

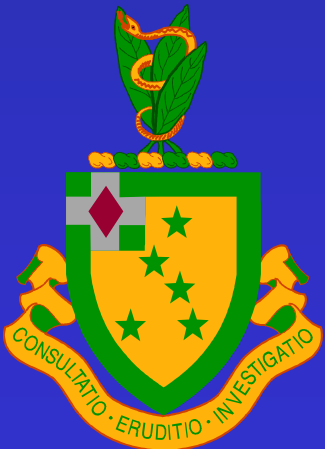
Diversity of Trace Elements and Toxic Metal Ions in Environmental Health and Human Diseases

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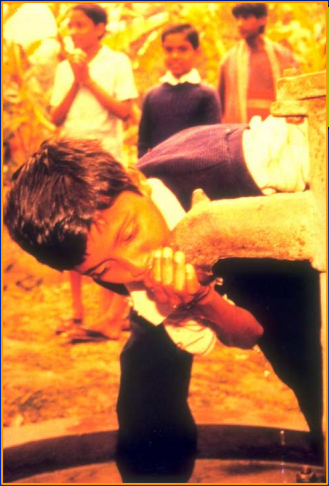
Outline

- **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).

**Non-
industrial**

**Drinking water
Food**

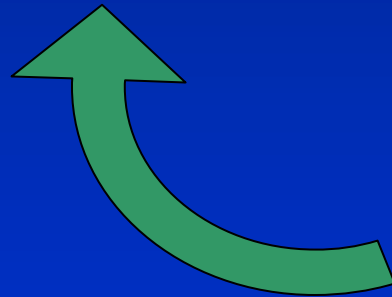
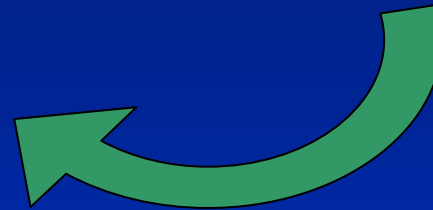


**Natural
deposits**



Industrial

**Agriculture
Mining/smelting
Coal burning
Micro-electronics**



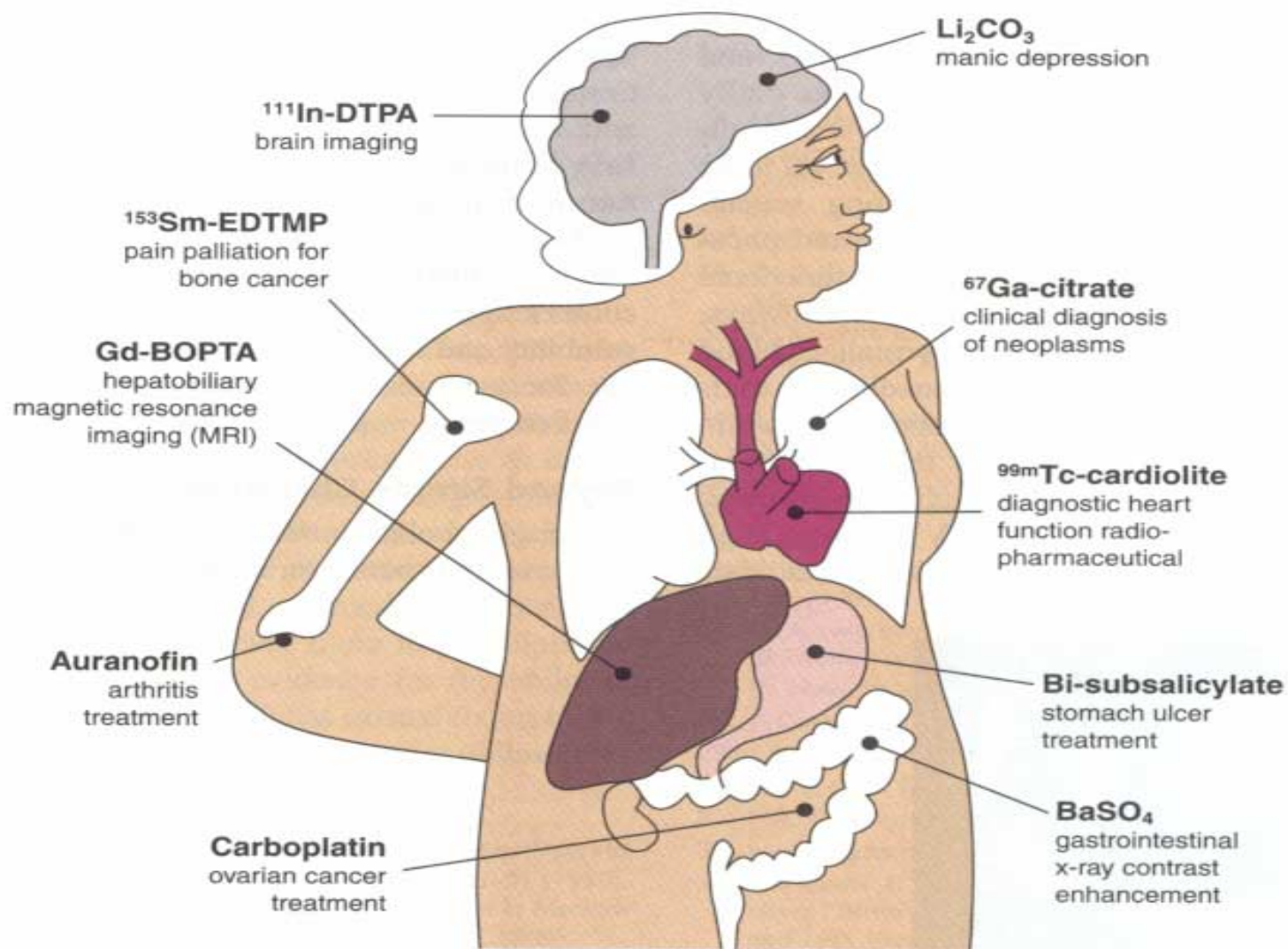
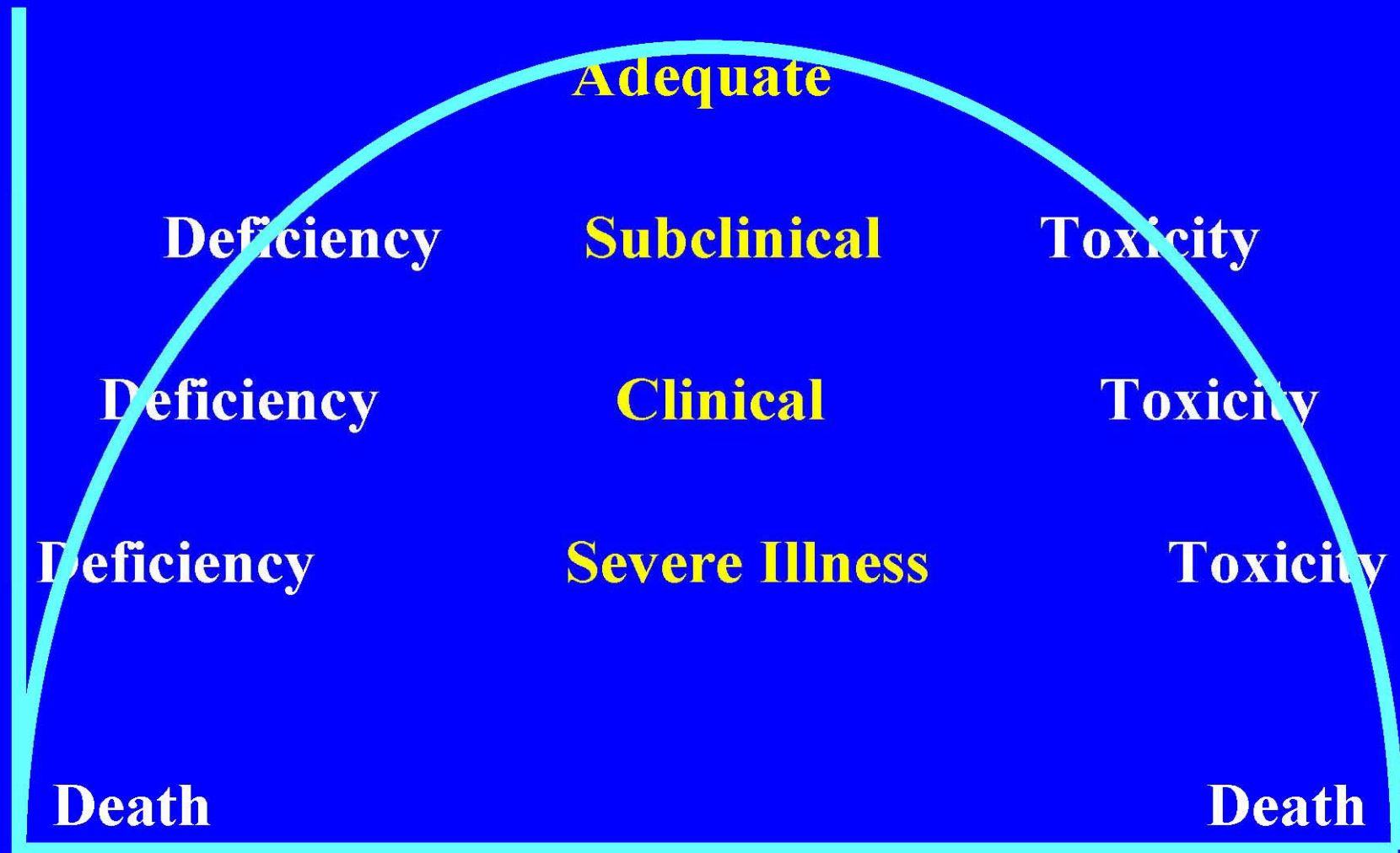


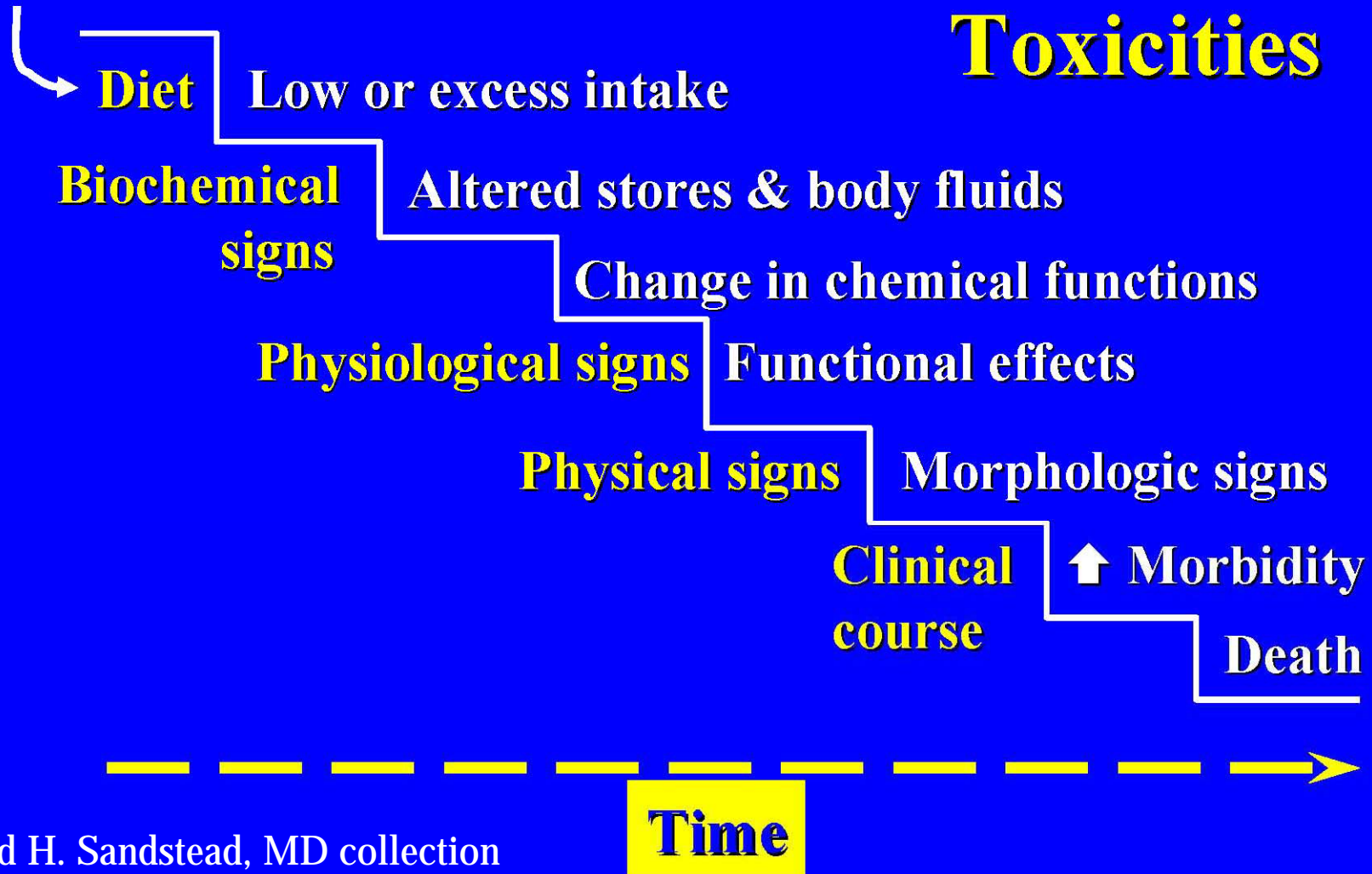
Fig. 1. Metal ions are important in diagnosis and therapy of a host of different human pathologies. Gd, ^{111}In , and $^{99\text{m}}\text{Tc}$ are used in medical imaging; ^{153}Sm and Au to relieve pain in bone cancer and arthritis, respectively; Bi to soothe upset stomach; and Li to calm bipolar psychosis.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

Spectrum of Nutrition Status



Geochemistry & Agriculture

Evolution of Deficiencies or Toxicities



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:

H																		He
Li	Be																	Ne
Na	Mg																	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr	
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe	
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn	
Fr	Ra	Ac	Rf	Ha	Sg	Ns	Hg	Mt	Uhh	Uhu								

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

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Mn	No	Lr

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- **Environmental Health and Diseases**
- **Concluding Remarks**

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.

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.

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

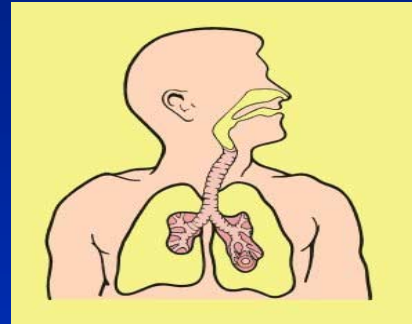
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Li	Be															B	C	N	O	Ne
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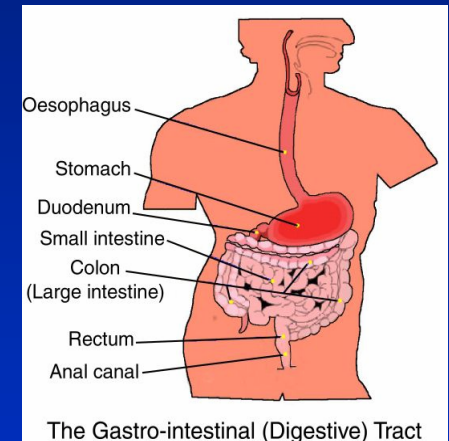
Trace Elements in Environmental Health

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

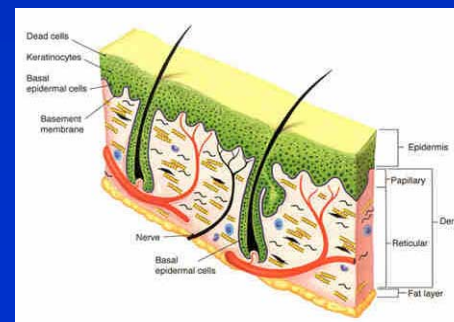
Inhalation



Ingestion



Dermal contact



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

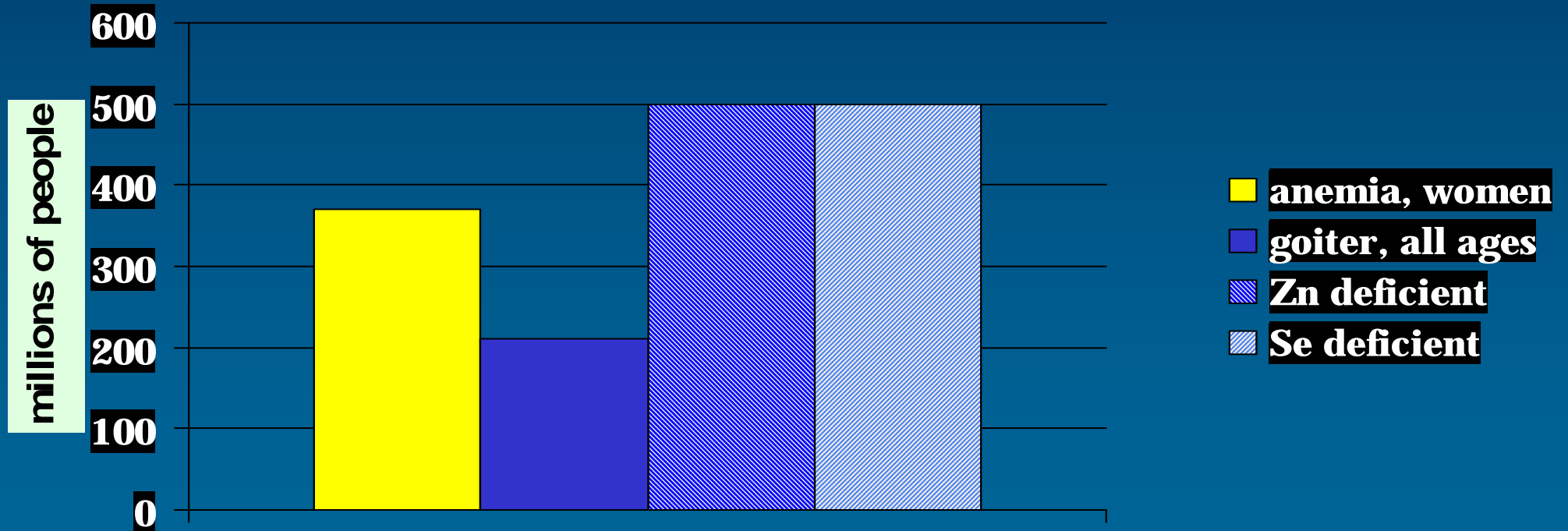
Examples:

<u>Element</u>	<u>Target Organ and/or Sites</u>
→ 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

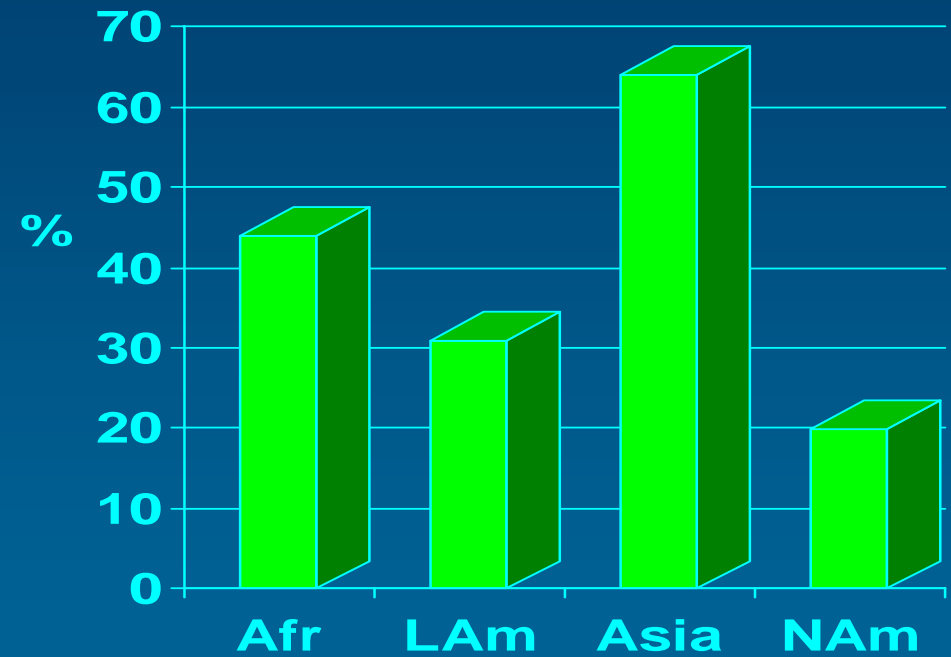
Deficiencies

Iron (Fe): The most widely abundant micronutrient

- Essential constituent of: Hemoglobin, myoglobin, e-transport enzymes, oxidases;
- Human Body: 2-6 g of 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 B₁₂
- **reduced work capacity**
- **20% of maternal deaths**
 - hemorrhage, heart failure
- **1/3 of child deaths**
- **impaired cognitive learning**



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

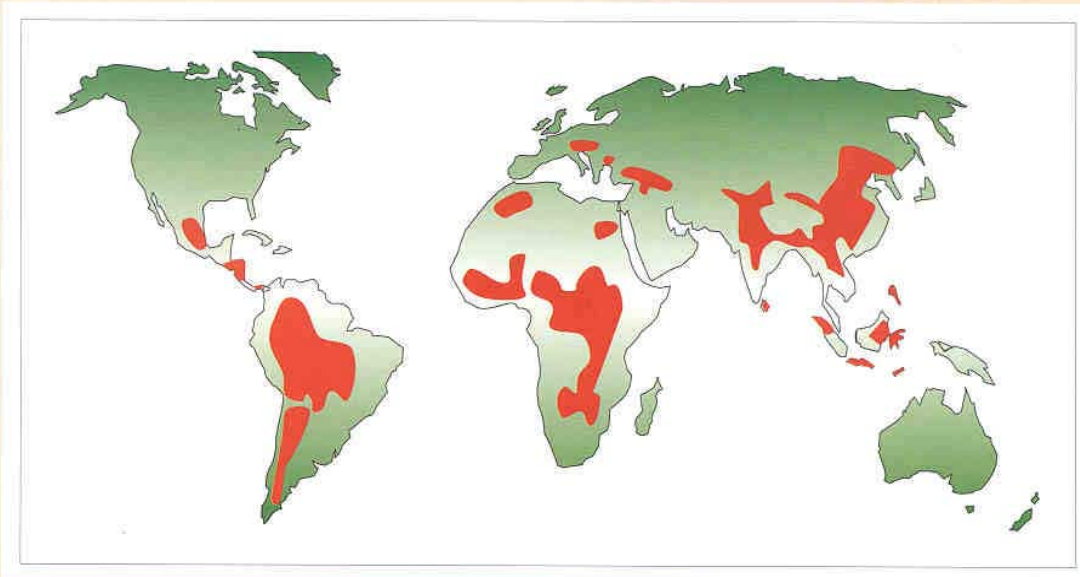
Dental and Skeletal

Metalloids:*

Arsenic

Skin lesions, cancer

Element deficiency - Iodine



Iodine Deficiency Disorders (IDD)



IDD and multi-causal disease involving factors such as:

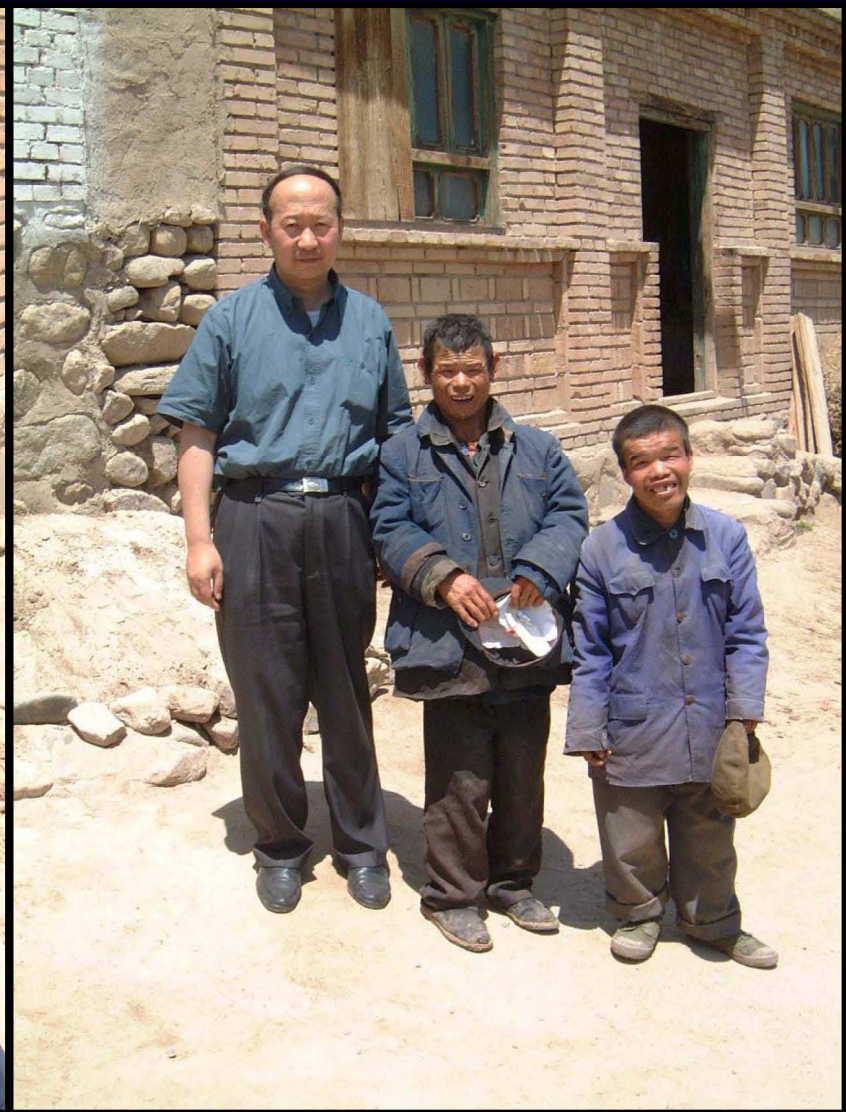
- trace element deficiencies
- goiter-inducing substances in foodstuffs (known as goitrogens)
- genetics

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

Cretinism



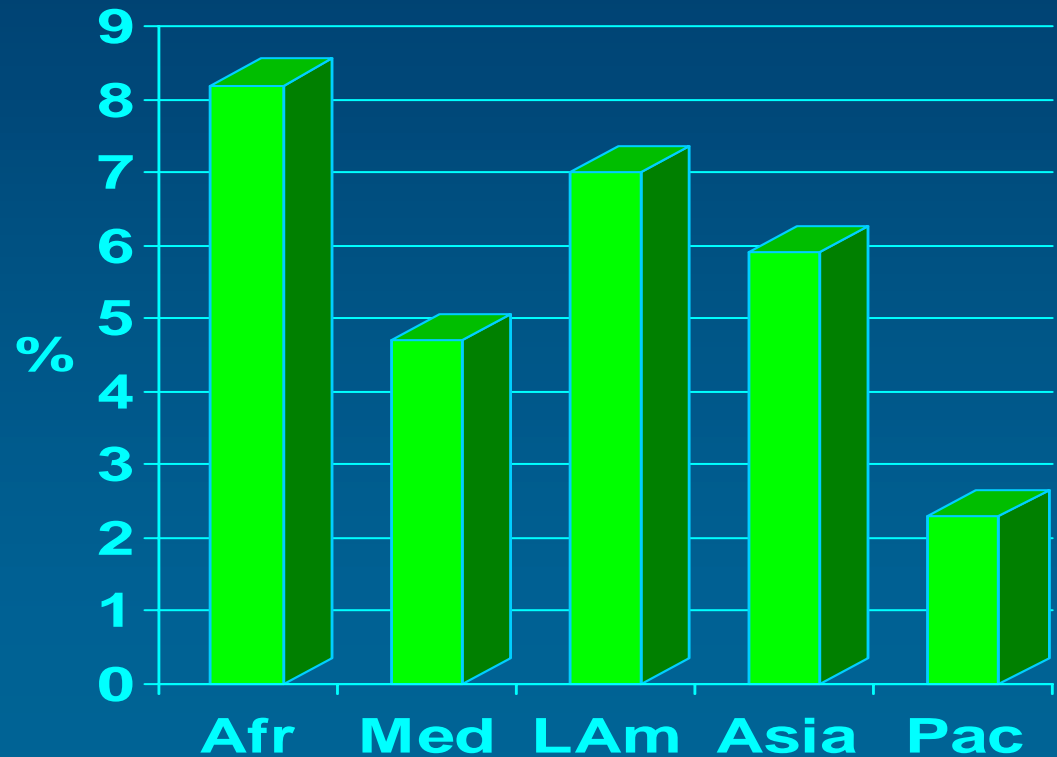
Subject, aged ~ 50 years



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

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)

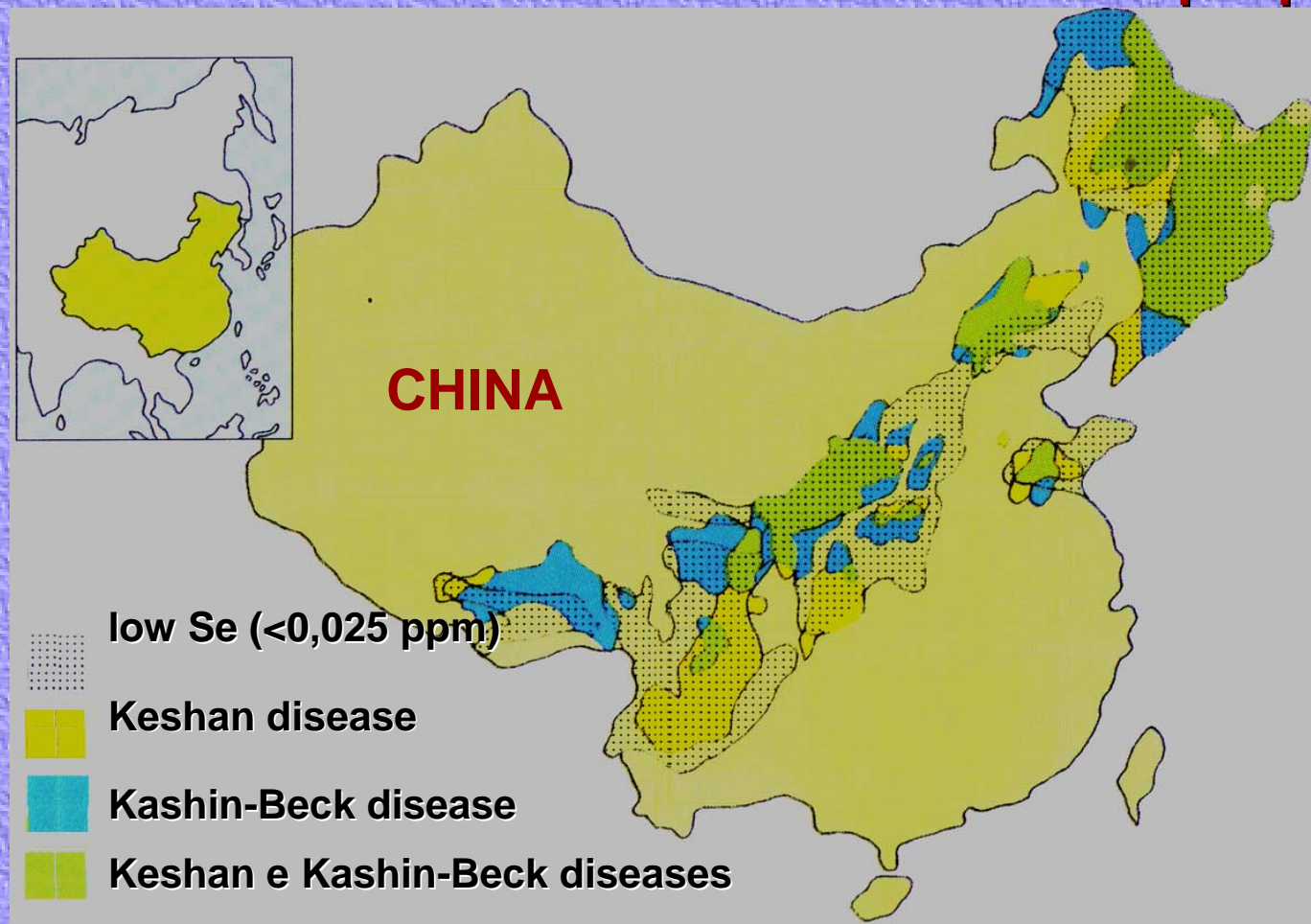
- **From Experimental Animal Studies:**
 - SeD alone: reduce activity of Se-enzymes, but no clinical effects;
 - SeD + vitamin E deficiency – lipid peroxidation, liver necrosis, cardiac necrosis
 - White muscle disease in sheep
- **Humans:**
 - Keshan cardiomyopathy
 - Kashin-Beck osteoarthopathy
- **Other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



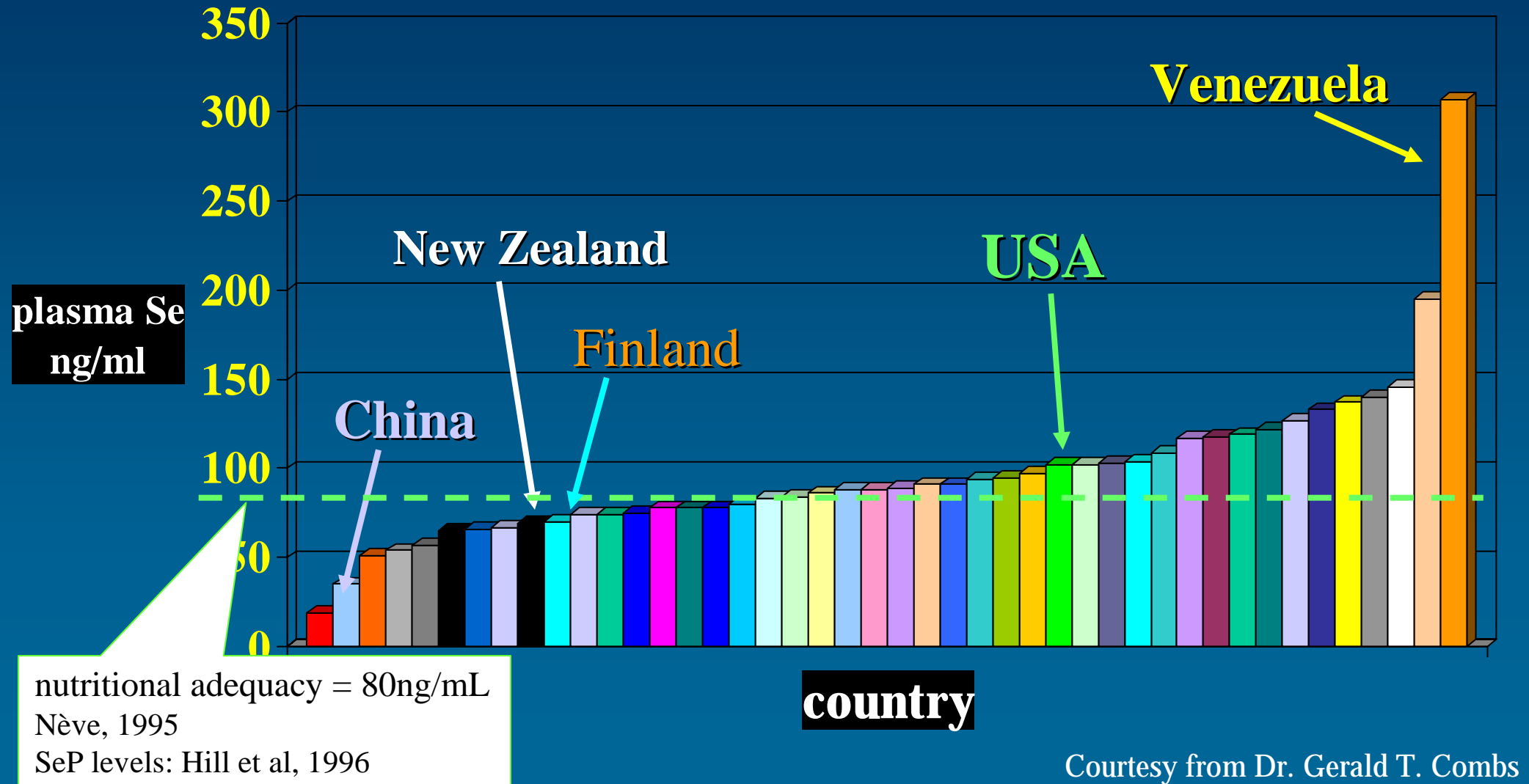
Keshan disease – weakening of the heart muscle
Kashin-Beck disease – muscular pains, other effects

Selenium Deficiency
Kashin-Beck Disease



Photo: Courtesy of Prof. Wang Zhilun, China

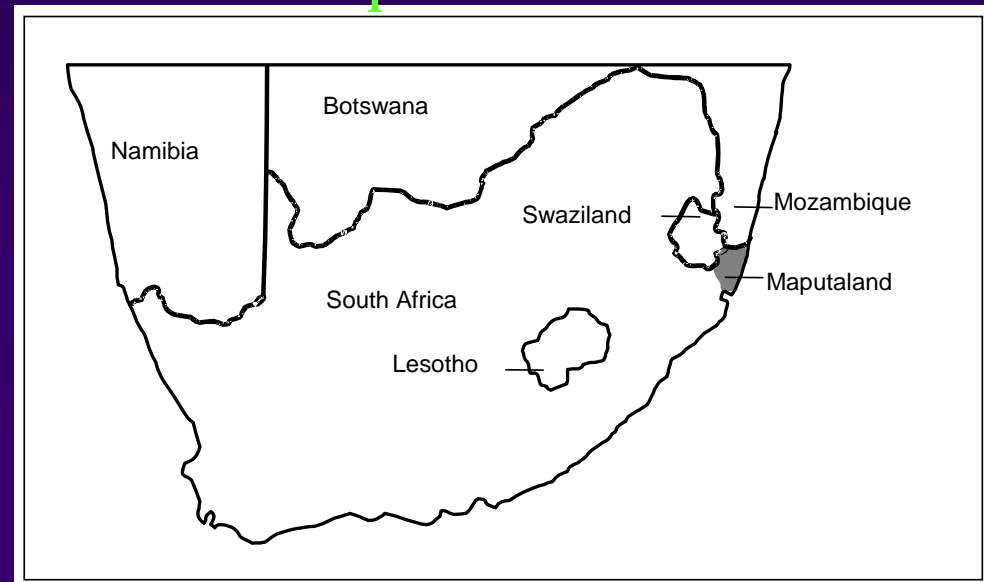
Worldwide Variation in Se status



Mseleni Joint Disease

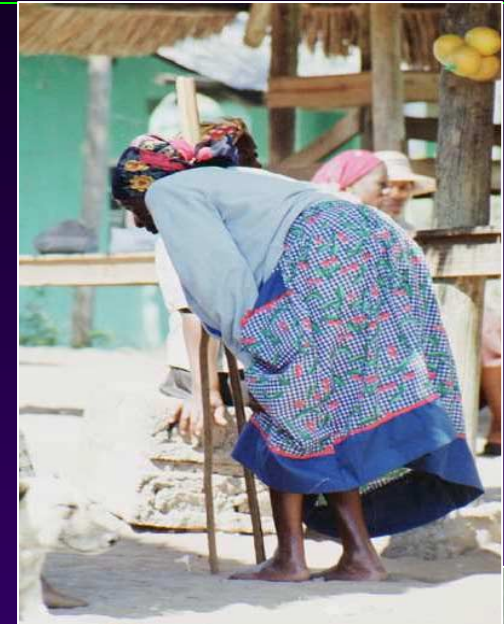
- Multiple epiphyseal displasia (long bones have malformed growth)
- Polyarticular osteoarthritis (arthritis of several joints)
- Protrusio acetabuli (hip disorder)
- Dwarfism

Maputaland



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(?)

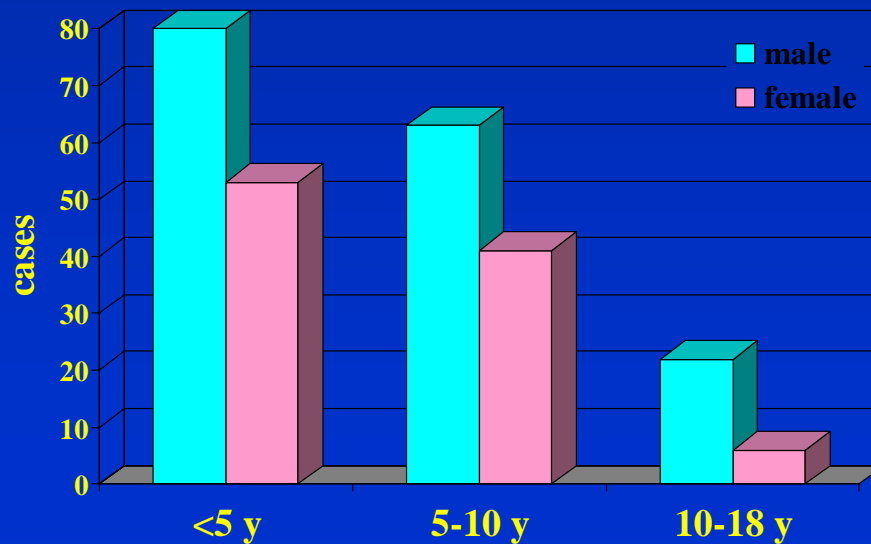
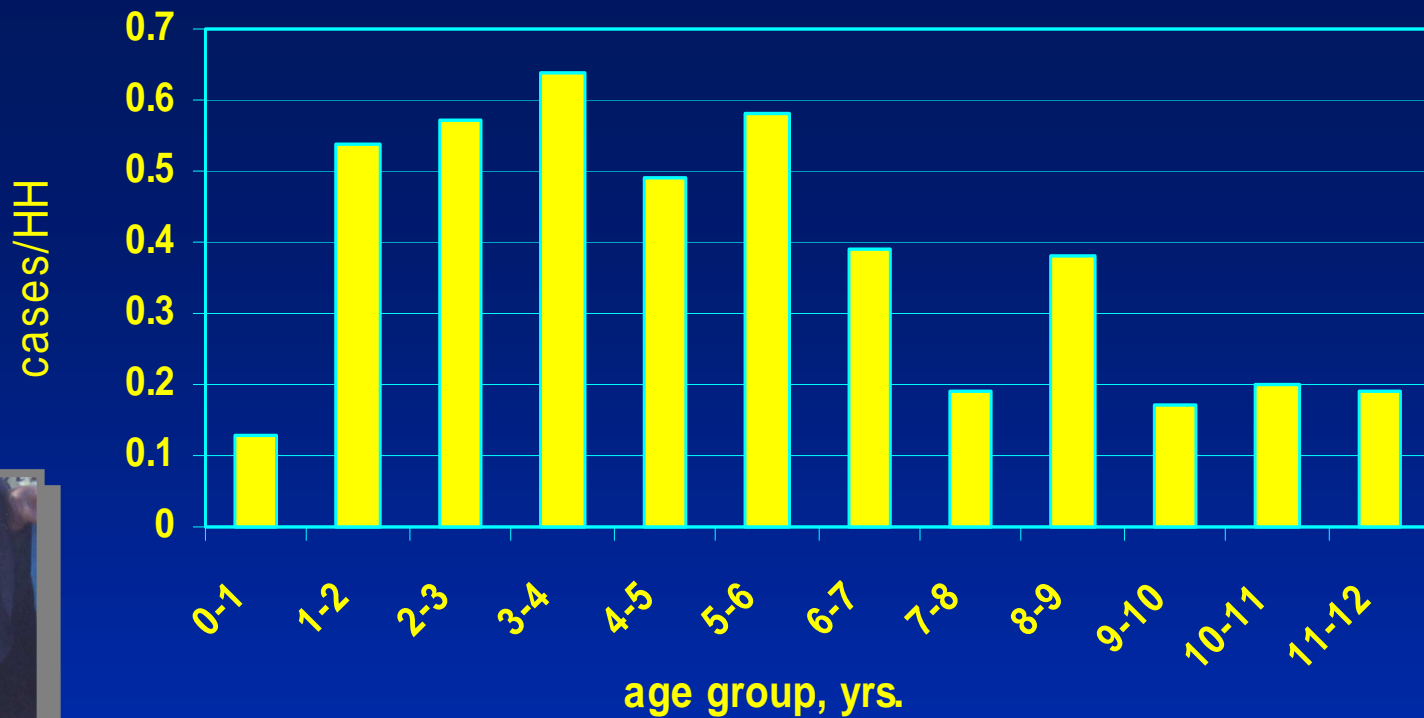
 - tachysterols (vit. D analogues)

 - fat, oxalates, DDT (?)



Photo Courtesy: Dr. Gerald F Combs, USDA

age and sex distribution of cases



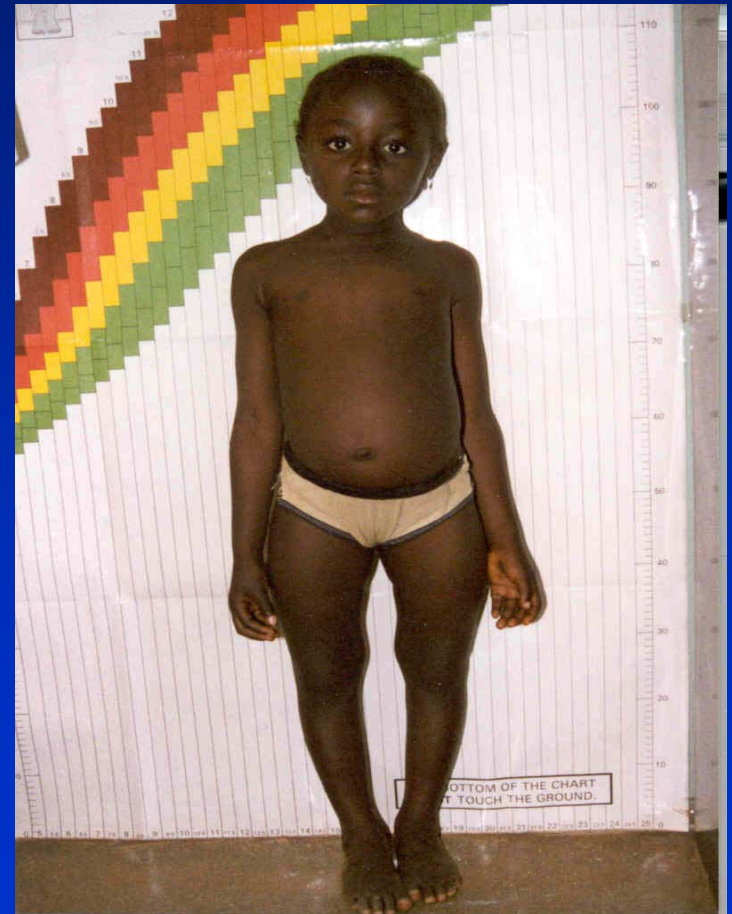
Calcium-supplementation study
(Combs et al. personal communication)

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



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**



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

