

# Lead Exposure and Osteoporosis

James R Campbell, MD, MPH

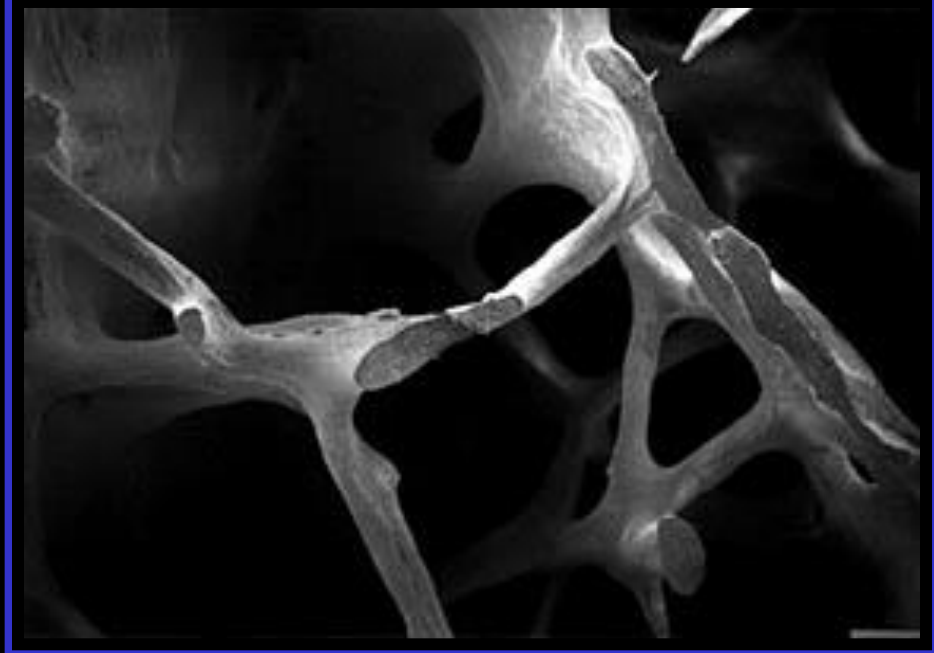
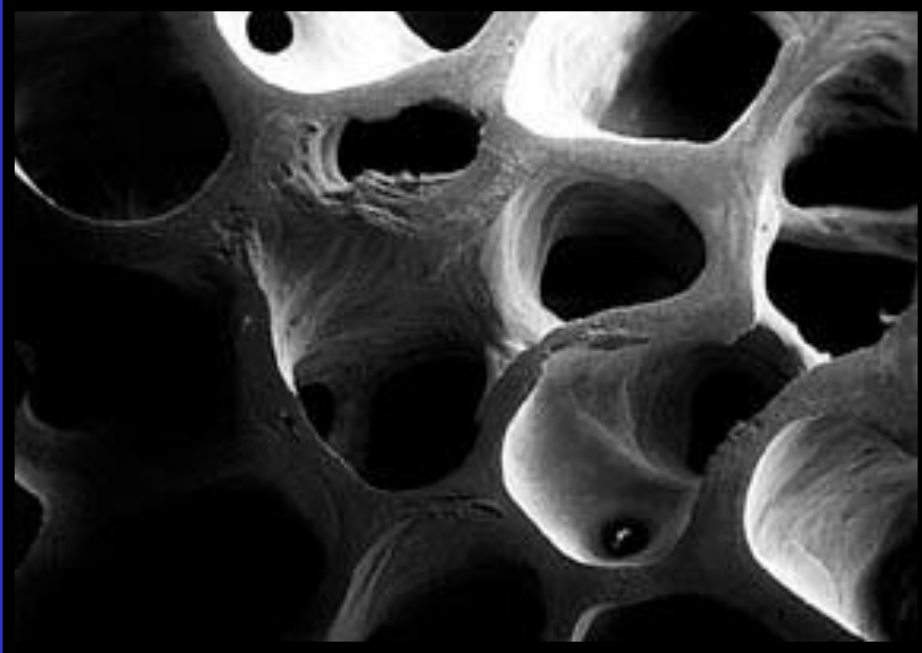
Associate Professor of Pediatrics

University of Rochester School  
of Medicine and Dentistry









Dempster, DW et al, J Bone Miner Res 1986; 1:15-21

# Impact of Osteoporosis

- 17% of women over age 50 years
- 6 million women have osteoporosis, and 17 million women have osteopenia
- 269,000 hospital discharges for hip fracture in 1991
- \$10-15 billion per year

# Impact of Osteoporosis

- Nearly 1/3 of patients with osteoporotic hip fractures enter a nursing home within a year
- 20% of patients die within 1 year after an osteoporotic hip fracture

Does lead poisoning  
cause osteoporosis?



Does lead poisoning  
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# Criteria to Establish Causation

- The exposure must precede outcome.
- Studies show an association between exposure and outcome.
- The association shows a dose-response relation.
- The association is strong.
- Studies show consistent results.
- There is a plausible biological mechanism.

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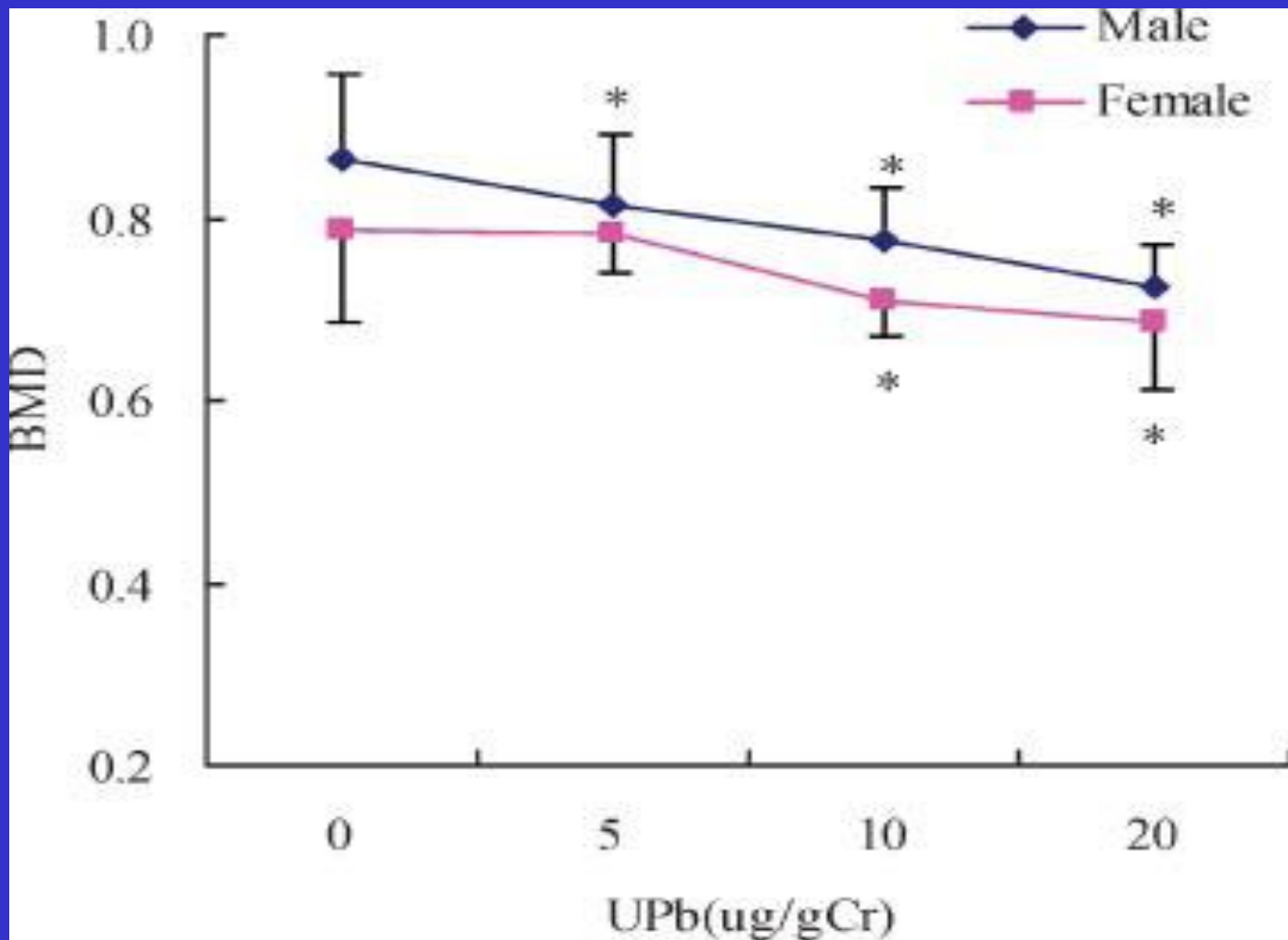
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# Lead and Bone Mineral Density NHANES Analysis

Measure	Female		Male	
	White	African-American	White	African-American
Adjusted mean (SE) BMD (g/cm <sup>2</sup> ) <sup>a</sup>				
Lowest	0.789 (0.006)	0.898 (0.010)	0.961 (0.007)	1.036 (0.011)
Middle	0.776 <sup>b</sup> (0.006)	0.882 (0.009)	0.944 <sup>c</sup> (0.006)	1.023 (0.010)
Highest	0.771 <sup>b</sup> (0.007)	0.873 (0.012)	0.934 <sup>c</sup> (0.009)	1.011 (0.013)

Campbell JR. Environ Health Perspect. 2007;115:1018-1022.

# Lead and Bone Mineral Density Occupationally Exposed Chinese



# Lead and Bone Mineral Density

## Female Lead Smelters

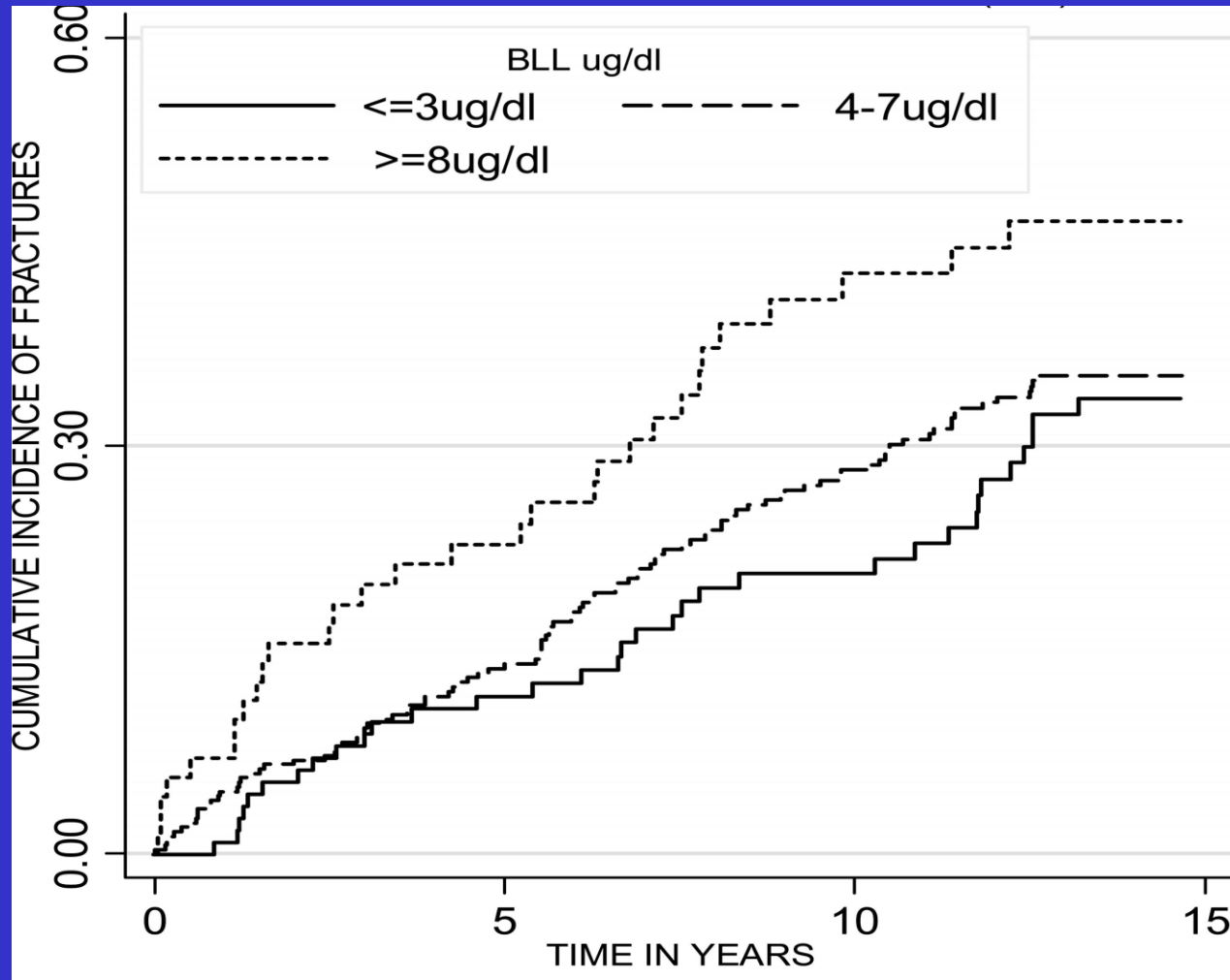
<u>Blood Lead Level Percentile</u>	<u>% Change in BMD from 1994 to 2000</u>
$\geq 90$ percentile	-10.38%
$< 90$ percentile	-1.33%

# Lead and Bone Mineral Density Study of Osteoporotic Fractures

	<i>Low</i>	<i>Medium</i>	<i>High</i>
Level ( $\mu\text{g}/\text{dl}$ )	$\leq 3$	4-7	$\geq 8$
<i>N</i> = 533	<i>N</i> = 122	<i>N</i> = 332	<i>N</i> = 79
BMD ( $\text{g}/\text{cm}^2$ )			
Total hip [mean (SD)]	0.77 (0.13)	0.76 (0.13)	0.72 (0.12)
Femoral neck [mean (SD)]	0.65 (0.11)	0.66 (0.12)	0.62 (0.09)
Calcaneus [mean (SD)]	0.41 (0.09)	0.42 (0.09)	0.39 (0.09)

# Lead and Fracture Incidence

## Study of Osteoporotic Fractures



Khalil N, et al. J Bone Miner Res 2008;23:1417–1425.



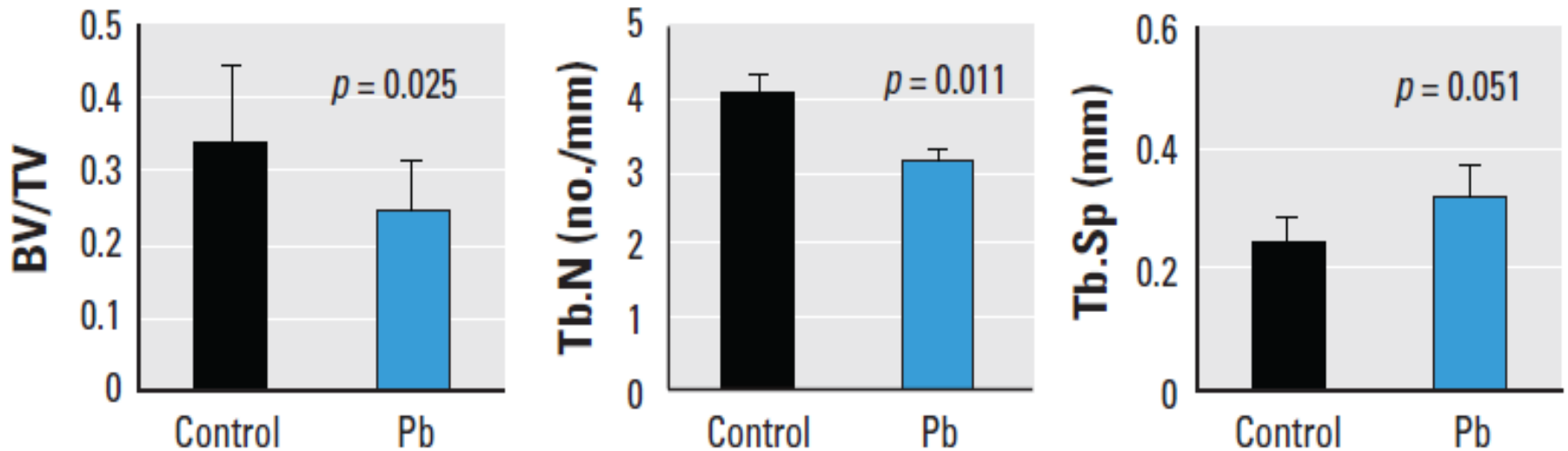
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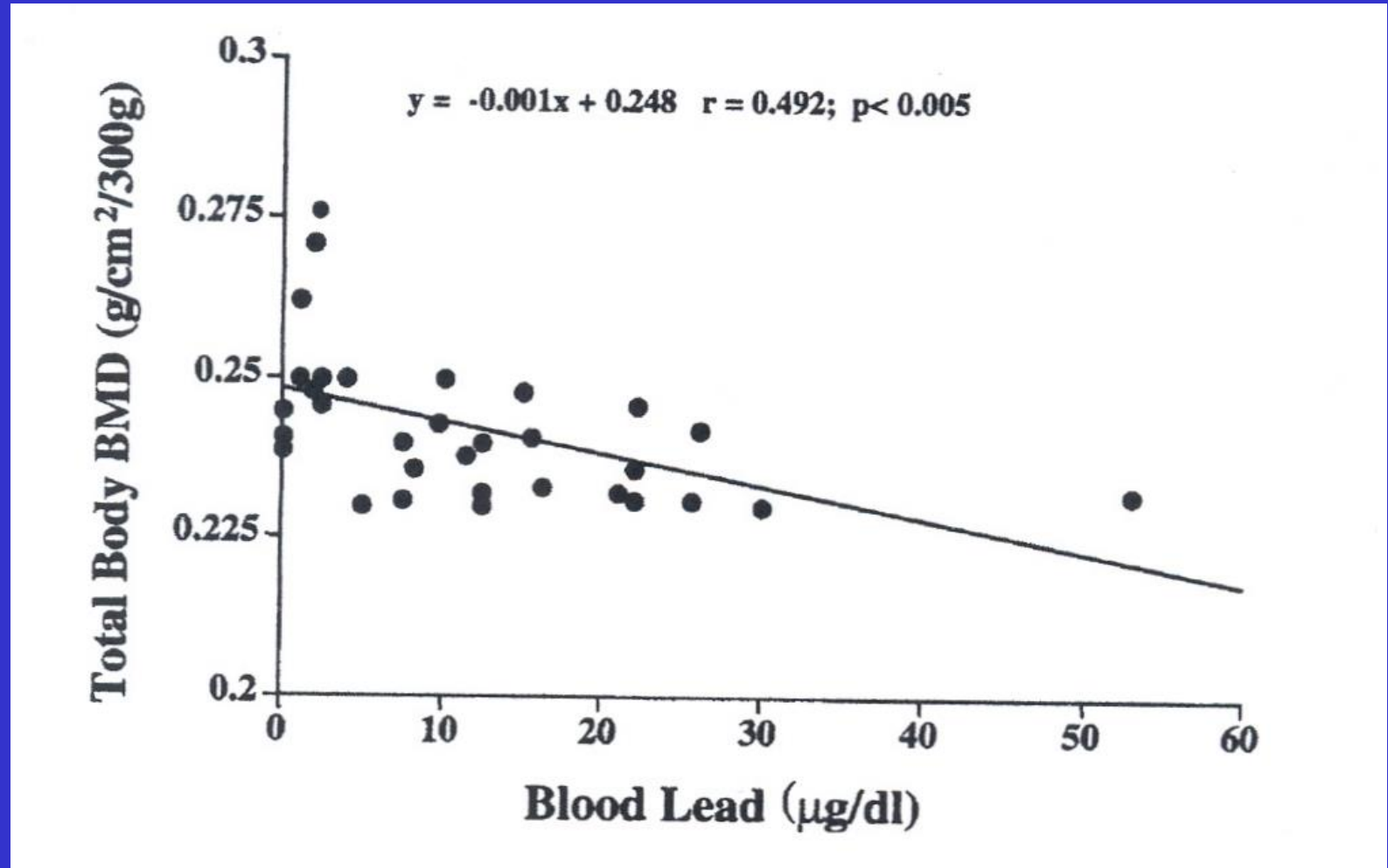
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# Lead and BMD in Mice



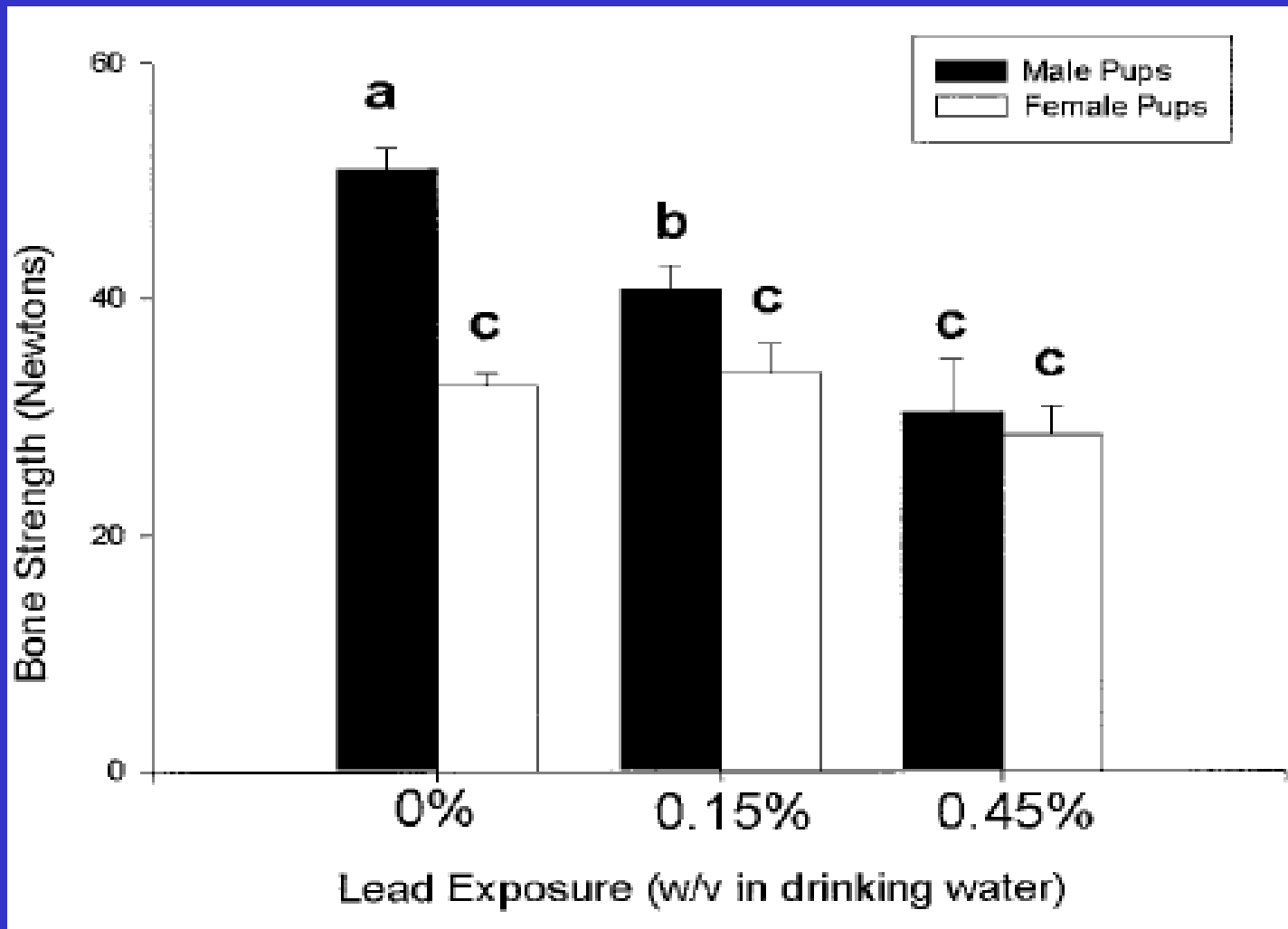
Beier EE. Environ Health Perspect. 2013;121:97-104

# Lead & BMD in Mice



Puzas JE, Campbell JR. Nutr Bone Health. 2004;363-376.

# Lead & Bone Strength in Mice



Ronis MJ. Toxicol Science. 2001;62:321-329.

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<u>Study</u>	<u>Unexposed BMD</u>	<u>Exposed BMD</u>	<u>Percent BMD of Exposed to Unexposed</u>
Campbell, 2005	0.789	0.771	0.98
Khalil, 2008	0.770	0.720	0.94
Sun, 2008	0.757	0.739	0.97
Potula, 2006	1.065	0.968	0.91



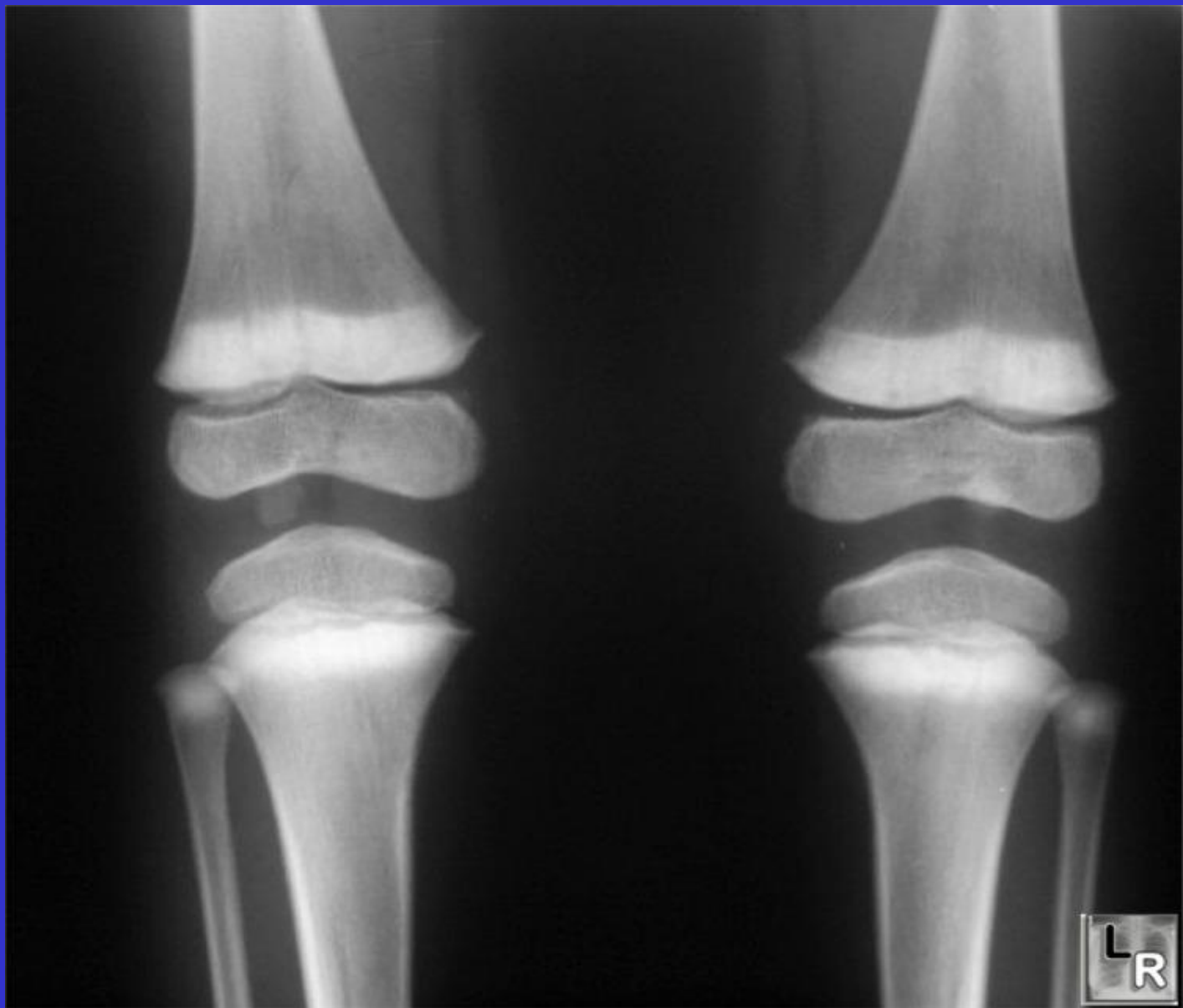
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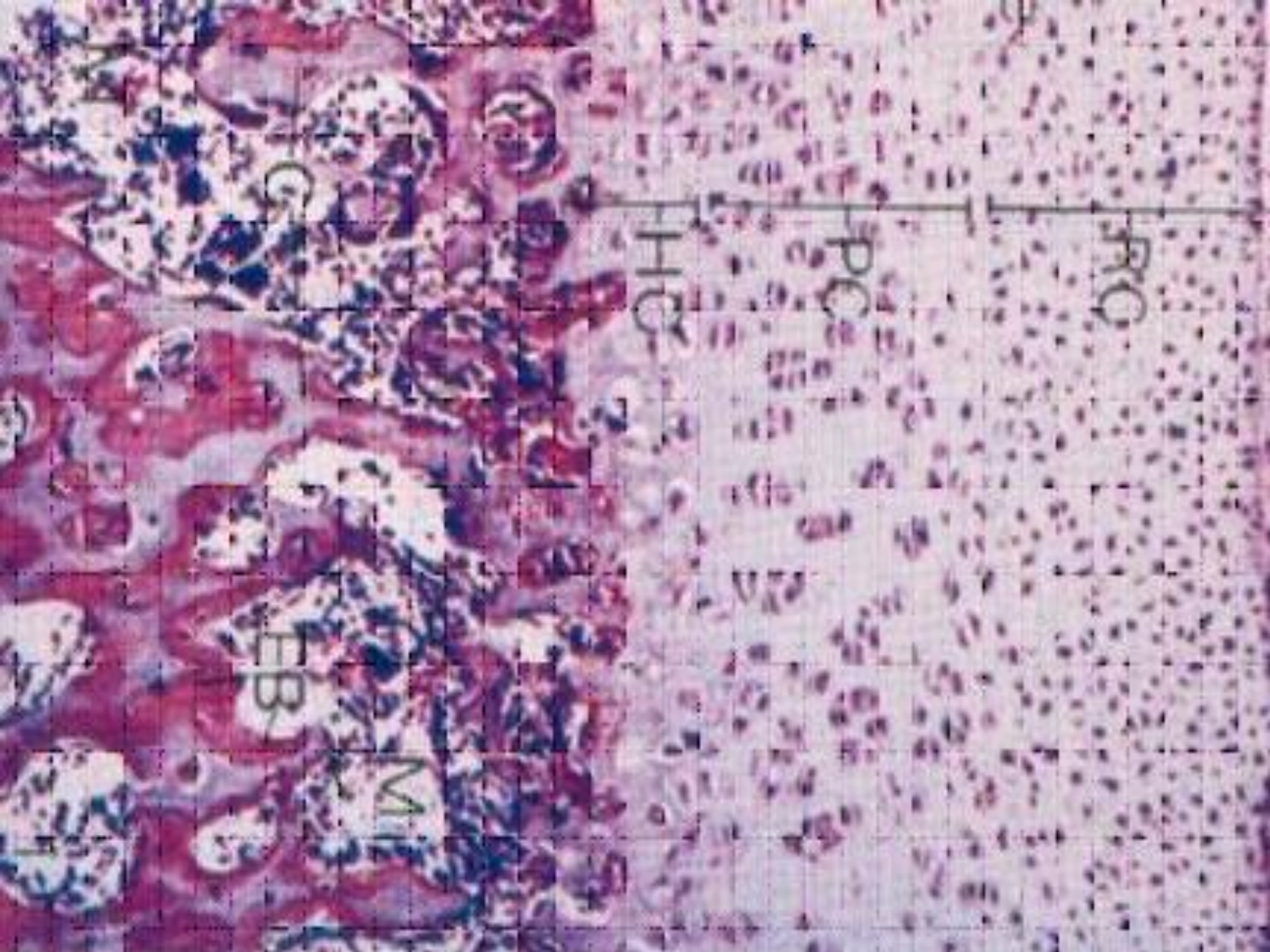
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FRO

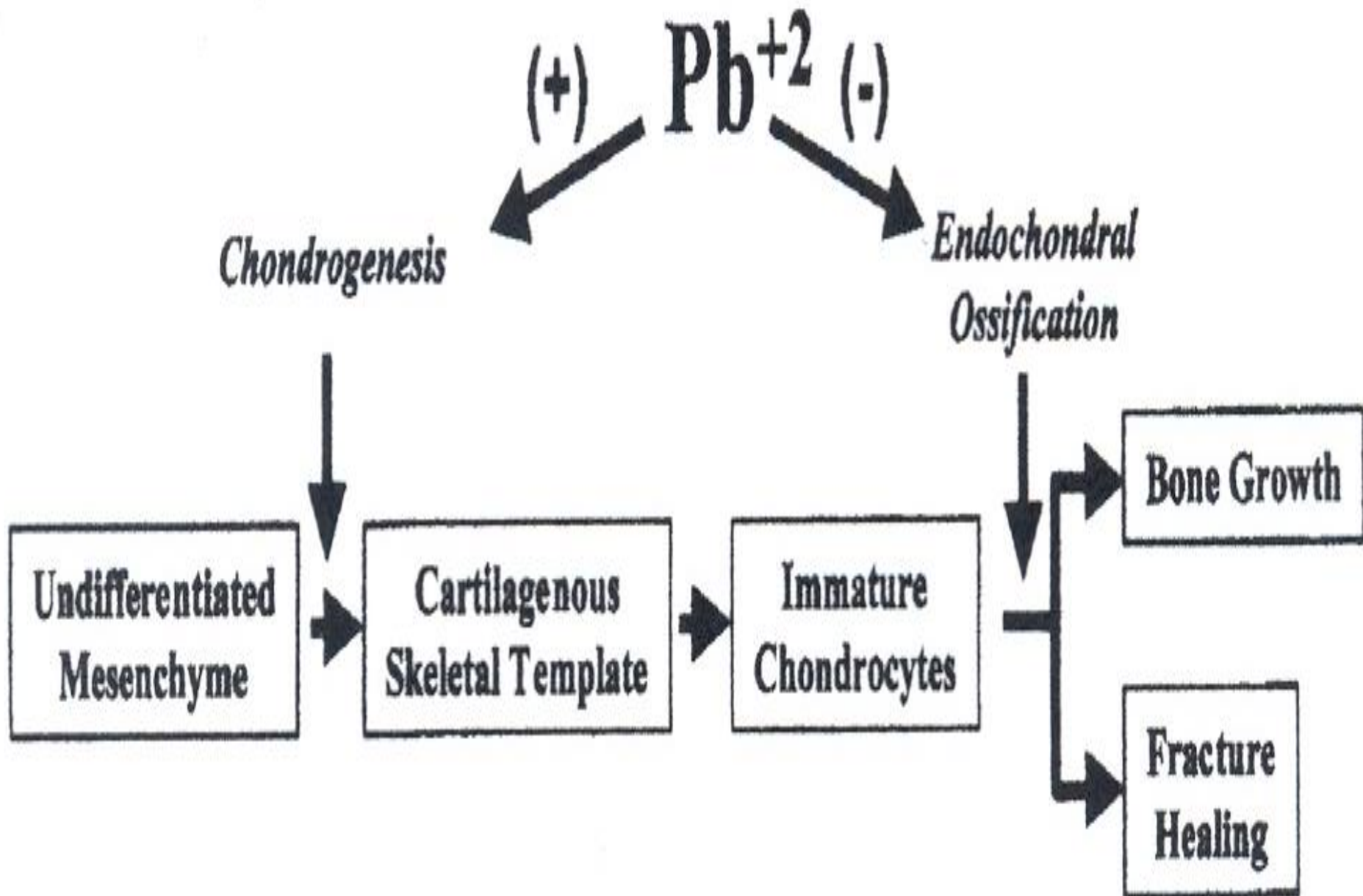
PC

HQ

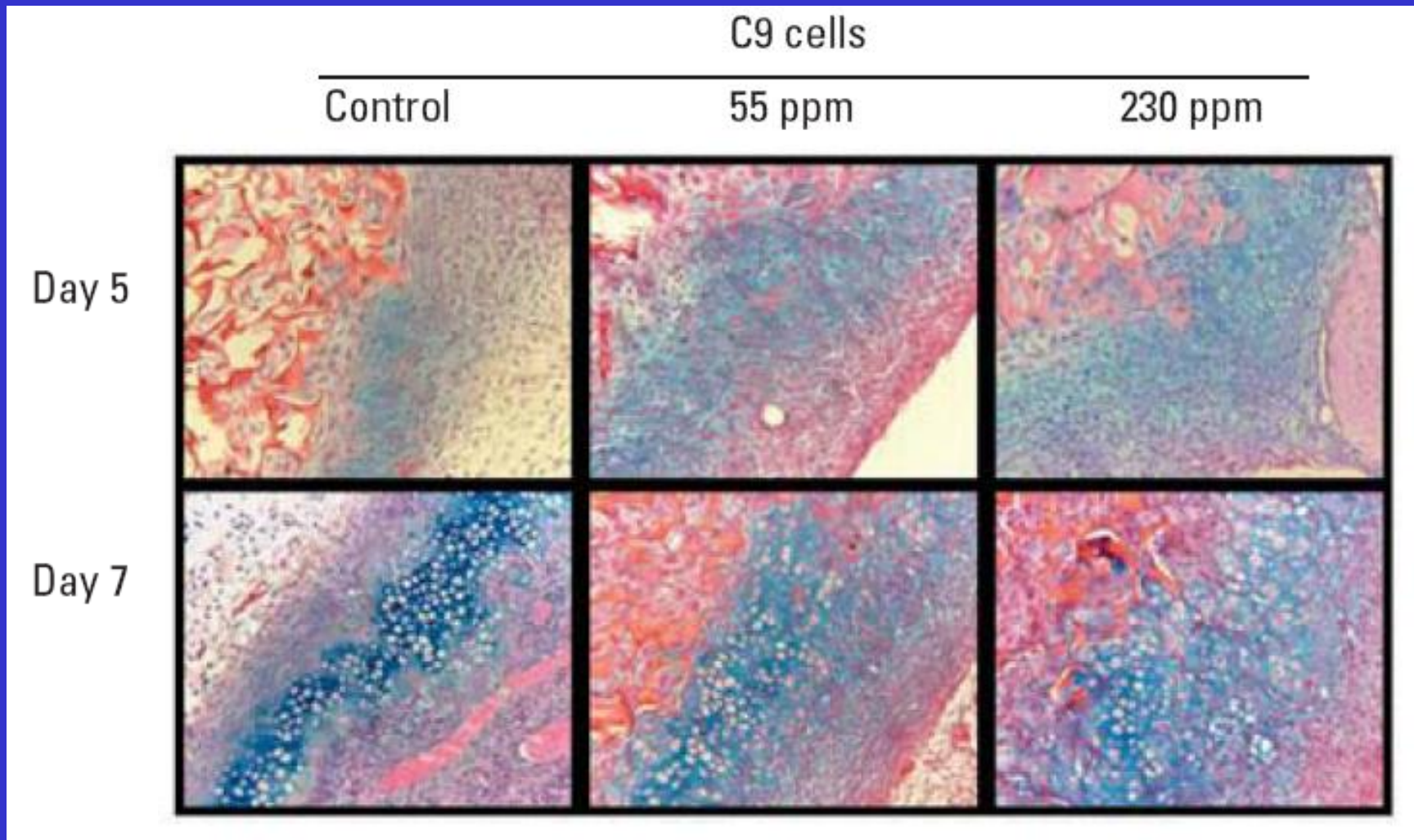
EB

MI



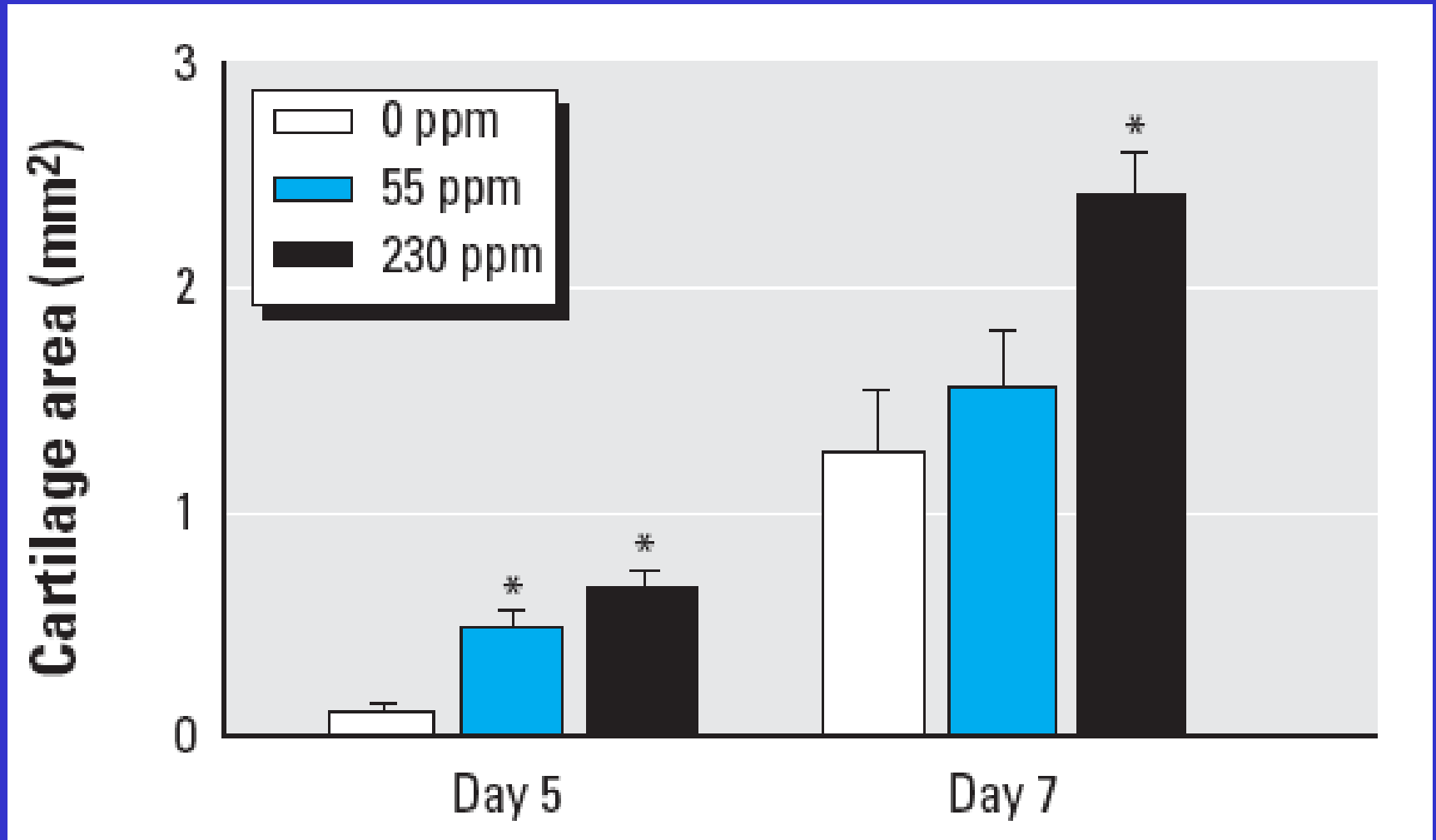


# Lead & Cartilage Formation



Zuscik MJ. Environ Health Perspect. 2007;115:1276-1282.

# Lead & Cartilage Formation



Zuscik MJ. Environ Health Perspect. 2007;115:1276-1282.



# Lead & Fracture Healing in Rats

**Lead in  
Water**

**0 ppm**



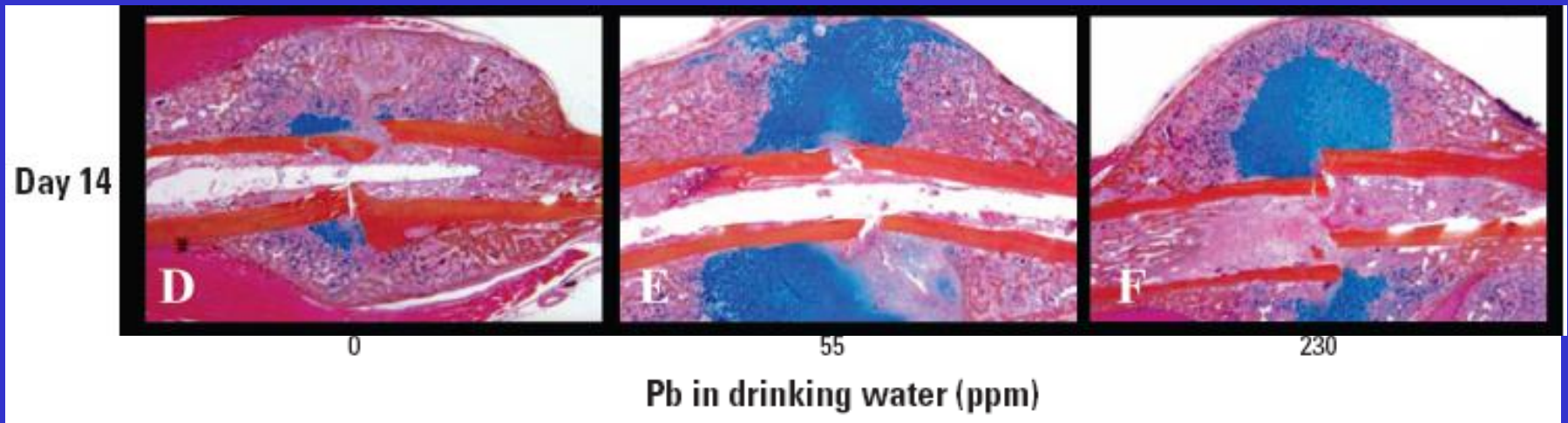
**55 ppm**



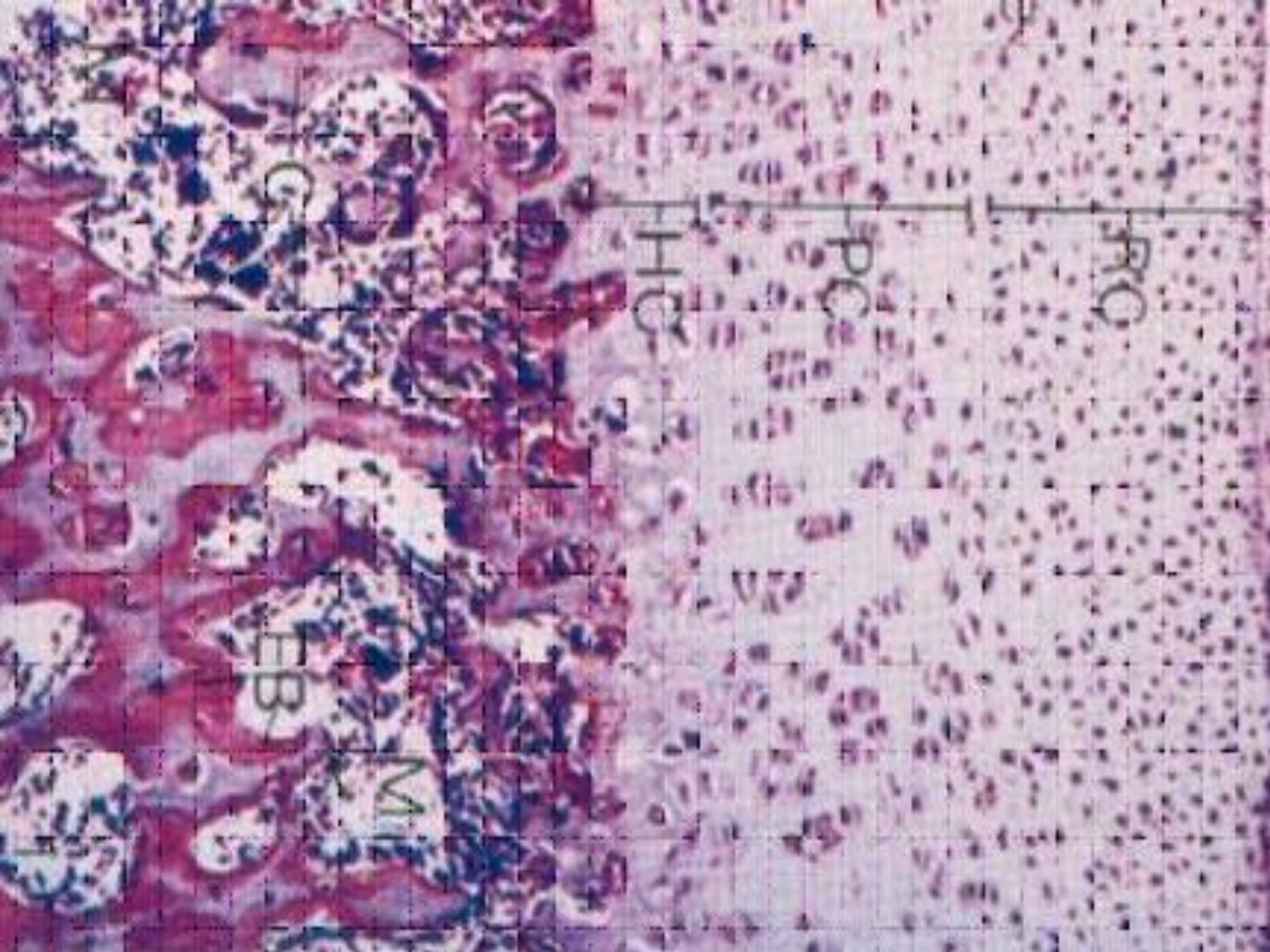
**230 ppm**



# Lead & Fracture Healing in Rats



Carmouche JJ. Environ Health Perspect. 2005;113:749-755.



FRQ

PC

HQ

EB

M



(+)  $Pb^{+2}$  (-)

*Chondrogenesis*  *Endochondral Ossification*

```
graph TD; Pb[Pb+2] -- "(+)" --> Chondrogenesis; Pb -- "(-)" --> EndochondralOssification[Endochondral Ossification]; UndifferentiatedMesenchyme[Undifferentiated Mesenchyme] --> CartilaginousSkeletalTemplate[Cartilaginous Skeletal Template]; CartilaginousSkeletalTemplate --> ImmatureChondrocytes[Immature Chondrocytes]; ImmatureChondrocytes --> BoneGrowth[Bone Growth]; ImmatureChondrocytes --> FractureHealing[Fracture Healing];
```

Undifferentiated  
Mesenchyme

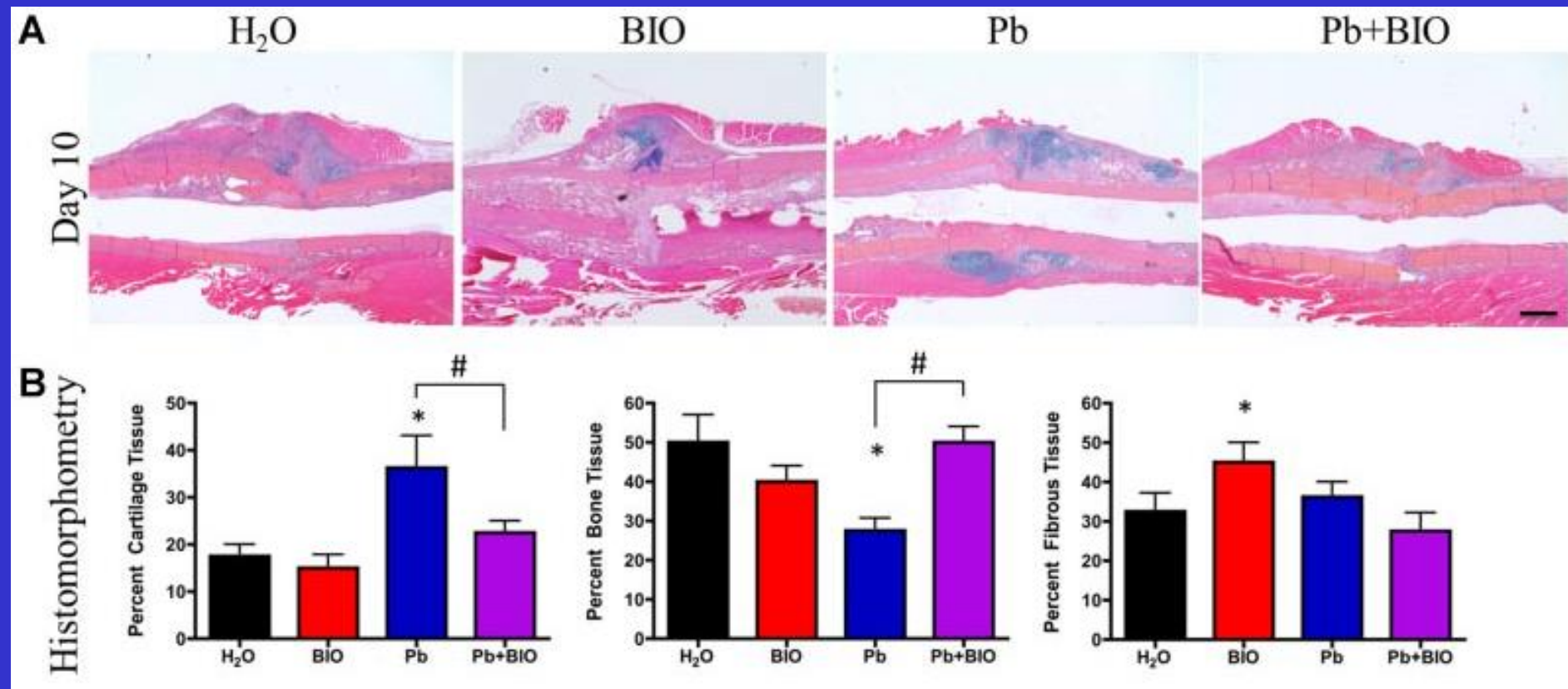
Cartilaginous  
Skeletal Template

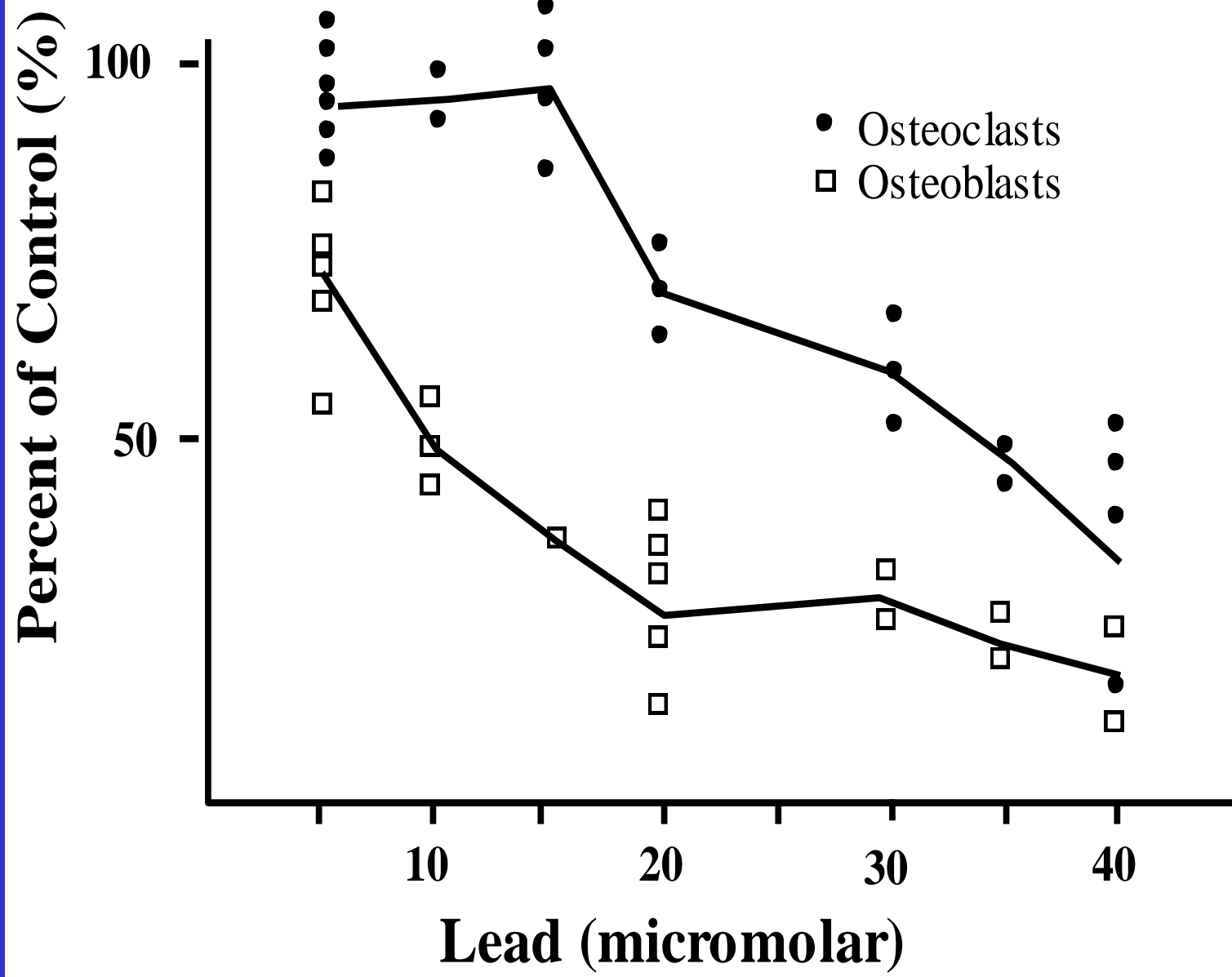
Immature  
Chondrocytes

Bone Growth

Fracture  
Healing

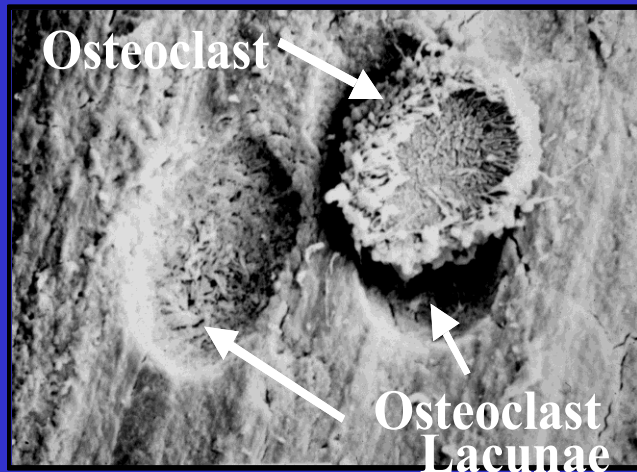
# Lead and Cartilage/Bone Formation





# In a normal skeleton.....

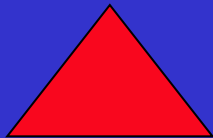
**Bone Resorption = Bone formation**



**- Lead**

*Bone resorption*      *Bone formation*

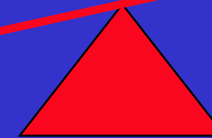
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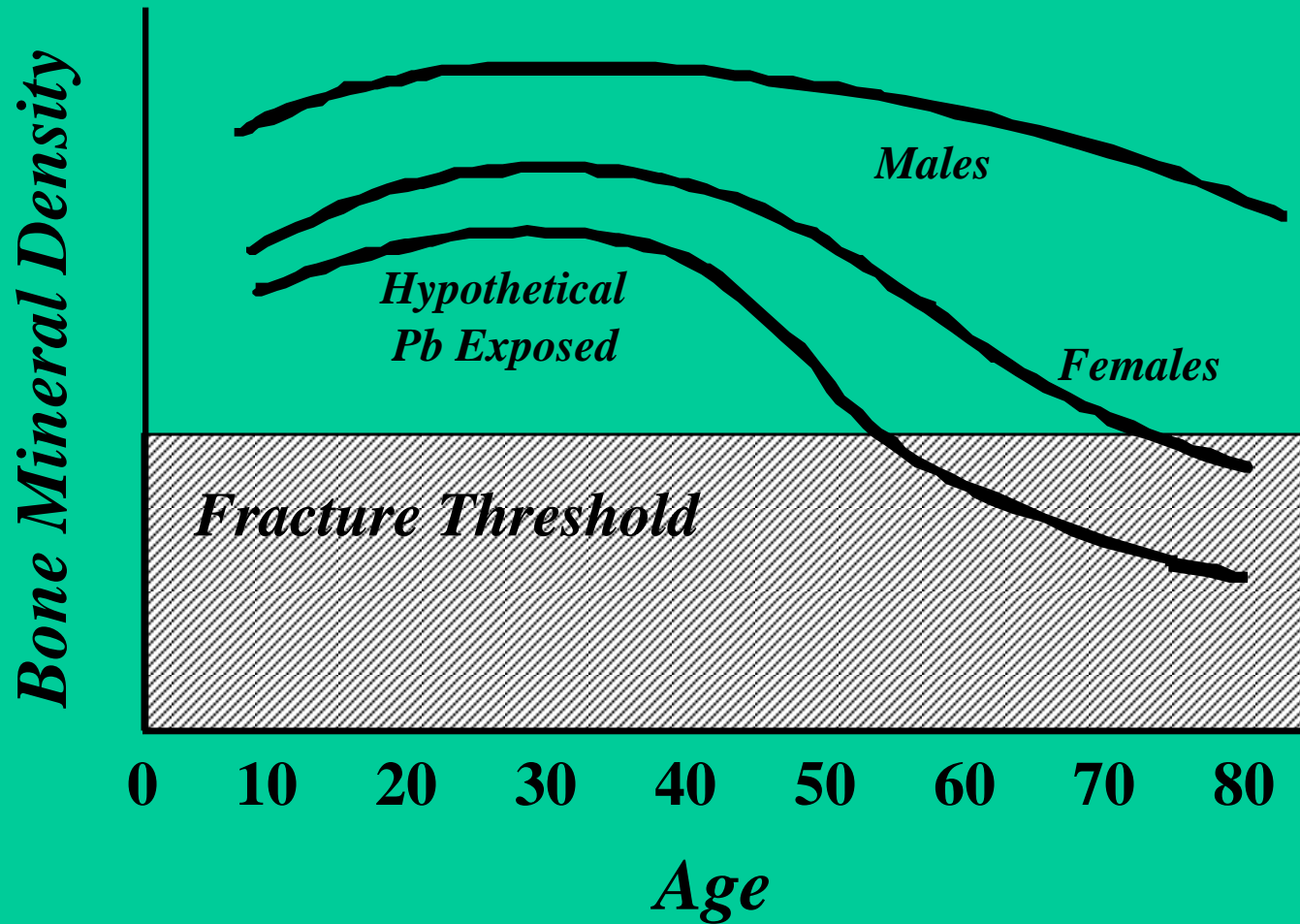
**+ Lead**

*Bone resorption*      *Bone formation*

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# Hypothesis





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Does lead poisoning  
cause osteoporosis?

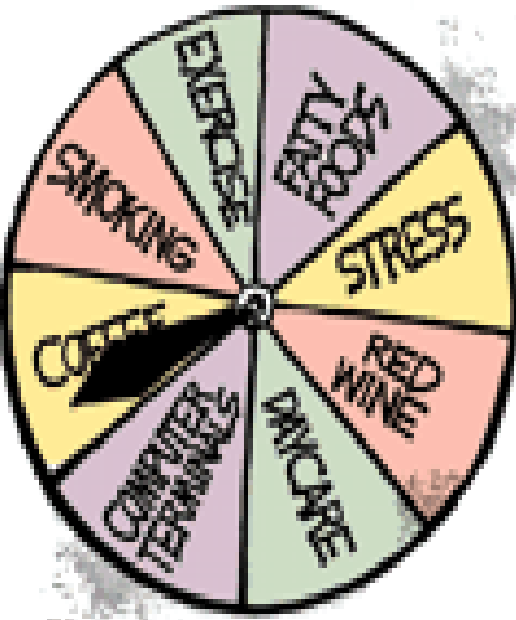
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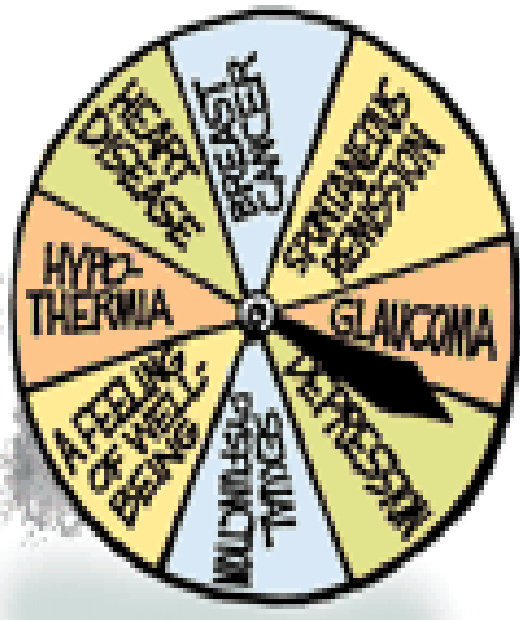
# Today's Random Medical News

from the New England  
Journal of  
Panic-Inducing  
Gobbledygook

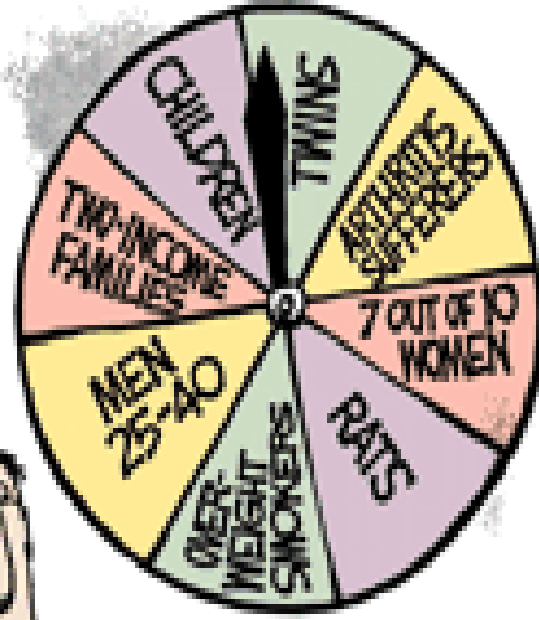
W.B. BRAMAN



CAN CAUSE



IN

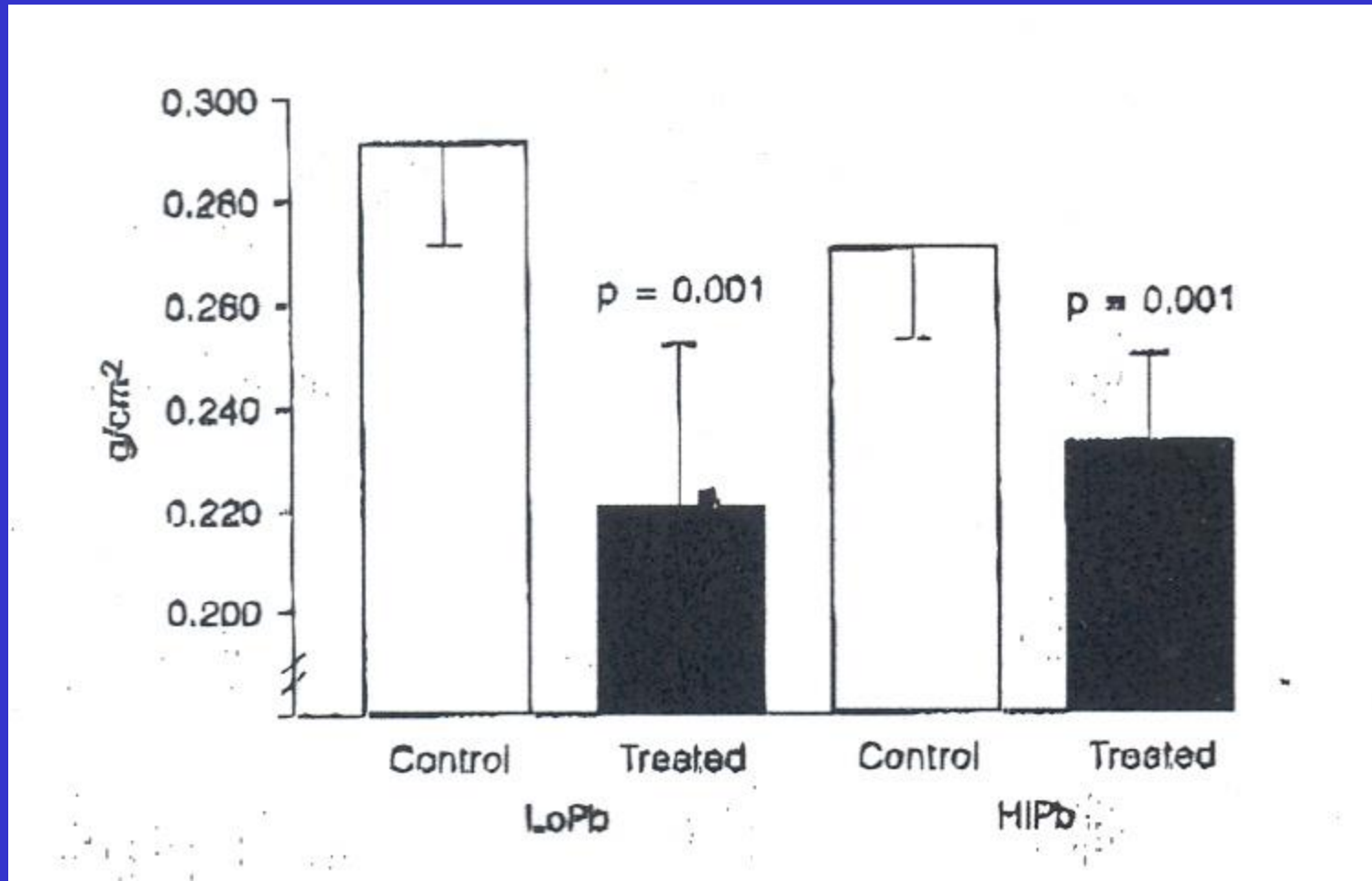


ACCORDING TO A REPORT RELEASED TODAY...



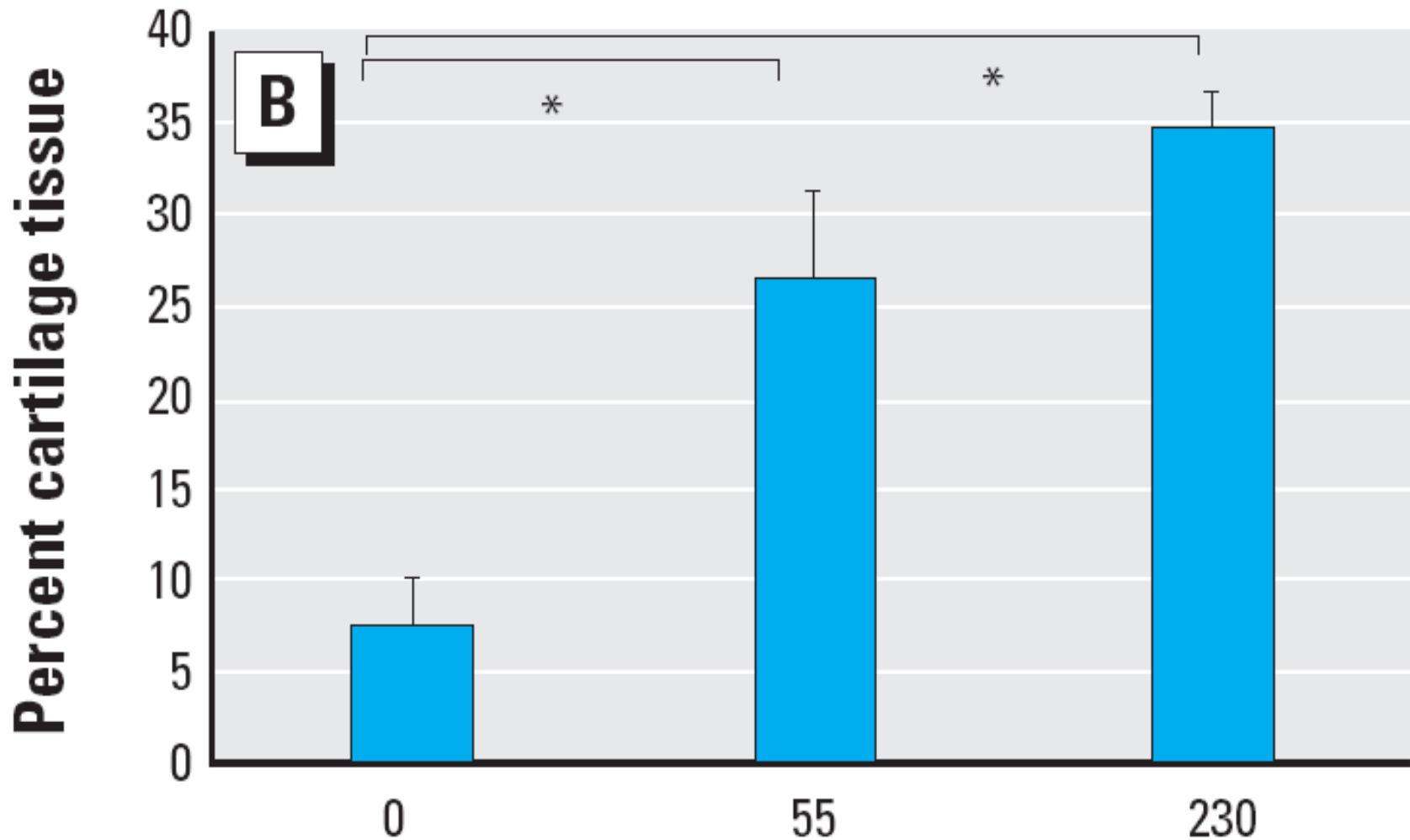


# Lead & BMD in Mice

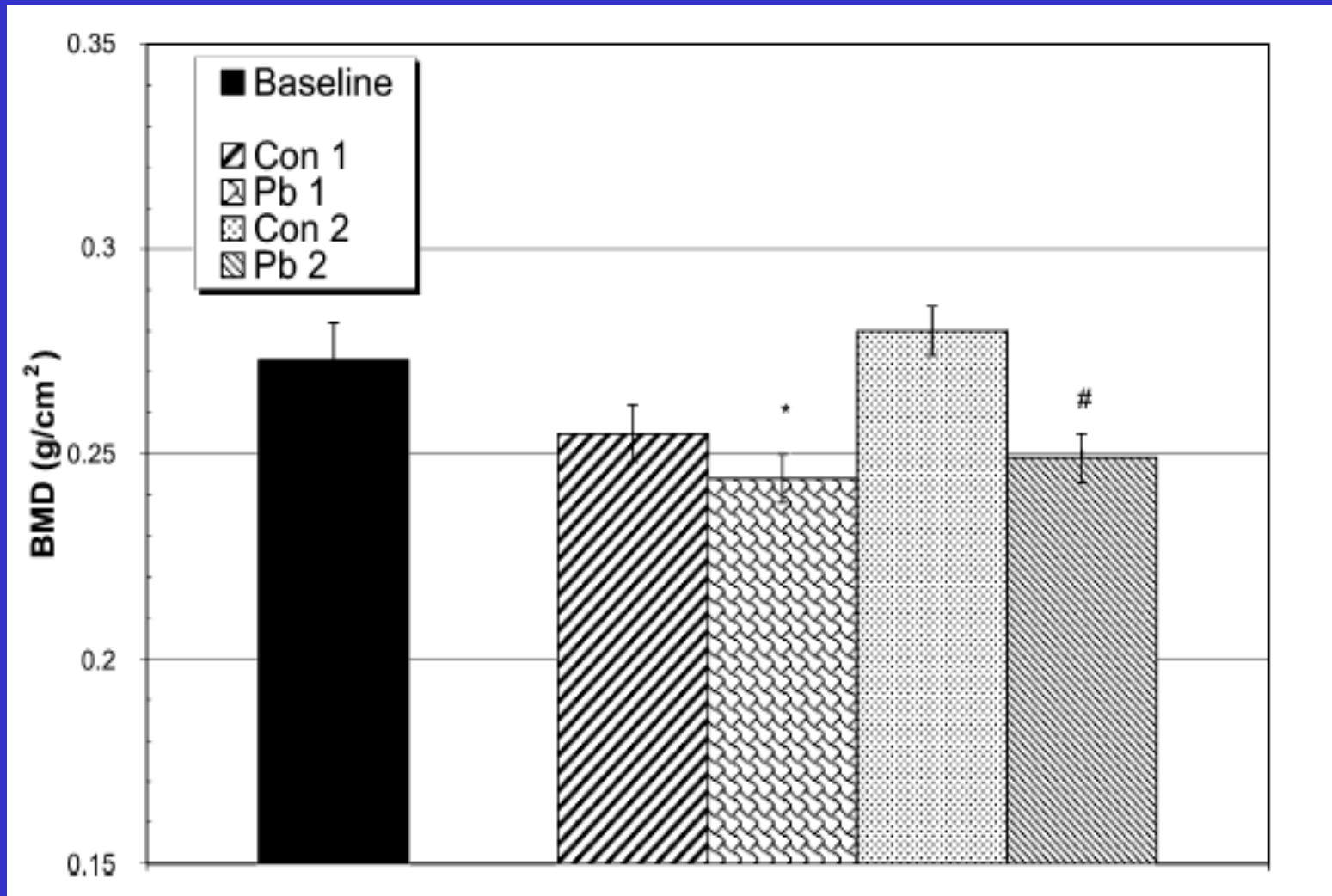


Gruber H. Miner Electrolyte Metab. 1997;23:65-73

# Lead & Fracture Healing in Rats



# Lead & BMD in Rats



Bagachi D. J Inorgan Biochem. 2005;99:1155-1164.

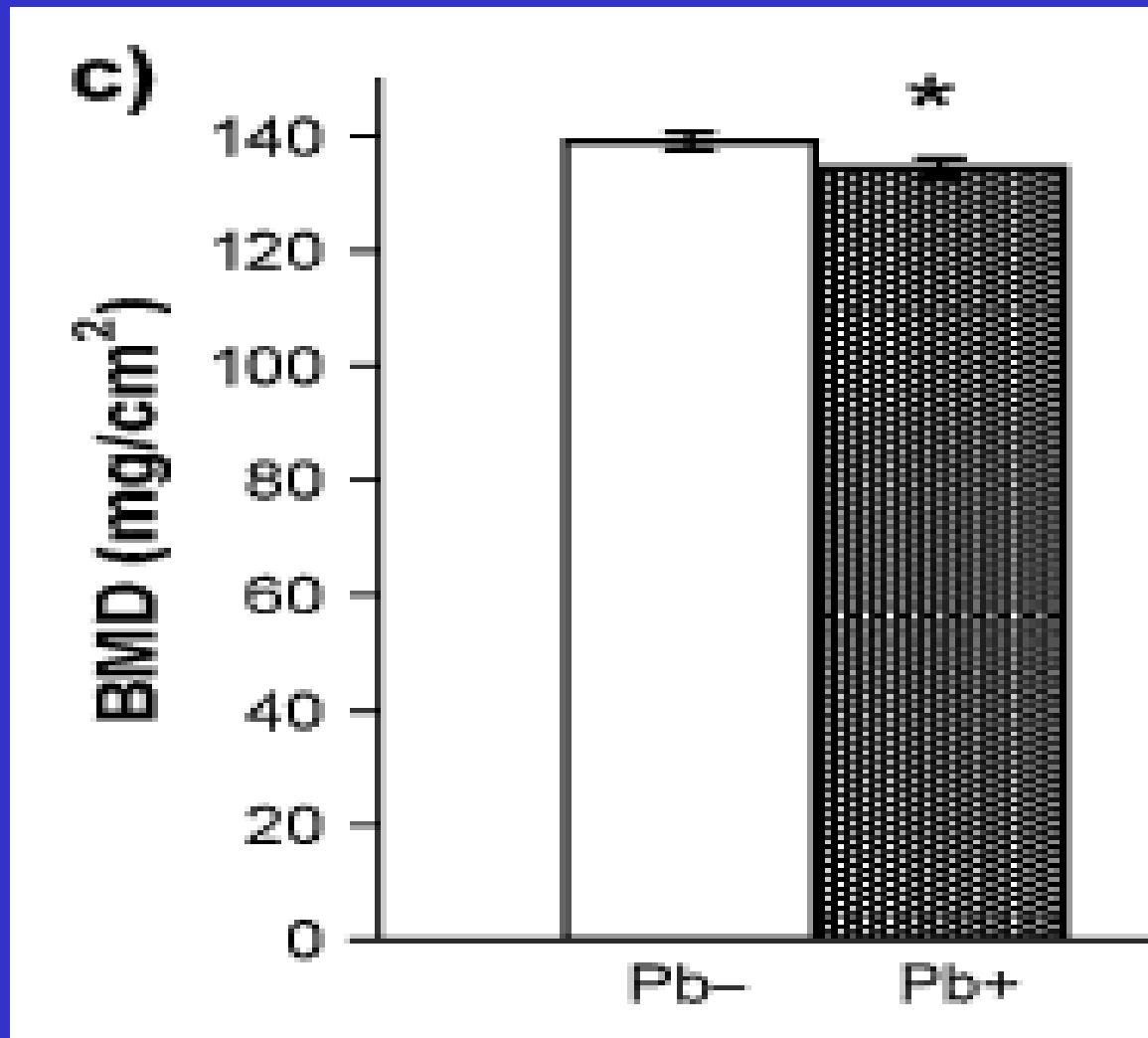


# Lead & Bone Turnover in Humans

Variable	Blood lead levels		Calcaneus-bone lead levels	
	≤90th	>90th	≤90th	>90th
	<i>M</i>	<i>M</i>	<i>M</i>	<i>M</i>
<b>Calcitropic hormones</b>				
Parathyroid hormone (pg/ml)	59.0	42.5*	59.12	43.83*
Vitamin D (pg/ml)	45.7	25.1*	48.56	46
Ionized calcium (mg/dl)	4.9	5.1	4.94	5.04
Total calcium (mg/dl)	8.9	9.2**	9.04	9.26
<b>Bone turnover markers</b>				
Urinary pyridinoline	47.2	77.8*	47.46	70.9**
Urinary deoxypyridinoline	11.6	20.2*	11.80	17.39**
Osteocalcin (ng/ml)	17.0	9.9	18.98	24.63

Potula V. Arch Environ Occup Health. 2005;60:195-204.

# Lead & BMD in Mice



Jamieson JA. Toxicol Science. 2006;92:286-294.

# Lead & BMD in Mice

<u>Measure</u>	<u>Control</u>	<u>Exp</u>	<u>P-value</u>
Tr* volume	21.8%	17.8%	0.041
Tr number	3.5	2.7	0.001
Tr thickness	64	56	0.028
Tr space	359	556	0.022

\* Trabecular

Escribano A. Calcif Tissue Int. 1997;60:200-3