Bush '82

Future Meetings

January 16-18, 1983

The International Embryo Transfer Society will hold its annual conference on January 16-18, 1983, at Colorado State University, Fort Collins. A workshop on the comparison of embryos among species, evaluation of embryo quality within species, and techniques of micromanipulation will be held on January 16. The main program, on January 17-18, will consist of invited papers on in vitro fertilization in bovines; embryo transfer in swine, sheep, and goats; induction of superovulation in mares; problems with superovulation and fertilization failure in bovines; and international movement of livestock. There will also be posters and movie sessions, as well as exhibits.

Registration for the workshop is $25.00. Registration for the main program is $50.00 for members, $85.00 for nonmembers. The fee for student affiliates is $10.00 and includes both the workshop and the main session. For further information contact Dr. Sarah Seidel, Executive Secretary, International Embryo Transfer Society, 3101 Arrowhead Road, La Porte, CO 80535 (303/482-1088).

March 14-16, 1983

The Fifth Charles River International Symposium on Laboratory Animals, "Biomedical Research: Importance of Laboratory Animal Genetics, Health, and Environment," sponsored by the Charles River Foundation, will be held at the Stadthalle in Heidelberg, Germany, on March 14-16, 1983. For advanced registration information, contact Symposium Chairman, Charles River Foundation, P.O. Box 430, Wilmington, MA 01887.

Articles

A SEARCH FOR ANIMAL MODELS AT ZOOS

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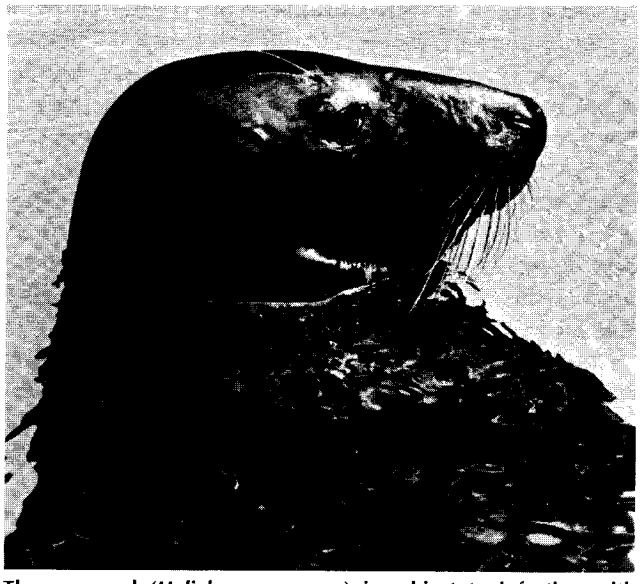
In the continuing search for animal models of human diseases, the wide variety of species housed in zoological parks is often overlooked. Although it is unlikely that these species will provide "ultimate" models, certain aspects of their diseases may be relevant to the human counterparts. For example, Dr. Fred Chu of the National Eye Institute recently contacted the National Zoo about studying ocular cystinosis in maned wolves (*Chrysocyon brachyurus*). He had come across reports (Bush and Bovée, 1978; Bovée *et al.*, 1981) of some work initiated at this facility, stemming from the necropsy of a maned wolf that died with urinary obstruction due to cystine calculi. Subsequent study of 42 maned wolves revealed that about 80 percent of the animals had excessive cystine in their urine. Some of the wolves came from other zoos or were live-trapped in their native habitat in South America. The maned wolf is endangered, and the implications of this familial disease become more ominous in this species, whose captive population is already small. Knowledge of this condition in maned wolves now demands breeding strategies to perpetuate the species. The resemblance of this amino acid disorder to cystinosis in humans is a valuable spin-off of these findings. Enter then Dr. Chu, who wishes to study the effects of cystinosis on the eyes. Other investigators also may want to establish whether there are manifestations of cystinuria in maned wolves that can shed further light on human cystinosis.

There are many examples of zoo animals that might provide clues to human disease processes. Dr. Timothy Meyer, working with Dr. Hostetter's group at the Brigham and Women's Hospital, Boston, Massachusetts, has been investigating the relationship of protein feeding to changing renal hemodynamics, which is felt to accelerate development of glomerular pathology in different species (Hostetter *et al.*, 1981). Of course, the majority of the work has centered around various strains of rats, but Dr. Meyer has also been interested in reviewing cases of kidney disease in large cats, which traditionally are maintained on high-protein diets and are known to develop renal disturbances in later life. In reviewing the pathology of large cats that died over the past 15 years at the National Zoo, three aged cheetahs (*Acinonyx jubatus*) were found to have pertinent glomerular changes.

Other aspects of disease processes may have some bearing on human disorders. In pinnipeds (seals, sea lions), for example, the pathogenesis of fungal dermatitis due to *Fusarium solani* is dependent on the ambient temperature of the animals' pools. When temperatures surpass 80°C, fungal dermatitis develops; when cooler temperatures prevail, the dermatitis goes into remission (Montali *et al.*, 1981a). *Fusarium solani* occasionally causes keratitis in humans (as well as in other animal species), and it is possible that cryotherapy would be of some benefit.

Research in zoo settings with the intent of providing



The grey seal (*Halichoerus grypus*) is subject to infection with *Fusarium solani*, a fungus that occasionally causes keratitis in humans. Study of this fungal dermatitis in pinnipeds may provide insights into treating the human disease. Photograph courtesy of Jessie Cohen, Office of Graphics and Exhibits, National Zoological Park, Smithsonian Institution, Washington, D.C.

comparative information is certainly not a new notion. A symposium sponsored by the Institute of Laboratory Animal Resources, National Academy of Sciences, in 1973 highlighted all of the major research efforts and accomplishments of many of the major zoos in the United States and Europe over the past century (NAS, 1975). At that forum, L. T. Goodwin of the Zoological Society of London pointed out that, as early as 1825, Sir Humphrey Davy, one of the founders of the society, had the perspicacity to develop a zoo in London for reasons to which we frequently allude today. As Davy put it, "It would well become Britain to offer another, and a very different series of exhibitions to the population of her metropolis; namely, animals brought from every part of the globe to be applied either to some useful purpose, or as objects of scientific research—not of vulgar admiration!" This thinking is particularly important during these times, when natural environments are diminishing and zoos can no longer be consumers of animals. Zoos have to establish and maintain captive breeding programs for selected endangered species, and this means keeping the animals as healthy as possible.

To carry out this obligation, zoo medicine is becoming highly sophisticated. A review of the status of zoo medicine in the United States several years ago (Schroeder, 1976) showed an increase in the construction of modern zoo hospitals and laboratories with sophisticated equipment, including data-storage devices and computers. There is an increasing volume of literature on the research involving medical problems and diseases in zoo species—some of this having significant implications for human medicine.

For the past 25 years, the East German Academy of Sciences, under the leadership of Dr. Rudolph Ippen, has sponsored symposia on the diseases of zoo animals. A wealth of information is contained in the published proceedings. In 1978, the National Zoo hosted the first symposium devoted to the comparative pathology of zoo species in the United States. Similarities between animals and human diseases were highlighted, and, although no perfect models surfaced, the spectrum of disease caused by agents or conditions resembling human types was found to be substantial (Montali and Migaki, 1980). Still, much of this literature on the medical aspects of zoo species is scattered about in proceedings from symposia, books, and a variety of journals. For the past several years, Dr. Murray Fowler of the University of California-Davis has been gathering together all of these sources of zoo medical information, under sponsorship of the Morris Animal Foundation, and is developing a computerized zoo medical data bank that will be available for use by interested scientists at some time in the near future. At Davis, Fowler teaches one of the few formal courses available anywhere on zoo medicine and has also compiled the first English language medical text on zoo medicine (Fowler, 1978). A new edition of this text is being planned for publication in 1984. Much zoo medicine currently is taught during internships and residencies in both clinical medicine and pathology, and there are well-defined programs in these areas at zoos in Washington, D.C., New York City, Philadelphia, and San Diego.

A few journals are devoted to zoo animal diseases. The American Association of Zoo Veterinarians, which is an affiliate of the American Veterinary Medical Association, publishes the *Journal of Zoo Animal Medicine.* A new quarterly journal, *Zoo Biology*, has just surfaced, and, in addition to information on management, husbandry, behavior, and so on, it plans to provide a section on medical problems of zoo animals (Maple, 1982).

A recent survey of research at American and European zoos by Dr. van Dan, Director of the Blijdorp Zoo, Rotterdam, The Netherlands, shows intensive research activity in many of the major zoos around the world. The list of projects is too numerous to publish but is available on an individual basis from Dr. van Dan. Research that is certain to have spin-off information pertinent to human medical needs includes projects dealing with infectious diseases, reproduction, and genetics, as well as degenerative disorders and cancer.

Dr. Robert Snyder at the Penrose Laboratory, a branch of the Philadelphia Zoo, has been working for years with the woodchuck (*Marmota monax*), a common rodent of the northeastern United States and Canada, as an animal model for the study of chronic viral hepatitis and primary liver cancer. He has found that the eastern subspecies, at least, is host to woodchuck

hepatitus virus (WHV), which is phylogenetically related to hepatitis B virus (HBV) of humans. He has also detected an incidence of hepatocellular carcinomas exceeding 60 percent among older animals with persistent WHV infections and an absence of liver cancer in animals with either negative serological evidence of the disease or with certain detectable antigens (WH) (Snyder *et al.*, 1981). Similar hepatitis viruses related to HBV and WHV have also been characterized in wild rodents, birds, and cheetahs. Dr. Mike Worley at the San Diego Zoo has apparently identified the virus and antibodies of feline hepatitis virus, which is particularly active in cheetahs and other large cats.

There is a major research effort in comparative reproductive endocrinology at San Diego, and most of the large zoos now are quite active in reproductive physiology. Embryo transfer and artificial insemination techniques are being pursued vigorously by the San Diego, Bronx, National, and other zoos. The Bronx Zoo made news last year with the first successful transplantation of a gaur (*Bos gaurus*) embryo into a Holstein cow, leading to the delivery of a normal gaur calf. The gaur, an "exotic" bovid, was once abundant in Southeast Asia but now is endangered.

Another relevant investigation at zoos has been the surveillance of their animal collections for lead levels. Studies (Zook, 1971) based on the earlier discovery that primates at the National Zoo developed chronic lead poisoning from paint-chewing (Sauer *et al.*, 1970) provided a model for lead toxicity in man. The Bronx Zoo is currently correlating tissue and blood levels of lead with levels of lead in the air and in food. This has been shown to be a good monitoring device for lead residues in the atmosphere that could potentially be toxic to humans. The recent findings indicate lower lead levels, possibly a reflection of the general decline in use of leaded gasoline in the United States.

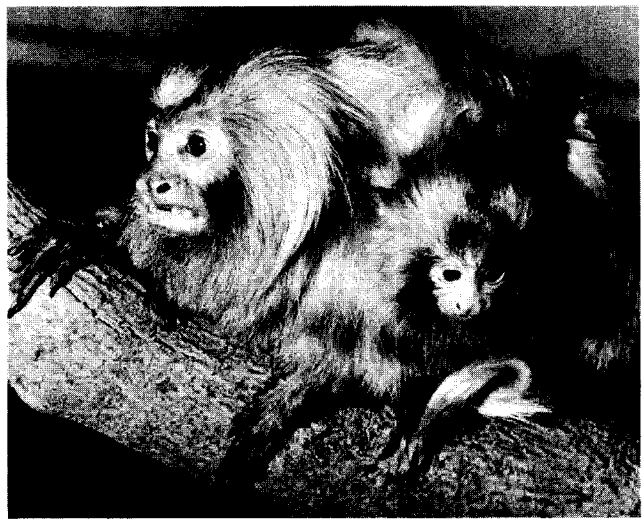
One very important subject for research in zoos is comparative genetics. It is important primarily because many zoos are struggling to perpetuate endangered species known to have limited gene pools. A stronghold for this type of research activity is with Dr. Kurt Benirschke's group at the San Diego Zoo. There, Dr. O. Ryder is doing comparative karyology primarily in equine species. He also performs in situ hybridization of DNA and has identified differences in mitrochrondrial DNA in several types of equids. With this basic information, he has been able to advise on the breeding of Przewalski horses (*Equus przewalskii*), the single surviving species of wild horses.

Trends toward limited genetic variability may not be solely a function of inbreeding in captivity. Researchers from the National Institutes of Health and several U.S. zoos, in collaboration with South African scientists, have recently established that the cheetah, an endangered species and a particularly difficult animal to breed in captivity, is relatively genetically monomorphic even in the wild (O'Brien *et al.*, 1981).

Genetic diseases are also under study at various zoos. Dr. Benirschke (1980) has been studying ruffed leumurs (*Lemur variegatus variegatus*) with *pectus excavatum* (funnel or cobbler's chest), a not uncommon congenital anomaly in man. In addition to the previously mentioned familial cystinuria in the maned wolf, familial diaphragmatic hernias, similar to those of the Morgagni type in humans, are being studied in golden lion tamarins (*Leontopithecus rosalia rosalia*) at the National Zoo (Bush *et al.*, 1980; Montali *et al.*, 1980).

Dr. Benirschke also studies placentas from every birth available at the San Diego Zoo and is actively pursuing the study of comparative neonatology. His major effort is the investigation of renal maturation as a possible index of prematurity in primates, carnivores, and hoofed mammals.

Comparative cancer studies would seem to have great potential in a zoo setting, mainly because the animals are subjected to a relatively constant environment and allowed to live out their life spans. Every day, it seems, a new inhaled or consumed substance is reported as a suspected carcinogen. Information concerning the experimental induction of tumors in laboratory animals mounts and numerous surveys of spontaneously occurring neoplasms in laboratory and domestic animals are available. There are many models available to study specific neoplasms, for example, murine, avian, and feline viral-induced hemopoietic tumors, and the models based on tumors produced by organic chemical carcinogens are innumerable. Despite the availability of these models, however, there are many remaining unknowns about the natural history of cancers in man and lesser



Golden lion tamarins (*Leontopithecus rosalia rosalia*) are studied at the National Zoo for familial diaphragmatic hernias similar to those of the Morgagni type in humans. Photograph courtesy of Jessie Cohen, Office of Graphics and Exhibits, National Zoological Park, Smithsonian Institution, Washington, D.C.

animals. Studying tumors that occur naturally in less familiar species should provide further comparative knowledge about the biological behavior of cancer. A recent overview of tumors in zoo animals cites the pertinent literature on this subject. (Montali, 1980).

One of the largest collections of cancers of nondomestic animals is housed at the Smithsonian Institution as the Registry of Tumors of Lower Animals. The collection is maintained by the National Institutes of Health under the directorship of Dr. John Harshbarger. A collection at the Philadelphia Zoo covers almost a century of necropsies, a significant number of which are cancers, of all classes of zoo species.

Of particular interest are clusters of tumors affecting related species. In one occurrence at the Philadelphia Zoo, 11 small carnivores (procyonids and viverrids) developed neuroepitheliomas of the nasal cavities. Most of these tumors evolved over a period of 12 years, and it is likely that some event took place earlier that created a carcinogenic condition (Montali *et al.*, 1982a). In another situation in 1964, a group of Asiatic bears at the San Diego Zoo developed cancer of the liver and biliary tract. Since then, similar cases in bears have been reported in London and Norway, and recently a sloth bear (*Melursus ursinus*) and a Malayan sunbear (*Helarctos malayanus*) from the National Zoo were both found to have extrahepatic biliary carcinomas that had metastasized widely. In man the cause of biliary cancers is unknown, but it appears to be associated with lithogenesis and perhaps carcinogenic substances in the bile. The bears, unike humans with biliary cancers, were without gallstones, and a change from the natural diet was a factor proposed to contribute to the development of these ursine neoplasms (Montali *et al.*, 1981b). Hormonal induction of vaginal leiomyomas in Indian rhinoceros (Montali *et al.*, 1982b) have also been studied and compared to leiomyomas of the human female reproductive tract.

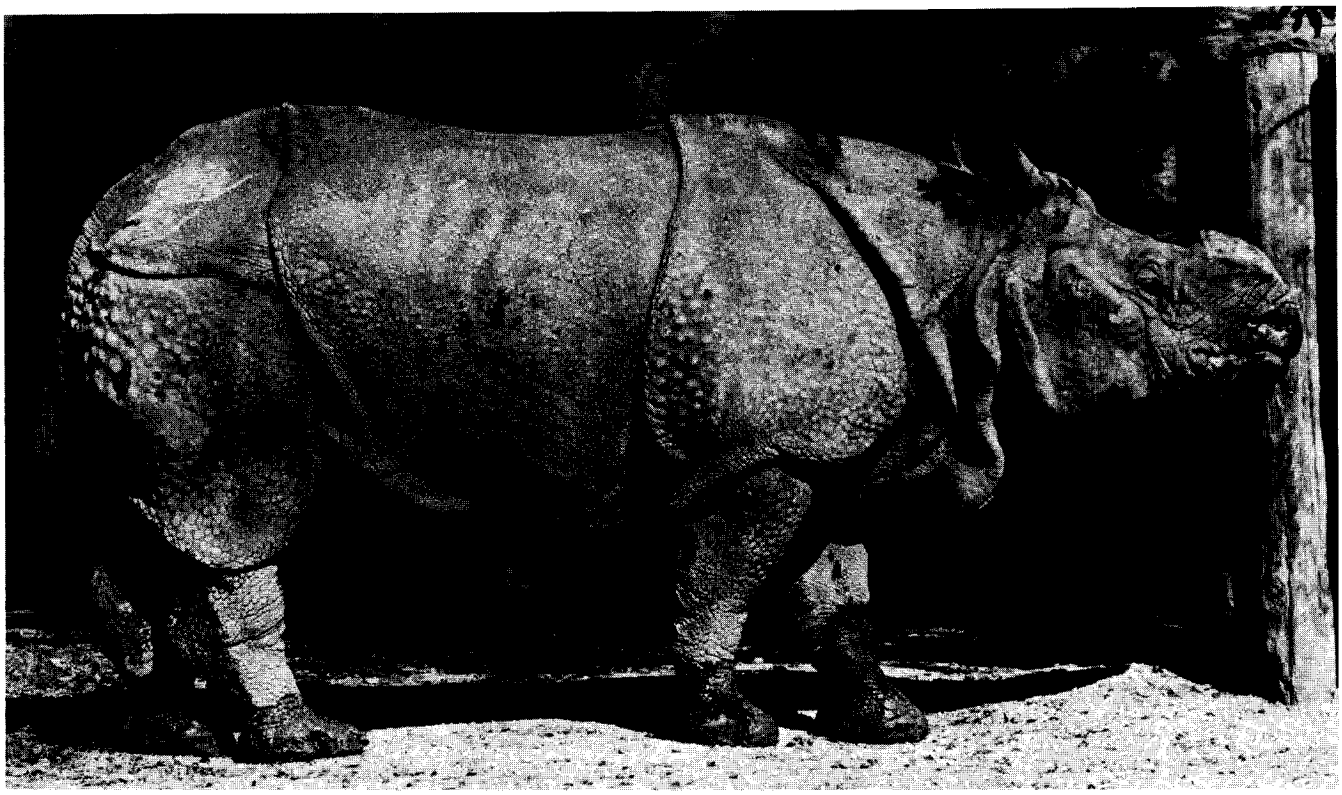
Malayan sunbears (*Helarctos malayanus*) can develop extrahepatic biliary carcinomas that resemble biliary cancers in man. Reprinted from the *Journal of the National Cancer Institute* 66(3):603-607, 1981, with permission of the authors.

Another fascinating subject is comparative pharmacokinetics in zoo species. Drug dosages generally are chosen empirically or are extrapolated from domestic animals and humans. However, extrapolation of doses works best when done between mammalian species. Dosages that provide therapeutic levels of key antibiotics have been determined recently to be considerably less in reptiles and greater in birds than in mammals (Bush *et al.*, 1978; Custer *et al.*, 1979). Mammalian dosages of gentamicin, a popular treatment for the gram-negative bacterial diseases that commonly affect reptiles, for example, are toxic in sick snakes and may produce fatal gout (Montali *et al.*, 1979).

Diseases occasionally have occurred in zoo animals that at first were considered potentially useful models but that, on careful study, proved otherwise. For example, in 1976 and 1977 there was a high incidence of fatal systemic mycoses in neonatal reindeer (*Rangifer tarandus*) at the National Zoo. Previously, there had been high mortality among the young of the herd. Many of the calves showed histologic evidence of deficient lymphoreticular organs. A familial immunodeficiency disorder was hypothesized and subsequently tested. Dr. Susan Hsu of Johns Hopkins University performed lymphocyte transformation studies, and gamma globulin levels were ascertained in the 1978 crop of reindeer. The neonates were determined to be immunocompetent, and the mycoses disappeared in subsequent years (Kennedy *et al.*, 1980).

Despite the great potential of a zoo as a resource for models, there are many limitations and, of necessity, some restrictions for use. There is little opportunity to conduct overly manipulative or invasive research procedures—probably less than would be allowed in clinical research trials involving human beings. Many of the species are difficult to work with or are difficult to breed, so that the number of animals available for study are limited. In fact, it is safe to say that over the past years, humans have served more as "animal models" for zoo species than is true of the reverse. This has been mainly due to the adaptation of sophisticated human medical procedures to use in zoos.

Most of the major zoos now bank pathology speci-



The hormonal induction of vaginal leiomyomas has been studied in the Indian rhinoceros (*Rhinoceros unicornis*) and compared to leiomyomas in the reproductive tract of human females. Photograph courtesy of Jessie Cohen, Office of Graphics and Exhibits, National Zoological Park, Smithsonian Institution, Washington, D.C.

mens, including fixed and frozen tissues and serum, which provide much useful research material for retrospective studies. A directory of zoos holding such specimens and other materials that can be used for teaching and research by interested scientists has been compiled by the Registry of Comparative Pathology, Armed Forces Institute of Pathology (RCP, 1981).

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COMPARATIVE PATHOLOGY AND EXOTIC ANIMALS

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This is a time in which zoos are in transition from the menageries of yesteryear to institutions that, in addition to providing amusement for the public, are developing coordinated programs of conservation and education. As a result, the health-related aspects of breeding and management are becoming more sophisticated. The close interaction of veterinary and other medical personnel with zoos has provided a means for studying, in unprecedented detail, many of the conditions encountered in zoo animals. The benefit accrues to zoo medicine, which often takes advantage of advances in human medicine and capitalizes on the fact that many professionals enjoy being able to contribute some of their expertise to creatures vastly different from their normal patients. Individuals with more traditional veterinary backgrounds also contribute in this way. In the course of diagnosing and investigating medical problems in zoo animals, many conditions are encountered that are of interest because they parallel disease states in other species, including man. In some instances the unique features of the zoo animals make them suitable for manipulation in model systems. In others the animals themselves are sufficiently rare, expensive, or difficult to work with that one must glean information from spontaneous disease, which may be enlightening in understanding basic biological mechanisms. To best capitalize on this situation it is essential to have good working arrangements between the zoo's management and medical staffs and the biomedical institutions with specialists in a variety of disciplines.

The Baltimore Zoo and the Division of Comparative Medicine of the Johns Hopkins University School of Medicine have a long history of such cooperation. This dates from the establishment of the Baltimore Zoological Society in 1967 by a group of individuals who included staff of the Johns Hopkins medical institutions. One of the initial purposes of the group was to establish a comprehensive program of medical care for animals housed in the zoo collection. Initially, the medical care was provided by members of the Hopkins staff, but as the scope of the medical activities grew, a full-time veterinarian was hired by the society. This individual also has an appointment in the Division of Comparative Medicine, which provides diagnostic pathology support for the zoo programs.

This interaction has provided numerous instances in which the expertise of a wide variety of medical experts has aided in the diagnosis of specific disease entities in