# Zinc Polymorphism in Type 2 Diabetes

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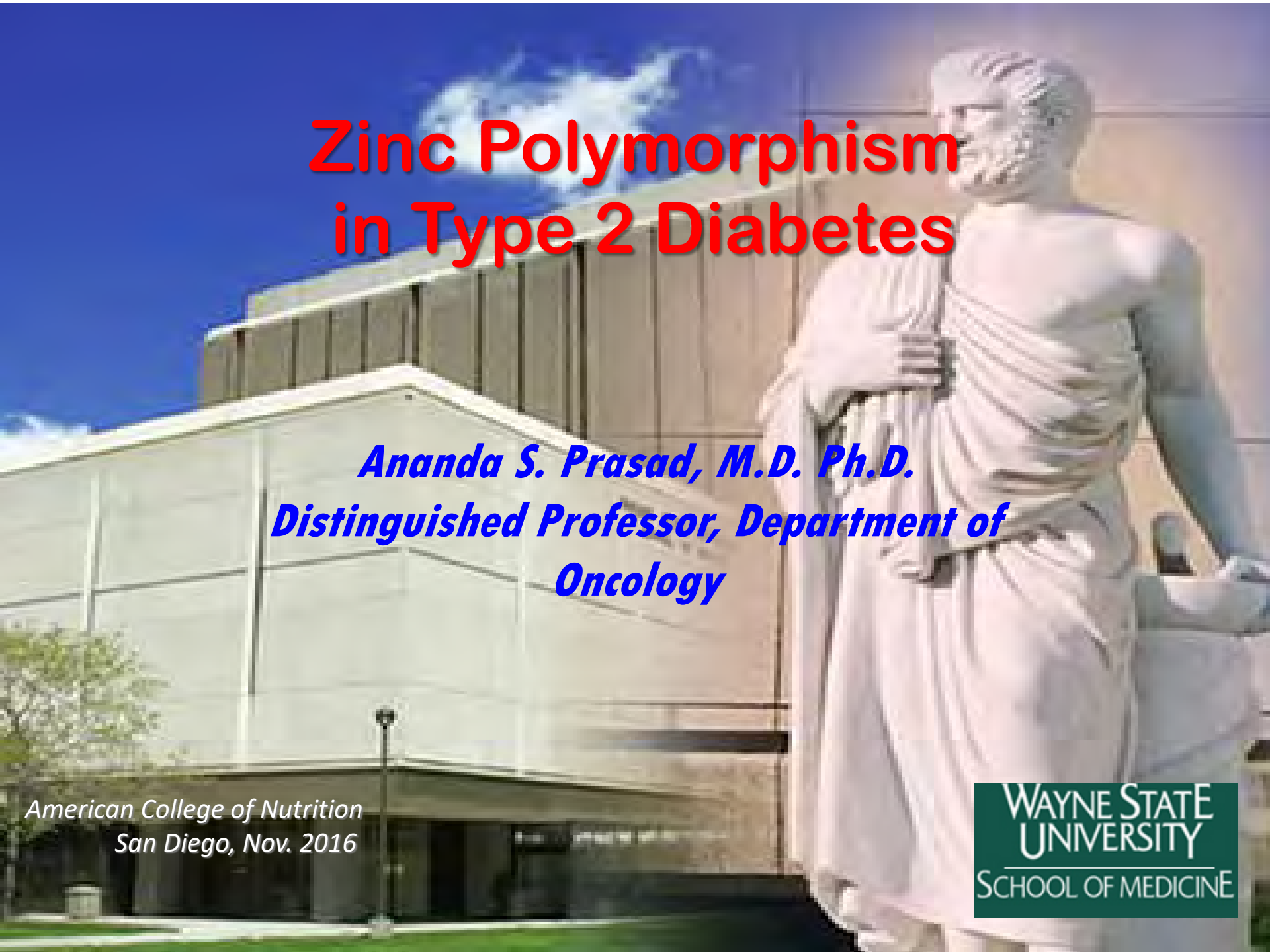
*American College of Nutrition*
*San Diego, Nov. 2016*



WAYNE STATE UNIVERSITY
SCHOOL OF MEDICINE

# Faculty Disclosure

| Commercial Interest | Nature of Relevant Financial Relationship (Include all those that apply) | |
|---|---|---|
| | **What was received** | **For what role** |
| • None | • N/A | N/A |

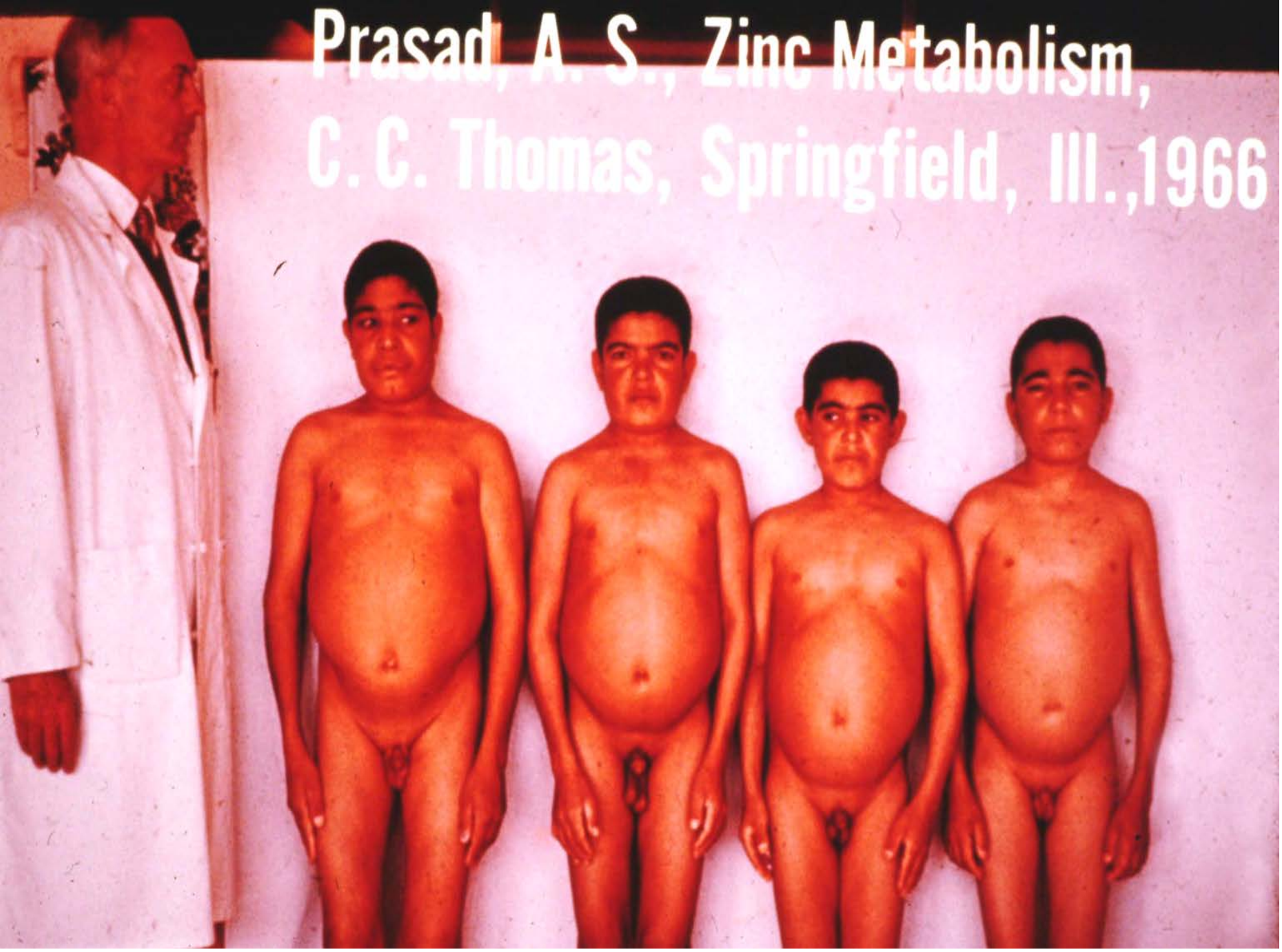
# Presentation Learning Objectives

After participating in this presentation, learners should be better able to:

- Understand role of zinc in insulin signaling
- Recognize that zinc deficiency is common in diabetes type 2 patients
- Understand the role of zinc in insulin resistance

# Zinc Deficiency in Microorganisms, Plants and Animals

1. RAULIN in 1869 - Aspergillus niger
2. SOMMER and LIPMAN in 1926 - Higher Plant Life
3. TODD, ELVEHJEM & HART in 1934 - Rats
4. TUCKER and SALMON in 1955 - Pigs
5. O'DELL and SAVAGE in 1958 - Poultry
6. Prasad et al in 1963 - Man


Prasad, A. S., Zinc Metabolism,
C. C. Thomas, Springfield, Ill.,1966

Cited in Nutrition Classics, Nutrition Review, July 1983

NUTRITION CLASSICS

THE
AMERICAN JOURNAL
OF MEDICINE

Volume 31, 1961
Pages 532-546

# Syndrome of Iron Deficiency Anemia, Hepatosplenomegaly, Hypogonadism, Dwarfism and Geophagia

ANANDA S. PRASAD, M.D., JAMES A. HALSTED, M.D. and
MANUCHER NADIMI, M.D.
*Shiraz, Iran*

# Zinc-Deficient Farm Boy

1915 75 1990 YEARS

LANDMARK ARTICLE

The Journal of

LABORATORY and CLINICAL MEDICINE

*Volume 61 Number 4 APRIL 1963*

Clinical and experimental

# Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypogonadism

ANANDA S. PRASAD, AUGUST MIALE, JR., Z. FARID, H. H. SANDSTEAD, and ARTHUR R. SCHULERT *Cairo, U. A. R.*

# CLINICAL MANIFESTATIONS IN ZINC DEFICIENT DWARFS

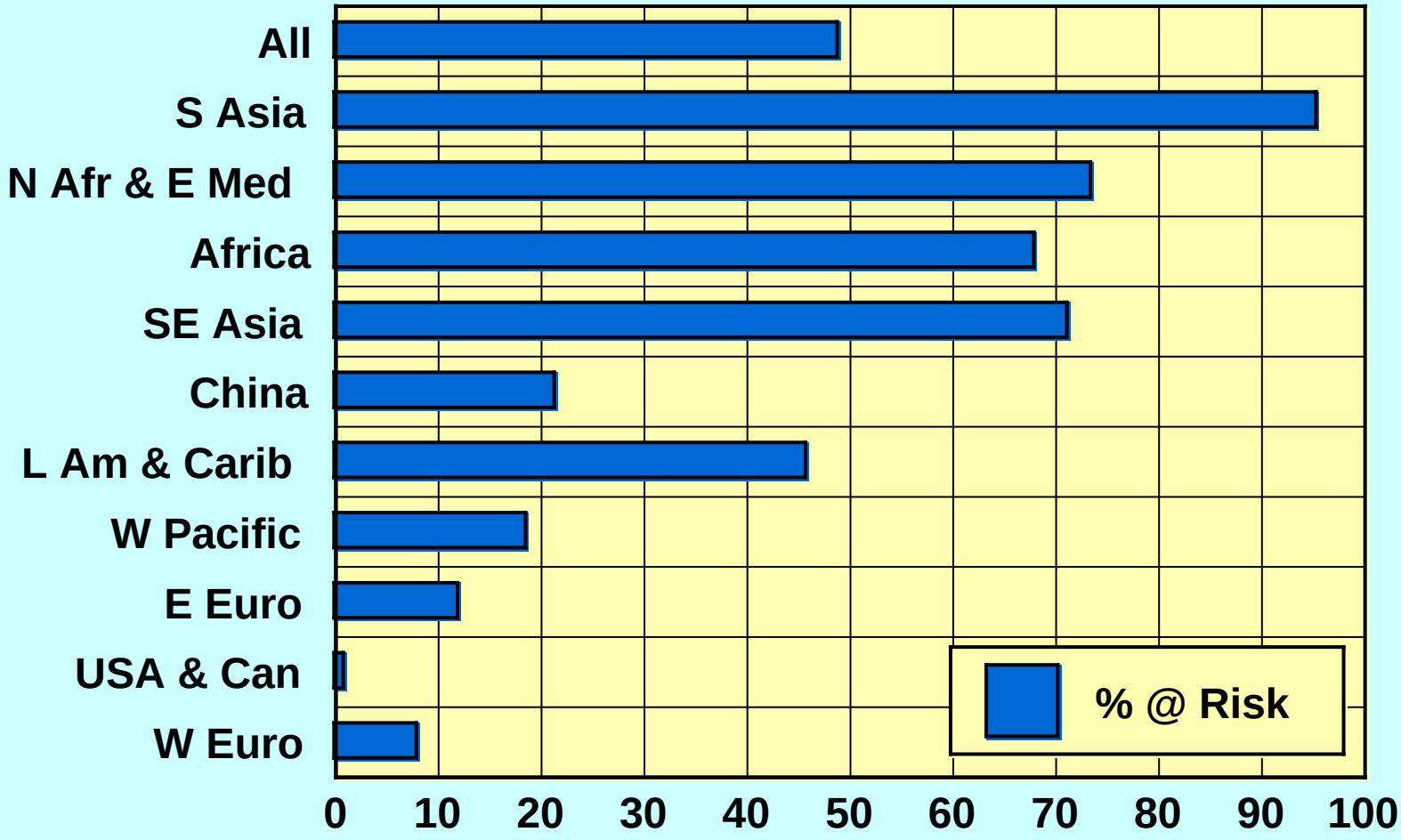
1. Growth Retardation
2. Hypogonadism in Males
3. Rough Skin
4. Poor Appetite
5. Mental Lethargy
6. Intercurrent Infections

# Prevalence of ZINC DEFICIENCY

**Nearly two billion subjects in the developing world have nutritional deficiency of zinc. In the developing world the diet consists of mainly cereal proteins with high phytate content which complexes zinc and decreases its availability.**

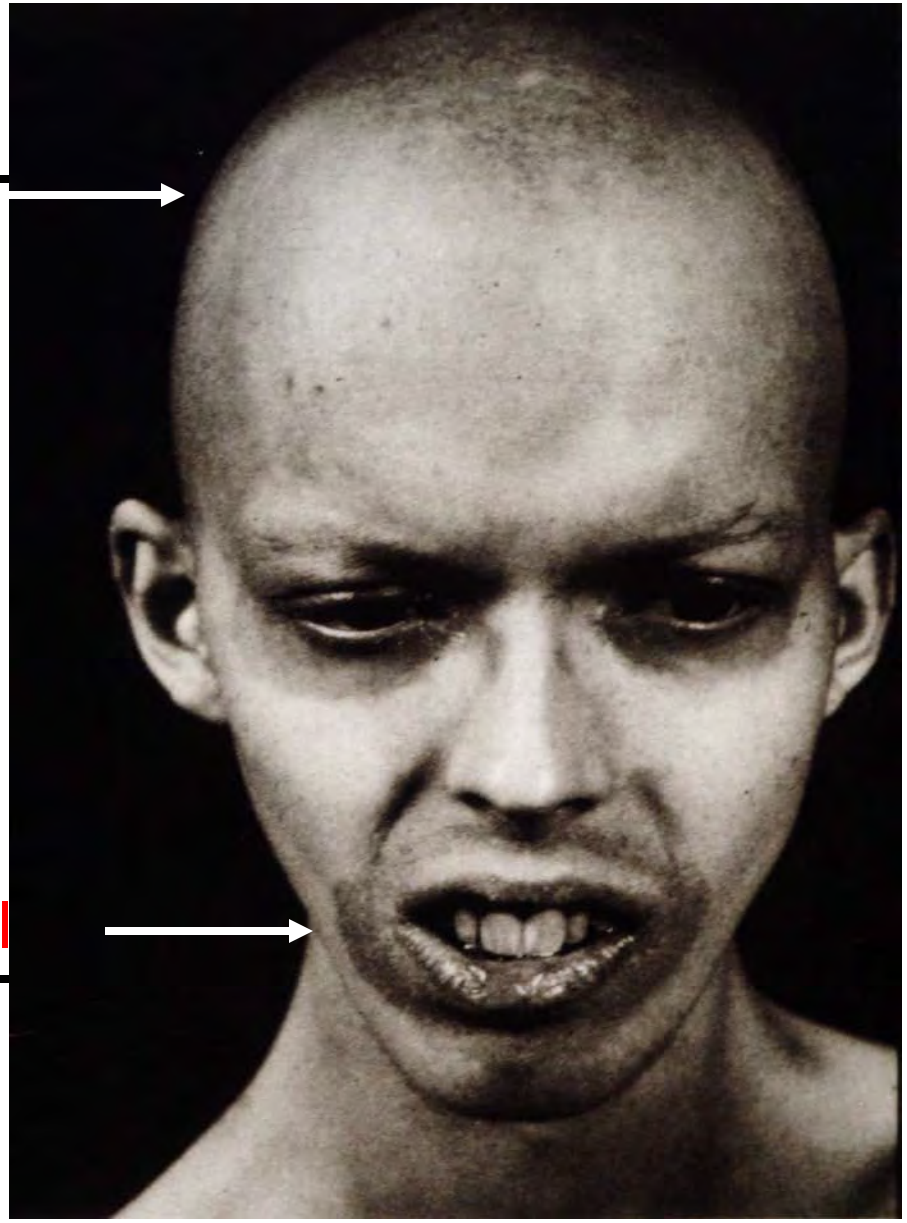
**Conditioned deficiency of zinc is also widely prevalent throughout the world. Zinc deficiency has been reported in patients with liver disease, chronic alcoholism, malabsorption syndrome, chronic renal disease, and other chronic diseases including malignancy.**

# Estimated Percentage of Population at Risk of Zinc Deficiency

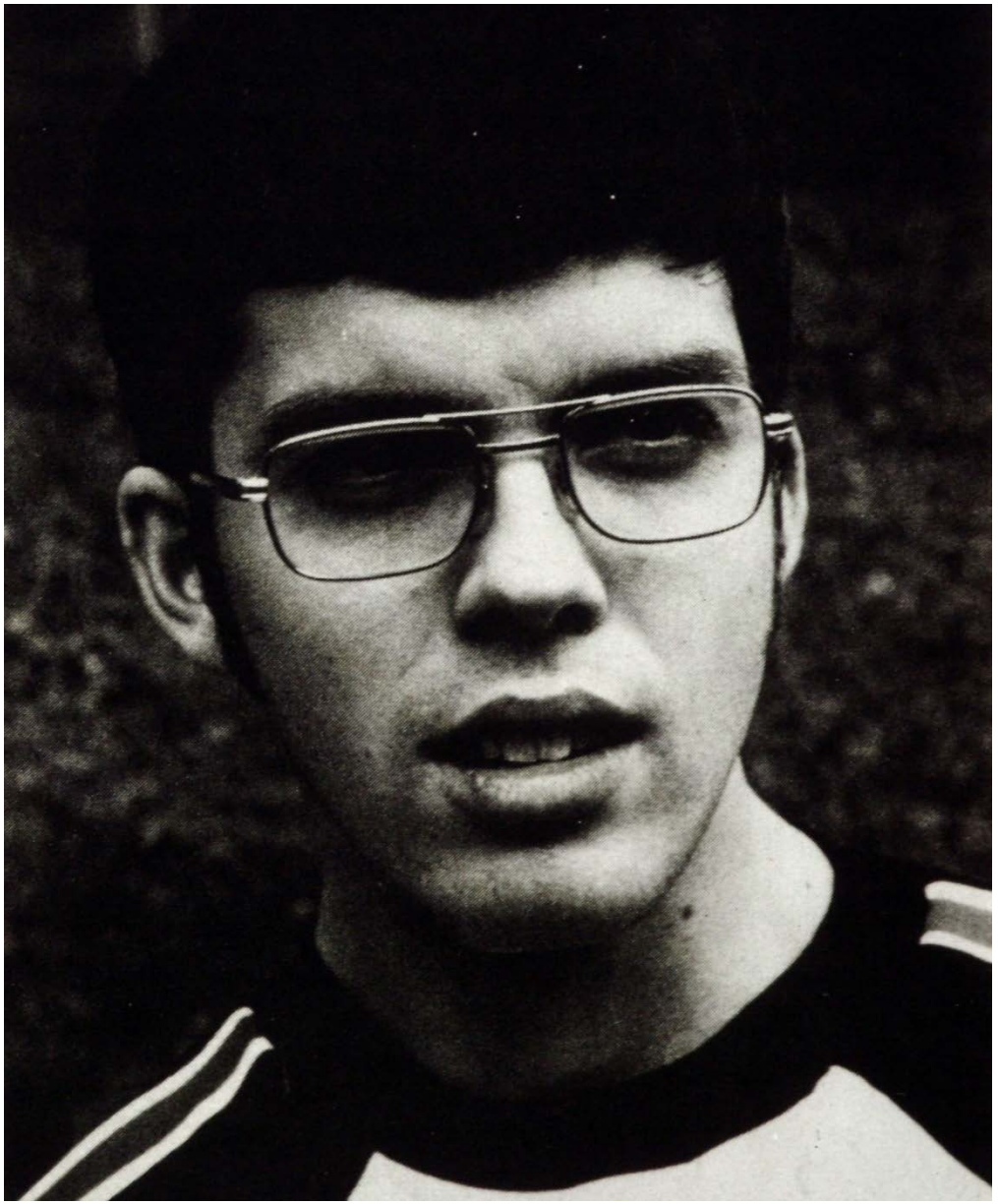



Brown, et al Food Nutr Bull 2001;22:113-25

# Patient With Severe Zinc Deficiency



# Photograph of Patient After Zinc Therapy



# " Mild" Deficiency of Zinc

## Manifestations:

**Neuro-sensory changes**

**Decreased serum testosterone**

**Oligospermia**

**Hyperammonemia**

**Anergy**

**Decreased NK activity**

**Decreased production of IL-2**

**Decreased thymulin activity**

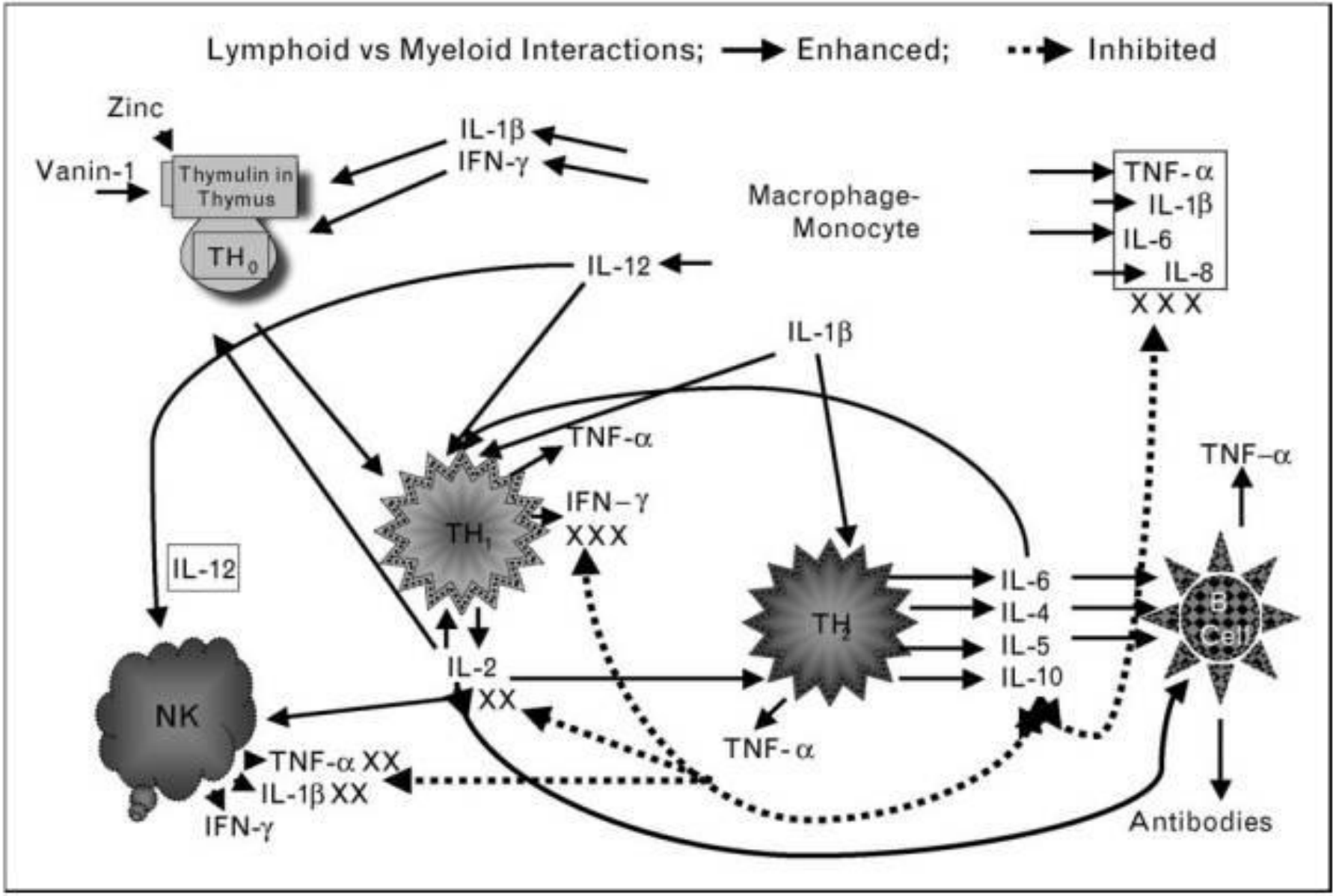
**Impaired cognitive functions**

## Observed in:

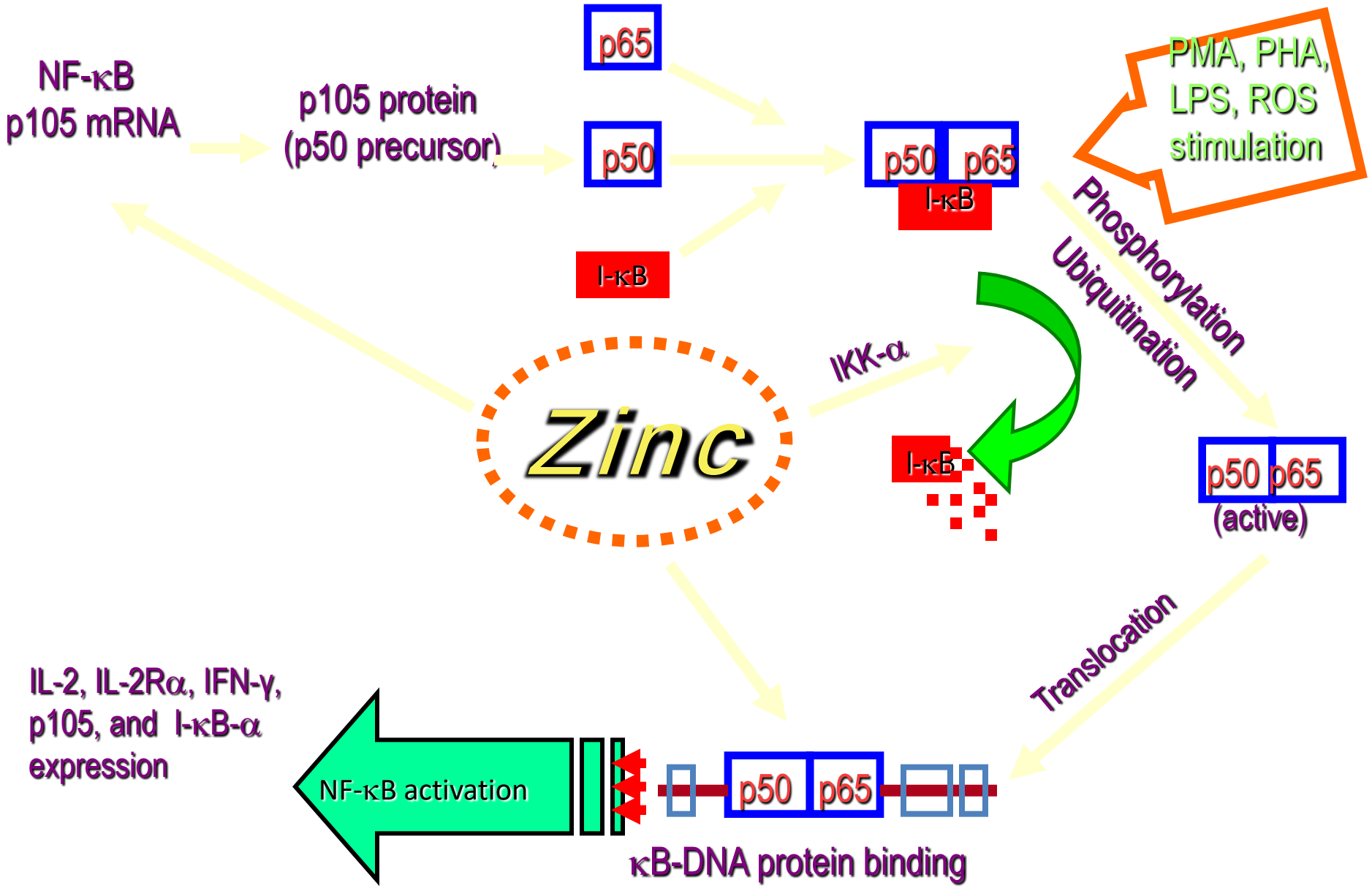
**Experimental human model studies.**

**Elderly**

**Pre-menopausal women**


Lymphoid vs Myeloid Interactions; → Enhanced; ⇢ Inhibited
Zinc
Vanin-1
Thymulin in Thymus
TH0
IL-1β
IFN-γ
IL-12
Macrophage-Monocyte
TNF-α
IL-1β
IL-6
IL-8
XXX
IL-1β
TNF-α
TH1
IFN-γ
XXX
IL-12
TNF-α
IL-2
XX
TH2
IL-6
IL-4
IL-5
IL-10
B Cell
TNF-α
NK
TNF-α XX
IL-1β XX
IFN-γ
TNF-α
Antibodies

# Effect of Zinc on NF-κB Activation in HUT-78 Cells



# REDUCTION OF MOLECULAR DIOXYGEN

$O_2 \xrightarrow{E} O_2^{\cdot -}$ (SUPEROXIDE ANION RADICAL)

$O_2^{\cdot -} \xrightarrow{E} O_2^{2-}$ (PEROXYL ANION)

$O_2^{2-} \xrightarrow{H^+} HO_2^- \xrightarrow{H^+} H_2O_2$ (HYDROGEN PEROXIDE)

$H_2O_2 \xrightarrow{E} OH^- \longrightarrow OH^{\cdot}$ (HYDROXYL RADICAL)

$OH^{\cdot} \xrightarrow{E} OH^-$

NET $O_2 + 4H^+ \xrightarrow{4E} 2H_2O$

## Therapeutic Impact of the Discovery of Essentiality of Zinc in Human

1. **In infants and children in developing countries with acute diarrhea and respiratory tract infections**
2. **Wilson's Disease**
3. **Common Cold**
4. **Sickle Cell Disease**
5. **Prevention of blindness due to age related macular degeneration (AMD)**
6. **Acyzol for Co poisoning (*Russian Study*)**
7. **Decreased incidence of infections in the elderly**

# Zinc supplementation in children with Acute Diarrhea

- Sazwal et al J Nutr 126: 443-450, 1996

For infants and children with acute diarrhea, zinc supplementation results in clinically significant reductions in the duration and severity of diarrhea.

20 mg elemental zinc daily resulted in 23% reduction in the risk of continued diarrhea and 34% reduction in mean number of watery stools per day

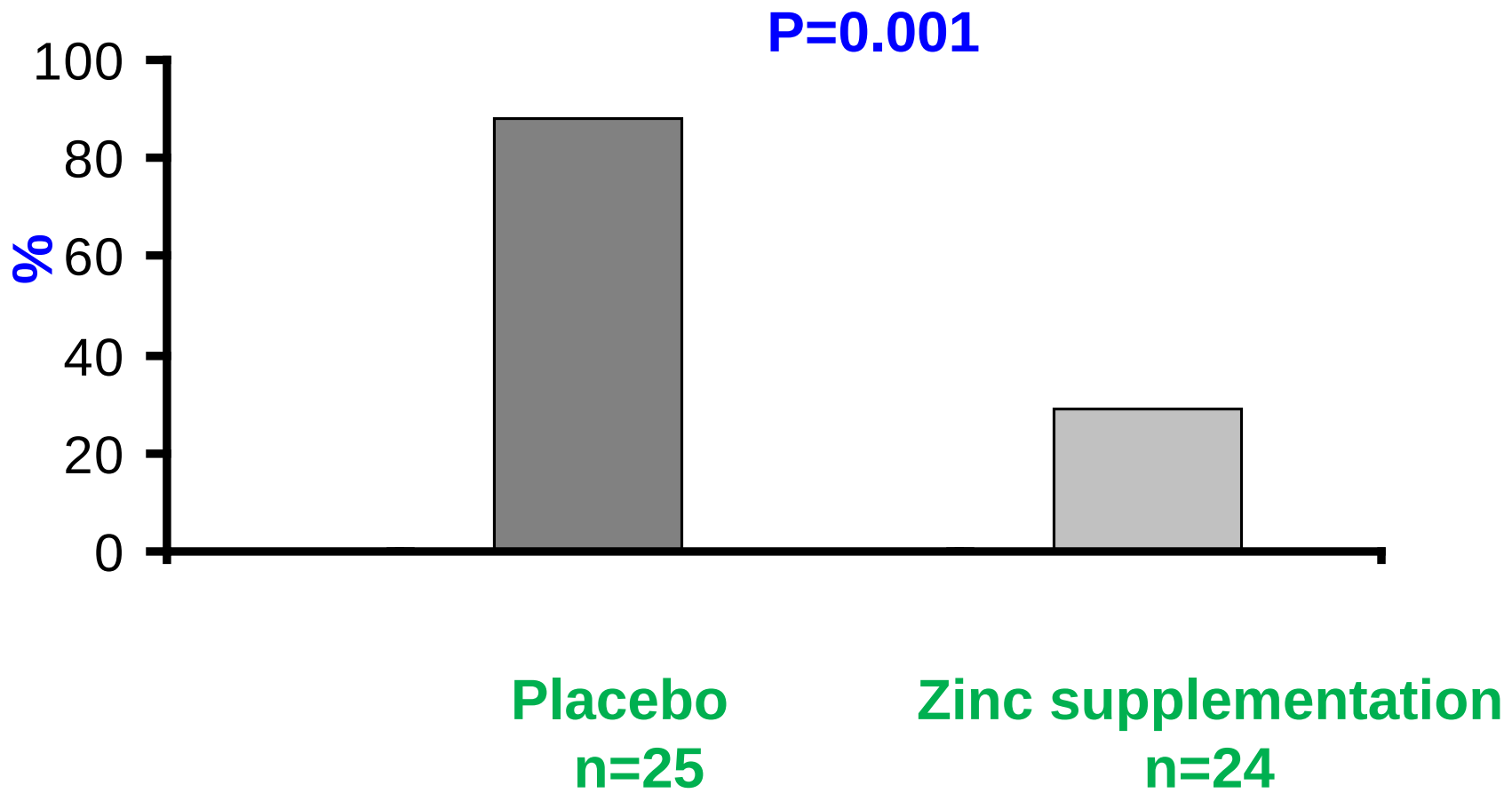
# Zinc supplementation in children with Acute Diarrhea

- Fischer, et al. Zinc and Infectious Disease: In L Rink ed Zinc in human health, IOS Press, 2011

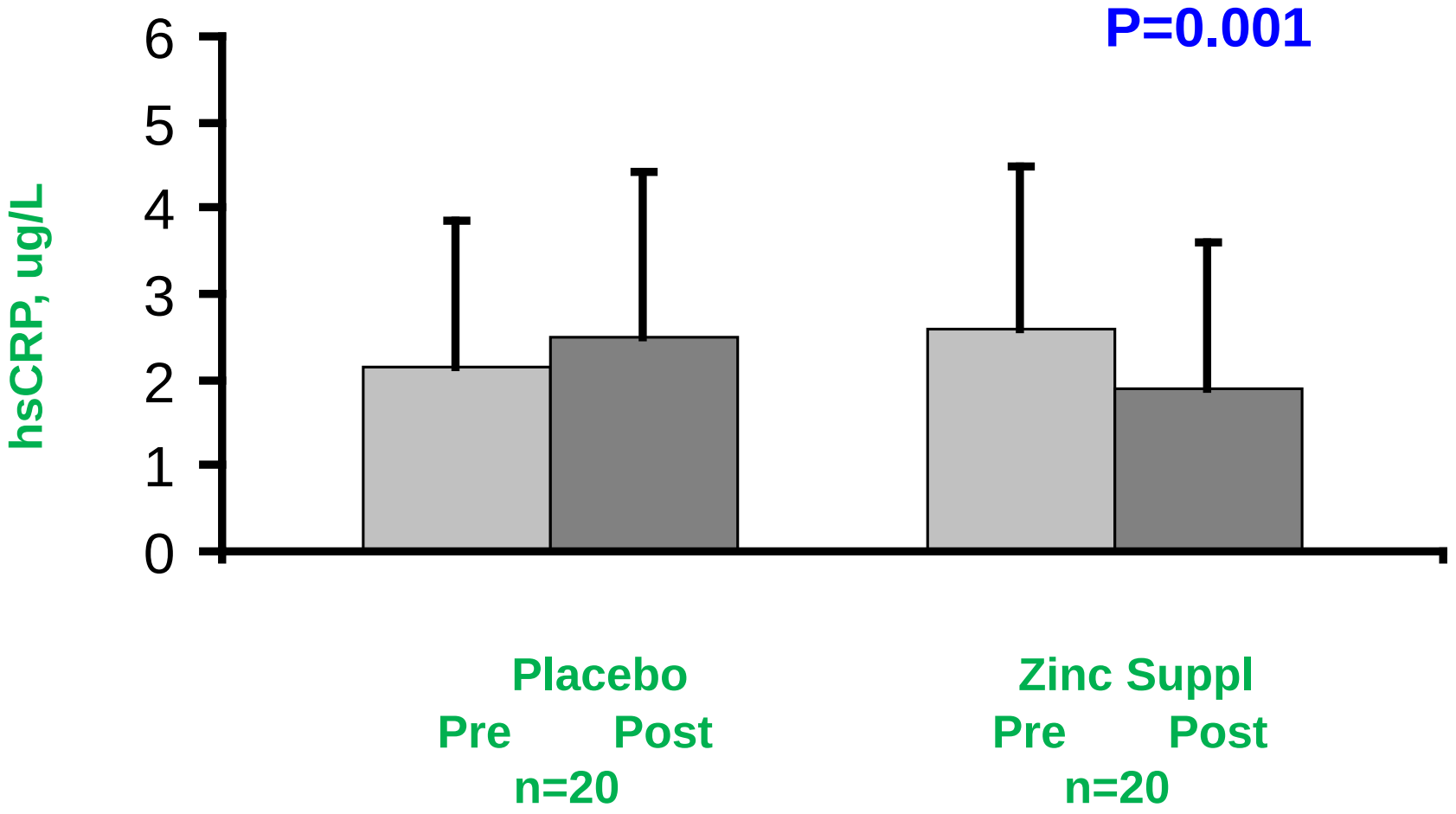
Zinc supplementation is recommended by WHO as an effective agent for the treatment of diarrhea and its prevention in children under 5 y of age.

WHO recommends this treatment for young children. This therapy also decreases risk of respiratory tract infections in young children.

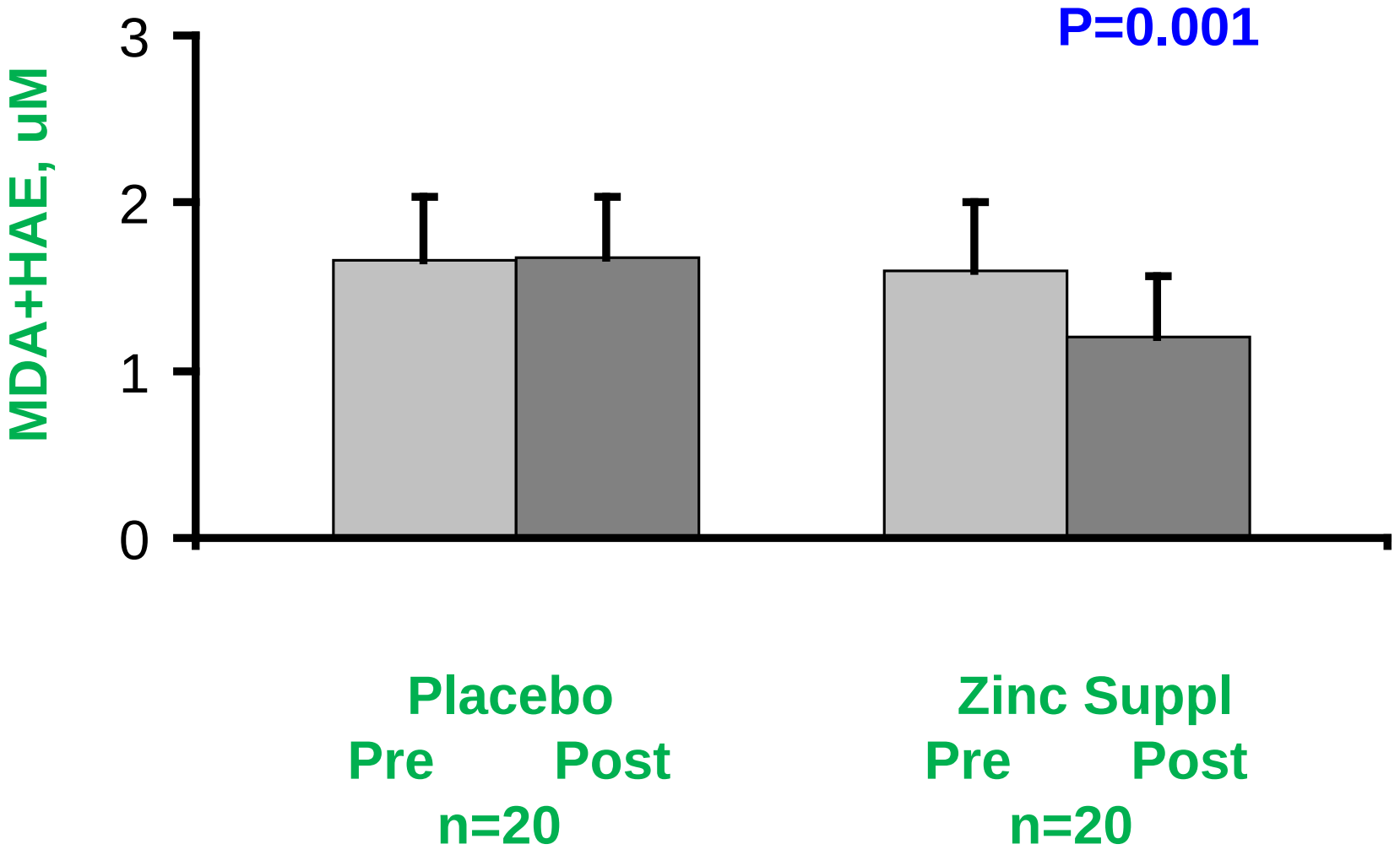
# Effect of zinc and placebo supplementation on incidence of infection in elderly subjects after 12M of supplementation



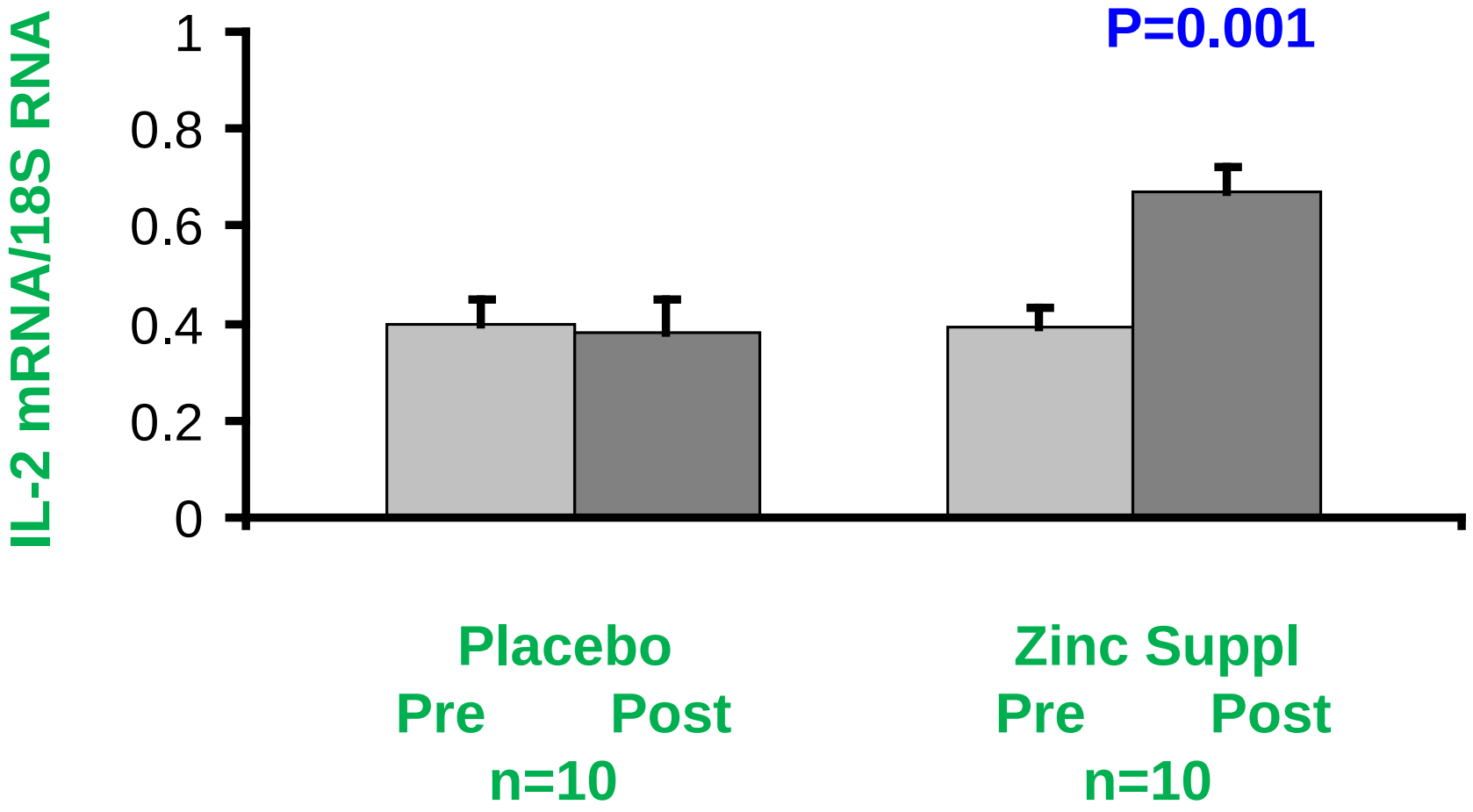
# Effect of zinc supplementation on plasma hsCRP in elderly after 6M of supplementation



# Effect of zinc supplementation on plasma MDA+HAE in elderly after 6M of supplementation



# Effect of zinc supplementation on IL-2 mRNA in PMNC isolated from elderly after 6M of supplementation



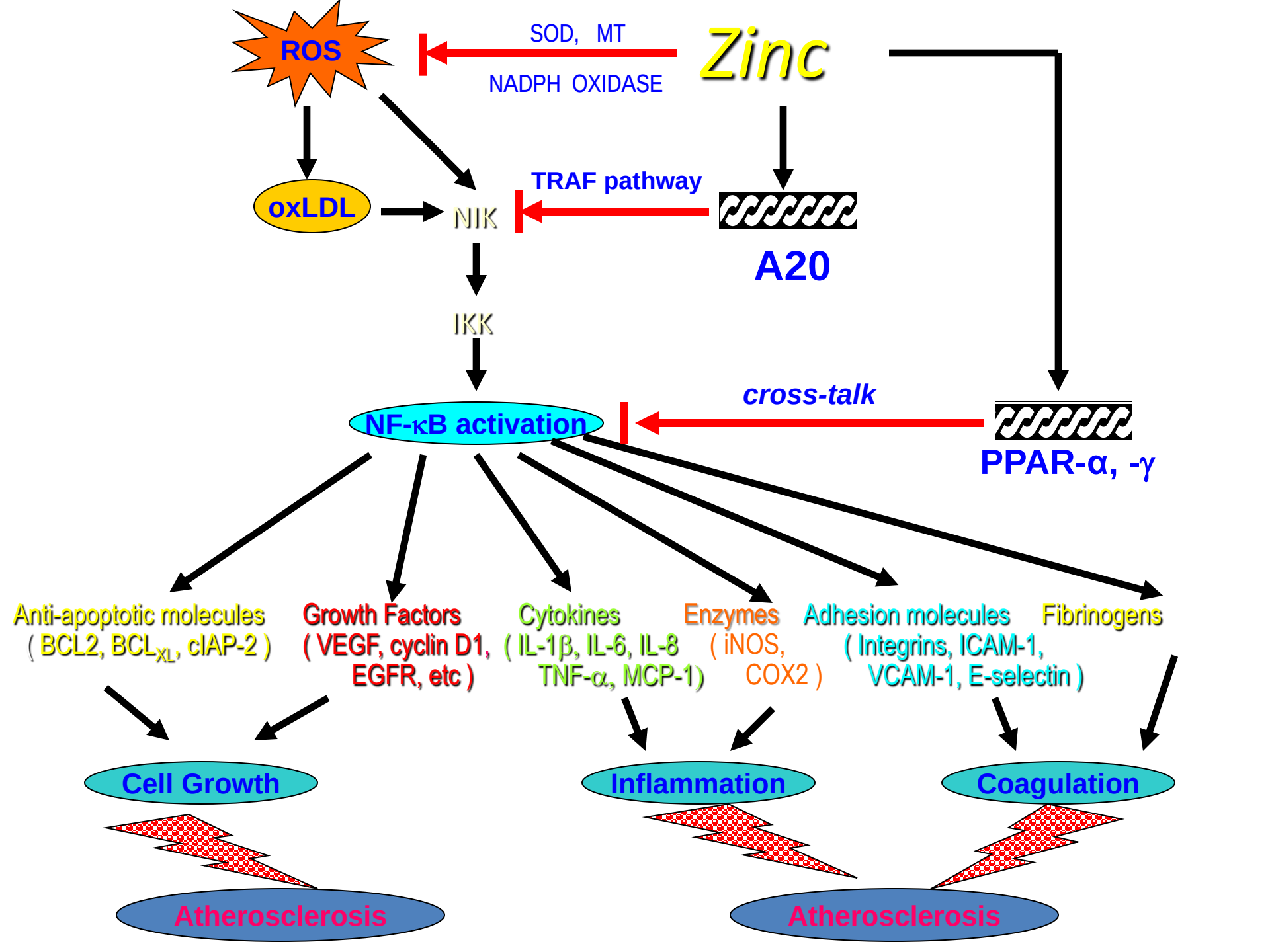

ROS
SOD, MT
NADPH OXIDASE
Zinc
oxLDL
NIK
TRAF pathway
A20
IKK
cross-talk
NF-κB activation
PPAR-α, -γ
Anti-apoptotic molecules
( BCL2, BCL$_{XL}$, cIAP-2 )
Growth Factors
( VEGF, cyclin D1,
EGFR, etc )
Cytokines
( IL-1β, IL-6, IL-8
TNF-α, MCP-1)
Enzymes
( iNOS,
COX2 )
Adhesion molecules
( Integrins, ICAM-1,
VCAM-1, E-selectin )
Fibrinogens
Cell Growth
Inflammation
Coagulation
Atherosclerosis
Atherosclerosis

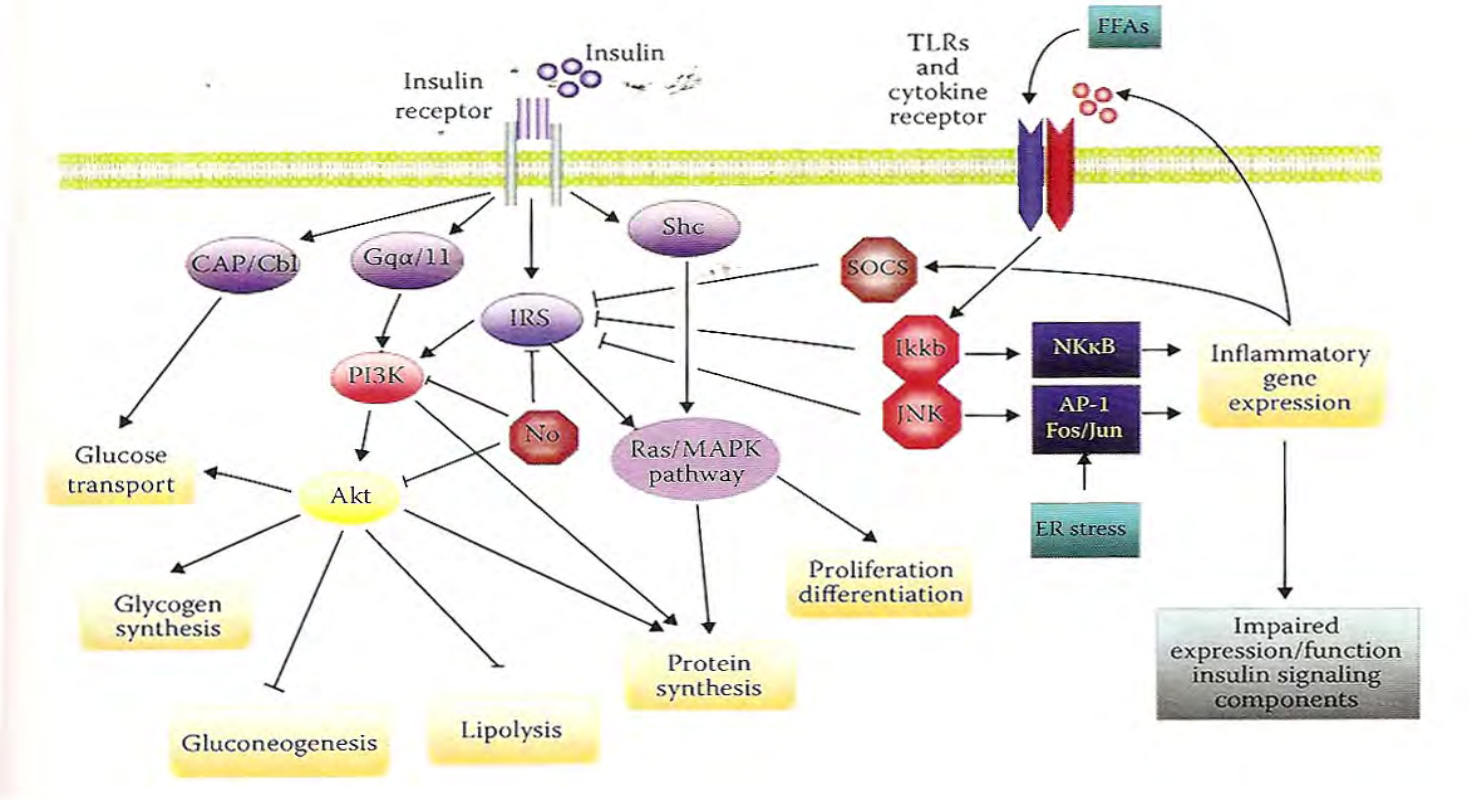
Table 1

Zinc in the Plasma, Lymphocytes, Granulocytes, Platelets and Urine and Nucleoside Phosphorylase Activity in the Lymphocytes in Diabetic and Control Subjects

| | Z I N C (Mean ± SD) | | | | | | Nucleoside Phosphorylase Activity in Lymphocytes ΔOD/h/mg protein (Mean ± SD) |
|---|---|---|---|---|---|---|---|
| | Plasma µg/dl | Lymphocytes $\mu g/10^{10}$ cells | Granulocytes $\mu g/10^{10}$ cells | Platelets $\mu g/10^{10}$ cells | Urine mg/24hr | Urine mg/g creatinine | |
| Diabetic subjects | 108.3±12.9 (16) | 44.6±7.42 (16) | 35.6±5.86 (16) | 1.49±0.29 (16) | 0.92±0.61 (14) | 0.71±0.64 (14) | 3.22±0.93 (11) |
| Controls | 120.2±7.9 (19) | 58.0±5.49 (19) | 45.0±5.59 (19) | 1.93±0.40 (19) | 0.26±0.19 (10) | 0.17±0.12 (10) | 4.1±0.32 (9) |
| P | <.01 | <.001 | <.001 | <.001 | <.003 | <.015 | <.01 |

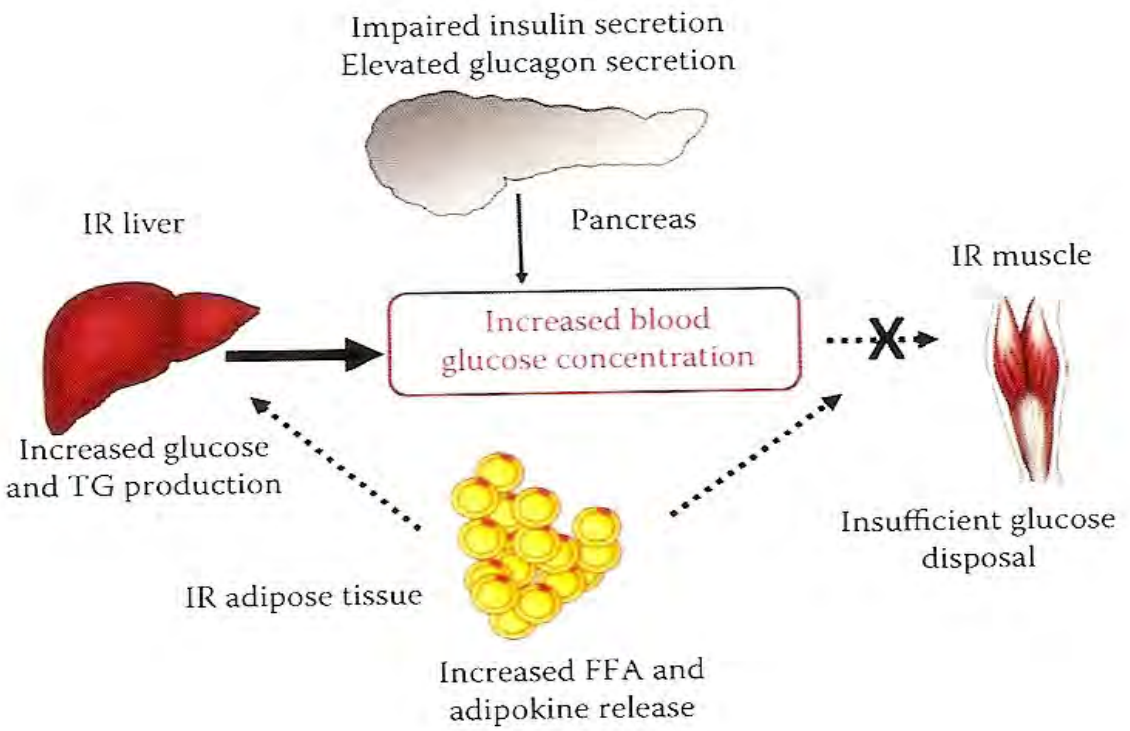
Note: Number in parenthesis indicates number of subjects.

# Insulin Signaling



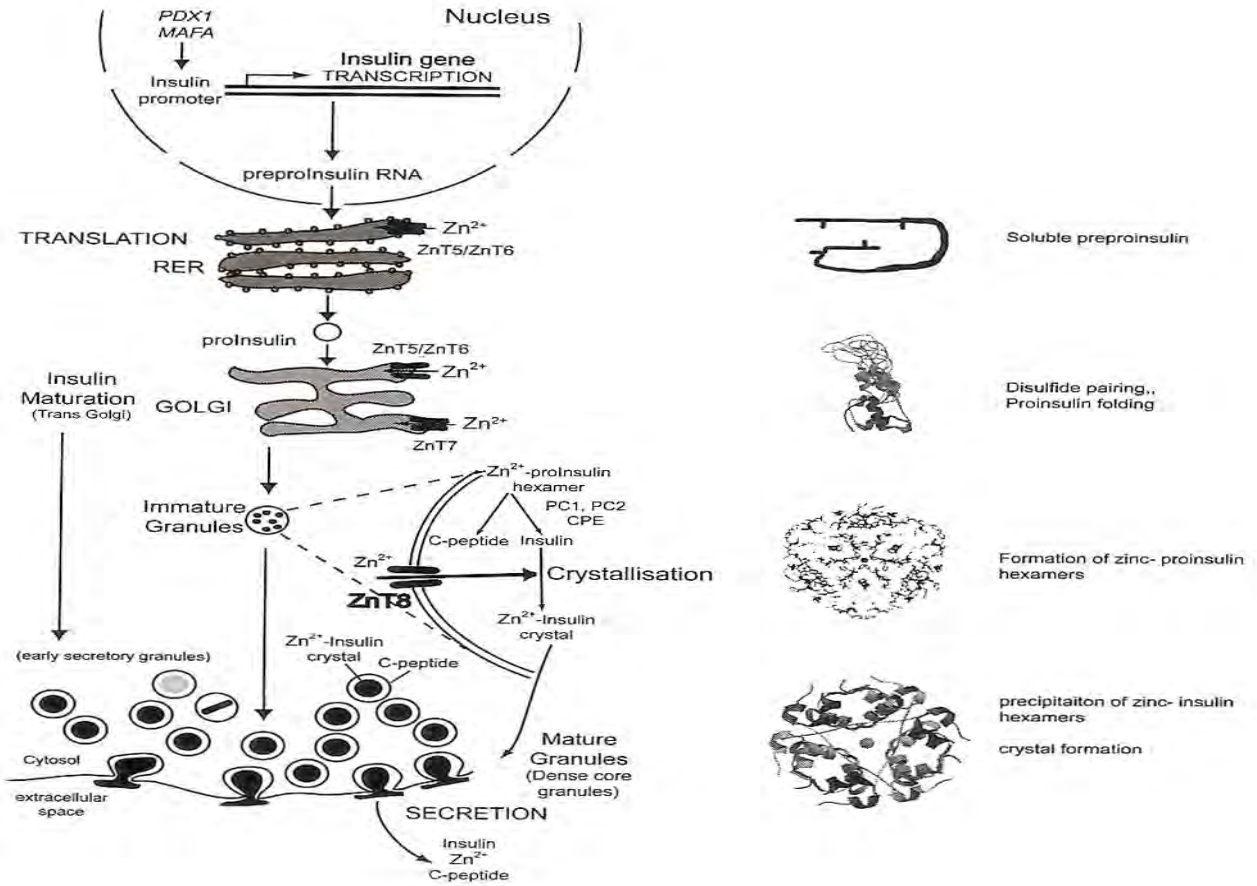

O.Melzer and M. Rothkopf, Metabolic Medicine and Surgery, CRC Press, 2015

# Impaired Insulin Secretion




O. Melzer and M. Rothkopf, Metabolic Medicine and Surgery, CRC Press 2015

# Requirement of Zinc for Insulin Synthesis




F. Chimienti et al, Zinc in Human Health, 10S Press, L. Rink (ed.)

# Presentation Clinical Actions

After participating in this presentation, clinicians should be better able to:

- Monitor and manage zinc status in Type 2 diabetes patients
- Understand the clinical effects of zinc supplementation in Type 2 diabetes patients