Mechanisms of calcium metabolism in the dairy cow; relation to hypocalcemia .

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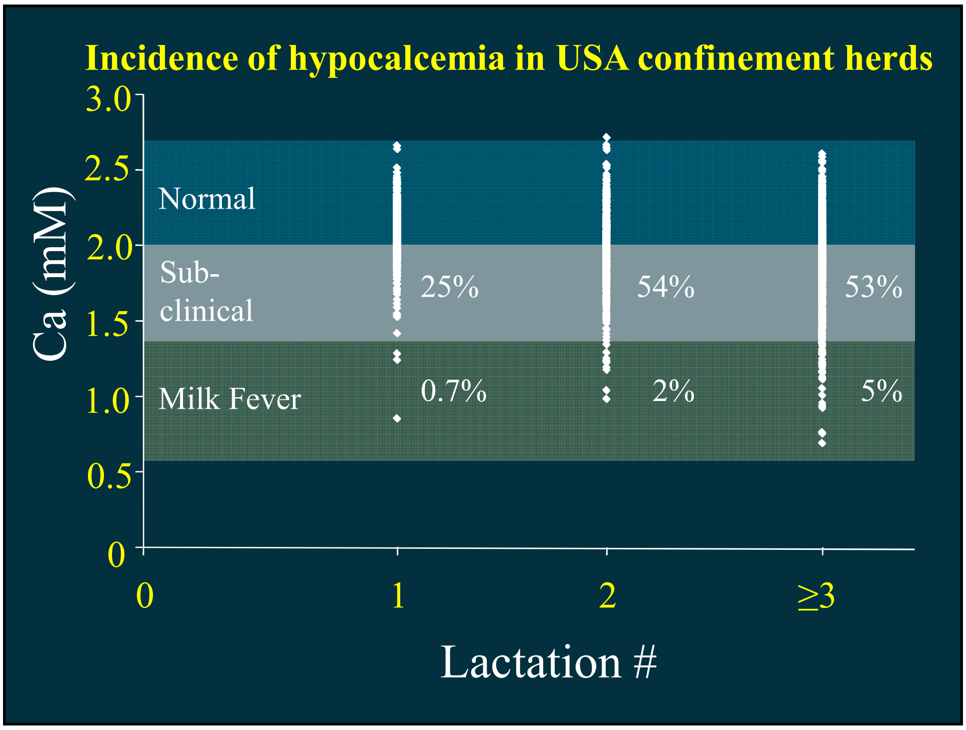
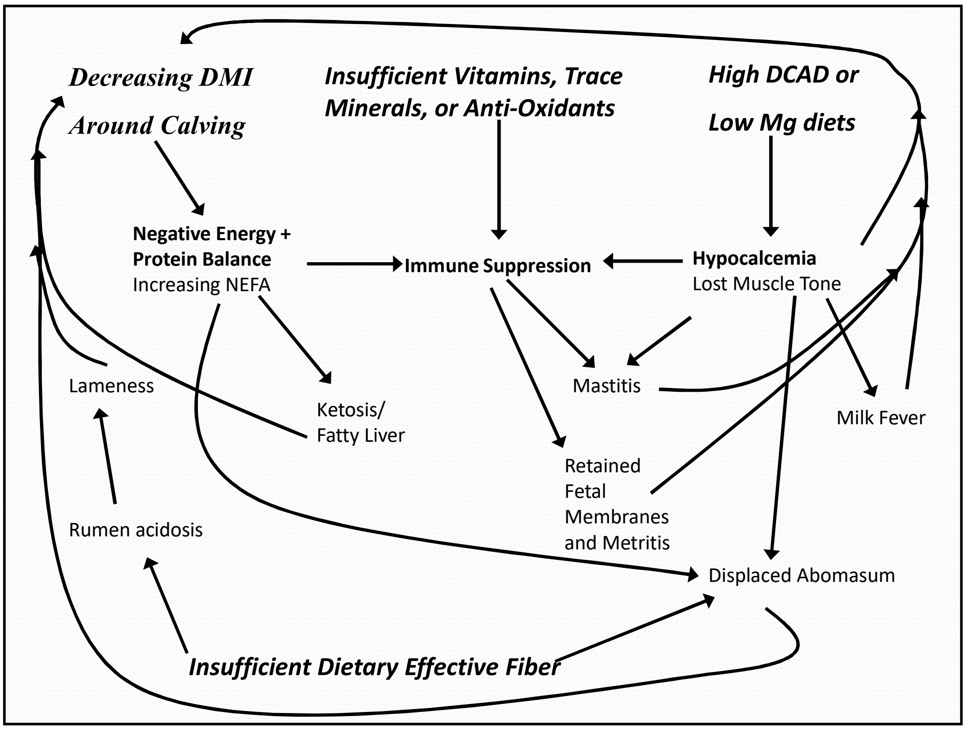




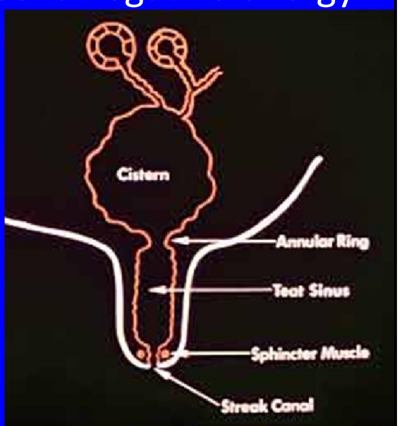
EFFECTS OF HYPOCALCEMIA AND MILK FEVER ON DISEASE RESISTANCE

1. Reduced feed intake ➔ worsens negative energy balance

2. Lack of muscle contraction

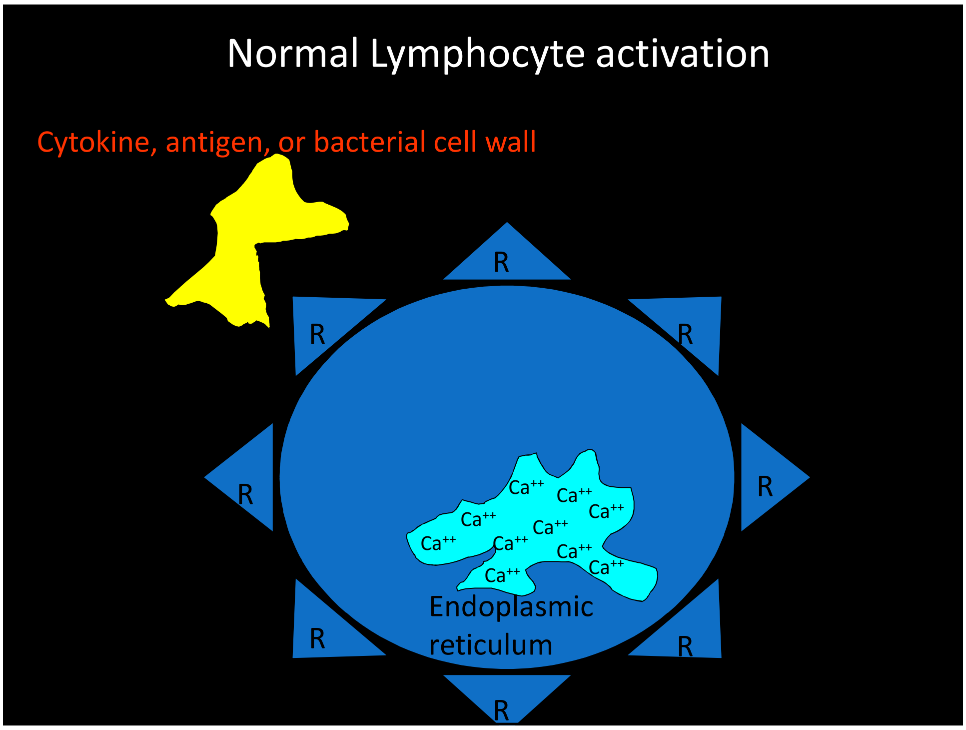
   - impairs teat sphincter closure

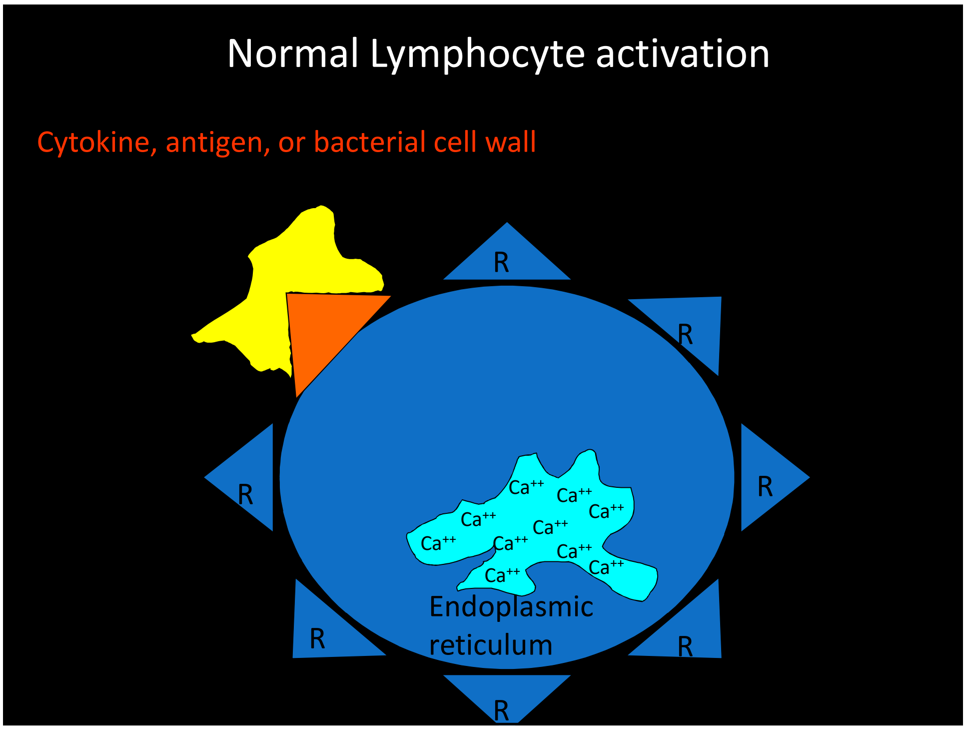
   - failure to expel contents of uterus after calving



3. Reduction in Immune Cell Response to Stimuli

   - Calcium is the “second messenger” of immune cells


Normal Lymphocyte activation
Cytokine, antigen, or bacterial cell wall
R
R
R
R
R
R
R
R
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Endoplasmic
reticulum


Normal Lymphocyte activation
Cytokine, antigen, or bacterial cell wall
R
R
R
R
R
R
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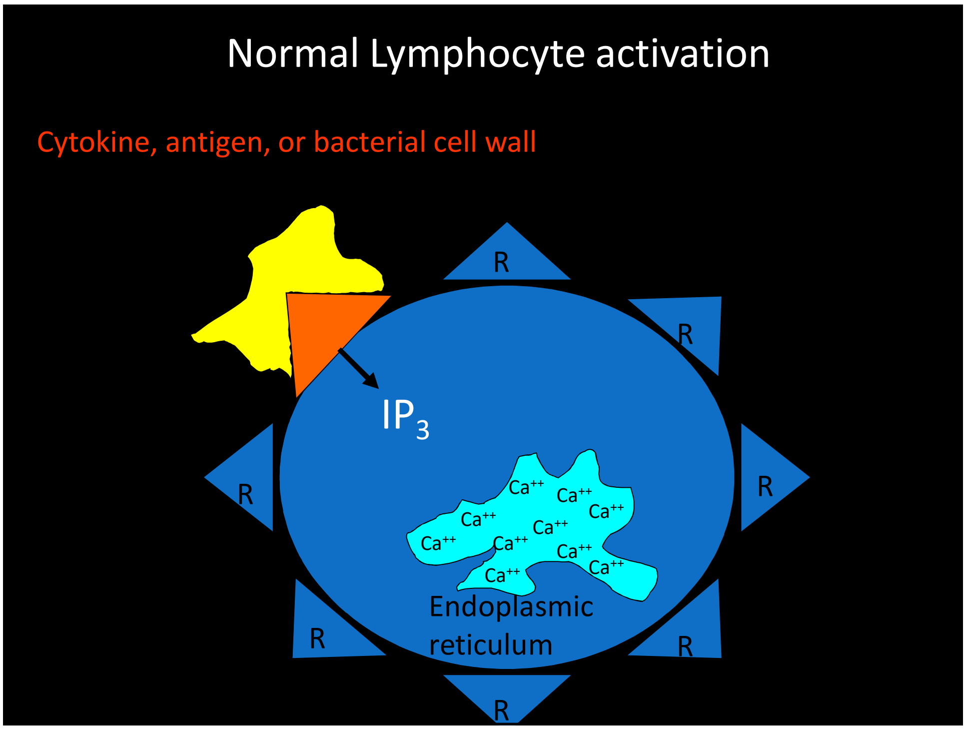
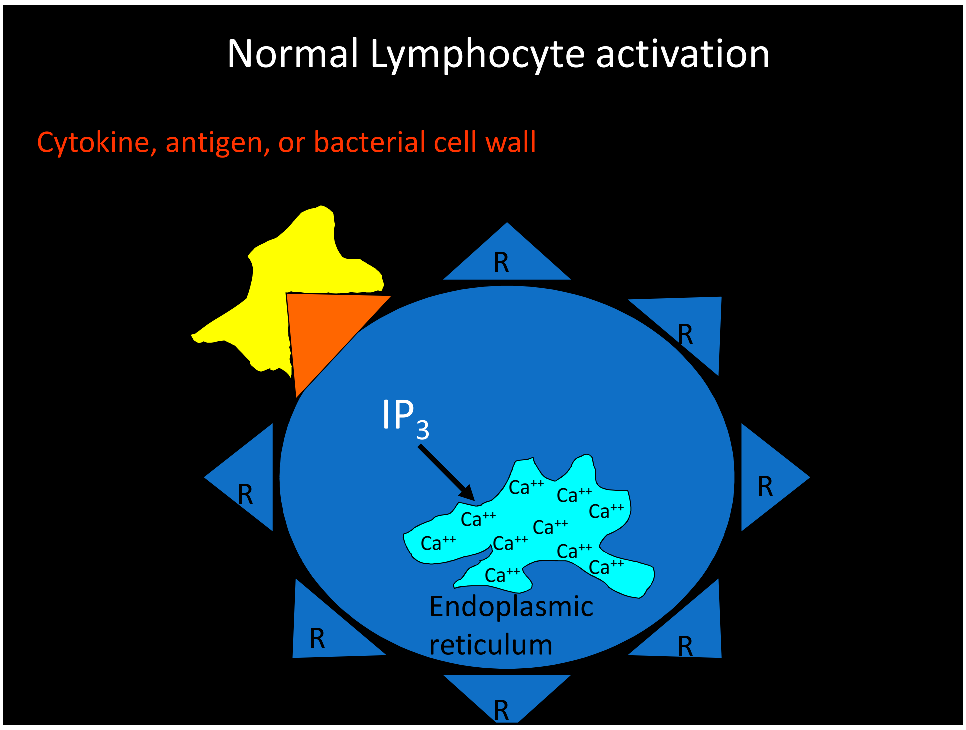
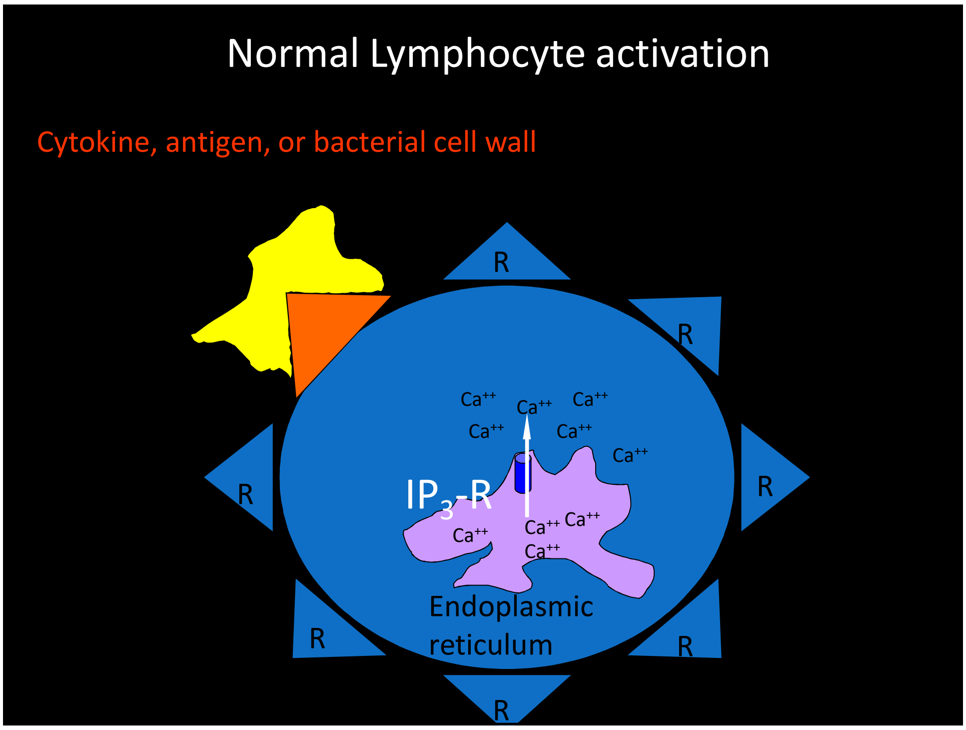
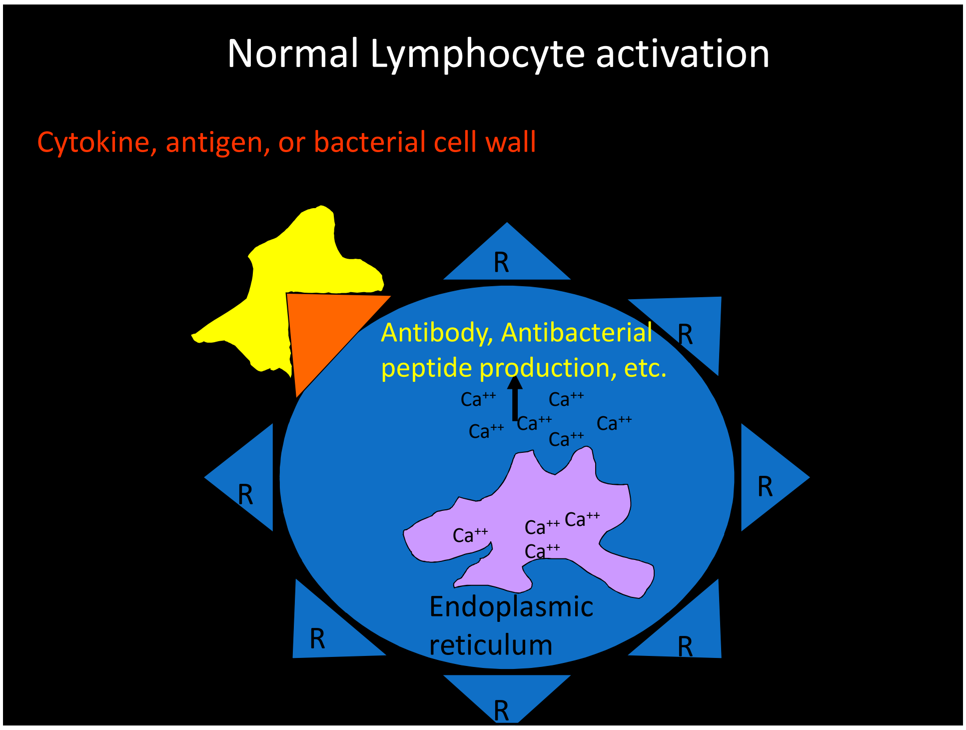
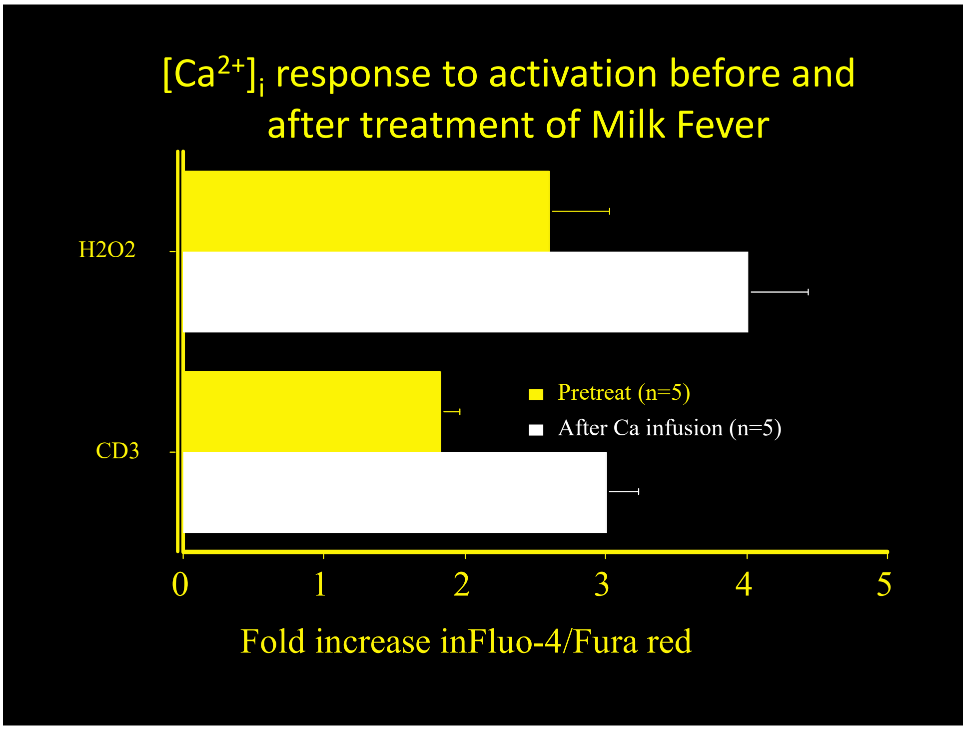
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Endoplasmic
reticulum

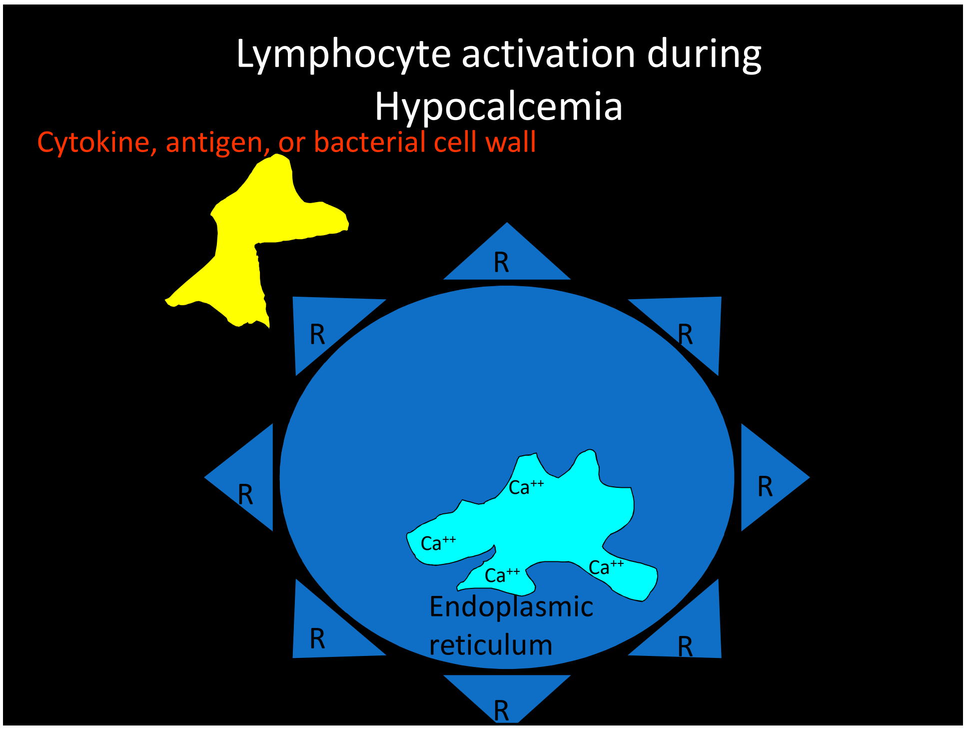

Normal Lymphocyte activation
Cytokine, antigen, or bacterial cell wall
R
IP3
Ca++
Endoplasmic
reticulum

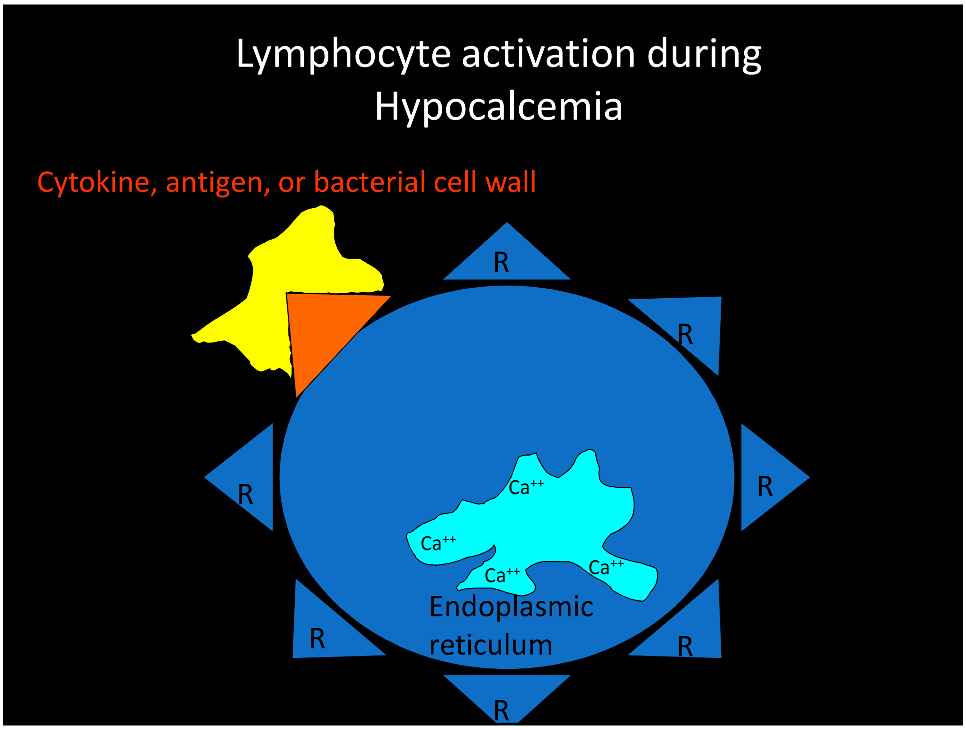

Normal Lymphocyte activation
Cytokine, antigen, or bacterial cell wall
R
IP3
Ca++
Endoplasmic
reticulum

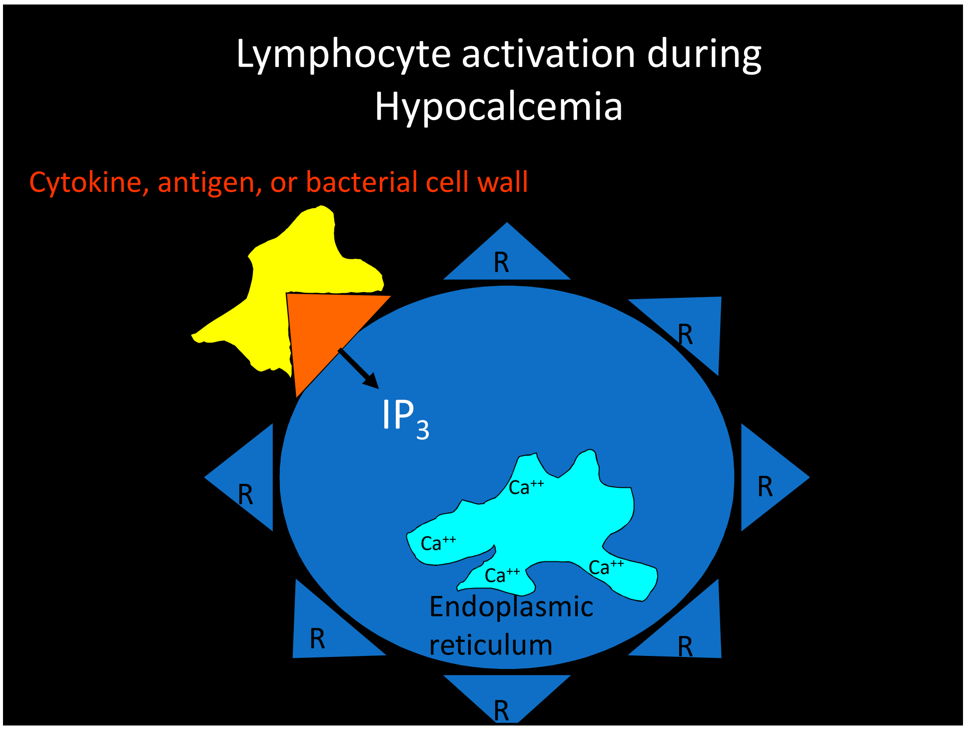

Normal Lymphocyte activation
Cytokine, antigen, or bacterial cell wall
R
R
R
R
R
R
R
R
Ca^{++}
IP_3-R
Endoplasmic reticulum


Normal Lymphocyte activation
Cytokine, antigen, or bacterial cell wall
Antibody, Antibacterial peptide production, etc.
R
R
R
R
R
R
R
R
Ca^{++}
Endoplasmic reticulum


[Ca2+]i response to activation before and after treatment of Milk Fever
H2O2
CD3
Pretreat (n=5)
After Ca infusion (n=5)
0
1
2
3
4
5
Fold increase inFluo-4/Fura red


Lymphocyte activation during Hypocalcemia
Cytokine, antigen, or bacterial cell wall
R
Ca++
Endoplasmic reticulum


Lymphocyte activation during
Hypocalcemia
Cytokine, antigen, or bacterial cell wall
R
R
R
R
R
R
R
R
Ca++
Ca++
Ca++
Ca++
Endoplasmic
reticulum


Lymphocyte activation during
Hypocalcemia
Cytokine, antigen, or bacterial cell wall
R
R
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R
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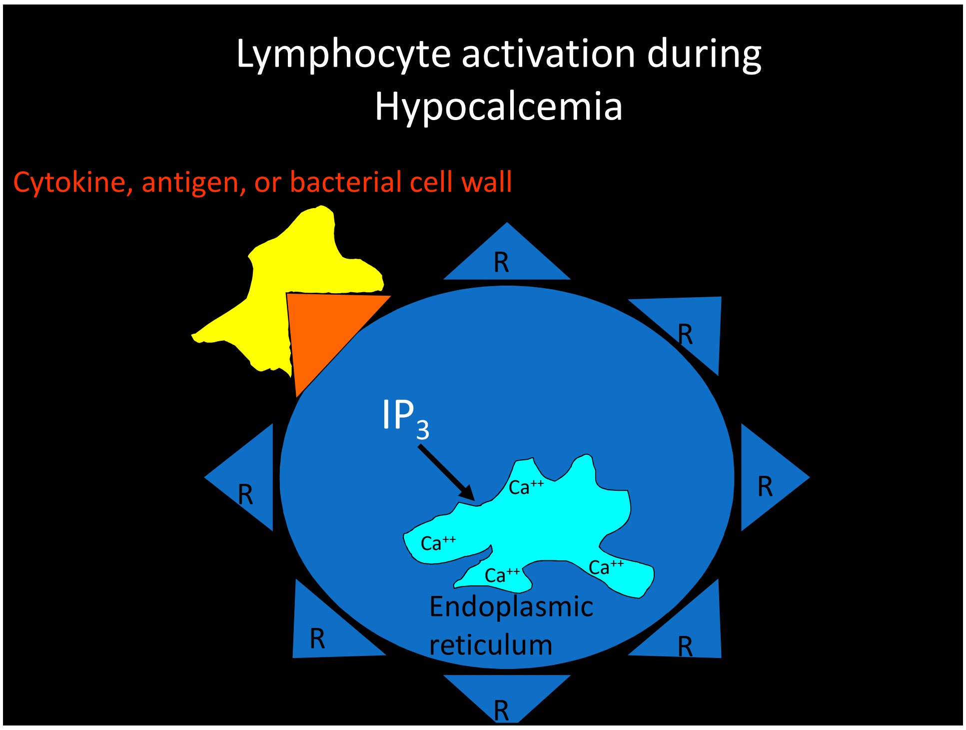
R
IP3
Ca++
Ca++
Ca++
Ca++
Endoplasmic
reticulum


Lymphocyte activation during Hypocalcemia
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R
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R
R
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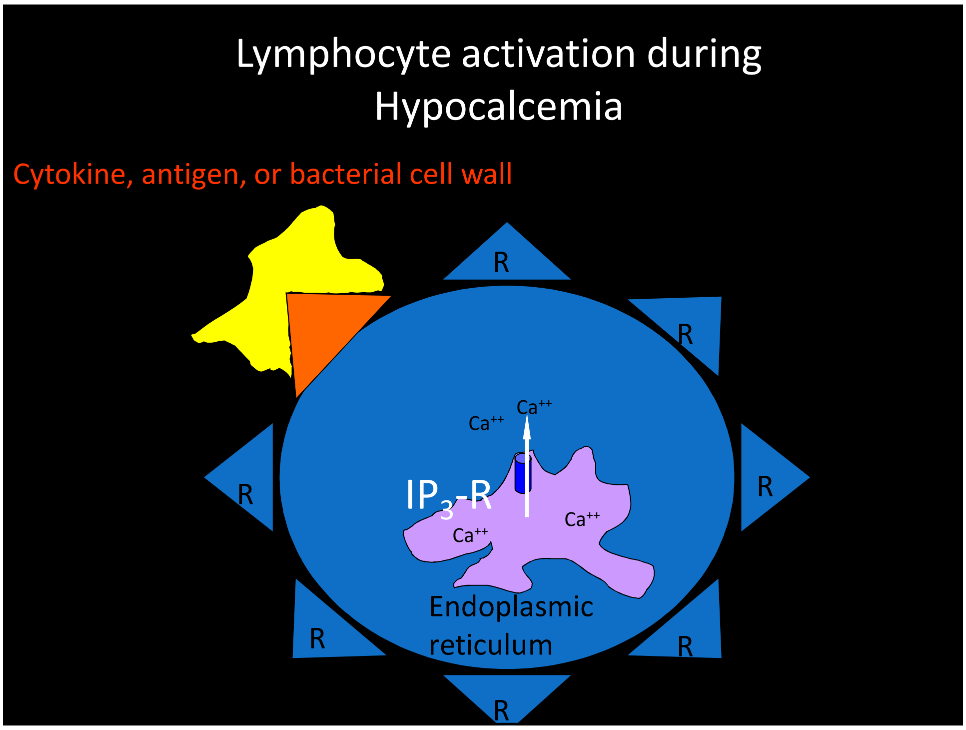
R
R
R
IP3
Ca++
Ca++
Ca++
Ca++
Endoplasmic reticulum


Lymphocyte activation during Hypocalcemia
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Ca++
Ca++
IP3-R
Ca++
Ca++
Endoplasmic reticulum

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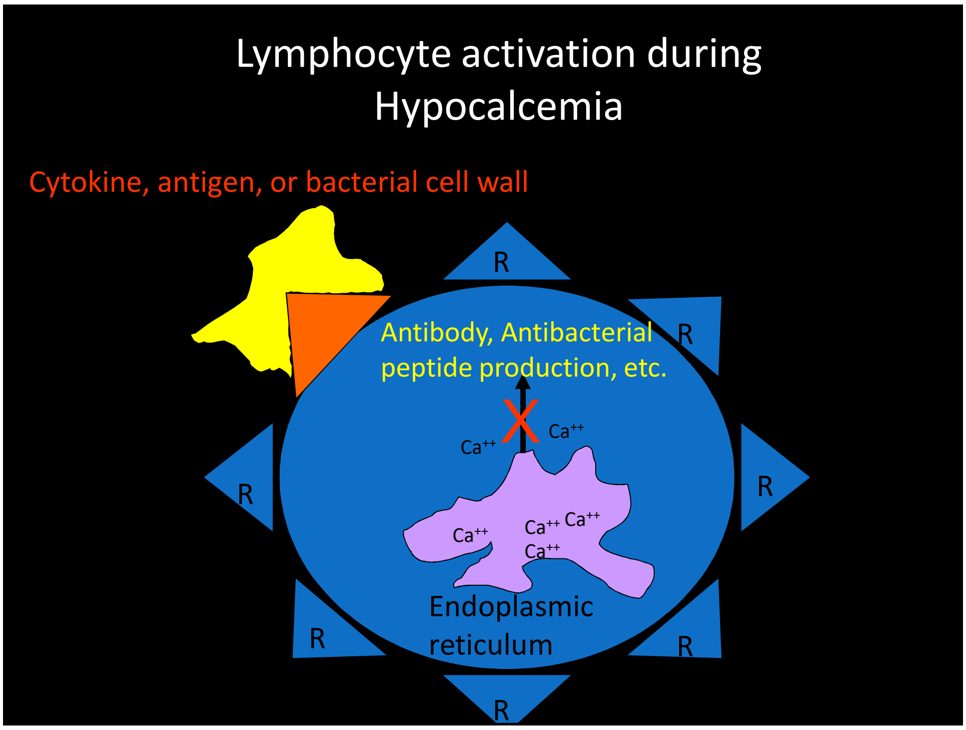


Ca Dynamics in the Periparturient Cow

Late Gestation

650 kg dairy cow needs to absorb:

7-8 g Ca to support daily maintenance requirement
= Endogenous fecal loss, urine loss

9-10 g Ca to support fetal skeleton development.

Total = 16-18 g Ca that must be restored to blood to maintain normal blood Ca concentrations

Primarily met by absorbing dietary Ca!

Ca Dynamics The Day of Calving

Maintenance – 7-8 g Ca

First Colostrum – 7.5 Kg X 2.3 g Ca / kg = 17.25 g Ca

Within 45 min of colostrum removal- Ca uptake by mammary = ¾ of 17.25 = 10-12 g Ca

2nd milking removal at 12 hrs – mammary sequestered 11 g Ca plus additional 3 g Ca (8.7 kg X 1.7 g Ca / kg= 14.8 g Ca)

Within 45 min of second milk removal - Ca uptake by mammary for next milk is another 8- 10 g Ca.

Total Ca loss from blood between calving and 14 hrs after calving can be 50 g Ca.

Increase in Ca Demand the first half day after calving

50 g Ca (post-calving ½ day) – 18 g Ca (precalving) =

~ 32 g Extra Ca that must be brought into blood to avoid hypocalcemia

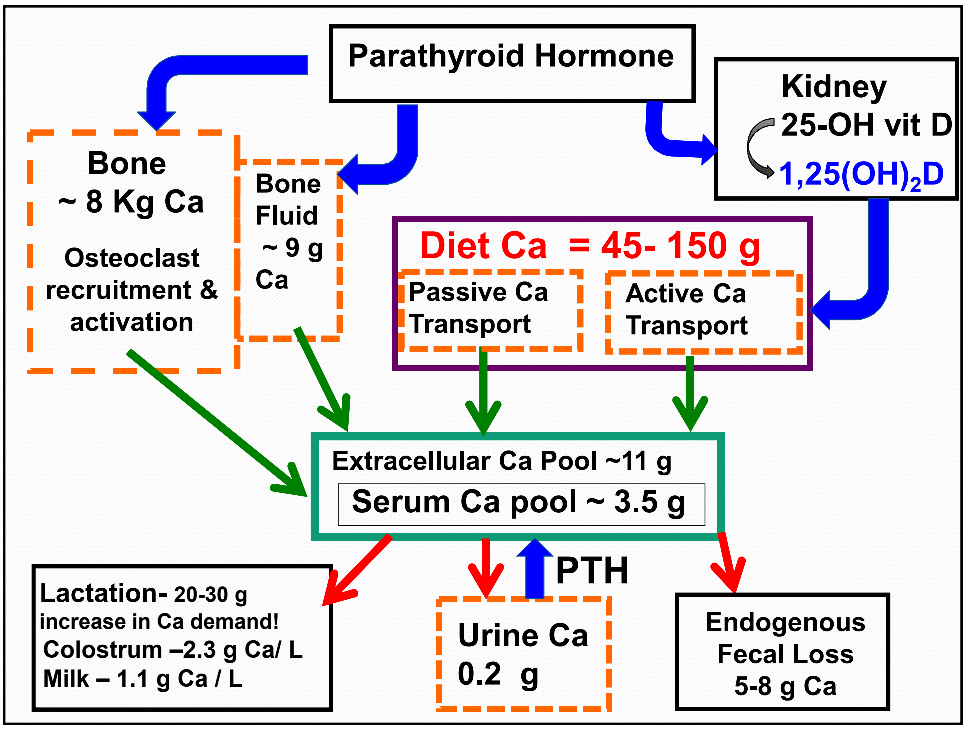
Ca Homeostasis Begins With The Parathyroid Gland

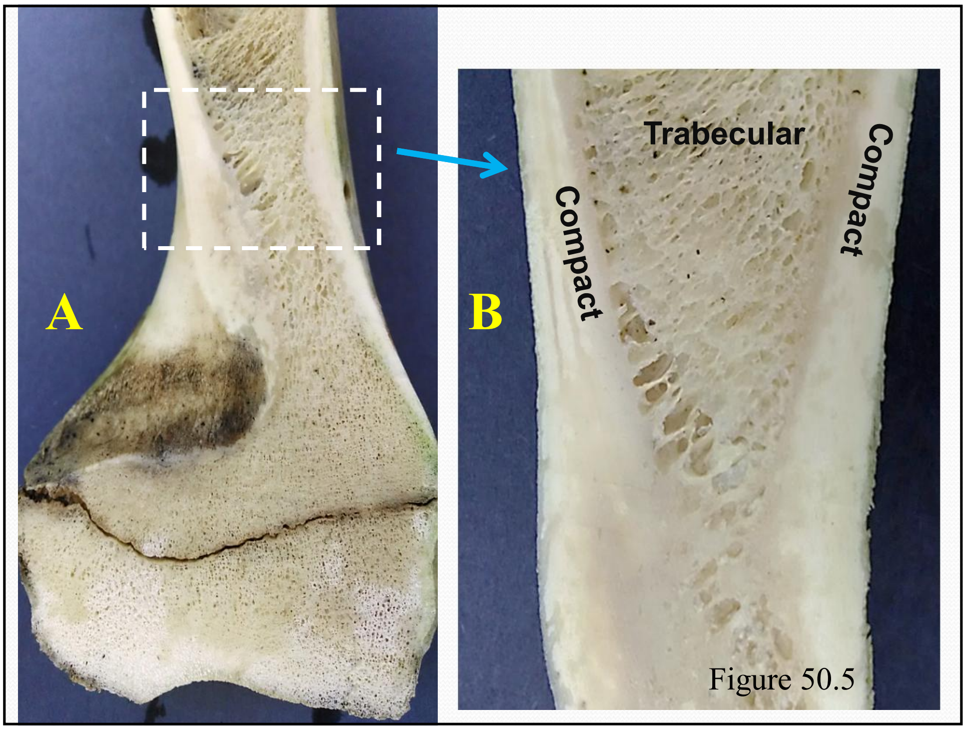
Parathyroid cells have a Ca- Sensing G-Protein Coupled receptor on their surface.

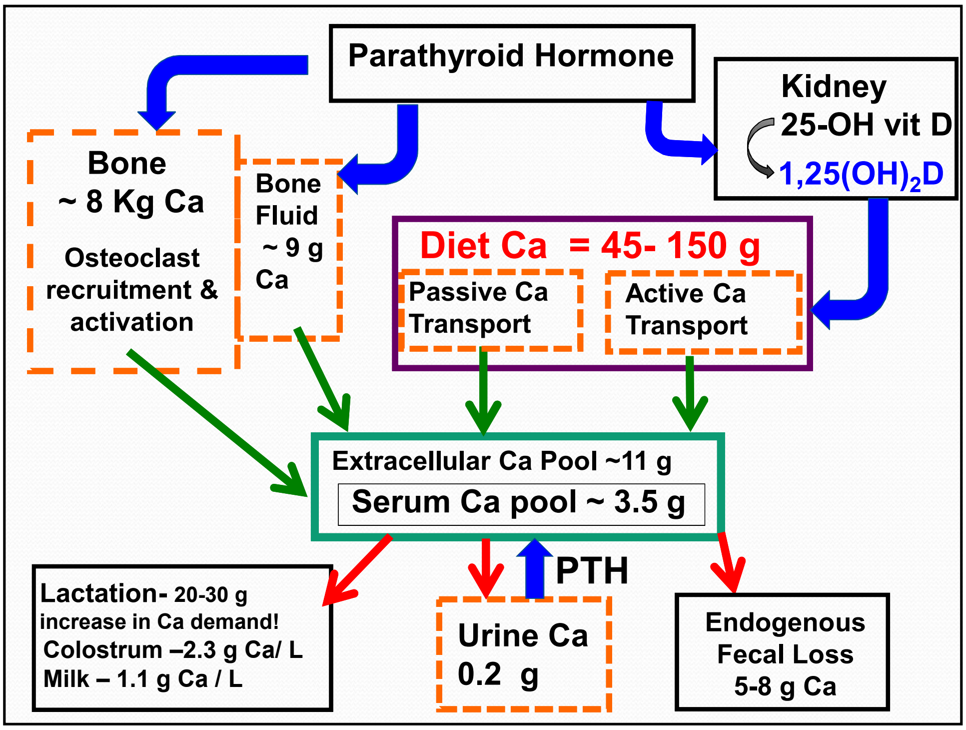
Lack of extracellular ionized Ca++ bound to the Ca-Sensing receptor elicits Parathyroid Hormone Secretion

Parathyroid Hormone Targets

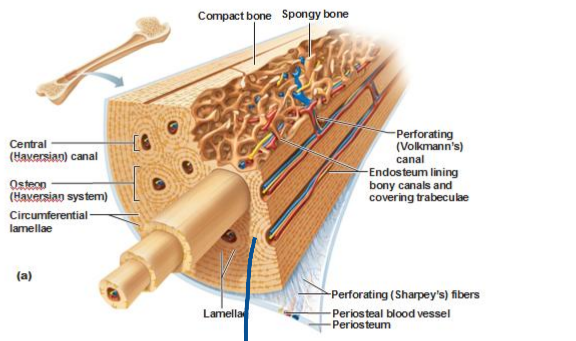
Kidney tubule cells
Bone osteocytes and osteoblasts
Salivary glands




A
B
Trabecular
Compact
Compact
Figure 50.5

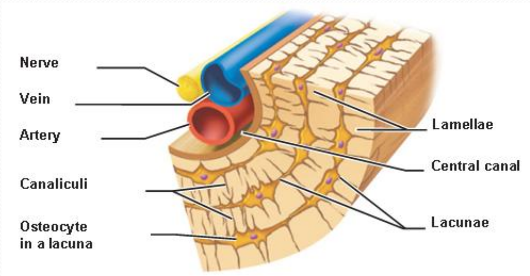

Parathyroid Hormone
Kidney
25-OH vit D
1,25(OH)2D
Bone
~ 8 Kg Ca
Osteoclast recruitment & activation
Bone Fluid ~ 9 g Ca
Diet Ca = 45- 150 g
Passive Ca Transport
Active Ca Transport
Extracellular Ca Pool ~11 g
Serum Ca pool ~ 3.5 g
PTH
Lactation- 20-30 g increase in Ca demand!
Colostrum –2.3 g Ca/ L
Milk – 1.1 g Ca / L
Urine Ca 0.2 g
Endogenous Fecal Loss 5-8 g Ca

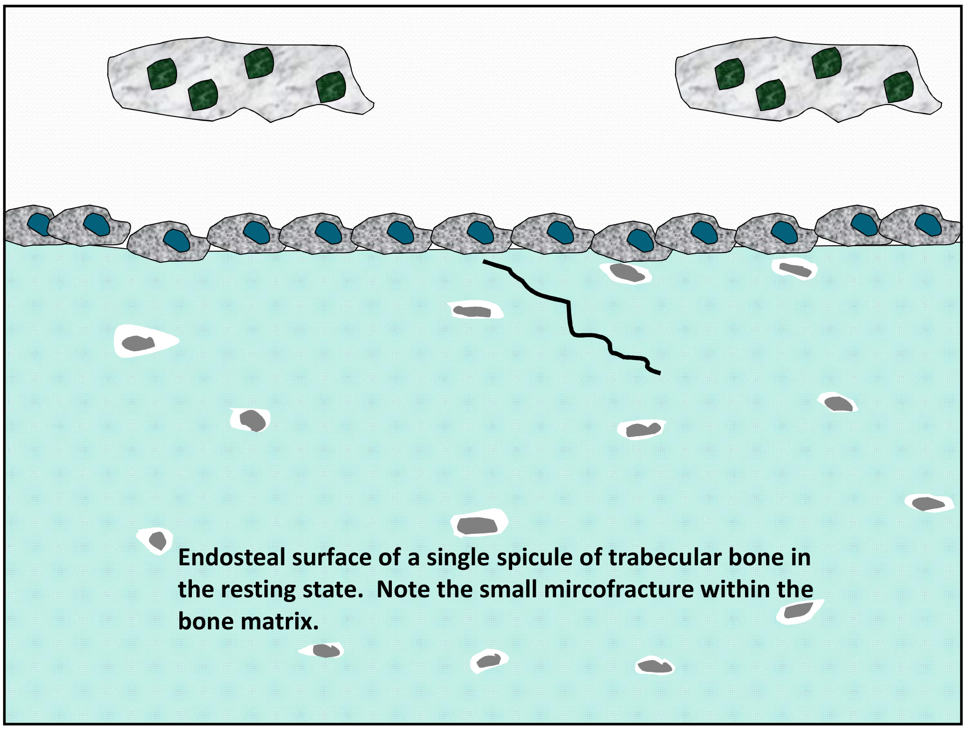
Microscopic Structure of Compact Bone

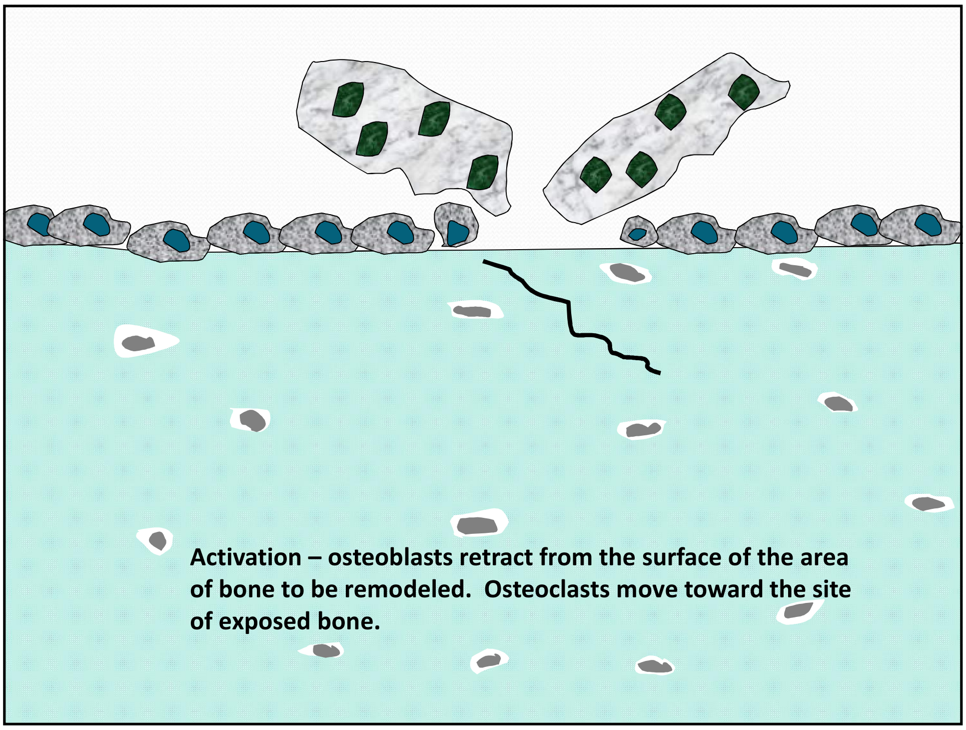


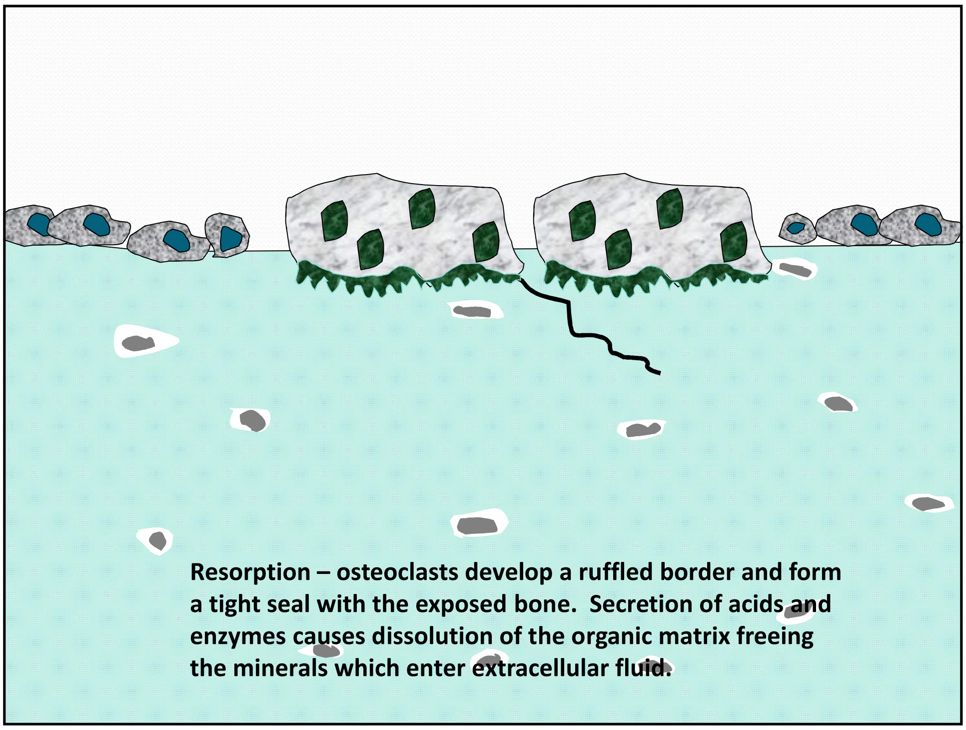
Osteocytic Osteolysis

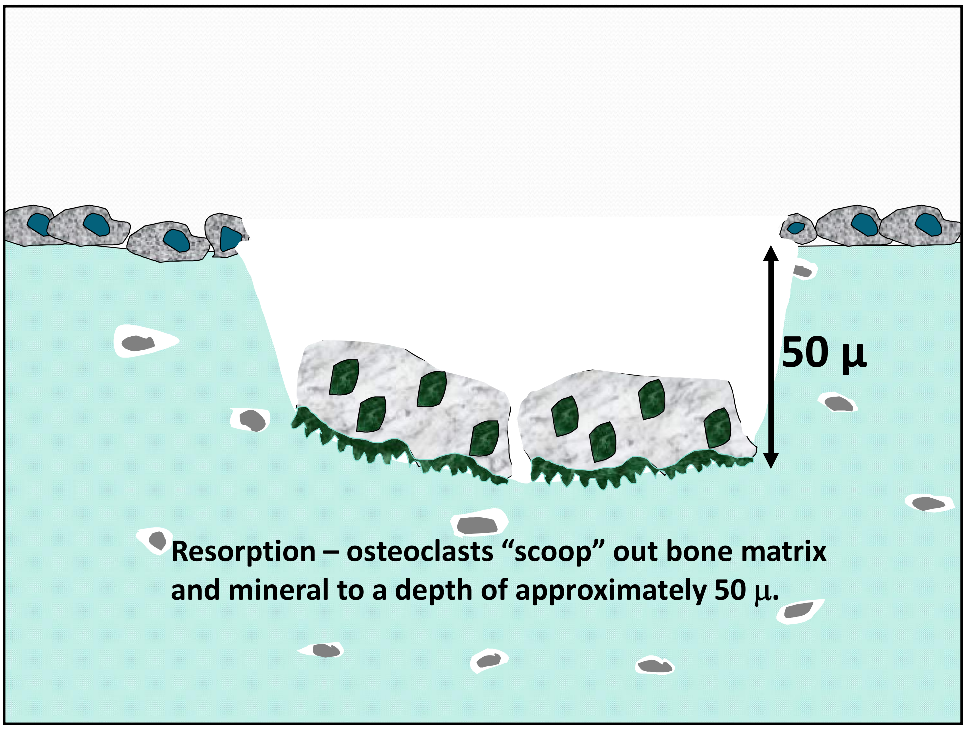
Ca within fluid surrounding each osteocyte and within canaliculi is pumped into blood under control of PTH

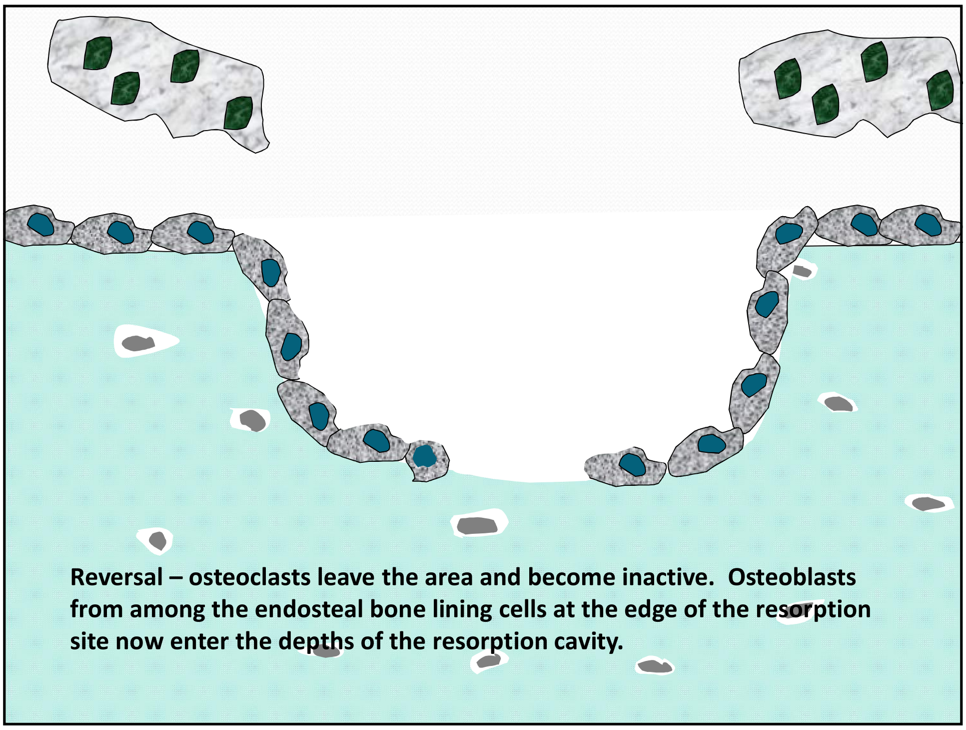





Activation – osteoblasts retract from the surface of the area of bone to be remodeled. Osteoclasts move toward the site of exposed bone.


Resorption – osteoclasts develop a ruffled border and form a tight seal with the exposed bone. Secretion of acids and enzymes causes dissolution of the organic matrix freeing the minerals which enter extracellular fluid.


50 µ
Resorption – osteoclasts “scoop” out bone matrix and mineral to a depth of approximately 50 µ.


Reversal – osteoclasts leave the area and become inactive. Osteoblasts from among the endosteal bone lining cells at the edge of the resorption site now enter the depths of the resorption cavity.

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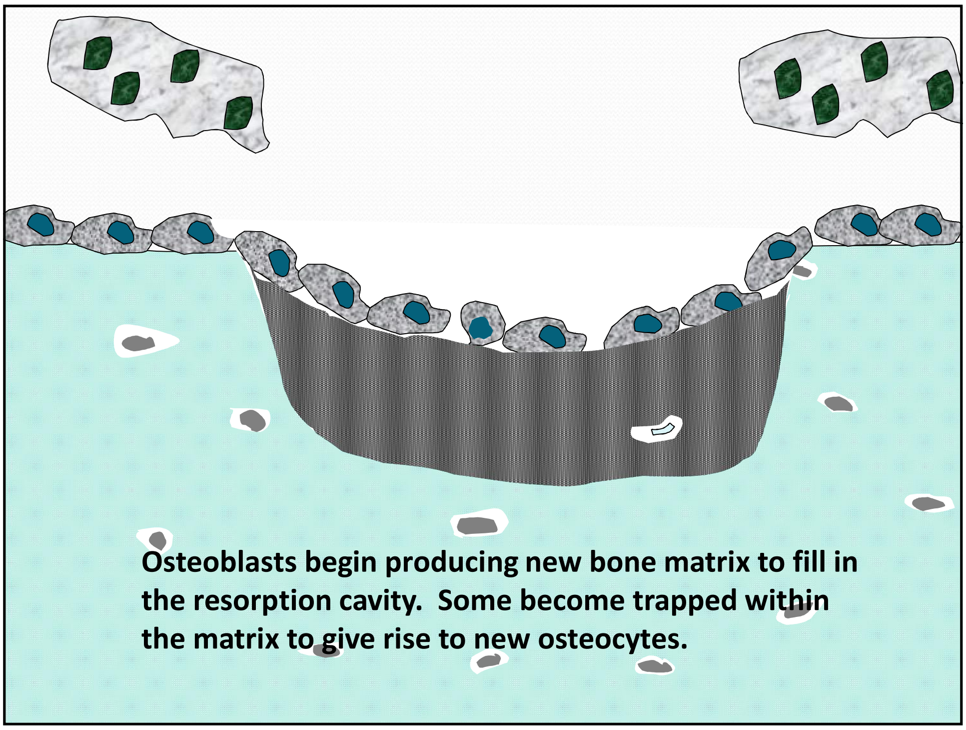
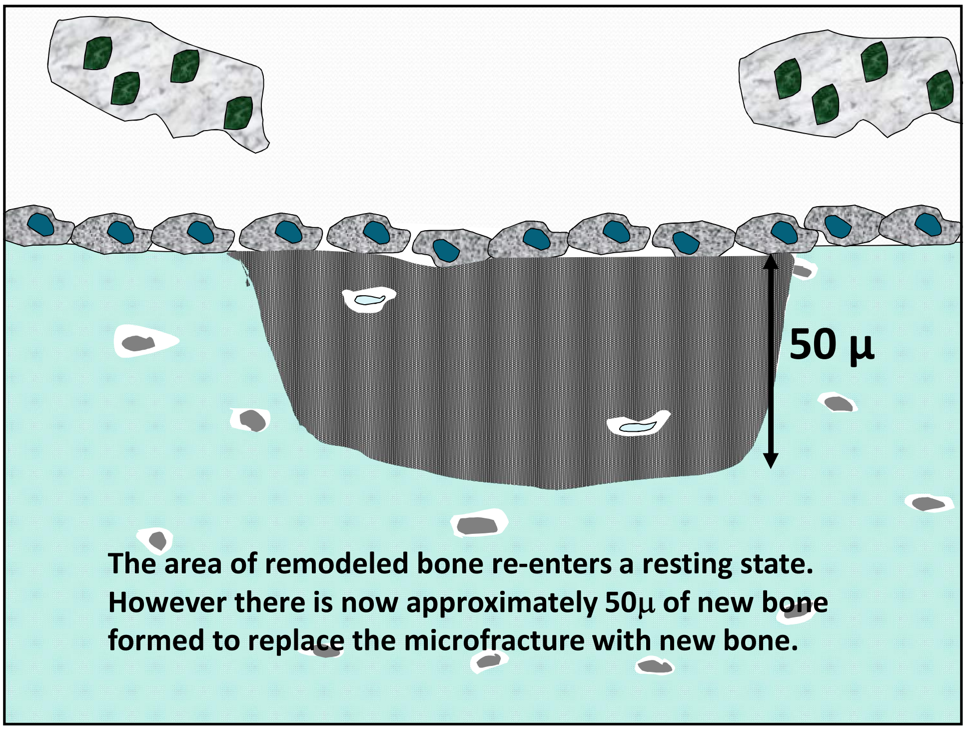
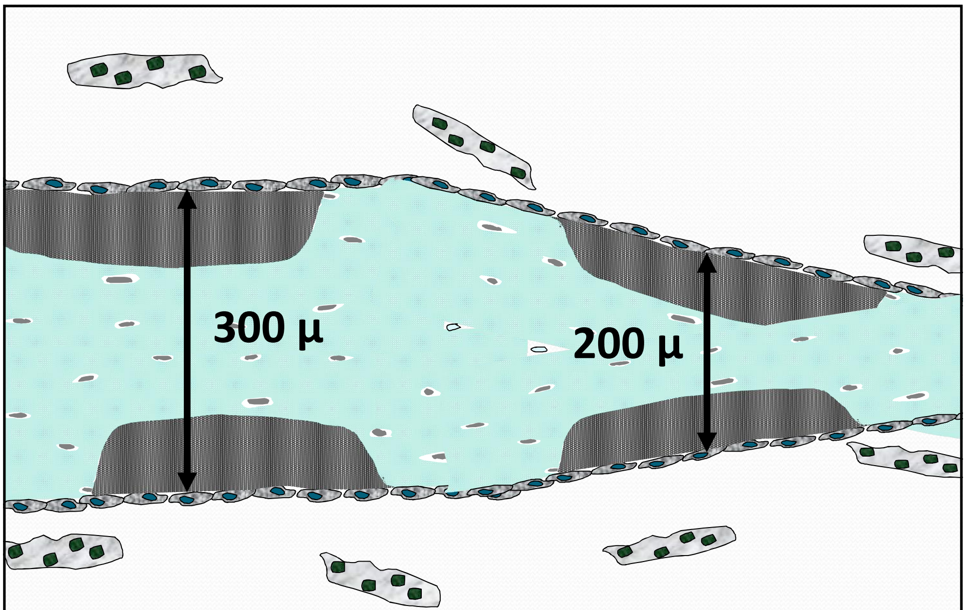
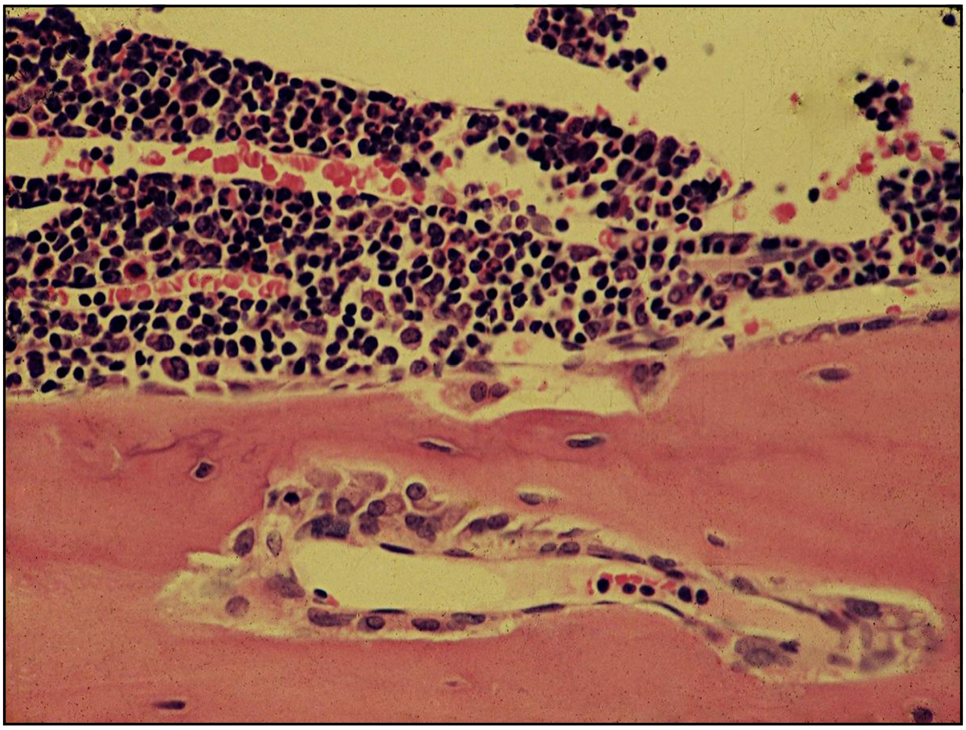






Normal Bone Remodeling – "Old" bone resorbed is replaced by New



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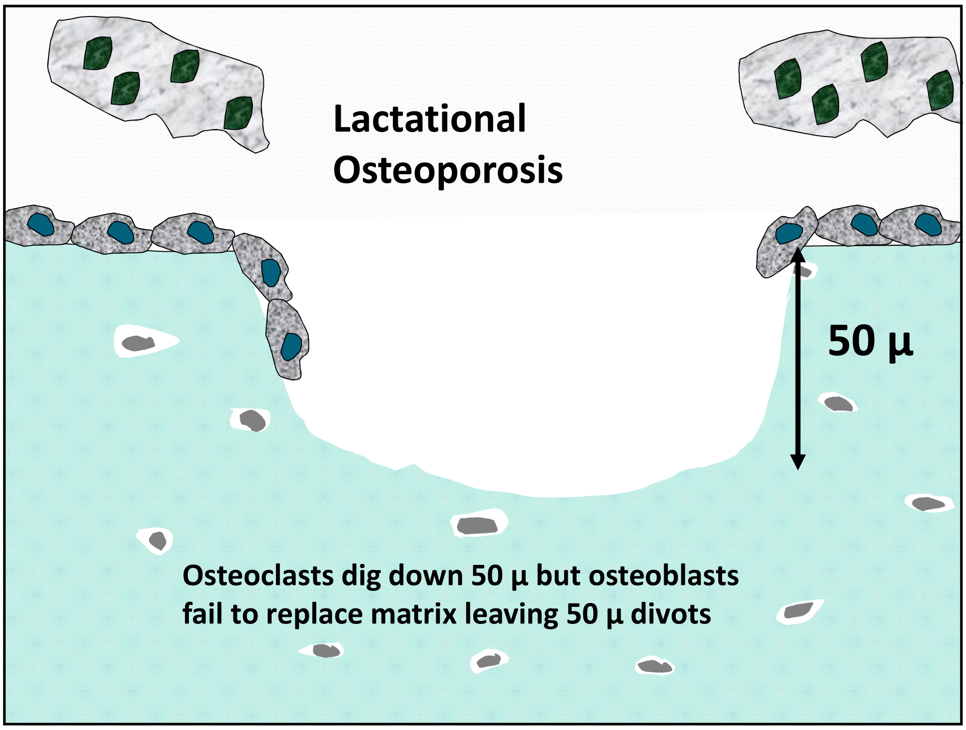
Lactational osteoporosis

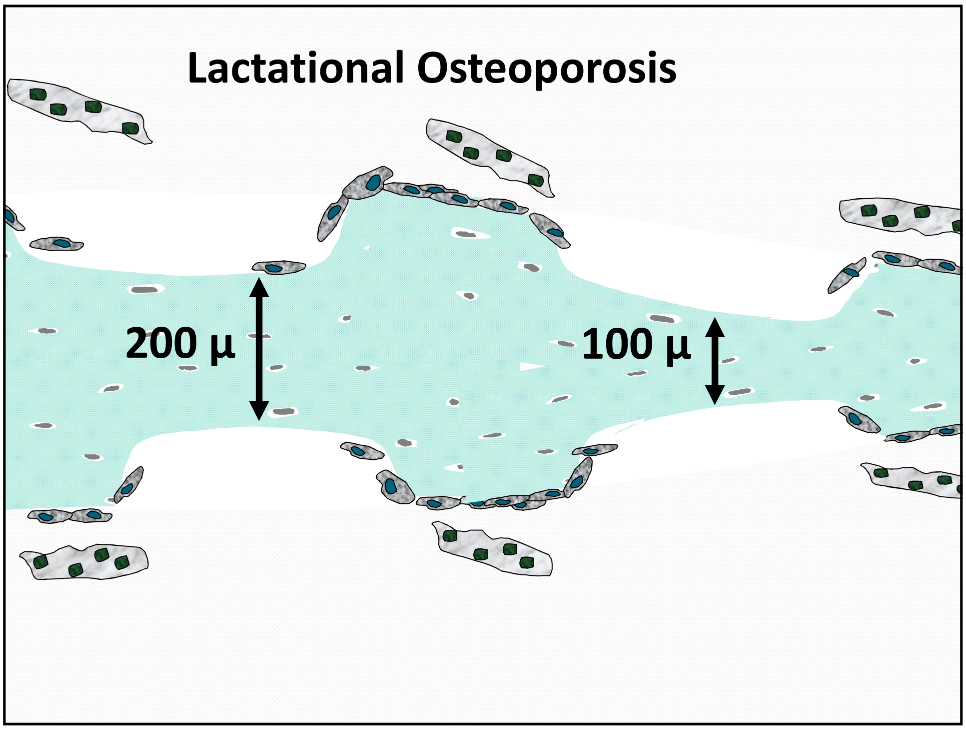
The need for calcium to support lactation causes a “disconnect” between the resorptive and reversal phases of the remodeling process. Mediated by PTH and perhaps PTH-rP (beyond first week of lactation?)!!

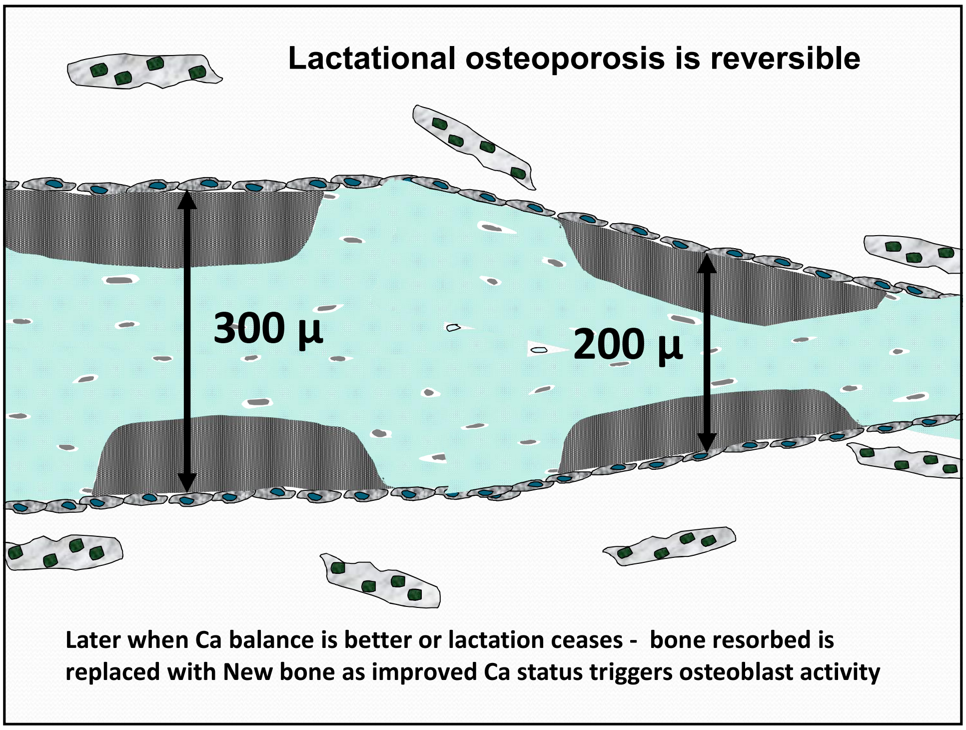
This occurs to some extent in all mammals even if diet calcium is adequate. PTH-rP made by mammary gland!!

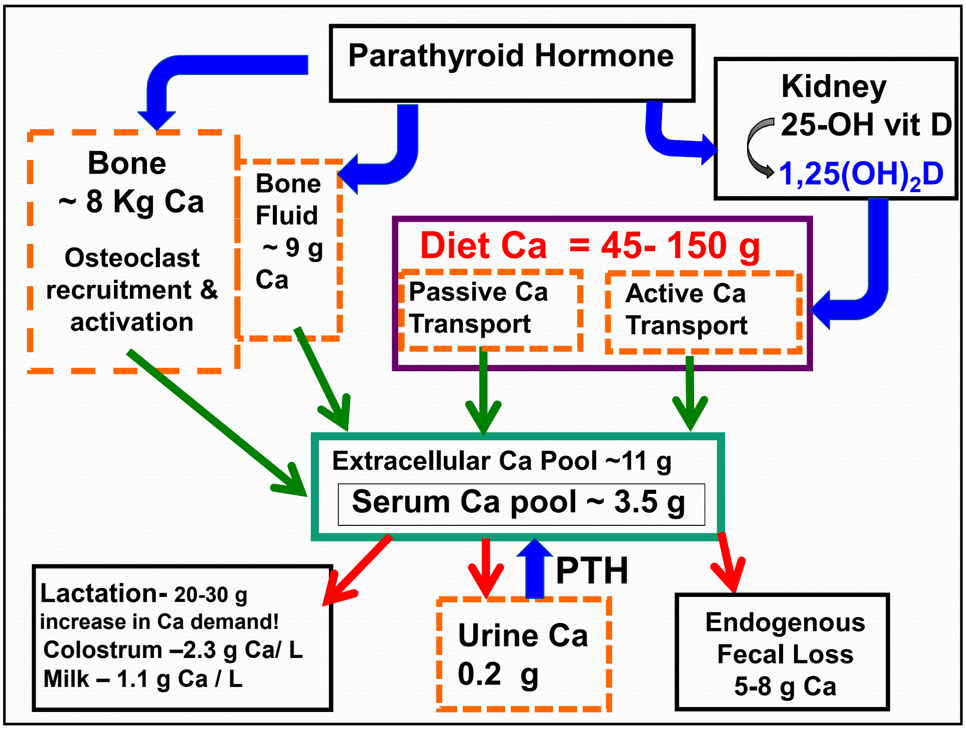
This resorbed bone is not replaced until some later point when dietary calcium absorption is sufficient to sustain calcium requirements of milk production, growth etc. About 5 weeks in a cow. By that point 10-13% of skeletal Ca will have been removed.

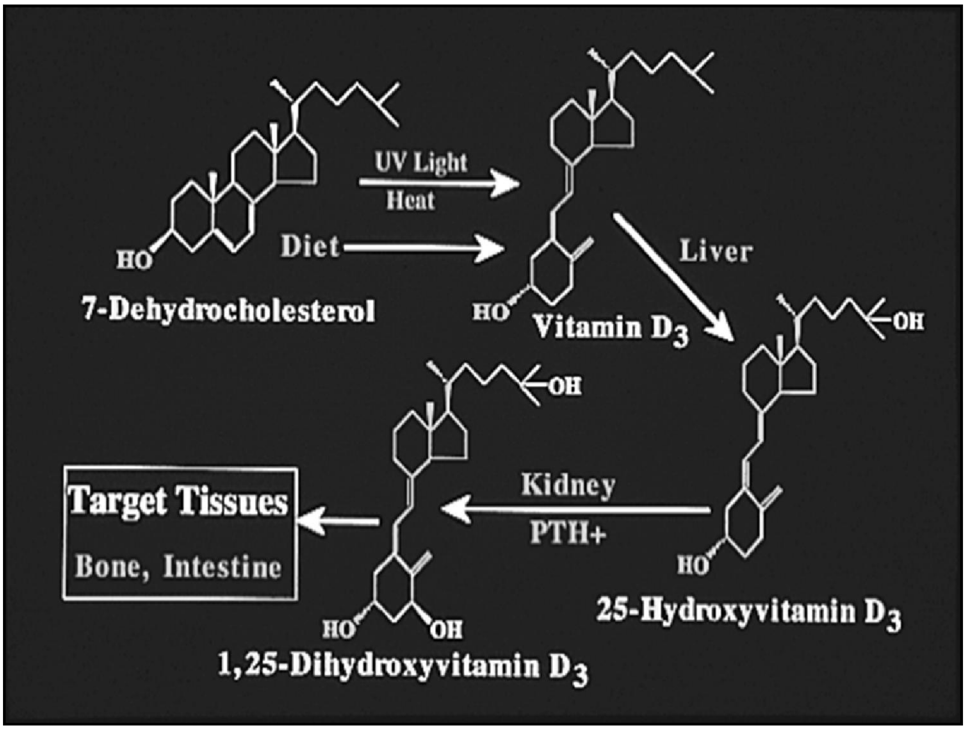
The resorbed bone can be successfully replaced in late lactation!!?

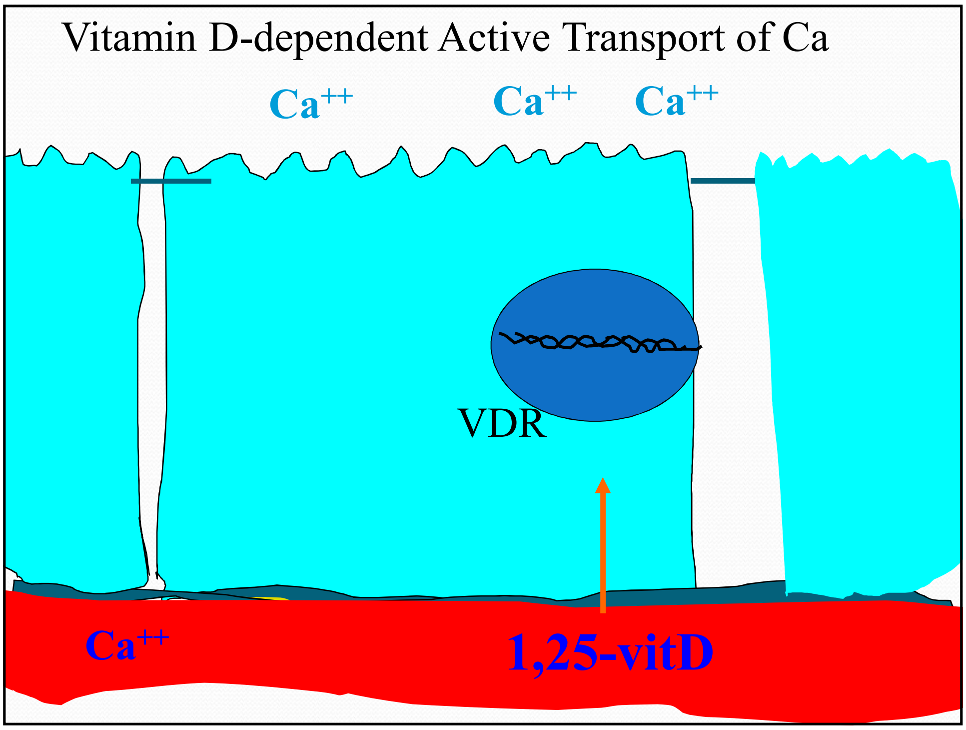


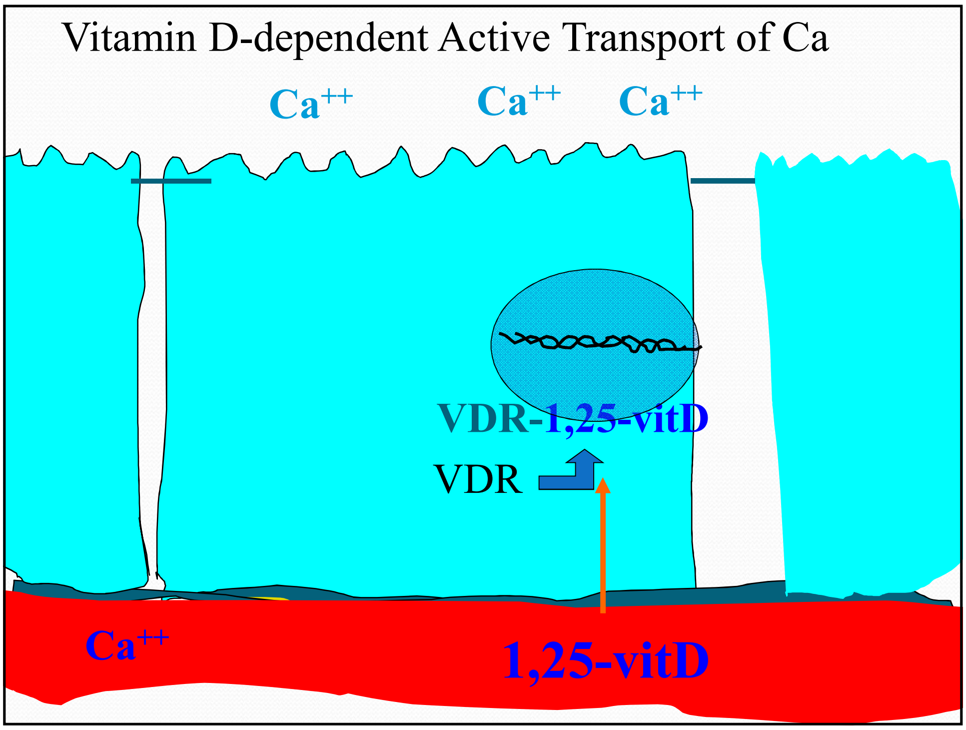

Lactational Osteoporosis
200 µ
100 µ

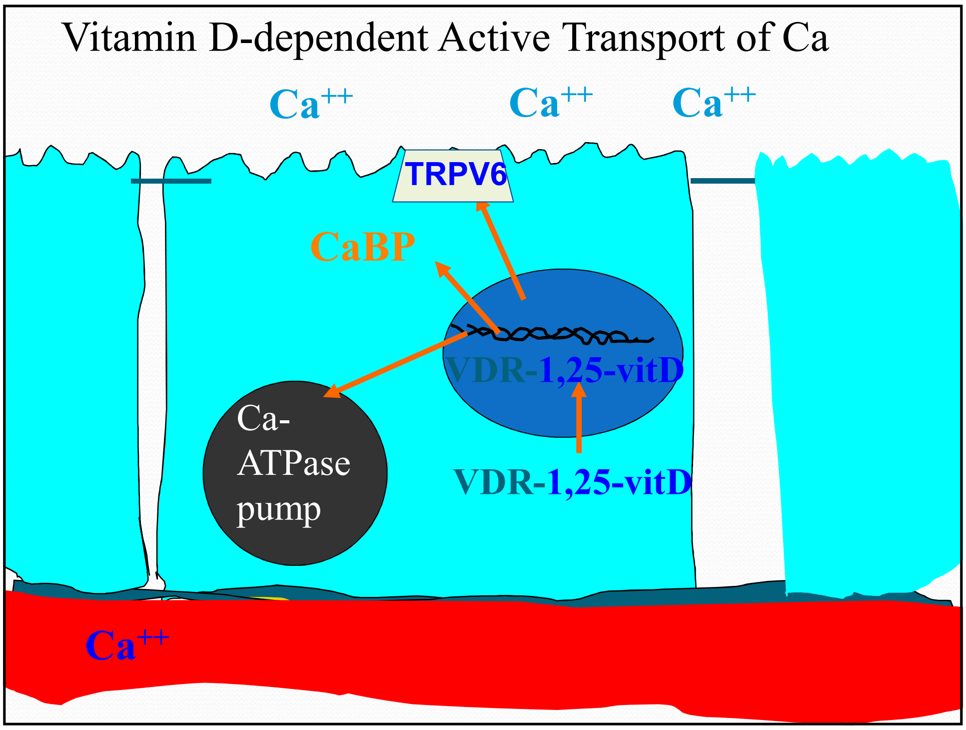

Lactational osteoporosis is reversible
300 µ
200 µ
Later when Ca balance is better or lactation ceases - bone resorbed is replaced with New bone as improved Ca status triggers osteoblast activity

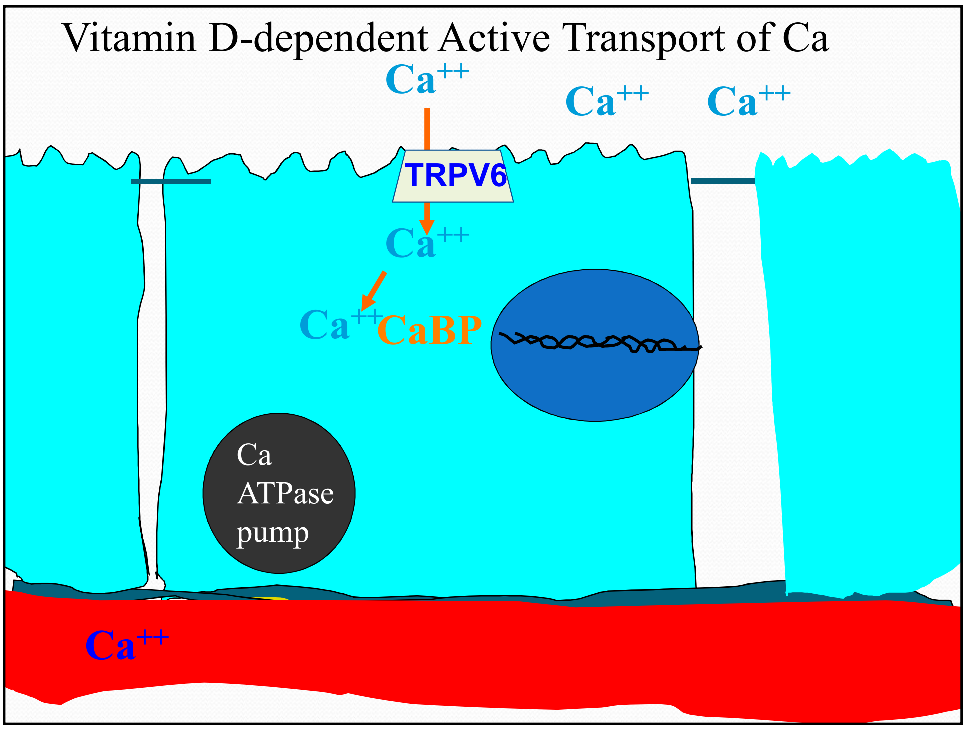

Parathyroid Hormone
Kidney
25-OH vit D
$1,25(OH)_2D$
Bone
~ 8 Kg Ca
Osteoclast recruitment & activation
Bone Fluid
~ 9 g Ca
Diet Ca = 45- 150 g
Passive Ca Transport
Active Ca Transport
Extracellular Ca Pool ~11 g
Serum Ca pool ~ 3.5 g
PTH
Lactation- 20-30 g increase in Ca demand!
Colostrum –2.3 g Ca/ L
Milk – 1.1 g Ca / L
Urine Ca
0.2 g
Endogenous Fecal Loss
5-8 g Ca

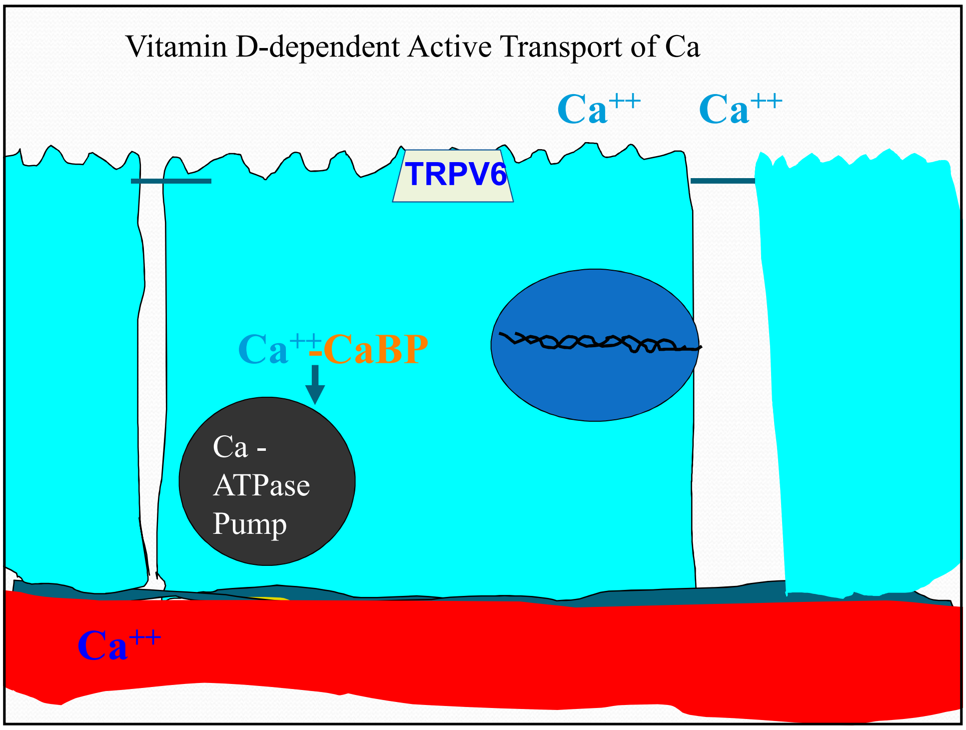

UV Light
Heat
Diet
HO
7-Dehydrocholesterol
Liver
HO
Vitamin D_3
OH
OH
Target Tissues
Bone, Intestine
Kidney
PTH+
HO
25-Hydroxyvitamin D_3
HO
OH
1,25-Dihydroxyvitamin D_3

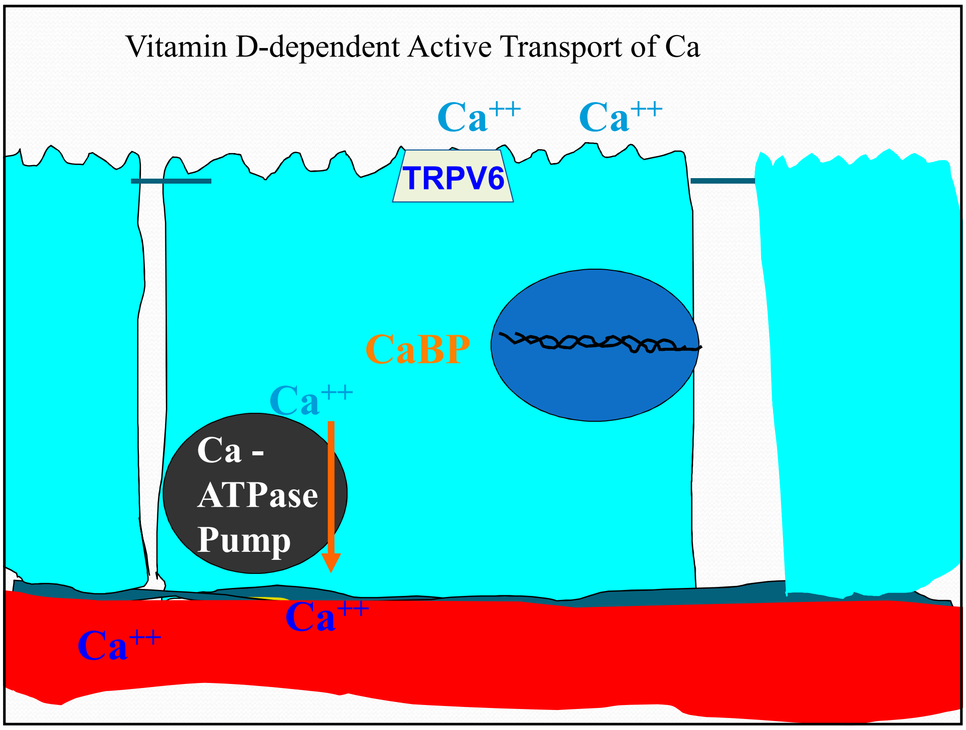

Vitamin D-dependent Active Transport of Ca
Ca++
Ca++
Ca++
VDR
Ca++
1,25-vitD

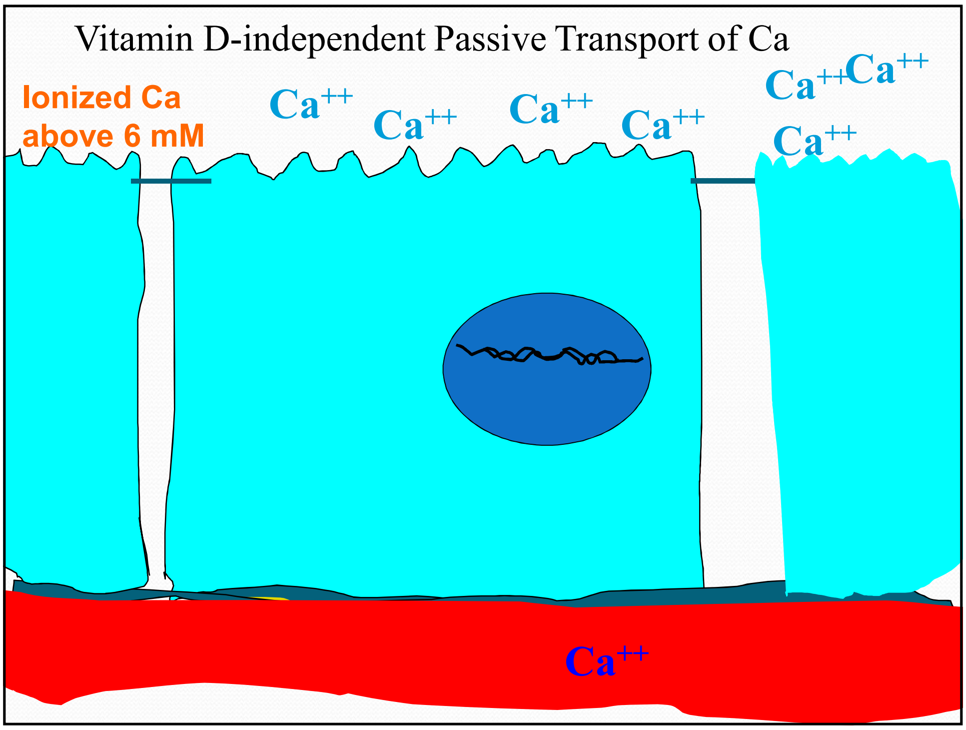

Vitamin D-dependent Active Transport of Ca
Ca++
Ca++
Ca++
VDR-1,25-vitD
VDR
Ca++
1,25-vitD

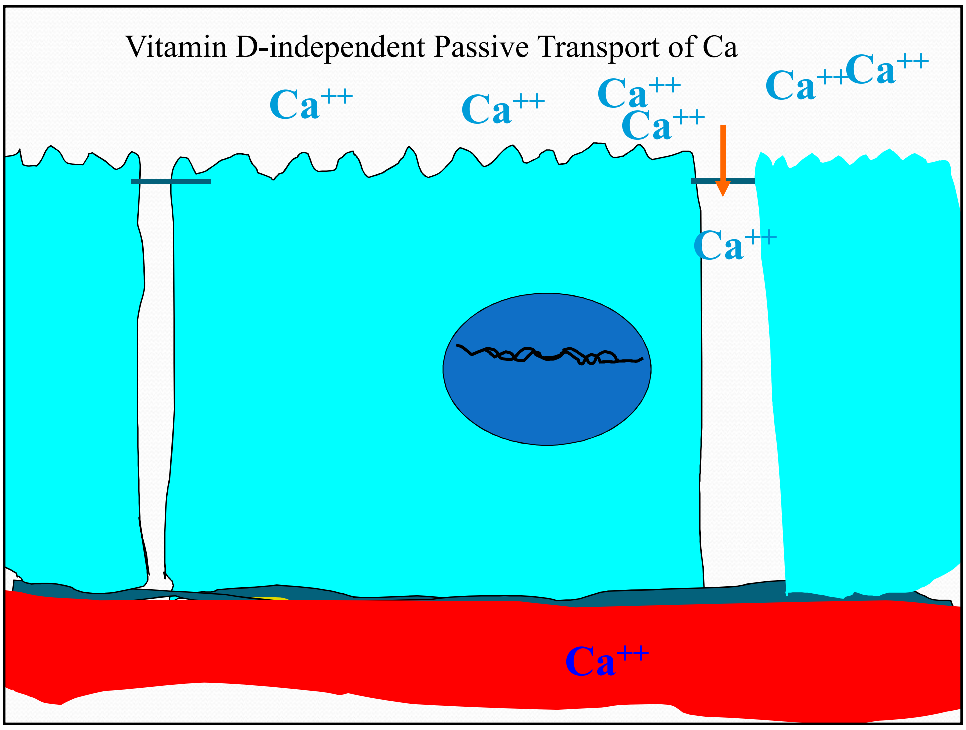

Vitamin D-dependent Active Transport of Ca
Ca++
Ca++
Ca++
TRPV6
CaBP
VDR-1,25-vitD
Ca-
ATPase
pump
VDR-1,25-vitD
Ca++

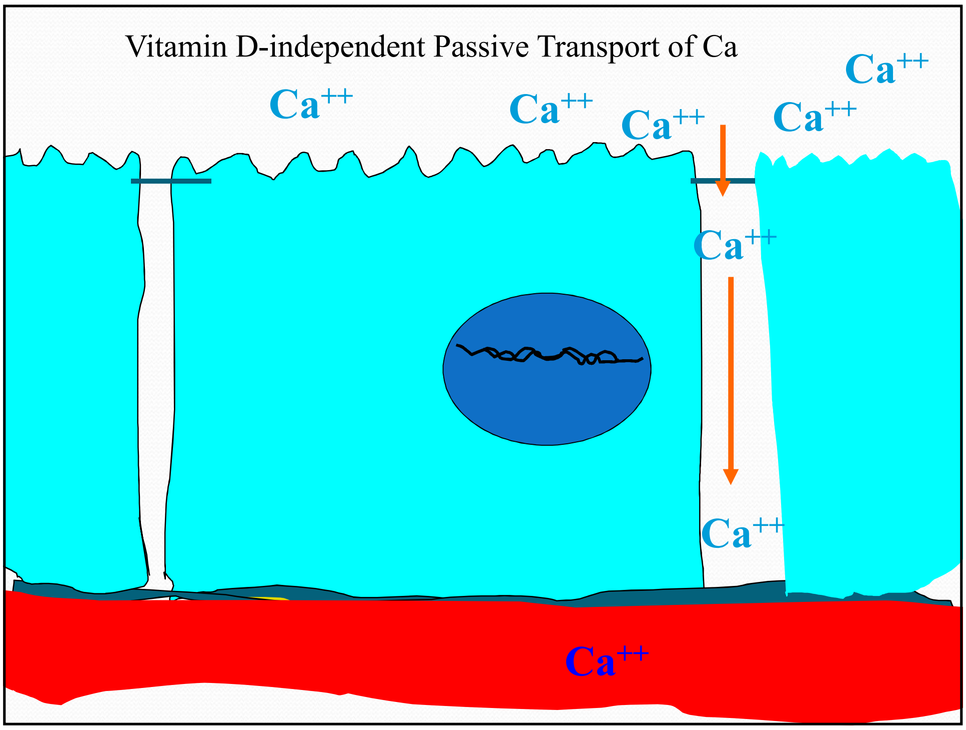

Vitamin D-dependent Active Transport of Ca
Ca++
Ca++
Ca++
TRPV6
Ca++
Ca++CaBP
Ca
ATPase
pump
Ca++

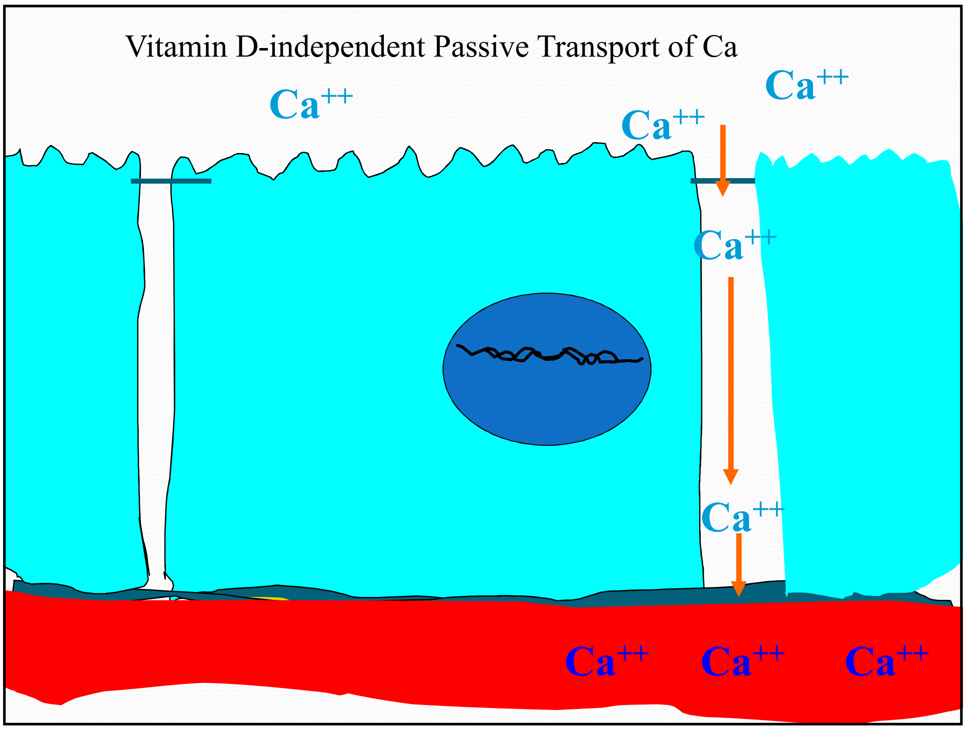

Vitamin D-dependent Active Transport of Ca
Ca++
Ca++
TRPV6
Ca++-CaBP
Ca -
ATPase
Pump
Ca++


Vitamin D-dependent Active Transport of Ca
Ca++
Ca++
TRPV6
CaBP
Ca++
Ca -
ATPase
Pump
Ca++
Ca++


Vitamin D-independent Passive Transport of Ca
Ionized Ca
above 6 mM
Ca++
Ca++
Ca++
Ca++
Ca++Ca++
Ca++
Ca++


Vitamin D-independent Passive Transport of Ca
Ca++
Ca++
Ca++
Ca++
Ca++Ca++
Ca++
Ca++


Vitamin D-independent Passive Transport of Ca
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++


Vitamin D-independent Passive Transport of Ca
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++

Ca Homeostasis – How long does it take to react?

Kidney

PTH promotes Ca reabsorption from tubular fluid within minutes (but normally brings <1 g Ca into blood).

Renal production of 1,25-dihydroxyvitamin D. Plasma 1,25-dihydroxyvitamin D can increase within 8*-16 hrs, and requires another 12-24 hrs for significant increase in proteins involved in Ca absorption to be produced.

Bone

Osteocytic Osteolysis – minutes to a few hours (~ 9 g Ca***)

Osteoclastic Resorption – 36-96 hr, depending on age of cow and diet . Can bring 800 – 1200 g Ca into blood

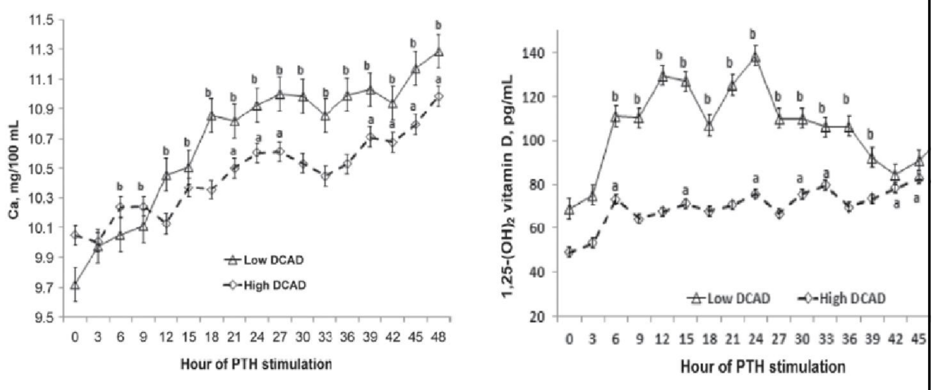
Why doesn't Ca Homeostasis work for all cows???

Aged cows lose vitamin D receptors in intestine

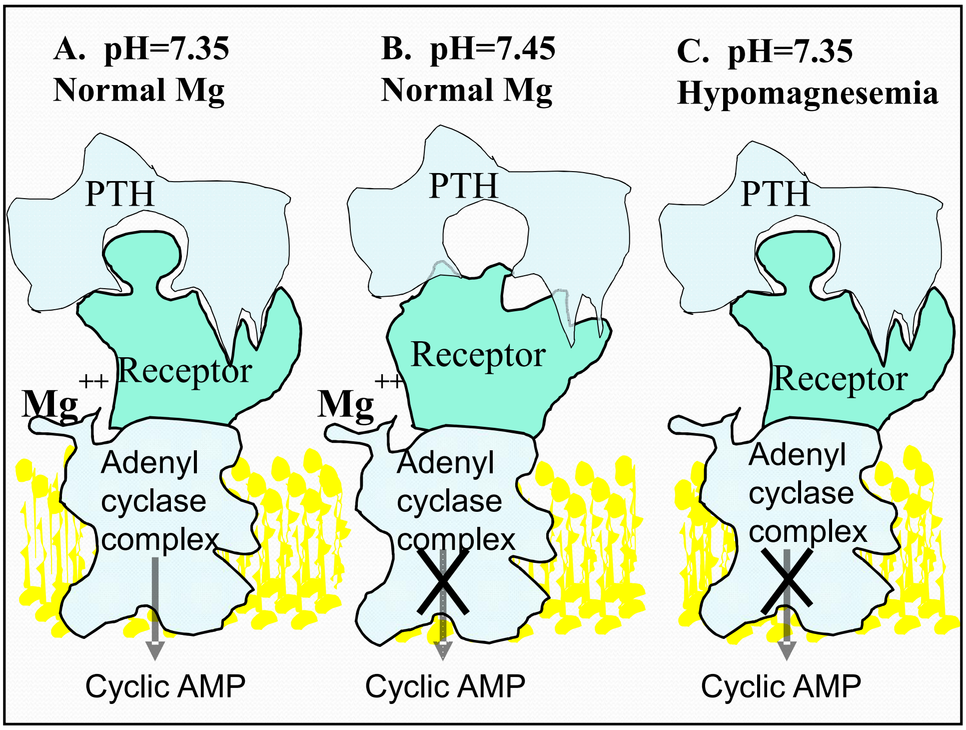
Aged cows have fewer sites of active bone resorption (fewer osteoclasts) capable of responding to PTH rapidly

BLOOD pH AFFECTS TISSUE RESPONSIVENESS TO PTH!

Cows fed high DCAD diets become alkalotic and fail to respond to PTH stimulation by increasing blood Ca and 1,25-(OH)2 Vit D production. THIS CAUSES SEVERE HYPOCALCEMIA



Goff et al



Acid-Base Physiology & Strong Ions

All solutions must be electrically neutral ., ie.

The number of + charges in a solution must equal the number of - charges in a solution.

Neutral solutions have an equal number of H^+ and OH^- particles in them. This results in a pH of 7.0

If K^+ ions are added to the solution it necessitates a loss of H^+ ions and a simultaneous increase in OH^- in the solution to achieve electroneutrality.

The pH increases.

Diet Cation-Anion Difference (DCAD) & Acid-Base Status

Diet Cations (Na^+, K^+, Ca^{++}, Mg^{++}, NH_4^+) absorbed into the blood will alkalinize the blood

Diet Anions (Cl^- , SO_4^{--} , PO_4^{--}) absorbed into the blood will acidify the blood.

NaCl has equal numbers of + and - charges

Both Na^+ and the Cl^- are absorbed into the blood with nearly 100% efficiency.
The blood gains an equal number of + and - charges.
NO CHANGE in Electrical charge = NO CHANGE in pH!!!

$CaCl_2$ also has an equal number of + and – charges

The Cl^- is absorbed with nearly 100% efficiency into the blood.
Less than 20% of the Ca in the salt is absorbed into the blood.

More – charges enter the blood than do + charges.
The blood becomes more negative necessitating a rise in H^+ = lower pH = More acidic blood

Milk Fever Prevention Strategies

1. ***Avoid high potassium forages for close-up cows so cows are less alkaline***
2. Add anions (Cl or Sulfate) to diet to reduce blood (and urine) pH.
3. Diet Mg = 0.4% must be available to cow

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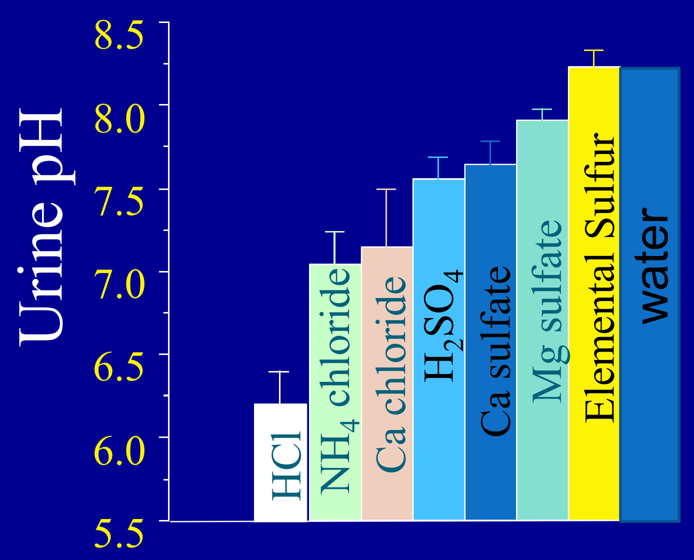
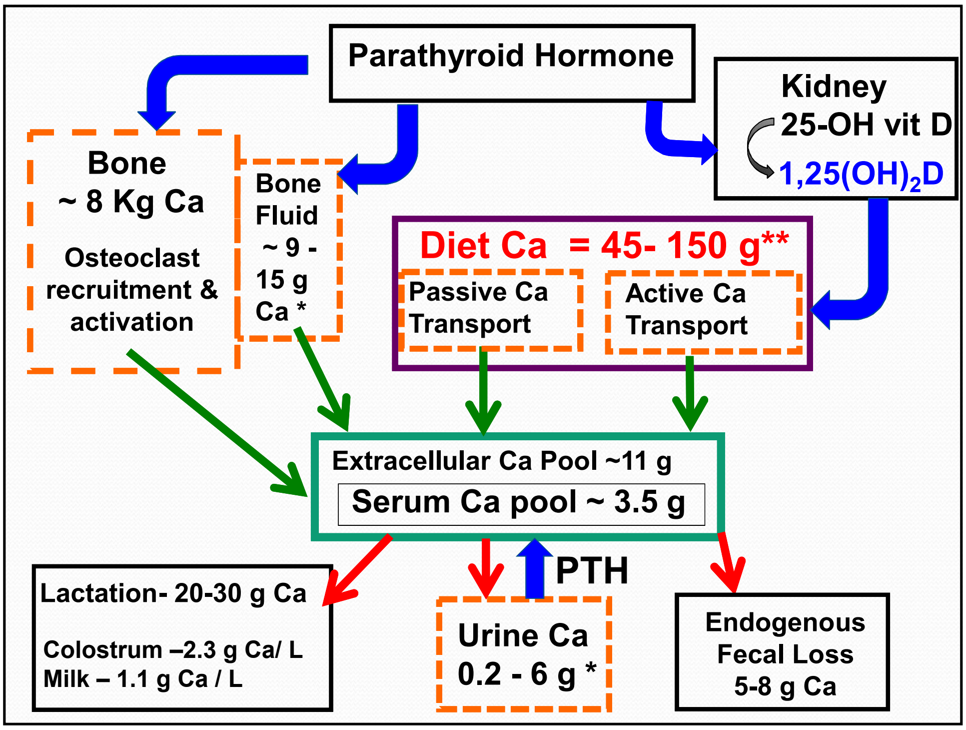
2 Eq of each anion source fed





DCAD Equations

Most Commonly Used Equation

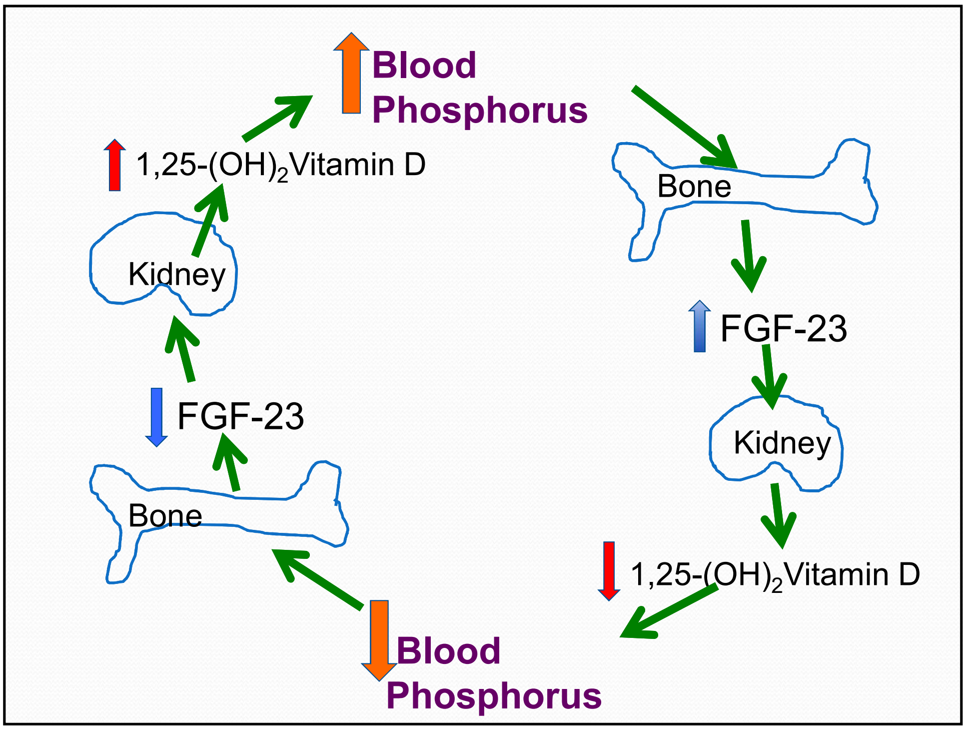
(mEq Na + mEq K) – (mEq Cl + mEq S)

Corrected for lower sulfate absorption

(mEq Na + mEq K) – (mEq Cl + 0.6 mEq S)

Minerals/DCAD for Close-up Diets

- Phos at .30-.35% , or lower???
- Mg at .4% to use passive absorption!!
- S between .22 and .4%
- Ca at .85-1.3% ??
- Na at .1-.12%
- K as close to 1% as possible
- Enough Chloride to ↓ urine pH.



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HOW MUCH Chloride do I add to the diet?

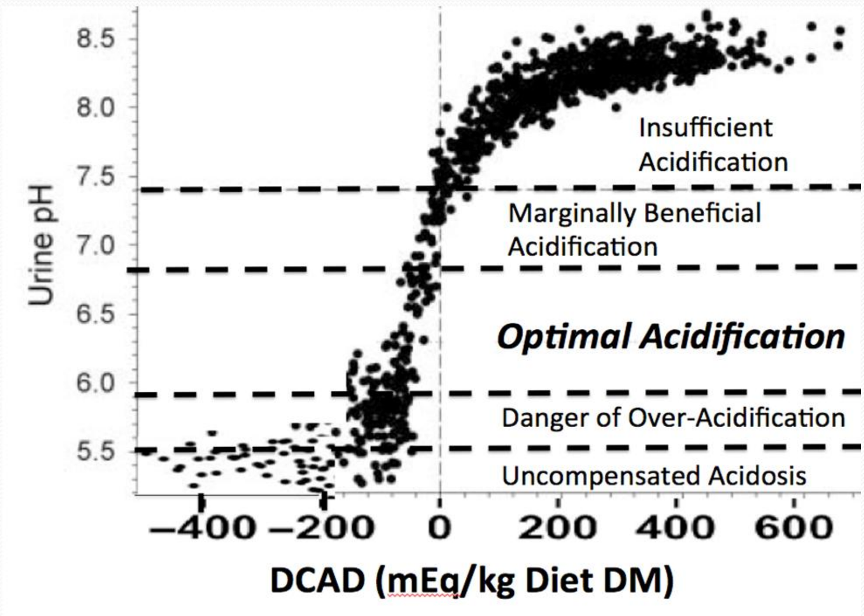
Enough to bring urine pH between 6.2 and 6.8 the week before calving. (Jersey target= 5.8-6.2)

When urine pH is below 5.3 in the cows you may have caused an uncompensated metabolic acidosis = trouble!!!!!

Thumbrule To Get Started with Anions

% Chloride needed = % K - 0.5

Example -If diet K is 1.3% then bring diet to 0.8 % Cl and check urine pH to fine tune diet



Adapted from Constable et al., 2017 and Charbonneau et al., 2006

Magnesium

Adult Ruminants absorb Mg across rumen wall ! Mg insoluble at rumen pH is NOT available.

- ***Active transport*** process efficient with low diet Mg BUT EASILY POISONED BY DIET K AND NITROGEN
- Second ***passive transport*** system exists, but requires high concentration of ionized Mg in rumen fluid to work

Keep diet Mg at 0.4% prepartum and early post-partum to take advantage of passive transport of Mg across rumen wall

MAKE SURE Mg Source is AVAILABLE to the cow. Finely ground, not overly calcined!

Magnesium sources

Pre-calving
- using $MgSO_4$ or $MgCl_2$ as “anions” also supplies readily available, soluble Mg.

-The better anion supplements on the market include Mg in this form to remove Mg worries pre-calving.

Post-calving
Magnesium Oxide – supply Mg and act as rumen alkalinizer.
* my experience; Low Mg = primary cause of mid-lactation milk fevers

Testing Magnesium Oxide Availability

Weigh out 3 g MgO into large vessel.

Add 40 ml of 5% acetic acid (white vinegar) slowly!!

Cap container and shake well, shake again at 15 min. Check the pH at 30 min mark.

Vinegar will be pH 2.6-2.8!

The best MgO will bring the pH up to 8.2.

The worst to just 3.8.

pH is a log scale so this represents >10,000 fold difference in buffering action.

Lean, et al 2014 Meta-Analysis

Studies contrasted use of anion supplements vs controls. Anions had to be fed at least 21 days pre-calving for inclusion in study.

Utilized 15 published studies with 34 diet comparisons.

Cows fed anions produced an average of 1.13 kg more Fat corrected milk / day for first 65 days in milk (or 73 kg 1st 65 days).

Anions cost $12 to $22 / cow

Milk price = 0.33 USD/ liter X 73 kg in 65 days = 24.11 USD

Over whole lactation – use 318 kg figure (Beede)
0.33 dollars/ L X 318 kg in 305 days = 104.94 USD

Relative risk Milk Fever has on other Disease Development in that lactation (Curtis et al 1985)

Ketosis – **23** fold increased risk (16 fold for RP)

All Mastitis – **5** fold increased risk

Coliform Mastitis - **11** fold increased risk

Retained Placenta – **4** fold increased risk

Reduced retained placenta, improved uterine health, less displaced abomasum, less mastitis? How many $$$$$????