

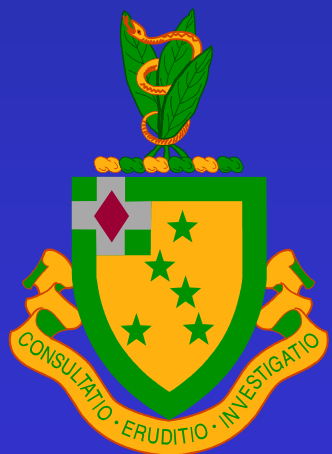
# *Diversity of Trace Elements and Toxic Metal Ions in Environmental Health and Human Diseases*

José A. Centeno

U.S. ARMED FORCES INSTITUTE OF PATHOLOGY

Washington, DC

Email: [centeno@afip.osd.mil](mailto:centeno@afip.osd.mil)

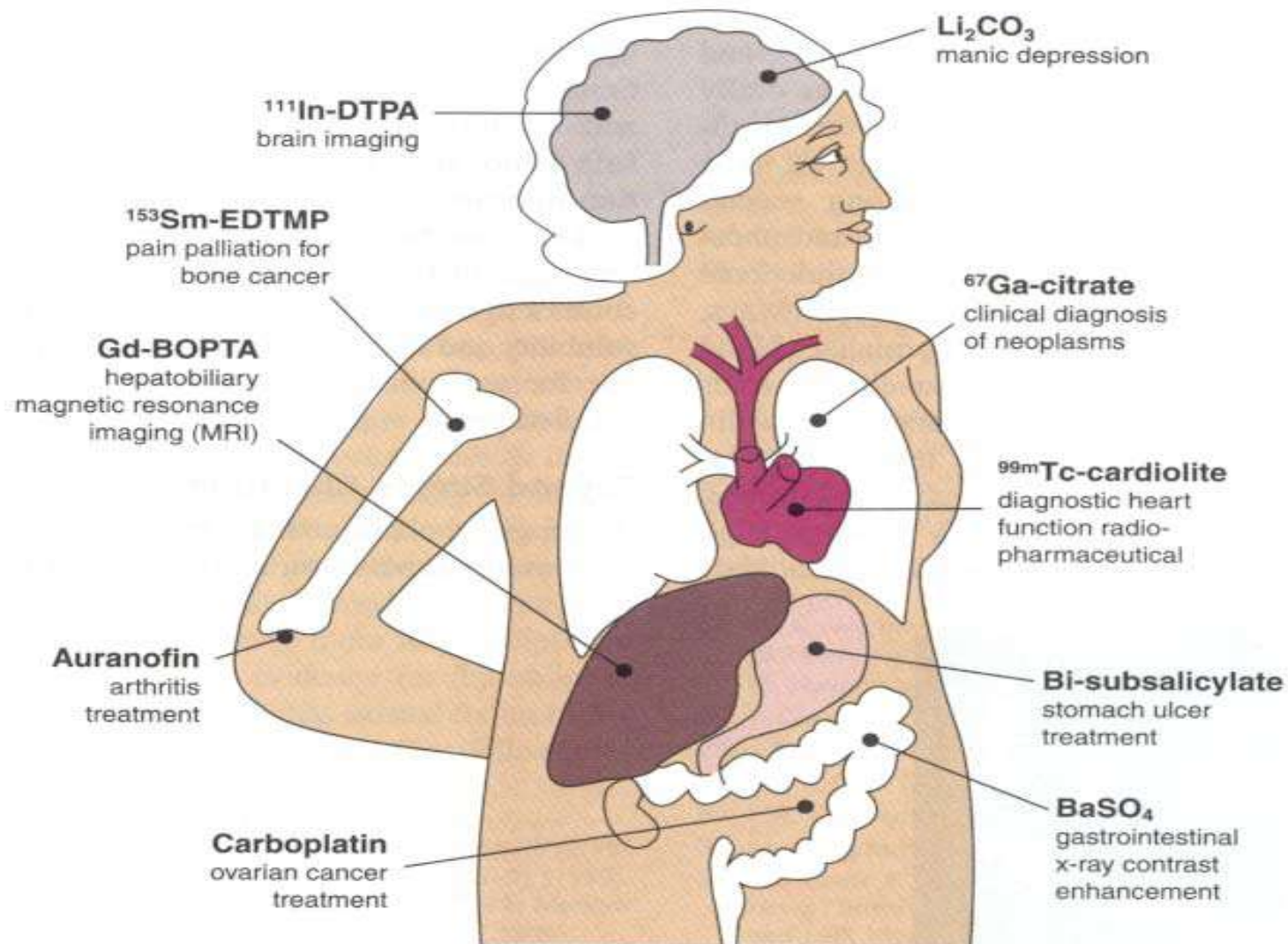


# Outline

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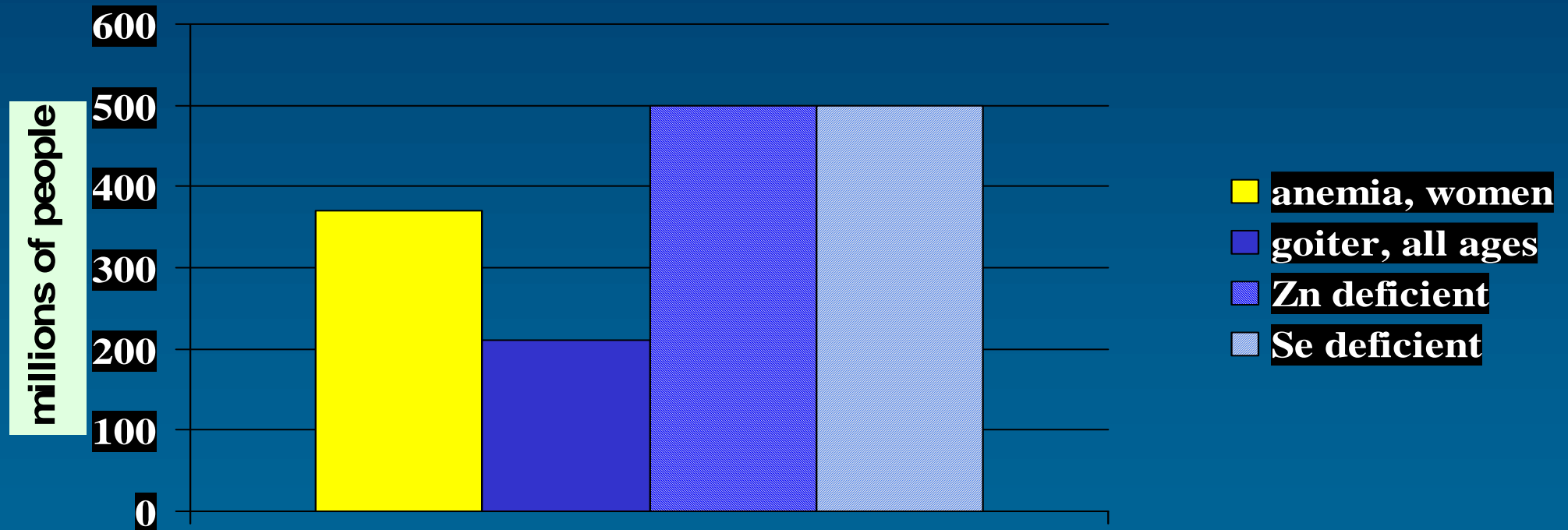
- **Introduction to Trace Elements, Metals and Metalloids**
- **Trace Elements and Known Biological/Toxicological Reactions**
- **Environmental Health and Diseases**
- **Concluding Remarks**

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



**Fig. 1.** Metal ions are important in diagnosis and therapy of a host of different human pathologies. Gd,  $^{111}\text{In}$ , and  $^{99\text{m}}\text{Tc}$  are used in medical imaging;  $^{153}\text{Sm}$  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.

# Trace Element Malnutrition in Developing Countries



Courtesy from Dr. Gerald T. Combs

# Criteria for Essentiality

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- 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 and diet
- **Concentration:** needed on mcg to mg

# The geoavailability-bioavailability continuum



Total metal content of an earth material

The geoavailable fraction

The bioaccessible fraction – that which is soluble in various body fluids (gastrointestinal, respiratory, perspiration, etc.)

The bioavailable fraction – that which is absorbed by the body, and transported within the body to a site of toxicological action

# Geoavailability

- That portion of a metal's or a metal-bearing compound's total content in an earth material that can be liberated to the surficial or near-surface environment (or biosphere) through mechanical, chemical, or biological processes.
  - Smith and Huyck (1999)
  - In order for a metal in an earth material to be bioaccessible and bioavailable, it must first be geoavailable



H																	He				
Li	Be															B	C	N	O	F	Ne
Na	Mg															Al	Si	P	S	Cl	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														
Fr	Ra	Ac	Rf	Ha	Sg	Ns	Hg														

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

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

Ce	Pr	Nd	Pm	Sm	Eu
Th	Pa	U	Np	Pu	Am



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<div>K</div>	<div>Ca</div>	Sc	Ti	V	<div>Cr</div>	<div>Mn</div>	<div>Fe</div>	Co	Ni	<div>Cu</div>	<div>Zn</div>	Ga	Ge	As	<div>Se</div>	Br	Kr				
Rb	Sr	Y	Zr	Nb	<div>Mo</div>	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	<div>I</div>	Xe				
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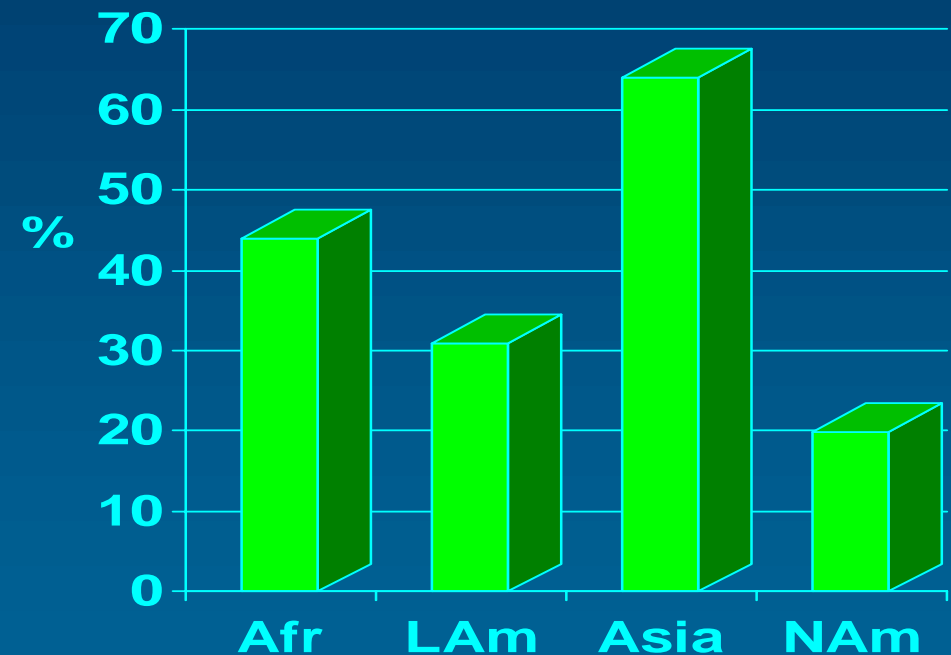
# IRON (FE)

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- 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);
- **Deficiency:** 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
- **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<sub>12</sub>
- **reduced work capacity**
- **20% of maternal deaths**
  - hemorrhage, heart failure
- **1/3 of child deaths**
- **impaired cognitive learning**





# Outline

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

## **ACTION OF MACRONUTRIENTS**

<b>Ca</b>	Strengthening of bones and teeth; muscular activity; blood coagulation; cellular permeability. Excess may originate liver and bladder stones and renal insufficiency.
<b>Cl</b>	Maintenance of blood pressure; vital as acid constituent during digestion.
<b>K</b>	Maintenance of corporeal fluids; muscular contractions and nervous impulses.
<b>Mg</b>	In bones, together with Ca; activation of muscular contractions; body temperature control; component of several enzymes.
<b>Na</b>	Active in hydrosaline equilibrium; transmission of nervous impulses and transport of metabolites.
<b>P</b>	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 <sub>12</sub> and in chemical reactions. Deficiency causes anemia. Excess causes heart failures.
Cr	Needed for metabolism of sugar. Deficiency may cause diabetes, intolerance to glucose etc. Excess may result in renal failures. Excess of Cr <sup>+6</sup> is carcinogenic.
Cu	Component of oxidizing enzymes during metabolism of energy sources; active in the synthesis of hemoglobin, in keratinization 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**

insulin potentiation

antioxidant protection

antioxidant protection; regulation of thymulin and IL-2

antioxidant protection, regulation of PG metabolism

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# Toxic Effects of Metals:

## *Cardiovascular*

### *Cardiomyopathy*

*Examples: Se, Co, Hg, Fe, Al, As, Au, Cr*

### *Atherosclerosis*

*Examples: Fe, Se, Mg, Ca, Cu*

### *Hypertension*

*Examples: Pb, As, Al, Hg*

❖ *From epidemiological studies*

# **Nephrotoxicity of Metals**

## ***The Culprits* <sup>(1)</sup>**

<b>Gold</b>	<b>Arsenic</b>
<b>Lithium</b>	<b>Mercury</b>
<b>Chromium</b>	<b>Bismuth</b>
<b>Platinum</b>	<b>Lead<sup>(2)</sup></b>
<b>Cadmium</b>	

**(1) More commonly renal changes: chronic tubulo-interstitial disease and vascular sclerosis;**

**(2) Pathognomonic feature: presence of intranuclear inclusion bodies.**

# Hepatotoxicity of Metals

## *The Culprits (1)*

Aluminum

Barium

Cadmium

Copper

Iron

Arsenic

Beryllium

Chromium

Gold

Lead



# Hepatotoxicity of Metals

## *Summary (2)*

- **Toxic (Chronic) Effects:**
  - Granulomas
  - Fibrosis, cirrhosis
  - Vascular lesion, e.g. veno-occlusive disease
  - Malignancies, e.g. angiosarcoma, cholangiocarcinoma, hepatocellular carcinoma

# **Toxic Effects of Metals:**

## ***Skin Lesions: Reaction patterns***

- I. Carcinogenesis
- II. Spongiotic dermatitis
  - Allergic contact dermatitis*
  - Primary irritant dermatitis*
- III. Granulomatous dermatitis
- IV. Pigmentation disorders

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- **Environmental Health and Diseases**
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**Non-  
industrial**



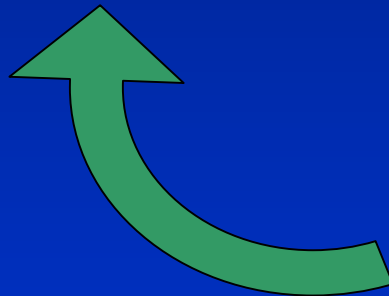
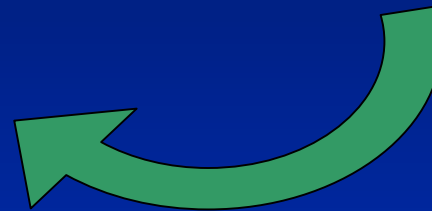
**Drinking water  
Food**

**Natural  
deposits**



**Industrial**

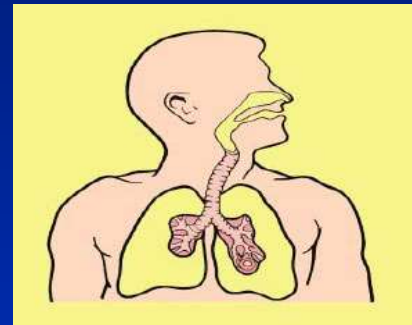
**Agriculture  
Mining/smelting  
Coal burning  
Micro-electronics**



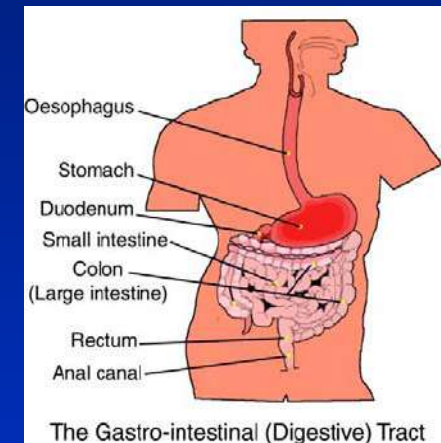
# Trace Elements in Environmental Health

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

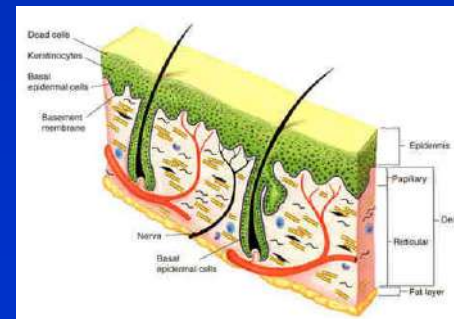
Inhalation



Ingestion



Dermal contact



# TRACE ELEMENTS AND TOXIC METAL IONS

*HEALTH EFFECTS*

*Deficiencies*

# 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

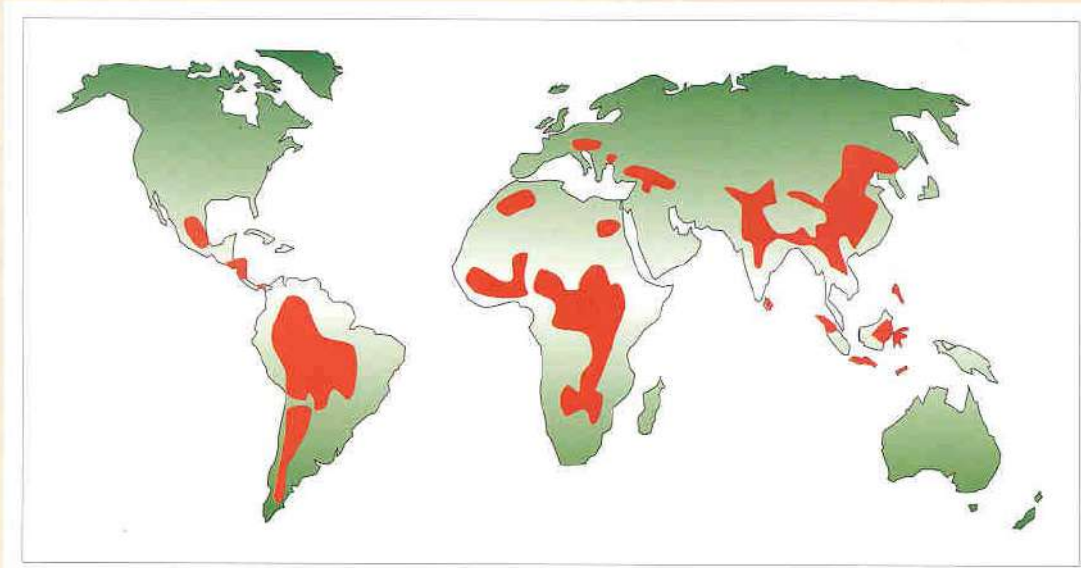
**Metalloids:\***

Arsenic

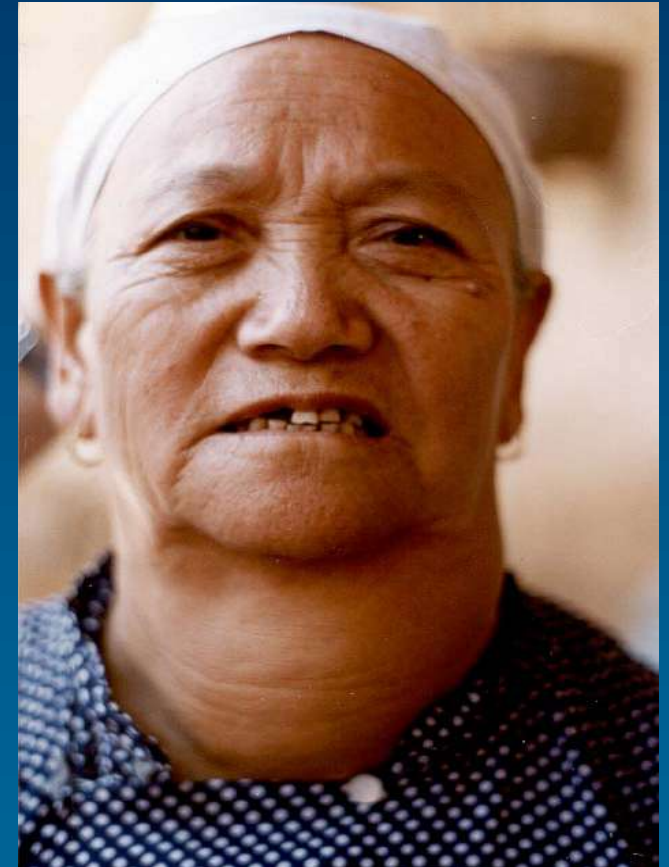
Skin lesions, cancer



## Element deficiency - Iodine



# Iodine Deficiency Disorders (IDD)



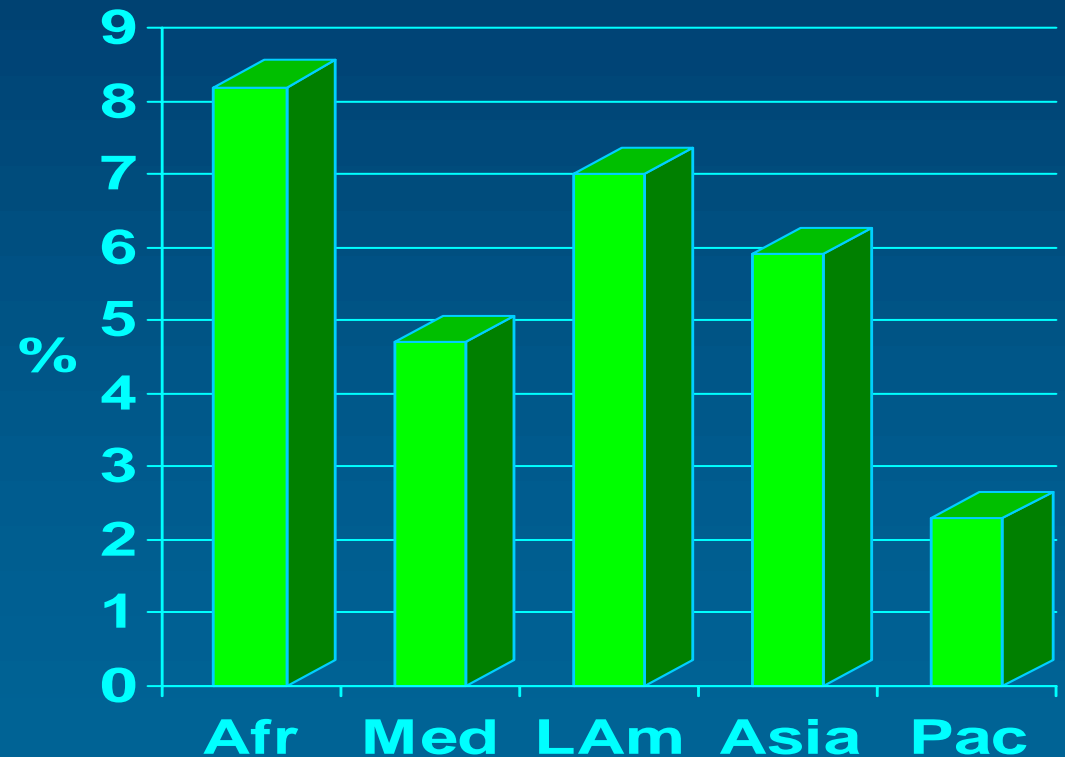
IDD and multi-causal disease involving factors such as:

- 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.

# 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



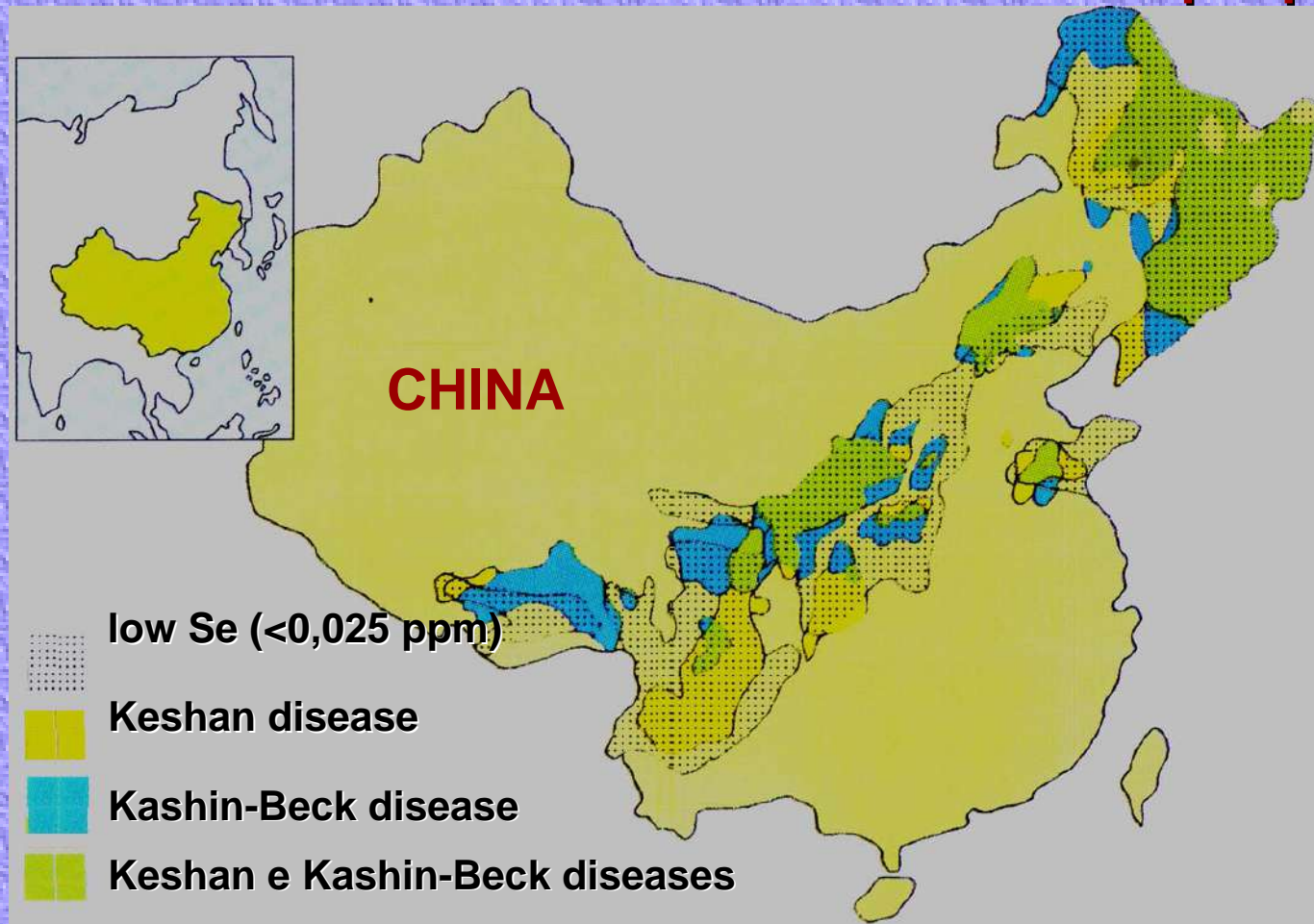
Courtesy from Dr. Gerald T. Combs

# 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
- impairs
  - thyroid hormone metabolism
  - T-cell function
  - resistance to RNA-viral disease

# 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



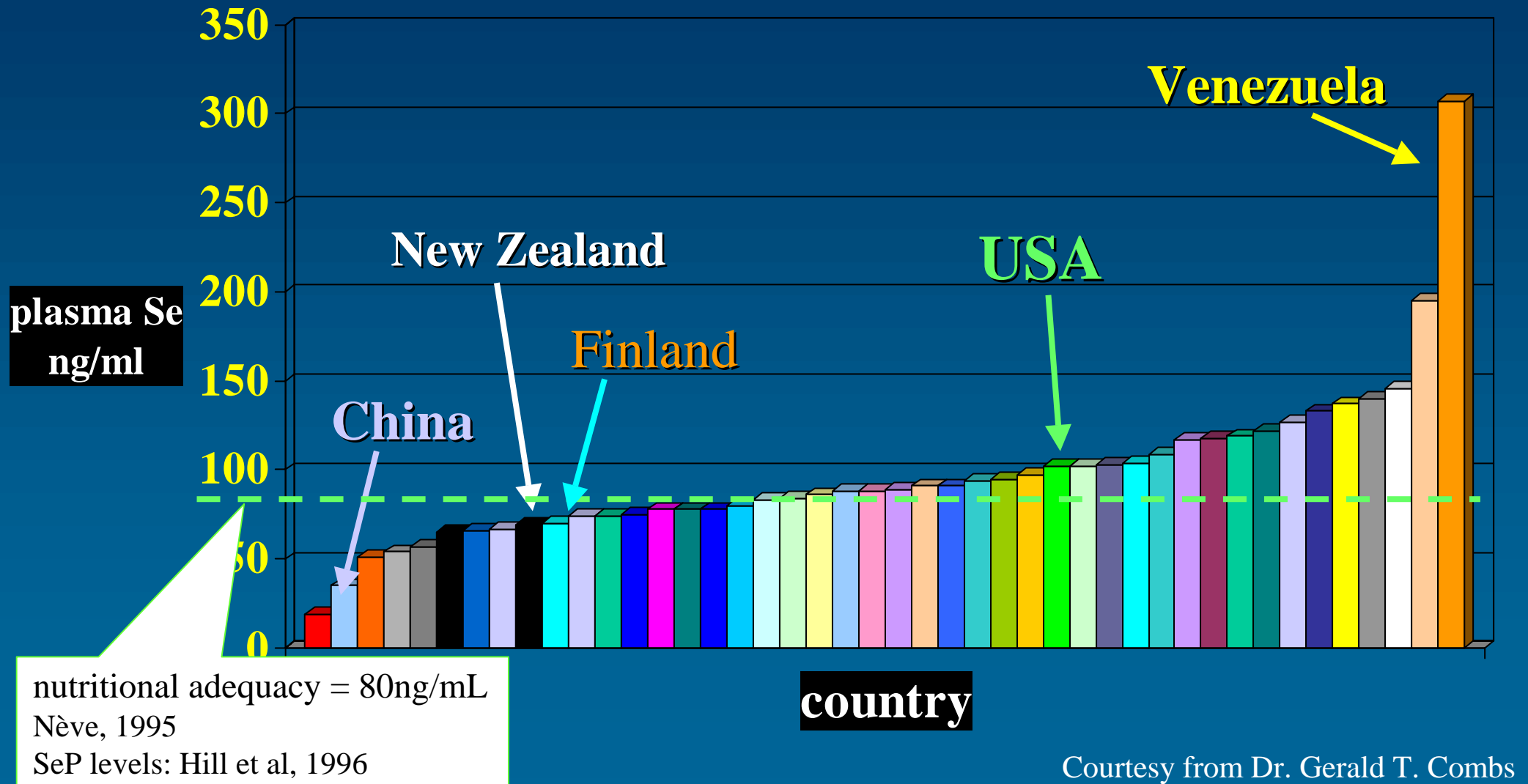
# Selenium Deficiency

## *Kashin-Beck Disease*



*Photo: Courtesy of Prof. Wang Zhilun, China*

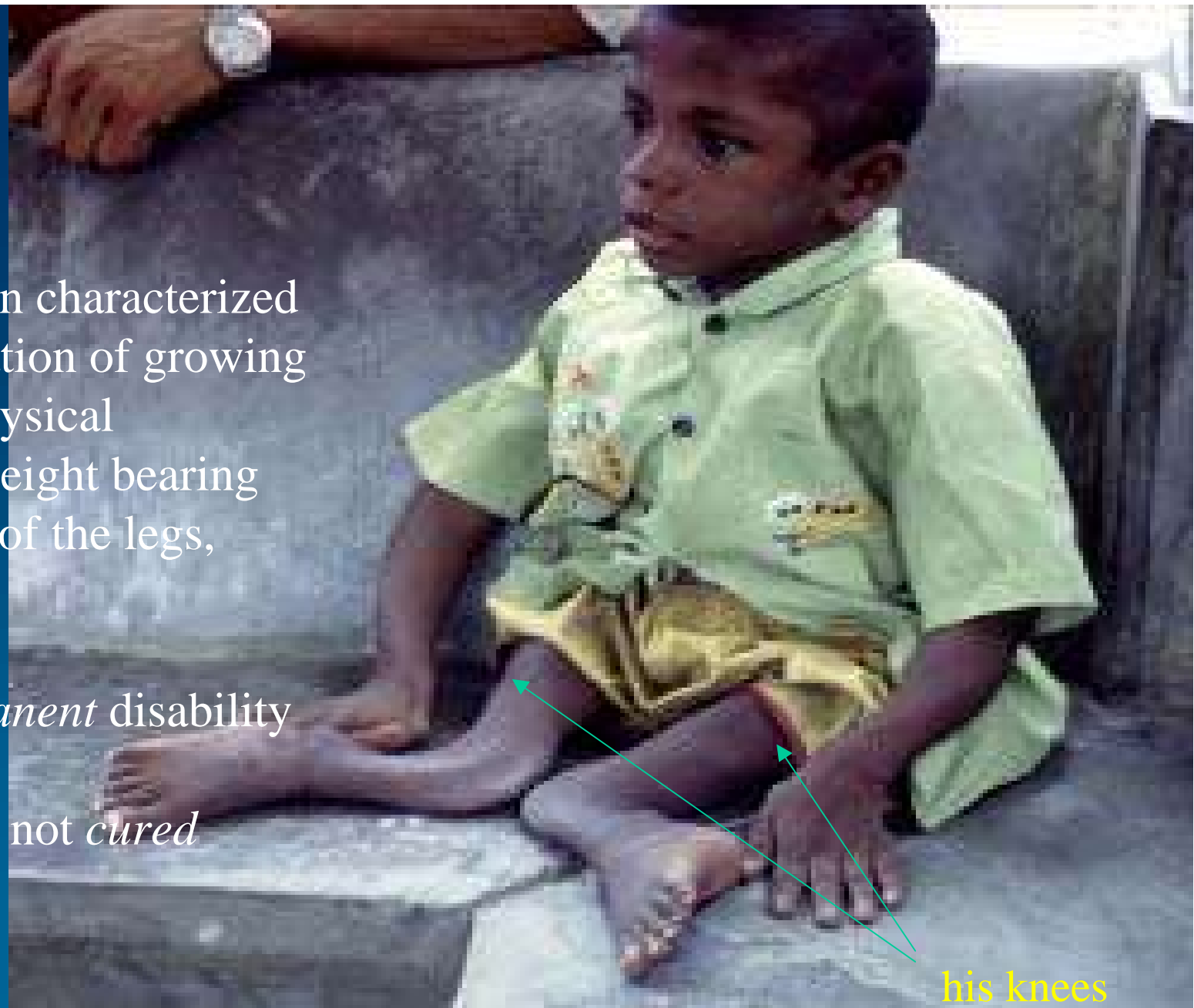
# Worldwide Variation in Se status



Courtesy from Dr. Gerald T. Combs

# 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(?)

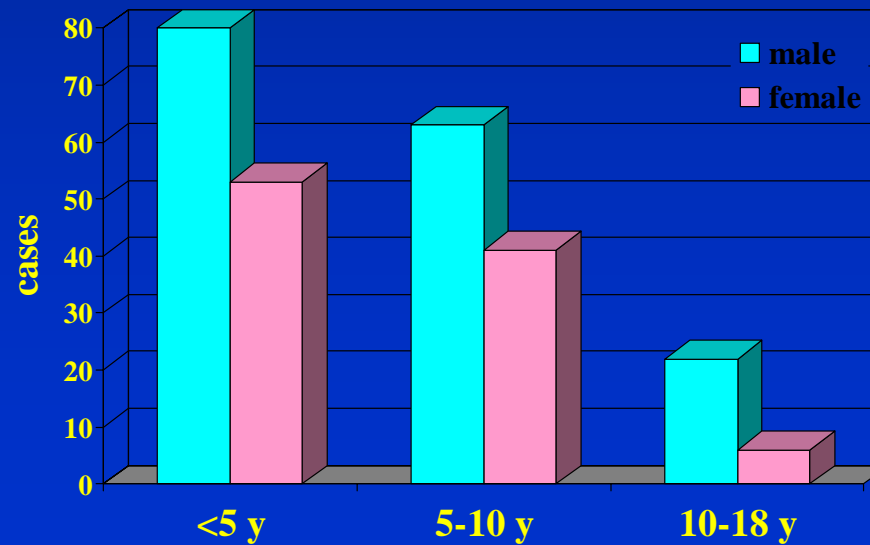
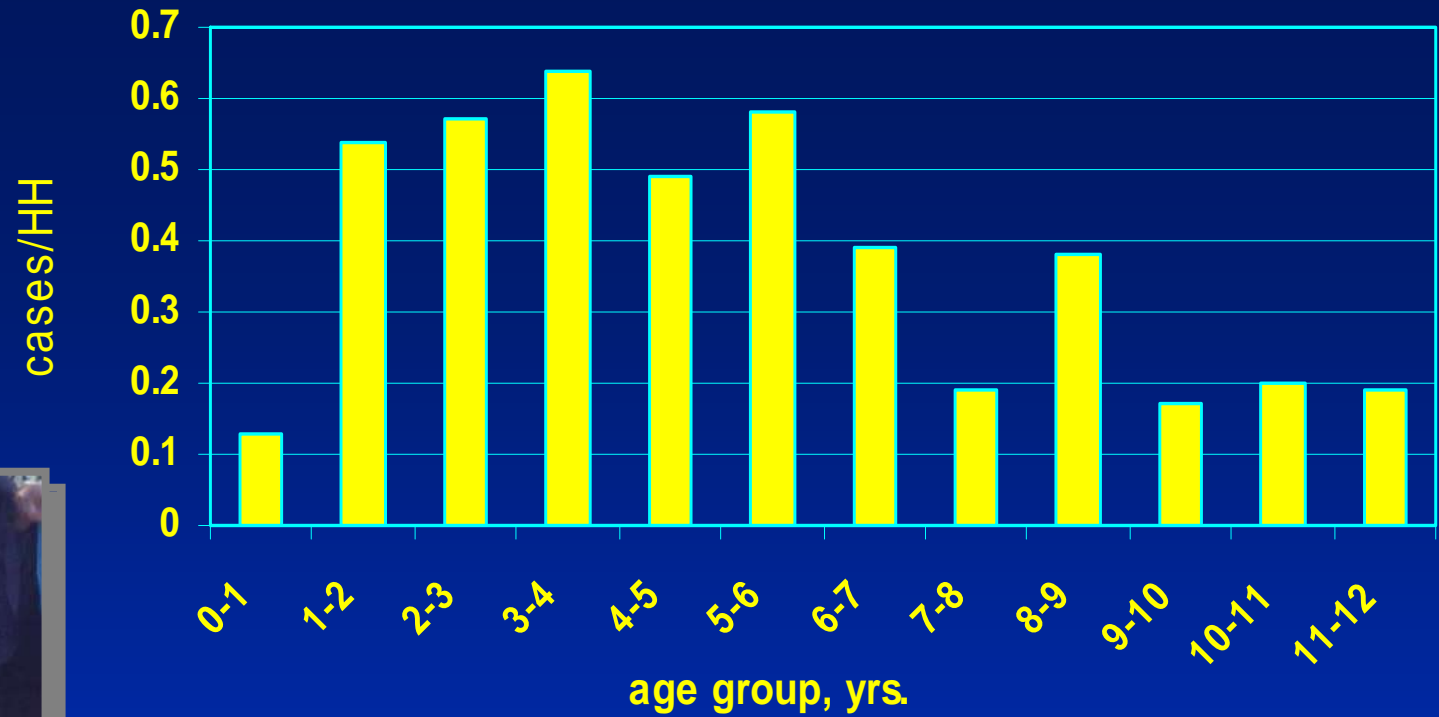
tachysterols (vit. D analogues)

fat, oxalates, DDT (?)



*Photo Courtesy: Dr. Gerald F Combs, USDA*

# age and sex distribution of cases



Courtesy from Dr. Gerald T. Combs

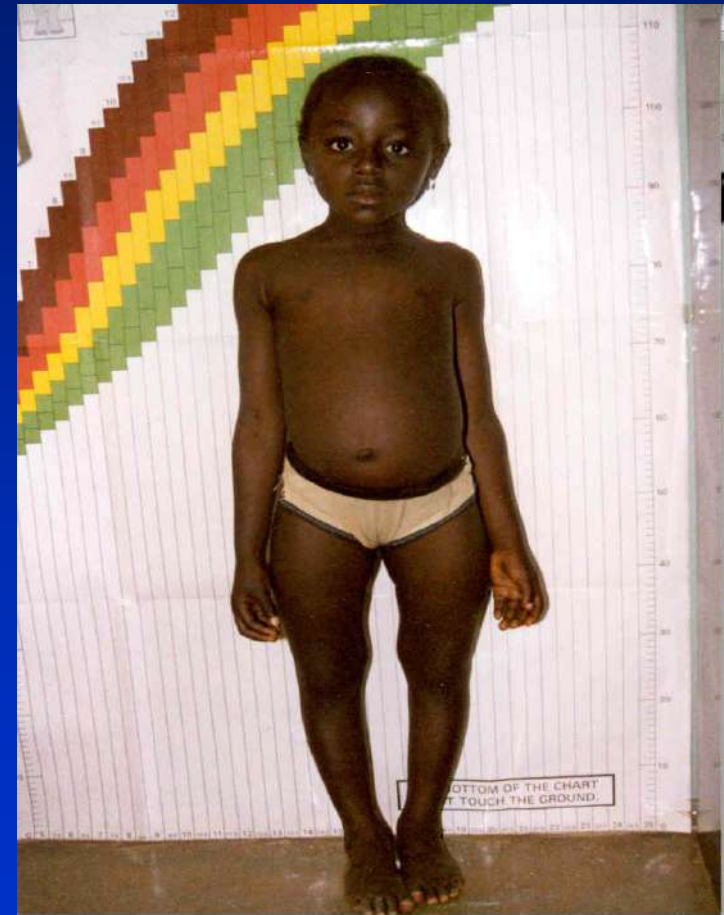
Calcium-supplementation study  
(Combs et al. personal communication)

**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

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## Dose-Response Relationship for Fluorine:

- $< 0.5 \text{ mg/L}$  : dental cavities may occur (risk)
- $0.5 - 1.5 \text{ mg/L}$ : no adverse effects
- $> 1.5 \text{ mg/L}$  : fluorosis risk

# ARSENIC EXPOSURE : GLOBAL IMPACT

## PEOPLE AFFECTED BY NATURALLY CONTAMINATED WATER AND SOILS



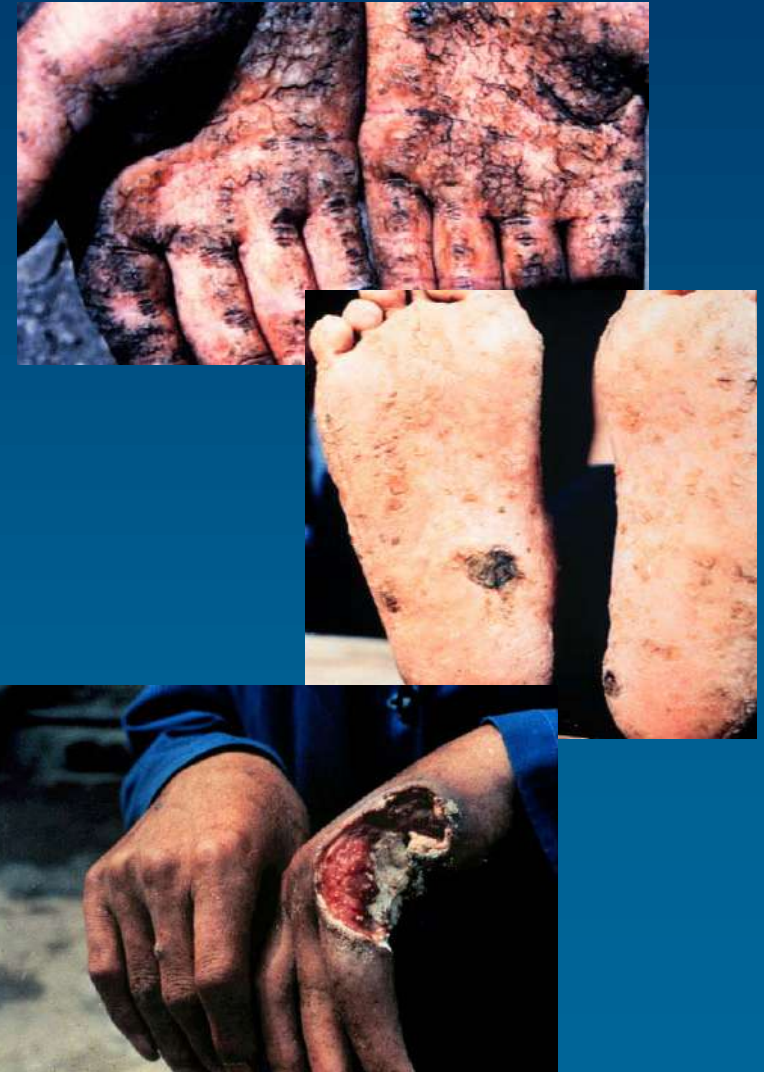


# Health Effects Associated with Arsenic Exposure

- 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

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

# SUMMARY

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- 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.