How faulty nutrition causes disease

Mammalian Pathobiology
PATB 4130/5130

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How does faulty nutrition develop?

- **Primary Malnutrition**
  - Protein-calorie undernutrition (starvation)
  - Dietary deficiency of specific nutrients

- **Secondary Malnutrition**
  - Nutrients present in adequate amounts but appetite is suppressed
  - Nutrients present in adequate amounts but absorption and utilization are inadequate
  - Increased demand for specific nutrients to meet physiological needs

Protein – calorie undernutrition

- Simply put = starvation
- Occurs in humans and animals
- **Primary** – mainly in underdeveloped nations but can also occur in more affluent industrialized countries
  - Estimated that ½ billion people suffer from mild to severe protein-calorie undernutrition
  - Estimated that 10 million individuals, mainly children die annually
Kwashiorkor – protein starvation

Marasmus – protein/carbohydrate starvation

Protein – calorie undernutrition

- **Secondary** – starvation secondary to some other condition
  - **Decreased intake**
    - Poor dentition
    - Dysphagia
    - Systemic disease → Anorexia
  - **Malabsorption or decreased utilization**
    - Biliary and pancreatic disease
    - Gastrointestinal disease – parasitism, inflammation, etc
  - **Increased requirements**
    - Requirements for growth versus adult maintenance
    - Pregnancy, trauma, burns, excessive losses

Yes – starvation does occur in animals
Starvation in Animals
Primary or Secondary

- **Secondary** – starvation secondary to some other condition
  - **Decreased intake**
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How would you develop an understanding of malnutrition involving specific nutrients as a cause of disease?
How would you develop an understanding of malnutrition as a cause of disease?

Requires an understanding of the role nutrients play in basic biochemical and metabolic pathways! What is their function? How do they relate to other nutrients?

This information will provide the potential mechanisms for malnutrition as a basis for specific diseases.

Even after knowing the metabolic function(s) of the nutrients; it can be difficult to directly correlate these mechanisms with specific lesions or disorders!

In many instances, specific nutritional deficiencies become more complex, involving multiple micronutrients

Example

Vitamin $B_{12}$ (cyancobalamin)

- Is an essential dietary nutrient for humans, absorption requires intrinsic factor, a carrier protein synthesized by parietal cells in the stomach
- There are only two known biochemical reactions requiring $B_{12}$
  - Methylation reaction to form folic acid required for DNA synthesis
  - $\text{Methylmalonyl-CoA} \rightarrow \text{Succinyll-CoA}$
- Diseases associated with $B_{12}$ deficiency
  - Pernicious anemia
  - Subacute combined degeneration of the spinal cord
For this lecture – two specific deficiencies will be covered to illustrate the diversity of diseases associated with nutrition

**Copper**

&

**Vitamin B₁ (thiamine)**

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**Copper – known functions**

- **Energy production** – cytochrome C oxidase
- **Connective tissue** – lysyl oxidase (collagen), ascorbate oxidase (bone)
- **Iron transport and heme synthesis** – ceruloplasmin
- **Neurotransmission** – monoamine oxidase
- **Myelin formation** – cytochrome C oxidase
- **Melanin formation** – tyrosinase
- **Antioxidants** – Cu,Zn superoxide dismutase

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**Copper – how do deficiencies occur?**

- **Primary**
  - Decreased dietary intake as in copper deficient soils (animals)
- **Secondary**
  - Decreased transport and utilization as in Menkes kinky hair disease (humans)
  - Decreased absorption due to antagonism by other nutrients in the diet (humans and animals)
    - Molybdenum
    - Sulfates
    - Zinc
Humans - Menkes Kinky Hair Disease

- Described in 1962
- Hereditary (x-linked recessive)
- Due to defective Cu-transporting ATPase (intestinal Cu uptake is normal but Cu cannot be transported to other tissues)
- 1/300,000 worldwide incidence (10X higher in Australia)

Menkes Kinky Hair Disease

- Clinical findings
  - Brain: Seizures, various abnormalities (cystic degeneration, nerve cell loss, etc)
  - Skin and hair: pili torti, trichorrhexis nodosa, hypopigmentation
  - Bone, connective tissue abnormalities
  - Blood vessels – phlebectasia, aneurysms

Cu - Other human maladies reported

- Motor neuron disease – degeneration of motor neurons in the ventral horns of the spinal cord
  - Late onset
  - At least some cases associated with overzealous zinc supplementation
  - Mechanism for copper deficiency?
Copper deficiency disease in animals

- Can be primary or secondary
  - Falling disease in cattle
  - Aneurysms*, arterial rupture
  - Abnormal bone formation*
  - Hair abnormalities*
  - Abnormal pigmentation*
  - Enzootic ataxia / swayback*
  
  *All of these share at least some similarities with Menkes kinky hair disease.

Left – gross photo of a pulmonary artery aneurysm

Right – Microscopic photo of an aneurysm

Left: Menkes infant

Right: Cu deficient calf
Copper deficiency – small ruminants
The deficiency can result in two syndromes: congenital neurologic disease at the time of birth (swayback) and a delayed form (enzootic ataxia).

- **Swayback**
  - Affects lambs, rarely kids
  - Clinical signs are evident at the time of birth
    - Dullness, depression, blindness, recumbency, flaccid limbs, may appear deaf

- **Enzootic ataxia**
  - Affects lambs & kids
  - Normal at birth; after birth up to about 6 months of age
    - Clinical signs are progressive incoordination, ataxia, may have some muscle atrophy

- **Lesions**
  - Cavitated, cystic areas in cerebral cortex resembling porencephaly
  - See enzootic ataxia

Thiamine (vitamin B₁) deficiency

- Humans and carnivorous animals have an absolute dietary requirement
- Ruminants and other herbivores can synthesize due to thiamine producing bacteria in the rumen and gut
- All tissues require thiamine but the effects of thiamine deficiency typically involve the heart and/or nervous system
Monogastrics - Thiamine (vitamin B₁) deficiency

- Mechanisms of deficiency
  - Inadequate intake (high carbohydrate diets, others)
  - Increased requirements (strenuous physical exertion, fever/disease, pregnancy, lactation, rapidly proliferating cancers)
  - Excessive loss (kidney disease – controversial)
  - Anti-thiamine factors in the diet (coffee, tea, thiaminases in foods such as fish, shellfish, some ferns)
  - Drugs (diuretics, 5-fluorouracil in cancer therapy)

Functions of Vitamin B₁

- Cofactor for enzymes in 3 metabolic pathways
  - Pentose phosphate pathway
  - Glycolysis
  - Tricarboxylic acid cycle

Thiamine deficiency diseases in humans

- **Heart:** wet Beriberi – rapid heart rate, cardiomegaly, congestive heart failure with edema (fluid retention)
- **Peripheral nerves:** dry beriberi – ‘burning feet syndrome’ muscle weakness
- **Brain:**
  - Wernicke’s encephalopathy – nystagmus (abnormal eye movements), disorientation, confusion, apathy
  - Korsakoff’s psychosis – memory deficits, amnesia
Areas of the brain affected in Wernicke's encephalopathy

Thiamine Deficiency in Carnivores
- Occurs in: dog, cat, mink, fox
- Due to feeding raw fish or to destruction of thiamine in feedstuffs.
- Also called Chastek's paralysis
Thiamine deficiency in herbivores

The disease and lesions in ruminants are considerably different than in monogastrics. In ruminants, the disorder commonly affects the cerebrum rather than brain stem.

Thiamine (Vit B₁) Deficiency
Ruminants – Causal relationships

- Thiaminase containing plants
- Acidosis with loss of ruminal thiamine producing bacteria and proliferation of thiaminase bacteria
- Amprolium

- No absolute deficiency?
  - Cobalt deficiency
  - *Sulfur induced – total intake (water & forage) should not exceed 0.3-0.4% or 3-4,000 ppm.
  - *Molasses – urea based diets
  - *Plants (Kochia scoparia)

In many instances, a causal relationship between absolute deficiency of thiamine and ‘polio’ has been elusive.

Lesions of polioencephalomalacia in ruminants
Overnutrition – If a little is good, more is better. Correct?

Have we mentioned a nutrient in past lectures that can cause disease if in excess?

What is the most prevalent condition associated with malnutrition in developed, industrialized nations?

obesity
Obesity increases the risk for...

- Ischemic heart disease
- High blood pressure
- Renal disease
- Diabetes mellitus
- Stroke
- Certain forms of cancer

Causes/risk factors of obesity

- **Kcal intake > Kcal burned**
  - Diet and lifestyle
- Genetics & neurobiological mechanisms
  - Leptin, grelin, orexin, adiponectin
- Medical and psychiatric illness
  - Example: hypothyroidism
- Socioeconomic status
  - Controversial
Sample Question #1

• Which of the following best describes the cause of edema in kwashiorkor?

  1. Blockage of lymphatics
  2. Increased venous hydrostatic pressure
  3. Decreased intravascular colloidal osmotic pressure
  4. Decreased hydrostatic pressure

Sample Question #2

• Name one disease or abnormality that may be observed with copper deficiency.