Diversity of Trace Elements and Toxic Metal Ions in Environmental Health and Human Diseases

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Outline

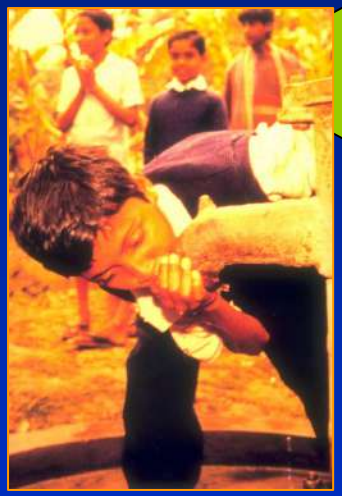
- **Introduction to Trace Elements, Metals and Metalloids**
- **Trace Elements and Known Biological/Toxicological Reactions**
- **Environmental Health and Diseases**
- **Concluding Remarks**

Suggested Reading: Essentials of Medical Geology (Selinus et al. 2005). Chapters on Nutrition (Gerald T. Combs), Biology of Trace Elements (Ulf Lindh)).

Natural deposits

Non-industrial

Drinking water
Food



Industrial

Agriculture
Mining/smelting
Coal burning
Micro-electronics

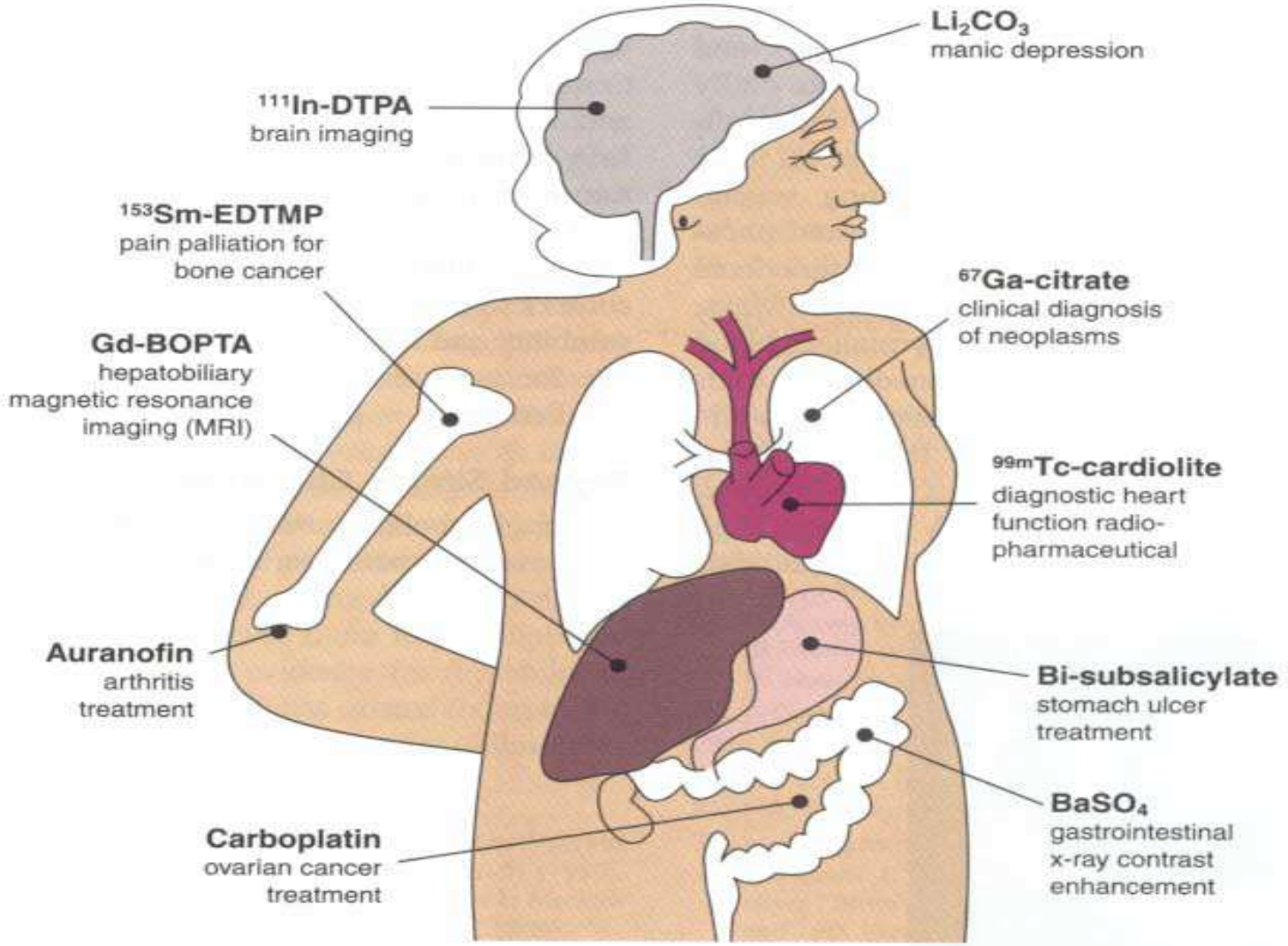
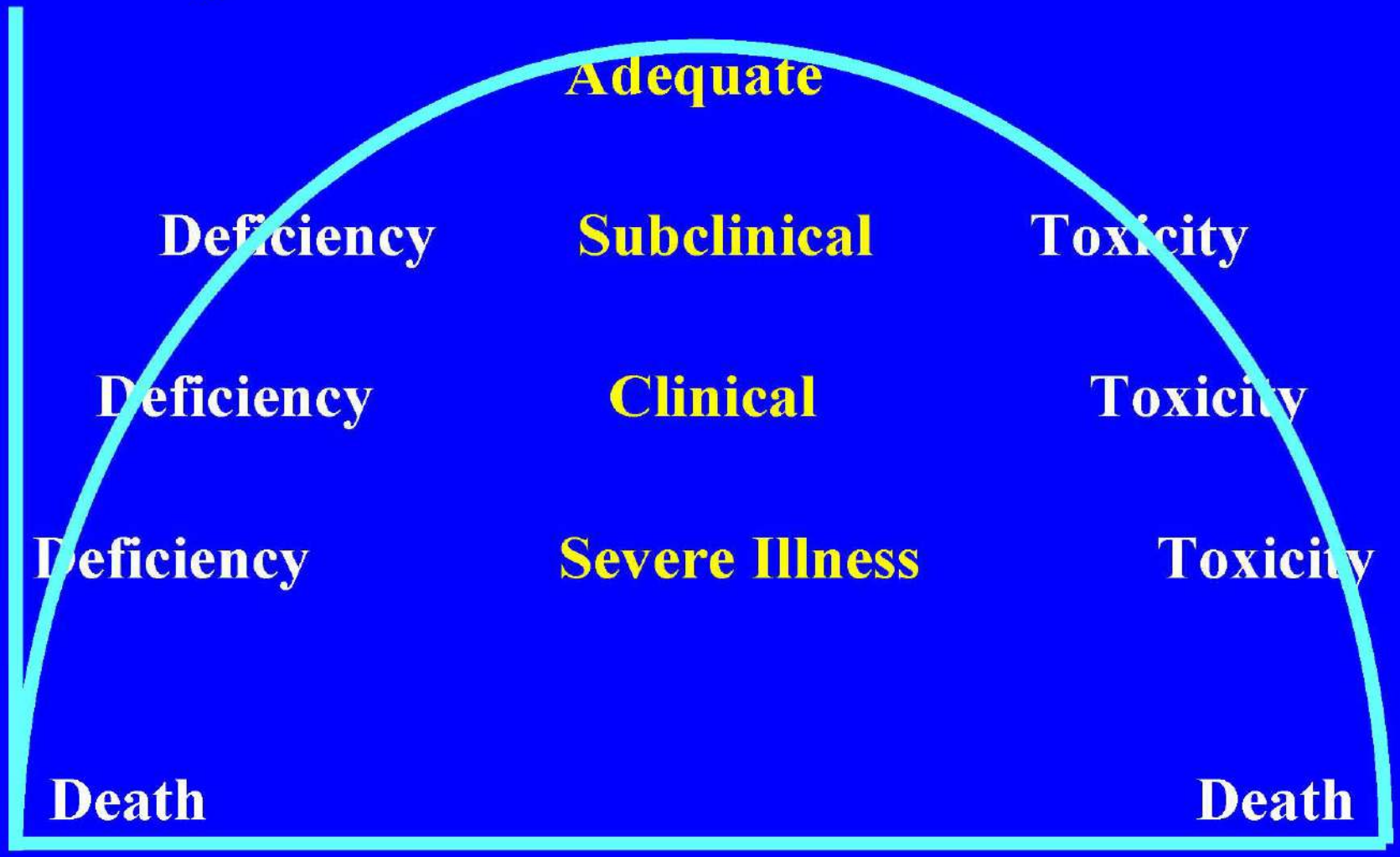


Fig. 1. Metal ions are important in diagnosis and therapy of a host of different human pathologies. Gd, ^{111}In, and ^{99m}Tc are used in medical imaging; ^{153}Sm and Au to relieve pain in bone cancer and arthritis, respectively; Bi to soothe upset stomach; and Li to calm bipolar psychosis. ^{67}Ga-citrate is used in clinical diagnosis of neoplasms (by SPECT imaging), and Pt is used for cancer treatment.

Science, Vol 300, May 2003

Spectrum of Nutrition Status



From Harold H. Sandstead, MD collection
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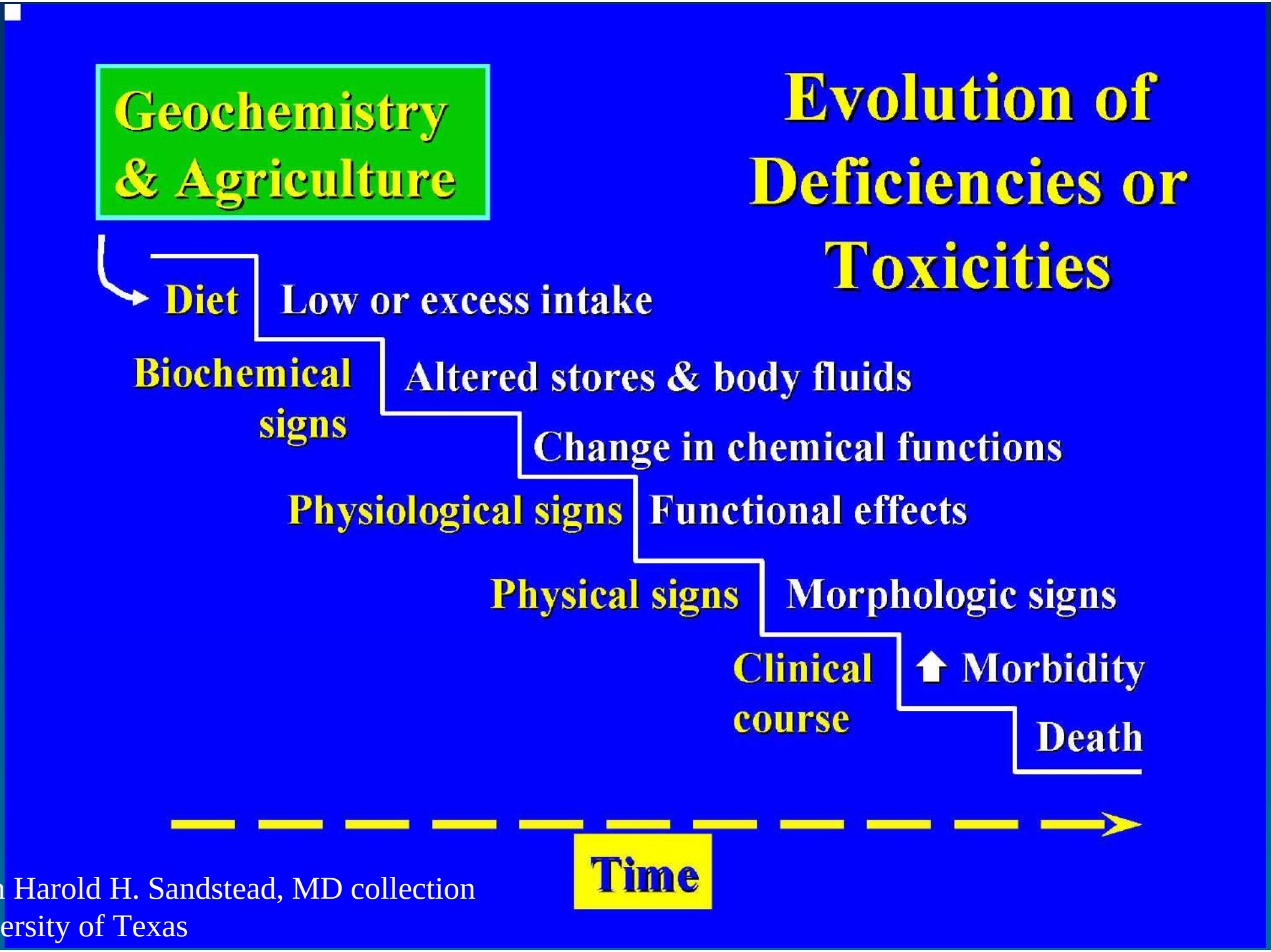

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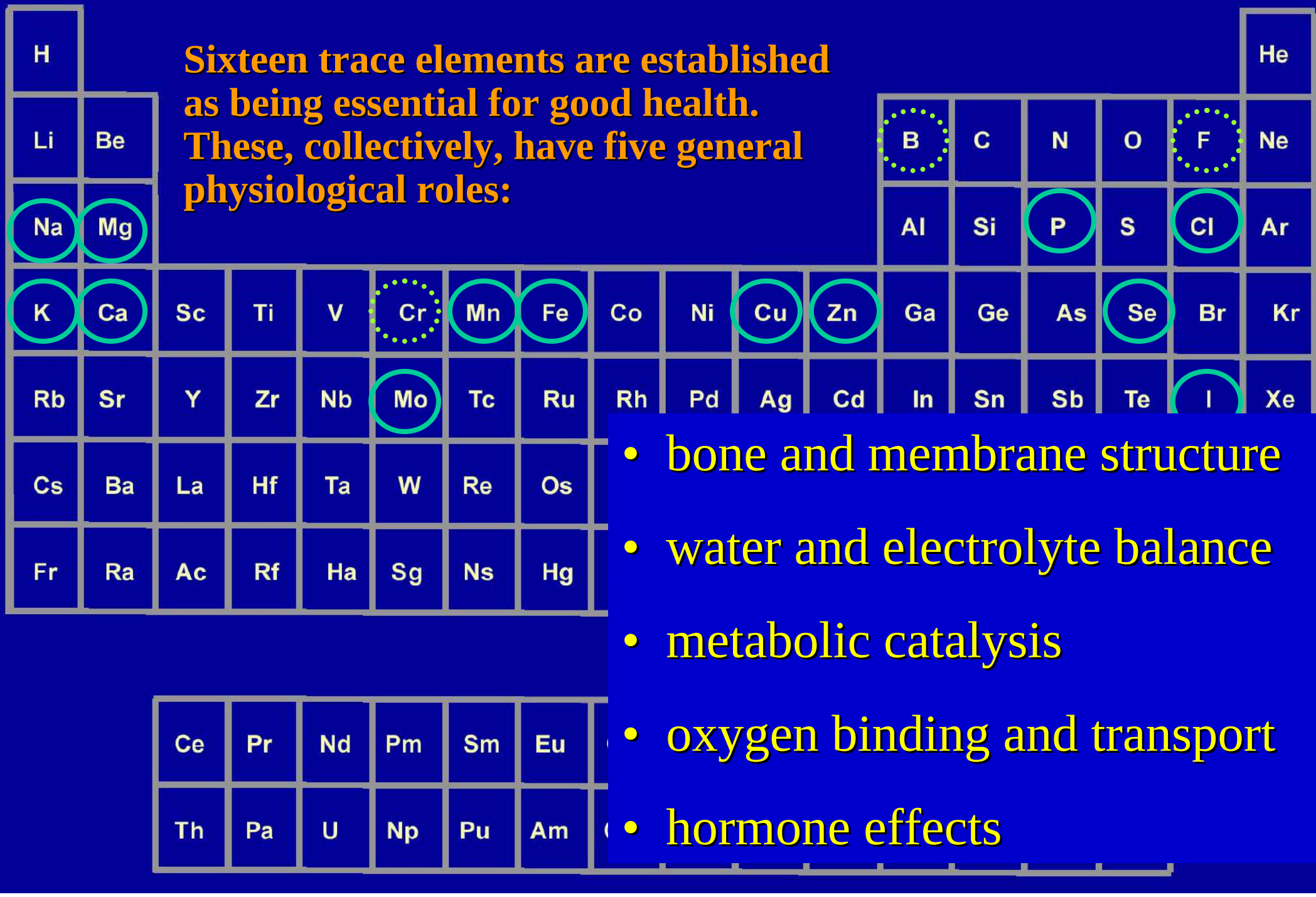
Geochemistry of Some Essential Elements Affects Human Health

- **Some essential elements whose geography is, or is presumed, directly related to human health:**
  - **I, Se, F, Cr, Mo, B**
- **Some essential elements whose geography is apparently not directly related to human health:**
  - **Fe, Zn, Cu, Ca, Mg**

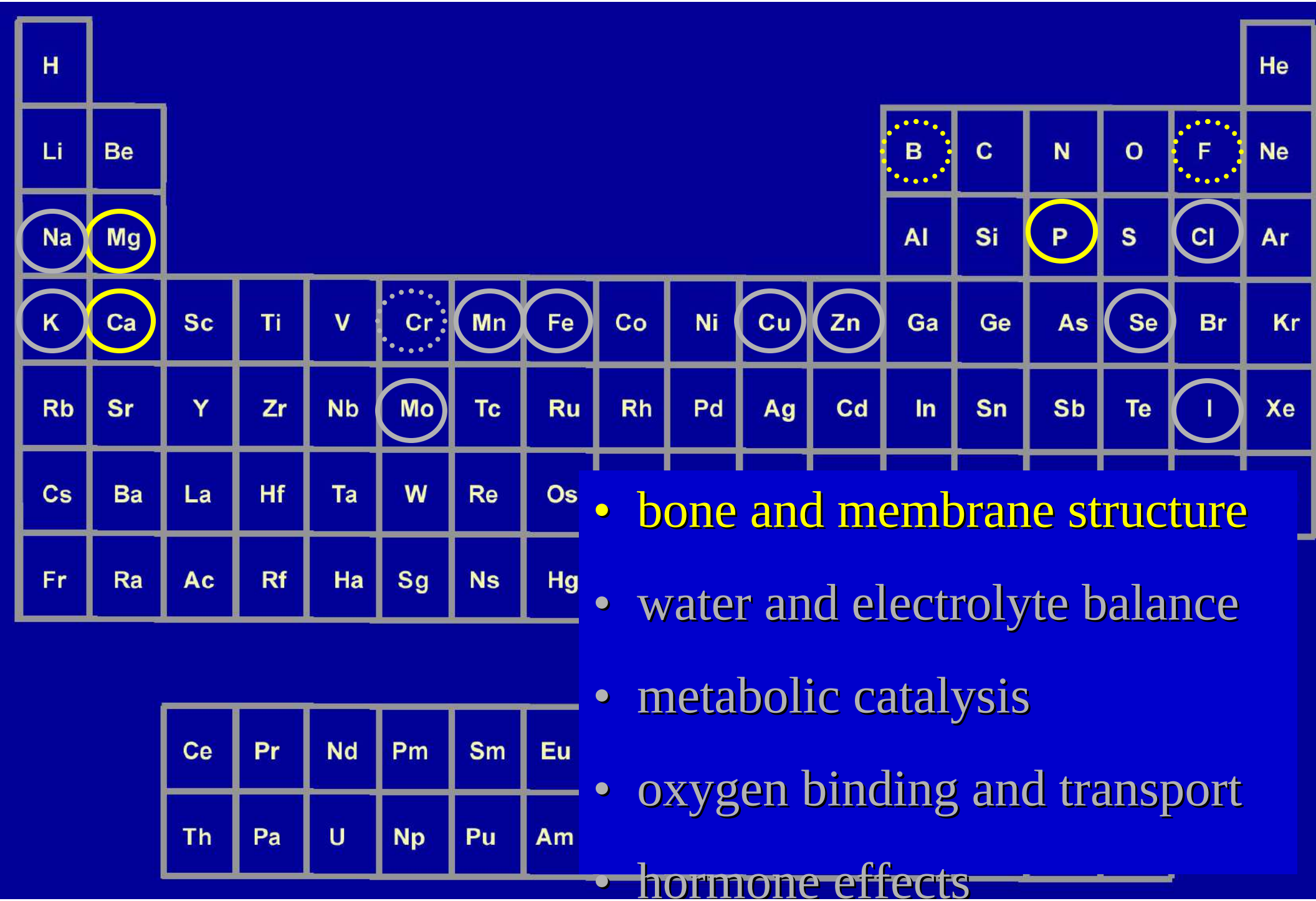
Criteria for Essentiality

- **Withdrawal or absence of the metal from the diet produces either functional or structural abnormalities, and that the abnormalities are related to or are a consequence of specific biochemical changes that can be reversed by the presence of the essential metal.**
- **Role: As catalyst in cellular functions.**
- **Sources: Must be obtained from air(oxygen), water an diet**
- **Concentration: needed on mcg to mg**

Sixteen trace elements are established as being essential for good health. These, collectively, have five general physiological roles:



- bone and membrane structure
- water and electrolyte balance
- metabolic catalysis
- oxygen binding and transport
- hormone effects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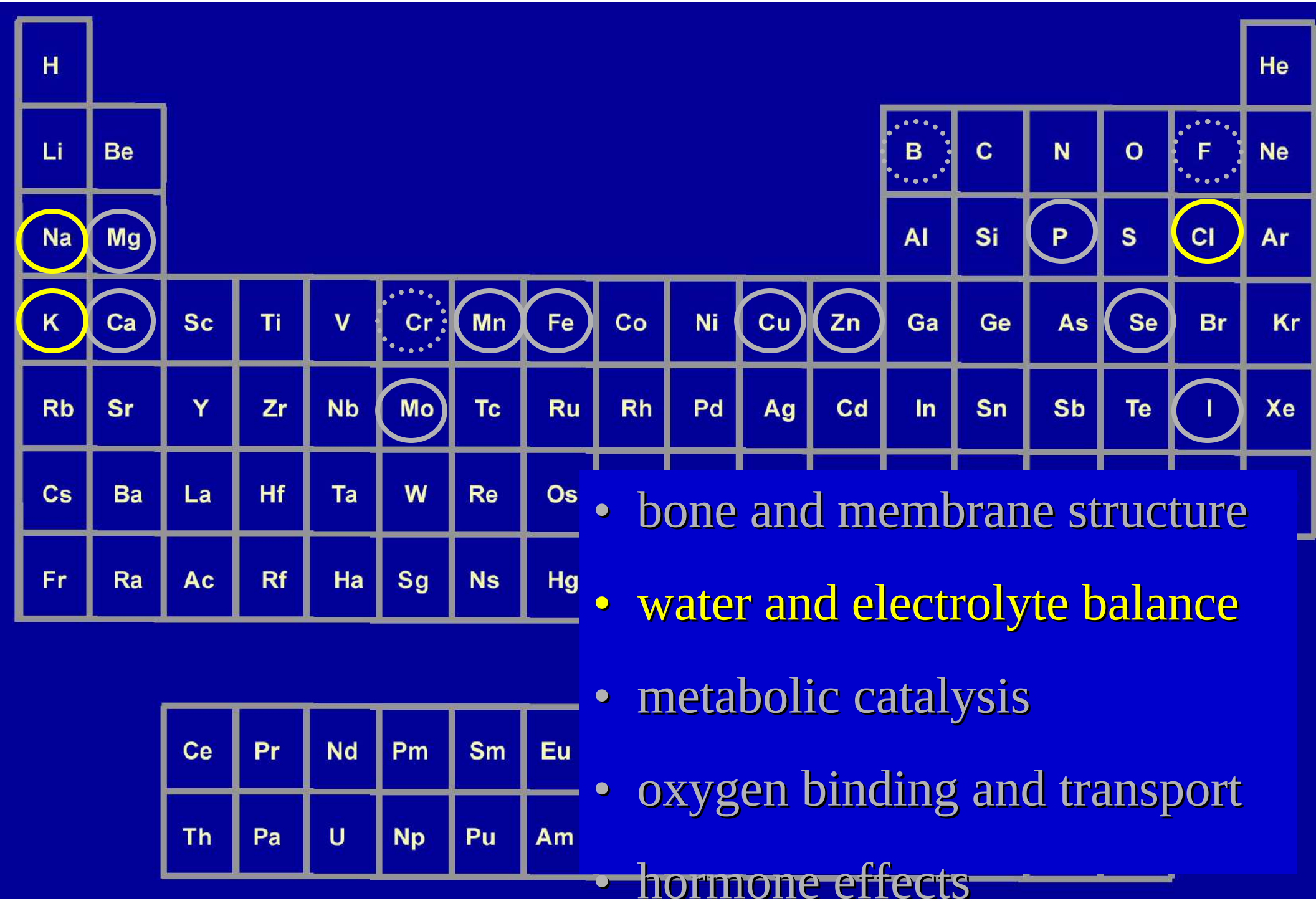
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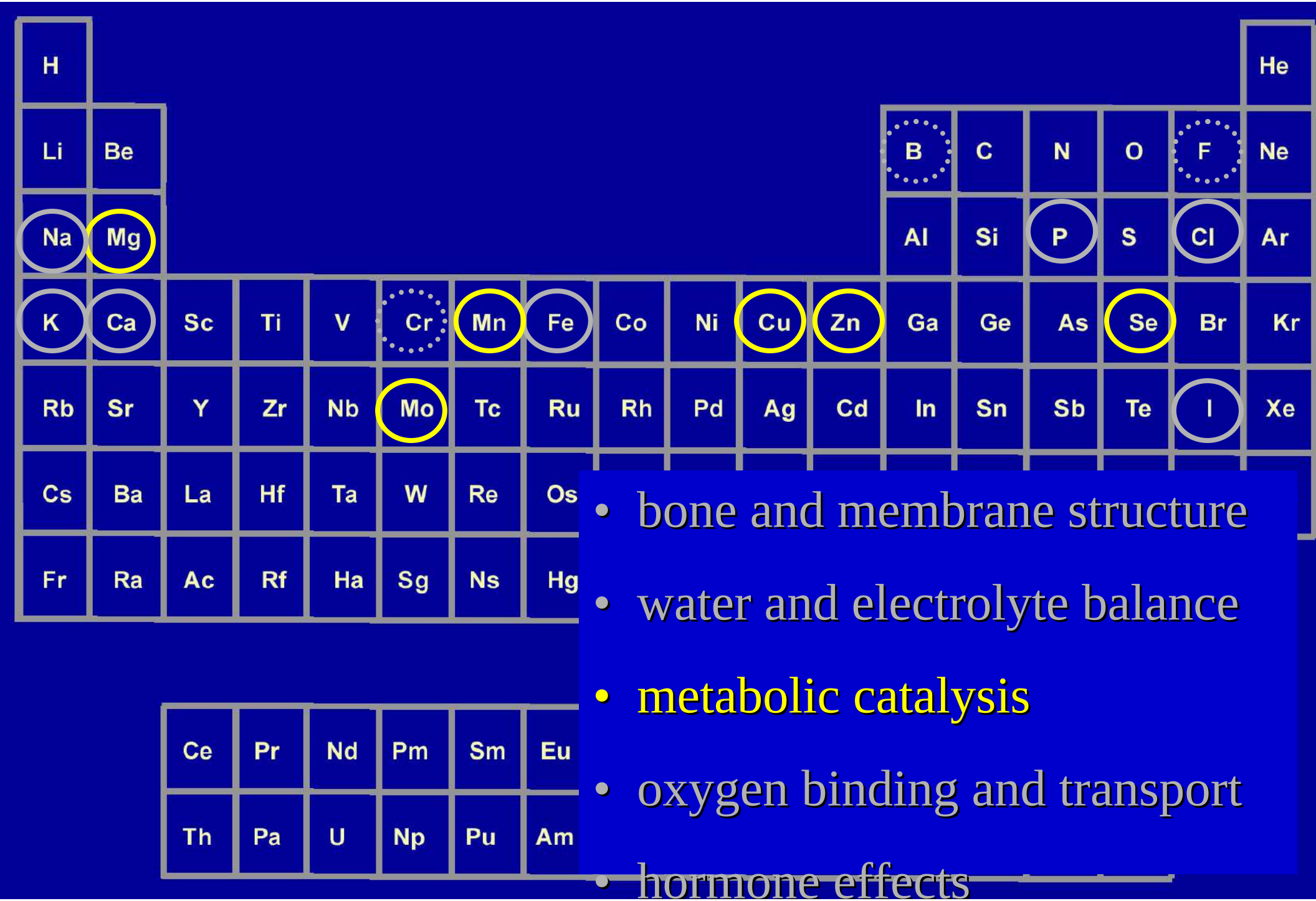
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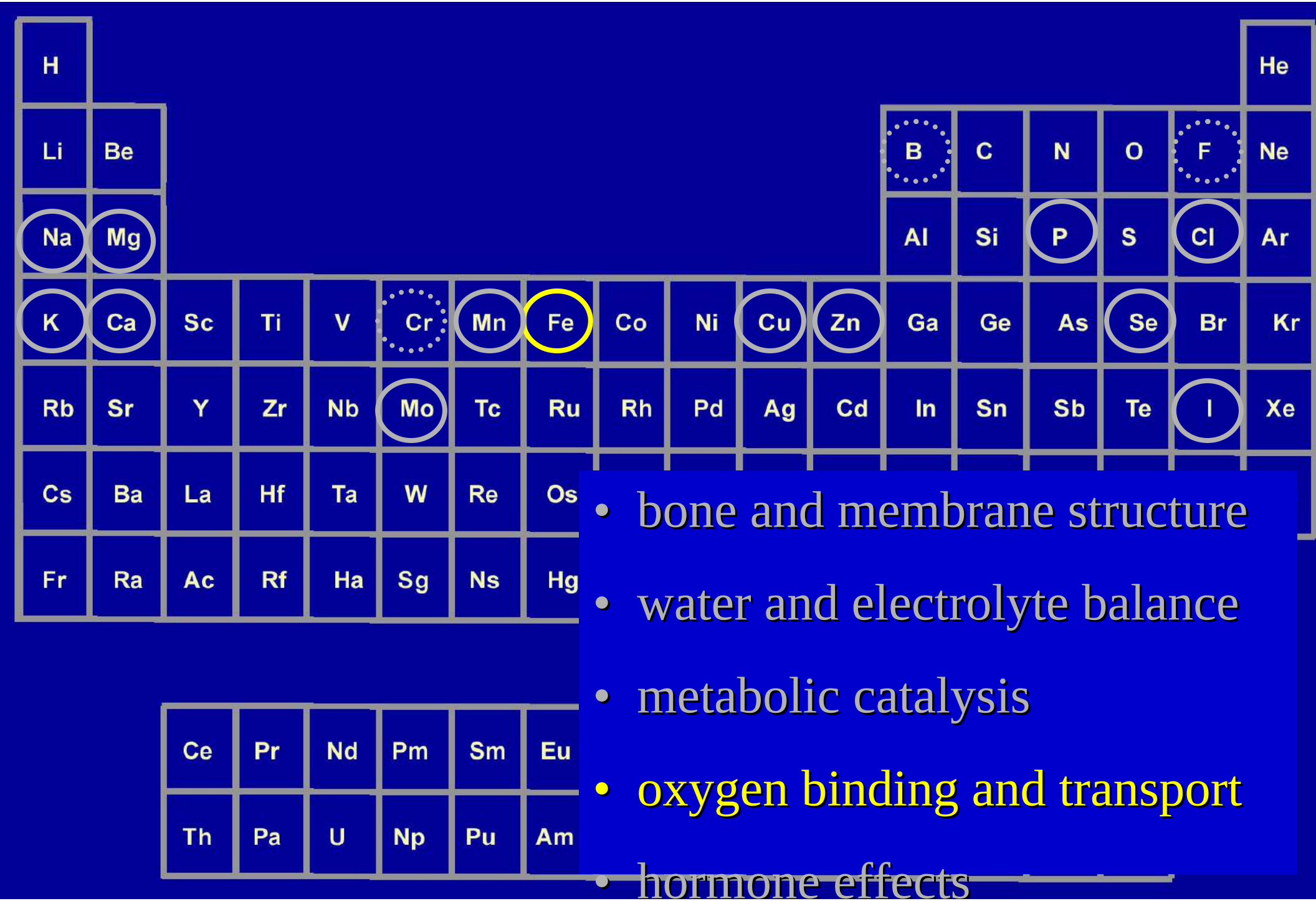
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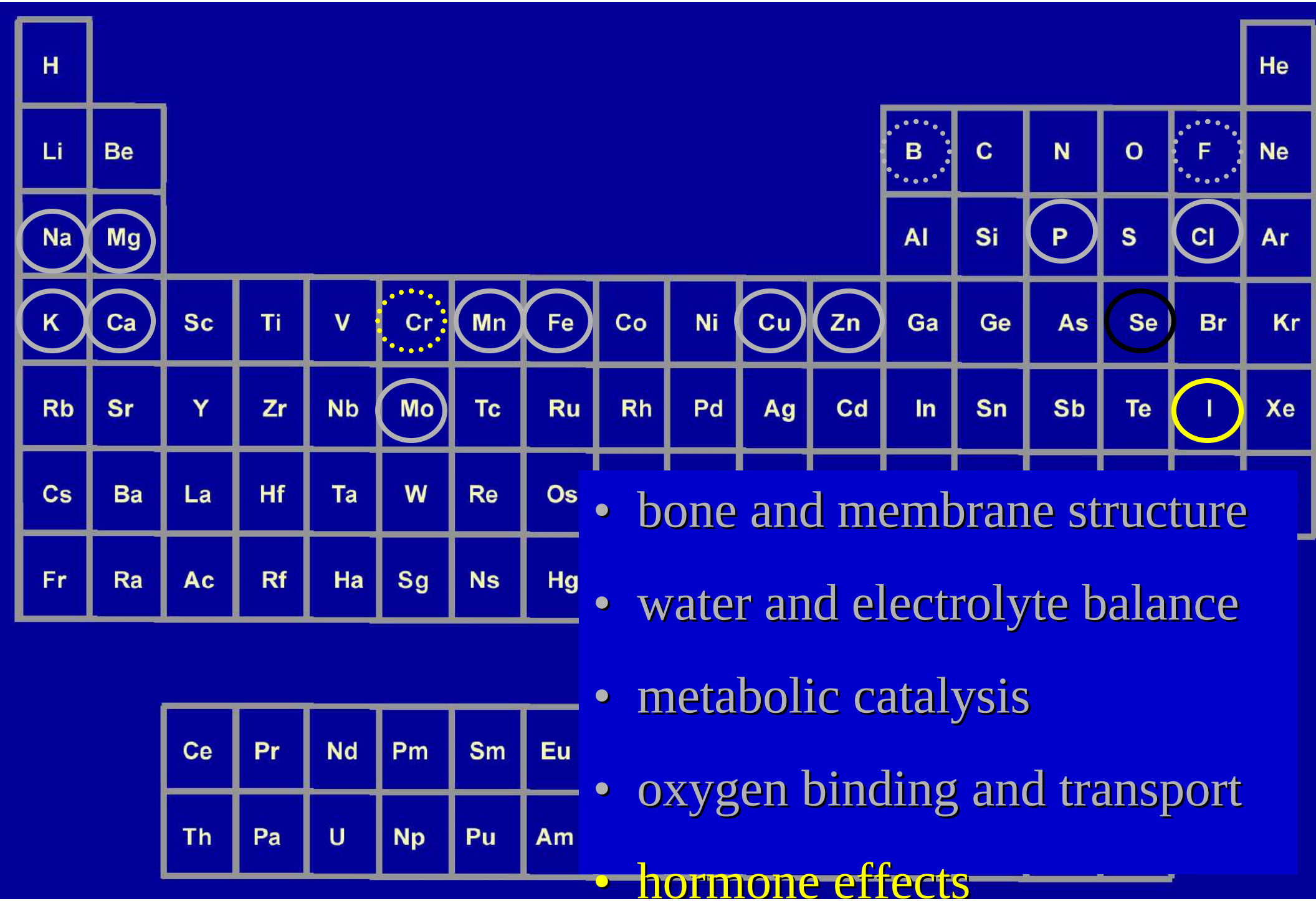
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ACTION OF MACRONUTRIENTS

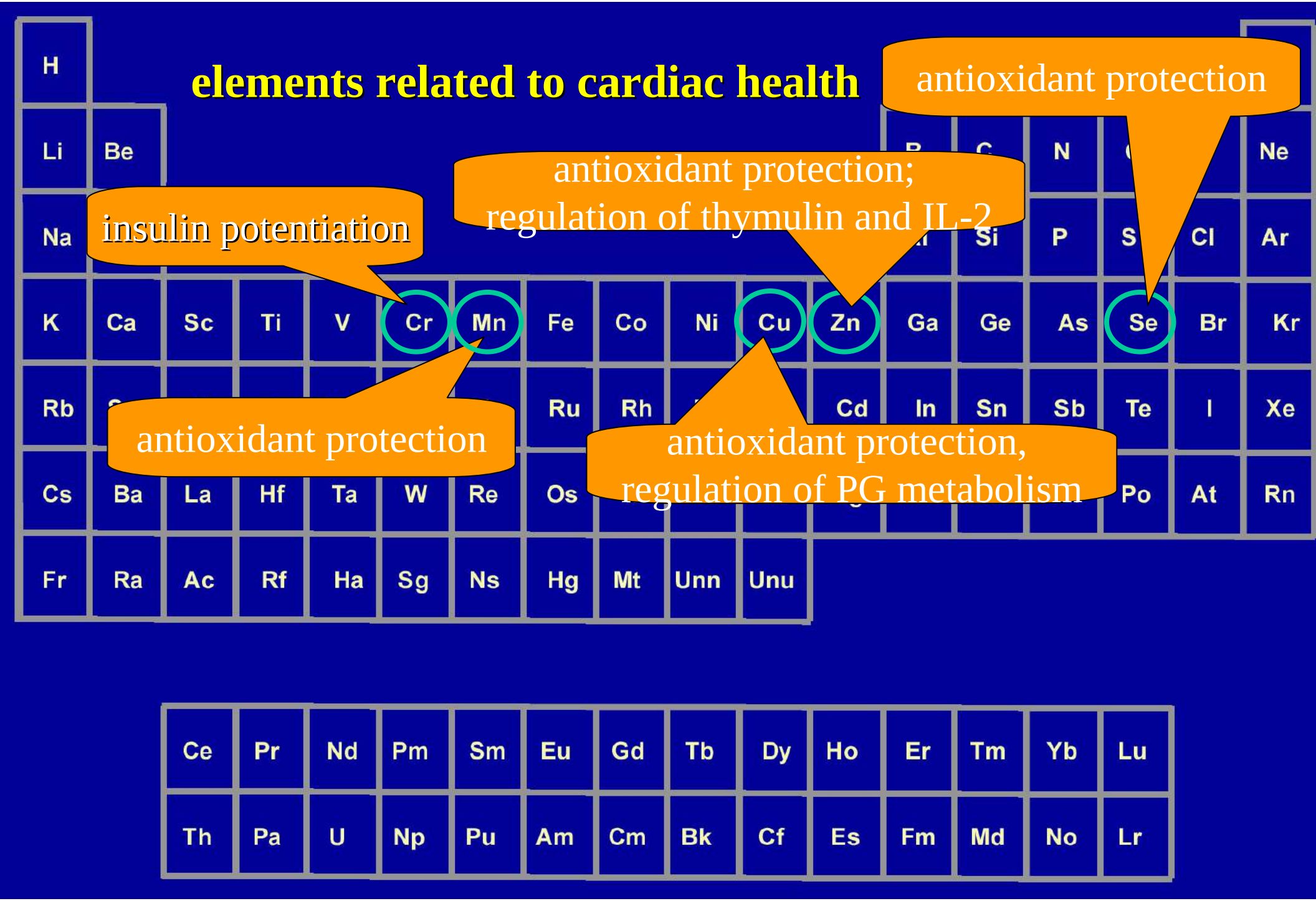
Ca	Strengthening of bones and teeth; muscular activity; blood coagulation; cellular permeability. Excess may originate liver and bladder stones and renal insufficiency.
Cl	Maintenance of blood pressure; vital as acid constituent during digestion.
K	Maintenance of corporeal fluids; muscular contractions and nervous impulses.
Mg	In bones, together with Ca; activation of muscular contractions; body temperature control; component of several enzymes.
Na	Active in hydrosaline equilibrium; transmission of nervous impulses and transport of metabolites.
P	Bone constituent as apatite; participates in most body chemical reactions. Excess turns hair and bones brittle.

Scarpeli, William (personal communication)

ACTION OF MICRONUTRIENTS

Co	Active in vitamin B_{12} and in chemical reactions. Deficiency causes anemia. Excess causes hearth failures.
Cr	Needed for metabolism of sugar. Deficiency may cause diabetes, intolerance to glucose etc. Excess may result in renal failures. Excess of Cr^{+6} is carcinogenic.
Cu	Component of oxidizing enzymes during metabolism of energy sources; active in the synthesis of hemoglobin, in keratization and in skin and hair pigments. Deficiency leads to osteoporosis and low number of white blood cells.
F	Give strength to teeth and bones, avoiding dental caries and osteoporosis. Excess causes fluorosis of teeth and bones.
I	Required by thyroidal hormones, temperature control, body growth, reproduction etc. Deficiency causes abnormal growth of the thyroid.

Scarpeli, William (personal communication)


elements related to cardiac health
antioxidant protection
antioxidant protection;
regulation of thymulin and IL-2
insulin potentiation
antioxidant protection
antioxidant protection,
regulation of PG metabolism
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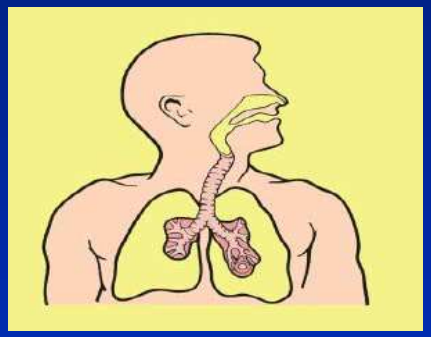
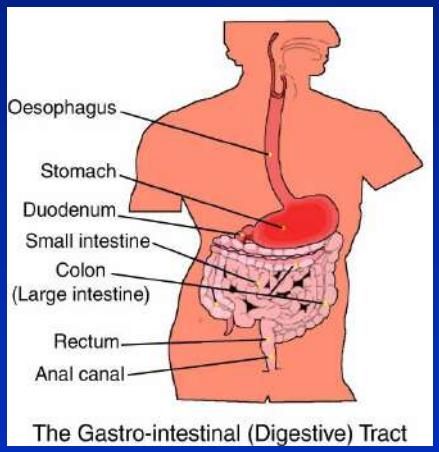
Trace Elements in Environmental Health

- **Exposure Routes:**
  - **Direct Absorption**
  - **Air (inhaling)**
  - **Drinking water**
  - **Diet (food chain)**
- **Metal-Induced Disease:**
  - **Carcinogenic**
  - **Teratogenic**
  - **Mutagenic**

Inhalation

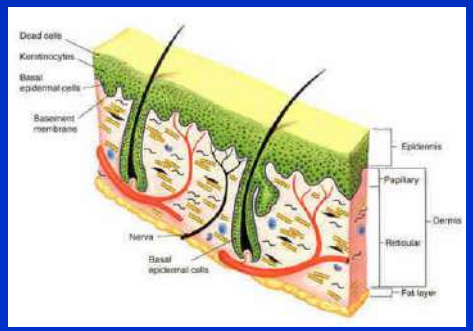


Ingestion



The Gastro-intestinal (Digestive) Tract

Dermal contact



Cancer and Site Specific Effects Associated with Exposure to Toxic Trace Metals

Examples:

Element	Target Organ and/or Sites
→ Cr	Lung, Liver, Kidney
→ As	Bladder, Liver, Lung, Skin, Vascular, Neurological changes
→ Cd	Lung, Kidney, Bladder, Vascular, Hypertension, Neurological changes
→ Hg	Neurological, lung, kidney, Brain
→ Pb	Neurological, IQ(children), Anemia

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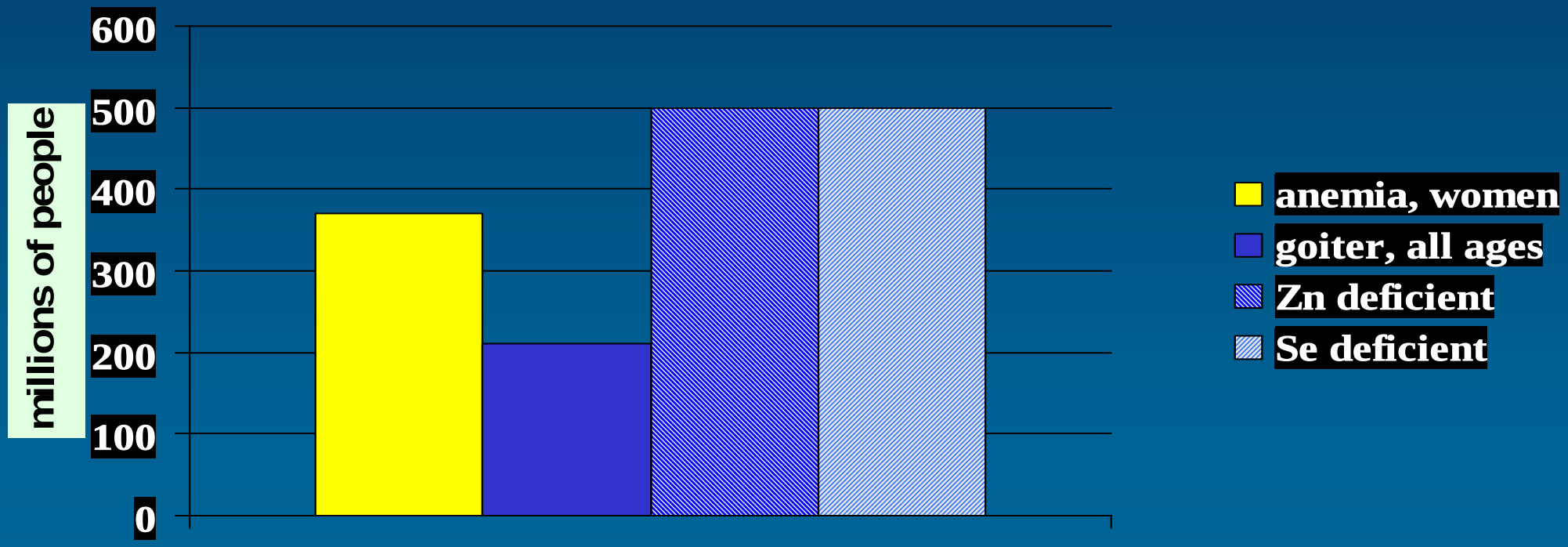
Trace Element Malnutrition in Developing Countries



Courtesy from Dr. Gerald T. Combs

TRACE ELEMENTS AND TOXIC METAL IONS

HEALTH EFFECTS

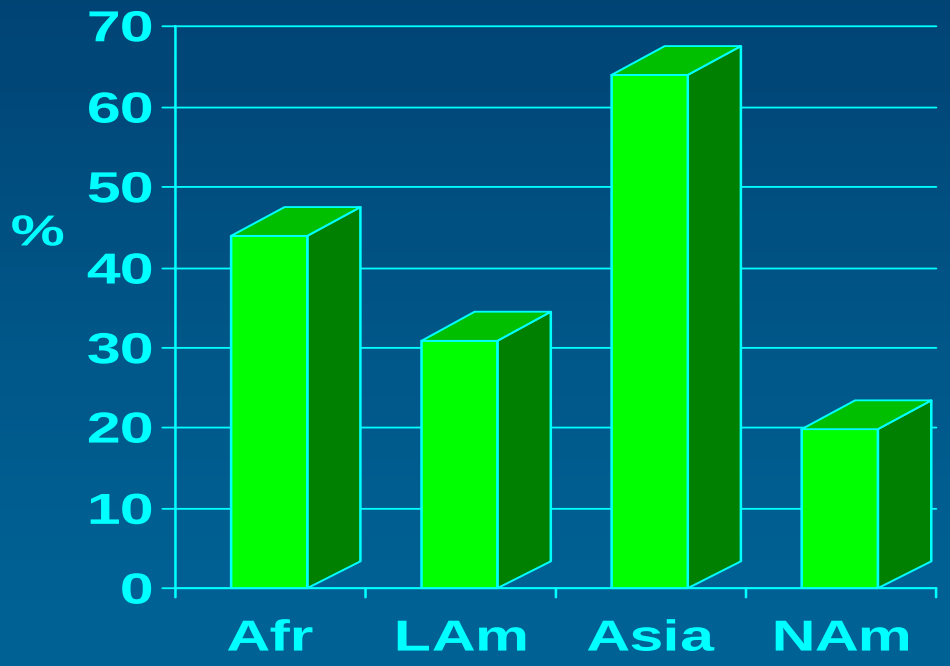
Deficiencies

Iron (Fe): The most widely abundant micronutrient

- Essential constituent of: Hemoglobin, myoglobin, e-transport enzymes, oxidases;
- Human Body: 2-6 g or iron ; metabolic function is to transport oxygen and electrons (redox agent);
- Iron Deficiency (ID): Anemia, fatigue, susceptibility to infection and impairment of cognitive development, increased risk of Pb poisoning;
  - *Pregnancy*: increases the risk of premature delivery, low birth weight and infant and maternal mortality
- Iron Toxicity: Liver and increase risk of coronary heart diseases (adults), Iron-overload (children)
  - *Clinical Signs* (Fe > 10-fold excess): cirrhosis, diabetes, heart failure, arthritis, and sexual dysfunction.

Global Prevalence of Anemia

- >2.1 B affected
  - 43% of women, 34% of men in developing countries
- multiple causes:
  - malaria, intestinal parasites
  - deficiencies of Fe, vit A, folate, vit B_{12}
- reduced work capacity
- 20% of maternal deaths
  - hemorrhage, heart failure
- 1/3 of child deaths
- impaired cognitive learning



Courtesy from Dr. Gerald T. Combs

Zn Deficiency (ZD)
Global Prevalence

- Similar to ID; likely widespread, but not well documented.
- Infants, children, pregnant and premenopausal women, and elderly at higher risk.
- impairs immunity, vit A utilization
- Some clinical effects of ZD:
  - Abortion
  - Growth stunting (children)
  - Development delay
  - Decrease immunity
  - Dermatitis
  - Decrease neuropsychological functions
  - Behavior problems
  - Dementia

Some causes of zinc deficiency

Primary

– Poor food choices
– Reduced bioavailability
– Geophagia

Secondary

- Blood loss
- GI diseases
  - Malabsorption
  - Inflammation
- Liver diseases
- Renal losses

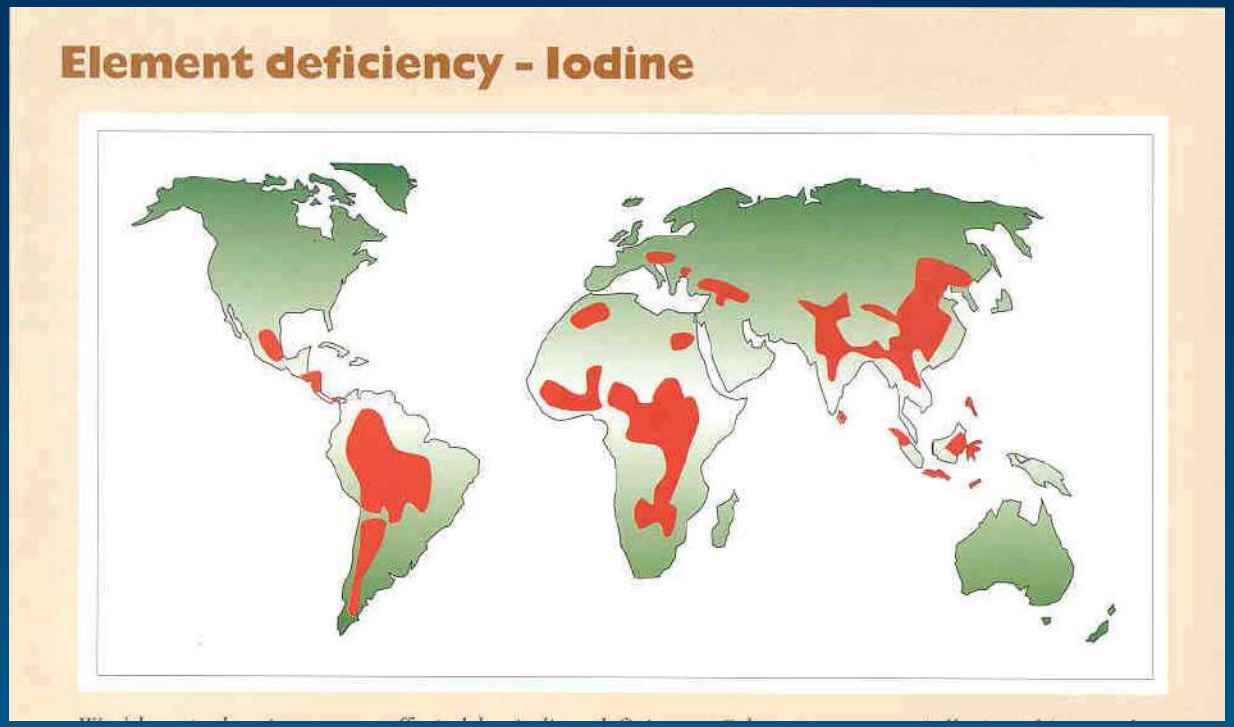
Effect of ZD on Dementia

74 year old bachelor farmer with severe malabsorption syndrome from gluten sensitivity

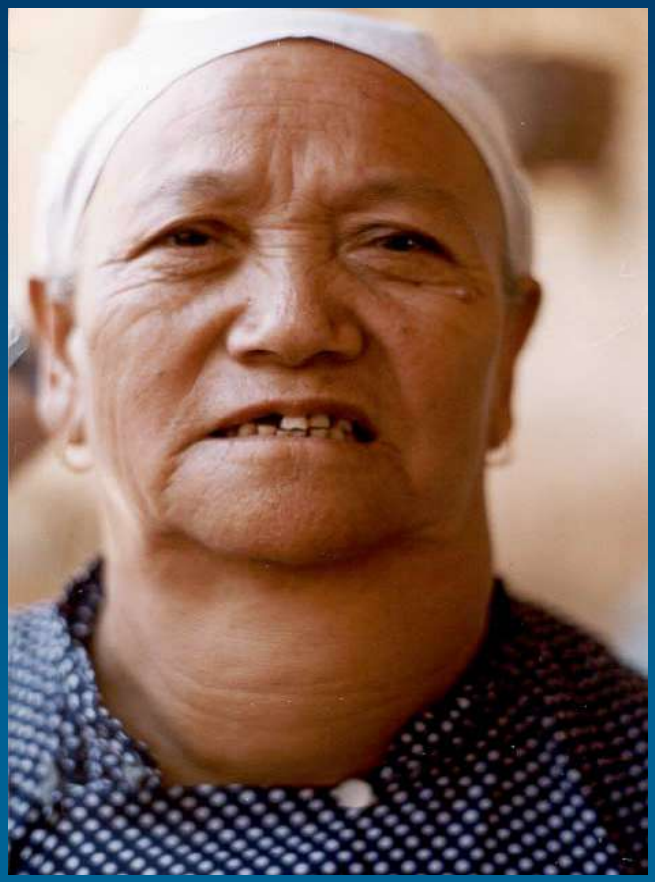
Collection of Harold H Sandstead, MD

TRACE ELEMENTS AND SELECTED ENDEMIC DISEASES OF SIGNIFICANCE IN MEDICAL GEOLOGY

Element	Disease
Selenium	Kaschin-Beck Disease *Degenerative osteoarthropathic disease* Keshan Disease *Chronic heart disease (cardiomyopathy)*
Iodine	Goiter and Cretinism
Fluorine	Dental and Skeletal
Metalloids:*	
Arsenic	Skin lesions, cancer



Iodine Deficiency Disorders (IDD)



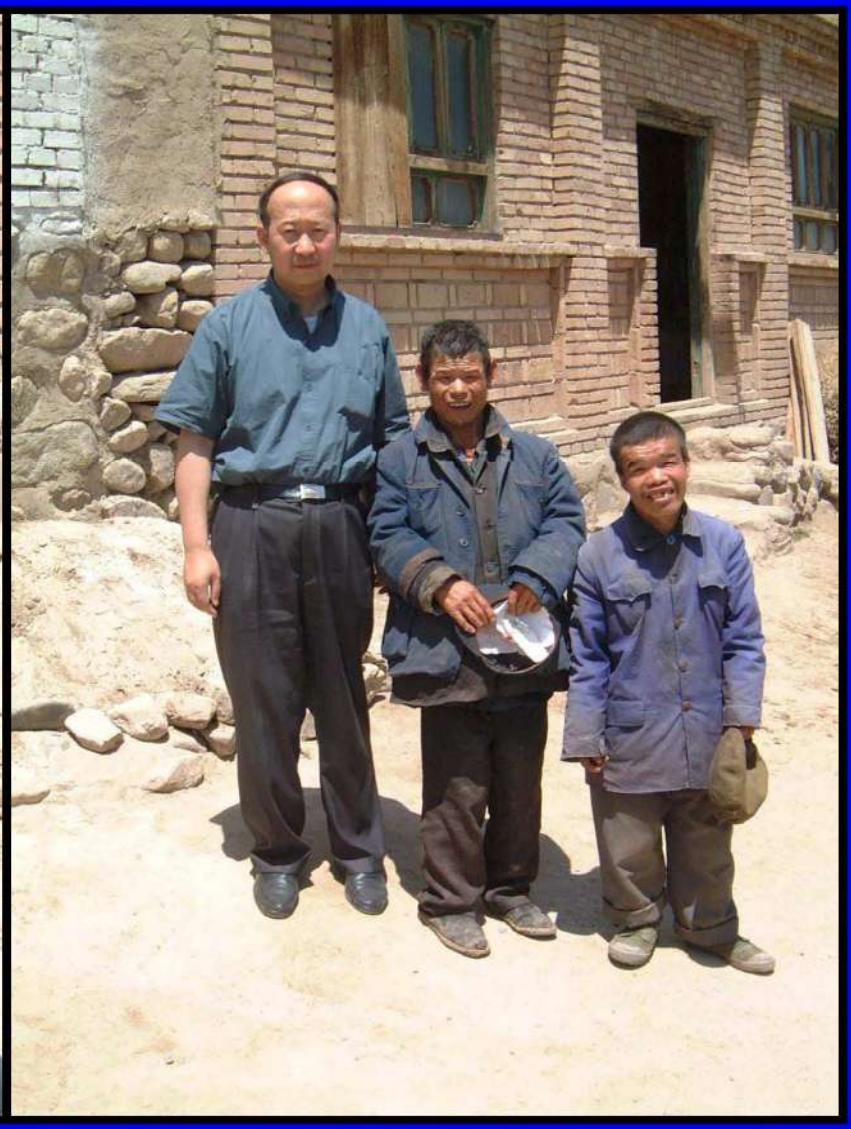
IDD and multi-causal disease involving factors such as:

- trace element deficiencies
- goiter-inducing substances in foodstuffs (known as goitrogens)
- genetics

IDD disorders include: goiter (enlargement of the thyroid), cretinism (mental retardation with physical deformities), reduced IQ, miscarriages, birth defects.

Cretinism

Subject, aged ~ 50 years

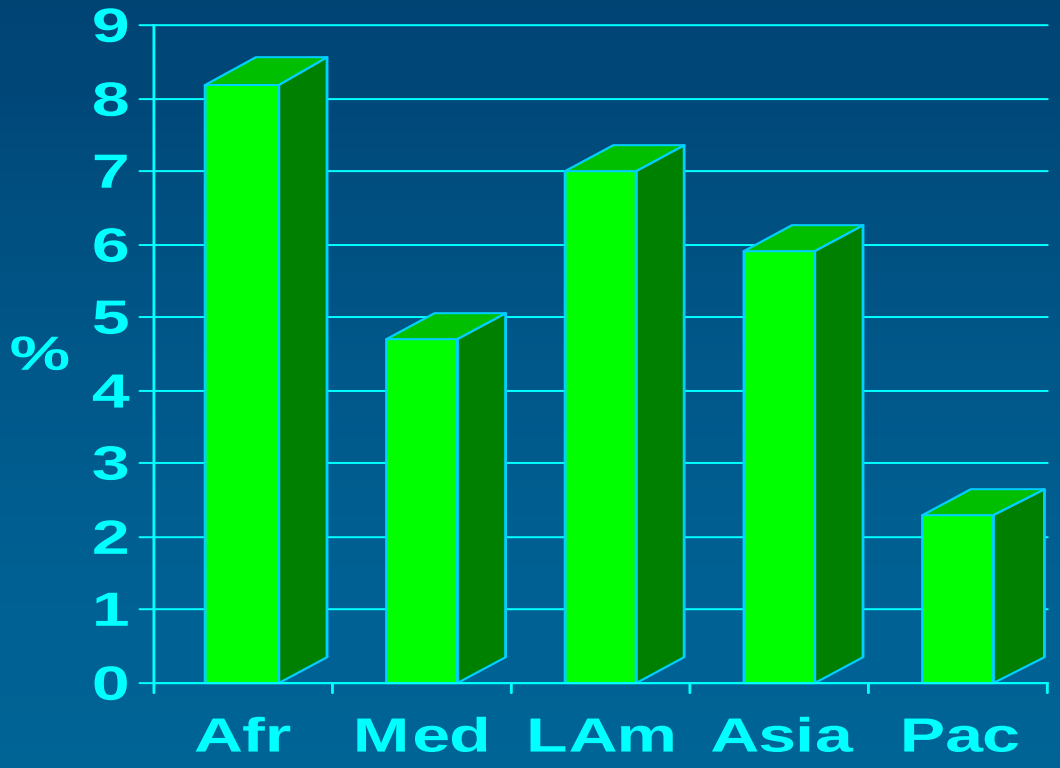


Subjects, aged ~50 & 30 years
with 5'9" physician

Collection of Harold H Sandstead, MD

Global Prevalence of I Deficiency Diseases

- >2 B at risk
- 740 M with goiter
- 20 M mentally retarded
- 6 M infants with cretinism (half in SE Asia) each yr



Courtesy from Dr. Gerald T. Combs

Abnormalities of Selenium Deficiency (SeD)

- **From Experimental Animal Studies:**
  - SeD alone: reduce activity of Se-enzymes, but no clinical effects;
  - SeD + vitamin E deficiency – lipid peroxidation, liver necrosis, cardiac necrosis
  - White muscle disease in sheep

- **Humans:**
  - Keshan cardiomyopathy
  - Kashin-Beck osteoarthopathy

- **Other effects - SeD impairs:**
  - thyroid hormone metabolism
  - T-cell function
  - resistance to RNA-viral disease

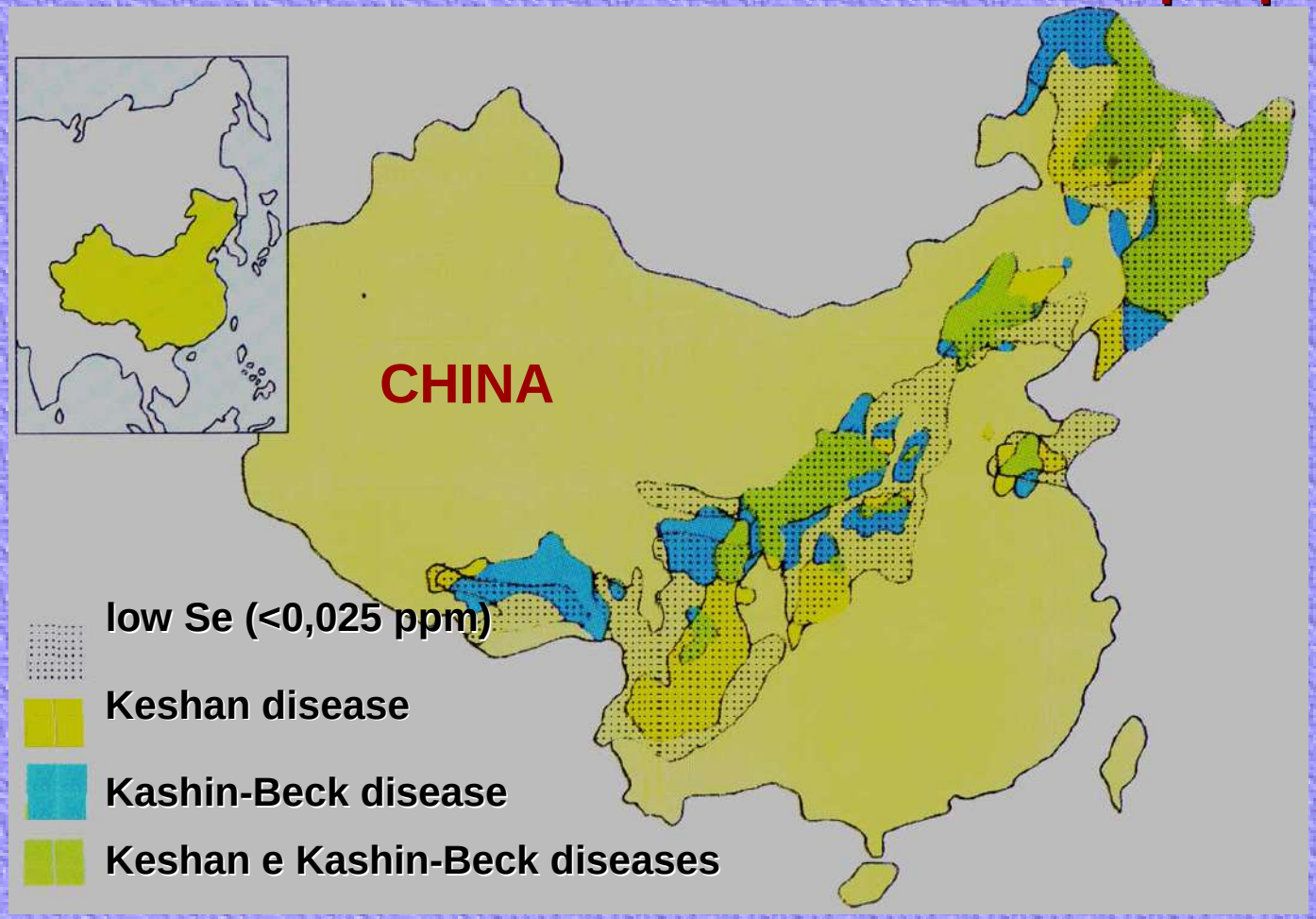
Global Prevalence of Se Deficiency

- 400 M people at risk in China
  - children: cardiomyopathy (Keshan Disease)
  - adolescents: chondrodystrophy (Kaschin-Beck Disease)

- 500-1000 M at risk worldwide

SELENIUM

A belt of low-Se rocks influences millions of people.



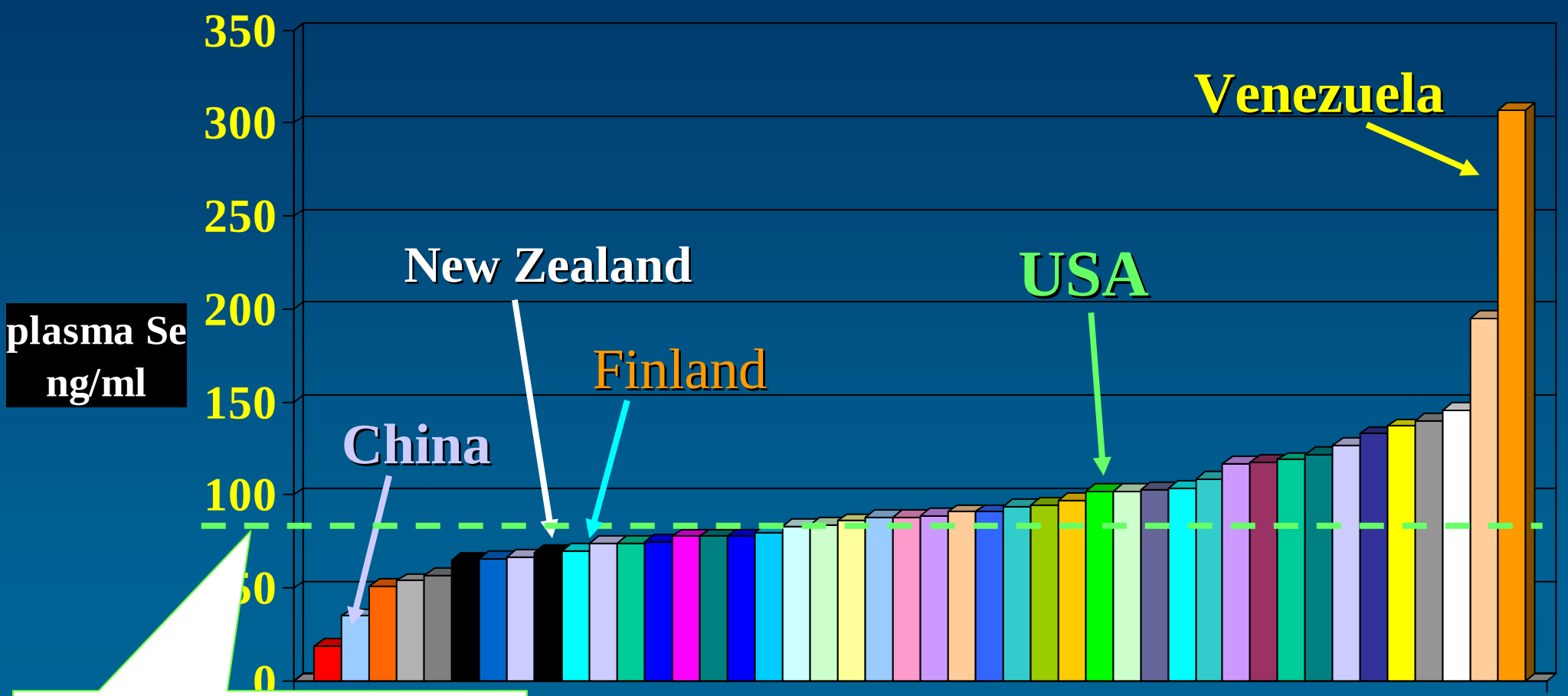
Keshan disease – weakening of the heart muscle
Kashin-Beck disease – muscular pains, other effects

Selenium Deficiency

Kashin-Beck Disease

Photo: Courtesy of Prof. Wang Zhilun, China

Worldwide Variation in Se status



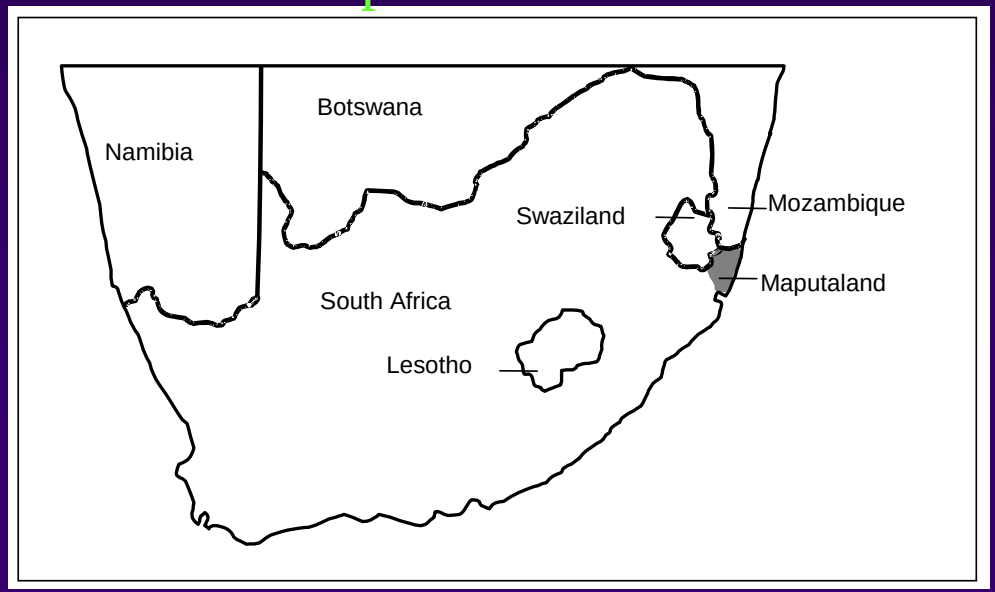
nutritional adequacy = 80ng/mL
Nève, 1995
SeP levels: Hill et al, 1996

Courtesy from Dr. Gerald T. Combs

Mseleni Joint Disease

- Multiple epiphyseal displasia (long bones have malformed growth)
- Polyarticular osteoarthritis (arthritis of several joints)
- Protrusio acetabuli

  (hip disorder)
- Dwarfism



MJD Research

- Medical
  - Low PO_4, F, Ca and Mg
  - Aflotoxins not present
  - Anemia due to parasites
  - Genetics inconclusive
  - Mg and Zn deficiency suspected
- Comparison with other diseases
  - Keshan-Beck and Se
  - Dwarfism and Zn

Soil Properties

- Near neutral pH 6.9
- < 4% clay (kaolinite and quartz)
- Low organic C ~1.6%
- Trace Element Deficiency: F, I, V, Se ;

  Others: Cu, Zn, B, N, P, K, S, Ca

Rickets:

- Disease of children characterized by under-mineralization of growing bones, leading to physical deformities of the weight bearing bones most notably of the legs, wrists and arms

- A source of *permanent* disability

- Can be healed but not *cured*

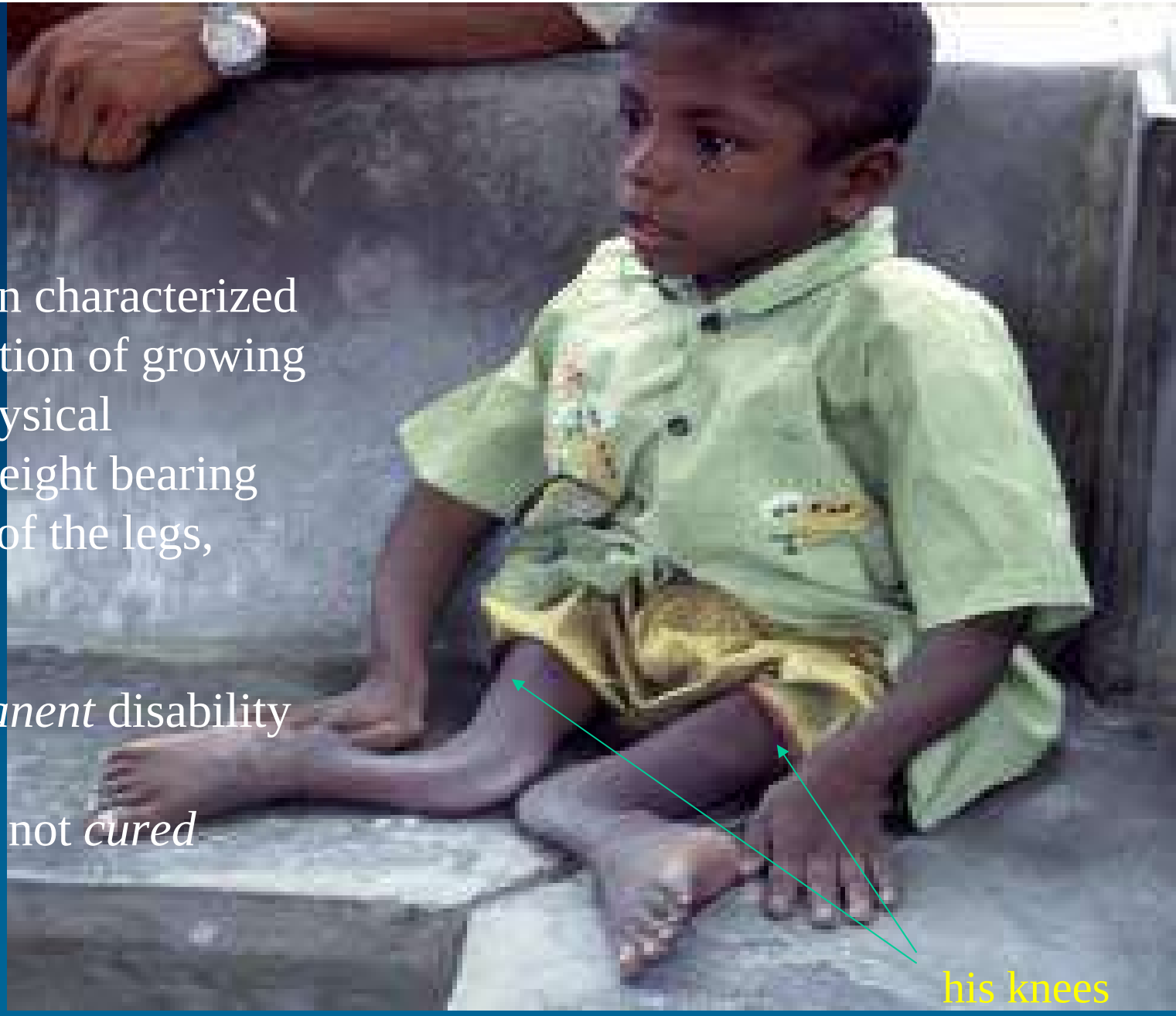


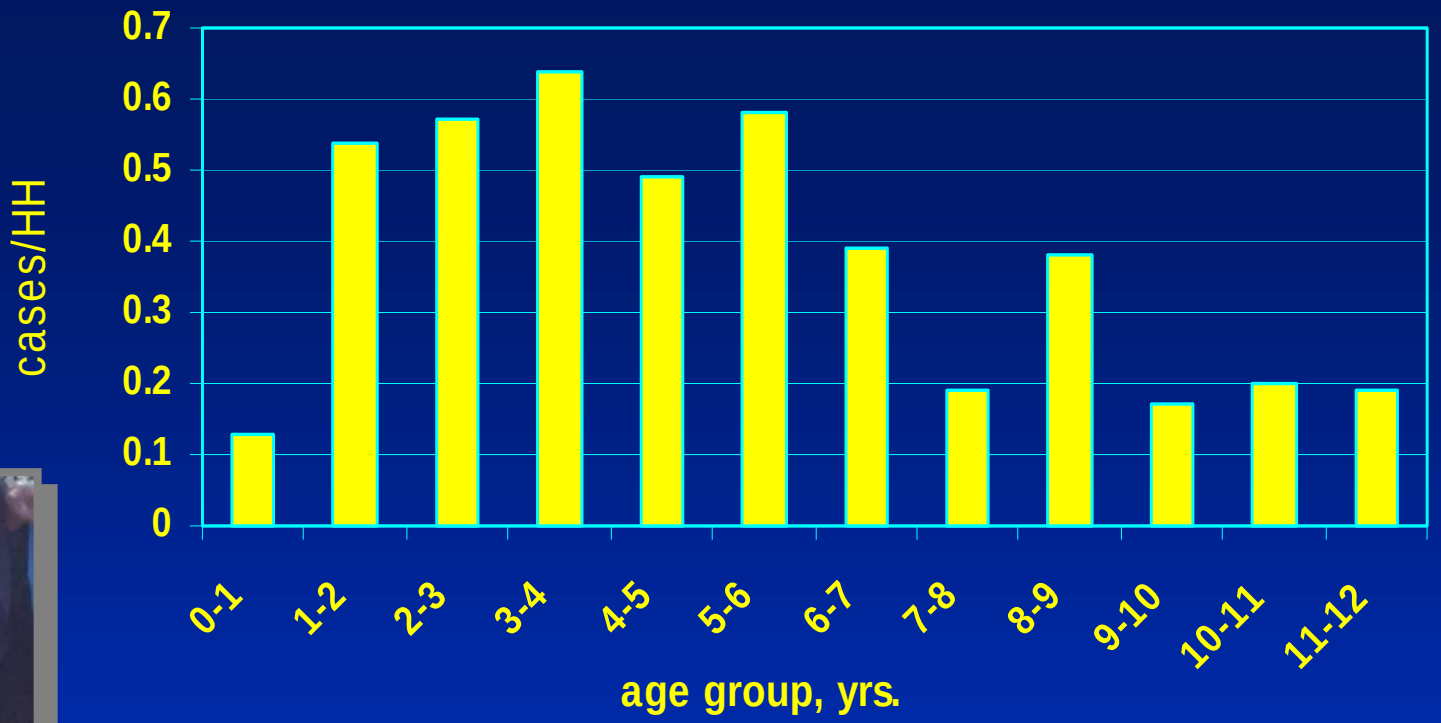
Photo Courtesy: Gerald F Combs, USDA

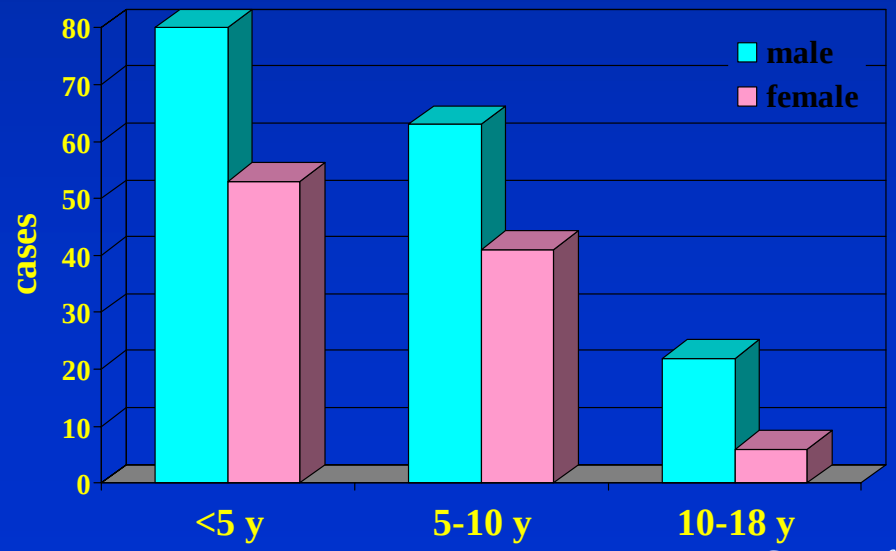
Rickets . . . caused by malnutrition . . .

- **deficiencies**
  - vitamin D (sunlight)
  - Ca, P, Mg, B (?)
- **imbalances/excesses**
  - P, Pb, Al, Sr, As(?)
  - tachysterols (vit. D analogues)
  - fat, oxalates, DDT (?)

Photo Courtesy: Dr. Gerald F Combs, USDA

age and sex distribution of cases





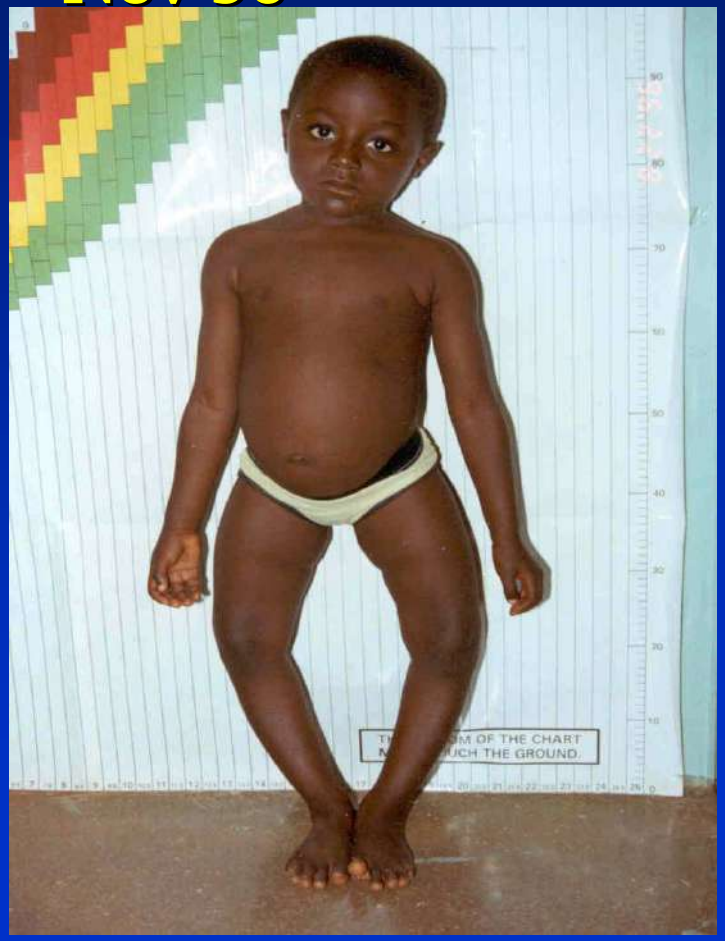
Courtesy from Dr. Gerald T. Combs

Calcium-supplementation study

(Combs et al. personal communication)

Pt 35A

Nov 96



Feb 98

Photos: Courtesy of Dr. Gerald F. Combs, USDA

TRACE ELEMENTS AND TOXIC METAL IONS

HEALTH EFFECTS

Excess

FLUORINE

Fluorine is an essential component of phosphates, as the hydroxy-fluor-apatite, a constituent of teeth and bones.

It is essential for healthy and strong teeth and bones, and to avoid osteoporosis.

The excess causes fluorosis, with mottled and harder teeth and bone calcification.

Fluorosis is common where drainage water is high in fluorine, and is consumed without adequate treatment, as in large areas of China, Ghana, Sri Lanka and other places.

More than 100,000,000 people have fluorosis.

Courtesy from Dr. William Scarpeli, Brazil

Fluorine in Drinking Water

Dose-Response Relationship for Fluorine:

- < 0.5 mg/L : dental cavities may occur (risk)
- 0.5 – 1.5 mg/L: no adverse effects
- > 1.5 mg/L : fluorosis risk

ARSENIC EXPOSURE : GLOBAL IMPACT

PEOPLE AFFECTED BY NATURALLY CONTAMINATED WATER AND SOILS

Selinus O, Alloway B, Centeno JA et al. "Essentials of Medical Geology" (2005)

Health Effects Associated with Arsenic Exposure

- Cancer: skin, lung, bladder, liver, kidney
- Cardiovascular disease
- Peripheral vascular disease
- Developmental effects
- Neurologic & neurobehavioral effects
- Diabetes Mellitus
- Hearing loss
- Portal fibrosis of the liver
- Lung fibrosis
- Hematological effects (e.g., anemia)

Tchounwou PB, Patlolla AK, Centeno JA. ***Toxicologic Pathology*** **31:575-588 (2003).**

Centeno et al. Environ Health Perspect 2002.

Outline

- Introduction to Trace Elements, Metals and Metalloids
- An Overview of Tissue Reactions to Toxic Trace Metal Exposures
- Environmental Health and Diseases
- Concluding Remarks

Armed Forces Institute of Pathology

SUMMARY

- Trace elements deficiency or excess contribute to a wide-spectrum of environmentally health-related problems.
- Disorders related to trace element deficiency are treatable (dietary supplements, etc.)
- Toxic metal ions may exhibit different toxicity depending on the chemical and physical form.
- Toxic metal ions may affect more than one organ system.
- Clinical and environmental health assessment (including risk assessment and risk management) studies of exposures to trace elements, toxic metals, and metalloids, must consider background exposure, natural modes of exposure, bioavailability, chemical/physical speciation, morphological characteristics, as well as dose-response relationships.

Cardiovascular effects of Cu deficiency

- cardiomyopathy
- ventricular aneurisms
- impaired contractile function
- arrhythmia
- hypertension in older animals; elevated BP in response to stressors
- depressed mitochondrial respiration
- myocardial apoptosis

Effect of Zinc Treatment on Dermatitis

Before

After

Collection of Harold H Sandstead, MD

Iodine Deficiency Goiter

Armed Forces Institute of Pathology Collection