IN THE BEGINNING...

• Adequate diet in 19th century
  – 12% protein
  – 5% minerals
  – 10-30% fat
  – 60-70% carbohydrates

• What caused diseases such as rickets, scurvy, and beri-beri?

Early Experiments

• Fed appropriate proportions to animals
  – Low survival

• What was missing from this diet?

• Other findings supported existence of essential micronutrients in diet

Case of Beri-Beri

• High incidence among prisoners in Dutch East Indies

• These prisoners were fed predominantly a diet of polished rice

• Providing the hulls of rice got rid of beri-beri

• Conclusion: Polished rice contained toxin that was neutralized by a substance in the hull

Scurvy Prevention

• Discovery of substance that prevent scurvy in sailors
  – Substance in citrus fruits

  German chemist, Funk, stated that a "vital amine" present in foods was required for health and survival
STUDY AT UNIVERSITY OF WISCONSIN

• Experiment on diary cattle
• Fed four groups same proportions
  – Each group’s entire ration from a single grain – corn, oats, wheat, or mixture
• Outcomes:
  – Corn diet → reproduced & produced large quantities of milk
  – Wheat diet → poor outcomes; many failed to survive
  – Oats diet → results between that of corn and wheat

FURTHER STUDIES

• Used white rat to study dietary components
  – Demonstrated that butter fat and cod liver oil contained a factor that prevented eye disease and supported growth
  – This was a fat soluble substance
• Discovered water-soluble factor that prevented neurological disease similar to beri-beri
• Another water soluble factor was found to prevent scurvy

“THE ENGLISH DISEASE”

• Sir Edward Mellanby concerned with high incidence of rickets in United Kingdom
  – Could rickets be due to a dietary deficiency?
• Fed Scottish diet (primarily oats) to dogs that were inadvertently kept indoors
  – Developed rickets
  – Cured with cod liver oil
• Must be Vitamin A!

“THE ENGLISH DISEASE”

• McCollum tested hypothesis about Vitamin A deficiency linked with rickets
• Destroyed the Vitamin A in cod liver oil
  – No longer prevented xerophthalmia or Vitamin A deficiency
  – HOWEVER… still cured rickets

HEALING RICKETS WITH UV LIGHT

• Physicians and researchers in Vienna & England noted that sunlight cured rickets
• Study at Univ. of Wisconsin
  – During summer goats had positive calcium balance
  – Goats brought indoors in winter → calcium decreased
  – Sunlight → calcium retention

HEALING RICKETS WITH UV LIGHT

• Observation of goats led to further studies with rats
• Irradiated rats, their food, and air in their cages
  – Irradiation in rat and food prevented/cured rickets
• Found that this activity was associated with non-saponifiable lipid fraction
  – Concluded that inactive lipid in diet & skin converted by UV light into active substance
• Process patented → industry had cure for rickets as major medical problem
IDENTIFICATION OF VITAMIN D

• Vitamin D₂ isolated from irradiation mixture of ergosterol
• In 1935 → 7-dehydrocholesterol isolated
• In 1937 → Vitamin D₃ identified

• D₃ natural form of Vitamin D
  – Formed in skin as result of UV irradiation of 7-dehydrocholesterol
  – Is Vitamin D truly at vitamin?
  – Is it normally produced in skin, not in natural foods?

VITAMIN D FORMS

<table>
<thead>
<tr>
<th>Ergocalciferol (Vitamin D₂)</th>
<th>Not naturally occurring in body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecalciferol (Vitamin D₃)</td>
<td>Naturally occurring</td>
</tr>
<tr>
<td>Calcidiol (25-hydroxyvitamin D₃)</td>
<td>Prohormone made in liver</td>
</tr>
<tr>
<td>Calcitriol (1,25-dihydroxyvitamin D₃)</td>
<td>Actives from made in kidneys</td>
</tr>
</tbody>
</table>

ROLE OF VITAMIN D

<table>
<thead>
<tr>
<th>Ergocalciferol (Vitamin D₂)</th>
<th>Absorption of calcium &amp; phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecalciferol (Vitamin D₃)</td>
<td>Helps body absorb calcium</td>
</tr>
<tr>
<td>Calcidiol (25-hydroxyvitamin D₃)</td>
<td>Not an active form of Vitamin D until the conversion to Calcitriol</td>
</tr>
<tr>
<td>Calcitriol (1,25-dihydroxyvitamin D₃)</td>
<td>Increases uptake of calcium from GI tract</td>
</tr>
<tr>
<td></td>
<td>Enhance effect of PTH on bone</td>
</tr>
<tr>
<td></td>
<td><strong>Increases calcium in blood</strong></td>
</tr>
<tr>
<td></td>
<td>Regulates cell growth</td>
</tr>
<tr>
<td></td>
<td>Immunomodulation</td>
</tr>
</tbody>
</table>

VITAMIN D3 ≠ VITAMIN D2

7-dehydrocholesterol → Ergosterol
Produced by skin by UVB → Fully active
Not produced in humans → 1/3 activity D3

VITAMIN D3 ≠ 1,25(OH)₂VITAMIN D₃

<table>
<thead>
<tr>
<th>VITAMIN D3</th>
<th>1,25(OH)₂D₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologically inactive</td>
<td>Steroid hormone</td>
</tr>
<tr>
<td>Does not bind to VDR</td>
<td>Acts through Vitamin D Receptor (VDR)</td>
</tr>
</tbody>
</table>

FOOD SOURCES OF VITAMIN D

<table>
<thead>
<tr>
<th>Very few sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty fish (salmon, tuna, mackerel)</td>
</tr>
<tr>
<td>Fish liver oil</td>
</tr>
<tr>
<td>Beef liver, cheese, egg yolks</td>
</tr>
<tr>
<td>Fortified foods → largest food source of Vitamin D</td>
</tr>
<tr>
<td>Cholecalciferol in milk or juices</td>
</tr>
</tbody>
</table>
Vitamin D is technically not a vitamin (an essential dietary factor).

Vitamin D is a PROHORMONE (steroid) produced photo-chemically in the skin from 7-dehydrocholesterol.

METABOLISM OF VITAMIN D

- Renal synthesis of calcitriol
  - Up-regulation by PTH
  - Down-regulation by fibroblast-like growth factor (FGF23)

- Calcitriol
  - Binds to vitamin D binding protein (DBP) → transported to target organs

VITAMIN D SYNTHESIS FROM SUNLIGHT

Only UV light between 270-320nm can produce Vitamin D3 (UVB).
WHAT ABOUT TANNING BEDS?

- Produce UVA & UVB
- Studies indicate ~20% skin exposed to sun or tanning bed resulted in increased concentrations of Vitamin D3 and 25-(OH)D3
- Not FDA approved to increase Vitamin D

Both QUANTITY (intensity) and QUALITY (wavelength) of UVB radiation are important determinants in Vitamin D3 synthesis.

Direct correlation between Vitamin D deficiency & latitude which person lives.

UVB must activate 7-dehydrocholesterol in the deepest layers of the epidermis.

Keratinocytes: Excretes keratin which waterproofs & strengthens skin

Melanocytes: Produce melanin (pigment) which darkens the skin

Greatest capacity for production of pre-vitamin D3 and vitamin D3

Highest concentrations of 7-dehydrocholesterol

Melanin absorbs UV light in the 290-320nm range.

- Serves as a filter for penetration into the stratum spinosum and stratum basale.
- Competes with 7-dehydrocholesterol for UV absorption.

Melanin is an effective natural sunscreen.

Darker skin (more melanin) interferes with cutaneous synthesis of Vitamin D.

African Americans with dark skin tone require 5-10 times the amount of sunlight necessary to produce similar (though still not as much) serum concentrations of Vitamin D.

In ideal atmospheric conditions, with clear skies, 30 minutes of whole body exposure (pale skin) to sunlight without clothes or sunscreen may result in synthesis of 10,000-20,000 IU of Vitamin D.

This quantity is enough to supply the body’s full needs.

>90% of Vitamin D requirement for most people comes from casual exposure to sunlight.

Exposure of arms & legs for 10-30 minutes between 10am-3pm twice per week is often adequate (depends on time of day, season, latitude, skin tone).

ALTERATION OF VITAMIN D3 PRODUCTION
Anything that influences penetration of UVB or alters amount of 7-dehydrocholesterol may affect cutaneous productions of Vitamin D3

7-dehydrocholesterol declines as we age
- 70 year old & 25 year old exposed to same sunlight exposure
- 70 year old makes ~25% of vitamin D₃ as the 25 year old

Clouds can eliminate up to 99% UVB radiation

Sunscreen absorbs UVB and some UVA
- SPF 8 → reduces capacity of skin to produce vitamin D₃ by >95%
- SPF 15 → reduces capacity by >98%

Latitude can drastically influence Vitamin D₃ production

Markedly decreased UVB in winter months

- UVB is at its highest between 10:00AM and 3:00PM during spring, summer, autumn
- Less cutaneous formation of vitamin D3 in early morning or late evening

**Vitamin D** is best known for its role in **calcium regulation**

**VITAMIN D RECEPTORS**
- 36 tissues express VDR
- Potential to produce biological response depends on availability of Vitamin D3


**ACTIONS OF VITAMIN D**

Without Vitamin D3:
- 10-15% dietary calcium (normal ~30%) and 60% phosphorus (normal ~80%) are absorbed
IT’S MORE THAN JUST CALCIUM REGULATION...

- The activity of Vitamin D3 expands beyond the regulation of calcium homeostasis
- Currently recognized to play vital roles in:
  - Adaptive immunity
  - Tumor suppression
  - Insulin secretion by β-pancreatic cells
  - Cardiac and blood pressure regulation
  - Brain and fetal development

VITAMIN D DEFICIENCY

FACTORS AFFECTING VITAMIN D

- Sun exposure
- Kidney disease
- Age
- Malabsorption syndrome
- Skin color

An estimated ONE BILLION people worldwide across all ethnicities and age groups have a vitamin D deficiency.

VIT D DEFICIENCY HIGHEST AMONGST:

- Elderly
- Institutionalized (67%)
- Hospitalized (57%)
- 2/3 of healthy young adults in Boston were vitamin D deficient at end of winter

A GLANCE AT THE DATA...

- >50% African Americans in US at risk
- Young adults that seldom see daylight or always use sunscreen at risk
- Boston → 84% African American men and women over age 65 were deficient
- Women and children in Saudi Arabia → high prevalence of osteomalacia and rickets
- 32% students & doctors at Boston Medical Center were vitamin D deficiency at end of winter
Vitamin D deficiency appears to be associated with a wide range of diseases

(A direct causal relationship remains unclear)

EFFECT ON BONES

Osteopenia
Osteomalacia (children & adults)
Rickets (children)

VITAMIN D & CANCER

• Levels of 25-hydroxyvitamin D <20ng/mL associated with 30-50% increased risk and higher mortality rate from colon, prostate, and breast cancer

• Nurses Health Study (~33,000 subjects)
  – Inverse relationship between colorectal cancer and median 25-hydroxyvitamin D, but not 1,25(OH)₂vitaminD₃

LIVING AT HIGHER LATITUDES

• Increased cases of Type 1 diabetes, Crohn's disease, Multiple Sclerosis
  – Living below 35° latitude first 10 years of life ↓ risk of MS 50%

• Increased risk of hypertension and CV disease

• Increased incidence of schizophrenia and depression

HYPERPARATHYROIDISM
IMMUNE SYSTEM IMPAIRMENT
• VDR expressed on B cells, T cells, and Ag presenting cells
  – All capable of synthesizing ACTIVE vitamin D
• Modulates immune cell function
• Influences natural & adaptive immunity
• Lack of vitamin D → poor immune function

CONTROVERSY
Sunscreen or no sunscreen?
Too much sun → fear of cancer
Too little sun → Vitamin D deficiency

RECOMMENDED DAILY INTAKE
• Two sets of guidelines
  – Institute of Medicine (IOM)
  – Endocrine Society

<table>
<thead>
<tr>
<th>Ages 1-18</th>
<th>Ages 19-70</th>
<th>Ages 71+</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDA (IU/day)</td>
<td>RDA (IU/day)</td>
<td>RDA (IU/day)</td>
</tr>
<tr>
<td>IOM</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Endoc. Society</td>
<td>600-1000</td>
<td>1500-2000</td>
</tr>
</tbody>
</table>

US ENDOCRINE SOCIETY CLASSIFICATION

<table>
<thead>
<tr>
<th>Vitamin D Status</th>
<th>Vitamin D levels (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>21-29</td>
</tr>
<tr>
<td>Sufficiency</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Toxicity</td>
<td>&gt;150</td>
</tr>
</tbody>
</table>

Source | Approx Vitamin D content
Salmon
  Fresh, wild (3.5 oz) | 600-1000 IU
  Fresh, farmed (3.5 oz) | 100-250 IU
  Canned (3.5 oz) | 300-600 IU
Sardines, canned (3.5 oz) | 300 IU
Mackerel, canned (3.5 oz) | 250 IU
Tuna, canned (3.6 oz) | 230 IU
Fortified milk (8 oz) | 100 IU
Fortified orange juice (8 oz) | 100 IU
Infant formula (8 oz) | 100 IU
Exposure to sunlight | 3000 IU
DIETARY SUPPLEMENTS

- Differ in chemical structure
- Manufactured differently
- Identical metabolism
- Both raise 25(OH)D levels
- At nutritional doses, both are equivalent
- At high doses, D$_2$ is less potent

VITAMIN D TOXICITY

PREVENTION OF EXCESS VITAMIN D

Melanin accumulation
Conversion to inactive metabolites

Excessive sun exposure & excessive food intake DO NOT cause Vitamin D toxicity
Toxicity most likely to occur from high intake of dietary supplements

TOXICITY

- Doses >50,000 IU can raise serum 25(OH)D to 300 ng/mL
- Doses >10,000 IU daily may cause kidney & tissue damage
- Doses of 5000 IU daily raised serum 25(OH)D to 100-150 ng/mL
- Leads to hypercalcemia, vascular & tissue calcification, damage to heart, kidney, and blood vessels
- Symptoms unlikely at daily intakes <10,000 IU (but there may be adverse effects over time)

TOLERABLE UPPER INTAKE LEVELS

<table>
<thead>
<tr>
<th>Age</th>
<th>Upper Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mos.</td>
<td>1000 IU</td>
</tr>
<tr>
<td>7-12 mos.</td>
<td>1500 IU</td>
</tr>
<tr>
<td>1-3 yr.</td>
<td>2500 IU</td>
</tr>
<tr>
<td>4-8 yr.</td>
<td>3000 IU</td>
</tr>
<tr>
<td>9-18 yr.</td>
<td>4000 IU</td>
</tr>
<tr>
<td>&gt;19 yr.</td>
<td>4000 IU</td>
</tr>
</tbody>
</table>

Generally, not recommended to take >2000 IU in supplement form without medical advice
IN SUMMARY...

• Vitamin D is a steroid hormone that is synthesized in the SKIN when activated by SUNLIGHT (UVB)

• Although Vitamin D is best known for its role in bone formation, receptors are found all over the body → NUMEROUS FUNCTIONS

MY TAKE HOME MESSAGE...

SOAK UP THE SUN

UV Index in the Middle of Summer

UV Index in the Dead of Winter