

# Consequences of vitamin B12 deficiency in embryonic development and neonatal survival



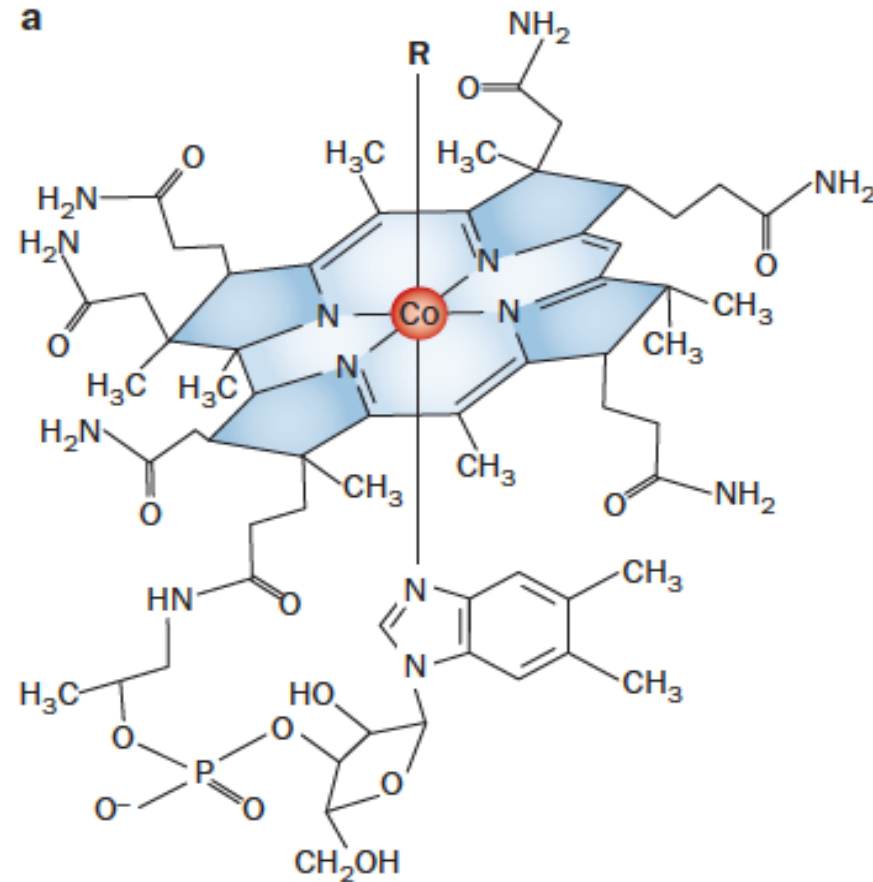
<https://www.swansonvitamins.com/blog/health-news-and-opinion/vitamin-b12-foods>

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# Vitamin B12 (cobalamin)



<https://www.swansonvitamins.com/blog/health-news-and-opinion/vitamin-b12-foods>



Nielsen *et al.*, 2012

# Several populations are at risk for vitamin B12 deficiency

- Who's at risk:
  - Decreased absorption
    - Older adults
    - Diseases involving malabsorption
  - Low intake
    - Low and middle income nations
  - Increased Need
    - Pregnant and nursing mothers



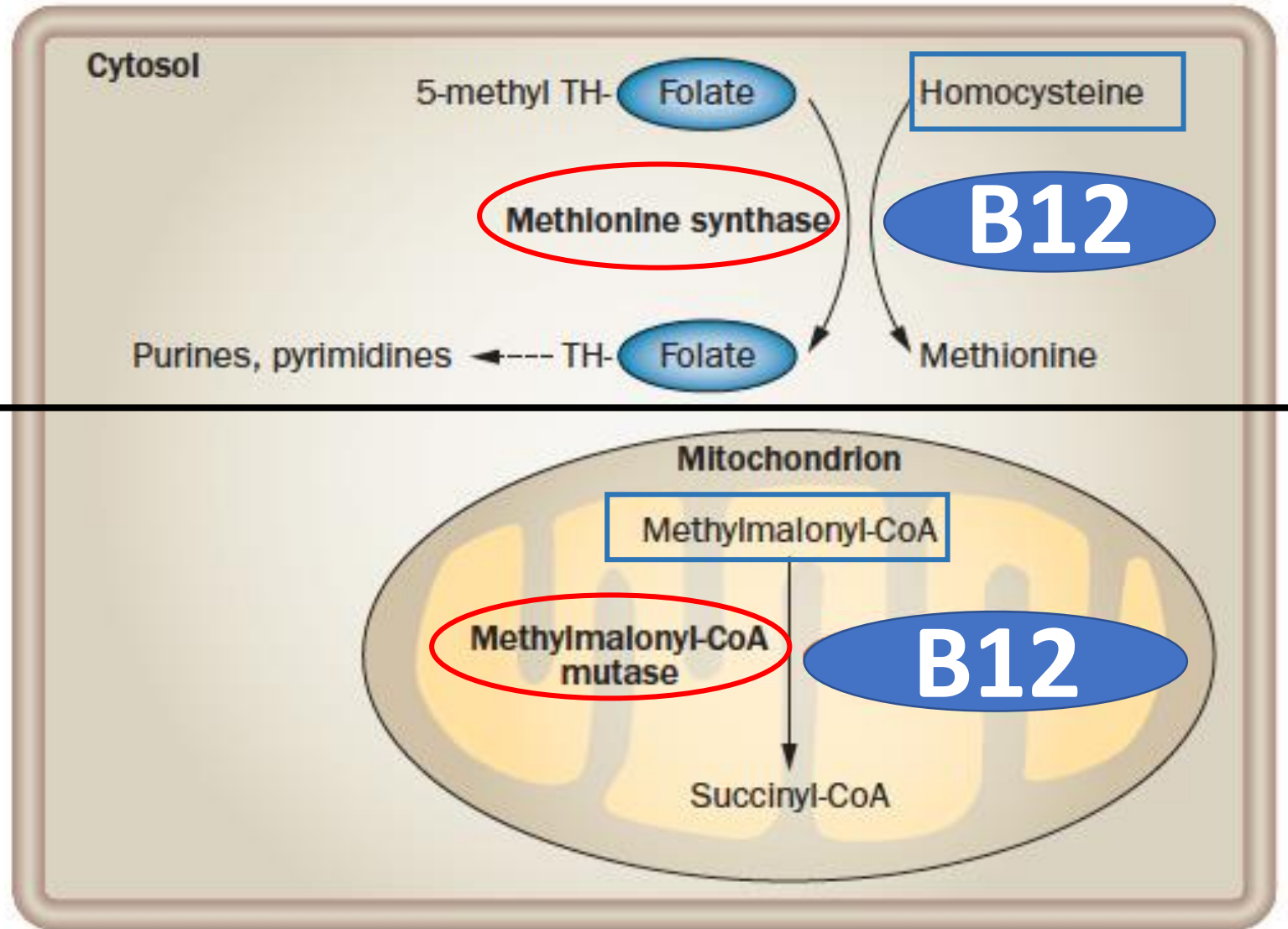
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- Deficiency results in:
  - megaloblastic anemia
  - Fatigue and weakness
  - poor memory, depression
  - peripheral neuropathy
- Risk factor for neural tube defects



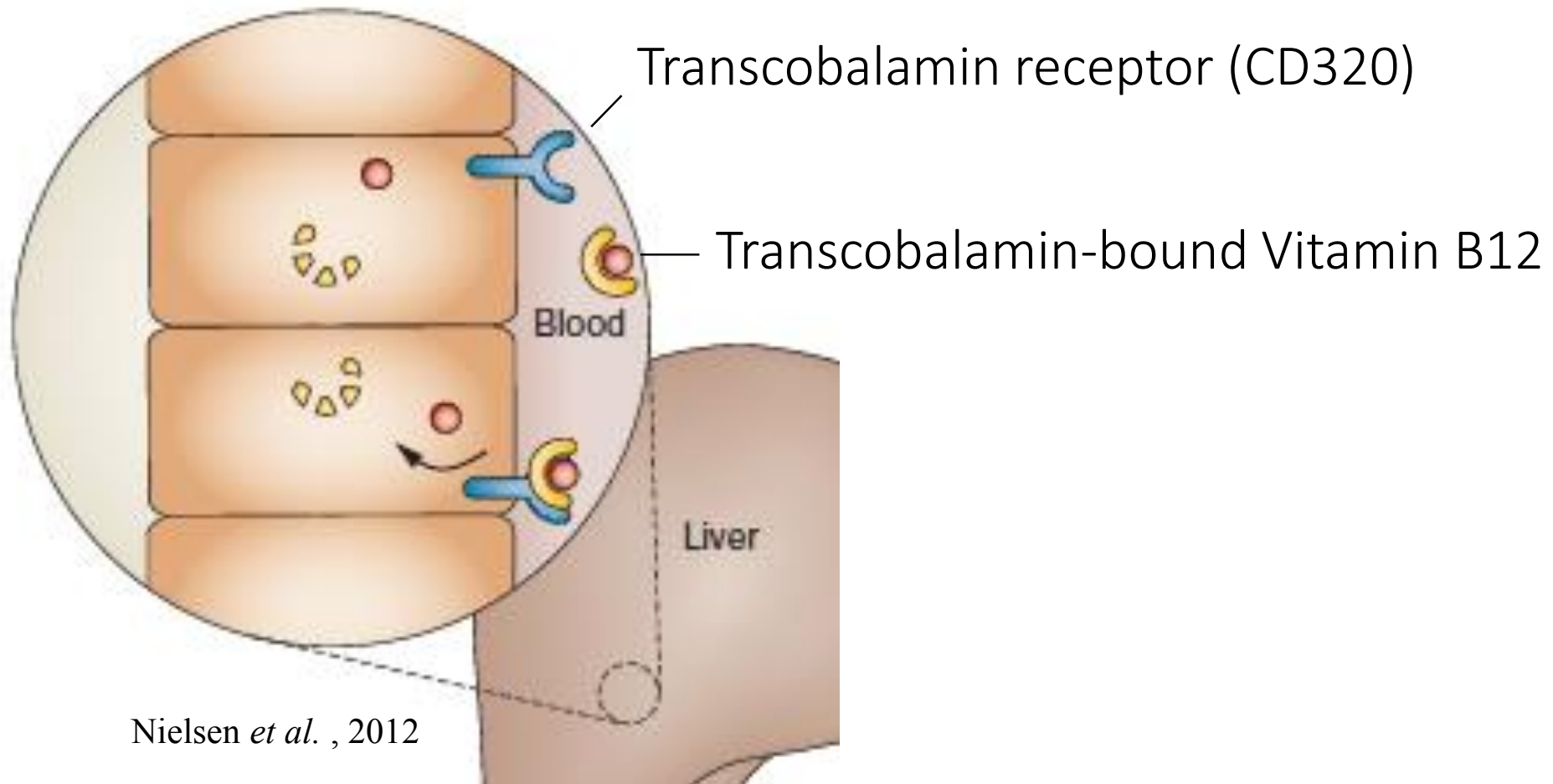
Vitamin B12 is required for 2 essential processes

**DNA**

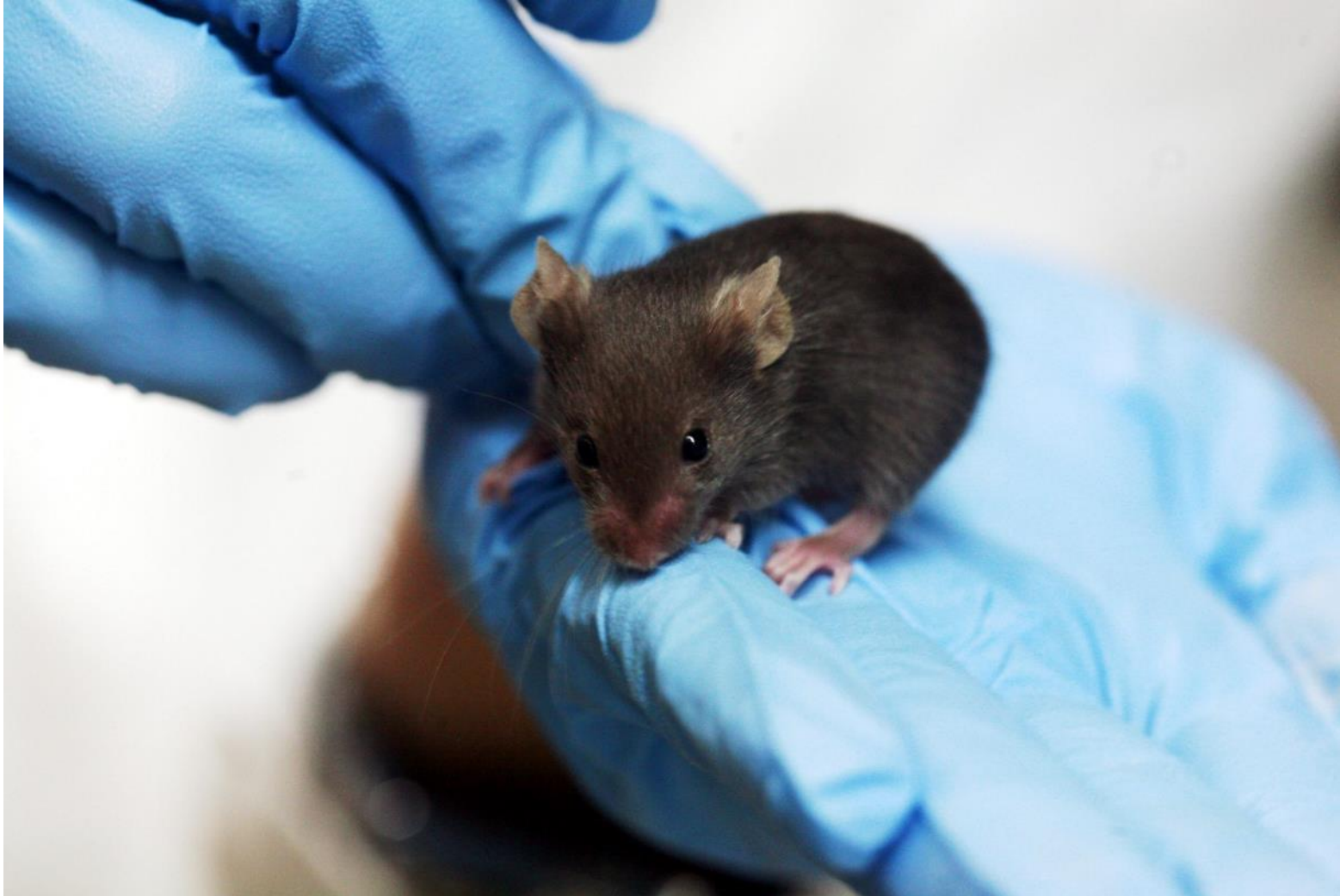


**ENERGY**

# CD320 receptor functions to transport vitamin B12 from blood into tissues



Mice are used to model vitamin B12 deficiency



# Vitamin B12 is required for 2 essential processes

**DNA**

Cytosol

5-methyl TH-

Folate

Homocysteine



Methionine synthase

**B12**

**MTR KO**  
-no offspring

Purines, pyrimidines

TH-

Folate

Methionine

**ENERGY**

Mitochondrion

Methylmalonyl-CoA



Methylmalonyl-CoA





**B12**

**MUT KO**  
-offspring  
perish  
as newborns

Succinyl-CoA

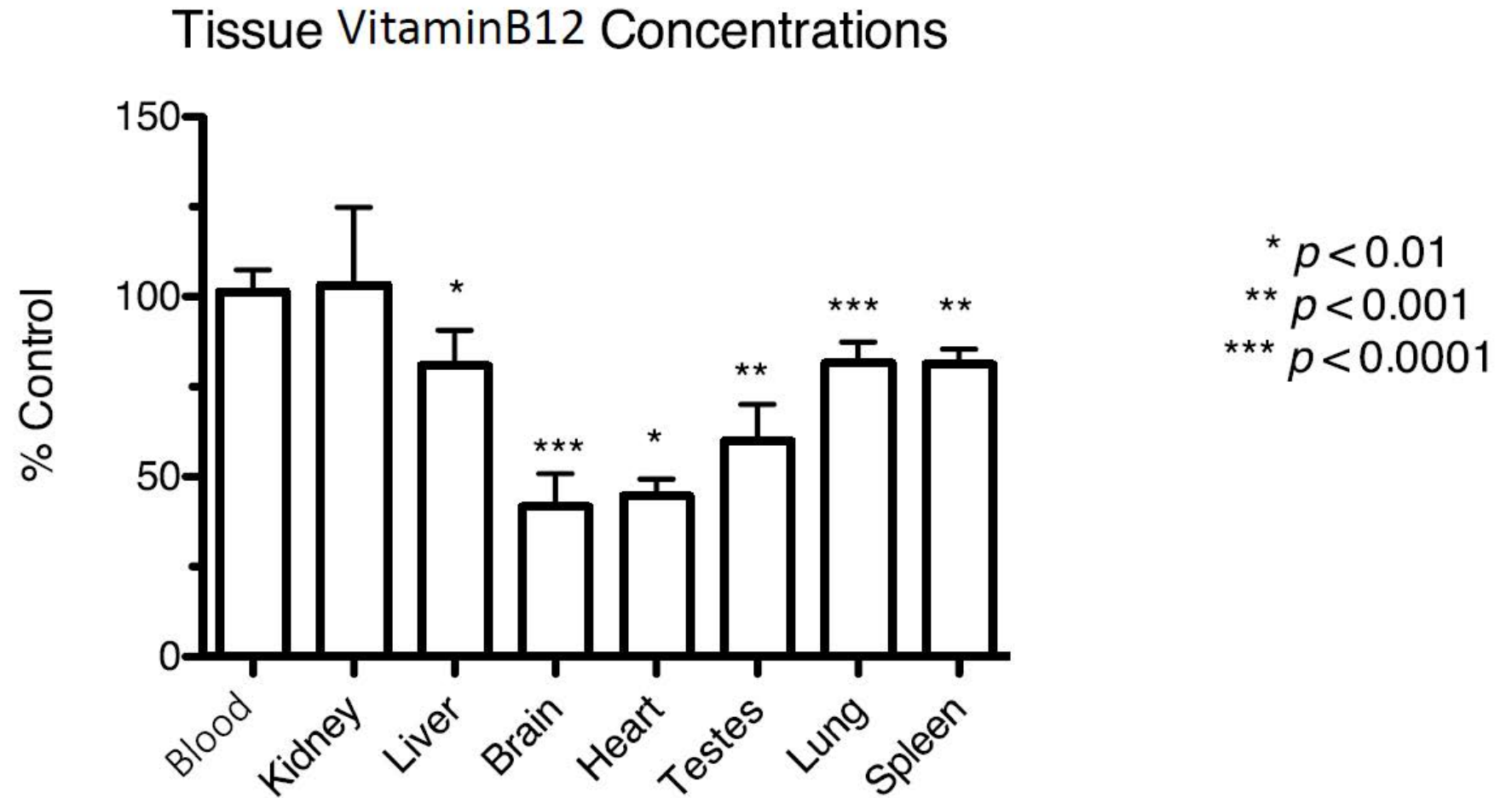
# Generate global *Cd320* KO

F1		X			
	<b>+/-</b>		<b>+/-</b>		
F2	<b>+/+</b>	<b>+/-</b>	<b>-/-</b>		
Observed	23	:	57	:	25
Expected	26	:	53	:	26

Mice can survive without *Cd320*!



# Are the *Cd320* KO mice deficient for vitamin B12 ?



# Can we stress the KO mice with B12-deficient diet?



Standard  
Diet



Soy Diet  
With vitamin B12



Soy Diet  
Vitamin B12-deficient

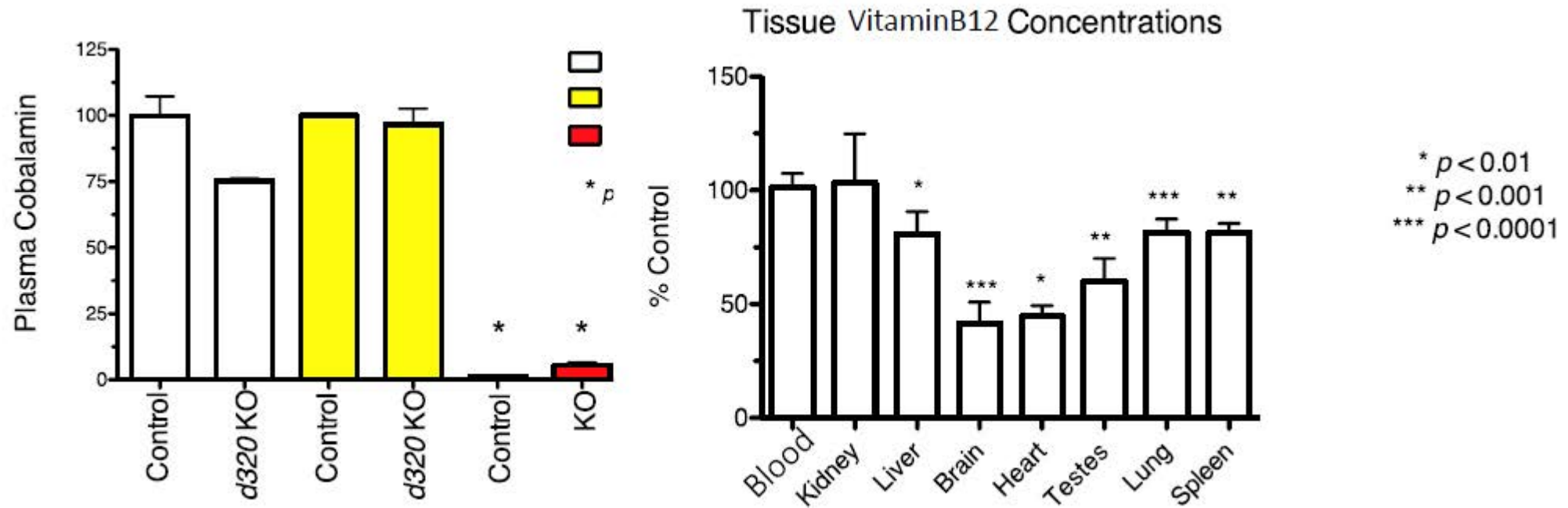
Vitamin B12

Yes

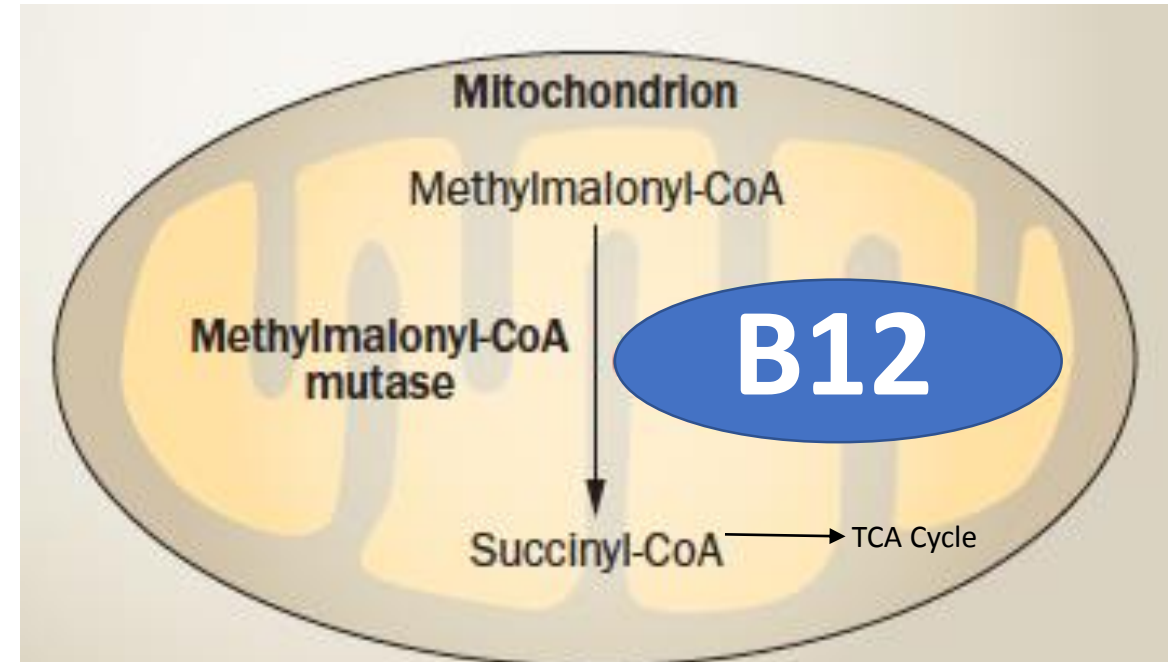
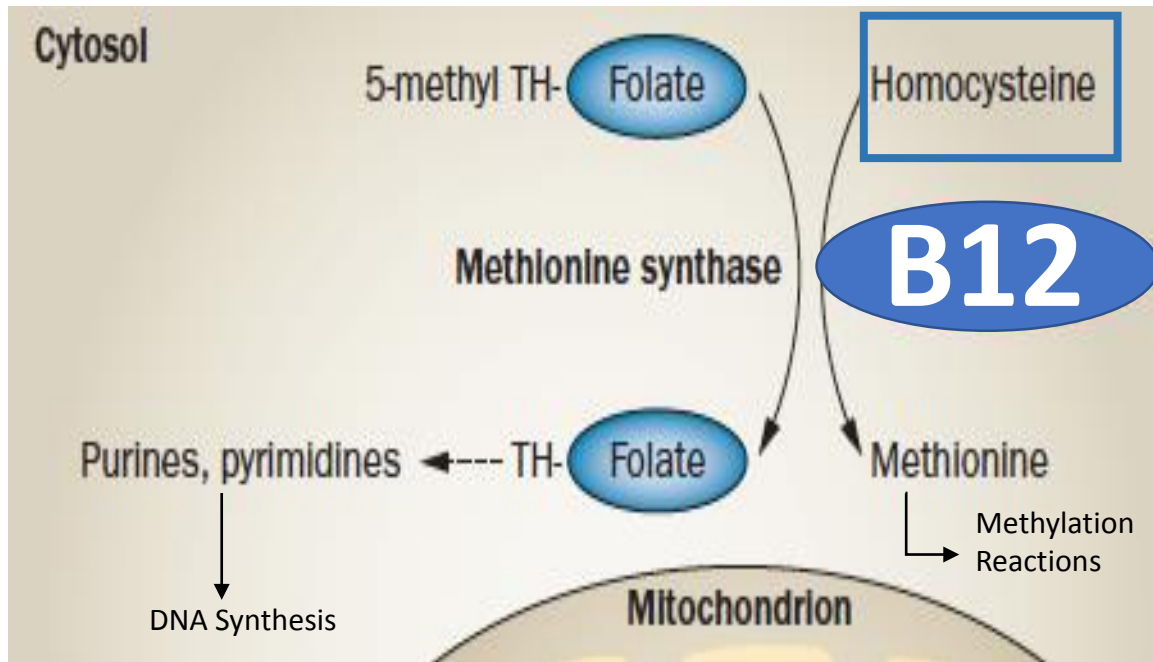
Yes

No

# Blood vitamin B12 concentration after 12 weeks on diet



# Blood MMA and homocysteine concentrations after 24 weeks on diet



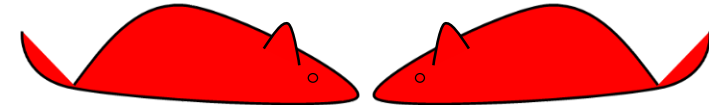
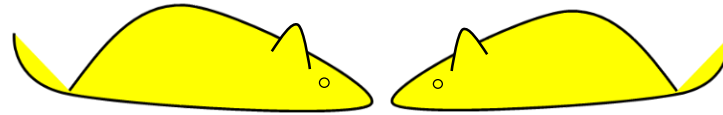


# Breeding mice on B12-deficient diet

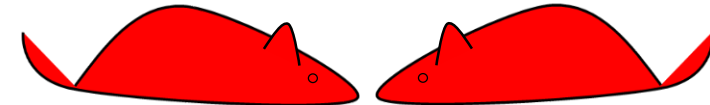
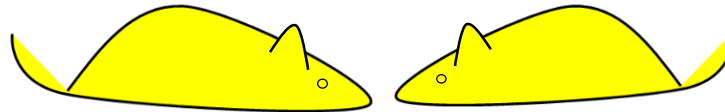
Vitamin B12 supplemented

Vitamin B12-deficient diet

Control

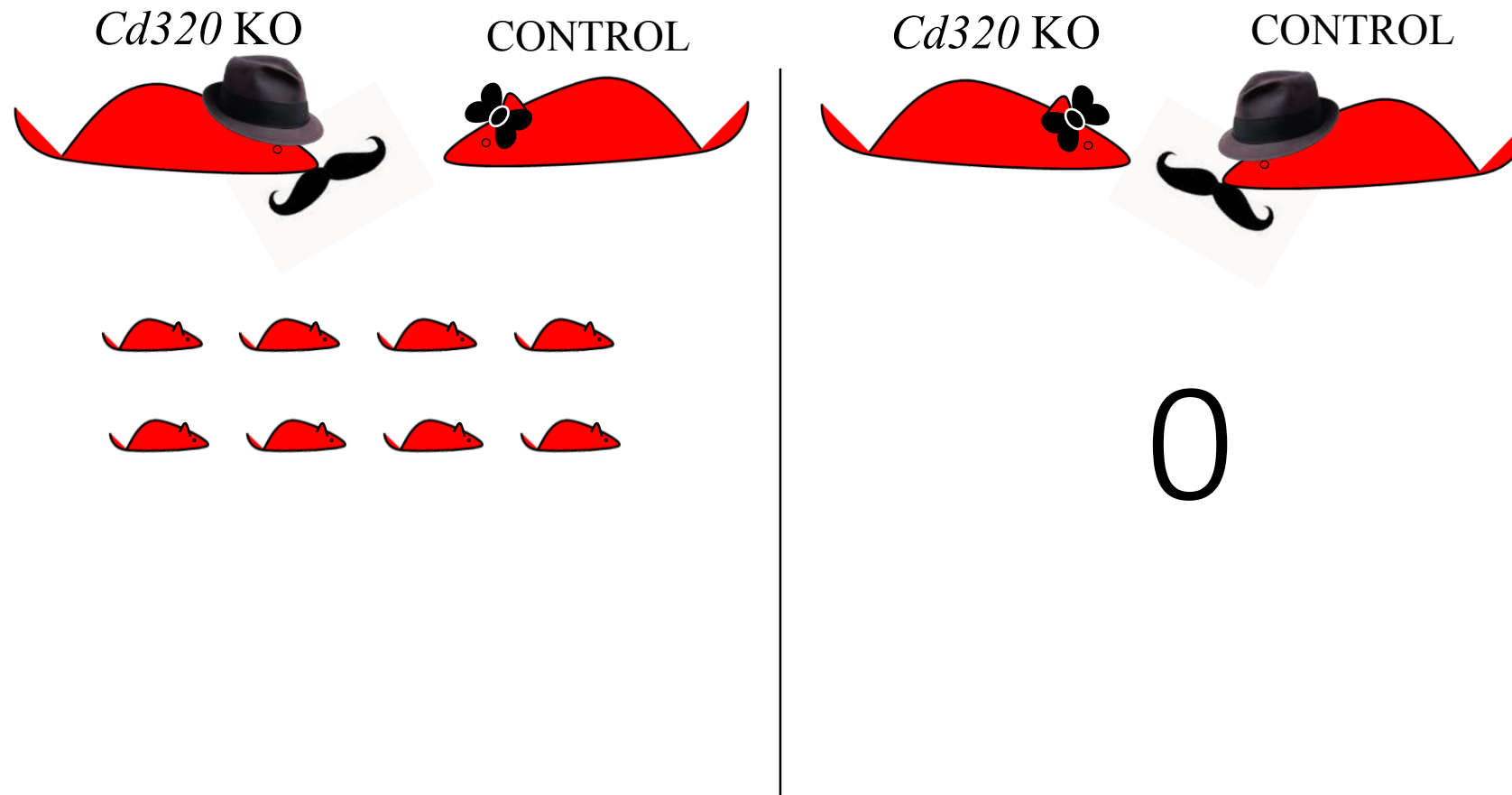


*Cd320* KO

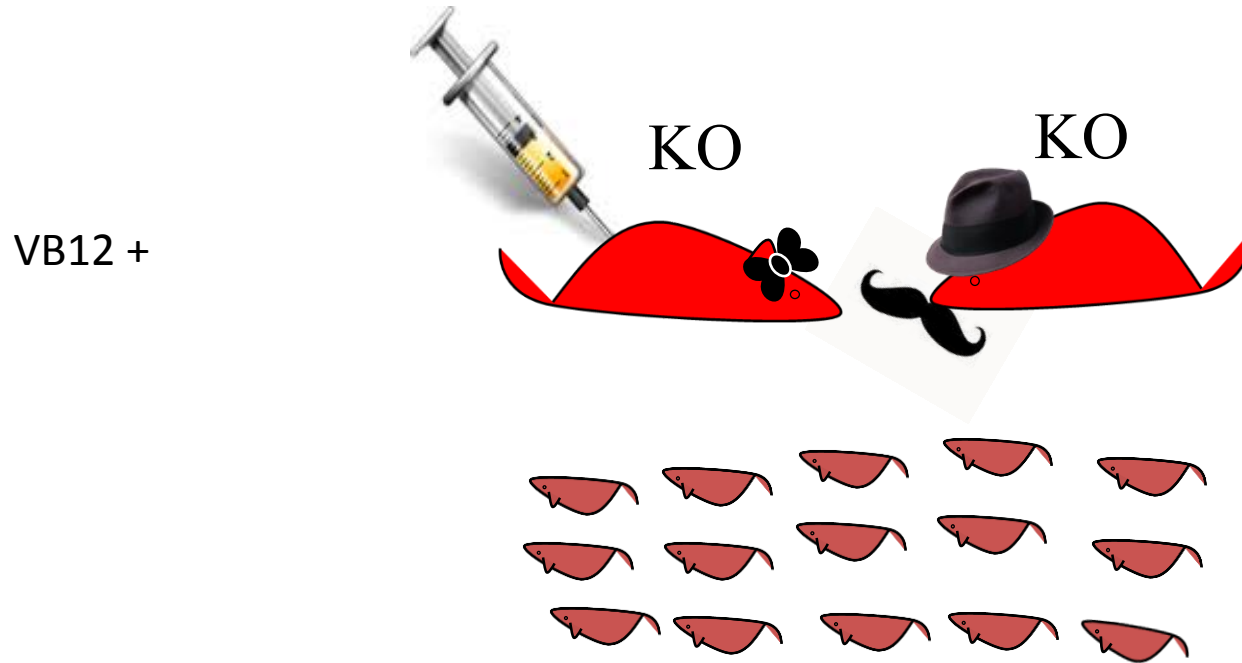


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# Reproductive defect in one or both sexes?



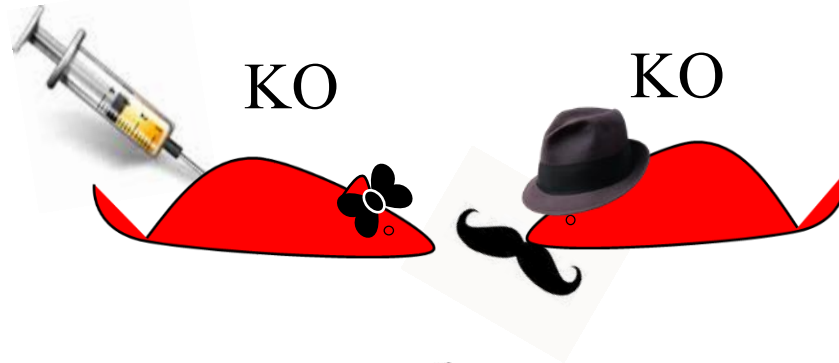
# Can vitamin B12 rescue the reproductive defect?



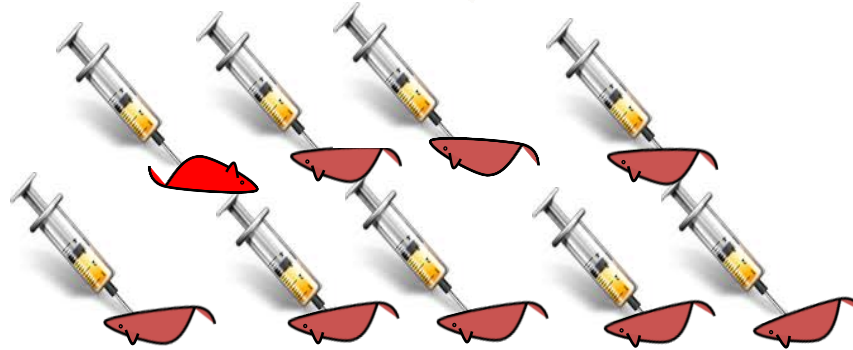
15 pups born – all died <24 hrs

# Can vitamin B12 rescue the newborn lethality?

VB12 +  
C-section (E17.5)



VB12 +

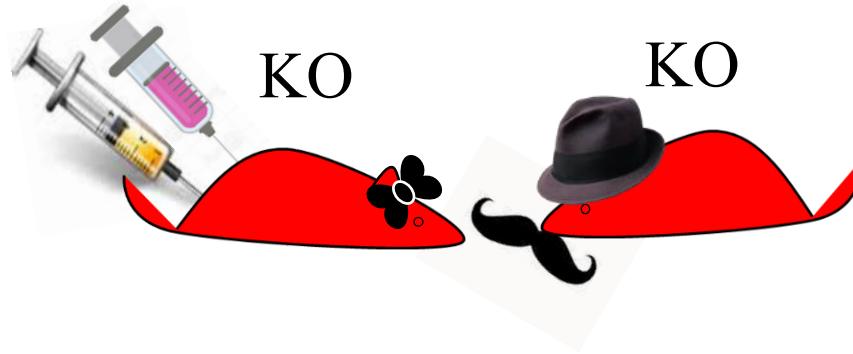


15 pups born – 1 survived to weaning



# Can vitamin B12 rescue the newborn lethality?

VB12 +  
Progesterone +  
C-section (E19.5)



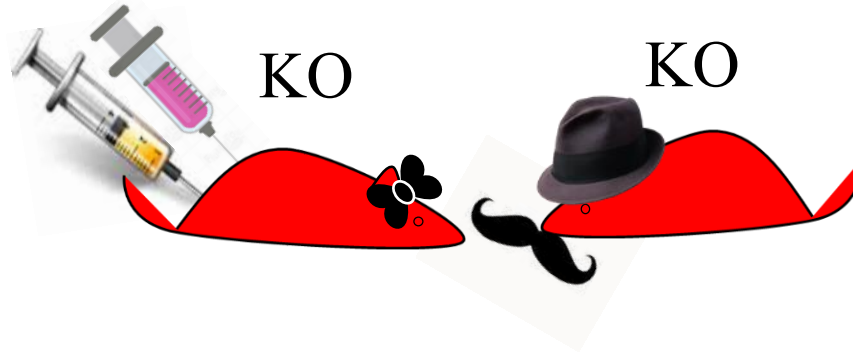
VB12 +



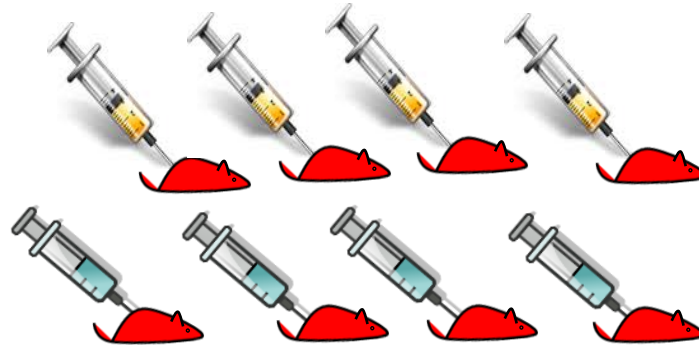
17 pups born – 14 survived to weaning

# Can vitamin B12 rescue the newborn lethality?

VB12 +  
Progesterone +  
C-section (E19.5)



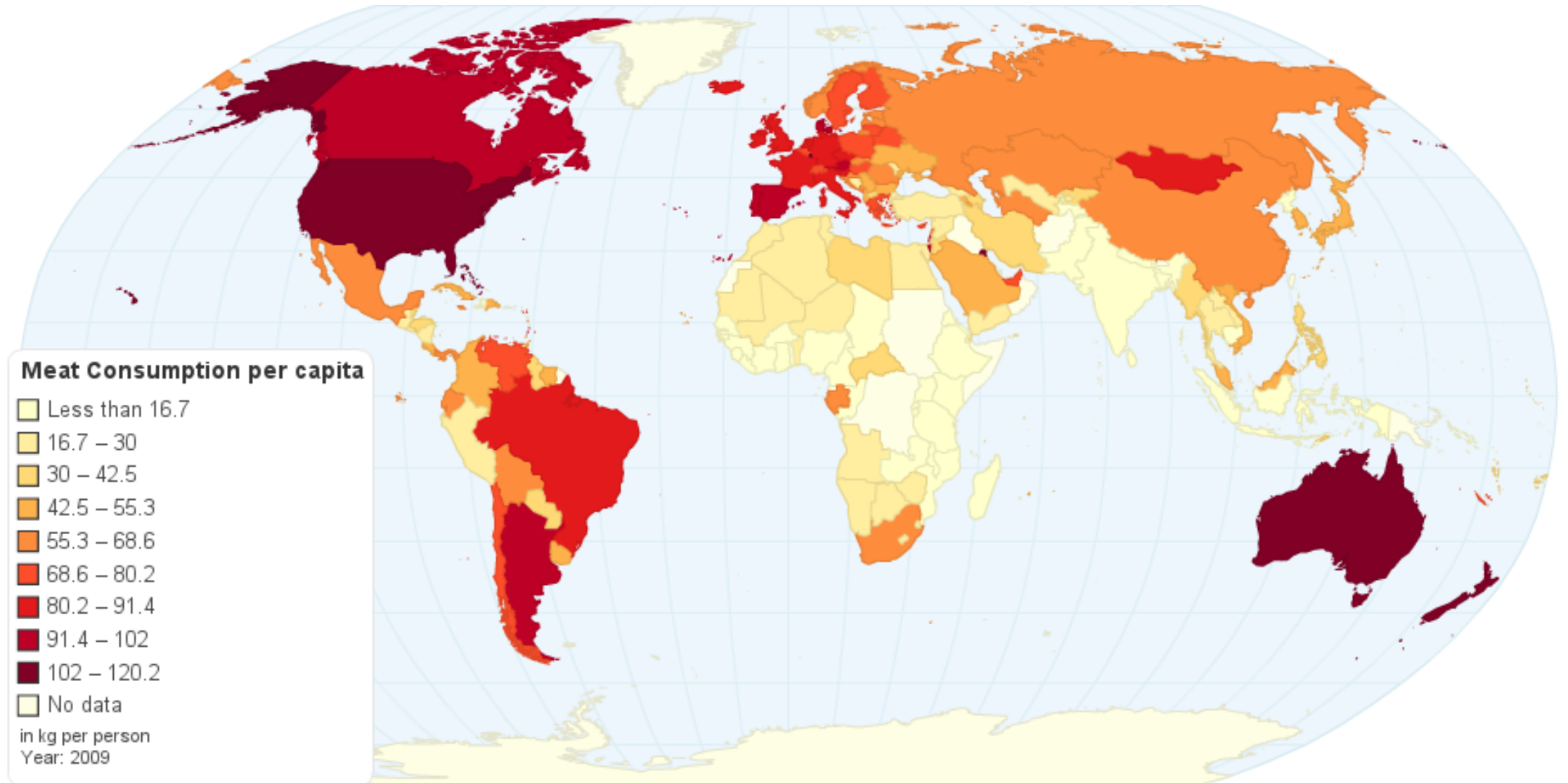
VB12 +



Saline +

15 pups born – 10 survived to weaning regardless of treatment

# Bringing it back to humans



# Looking at Development





# Microphthalmia



LEFT: Normal



RIGHT: abnormal

# Birth defects have been seen in some offspring

CONTROL



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*Cd320* KO



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# Conclusions

- Metabolic phenotype
  - Higher homocysteine
    - Specifically in female KO
- Reproductive defect
  - Perish early during embryonic development
  - Rescue development with vitamin B12 injection
  - Perish shortly after birth
  - May be rescued by vitamin B12 injection

# Future Questions to Address





# Future Journey



JOHNS HOPKINS   
CENTER FOR AMERICAN  
INDIAN HEALTH

**HELLO**  
MY NAME IS

*Future M.D.*

# Acknowledgements

- **NHGRI Gene and Environment Interaction Section**
  - Lawrence Brody
  - David Bernard
  - Faith Pangilinan
  - Courtney Benoit
  - Nadia Huerbi
- **NHGRI Transgenic Mouse Core**
  - Jun Cheng
  - Karen Hazzard
- **Trinity College – Dublin**
  - Anne Molloy
  - Clare Horan