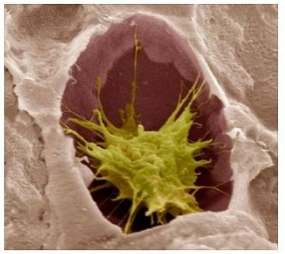
‘Salix’ and Calcium and Bones *IS* there a connection??

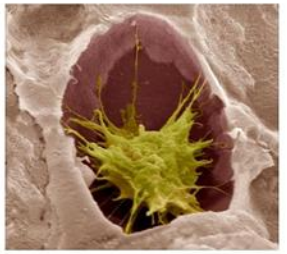
Calcium Homeostasis (in the horse)



- The horse differs considerable from other species with regard to calcium homeostasis
- Plasma calcium concentration is ***not*** affected by breed, calcium intake, exercise or housing.
  - Phosphorus is negatively correlated with age and positively with intake.
- Vitamin D ***does not*** play a large roll in calcium homeostasis.

Briedenback et al. Vet Res 1998, 29:73

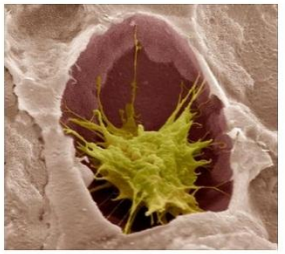
Calcium Homeostasis General



- Dietary calcium is absorbed primarily from the duodenum in horses.
- Calcium is absorbed both actively (energy requiring transporters) and passively by diffusion.
- Calcium is exchanged with bone according to needs of growth, exercise etc.
- ***Excess*** calcium is excreted in the urine and feces.
- Renal failure in horses is characterized by hypercalcemia!
  - ***This is different from all other species!***

Sprekeler et al. BMC Veterinary Research 2011, 7:65

Calcium Homeostasis (in the horse)



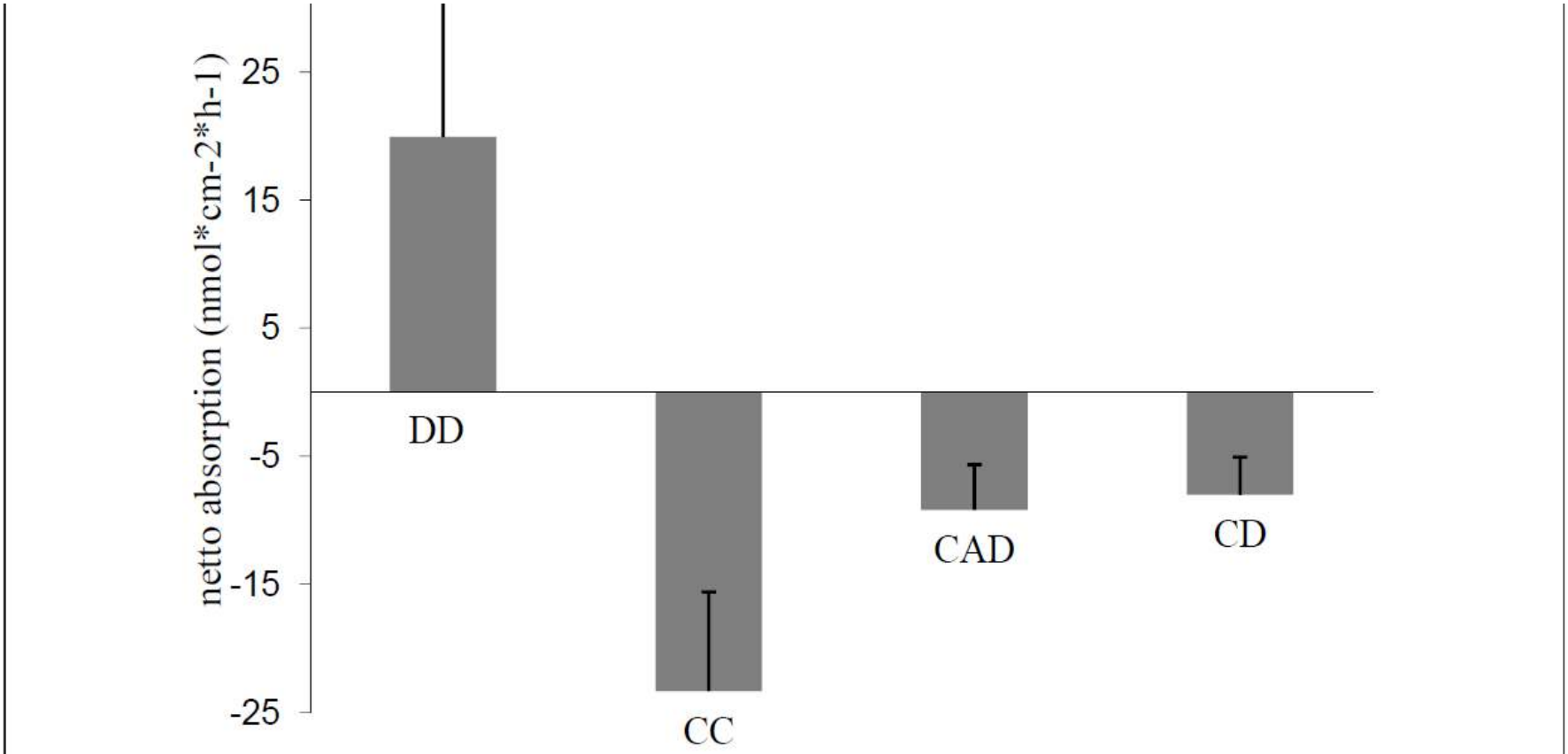
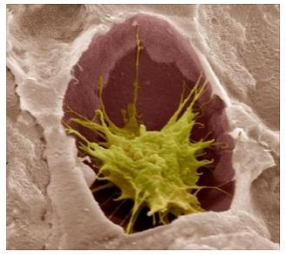


Figure 6 Ussing chamber. Ex-vivo Ca^{2+} absorption in different intestinal segments (duodenum = DD, cecum = CC, colon descendens dorsale = CAD, colon descendens = CD) was measured by the Ussing chamber technique. Positive flux rates (absorption) from the mucosal to the serosal sides were measured in the duodenum, while in the remaining segments (CC, CAD, CD), the negative flux rates (secretion) were determined.



Site of calcium absorption

Site of calcium excretion

Site of calcium excretion

Pharynx

Oesophagus
(1 1/2 metres)

Stomach
(10 litres)

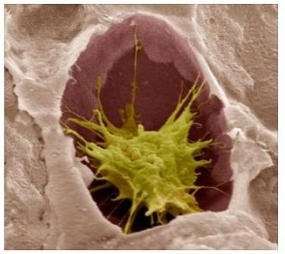
Buccal Cavity

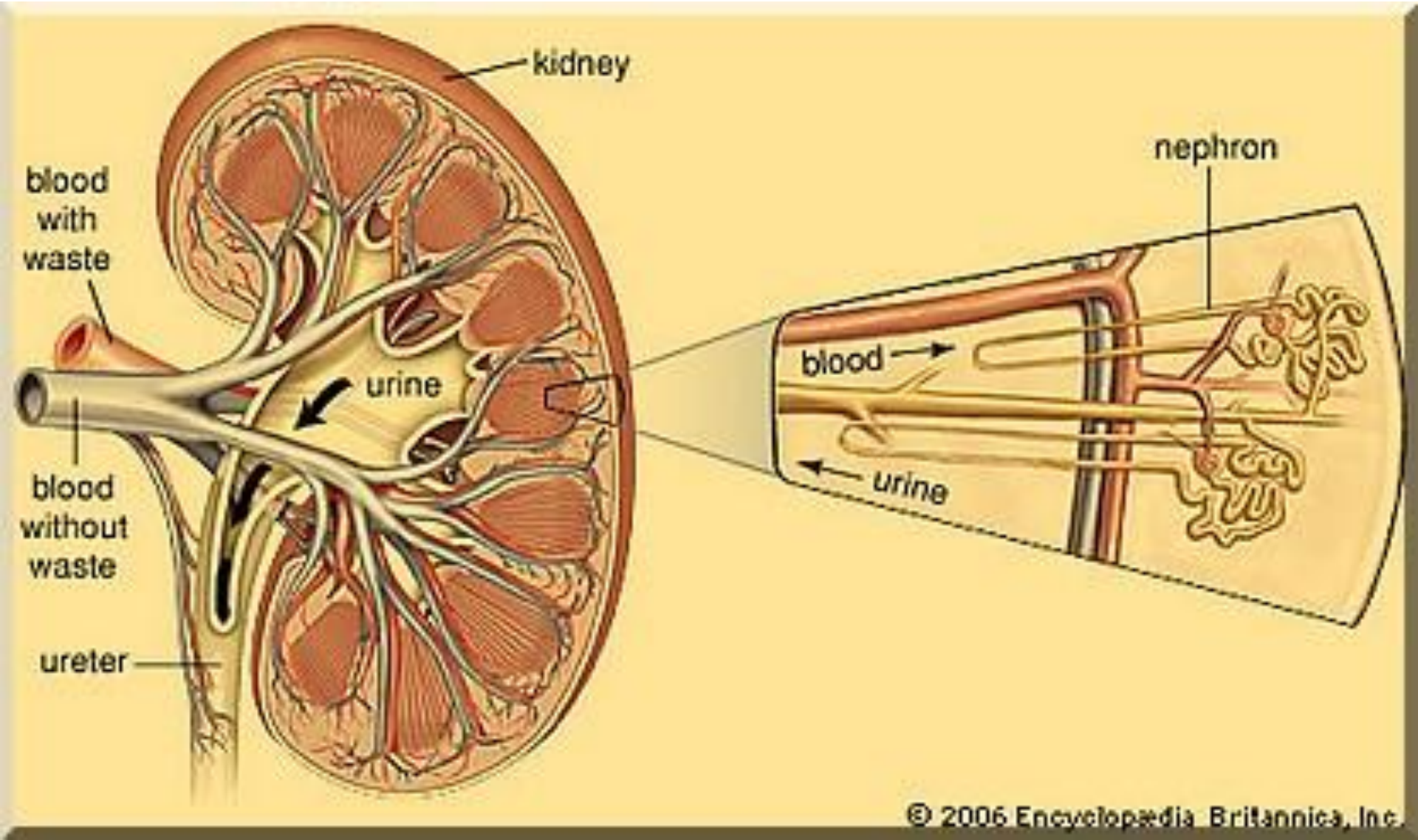
Small Intestine
(50 litres, 20 metres)

Caecum
(30 litres)

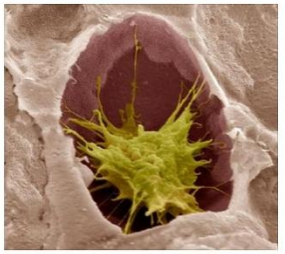
Large Colon
(70 litres, 3 1/2 metres)

Calcium Homeostasis
Renal Handling





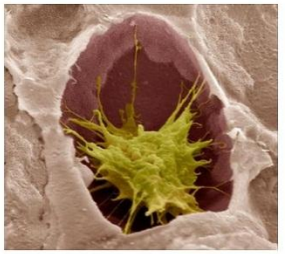
Calcium in the Urine

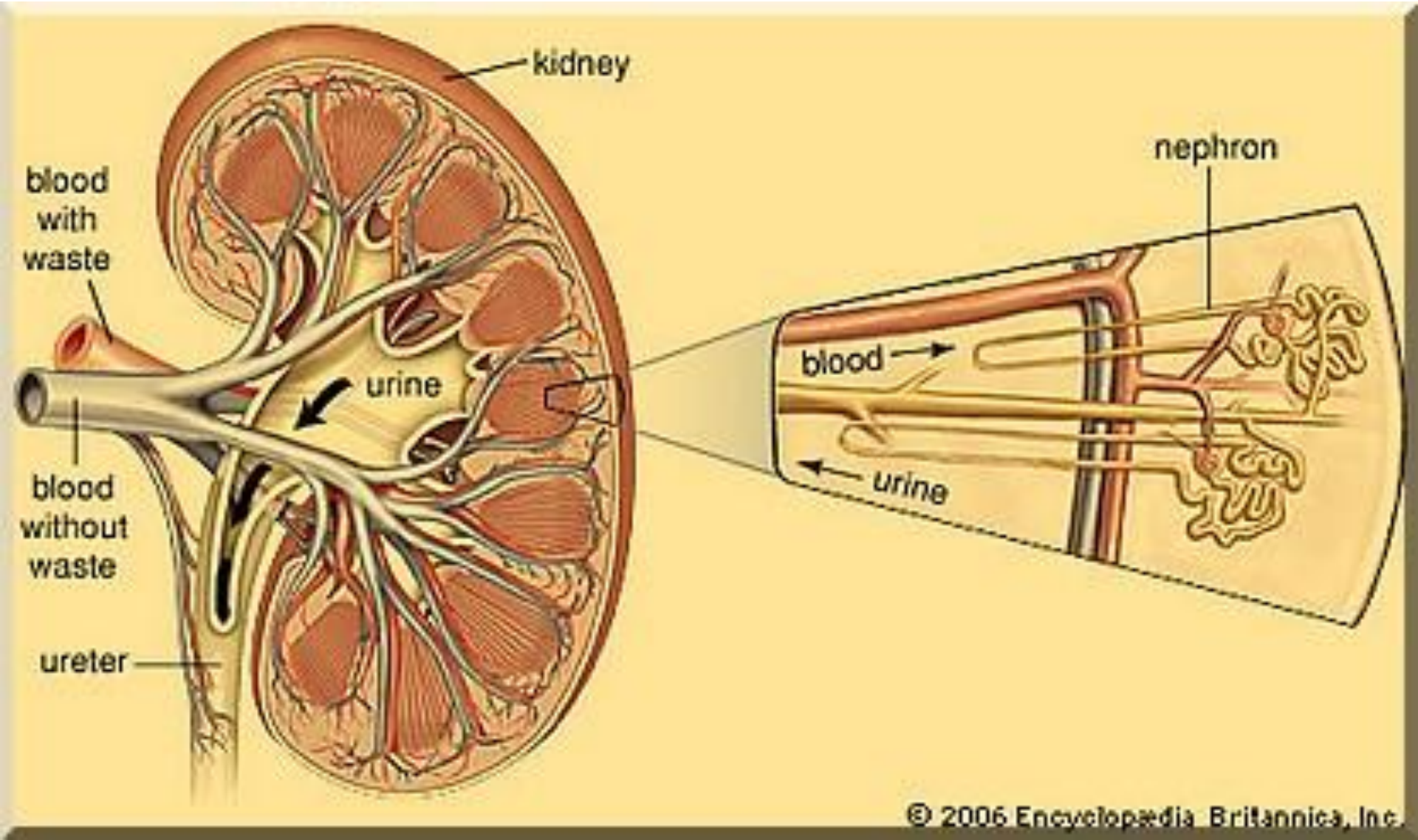


- In one study, the concentrations of Ca and P in urine samples changed markedly when groups of 4 mares were fed diets containing between 1.0 to 3.9 g Ca/kg and from 1.5 to 6.1 g P/kg, *but* **serum concentrations of Ca remained constant**.
- When horses are fed adequate calcium, the Ca-%Cr is greater than 2.5% and P-%Cr is less than 4%.
- When a low Ca (1.0 g/kg) and high P (4 g/kg) diet is fed, the excretion of Ca and P change markedly within 3 days.
- *Diet determines urinary but not serum or plasma calcium concentrations overall.*

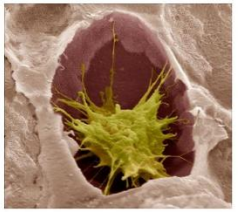
Caple et al, Aust Vet J. 1982, 58:125

Calcium Homeostasis
Renal Handling





A. Site of action of diuretics



Carbonic anhydrase inhibitors
(e.g., acetazolamide)

Na^+ and HCO_3^- reabsorption

Thiazide diuretics

Na^+-Cl^- symport

Aldosterone antagonists
(e.g., spironolactone)

Na^+ channel
(indirect effect)

Loop diuretics
(e.g., furosemide)

Na^+-$2Cl^-$-K^+ symport

Amiloride

Na^+ channel
(direct effect)

NaCl reabsorption ↓ → → H_2O reabsorption ↓ → ECF volume ↓

Proximal convoluted tubule

Loop of Henle

Distal tubule

10%

60%

15%

Thick ascending limb

10%

Collecting duct

Cortical

72%

9%

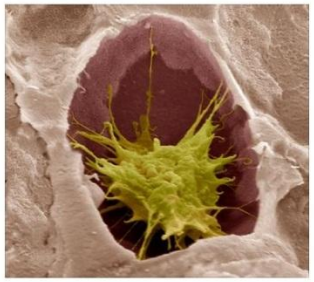
20%

100% Mg

100% Ca/Na

Thin descending limb

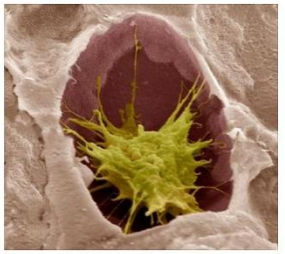
Medullary



3%

>5%

Salix and Dehydration



- Purposeful dehydration of horses over 36 hrs using water deprivation and every 8 hour Salix administration (1 mg/kg) resulted in:
  - Average 23 kg weight loss (5.5% BW)
  - NO change in plasma electrolyte concentrations
  - Increased total protein
  - Increased lactate
  - NO change in PCV, minor decrease in splenic volume (decreased ~3.9 L from ~25.5 L)

Nolen-Walston et al. J Vet Intern Med, 2011, 25:570

J Vet Intern Med 2003;17:887–895

Furosemide Continuous Rate Infusion in the Horse: Evaluation of Enhanced Efficacy and Reduced Side Effects

Anna M. Johansson, Sarah Y. Gardner, Jay F. Levine, Mark G. Papich, D. Heath LaFevers, Laura R. Fuquay, Virginia H. Reagan, and Clarke E. Atkins

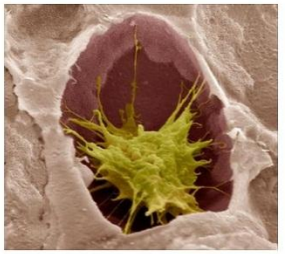
Table 1. Urinary electrolyte excretion during infusion or after bolus administration of furosemide. Values were obtained from well-mixed total urine produced during the first 8 hours and during 24 hours of treatment.[a]

		Electrolyte Concentration in Urine (mmol/L)				Total Electrolyte Excretion in Urine (mmol)			
		8-Hour Urine		24-Hour Urine		8-Hour Urine		24-Hour Urine	
		Median	(25th, 75th)	Median	(25th, 75th)	Median	(25th, 75th)	Median	(25th, 75th)
Na	IA	96	(86, 100)	91*	(82, 92)	564	(460, 602)	1,178	(991, 1,245)
	CRI	91	(88, 95)	66*	(65, 70)	909	(778, 1,227)	959	(916, 1,399)
K	IA	52	(44, 66)	65*	(56, 74)	315*	(298, 345)	764*	(709, 904)
	CRI	55	(55, 59)	82*	(79, 92)	537*	(528, 701)	1,133*	(1,110, 1,229)
Cl	IA	138	(124, 133)	129	(125, 130)	723*	(693, 866)	1,596	(1,457, 1,767)
	CRI	140	(140, 141)	124	(122, 125)	1,330*	(1,245, 1,918)	1,776	(1,657, 2,378)
Ca	IA			6.0*	(5.1, 6.5)			73.3*	(65.0, 73.5)
	CRI			6.5*	(6.4, 8.5)			102.7*	(96.0, 117.2)
Mg	IA			2.7	(2.3, 3.9)			33.7	(29.6, 58.5)
	CRI			2.8	(2.5, 2.8)			34.4	(33.4, 57.6)

[a] Data presented as median (25th, 75th percentiles). IA, intermittent administration of furosemide (1 mg/kg q8 IV); CRI, continuous rate infusion of furosemide (0.12 mg/kg/h, preceded by a loading dose of 0.12 mg/kg IV); Conc, concentration; Na, sodium; K, potassium; Cl, chloride; Mg, magnesium; Ca, calcium.

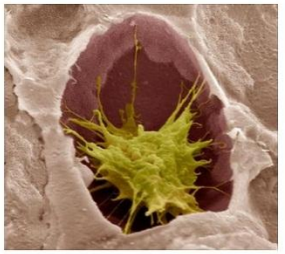
* Significant difference between methods, $P < .05$ (Wilcoxon signed-rank test).

Salix, Exercise and Calcium

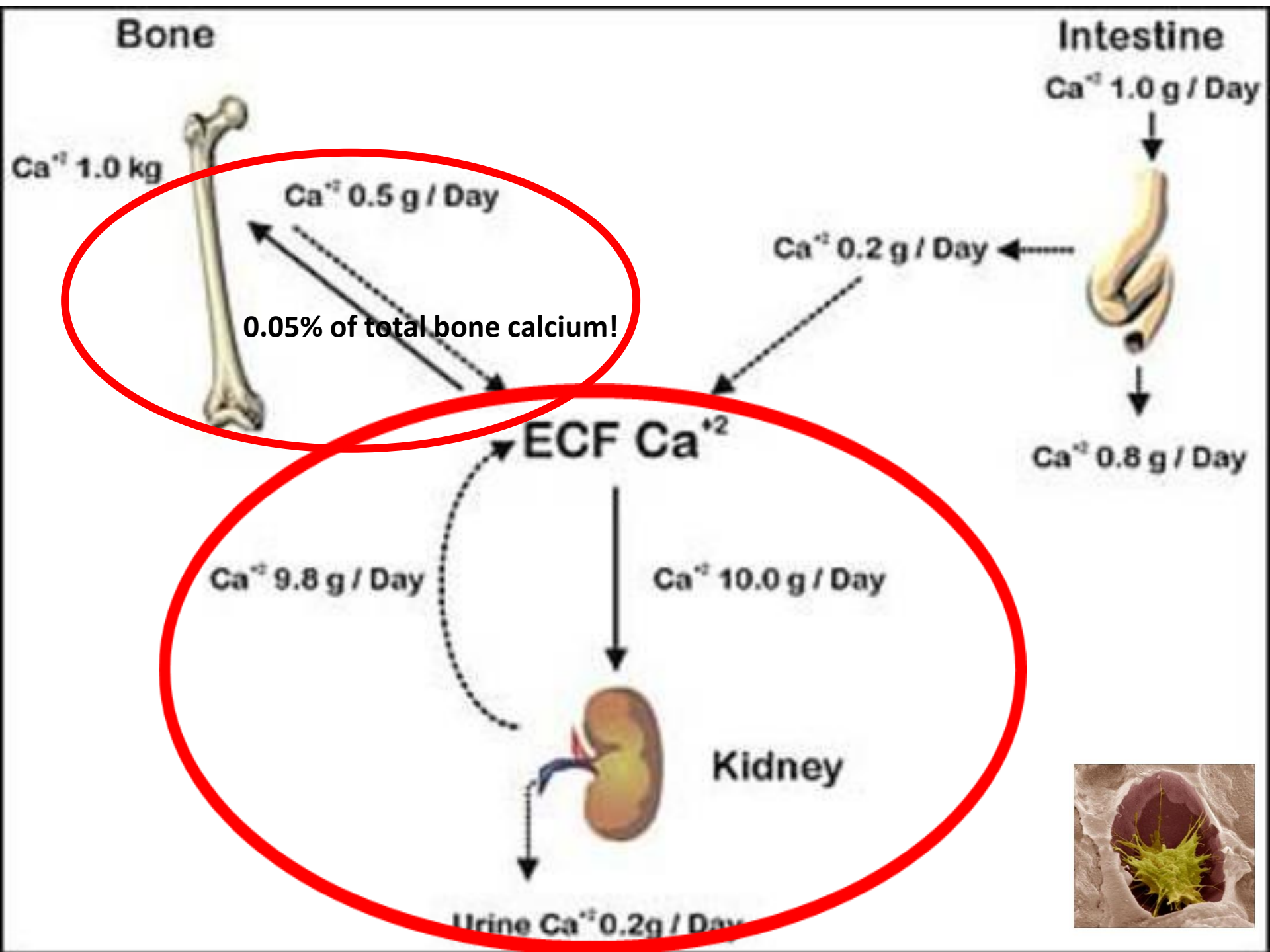


- The question becomes ‘Why’?
- We haven’t yet discussed **BONE**.
- The horse is a cursorial animal, with musculo-skeletal structure adapted to maximize locomotor efficiency at an early age to avoid predation.
- Distal to the carpus and tarsus, load is borne mainly through the third metacarpal (Mc3) or third metatarsal bone (Mt3).

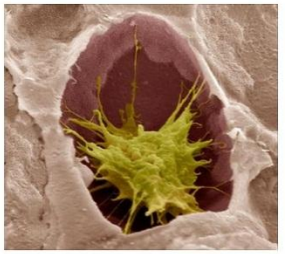
Salix, Exercise and Calcium



- Horses often begin training in their second year of life, and this, together with the morbidity and mortality associated with athletic pursuits in horses, has driven considerable study of the effects of exercise on bone in the horse.
- Bone tissue will adapt if the forces acting upon it cause the deformation (strain) sustained by the bone to exceed certain values, but if that strain value is not exceeded, then the bone will not respond to increase its resistance to the deforming forces (Frost et al. 2002).

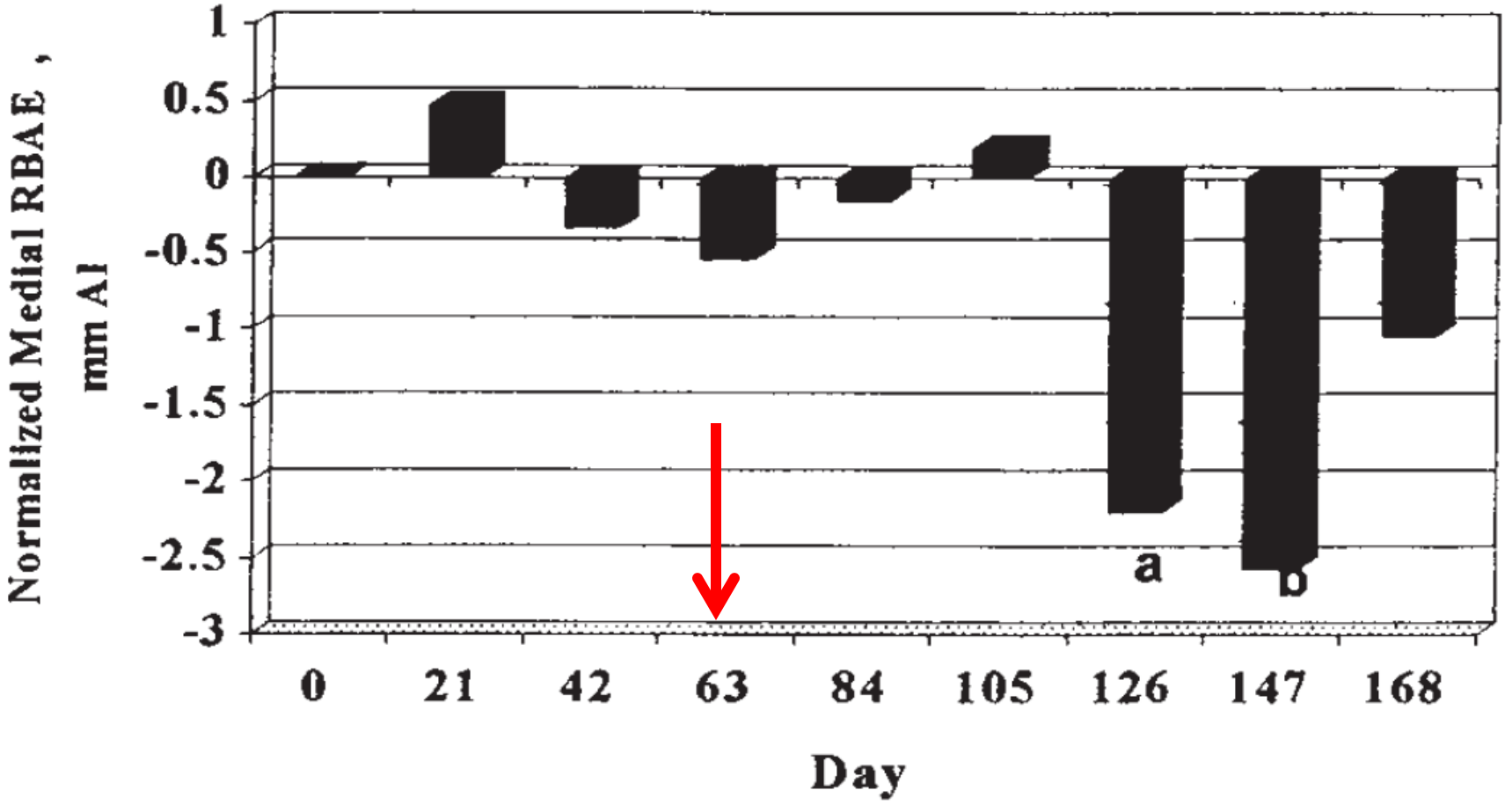

Bone
Intestine
Ca+2 1.0 kg
Ca+2 0.5 g / Day
Ca+2 0.2 g / Day
Ca+2 1.0 g / Day
0.05% of total bone calcium!
ECF Ca+2
Ca+2 0.8 g / Day
Ca+2 9.8 g / Day
Ca+2 10.0 g / Day
Kidney
Urine Ca+2 0.2g / Day

Exercise and Bone Density



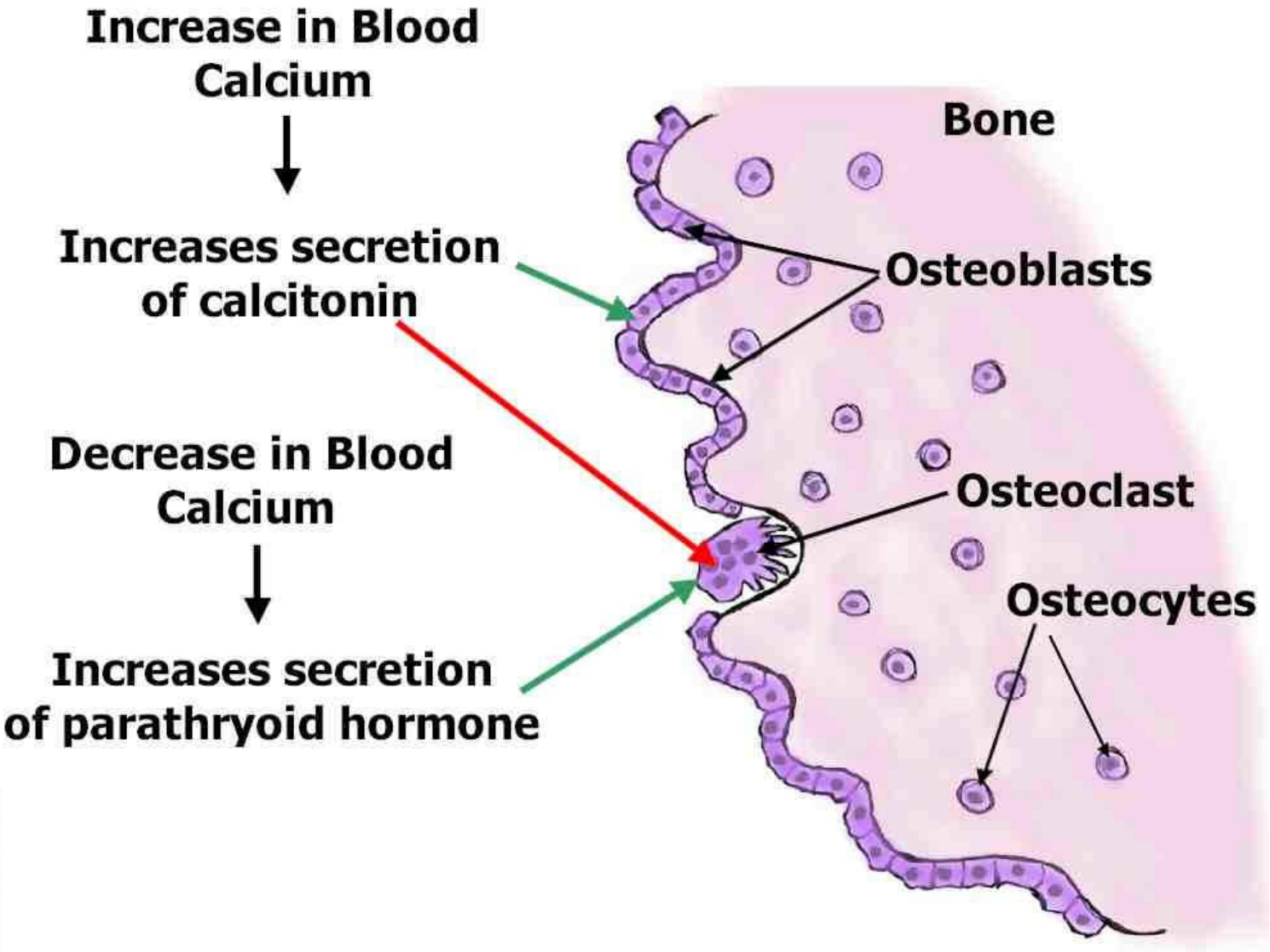
- Research indicates that both young and mature horses experience an initial decrease, followed by an increase, in bone density after the onset of training.
  - Nielsen BD et al. Modifications of the third metacarpal bone in young horses as a result of race training. Proc 14th Equine Nutr Physiol Symp 1995;p.102.
  - Nielsen Bdet al. Characterization of changes related to mineral balance and bone metabolism in the young racing quarter horse. J Equine Vet Sci 1998b;18:190

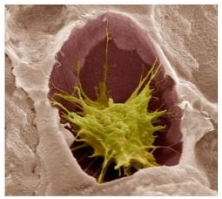
Exercise and Bone Density



[a] Mean different from d 0 ($P < .001$), [b] Mean different from d 0 ($P < .02$)

Hormonal Control of Bone Remodeling





PTH and Salix

- Long term (>2 years) loop diuretic treatment of women actually resulted in increased bone density compared to those not treated, *despite* increased calcium urinary losses.
- PTH concentrations were increased and overall calcium balance was neutral.
    - Rejbmark et al. Journal of Internal Medicine 2005; 257: 176–184

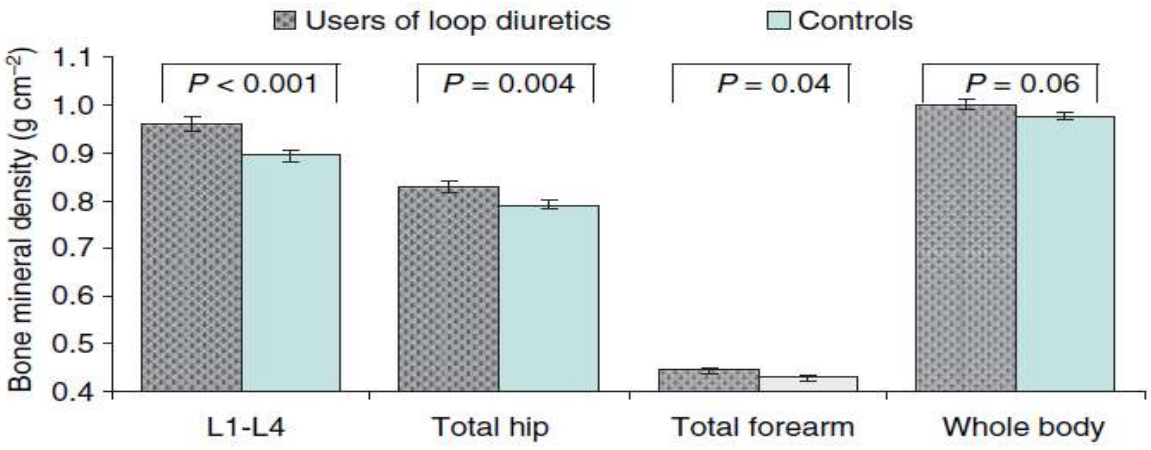
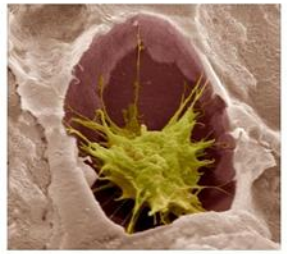


Fig. 1 Bone mineral density in users ($n = 140$) and nonusers ($n = 140$) of loop diuretics (mean ± SEM).

In Summary…….



- In the young horse, exercise induces a significant remodeling and modeling response in bone. Maintenance of that bone content requires further exercise; however, exercise must be below a critical threshold at which exercise can induce disease.
- Exercise has been shown to maintain bone mineral density and strength *even in the face of calcium insufficiency*.
  - Inman et al. J Appl Physiol. 1999 Jul;87(1):189-95
- Urinary calcium loss associated with Salix is ***not dissimilar*** to that of the horse at exercise after 24 hours and may not be contributor to any alteration in bone strength or the remodeling process.
- More research specifically examining the question of Salix and bone remodeling is required.

Lasix/Salix/EIPH

Apples to Apples…What is the Science?

Pamela A Wilkins DVM, MS, PhD, DACVIM-LAIM, DACVECC

Professor Equine Internal Medicine and Emergency and Critical Care

THURSDAY, JANUARY 24, 2013
Thoroughbred Daily News
EIPH Expert Panel Consensus Statement

“Exercise Induced Pulmonary Hemorrhage (E.I.P.H.) is a consequence of the high pulmonary vascular pressures achieved by elite athlete horses during strenuous exercise. A similar condition occurs in racing greyhounds and has been reported in some elite human athletes”

“E.I.P.H. has a detrimental effect on performance in Standardbreds and Thoroughbreds”.

“The only treatment that has been shown to prevent the occurrence and decrease severity of E.I.P.H. in Thoroughbred racehorses is furosemide.”

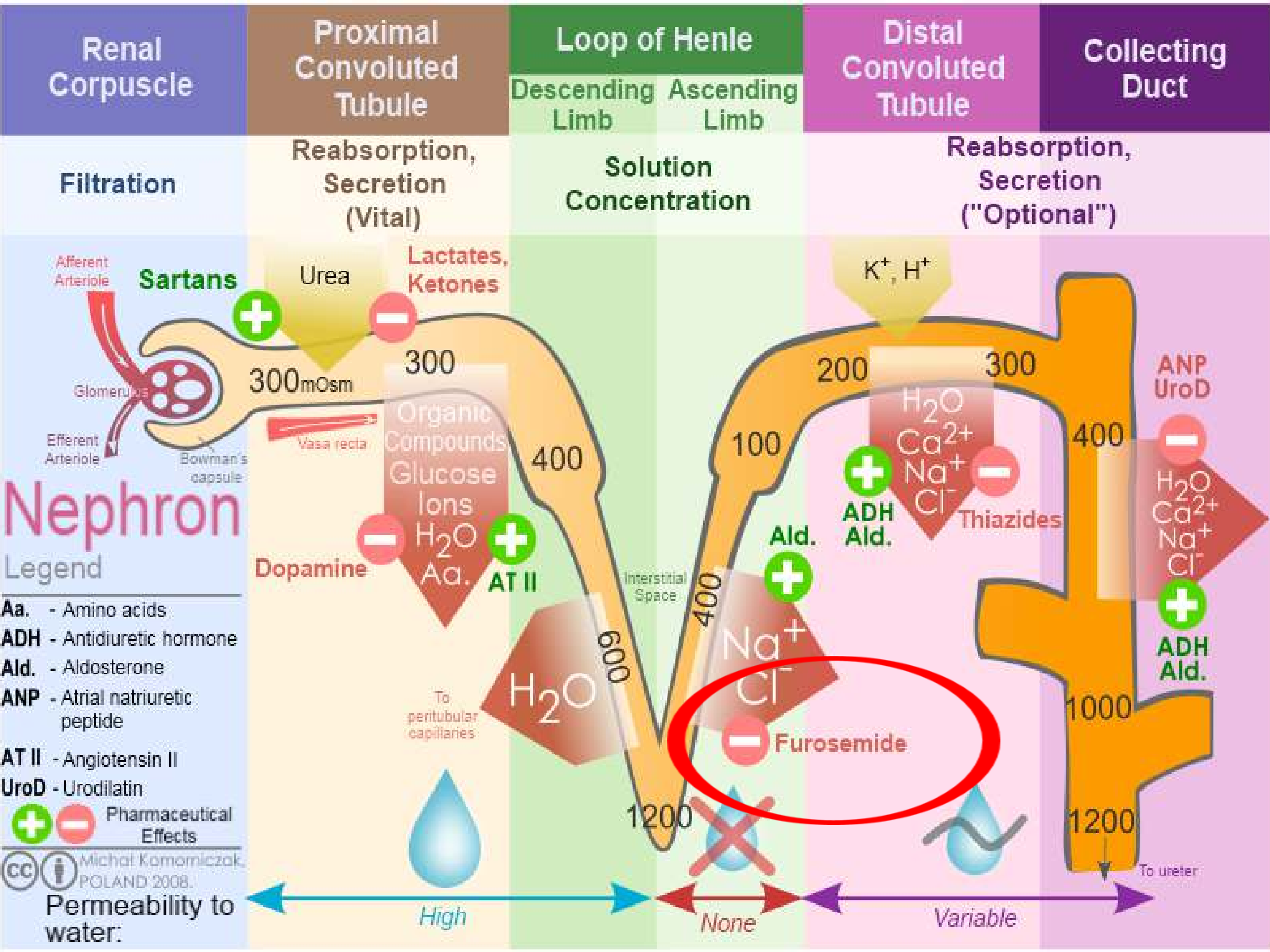
“On average, horses administered furosemide have better performance.”

“Horses administered furosemide on a routine basis have not been recognized to experience detrimental effects.”

“Furosemide does not mask detection or other agents when modern analytical methods are used.”

An incoherent debate?

- "…..the Salix (*sic* Lasix or furosemide) debate stands alone in its incoherency and lack of reliance on the ***science*** *(my emphasis)* behind its use."
- "Indeed, the ***science*** (*my emphasis*) speaks for itself yet the ***misanthropes*** insist that administering Salix and other potent medications is the "humane" thing to do."
- "Well at least we can be thankful that there won't be rivers of blood gushing down the backside. The sensationalism is simply too much to tolerate anymore."
    - JANE ALLIN, Posted on Tuesday's Horse on Nov 24, 2012 by VG Farrell.
    - http://tuesdayshorse.wordpress.com/2012/11/24/forgotten-side-of-the-salix-debate-the-calcium-connection/

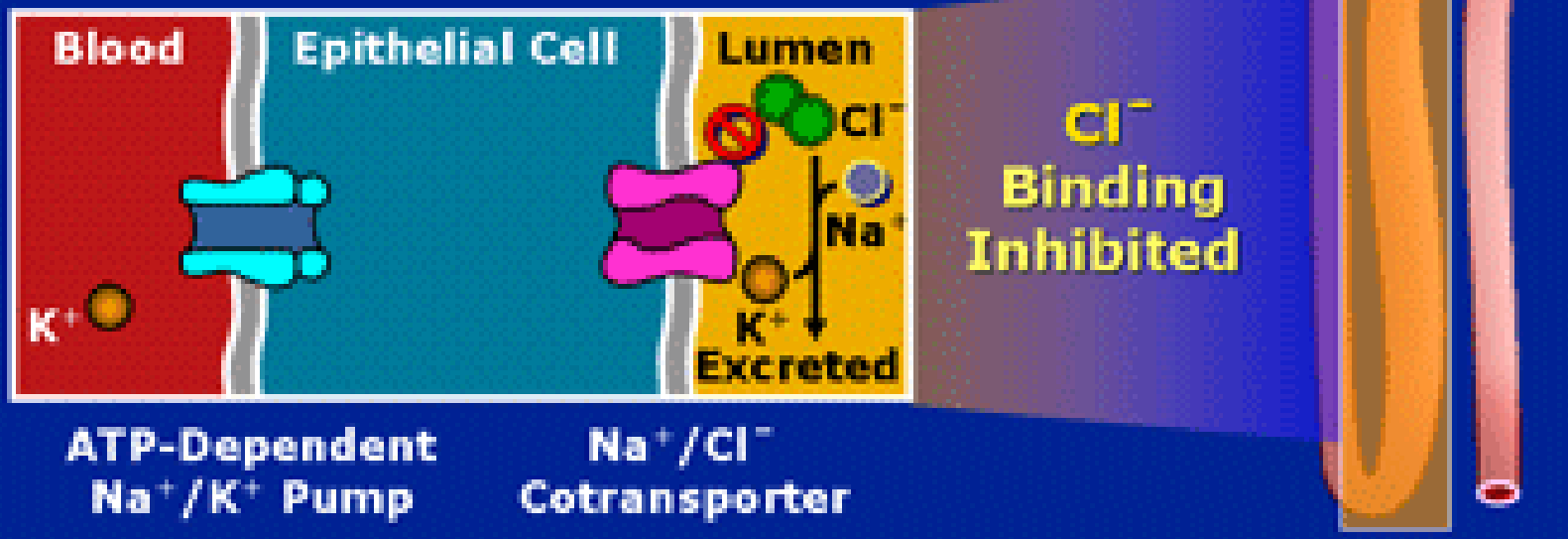


Renal Corpuscle
Proximal Convoluted Tubule
Loop of Henle
Descending Limb
Ascending Limb
Distal Convoluted Tubule
Collecting Duct
Filtration
Reabsorption, Secretion (Vital)
Solution Concentration
Reabsorption, Secretion ("Optional")
Afferent Arteriole
Sartans
Urea
Lactates, Ketones
K+, H+
300mOsm
300
Glomerulus
Efferent Arteriole
Vasa recta
Bowman's capsule
Organic Compounds Glucose Ions H2O Aa.
400
100
200
300
H2O Ca2+ Na+ Cl-
ADH Ald.
Thiazides
ANP UroD
400
H2O Ca2+ Na+ Cl-
ADH Ald.
Nephron
Legend
Aa. - Amino acids
ADH - Antidiuretic hormone
Ald. - Aldosterone
ANP - Atrial natriuretic peptide
AT II - Angiotensin II
UroD - Urodilatin
Pharmaceutical Effects
Dopamine
AT II
H2O
600
Interstitial Space
400
Na+ Cl-
Ald.
Furosemide
To peritubular capillaries
1200
1000
1200
To ureter
Michał Komorniczak POLAND 2008.
Permeability to water:
High
None
Variable

Loop Diuretics

Mechanism of Action

Sodium and chloride are not reabsorbed, resulting in increased excretion of these ions



ATP = adenosine triphosphate

Morrison RT. *Med Clin North Am.* 1997;81:689-704;
Brater DC. *Am J Med Sci.* 2000;319:38-50.