Pathobiochemistry of Zinc Metabolism and Diagnostic Principles in Zinc Deficiency

Pathobiochemie des Zinkstoffwechsels und Diagnostik Zink-bedingter Mangelerkrankungen

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Summary: Zinc plays an important role in numerous biological processes of the human organism. As a result, zinc deficiency is often associated with a decline in enzymatic and immunological reactions that frequently improve dramatically after zinc substitution (e.g. acrodermatitis enteropathica).The manifold biological roles of zinc often prevent a clear understanding of the pathogenesis of diseases depending on or connected with zinc deficiencies. The bivalent character of zinc means that it cannot deliver an additional electron in contrast to copper and iron. This is the reason why it does not take part in redox reactions. It is, however, a strong electron acceptor and has a high affinity for electron donators. Like most of the trace elements, it prefers to form complexes with amino, carboxy or thiol groups of amino acids and proteins. The binding of zinc stabilizes the conformation of structural domains in some macromolecules important for genetic expression, cell division and growth. Above all, its special role bases on its function as partner of numerous enzyme-controlled metabolic processes. More than 300 enzymatic reactions are known to depend on the presence of zinc. Zinc containing metallo-proteins like metallothionein, thymulin, steroid receptors and gene regulatory proteins take part in the metabolism of carbohydrates, lipids and proteins and in the synthesis and catabolism of nucleic acids. Clinically a zinc deficit is often associated with diarrhea and growth retardation. The typical skin manifestations, acrodermatitis enteropathica, are characterized by psoriasis-like, erythematous, vesiculobullous and crusty inflammations of the skin near the orifices. At the same time multiple perionyxes can be found at the aeral area (paronychia).

Keywords: Zinc/metabolism; Zinc/deficiency; Metalloproteins; Metallothionein; Enzymes; Immunity; Acrodermatitis.

Zusammenfassung: Zink spielt bei zahlreichen biologischen Vorgängen im menschlichen Organismus eine bedeutende Rolle. Daraus resultiert, daß ein Zinkmangel häufig verbunden ist mit Einschränkungen enzymatischer und immunologischer Reaktionen, die sich durch Zinksubstitution schnell beheben lassen (z.B. bei Akrodermatitis enteropathica). Die vielfältigen biologischen Funktionen des Zinks verstellen häufig den Blick auf die Pathogenese von Krankheiten, die durch einen Zinkmangel zustande kommen oder mit einem solchen im Zusammenhang stehen. Wegen seiner Zweiwertigkeit kann Zink im Gegensatz zu Kupfer und Eisen kein Elektron abgeben und nicht an Redoxreaktionen teilnehmen. Zink ist ein starker Elektronenakzeptor mit einer hohen Affinität zu Elektronendonatoren. Es bevorzugt wie die meisten Spurenelemente die Bildung von Komplexen mit Amino-, Carboxy- und Thiolgruppen von Aminosäuren und Proteinen. Zinkbindungen stabilisieren die Konformation struktureller Domänen in Makromolekülen, die für die genetische Expression, die Zellteilung und das Zellwachstum von Bedeutung sind. Weiterhin basieren spezifische biologische Eigenschaften von Zink auf seiner Rolle als Partner zahlreicher Enzym-kontrollierter Stoffwechselprozesse. Bisher sind über 300 enzymatische Reaktionen bekannt, bei denen die Anwesenheit von Zink erforderlich ist. Zink-enthaltende Metalloproteine wie Metallothionein, Thymulin, Steroidrezeptoren oder Genregulatorproteine nehmen aktiv am Kohlenhydrat-, Lipid- und Proteinstoffwechsel sowie an der Synthese und am Katabolismus von Nukleinsäuren teil. Klinisch ist ein Zinkdefizit häufig vergesellschaftet mit Diarrhöen und Wachstumsretardierung. Zinkmangel äußert sich vor allem in Hautveränderungen, der Acrodermatitis enteropathica, die sich in der Umgebung der Körperöffnungen durch Psoriasis-ähnliche, erythematöse, vesikulo-bulöse und krustöse Dermatitiden manifestiert. An den Akren der Hände finden sich gleichzeitig vermehrt Nagelfalzentzündungen (Paronychien).

Schlüsselwörter: Zink/Stoffwechsel; Zink/Mangel; Metalloproteine; Metallothionein; Enzyme; Immunität; Akrodermatitis.

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Of 70 inorganic elements detectable in human tissues and body fluids, 22 are considered to have more or less specific functions in the human organism. They are subdivided into minerals and trace elements (mass concentrations below 100 mg/l). Eight of the cationic trace elements are classified as being essential (Zn, Cu, Se, Mn, Cr, Mo, Ni, Co). Within this group zinc seems to be the most important.

What does the word "essential" mean? "Essential elements are designed since their removal from the nutrition causes reproducible pathological changes which can be uniquely reversed by adding each essential element back into the otherwise complete diet" [1]. So, depletion of elements can lead to clinically recognizable disorders with more or less characteristic and well defined failures.

Essential trace elements have well described functions in specific biological processes and are not interchangeable in most cases. The absence of an essential trace element in nutrition over a long period of time cannot be compensated and leads to decreased metabolic reactions with more or less typical deficiency symptoms. Zinc, copper, selenium, chromium and molybdenum represent a group of trace elements with changing valences and - in consequence - a large variety of different functions in organisms. All elements of the group have different functions in the human organism that can be highly specific on one side and sometimes interchangeable with other trace elements on the other side. In human metabolism zinc ions are key structural components of a large number of proteins with highly specific functions. This fact particularly underlines the outstanding significance of zinc among other essential trace elements.

Regularly the biological function of a specific trace element reflects its individual physico-chemical properties. Zinc is one of its best examples. In general obvious clinical symptoms are not at all the conclusive consequence of the absence or a significant reduction of trace elements and consecutive decreased functions of biological processes. This phenomenon makes the detection of typical lack symptoms so troublesome. Symptomatic clinical pictures are extremely rare and very often combined with other deficiencies. A further complication in the diagnosis of a trace element deficiency arises by inhibited absorption caused by food shortage [2, 3, 4] and by interaction with other trace elements [5, 6], particularly well known with respect to zinc and copper [7, 8, 9, 10] or iron [11, 12].

Zinc metabolism

The methodological advances in the field of trace element analyses, of atomic absorption spectroscopy in particular, have made zinc determinations safe and reliable today [13]. For most analytical procedures the detection limits of zinc in biological material are distinctly lower than the reference values. From the analytical point of view, this makes the recognition of zinc deficiencies possible today without any major problems. However, zinc in whole blood or serum is not an optimal indicator among the laboratory-based criteria for the detection of a marginal zinc deficiency. Therefore zinc-binding capacity and zinc tolerance tests have recently been proposed to give better information [14].

Homeostatic equilibrium of a nutrient is a characteristic of healthy persons. For zinc, the nutrition containing phytate and the pancreatic state have been shown to be important for the maintenance of zinc homeostasis. Two pancreatic labile pools of zinc are secreted, one forms complexes not affected by phytate and another is labile and readily available for complexation [15].

The acrodermatitis enteropathica mutation causes severe disorders in newborns and infants resulting from an inability to absorb enough zinc from breast milk or food. An acrodermatitis enteropathica mutation affects zinc uptake in the intestine which subsequently affects the activity of various zinc-dependent enzymes that prevent both the zinc binding to the cell surface and its translocation into the cell. A genetic defect in the tryptophan pathway and the role of piculinic acid have been discussed to be responsible for the etiology of the congenital form of acrodermatitis enteropathica [16]. However, the specific biochemical lesion has not been identified yet.

Similar severe clinical symptoms occur secondary to total parenteral nutrition without zinc. Unbalanced nutrition excluding zinc, cereal proteins containing high amounts of organic phosphor compounds and large quantities of phytates [17] lead to more or less moderate symptoms concerning problems with healing ulcers, acrodermatitis, alopecia, diarrhoea, poor appetite, mental lethargy, intercurrent infections [18] due to cell-mediated immune dysfunctions, abnormal taste acuity and abnormal dark adaptation [19]. Even though the mechanism of action is still unknown, it could be shown that zinc was successful in reducing the duration of symptoms of the common cold [20, 21, 22, 23]. Moreover, zinc supplementation has been proved to prevent from infectious diseases of the respiratory tract [24, 25, 26]. Zinc, as a stabilizer and inhibitor of many functions, contributes to the integrity of biomembranes [27]. This has an influence on many areas of cellular and humoral immunity.

The main source of zinc deficiency are pathological conditions of the intestine. This depends either

1. on malnutrition derived from diseases of the digestive tract [28, 29, 30, 31, 32, 33, 34, 35, 36],
2. on surgical removal of substantial parts of the digestive tract,
3. on intestinal competitive interactions between zinc and other trace elements or food shortages or
4. on the biochemical inability of the intestinal wall to absorb zinc.

The question is whether zinc is absorbed by active or passive diffusion in the small intestine, mainly in the duodenum and ileum [37]. The understanding of

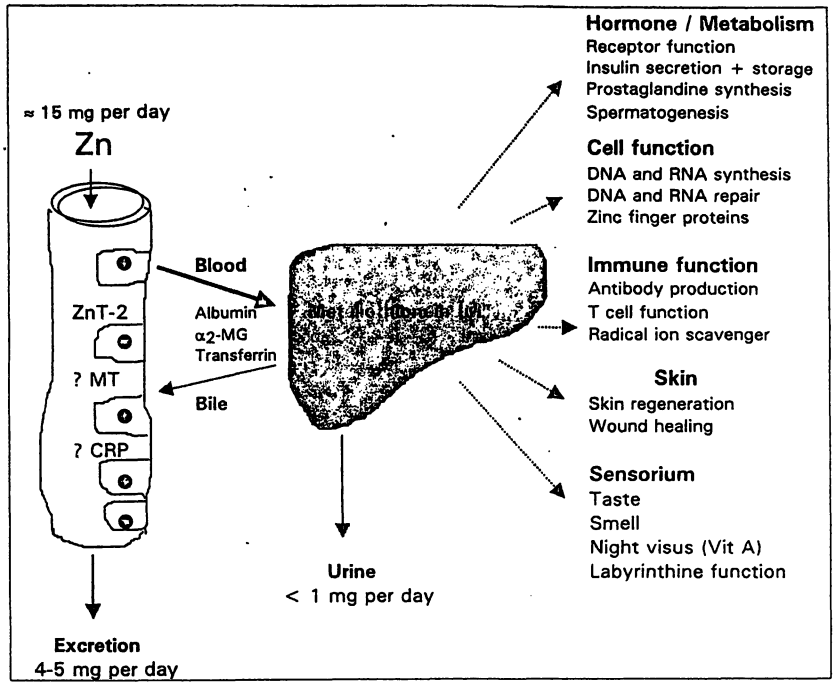

Figure 1 Zinc absorption and metabolism. Abbreviations: ZnT-2, Zinc transporter 2; MT, Metallothionein; CRP, Cysteine-rich protein; α_2-MG, α_2-Makroglobulin

mechanisms controlling zinc absorption at the molecular level has advanced recently. Four putative zinc transporters (ZnT1-4) have recently been described from which ZnT-1 is important for the absorption of zinc. For the regulation of zinc, ZnT2-4 seem to be involved in the zinc efflux or uptake into the vesicles of different organs (ZnT-2 in intestine, kidney and testis, ZnT-3 in neurons, ZnT-4 in mammary gland and brain). ZnT-1 expression is regulated by dietary zinc intake and is localized to the basolateral membrane of the small intestine, suggesting an orientation that is consistent with zinc absorption [38, 39, 40, 41]. It is still a matter of discussion whether metallothionein or other metalloproteins like cysteine-rich protein [42, 43] play an additional regulating role in the zinc absorption [44, 45] and binding to transport proteins in the blood [46] like α_2-makroglobuline (where zinc is not exchangeable), albumin (where zinc is exchangeable), transferrin (where zinc is easy exchangeable) or other less important proteins.

Having passed the absorption barrier zinc is transported to the liver where main parts of its metabolism are regulated specifically by metallothionein [47, 48, 49]. From here the distribution within the organism is organized depending on actual needs (Fig. 1). Regularly muscle and bone have the highest concentrations followed by the skin and the gastro-intestinal tract [50]. In comparison, the relative size of the blood zinc pool is only one percent of the total body pool. The kinetics of zinc [51, 52, 53] and its distribution between the different organs and tissues very much depend on actual demands from those organ sites that currently need zinc for their biochemical processes. This fact makes the discovery of zinc deficiencies by determinations in whole blood or plasma so difficult. Best information comes from stable isotope techniques [54, 55, 56] which, however, are of minor importance for the daily use of practitioners or clinicians who have to consider a zinc deficiency.

Biochemical structures and functions

The bivalent character of zinc means that it cannot deliver an electron in contrast to copper and iron. This is the reason why it does not take part in redox reactions of the metabolism. It is, however, a strong electron acceptor and has a high affinity for electron donators such as thiolates or amines [57] depending on its oxidation state. Like most of the trace elements, it prefers to form complexes with amino-, carboxy- or thiol-groups of amino acids and proteins [58].

All dysfunctions in zinc deficiency depend on the key role of zinc in some biological reactions in the human metabolism (Tab. 1). The binding of zinc stabilizes the folded confirmation of structural domains in some proteins and macromolecules [59, 60, 61] important for genetic expression [62, 63, 64], cell division and growth [65]. Above all, this special role bases on its properties as partner of numerous enzyme-controlled metabolic processes. To date, more than 300 enzymatic reactions [66] are known to depend on the presence of zinc.

Table 1 Sources and functions of important endogenous zinc-binding ligands

Name	Source	Function
Enzymes		
RNA polymerase	bacteria, viruses	promoter, recognition
Deoxythymidine kinase	eucaryonts	activator
Deoxy-RNT transferase	viruses, thymus	activator (?)
5'-Nucleotidase	bacteria	activator (?)
Alcohol dehydrogenase	vertebrates, plants	activator
Protein kinase C	mammals	activator
Superoxide dismutase	bovine erythrocytes	co-activator
Leucine aminopeptidase	bovine lens, pig kidney	co-activator
Phospholipase C	mammals	co-activator
Alkaline Phosphatase	mammals, bacteria	catalysis, co-activator
DNA polymerase	eucaryonts	catalysis
Reverse transcriptase	viruses	catalysis
tRNA synthetase	E. coli	catalysis
Nucleoside polymerase	calf thymus	catalysis
Carboxypeptidase A	vertebrates	catalysis
Carboxypeptidase B	mammals	catalysis
Collagenase	mammals, bacteria	catalysis
Endopeptidases	peptide hormones	hydrolysis
Hormones		
Insulin	pancreas	secretion, storage
Growth hormone	brain	activator (?)
Thymulin	thymus	T cell differentiation
Steroid receptors	glucocorticoid, estrogen	genetic expression
Angiotensin-converting enzyme	mammals, bacteria	catalysis
Carrier and structure proteins		
Transferrin	liver	transport
Albumin	liver	transport
α_2-Macroglobulin	liver	transport
Metallothionein	tissue, liver	inducer, metal transfer

Zinc serves two different coordinating points in the human metabolism: the metalloproteins and the catalysis or co-action of enzyme activities [67]:

Metalloproteins (Tab. 2 at the top)
Zinc containing metalloproteins like metallothionein, thymulin, steroid receptors and gene regulatory proteins take part in the metabolism of carbohydrates, lipids and proteins and in the synthesis and catabolism of nucleic acids [68, 69, 70, 71]. The ability of zinc to be bound specifically appears to be responsible for the evolution of the wide range of zinc-stabilized structural domains now known to exist. Taking metallothionein as a representative of metallo-proteins, the molecule has 2 clusters containing 3 and 4 zinc atoms at the C-terminal and N-terminal region, respectively (Fig. 2). During the metallothionein synthesis the zinc induction is mediated through distinct transcriptional control of the genes coding for metallothionein with the number of their specific mRNA transcripts increasing in response to many other inducers, e.g. zinc itself [72, 73] and other trace metals, cytokines, interferon and hormones like epinephrine and glucocorticoids [74]. The reason for the existence of so many inducers is unknown.

The metabolism of zinc mainly occurs in the hepatocytes of the liver (Fig. 3). Metallothionein is the central protein regulating and serving both a fast and a slow zinc pool. The first binds zinc very loosely so that it can equilibrate with extracellular zinc or create complexes; the latter is the larger part and is identified by rather strong bounds to metalloproteins. This pool seems to protect the hepatocytes against an intracellular zinc deficiency and depends very much on the function of the liver. It is not available as a central zinc pool in case of a general zinc deficiency.

With regard to gene regulating proteins, many nucleoproteins involved in DNA replication and transcription contain zinc atoms. Up to date more than 10 activator proteins comprise zinc including transcription factor proteins, gene 32 protein as a substrate for replication and repair enzymes, Gal4 protein [75] as activator for the galactose metabolism and glucocorticoid and estrogen receptors. As regulators of gene expression the zinc-binding finger-loop domains [76, 77] in DNA-binding proteins have found an increasing interest in understanding the essentiality of zinc for the gene expression [78, 79, 80]. In this procedure zinc ions act as framework in order to stabilize the folding of the domain for a high-affinity

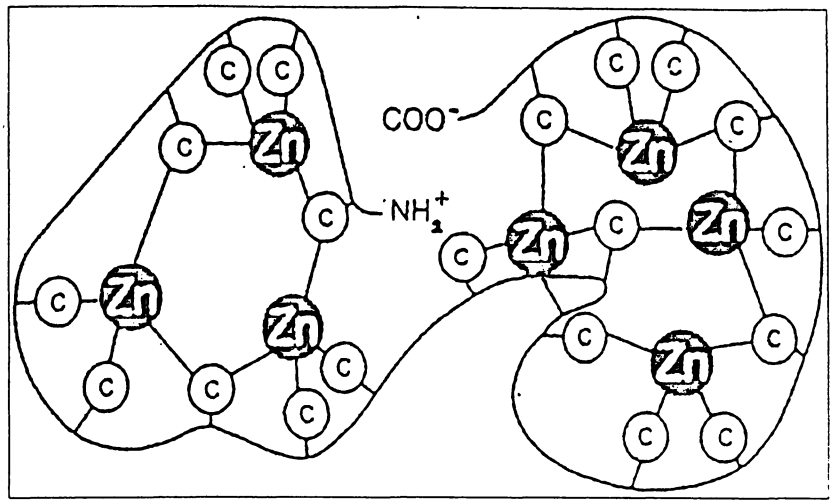

Figure 2 Metallothionein. Each zinc atom is tetrahedrally coordinated to four thiolate bondes

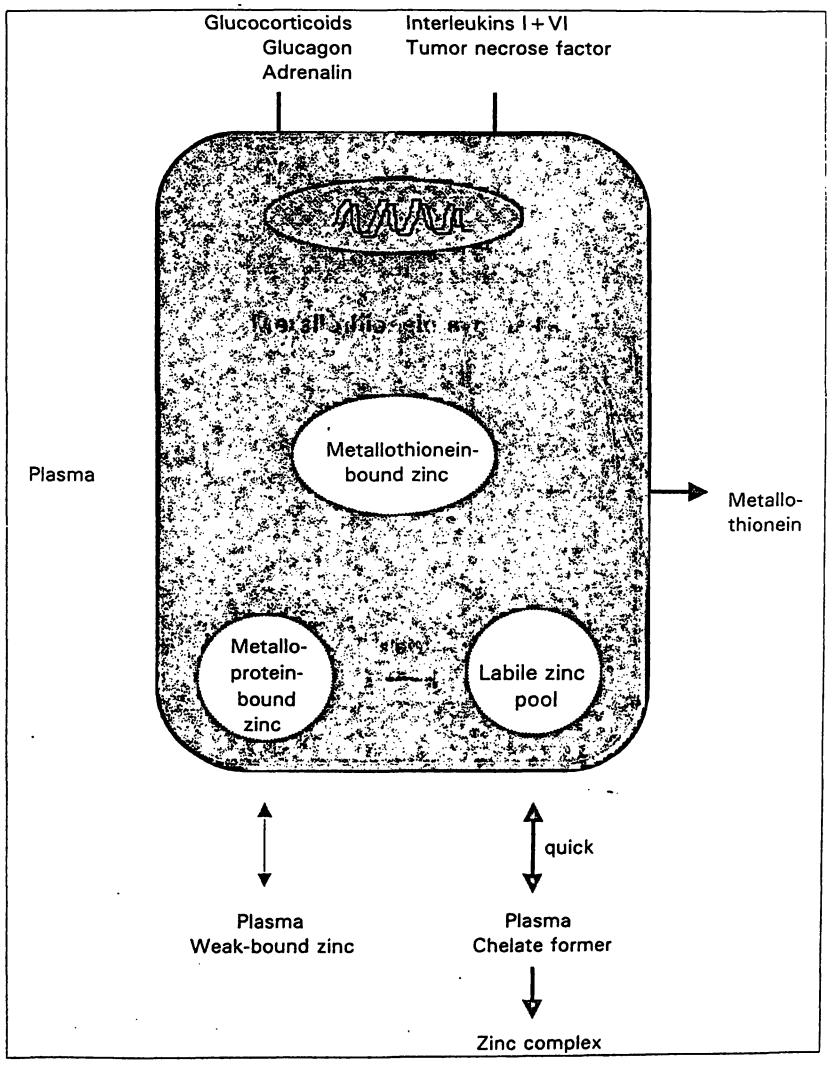

Figure 3 Regulation of zinc by metallothionein in hepatocytes

and site-specific binding of the double-stranded DNA.

Besides the regulation of the zinc metabolism and the genetic expression, the elementary task of all zinc holding metalloproteins is the participation in the cellular protective function by detoxifying heavy metals, stabilizing membranes and acting as radical ion scavenger [81, 82, 83, 84, 85]. The cell membrane is naturally defended against destructive oxygen radicals by metalloproteins promoting the protection of thiol-groups by constructing stable mercaptides. Moreover in combination with numerous zinc-dependent enzymes zinc performs a manifold network of regulatory bio-catalytic mechanisms, controlling responsibilities and protective functions [86]. Best examples are the T-cell maturation regulating thymulin of the thymus epithelic cells [87, 88, 89] and the regulating central role of metallothionein in the liver and possibly in the small intestine.

Zinc enzymes (Tab. 2 at the bottom)

The number of zinc enzymes for which structural data are available is increasing rapidly [90]. More than 300 need zinc in various intensities and with different specificities: whether as an indispensable structural part of the enzyme molecule or as catalytic factors or as coactive associates.

1. Structural zinc atoms

In this group zinc-ions establish a strong coordinative bond and are thus important for the stability of the enzyme protein. The catalytic function of enzyme proteins will be totally destroyed by tearing out the metal-ion, e.g. by chelating agents. The best-known metalloenzyme characterized by a high zinc content is the carbonate dehydratase (carbonic anhydrase) that hydratizes carbon dioxide to carbonic acid in erythrocytes and in the kidney. A further representative of this array of zinc-incorporating enzymes is the protein kinase C

Table 2 Tasks and functions of zinc in zinc proteins or zinc enzymes

	Function
Zinc proteins	
Metallothionein	
Mammalian Eukaryotes Plants	Stabilization of membranes Radical ion scavenger Detoxification of heavy metals Metal transfer to glutathion Metal transfer to thymulin
Gene regulatory proteins	
Transcription factor protein	Activating transcription by RNA polymerase
Gene 32 protein (gp32)	Substrate for replication and repair enzymes
Glucocorticoid receptor	Specific binding of cortisol
Estrogen receptor	Specific binding of estrogene
GAL4 protein	Gene activation for galactose metabolism
Zinc enzymes	
Structural function	
Alcohol dehydrogenase Aspartat transcarbamylase Protein kinase C	Primary structure and conformation Control of scaffolding of peptide chains Recognition, verification, specificity
Coactive function	
Phospholipase C	Ligand bridge between two zinc atoms
Alkaline phosphatase	Catalytic unit by ligand bridge with magnesium
Leucine aminopeptidase	Catalytic unit by ligand bridge with magnesium
Superoxide dismutase	Catalytic unit by ligand bridge with copper
Catalytic function	
Oxidoreductases	Acting on oxygen donors or hydrogen acceptors (Dehydrogenases, Reductases)
Transferases	Transferring groups or residues (Transferases, Polymerases)
Hydrolases	Acting on acid anhydrids, protein or peptid bonds (Phosphatases, Peptidases, Proteases, Kinases)
Lyases	Cleavage of C-C-, C-0- and C-N-bonds (Decarboxylases, Aldolases, Dehydratases)
Ligases	Joining of two molecules with high energetic bonds (Synthetases, Carboxylases)

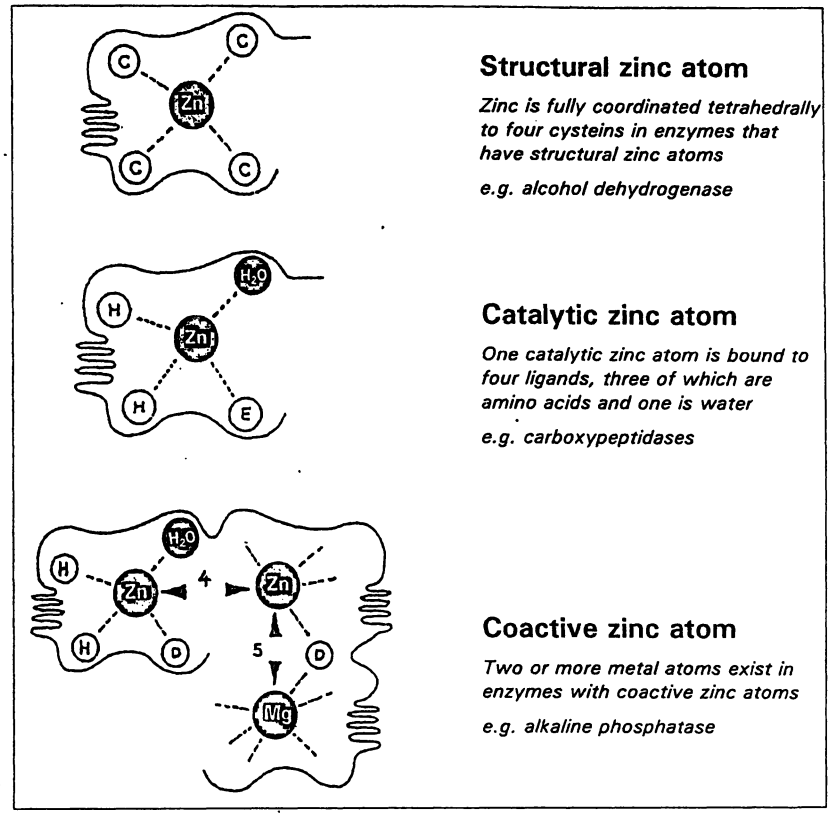

Figure 4 Zinc binding sites in zinc enzymes

in membranes and in cytosol and the enhancement of plasma membranes by the inhibition of ATPase or phospholipase A_2. Another example is the alcohol dehydrogenase that dehydrates alcohols to aldehydes and ketones. In this group of enzymes zinc is incorporated tetrahedrally to characteristic amino acids within the molecule (e.g. 4 cysteines in alcohol dehydrogenase or 3 cysteines and 1 histidine in protein kinase C) (Fig. 4 top).

2. Coactive function within enzymatic reactions

Coactive zinc atoms enhance or diminish catalytic functions in combination with another metal atom in the same enzyme. In this function it is not indispensable of itself for either enzyme stability or activity. This structure is characterized by an amino acid ligand bridge between two zinc atoms or a zinc atom and an other metal in the same molecule (Fig. 4 bottom). In phospholipase C two zinc atoms occur and in alkaline phosphatase one zinc and one magnesium atom are found.

One of two known mechanisms important for radical ion scavenging is the catalysis of hydrogen superoxide reduction during the oxidation of fatty acids, amino acids, alcohol or purines by means of the zinc-dependent superoxide dismutase. It contains bridged zinc and copper atoms. Another is the reduction of hydroperoxides by the selenium-dependent glutathione peroxidase.

3. Catalysis of enzyme activities

Within this important and wide group of enzymes zinc participates directly in the enzyme catalysis. In its absence the enzyme becomes inactive. Usually one zinc atom per enzyme molecule is bound to four ligands. Three of them are amino acids, the fourth ligand is water that can be ionized or displaced and thus enables the catalytic function (Fig. 4 middle).

All six classes of enzymes include those which need zinc as associates whether as structural framework or as catalytical activator or as co-factor (Tab. 3). The group of enzymes using zinc as catalytical activator is the largest. Above all many hydrolases (e.g. phosphatases, peptidases or kinases necessary for the transfer of phosphate) need the presence of trace elements, zinc in particular, for their catalytic activity. In this context trace elements have the responsibility to meet the conditions for the identification, the linkage and the chemical conversion of substrates in the apoproteins.

The specificity of zinc as catalytical enzyme activator varies from enzyme to enzyme. Sometimes other

trace elements like cobalt are able to replace zinc while the enzyme activity can be retained independent of an increased presence of cobalt.

Cellular and humoral immunity

A number of trace elements have regulatory functions in the immune system. Particularly with concern to zinc, a growing number of publications confirm the important role of these trace metals in the immunological response [91, 92, 93, 94, 95, 96, 97, 98]. Thus trace elements have a considerable influence on relevant metabolic processes (e.g. by regulating leptin concentrations [99]) and corresponding cell proliferation, above all as co-factors of cell enzymes.

The role of zinc in the effectiveness of humoral and cellular immunity is focused on a reduced thymus activity and antibody production [100]. Zinc has special functions in antigen-specific reactions (T-lymphocyte-dependent cellular immunity and antibody response by means of antigen-stimulated B-lymphocytes) and in non-specific mechanisms (phagocytosis, complement system, lysozyme functions [101]). These functions (Fig. 5) can only be fulfilled by zinc and cannot be replaced by any other trace element.

1. Promotion of lymphocyte proliferation

Zinc supports and reinforces humoral and cell-mediated immunity by acting as adjuvant facilitating proliferative responses to stimulations by mitogens such as polyhemagglutinin, concanavalin A and lipopolysaccharides. Restricted activities of plasma membranes derived from the inhibition of ATPase or phospholipase A_2 base on the absence of zinc. With regard to lymphocyte transformation zinc shows a direct supportive influence on the synthesis of DNA and RNA either by enzyme stimulation or by bond changes of the unspecific histones [102].

2. T-cell differentiation

The T-lymphocytes responsible for the cellular immune response undergo a specific maturation process in the thymus, which is regulated by thymulin [103] (thymosin, formerly thymus-factor) before they begin to circulate in the peripheral blood and in the lymphatic organs as immune-competent pre-active cells waiting for appropriate signals to become active. Thymulin, a peptide hormone from thymus epithelic cells

Table 3 Zinc enzymes

Structural Enzymes	Catalytic Enzymes	Co-Factors
1. Oxidoreductases		
Alcohol dehydrogenase	Alcohol dehydrogenase Sorbitol dehydrogenase	Superoxide dismutase
2. Transferases		
Aspartate transcarbamylase *(E. coli)*	RNA polymerase Reverse transcriptase Nuclear poly (A) polymerase	-
3. Hydrolases		
Protein kinase C α-Amylase *(B. subtilis)*	Alkaline phosphatase Leukotriene A_4 hydrolase Aminopeptidase Phosphodiesterase Carboxypeptidases Dipeptidase Neutral protease Hemorrhagic protease Collagenase Elastase *(P. aeroginosa)* ACE	Alkaline phosphatase Fruc-1,6-phosphatase Aminopeptidase Phospholipase C
4. Lyases		
Carbonate dehydratase (=carbonic anhydrase)	δ-ALA dehydratase Fruc-biphosphate aldolase Glyoxalase I	
5. Isomerases	DNA topoisomerase I (?)	-
6. Ligases (Synthetases)		
	tRNA synthetase Pyruvat carboxylase (?)	-

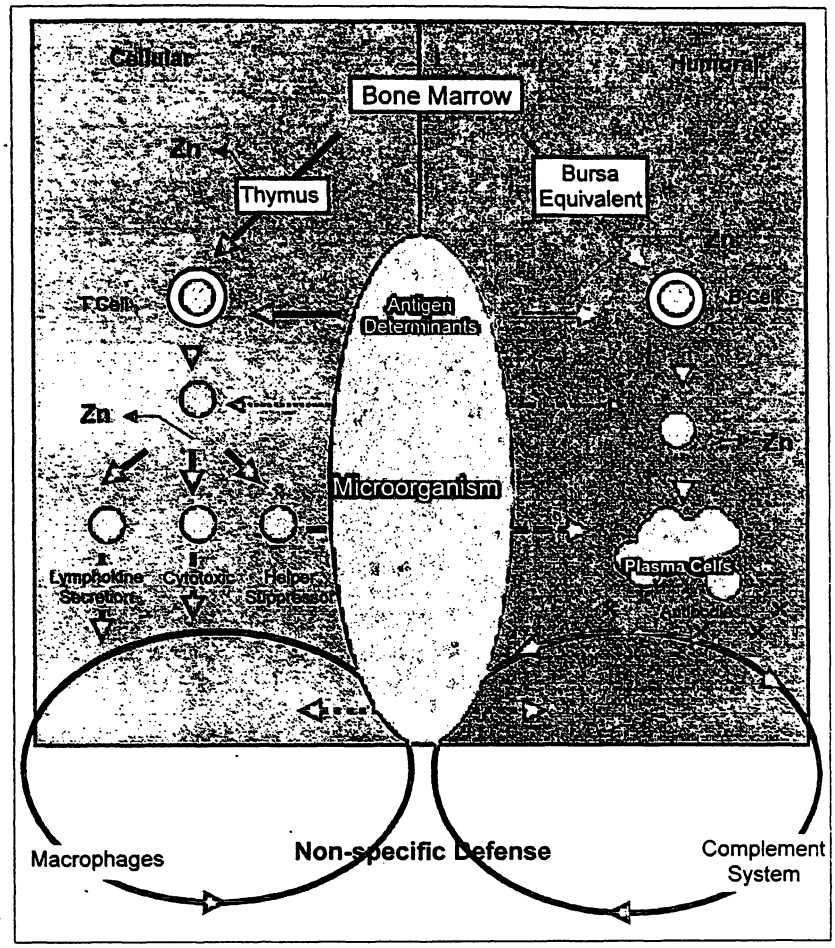

Figure 5 The role of zinc in the cellular and humoral immunity

plays a decisive role in the sequence of T-cell maturation. It requires zinc as an essential structural factor in order to be biologically effective [104]. In the absence of zinc, or when zinc has been replaced by other trace elements (e.g. aluminum or copper) the hormone loses its biological effectiveness. Thus zinc acts as a T-cell-specific growth factor [105, 106].

3. Induction of blastogenesis

Although the main interest in zinc is due to its influence on T-cells and on lymphatic proliferation, some influence on B-cells has to be mentioned. With regard to the production of platelet-forming cells the zinc-induced blastogenesis of human B-cells in peripheral blood and spleen is comparable to that attained through a direct mitotic impulse. Zinc and other trace elements like copper or nickel modify the immune response either directly by altering the reactive partners or by modulation of the autologous T-cell response. Even if the mechanism is not sufficiently understood yet the empirical effect is obvious with regard to the cellular immunity.

4. Suppression of histamine release

On the surface of basophilic leukocytes [107] and mast cells IgE causes biological processes leading to a release of mediators for humoral immunity. Histamine and slow-reacting substances of anaphylaxis like leukotrienes are released causing unspecific inflammations with bronchial constrictions and blood vessel dilatations. Zinc, in physiological concentrations (ca. 500 µg/l) suppresses the release of these substances by competitive blockade of the calcium uptake caused by anti-IgE activation. Low concentrations of zinc, therefore, lead to an increased humoral immune response.

In summary zinc has a significant effect on the immune defense. An extended reduction of food intake, a prolonged parenteral feeding without trace element substitution in particular, precede the depletion of body zinc. This depletion leads to immunological changes [108] which, initially, are subclinical and scarcely recognizable; at an advanced stage, however, this can lead to life-threatening infections [109, 110, 111], in particular in the pediatric population [112, 113] and in elders [114, 115]. Cell-mediated immuni-

ty, antibody reaction and affinity, the complement system and phagocyte activity [116] are distinctly affected.

Severe changes in elementary body reactions such as structure, function and activity of the immune system result in significant reductions of antibody response both of T-cell-dependent and independent antigens, the cytolytic T-cell reactions and the activities of natural killer cells with spontaneous cytotoxic potential.

The activity of the nucleoside phosphorylases, of T-cells in particular, is clearly reduced. Treatment with zinc leads to an improvement of clinical symptoms and an objective normalization of the biochemical functions [117]. Especially during the period of reconvalescence after illnesses associated with an inadvertently reduced zinc intake or an increased loss of minerals and trace elements substitution is important, since during this phase great demands are made upon cellular immunity.

Clinical significance of zinc deficiency

Many diseases and clinical syndromes have proved to be associated with diverse features of zinc deficiency. Diseases recognized to be complicated by zinc deficiency include malnutrition, a variety of intestinal diseases like Crohn's disease, sprue, bowel syndrome and after jejunal ileal bypass, as well as alcoholic liver disease and sickle cell anemia.

Less than a recommended dietary minimum supplementation of 15 mg zinc per day for a longer period of time leads sooner or later to clinical signs of zinc deficiency in humans. As a matter of priority, zinc deficiency manifests itself in moderate or severe forms of damages in which the skin of mouth, nose, ears and anal areas (orifices) and skin and nails of fingers and toes (acra) are affected (Fig. 6 and 7). Besides these foreground symptoms delayed wound healing [118, 119], growth retardation [120, 121], male hypogonadism [122, 123] and abnormal neurosensory changes [124] have been observed. The reasons for the absence or abnormal decreases of zinc concentrations are varied:

As is the case with all trace elements, the development of any clinical symptoms corresponding to deficiency within tissues cannot be recognized until there has been a highly significant and persistent decrease in the body zinc concentration for some time. An early or timely recognition of impending zinc supplementations and thus a premature provision for clinical symptoms based on zinc deficiency is often irrelevant and misleading when derived from blood and impossible by examining hair. Tissue damage, e. g. due to surgical procedures, results in a rapid but relatively transient decrease in the blood zinc levels. True zinc deficiency of the tissue due to prolonged inadequate intake often does not lead to recognizable blood zinc alterations because reserve supplies will be released from the musculature and osseous or parenchymal tissues. However, there is no indication that any organs perform a real storage function. On the contrary, high concentrations always reflect high turnover states due to underlying enzymatic metabolic processes requiring zinc as a cofactor.

Immunological alterations due to a zinc deficiency result in symptoms with an initially subclinical course. These alterations are hardly recognizable although later on, during advanced stages, they may lead to immunodeficiencies with infections which are difficult to manage [125].

The genetic type of congenital acrodermatitis enteropathica is characterized clinically by impaired wound healing as well as erythematous-pustular dermatitis involving the extremities and the areas around the body orifices [126, 127]. Immunologically the disease reveals itself by more or less pronounced thymic atrophy, lymphopenia, delayed hypersensitivities, and decreased natural killer-cell activity. This is hardly distinguishable from the acquired symptoms observed in cases of deficient zinc supplies due to a shortage in the breast milk or to impaired absorption. Furthermore, the symptoms and the etiology are easy to distinguish from acrodermatitis chronica atrophicans as an uncommon late cutaneous manifestation of Lyme disease which follows disseminated *Borrelia burgdorferi* infection [128].

Since ancient times the use of zinc for wound healing was well-known and commonly used [129]. But there is no evidence of benefit from the general use if zinc deficiency is not present. In case of a zinc deficiency, however, the zinc supplementation (100-400 mg zinc sulfate per day) leads to dramatic improvements and to an restitutio ad integrum with regard to superficial damages of the skin.

Conclusion

Zinc has an important function in numerous biological processes within human beings, first of all as catalyst for many enzyme-related metabolic processes and as essential part of some specific proteins. It takes part in the synthesis of nucleic acids and proteins and helps to protect the integrity of biomembranes. It has a decisive influence on the immune reaction predominantly in the lymphocyte proliferation and differentiation. As a result, zinc deficiency is often associated with a decline in enzymatic and immunological reactions that frequently improves dramatically after zinc substitution.

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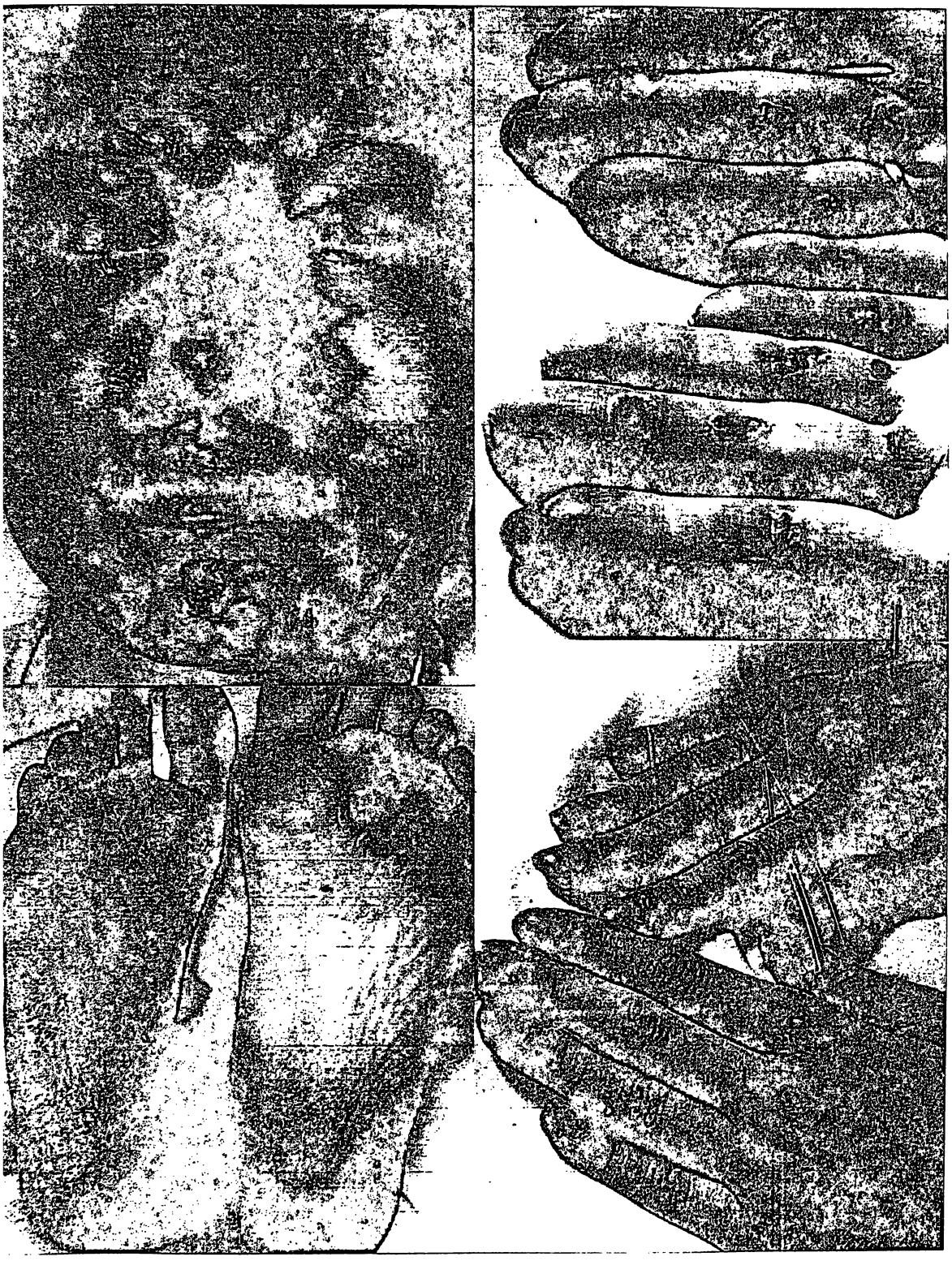

Figure 6 Acrodermatitis enteropathica in a 29-year-old woman (G. F.)

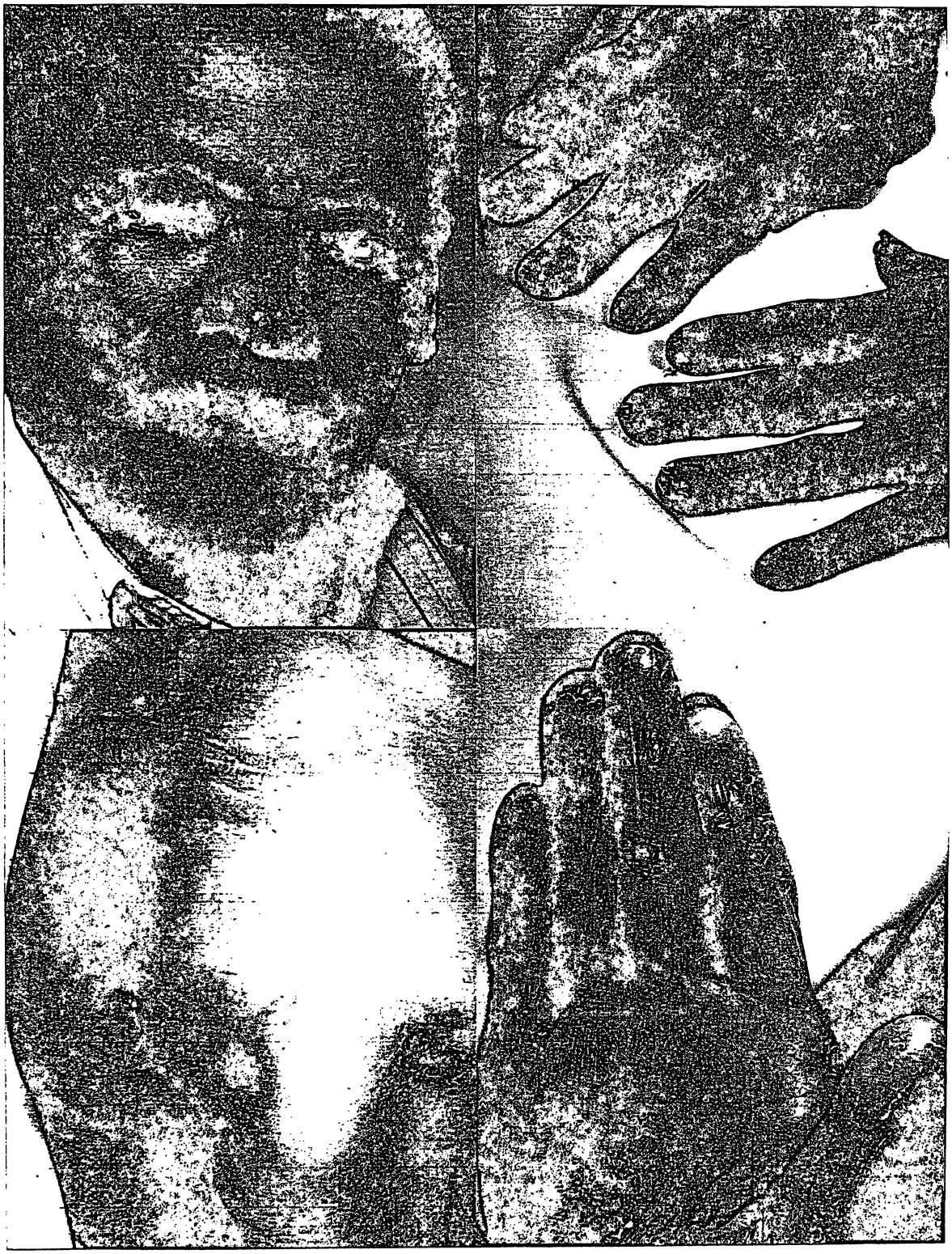

Figure 7 Acrodermatitis enteropathica in a 75-year-old man (R. W.)

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