter 80 to 92 nm) that were morphologically consistent with herpes virions (Fig. 1B). The cell type affected by this disease showed that this virus had a predilection for endothelial cells (endotheliotropism), which is unusual for any of the previously characterized herpesviruses. The high fatality rate was attributed to acute myocardial failure from capillary injury and leakage due to endothelial cell damage caused by the presence of the herpesvirus. A similar case was previously reported in a young Asian elephant from a circus in Switzerland (*3*, *4*).

Cultures or other evidence of concurrent infection were negative for pathogenic bacteria, and no viruses could be cultivated from the three most recent cases (Table 1, cases 1 to 3) when a variety of permissive cell lines (Vero and MARC African green monkey kidney cells, embryonating chicken eggs, baby hamster kidney cells, rabbit kidney-13 cells, equine dermal cells, and human foreskin fibroblasts) as well as Asian and African elephant fibroblasts were used. In addition, there was no serological evidence of exposure in any of the affected elephants tested or selected herdmates to viruses known to target car-

[1]Smithsonian, National Zoological Park, Washington, DC 20008, USA. [2]Johns Hopkins School of Medicine, Baltimore, MD 21205, USA. [3]PathoGenesis Corporation, Seattle, WA 98119, USA. [4]University of Tennessee, Knoxville, TN 37901, USA. [5]Institute for Zoo Biology and Wildlife Research, D10305 Berlin, Germany. [6]Southwest Missouri State University, Springfield, MO 65804, USA. [7]Dickerson Park Zoo, Springfield, MO 65803, USA.

*To whom correspondence should be addressed. E-mail: lkrichma@welchlink.welch.jhu.edu

diovascular tissue, including bluetongue virus, epizootic hemorrhagic disease of deer, equine arteritis virus, and encephalomyocarditis virus. Only one case (case 8) had evidence of a concurrent infection in which encephalomyocarditis virus (EMCV) was cultured from a lymph node, despite the animal being seronegative for EMCV. Histological and ultrastructural evidence for an endotheliotropic herpesvirus was the only common element linking these elephant cases together.

The index case for this endothelial disease occurred in 1995 in a 16-month-old Asian elephant born at the National Zoological Park (Table 1, case 1). We then diagnosed another case in an 11-month-old African elephant (case 2) in 1996 and in a 17-month-old Asian elephant (case 3) in 1997. We identified six additional Asian elephant cases of endothelial disease that occurred between 1983 and 1993 (cases 4 to 7, 9, and 10) by searching elephant studbook mortality records (held by the American Zoo and Aquarium Association, or AZA) and obtaining pathology reports, microscope slides, and tissues from elephants that matched the case definitions that we had established for this disease. Eight of 10 animals with confirmed disease were relatively young (from 18 months to 7 years), and there was no sex predilection. The elephants were in zoos at a wide range of locations in North America at the time of their death. These cases occurred as single events, with no knowledge by anyone at the time that a herpesvirus infection was responsible for the mortalities. Two facilities experienced two cases several years apart, whereas elephant calves were raised subsequently at three zoos with a single case and no further losses from the herpesvirus.

Asian elephants dying at zoos in California and Hawaii (cases 11 and 12) were also highly suspect of having this disease according to recorded clinical and pathological findings, but neither histologic slides nor tissues were available for confirmation by our group. Similarly, other deaths occurred in young Asian elephants before 1980, but pathological material and detailed documentation were not available. Between 1983 and 1996, 34 Asian elephants were born in North America. Seven of these animals have died with lesions attributed to the endotheliotropic herpesvirus disease, and one recovered after pharmacological intervention (case 3). African elephant births in North America have been few, with only seven births in the same time period and two deaths due to this disease.

Herpesvirus could not be cultured from the tissue of any elephants with endothelial disease, so we turned to a molecular approach. Initially, using nested polymerase chain reaction (PCR) with consensus redundant oligonucleotide primers that target portions of the terminase and DNA polymerase genes (*5, 6*) of all known herpesvirus genomes, we confirmed the presence of herpesviruses that are different from any other known species. Later, direct single-round PCR (*7*) was also performed on DNAs extracted from affected tissues of 10 diseased animals and appropriate negative controls (Fig. 2) (*8*). DNA from tissues of all seven of the affected Asian elephants tested (cases 1, 5, 7, and 9 shown), and in the blood of the

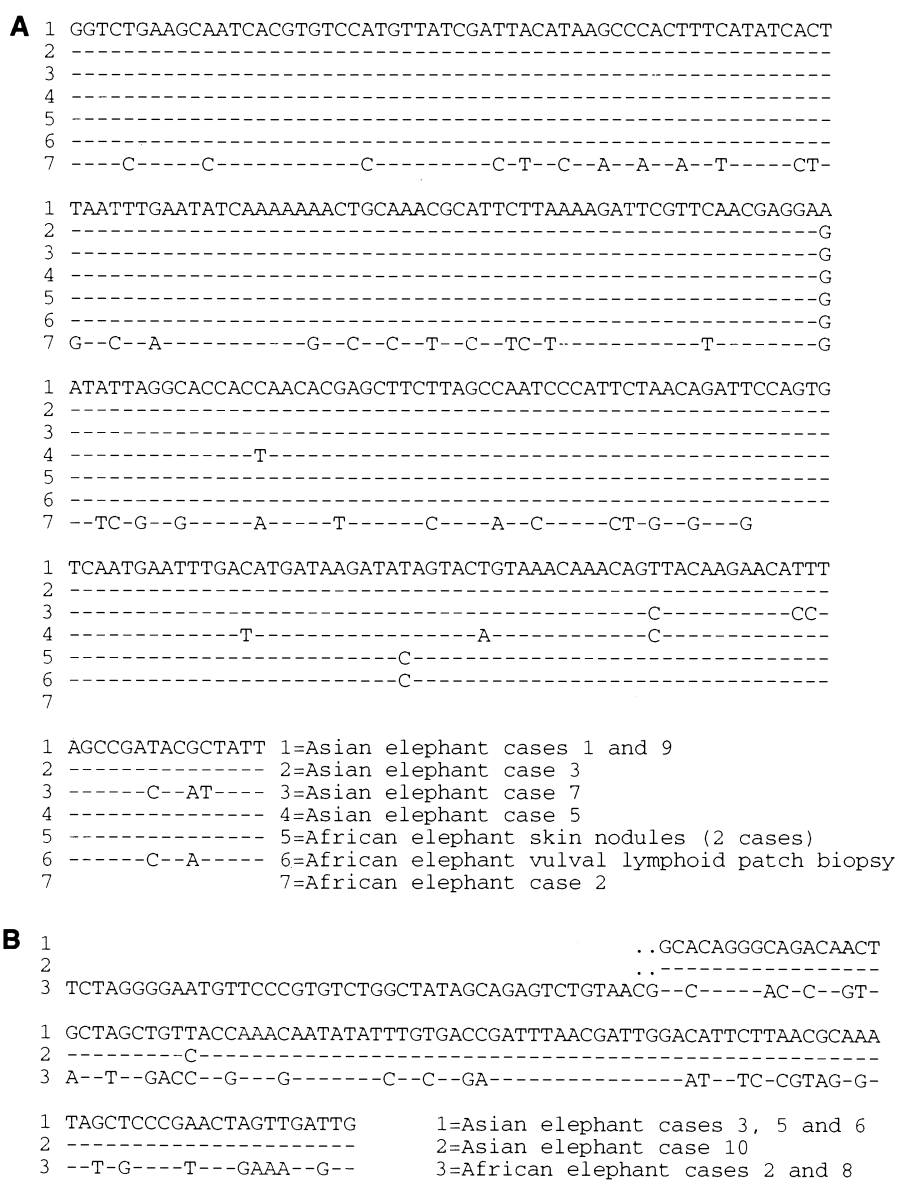

Fig. 3. DNA sequences of PCR products obtained from several samples of Asian elephant endothelial disease differ from those of African elephant endothelial disease but are nearly identical to those from skin and vulval lesions in African elephants. (**A**) Comparison of DNA sequences encoding amino acids from positions 386 to 496 (in HSV-1) from the terminase PCR products obtained from the heart tissue of five Asian elephants (cases 1, 3, 5, 7, and 9) and one African elephant (case 2) that died with endotheliotropic herpesvirus infection, and from skin papillomas from two asymptomatic African elephants and a vaginal lymphoid patch biopsy from a wild, asymptomatic African elephant. With the exception of the heart tissue from the African elephant, the DNA sequences are nearly identical, with at most a 5-bp difference. DNA sequences from African elephant case 2 are 80% identical to the Asian elephant terminase sequences. The complete DNA sequence of the 373-bp PCR product from Asian elephant case 1 has been deposited in GenBank (accession number AF117265). (**B**) Comparison of DNA sequences encoding amino acids from positions 824 to 872 (in HSV-1) from DNA polymerase PCR products obtained from heart tissue from two African elephants (cases 2 and 8) and four Asian elephants (cases 3, 5, 6, and 10) that died with endotheliotropic herpesvirus disease. The African elephant DNA sequences are identical, and the Asian elephant DNA sequences are 65% homologous to the African elephant sequences. The complete DNA sequence of the 180-bp PCR product from African elephant case 2 has been deposited in GenBank (accession number AF117266). Dashes indicate nucleotides that are identical to the topline reference case.

single survivor during the course of her illness (Asian elephant case 3), encoded herpesvirus terminase sequences that had only minor variability at the nucleotide level (Fig. 3A). Initially, no terminase PCR products were obtained from African elephants with endothelial disease, and conversely, DNA polymerase–directed PCR generated products from the African cases only, but not from

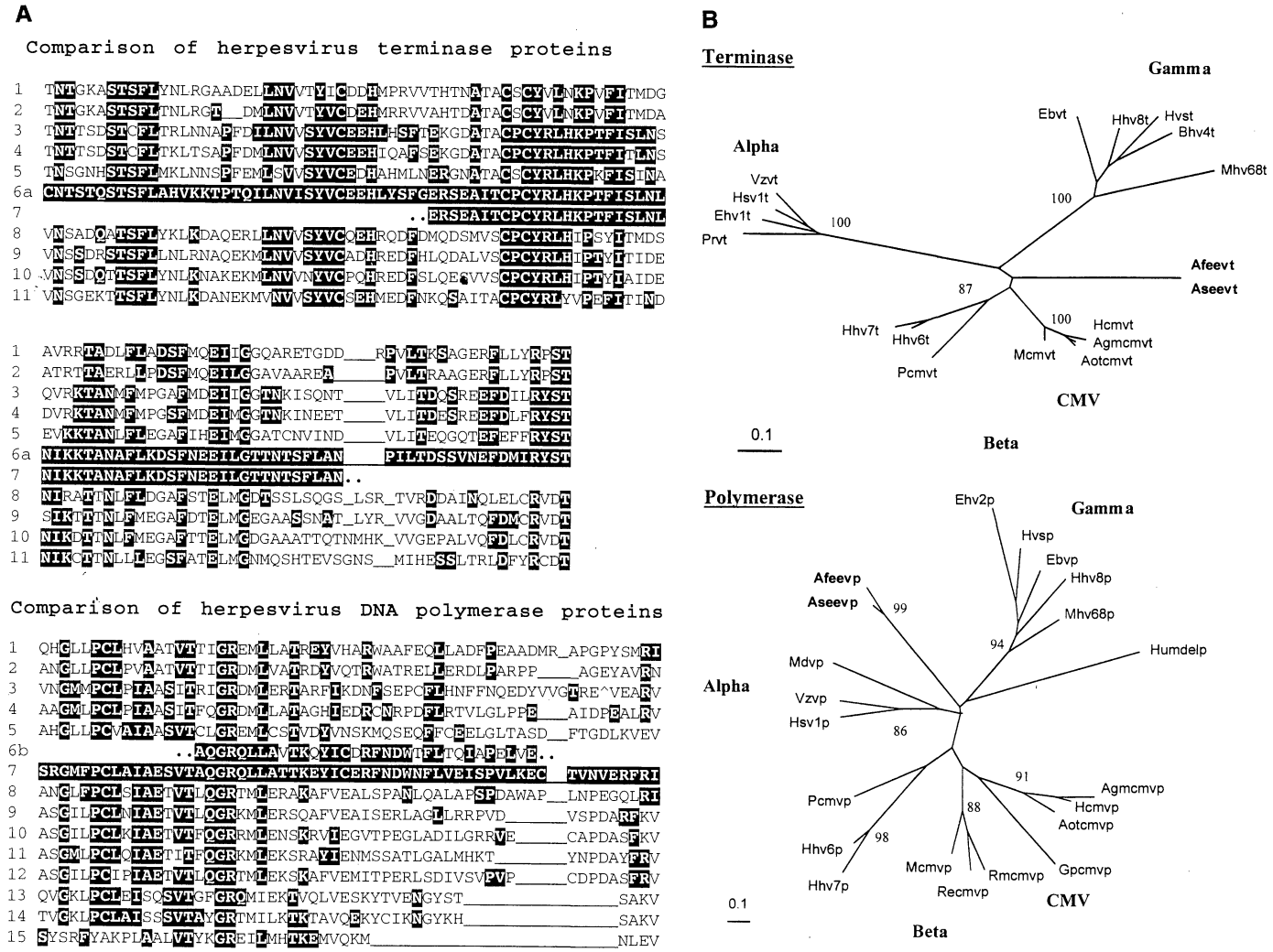

Fig. 4. Confirmation that the DNA sequences found in Asian and African elephant endothelial disease and African elephant skin lesions encode herpesvirus proteins but are not closely related to any known herpesvirus subfamilies. (**A**) Amino acid sequences of portions of the terminase and DNA polymerase proteins from selected human and animal herpesviruses compared to the Asian and African elephant herpesviruses and cellular DNA polymerases. Positionally matching amino acids that are identical to those in the Asian elephant versions in terminase and African elephant versions in polymerase are highlighted. The regions shown correspond to amino acid positions 386 to 496 in HSV-1 terminase (=UL 15) and 824 to 882 in HSV-1 DNA polymerase (=UL 30). (**B**) Phylogenetic relationship between elephant endotheliolytic herpesvirus and other representative herpesviruses within the terminase (t) and DNA polymerase (p) protein sequences. The diagrams were generated by the ProtDist (PAM) Neighbor program (unrooted) using a 111–amino acid segment of terminase or a 48–amino acid segment of DNA polymerase from about 20 different herpesviruses representing human and animal examples of alpha-, beta-, and gammaherpesviruses, including all known cytomegalovirus (CMV) species. Mouse gammaherpesvirus MHV68 terminase and human delta DNA polymerase (Humdel) were used as an outgroup. The Asian and African elephant endotheliolytic viruses are denoted Aseev and Afeev, respectively. The naming convention for the other viruses used is as follows. **Alphaherpesviruses:** Hsv1, herpes simplex virus 1 (HHV1 or HSV1); Vzv, varicella-zoster virus (HHV3 or VZV); Ehv1, equid herpesvirus 1 (EHV1); Prv, suid (pig) herpesvirus 1 or pseudorabies virus (SuHV1 or PRV). **Gammaherpesviruses:** Bhv, bovine herpesvirus 4 (BoHV4); Hvs, herpesvirus saimiri 2 (SaHV2 or HVS); Hhv8, human herpesvirus 8 or Kaposi's sarcoma–associated herpesvirus (HHV8 or KSHV); Ebv, Epstein-Barr virus (HHV4 or EBV); Mhv68, mouse herpesvirus 68 (MuHV4 or MHV68). **Betaherpesviruses:** Agmcmv, African green monkey cytomegalovirus (CeHV5); Aotcmv, herpesvirus aotus 1 or owl monkey cytomegalovirus (AoHV1); Hcmv, human cytomegalovirus (HHV5 or HCMV); Mcmv, mouse cytomegalovirus 1 (MuHV1 or MCMV); Pcmv, swine cytomegalovirus (SuHV2 or PCMV); Gpcmv, cavid (guinea pig) cytomegalovirus (CaHV2); Recmv, rat cytomegalovirus English strain; Rmcmv, rat cytomegalovirus Maastricht strain (MuHV2); Hhv6, human herpesvirus 6 (HHV6); Hhv7, human herpesvirus 7 (HHV7).

the Asian elephants with endothelial disease.

To compare the same viral genes derived from both Asian and African elephants, we constructed new specific primers based on the initial sequences obtained for cases 1 and 2. This approach resulted in PCR products from the DNA polymerase gene of four Asian elephant cases (3, 5, 6, and 10) that were nearly identical to each other at the nucleotide level (Fig. 3B). However, sequence comparison of the herpesvirus DNA polymerase regions from the two elephant species showed only a 76% protein identity between the viruses detected in Asian and African elephant cases (Fig. 4A), with 65% identity at the nucleotide level (Fig. 3B). This indicates that two different species of herpesviruses are present in the elephants studied here. Similarly, PCR products from the terminase gene region were also obtained from African elephant case 2 once a second set of specific primers was constructed (*7*). Sequence comparison of the terminase gene region from the two elephant species showed 80% identity at the nucleotide level (Fig. 3A), although in this case the changes were all synonymous and the encoded proteins showed 100% amino acid identity (Fig. 4A).

Control samples that proved negative in this study included heart or liver tissue (or both) from four Asian and four African elephants that died from conditions unrelated to endothelial disease (Fig. 2). Additionally, DNAs extracted from peripheral blood (*8*) of 27 asymptomatic Asian and 13 African elephants, including herdmates from facilities where herpesvirus deaths had occurred, were negative for herpesvirus using PCR primer sets specific for both viruses.

The finding of intranuclear inclusion bodies only in endothelial cells of elephants that have died with the characteristic disease provides histomorphological evidence of their tropism for these vascular cells. In fact, these endothelial inclusion bodies found in all nine elephants that died of the herpesvirus infection are histological hallmarks that may be pathognomonic for this disease. The endotheliotropic disease associated with the elephant herpesviruses, in conjunction with prominent intranuclear inclusion bodies, suggests that these viruses have some of the characteristics of betaherpesvirus (*9*). Indeed, the proteins encoded by the PCR-amplified DNA obtained from each of the eight Asian and two African elephants that were affected with the disease are clearly those of herpesviruses, but they are distinct from any of the currently known herpesviruses (Fig. 4). Comparison of amino acid sequences that are characteristic for each subfamily (Fig. 4A) and the results of a phylogenetic tree analysis (Fig. 4B) reveal that the terminase protein of the elephant herpesviruses shows slightly greater similarity to betaherpesviruses than to alpha- or gammaherpesviruses, but it is clearly not that of a cytomegalovirus (CMV). Similarly, the elephant virus DNA polymerase proteins do not fit into any of the herpesvirus subgroups (Fig. 4) (*10*). These findings, together with the unique pathogenesis, suggest that the causative agents of elephant endothelial disease either are outliers of mammalian betaherpesviruses or may belong in a previously unrecognized subfamily.

In many of the facilities with herpes-related elephant deaths, African and Asian elephants are known to have had direct or indirect contact with each other. Because localized cutaneous herpesvirus lesions have been reported in African elephants (*11*), preserved samples were obtained from skin papillomas from otherwise asymptomatic, wild-born African elephants that were imported to Florida in the early 1980s. We also obtained a skin papilloma from a wild bull elephant from the Kruger National Park in South Africa, as well as biopsy specimens of vulval lymphoid patches (*12*) from wild African elephants from Zimbabwe. Histologically, intranuclear inclusion bodies were present within epithelial cells of the deep epidermis in the skin papillomas (Fig. 1C), which contained both filled and empty herpes-like nucleocapsids, including capsids apparently undergoing envelopment at the nuclear membrane (Fig. 1D). The vulval lymphoid patch biopsies did not have light or electron microscopic evidence of viral particles. Surprisingly, in each of these African elephant tissues, we obtained PCR products of the terminase gene region (Fig. 2A) that, when sequenced, proved to encode protein sequences identical to those obtained from the eight Asian elephants with endotheliotropic herpesvirus disease (Figs. 3A and 4A). Control samples that proved negative included pustular skin lesions from two African and three Asian elephants without evidence of inclusion bodies, and suppurative or noninflammatory vulval lesions from one Asian and two African elephants.

Although the number of cases is currently small, this may be evidence for the existence of a herpesvirus that is indigenous to and nonlethal in African elephants (perhaps latent in the lymphoid patches and productive in the papillomas). When this virus is present in captive African elephants and inappropriately cross-infects young Asian elephants, the resulting primary disease is apparently lethal. We further suggest that the endothelial disease fatalities in the African elephants may have originated as an indigenous Asian elephant herpesvirus. It is also possible, but less plausible, that endothelial disease is a result of reactivation of a latent infection and that some other stressor contributes to reactivation and dissemination of these herpesviruses. However, only cross-species infection can account for the same virus being present in the diseased, young captive Asian elephants as in the asymptomatic adult African elephants in the wild. The status of herpesviruses in wild Asian elephants is currently unknown, because it has not yet been possible for us to obtain elephant tissue samples from Asian countries.

We also have shown by similar pathologic and molecular studies of the Asian circus elephant from Switzerland (*3*) and from an aborted Asian elephant fetus from a German zoo that they were infected with the same herpesvirus obtained from both the diseased North American Asian elephants and the asymptomatic African elephants (*13*). When an orphan elephant from India died in 1997, 2 months after arrival at a zoo in Jerusalem, we noted morphologic evidence of the same herpesvirus infection described here. These findings indicate that the elephant endothelial herpesvirus disease is likely to be worldwide wherever Asian and African elephants have come together. We suggest that these elephant herpesviruses have contributed to a substantial proportion of captive-born ele-

Table 1. Cases of endotheliotropic herpesvirus infection in elephants in North American zoos. Case 3 was the only survivor.

	Elephant	Species	Origin	Age	Sex	Onset	Location	Course (days)
Recent cases	1	Asian	Washington, DC	16 months	F	1995	Washington, DC	5
	2	African	California	11 months	M	1996	California	3
	3	Asian	Missouri	17 months	F	1997	Missouri	10
Retrospective cases	4	Asian	New York	18 months	M	1983	New York	5
	5	Asian	Florida	26 years	F	1986	Ontario	1
	6	Asian	Texas	4.5 years	M	1988	Ontario	3
	7	Asian	Texas	2.5 years	F	1991	Illinois	2
	8	African	Texas	13 years	F	1991	Texas	4
	9	Asian	Missouri	18 months	F	1993	Missouri	3
	10	Asian	Oklahoma	7 years	M	1993	Oklahoma	?
Unconfirmed cases	11	Asian	California	Adult	F	1980	California	1
	12	Asian	Hawaii	5 years	F	1986	Hawaii	1

phant mortalities and that an accurate accounting of this disease has been limited by the unavailability of case material before the 1980s.

The only known survivor of infection by this herpesvirus, Asian elephant case 3, was diagnosed very early in the course of the disease in November 1997 by clinical findings and positive PCR results on peripheral blood. The elephant's clinical recovery in this case was attributed to the use of an antiherpesvirus drug, famciclovir (*14*). The favorable drug response shows promise for treatment of future cases of this disease. We are continuing an intensive investigation of these viruses, as we believe the disease they cause represents a threat to elephant conservation. Our findings also have implications for management practices in facilities keeping both African and Asian elephants and in protecting natural elephant habitats from virulent forms of the virus. There is also an urgent need to develop serological tests that can discriminate between the two viruses and permit identification of possible asymptomatic carrier animals.

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7. Initially, consensus primer PCR was performed using a published set of redundant primers for the terminase and DNA polymerase gene regions. Specific single primer sets for the elephant herpesvirus terminase and DNA polymerase gene regions were constructed from the sequence initially obtained from elephant cases 1 and 2: terminase primers for Asian elephants (5′-GTACGTCCTTTCTAGCTCAC-3′ and 5′-GTGTCGGCTAAATGTTCTTG-3′), terminase primers for African elephants (5′-AATGTGATATCCTACGTATG-3′ and 5′-GTACTATATCTTATCATGTC-3′), and DNA polymerase primers for both elephant species (5′-GTGTCTGGCTATAGCAGAGT-3′ and 5′-CACATCGATACGGAATCTCT-3′). PCR amplification was performed with nonredundant primers in a 50-μl reaction volume containing PCR SuperMix (Gibco/BRL–Life Technologies, Gaithersburg, MD), 0.3% (v/v) glycerol, and 20 pmol of each primer. Thirty-six cycles of PCR were completed using the following protocol: denaturation at 94°C for 1 min, annealing at 50°C for 1 min, and extension at 72°C for 2 min. The final extension was performed at 72°C for 7 min. The PCR product was visualized on a 1.5% agarose gel stained with ethidium bromide. A second round of PCR was needed to detect the African elephant vulval lymphoid patch product using the same terminase primers under identical conditions. Some PCR products were cloned using the TA Cloning kit (Invitrogen) and sequenced, and others were sequenced directly from the PCR products.
8. DNA was extracted from ~100 μm of paraffin-embedded, formalin-fixed tissue with the Ex-wax kit (Oncor, Gaithersburg, MD). After precipitation, DNA was resuspended and amplified by PCR. DNA was extracted from 200 μl of whole blood (either fresh or frozen at −80°C) using Gentra System (Minneapolis, MN) capture columns according to the manufacturer's protocol.
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Three-Dimensional Structure of a Recombinant Gap Junction Membrane Channel

Vinzenz M. Unger,[1]* Nalin M. Kumar,[1] Norton B. Gilula,[1] Mark Yeager[1,2]†

Gap junction membrane channels mediate electrical and metabolic coupling between adjacent cells. The structure of a recombinant cardiac gap junction channel was determined by electron crystallography at resolutions of 7.5 angstroms in the membrane plane and 21 angstroms in the vertical direction. The dodecameric channel was formed by the end-to-end docking of two hexamers, each of which displayed 24 rods of density in the membrane interior, which is consistent with an α-helical conformation for the four transmembrane domains of each connexin subunit. The transmembrane α-helical rods contrasted with the double-layered appearance of the extracellular domains. Although not indicative for a particular type of secondary structure, the protein density that formed the extracellular vestibule provided a tight seal to exclude the exchange of substances with the extracellular milieu.

Gap junction membrane channels are macromolecular complexes that allow the direct exchange of small molecules and ions between neighboring cells (*1*); thus, these channels have an important role in maintaining homeostasis within tissues. Electrophysiological measurements, as well as dye-transfer studies in vivo, have revealed that signal transmission through gap junctions can be modulated by a variety of molecules and physiologic conditions [reviewed in (*2–5*)].

A diverse multigene family of polytopic gap junction membrane proteins are known as connexins (*5, 6*). Several human diseases have been related to connexin mutations, such as the X chromosome–linked form of Charcot-Marie-Tooth disease (*7, 8*); the most common form of nonsyndromic neurosensory autosomal recessive deafness (*9, 10*); and, possibly, developmental anomalies of the cardiovascular system in some patients (*11*). In addition, transgenic mice lacking α_1 connexin43, the principal gap junction protein in the heart, die soon after birth and exhibit developmental malformations (*12, 13*). Heterozygotes are viable but display slowed ventricular conduction (*14*).

Previous analyses of gap junction structure have been limited to relatively low resolution, which is partially due to the heterogeneity of the specimens (*15*). A model based on electron microscopy and x-ray–scattering experiments suggests that the intercellular channel is formed by the end-to-end interaction of two oligomers

[1]The Scripps Research Institute, Department of Cell Biology, 10550 North Torrey Pines Road, [2]Division of Cardiovascular Diseases, Scripps Clinic, 10666 North Torrey Pines Road, La Jolla, CA 92037, USA.

*Present address: Max-Planck-Institut für Biophysik, Abteilung Strukturbiologie, Heinrich-Hoffmann-Strasse 7, D-60528 Frankfurt am Main, Germany.

†To whom correspondence should be addressed. E-mail: yeager@scripps.edu