

IRON STORAGE DISORDERS IN CAPTIVE WILD MAMMALS: THE COMPARATIVE EVIDENCE

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Abstract: Excessive burden of iron, or iron storage disease (ISD), has been reported in a large variety of captive mammal species, including browsing rhinoceroses; tapirs; fruit bats; lemurs; marmosets and some other primates; sugar gliders; hyraxes; some rodents and lagomorphs; dolphins; and some carnivores; including procyonids and pinnipeds. This report collates the comparative evidence for species' susceptibility, recognizing that the data for mammal species are limited. Differences reported in the occurrence of ISD between facilities, or within facilities over periods that span management changes, have been reported in individual cases but are underused in ISD research. Given the species composition, the hypothesis that evolutionary adaptations to the iron content and availability in the natural diet determine a species' susceptibility to ISD (in the face of deviating iron content and availability in diets offered in captivity) seems plausible in many cases. But exceptions, and additional species putatively susceptible based on this rationale, should be investigated. Whereas screening for ISD should be routine in zoo animal necropsy, screening of live individuals may be implemented for valuable species, to decide on therapeutic measures such as chelator application or phlebotomy. Whatever the reasons for ISD susceptibility, reducing dietary iron levels to maintenance requirements of the species in question seems to be a logical, preventive measure.

Key words: Iron metabolism, phylogeny, nutrition, hemochromatosis, hemosiderosis.

INTRODUCTION

Excessive iron storage (also referred to as iron storage disease [ISD]) is a condition in which higher amounts of iron than normal are in circulation, iron is deposited within the body, or both. Sometimes, the finding is directly associated with clinical signs, disease, or mortality, but sometimes it is just a major incidental finding at necropsy without evident involvement in the fatality. There are many excellent reviews on the problem in humans or animals in general.^{33,36,65,77} For the zoo veterinarian, ISD is important because it has been described in a large variety of captive wild animal species.^{16,26,58,88}

In zoo animal medicine, zoo veterinarians strive for species-specific knowledge on a huge variety of species. If possible, species-transcending rules are sought. ISD can occur as a consequence of an infectious disease or prolonged fasting.^{3,58} Therefore, is not easy to judge whether case reports of ISD represent a species-specific susceptibility in

terms of iron metabolism, where clinical effects of the disease lead to secondary problems such as infections or wasting, or whether these conditions were triggered by other causes and secondarily led to ISD. Similar to the comparative method in physiology, lists of species in which ISD has been reported can be used to distill some general rules, either on a phylogenetic level (artiodactyls vs. primates²⁶), physiologic level (foregut vs. hindgut fermenter¹⁶), or ecologic level (frugivores vs. carnivores⁵⁸).

However, the quality of such interpretations is often limited by the data. Which species are actually susceptible to the problem and, maybe even more importantly, which species are not? A lack of reports that reliably document the absence of a problem may be even more compromising to progress in comparative approaches. A small retrospective evaluation of the occurrence of ISD in a lemur collection⁸⁵ may serve as an example. In a set of 35 adult animals of known age, six animals were reported positive for ISD, a mere 17% of all individuals. However, the necropsy reports of these six animals were the only reports in which the investigation of ISD had been actively noted. Thus, no negative result had been reported in any other case. Thus, the interpretation could change to an occurrence of 100% of all animals in which the problem had been actively investigated. In a comparative view, it can only be assumed that species for which no records of ISD exist to date may not be particularly susceptible, but recent additions to the list of potentially

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susceptible species^{24,83} should warn against such a silent assumption.

Comparative surveys that analyzed a large variety of animals and documented the results (both positive and negative) on a species-specific level are very rare. Consensus on whether a species, or a certain taxonomic group, is susceptible to ISD therefore still rests, in many cases, on a certain common agreement and shared experiences rather than statistical data evaluations. Politically, different interests may be at stake: researchers who strive for publications by “adding new species to the list,” laboratories that want to promote their services, nutritionists who want to emphasize the relevance of nutritional management, and facilities that do not want to be obliged to change existing husbandry routines. It is therefore critical that evidence is compiled and evaluated as objectively as possible and that decisions are made not only based on positive evidence, but also on a sober rationale. Interestingly, the relevance of ISD has been accepted for a long time in many captive wild bird species,⁵⁵ whereas its relevance for many captive mammal species seems less accepted, and may be less evident.

In this report, an overview of the literature regarding ISD in captive wild mammal species is provided. In addition, proposed explanations for observed patterns and treatment options that have been used or suggested are discussed.

REPORTS ON ISD IN CAPTIVE WILD MAMMALS

When surveying the large list of animal species for which ISD has been reported (Tables 1–4), it is important to consider the basis on which the judgement of susceptibility is made. For the tables, the reports are divided into single case reports (individual cases), case series (more than one case at one or two facilities), epidemiologic surveys (cases at three or more facilities), age dependence (demonstration of an increase in iron levels with age), and comparisons with data from free-ranging individuals. Results of the few experimental approaches (in the form of intervention trials, including veterinary intervention in individual cases, or as controlled studies) are included in the text. Iron status is usually judged at necropsy by using histopathology with special stains, mostly in liver tissue, as iron levels in liver tissue as quantified by chemical analysis, or in live animals, as iron analytes⁹⁶ in serum samples. It should be noted that this list only indicates species in which excessive iron storage has been

Table 1. Reports of excessive iron storage in nondomestic perissodactyls (tapirs and rhinos).

Species	Individual case ^{a,b}	Case series ^{a,b}	Epidemiologic survey ^{a,b}	Age dep. ^{a,b}	Comparison free-range ^{a,b}
Tapirs					
Malayan tapir (<i>Tapirus indicus</i>)		(+) histo ²	(+) blood ⁷³	(+) blood ⁷³	
Mountain tapir (<i>Tapirus pinchaque</i>)			(+) blood ⁷³	(+) blood ⁷³	
Baird's tapir (<i>Tapirus bairdii</i>)		(+) histo ²	(+) blood ⁷³	(+) blood ⁷³	(+) blood ^{45,73}
Brazilian tapir (<i>Tapirus terrestris</i>)	(+) histo ^{2,53}	(+) histo, blood ⁷⁶			
Rhinos					
Sumatran rhinoceros (<i>Dicerorhinus sumatrensis</i>)		(+) histo ⁸⁸	(+) blood, tissue ^{22,71}		
Asian one-horned rhinoceros (<i>Rhinoceros unicornis</i>)			(-) blood, tissue ^{22,71}		
White rhinoceros (<i>Ceratotherium simum</i>)			(-) blood, tissue ^{22,71,88}	(-) tissue ⁸⁸	(-) blood ²²
Black rhinoceros (<i>Diceros bicornis</i>)	(+) blood ⁴³	(+) histo ⁸⁰	(+) histo, tissue, blood ^{22,71,72,88}	(+) blood, tissue ^{22,88}	(+) histo, blood, tissue ^{22,56,64,71,72}

^a (+), positive for excessive iron storage; (-), negative for excessive iron storage.

^b histo, diagnosed by histology; blood, diagnosed by blood parameters; tissue, diagnosed by liver tissue iron content; age dep., age dependence.

Table 2. Reports of excessive iron storage in bats.

Species	Individual case ^{a,b}	Case series ^{a,b}	Age dep. ^{a,b}
Short-tailed leaf-nosed bat (<i>Carollia perspicillata</i>)		(+) histo ⁴⁶	
Straw-colored fruit bat (<i>Eidolon helvum</i>)	(+) histo ⁵⁷		
Egyptian fruit bat (<i>Rousettus aegyptiacus</i>)		(+) histo, blood, tissue ^{19,34}	(-) tissue ³⁴
Island flying fox (<i>Pteropus hypomelanus</i>)		(-) histo, blood, tissue ³⁴	
Indian flying fox (<i>Pteropus giganteus</i>)		(+) histo, blood ¹⁹	
Gray-headed flying fox (<i>Pteropus poliocephalus</i>)		(+) histo, blood ¹⁹	

^a (+), positive for excessive iron storage; (-), negative for excessive iron storage.

^b histo, diagnosed by histology; blood, diagnosed by blood parameters; tissue, diagnosed by liver tissue iron content; age dep., age dependence.

reported. This does not automatically imply clinical relevance. It also should be noted that parameters of iron metabolism may vary within species among different free-ranging populations,^{22,62,64} making the establishment of clear-cut reference ranges difficult, as well as the interpretation of differences between populations of captive vs. free-ranging specimens. In addition, without further investigations of the health status, values measured in free-ranging specimens may not necessarily indicate the optimum for the species⁹⁵ but might give an indication of the conditions the species has adapted in the course of evolution (if the habitat of the free-ranging specimens is representative of the species' natural niche).

Perissodactyls

Among mammals, one group of animals in which a larger number of reports on ISD exist are the perissodactyls, and in particular, the black rhinoceros (*Diceros bicornis*). Many aspects of ISD in rhinoceros species are discussed in the other contributions in this issue. Rhinoceroses are an ideal study population because they can easily be bled if trained, and because differences between the rhinoceros species are blatant and consistent. The black rhinoceros and the Sumatran rhinoceros (*Dicerorhinus sumatrensis*) have been shown to have excessive iron stores in terms of histopathology, liver tissue wet chemistry, and serum iron analytes in various studies, by independent research groups (Table 1). The condition increases with age or time in captivity. Comparisons with free-ranging specimens show that the problem is related to captivity, and comparisons with the white rhinoceros (*Ceratotherium simum*) and greater Asian one-horned rhinoceros (*Rhinoceros unicornis*) show that it is restricted to the two browsing rhino species (black and Sumatran) but does not affect the more grazing rhino species (white and greater Asian one-horned). The etiolo-

gy, the physiologic peculiarities of rhinos, and the pathologic implications of ISD are the subjects of discussion in other contributions of this issue.

For tapirs, similar observations have been made, but by a smaller number of research groups; again, differences between free-ranging and captive animals exist, and measures of iron metabolites increase with age (Table 1). There are indications for differences in dietary iron levels between diets in captivity and those of free-ranging animals, both for browsing rhinos⁹ (see contribution by Helary et al. in this issue) and tapirs,¹⁵ although comprehensive surveys are lacking.

Any debate regarding the clinical relevance of ISD in perissodactyls has been overcome by unequivocal histopathological and biochemical evidence of significant organ damage directly attributable to chronic iron toxicity.⁷¹ The common acceptance of a species-specific problem is evident in the formulation of feeding guidelines with recommendations to restrict iron. Given the value of rhinoceroses, experimental approaches to understand ISD are restricted to therapeutic measures such as regular phlebotomy. Therapeutic phlebotomies have been performed successfully in black rhinos, as presented during the ISD workshop from which this special issue was derived; results of the procedure have not been published so far.

Chiroptera

ISD has been recognized in several bat species (Table 2). ISD was triggered in a bat colony by accidental excessive dietary iron supplementation (*Rousettus aegyptiacus*).⁴⁴ There seems to be little controversy about the relevance of ISD in bats. Epidemiologic surveys and comparisons with free-ranging specimens are lacking in bats; however, the large number of animals usually kept at one facility automatically increases the caseload.

Table 3. Reports of excessive iron storage in primates.

Species	Individual case ^{a,b}	Case series ^{a,b}	Epidemiologic survey ^{a,b}	Age dep. ^{a,b}	Comparison free-range ^{a,b}
Lemurs			(+) histo, blood ^{1,31}	(+) tissue ³⁹	
Giant mouse lemur (<i>Mirza coquereli</i>)		(+) histo ⁸⁵			
Gray mouse lemur (<i>Microcebus murinus</i>)		(+) histo ³⁹			
Fat-tailed dwarf lemur (<i>Cheirogaleus medius</i>)		(+) histo ³⁹			
Aye-aye (<i>Daubentonia madagascariensis</i>)		(-) histo ³⁹			
Diademéd sifaka (<i>Propithecus diadema</i>)		(-) histo ³⁹			
Coquerel's sifaka (<i>Propithecus coquereli</i>)		(-) histo ³⁹			
Verreaux's sifaka (<i>Propithecus verreauxi</i>)		(-) histo ³⁹			
Golden-crowned sifaka (<i>Propithecus tattersalli</i>)		(+) histo, blood ^{39,96}			
Brown lemur (<i>Eulemur fulvus</i>)	(+) histo ^{40,90}	(+) histo, blood ^{39,96}			
Black lemur (<i>Eulemur macaco</i>)	(+) histo ⁵	(-) blood ⁹¹ , (+) histo, blood, tissue ^{39,40,90,96}		(+) tissue ⁹⁶	(-) blood ⁵¹
White-fronted brown lemur (<i>Eulemur albifrons</i>)		(+) histo ⁴²			
Collared lemur (<i>Eulemur collaris</i>)		(-) blood ⁹⁶			
Crowned lemur (<i>Eulemur coronatus</i>)	(+) histo ^{40,90}	(-) blood ⁹⁶ , (+) histo ³⁹			
Mongoose lemur (<i>Eulemur mongoz</i>)		(-) histo, blood ^{39,96}			
Bamboo lemur (<i>Hapalemur griseus</i>)		(-) blood ⁹⁶ , (+) histo ³⁹			
Ring-tailed lemur (<i>Lemur catta</i>)	(-) histo ¹⁶ , (+) histo, blood ^{39,40,99}	(-) histo, blood ^{96,97} , (+) histo, blood ^{42,90,96}		(-) tissue ⁹⁶	(+) blood ^{29,62}
Black and white ruffed lemur (<i>Varecia variegata</i>)	(+) histo ^{16,17}	(-) blood ⁹⁶ , (+) histo, blood ^{39,40,90,100}	(+) blood ¹⁷	(+) blood ¹⁷	(+) blood ^{18,50}
Red ruffed lemur (<i>Varecia variegata ruber</i>)	(+) histo, blood ^{40,81}	(+) histo, blood, tissue ^{42,90,96}		(-) tissue ⁹⁶	(+) blood ^{30,50}
Marmosets (Callitrichidae) ^c	(+) histo ¹⁶	(+) histo, tissue ^{6,7,20,26,41,49,63,90,94}	(+) blood ³¹	(-) tissue ⁹⁰	
Capuchins/squirrel monkeys (Cebidae)		(-) histo ²⁶			
Muriqui (<i>Brachyteles</i> spp.)		(+) histo ⁸³			
Woolly monkeys (<i>Lagothrix</i> spp.)		(+) histo, blood ^{26,31}			
Macaques/baboons	(-) histo ¹⁶		(-) hist, blood ^{31,58}		
Blue monkey (<i>Cercopithecus mitis</i>)	(+) histo ¹⁶		(+) histo ⁵⁸		
Colobinae			(-) blood ³¹		
Great apes		(+) histo ⁶⁶			
Siamang (<i>Hylobates syndactylus</i>)			(+) histo ⁵⁸	(+) histo ⁵⁸	(+) histo ⁵⁸
Gorilla (<i>Gorilla gorilla</i>)			(-) histo ⁵⁸		
Orangutan (<i>Pongo pygmaeus</i> , <i>Pongo abelii</i>)	(+) histo ⁵⁸		(-) histo ⁵⁸		

^a (+), positive for excessive iron storage; (-), negative for excessive iron storage.

^b histo, diagnosed by histology; blood, diagnosed by blood parameters; tissue, diagnosed by liver tissue iron content; age dep., age dependence.

^c Because most investigations do not differentiate between individual marmoset species, all publications are summarized under Callitrichidae.

Table 4. Reports of excessive iron storage in various mammals.

Species	Individual case ^{a,b}	Case series ^{a,b}	Epidemiologic survey ^{a,b}
Sugar glider (<i>Petaurus breviceps</i>)		(+) histo ²⁴	
Elephant shrew (Macroscelididae)	(+) histo ¹⁶		
Lesser hedgehog tenrec (<i>Echinops telfairi</i>)		(+) histo ^{92,93}	
Rock hyrax (<i>Procavia capensis</i>)	(+) histo ³⁵	(+) histo ⁷⁹	(+) histo ⁹⁸
Afghan pica (<i>Ochotona rufescens</i>)		(+) histo ⁵⁹	
Mara (<i>Dolichotis patagonum</i>)	(+) histo ¹⁶		
Prehensile-tailed porcupine (<i>Coendu</i> spp.)	(+) histo ⁵⁸		
Rock cavy (<i>Kerodon rupestris</i>)	(+) histo ⁵⁸		
Kangaroo rat (<i>Dipodomys</i> spp.)	(+) histo ⁵⁸		
House shrew (<i>Suncus murinus</i>)		(+) histo ⁵⁸	
Artiodactyla (general)		(-) histo ¹⁶ , low-incidence histo ²⁵	
Reindeer (<i>Rangifer tarandus</i>)	(+) histo ²⁶		
Bay duiker (<i>Cephalophus dorsalis</i>)	(+) histo ⁵⁸		
Dikdik (<i>Madoqua</i> spp.)	(+) histo ⁵⁸		
Bottlenose dolphin (<i>Tursiops truncatus</i>)	(+) histo ⁹⁵	(+) blood ^{48,95}	
Coati (<i>Nasua</i> spp.)			(+) histo ^{11,58}
Raccoon (<i>Procyon lotor</i>)	(+) histo ¹⁶		
Red panda (<i>Ailurus fulgens</i>)	(+) histo ¹⁶		(+) histo ⁵⁸
Giant panda (<i>Ailuropoda melanoleuca</i>)	(+) histo ⁹⁹		
Cheetah (<i>Acinonyx jubatus</i>)			(+) histo ⁵⁸
Snow leopard (<i>Panthera uncia</i>)			(+) histo ⁶⁷
Northern fur seal (<i>Callorhinus ursinus</i>)	(+) histo, tissue ³⁸	(+) blood ^{38,60}	
California sea lion (<i>Zalophus californianus</i>)	(+) histo, tissue ³⁸	(+) blood ³⁸	

^a (+), positive for excessive iron storage; (-), negative for excessive iron storage.

^b histo, diagnosed by histology; blood, diagnosed by blood parameters; tissue, diagnosed by liver tissue iron content.

It has been suggested that ISD does not occur in vampire bats,¹⁹ although epidemiologic data are missing. An attempt at chelation therapy did not lead to the desired success in Egyptian fruit bats (*Rousettus aegyptiacus*).¹⁹ In straw-colored fruit bats (*Eidolon helvum*), it could be demonstrated that dietary tannic acid reduces iron absorption,⁵⁷ similar to findings in birds.^{69,87}

Primates

Among primates, excessive iron storage has been particularly investigated in lemurs and marmosets. Several, but not all, surveys of lemur pathology indicated a very high incidence of excessive iron storage in many, but not all, lemur species, and differences between free-ranging and captive specimens are evident (Table 3). Differences between lemur species were recognized early on, with ring-tailed lemur (*Lemur catta*) apparently not being very prone to ISD.^{1,39,100} In contrast, a recent comprehensive retrospective evaluation of the incidence and severity of hemosiderosis at one institution showed that although hemosiderosis was present in many cases, it was not considered excessive or associated with the cause of death.³⁹ The authors suggested that this

could be due to the particular management at this facility. Because this facility had been part of a previous survey, in which the occurrence of hemosiderosis had been reported in all animals and stressed as an important health issue,¹ this facility could represent a good example of how an improved management may help alleviate a putative health issue. At the same facility, from the same period in which low hemosiderosis was reported, serum iron analytes also did not indicate ISD.⁹⁶ It would be interesting to see whether copying the management practiced at that institution could reduce the occurrence of ISD in other lemur facilities. Alternatively, because the reports of that facility represent the most recent, large-scale case series published to date, this also might be an effect of a globally improved lemur husbandry and feeding regime.

Diets of free-ranging lemurs seem to be lower in dietary iron and higher in substances that reduce iron availability (polyphenols such as tannins) than diets fed to these animals in captivity.^{91,100} The dietary iron levels of 117, 61, and 37 ppm dry matter measured in fruits, leaves, and flowers, respectively, consumed by free-ranging black-and-white ruffed lemurs (*Varecia variegata*) in Madagascar⁸⁴ and the 65 ppm dry matter

measured in the diet of free-ranging ring-tailed lemurs on St. Catherine's Island, Georgia, USA,²³ are lower than the 110–190 ppm dry matter measured in some typical zoo diets.^{97,100} There is one report of a massive dietary intervention that reduced the amount of iron and vitamin C, and presumably also decreased iron availability by adding sources of tannin to the diet, thereby reducing the serum transferrin saturation when comparing measurements before and after the intervention.¹⁰⁰ It must be noted that that study did not include a control group whose iron metabolites were evaluated after a similar amount of time elapsed without dietary intervention.¹⁰⁰ Phlebotomy and chelation therapy have been performed with some success in individual lemurs.^{17,81}

Various investigations have documented that excessive iron storage occurs regularly in marmosets (Table 3). Miller et al.⁶³ stated that "hemosiderosis may be an important factor affecting the results in any research involving marmosets." In a controlled, prospective feeding study, ISD was triggered, with clinical consequences, by a diet of 350 ppm iron in dry matter.⁶³ Comparisons with free-ranging specimens are lacking to our knowledge. It has been suggested that Goeldi's marmoset (*Callimico goeldii*) may be less susceptible than other marmosets.⁴¹

Excessive iron storage also has been described in some other South American primates (*Brachyteles* and *Lagothrix* spp.), but not in squirrel monkeys, macaques, or baboons (Table 3). A case series has been described in siamangs.⁶⁶ Evidence for great apes is contradictory, with reports on ISD occurring in captive but not free-ranging gorillas.⁵⁸ However, in a serum survey, transferrin saturation in gorillas or other great apes was not particularly high.³¹

Other mammals

Excessive iron storage has been reported in a large variety of other mammals, including the rock hyrax (*Procapra capensis*) and some rodents and lagomorphs that may have a similar ecology, for example rock cavies (Table 4). In artiodactyls, the problem seems to occur rarely in adult animals.²⁵ Potential differences between cervids and bovids have been suggested, with a higher susceptibility in cervids (in particular reindeer).²⁵ However, potential seasonal effects (with reduced food intake in the winter as reported in free-ranging cervids³ or bears⁷⁸) have not been accounted for in these findings. In dolphins and in some pinnipeds, the condition also has been observed (Table 4).

Although red pandas (*Ailurus fulgens*) may be affected more frequently,⁵⁸ only two individual cases in giant pandas (*Ailuropoda melanoleuca*) have been reported previously.⁹⁹ Hemosiderosis in snow leopards (*Panthera uncia*) is commonly associated with veno-occlusive disease and might be secondary to that problem.⁶⁷ Causes for hemosiderosis in captive vs. free-ranging cheetahs (*Acinonyx jubatus*) have not been elucidated but may well be secondary to other problems.⁵⁸

POSSIBLE ETIOLOGY

Differences in the amount and bioavailability of iron between natural forages and captive diets are most often cited when discussing possible etiologies for ISD among affected species. The rationale is that affected species did not have to evolve mechanisms to protect them against iron overload, because their natural diet provides them with lower levels of available iron than the diet in captivity. Although differences in the iron content of ingested diets have, to our knowledge, not been demonstrated for any mammal species except for the black rhinoceros,⁴⁴ some results of analyses of individual food items, and common sense, support this view. Many herbivores that rely on leaves or fruit in the wild may consume, in captivity, diets that have 1) a higher absolute iron content, because of the ingestion of forages with higher iron levels, complete feeds not especially designed for limited iron intake,^{9,15} or both; and 2) a higher iron availability because of the absence of secondary compounds (such as tannins and other polyphenols) that occur in their natural forages.^{57,91}

These considerations could theoretically apply to many herbivores cited in the tables in this article, including fruit bats, hyraxes, pandas, folivorous and frugivorous primates, tapirs, browsing rhinos, and even the marmosets and sugar gliders whose natural diet consists of a large portion of gums and saps, possibly lower in iron than the diet offered in captivity.⁵⁸ The diet of one pika species also has been shown to contain tannins.²¹ Manufactured complete feeds often inadvertently contain high amounts of iron, not because it is added deliberately, but because it is contained in various ingredients, especially in sources of other minerals, such as calcium carbonate or phosphorus sources,^{14,19,46} and because of small inevitable abrasions from the processing machinery. Such feeds usually do not include tannins or other substances that reduce iron availability.

Species that feed on invertebrates in the wild but receive vertebrate meat in captivity may

experience higher iron availability in captivity. Heme-iron, the iron in vertebrate meat, has a higher availability than nonheme iron. This concept may apply both for insectivores (such as tenreks, shrews, and insectivorous bats) and omnivores (such as coatis and raccoons) that rarely ingest vertebrate prey in the wild but receive mammal meat sources in captivity¹¹ and also for marine mammals that receive fish rather than squid.⁵⁷ Note that these criteria all also apply for frugivorous and insectivorous birds.⁸²

In this concept, herbivores that feed on grasses did have to evolve protection mechanisms against iron overload because of inadvertent ingestion of soil when grazing;⁴⁵ hence, for example, the absence of ISD reports in grazing rhinoceros species. Although the iron in soil is commonly thought to be of low availability, reports on anemic conditions when foals⁴ or piglets^{27,54,101} are kept off soil indicate that soil can be a relevant source of iron. The molecular and genetic bases for differences in iron metabolism and hence susceptibility to ISD are the subject of ongoing research.³⁷

The flip-side of this argument evidently is that if this view about evolutionary adaptations to dietary iron levels was completely correct, ISD would be expected in additional species that match these criteria. On the one hand, it is likely that more species for which these criteria apply may be found susceptible to ISD in the future, as in the recent case of the frugivorous and folivorous muriquis⁸³ or the insectivorous tenreks.^{91,92} On the other hand, there is the group of browsing ruminants that seems to be little affected.^{16,26,58} Reports of ISD are also missing from folivorous or frugivorous sloths, or from other folivorous monkeys, such as howlers. Putative differences as reported between gorillas and orangutans,⁵⁸ between some lemur species,¹ or between the true lemurs and the sifakas (Table 3) are difficult to explain on the basis of the diet argument. Other species-specific characteristics must play a role.^{39,96} It has been suggested that due to a putative increase in iron availability during foregut fermentation, foregut fermenters had to evolve mechanisms preventing ISD.¹⁶ Although this conveniently explains the seemingly low susceptibility of ruminants, camelids, hippos, macropods, or sloths, the report on colobine monkeys⁵⁸ does not fit this pattern. One reason could be that due to the general ill-thrift of foregut fermenting primates in captivity,^{32,68} non-dietary causes for ISD, such as starvation, or

infection before death and necropsy are responsible in this group.

Nondietary causes for ISD can be assumed in some special cases, such as the veno-occlusive disease in snow leopards.⁶⁷ Because excessive iron deposition in the liver is associated with insulin resistance in humans,^{33,61} potential relationships between ISD and obesity should be investigated in affected species. Because hindgut fermenters broadly seem to be more susceptible to obesity than foregut fermenters,¹⁰ this relation would link with a difference between digestion types. A link with obesity could explain the observation that ISD does not seem to be a problem in lemurs if they are fed adequate amounts of fiber.⁵² However, given that black rhinoceroses seem less prone to obesity in captivity than the grazing rhinoceros species,¹² insulin resistance might be a less likely association with the difference in ISD susceptibility between rhinoceros species. Whatever the underlying etiology, differences in individual susceptibility, potentially in some instances due to hereditary predisposition, have been suggested in several species.^{48,63,72}

IMPLICATIONS FOR ZOO ANIMAL MANAGEMENT

The most important question, given this (most likely incomplete) list of putatively susceptible species, is whether clinical relevance of the problem is suspected on a species level, an individual level, or both. Clinical relevance, in terms of biochemical or morphological evidence of pathologic changes, or in terms of clinical improvement with therapeutic intervention, has been reported for species as diverse as hyraxes,⁷⁹ pikas,⁵⁹ marmosets,^{41,63} individual lemurs,⁸¹ fruit bats,^{19,34} and dolphins.⁴⁸ Although these cases should not be used to claim global relevance of all reported findings of excessive iron storage, they might serve as incentive to consider options of preventing the problem. Again, it should be noted that such preventive and therapeutic measures are routine in many avicultural settings and in private pet bird practice.⁵⁵

The necropsy of all deceased specimens of species suspected to be susceptible to ISD should include specific stains for iron deposits and an evaluation of iron storage. Ideally, all mammals should be checked for ISD at necropsy to increase the documented cases of negative findings. In addition, screening protocols based on blood measurements (in tandem with medical training programs that reduce the need for anesthetic intervention) should be instigated for susceptible

species.¹⁷ The problems associated with interpreting results from blood analyses need to be acknowledged: although comparisons with other individuals of the same species, with values taken from the same individual over time, or comparisons with data obtained from free-ranging animals can direct interpretations, there are no clear-cut reference ranges. In human medicine, the detection of elevated serum iron metabolites is the first step in a series of measures that include the ruling out of secondary causes of ISD (e.g., toxic hepatitis or inflammatory diseases involving the liver) and genetic screening for hereditary hemochromatosis.⁶⁵ In zoo animal medicine, the ruling out of other causes also should be performed by veterinarians, but a confirmation of diagnosis by genetic screening is not feasible in zoo animals to date. A consequence is that any treatment instigated must be accompanied by a close health monitoring of the patients.

The treatment of affected individuals includes phlebotomy,^{17,34,48,70} the application of iron chelators,⁸⁰ and a reduction of (available) dietary iron levels.^{28,100} All these measures represent considerable effort. Especially, the prophylactic screening of live animals via blood testing in the absence of clinical signs, and the treatment of animals with regular phlebotomy, may be subject to practical, financial, or even ethical concerns.¹⁷ Outside of the United States, the absence of laboratories that measure ferritin in rhinoceroses, lemurs, or other species may by necessity restrict serum evaluations to serum iron and transferrin saturation, even though the full panel of iron metabolites would be desirable.⁹⁷ When ferritin assays are unavailable, transferrin saturation is a useful and readily available backup option for monitoring iron status. Nonetheless, enzyme-linked immunosorbent assays of ferritin by using species-specific reagents remain the standard for noninvasive estimates of total-body iron burdens.

Adjusting the dietary iron levels so that requirements are not exceeded would represent the most practical approach if limiting iron in diets was not so difficult or against historical feeding traditions. The fact that it is the iron-limited diets that are more difficult to produce and therefore expensive, rather than iron-fortified diets, may contribute to a reluctance of changing feeding regimes. The inertia of established patterns is exemplified by the observation that a decade after the finding that diets containing iron at levels of ≥ 350 ppm dry matter can have serious deleterious effects on marmoset health,⁶³ commercial feeds designated for marmosets are still being sold that

contain declared iron levels in excess of that threshold (Clauss, pers. obs.). Nevertheless, the number of iron-controlled diets for captive mammals is increasing. When feeding animals potentially susceptible to ISD, commercial feeds high in iron should be avoided. In large herbivores such as rhinoceroses or tapirs, the use of such feeds can possibly be minimized beyond what is current practice in many institutions. Special attention should be paid to the use of mineral supplements, in particular calcium sources that may contain high iron levels, and mineral supplements without iron should be used. The offer of vertebrate meat to susceptible species that feed on invertebrates in the wild should be restricted.¹³ The deliberate inclusion of tannins or other polyphenol sources,⁷⁵ although successful in individual experiments^{57,100} and not evidently harmful in others,^{8,9} cannot be recommended at present without further research.^{13,52} Admittedly, information on the actual iron requirements of most species in question does not exist. Current feeding regimes should either be adjusted within reasonable boundaries right away, such as reducing iron levels to maintenance recommendations of model species, with accompanying health monitoring measures, or (further) adjusted on the basis of necropsy findings or screening of live animals.

FUTURE RESEARCH

The overview given in Tables 1–4 leaves much to be desired in terms of comparative information. In particular, studies targeting systematic species catalogs with respect to excessive iron storage would be welcome. In apparently susceptible species, comparisons with free-ranging specimens and across different age groups and time in captivity would yield important information. To assess the conditions triggering ISD, studies within species but either across time that span management changes or across a multitude of institutions could provide relevant insights. For example, changes over time in the incidence of ISD in callitrichids in one zoo were possibly due to change in dietary regime;⁹⁰ the same may be true for lemurs from a facility that participated in two major reviews of lemur pathology.^{1,39} Differences in ISD incidence between facilities have been suggested sporadically, for example, in marmosets.²⁵ For lemurs, new investigations that compare multiple institutions are recommended,⁹⁷ similar to epidemiologic studies investigating other disease complexes.¹⁰²

The recording of health problems associated with the finding of excessive iron storage is

important, including periods of anorexia before necropsy or live screening. Because excessive iron deposition in the liver is associated with insulin resistance in humans,^{33,61} one could speculate that the development of obesity, as for example reported for lemurs,⁸⁵ could not only result from general overfeeding but also from a high prevalence of ISD. Therefore, recording body masses of animals should be part of a comparative assessment.

The need for prospective studies is recognized,⁹⁶ but in long-lived species such as lemurs or rhinoceroses, these studies may not be feasible in terms of long-term commitments. Smaller susceptible species of lesser conservation concern, for example, hyraxes, could be used as mammal models for ISD in feeding and intervention studies. The quantification of iron absorption, with the aim of comparing different species,^{40,57} may be most feasible in smaller species.

Assessing biochemical and genetic parameters of iron metabolism beyond the typical serum iron, total iron binding capacity, transferrin saturation, and ferritin should accompany any future studies.³⁷ Interspecies comparative studies are particularly valuable when all members of a species are either susceptible to ISD or not, such as browsing vs. grazing rhinoceroses. These type of studies provide unique opportunities to investigate the molecular genetics of iron homeostatic control mechanisms to detect interspecies variations. Comparisons between fruit bats and vampire bats with their different ISD propensities and dietary iron loads would likely be highly rewarding, and such studies have been initiated. Yet, it should be remembered that regardless of further research to do, the reduction of dietary iron levels to maintenance requirements need not be considered a bold, but rather a logical, first step.

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