An Historical Perspective:
IRON OVERLOAD DISEASE IN
BROWSER RHINOCEROSSES

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“When the situation was manageable it was neglected, and now that it is thoroughly out of hand we apply too late the remedies which then might have effected a cure.”
CLINICAL PROBLEMS IN CAPTIVE RHINOCEROSSES

REPRODUCTION: White, Indian, Sumatran
INFECTIOUS DISEASES: Black, Sumatran
HEPATIC/G.I.: Black, White, Sumatran
SUDDEN DEATH: Black, White, Sumatran
HOOF DISORDERS: Indian, Black
RENAL/NEOPLASTIC: White, Black, Indian
OBESITY, BODY DECONDITIONING: (All)
ANEMIA, IRON OVERLOAD Black, Sumatran
RBC “ABNORMALITIES”
(All species variably affected)

Enzyme “deficiencies”

Very low metabolic energy (2-5% ATP)

Impaired antioxidant capacity (Heinz bodies)

Reflect other tissues?
ACUTE HEMOLYTIC ANEMIA

Most frequent cause of death in captive black rhinos before preventative measures (75%)

**Oxidant stress** $\rightarrow$ premature RBC death $\rightarrow$ **Hemoglobin** release & degradation $\rightarrow$ tissue deposits of iron pigments (**Hemosiderin**) 

**ISD** called “**Hemosiderosis**”
NECROPSY REPORTS

HEMOLYTIC ANEMIA
or
IRON STORAGE DISEASE
???
Joseph E. Smith, DVM, PhD (1938 - 1998)
“SILENT” DISORDERS

Hypertension
Arteriosclerosis
Diabetes
Alzheimer’s Disease
Iron Storage Disease
IRON CYCLING
IRON: The ‘Goldilocks’ Metal

BIOLOGICALLY ESSENTIAL
Hemoglobin, myoglobin, enzymes

DEFICIENCY
Most common anemia worldwide

HEREDITARY OVERLOAD
Hemochromatosis (HFE mutations)
Most common U.S. genetic disorder

HIGHLY TOXIC IN FREE FORM
IRON STORAGE DISEASE

All African black & Sumatran rhinos born or brought into captivity are affected.

Total body iron loads correlate with time in captivity, reaching tenfold in 3-5 yrs.

Massive (>1,000x) overloads are common among long-term captives.
EVIDENCE FOR IRON OVERLOAD

BLOOD STUDIES (>250 rhinos, 4 sp.)
- Serum Iron
- Transferrin Saturation
- Ferritin

NECROPSY STUDIES (>60 rhinos, 5 sp.)
- Histopathology (iron stains)
- Quantitative tissue iron analyses
SERUM IRON ANALYTES

IRON

TRANSFERRIN (transport protein)
(Total Iron Binding Capacity)

TRANSFERRIN SATURATION (%)

FERRITIN (storage-protein complex)
Correlates with total body burden
CAPTIVE WHITE RHINOS

Serum ferritin concentration (ng/ml) vs. Time in captivity (months)

- Non Captive Black
- free-ranging White
- Equine
- Human
- straight line
- Captive Indian
- Captive White
CAPTIVE SUMATRAN

Free-ranging species

Equine

Human

D. bicornis

C. simum

X + 1SD

Normal laboratory control ranges

Time in captivity (months)
CAPTIVE BLACKS
SERUM FERRITIN IN BLACK RHINO CALVES
NECROPSY PATHOLOGY (LUNG)

WHITE RHINO

BLACK RHINO
NECROPSY PATHOLOGY
(LIVER)

WHITE RHINO
BLACK RHINO
LIVER CARCINOMA IN A BLACK RHINO
BIOCHEMICAL EFFECTS
OF EXCESS FREE IRON

Catalytic production of
“Reactive Oxygen Species”
Hydroxyl free radicals,
superoxide, peroxides

Oxidative damage
Molecular, organelle,
cellular, organ
CLINICAL CONSEQUENCES OF IRON OVERLOAD

Cellular damage in multiple organs → dysfunction, failure
Increased vulnerability to INFECTIONOUS DISEASES
ROLE OF IRON OVERLOAD IN INFECTIOUS DISEASES

Iron available to invading organisms (loss of “nutritional immunity”)

Increased virulence of microbes (TB)

Susceptibility to exotic organisms

Impaired white cell function
CAPTIVITY-INDUCED IRON STORAGE DISEASE

An anthropogenic pandemic across multiple taxa....

Causes & Correctives....?
ETIOLOGIC POSSIBILITIES

NUTRITIONAL FACTORS
Browsers vs. grazers:
Tannin, fiber, phytates, phenols, phosphate, L-mimosine, DHBA?

GENETIC PREDISPOSITIONS
Molecular regulators of iron:
Hepcidin, ferroportin, hemojuvelin, HFE, TfR-2
MOLECULAR REGULATION OF IRON BALANCE

FERROPORTIN:
Channel for intracellular iron $\rightarrow$ plasma

HEPCIDIN:
Blocks ferroportin channel
HEPCIDIN DEFICIENCY

LOSS OF FERROPORTIN MODULATION

→ Unrestricted flow of dietary and storage iron into plasma

→ IRON OVERLOAD DISORDERS (Hemochromatosis)
**EVOLUTIONARY ASPECTS**

-5 B.y.a: Primodial atmosphere = volcanic gases
-4 B.y.a: $H_2O$ condensation → hydrosphere
-3 B.y.a: Anaerobic (reducing) atmosphere
-2 B.y.a: Bacteria & eukaryotes arise
-1 B.y.a: Blue-green algae & photosynthesis → oxygen, ozone → terrestrial life forms
-350-230 M.y.a: Oxygen = 35% → 15-21%
-100 M.y.a: Modern mammals & birds arise
-50-60 M.y.a: Browser rhinos appear
-25 M.y.a: Savannah grasslands → grazers arise
PREVENTION & THERAPY OF IRON OVERLOAD

THERAPY
Chelating drugs

PREVENTION
Phlebotomies
PHLEBOTOMY RATIONALE

Blood contains measureable hemoglobin iron (≈0.5g/L)
Phlebotomy induces slight anemia
Anemia mobilizes storage iron for new red cell production
Can be quantitatively monitored
RHINO ISD
HISTORICAL CHRONOLOGY

1993: White Oak Conference
1995: Smith et al JZWM
1999: St. Louis Int’l Conference, AAZV
2000: AAZV (Tapirs)
2003: IRKA (Phlebotomy protocol)
2004: AAZV (Phlebotomy protocol)
2005/6: IRKA
2011: Orlando Conference
2012: JZWM Special Supplement
SUMATRAN RHINO CAPTIVE BREEDING PROGRAM

“Emi”
Los Angeles Zoo
PHLEBOTOMIES:
COST/BENEFIT ANALYSIS

Potential Costs:
- Restraining chute (?)
- Staff time: training, performance
- Venesection supplies
- Laboratory monitoring
“TIPPING POINTS”

POPULATION SUSTAINABILITY

BIRTH/DEATH RATIOS:

> 1 → POPULATION GROWTH

< 1 → EXTINCTION

AFRICAN RHINOS = 1.0 ± 2-6%
HUMAN ISD (HEREDITARY HEMOCHROMATOSIS)

SYMPTOM ONSET = 30-50 yrs

UNTREATED → LIVER CIRRHOSIS → CANCER (>60 yrs old = 50%)

PHLEBOTOMIES in PRECIRRHOTICS → NORMAL LIFE SPANS
PHLEBOTOMIES: POTENTIAL BENEFITS

Long-Term Captives:
- Decrease toxic iron overburdens
- Increase quality of life
- Avoid euthanasia for organ dysfunction/failure
- Extend longevity (?)
PHLEBOTOMIES: POTENTIAL BENEFITS

Juveniles & Newly Captive:

- Prevent iron accumulation ➔ ISD
- Increase high quality of life
- Extend life expectancy 20-30%
- Extend reproduction 1-2 cycles
- Alter tipping point ➔ sustainability
Captivity induces pathological iron overloads (ISD) in browsers. Iron toxicity causes cell & organ dysfunction and increases virulence of microorganisms. Periodic phlebotomies can reduce iron loads &/or prevent ISD in young or newly captured animals.
“A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather its opponents eventually die, and a new generation grows up that is familiar with it.”

Max Planck
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