CHAPTER IV

TRACE ELEMENTS AND DEFICIENCY DISEASES
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In this Chapter, role of trace elements in human disease-states, has been discussed along with a brief review of literature thereon. In view of the variations in metal-ion concentrations of tissues and body fluids, commonly observed in many disease-states, assay of chromium, zinc and cadmium in the whole blood of normal subjects, diabetics and hypertensives was undertaken. As severe copper deficiencies of dietary origin are rare in humans, estimation of copper was not done. Determination of chromium-content in hair of diabetics and normal subjects is also reported in this Chapter.

These investigations were undertaken to ascertain if assay of trace elements could be of any diagnostic importance and clinical application in two common disease states - diabetes mellitus and hypertension.

IV.1: INTRODUCTION

Trace elements and the many avenues of approach to medical problems which they seem to offer, have generated much speculation and many hypotheses in regard to their role in human diseases. The obvious experimental difficulties in appraising the functional
significance of trace elements in normal and disease-states have often led to confusion as to their true role. Trace metals have been invoked as mechanistic factors to explain disease-states as diverse as cancer, arteriosclerosis, hypertension, arthritis, porphyria, lupus erythematosus, multiple sclerosis and amyotrophic lateral sclerosis. Variations in metal-ion concentration of tissues and body fluids are commonly observed in many disease-states.

ZINC:

When one considers the ubiquitous nature of zinc, it is not surprising that it appears to influence many body-systems and functions including growth, bone formation, brain development, behaviour, reproduction, fetal development, sensory functions, immune mechanisms, membrane stability and wound healing. Some of the best known mammalian enzymes that contain zinc in their active site include pancreatic carboxypeptidase, carbonic anhydrase, alcohol dehydrogenase, etc.

Studies in the Middle-East\textsuperscript{1,2} first showed that zinc deficiency does occur in humans. The deficiency symptoms found in the population where zinc intake was presumed inadequate were dwarfism, hypogonadism and iron-deficiency anaemia. The accelerated-rate of wound healing\textsuperscript{3} and the improved sense of taste\textsuperscript{4} observed after zinc supplements were administered indicate that zinc nutrient in the subjects studied was less than
optimum. Marginal zinc deficiency has been identified in survey\textsuperscript{5} of children. Of 150 apparently-healthy children from middle income families, 8% of them displayed deficiency-symptoms which included low levels of zinc in the hair (below 70 \text{ug per g}), impaired taste, poor appetite and suboptimal growth. When zinc intake was increased, the children showed improvement. Several studies\textsuperscript{6,7} have shown a high incidence of low levels of plasma and hair-zinc in growth-impaired children, suggesting zinc deficiency as a possible cause of their poor growth. Part of the problem, undoubtedly, can be attributed to genetic and other factors that affect growth and part to the adequacy of the available measures of zinc status\textsuperscript{8}.

Low plasma-zinc concentration are common in acute and chronic infections, cirrhosis of the liver, chronic alcoholism, renal disease, protein-energy malnutrition, cardiovascular diseases, pernicious anaemia, sickle-cell disease, some types of cancer and in patients on extended parenteral feeding\textsuperscript{9}.

Considerable interest in the nutritional role of zinc in animals developed from the discovery of zinc-deficiency in pigs fed on high calcium diets\textsuperscript{10}. There has been some interest in the biochemistry of zinc, notably in blood, in several human diseases\textsuperscript{11}. Rosner and Garfstein\textsuperscript{12} measured zinc levels in erythrocytes and
plasma of patients with various disorders. Erythro-
cyte-zinc and magnesium levels were found to be
elevated in patients and plasma zinc was significantly
decreased. Plasma-zinc in normal individuals ranged
between 97 and 234 mg/100 ml with a mean of 138.
Frout et al. measured the plasma levels of zinc in
60 diabetic subjects and no relationship was observed
between the plasma levels of zinc and the calculated
total zinc-intake from previous zinc-insulin adminis-
tration. The mean level of plasma zinc was found to
be 121 ± 44 mg percent. There was no significant
difference between the mean plasma-zinc levels for
patients with severe diabetes. Vikblandh measured
the plasma zinc levels in 13 patients with diabetes
mellitus and found a mean value of 125 ± 15.4 mg percent.

The level of plasma zinc in normal subjects
was reported to be 120 ± 19 mg percent by Vallee et al.,
Davis et al. found the plasma zinc values in normal
men to be 95 mg percent and 96 mg percent in women.
They observed that zinc levels in patients with diabetes
mellitus, cardiovascular diseases and anaemia has been
within normal limits. Pidduck et al. reported the
plasma zinc and copper values in normal subjects to be
70-240 mg percent and 132 mg percent, respectively.
They did not find significant differences in the plasma
zinc and copper concentrations between diabetics and
normals. Zinc and cadmium were determined in kidney
cortex, liver and pancreas from 292 subjects in Sweden. In the liver and pancreas, zinc was found to have a normal distribution, average 45.3 μg/g and 26.9 μg/g, respectively. Zinc was shown to accumulate with age in kidney cortex in a way similar to cadmium. Kumar and Rao estimated zinc in the urine and plasma of normal subjects and diabetics. They observed high concentration of zinc in the urine and low concentrations in the plasma and blood cells of diabetics. In normal subjects the plasma zinc was found to be 123.2 μg percent and 83.7 μg percent in diabetics.

**Cadmium:**

Although evidence of cadmium requirement for growth in the rat has been reported, further confirmation and elucidation of its possible physiological function is needed. Studies by Schroeder on trace metals implicated cadmium in the development of hypertension in the rat. In human beings zinc-cadmium ratio has been shown to be a contributing cause of high blood pressure.

The effect is not universal, however, suggesting that dietary factors may have role in counteracting the effect of cadmium. Ashby et al. observed that acute administration of subcutaneous cadmium (0.1 - 1.5 mg/kg) to male rats resulted in high plasma-concentrations of copper, 24 hours after treatment. In contrast, plasma-
zinc and iron levels were markedly reduced. Simultaneous parenteral administration of zinc did not counteract the effect. These results suggest that cadmium blocks the excretion of copper into the bile leading to an accumulation of copper in the liver. Cadmium produces a variety of pathological effects in various organs after injection into the experimental animals and after accidental ingestion by man\textsuperscript{24,25}. Many of the observed toxic effects of cadmium are thought to be the results of induced secondary deficiencies in such essential trace elements as zinc, copper, Fe and Ca, since the uptake of cadmium both antagonises and is antagonised by the uptake of these metals\textsuperscript{26}. It has been reported\textsuperscript{27} that the tissue accumulation of cadmium in rats was associated with an increased concentration of copper in the kidney and increased concentration of zinc in the liver.

For the non-industrially exposed human being food is the main source of cadmium. Surveys of cadmium concentration in various food-stuffs and estimates of intakes by man have been given\textsuperscript{28}.

Zinc protects against many of the acute effects of cadmium while copper reduces cadmium-induced anaemia\textsuperscript{26}. At present the mechanism of the antagonism of copper and zinc metabolism by cadmium is unknown.

Accumulation of cadmium in the kidney or an increase in the renal $\text{Cd}^{2+}/\text{Zn}^{2+}$ ratio has been
considered\textsuperscript{29} to be a causative factor in human hyper-
tension. Response to cadmium is affected by various
factors such as sex, age, stress, health, nutrition
and pattern of exposure. Cadmium may be a greater
hazard in areas where anaemia is endemic or in children
and pregnant women, in whom iron and calcium intake may
be inadequate\textsuperscript{30}. It may be more toxic in certain groups
of people (as in Egypt and Iran) that suffer from zinc
deficiency or in regions where protein deficiency and
malnutrition are current problems\textsuperscript{31}.

Hypertension is one of the most common chronic
diseases in the civilised countries and it appears to
be linked\textsuperscript{32} to environment and age. The ratio of zinc
to cadmium on the earth's crust is 500 : 1000. Schroeder
came to the conclusion that cadmium in kidneys in
relation to zinc is a contributory, if not sometimes
the whole, cause of high blood pressure\textsuperscript{28}. In areas
where the ratio is low, the incidence of hypertension
is high and vice-versa, based on the kidneys of 400 or
more human subjects from around the world. The source
of accumulation of cadmium in the kidney of man with
age is food, water and air. If cadmium can displace
zinc in the body, it is likely that food containing
more than usual amounts of zinc might slowly lead to
accumulation of cadmium.
It is very likely that cadmium in drinking water and other fluids is more readily absorbed from the intestinal tract than cadmium bound to foods. Therefore, we must examine tap water and other thirst-quenchers for cadmium. Schroeder has reported that natural soft water has 1.5 µg/L cadmium whereas galvanised iron pipes had 6.3 µg/L which exceeds the limit of cadmium in potable water (10 µg/L).

**Chromium:**

Chromium is associated with glucose metabolism, possibly as a cofactor for insulin. An organic form of trivalent chromium, glucose-tolerance factor (GTF) is believed to be the biologically active form of chromium. Existence of mild chromium deficiency in human is suggested by demonstration of chromium-responsive disturbances in glucose metabolism. In studies with human diabetics, improved glucose-tolerance tests were reported following chromium supplementation for some subjects, whereas others did not respond. Chromium supplementation also has been reported to restore glucose tolerance in children suffering from Kwashiorkor or protein-energy malnutrition, and in patients on extended parenteral nutrition. A possible relationship between chromium-deficiency and cardiovascular diseases has been postulated on the basis of limited epidemiologic and experimental evidence. A recent study observed regression of cholesterol-induced
atherosclerotic plaques in rabbit aortas, after intra-peritoneal administration of potassium chromate. Although these findings are interesting, much remains to be learnt about chromium metabolism in humans and of the possible consequences of inadequate chromium intake.

J.B. Morgan has determined the hepatic-chromium content in diabetic subjects to elucidate a possible relationship between chromium-deficiency and diabetes mellitus in the elderly subjects. Improvement of impaired carbohydrate metabolism by Chromium(III) in malnourished infants has been studied by Hopkins et al. Levine et al. have studied the effect of oral chromium supplementation on the glucose tolerance of elderly human subjects and their findings support the possibility that chromium may lead to the impairment of the GTF in some elderly subjects. The role of chromium(III) in hypoglycemia and in impaired glucose-utilization in kwashiorkor has been investigated by Majaj and Hopkins and Carter et al.

IV.2: EXPERIMENTAL

WHOLE BLOOD: 45-subjects in the age group 30-50 were selected for the present investigations. Out of these, 15 were healthy normal subjects, 15 Diabetics and 15 hypertensives were chosen from among the patients
of D. k. Hospital of local J.N.M. Medical College. Age and sex of all these subjects were noted. Venous blood samples were drawn into a 10-ml syringe which had previously been wetted with sodium citrate. The blood samples were dried in silica crucibles and ashed in a muffle furnace. Estimation of the trace elements was done as detailed in Chapter II.

**Hair:** Hair samples of ten diabetics and ten normal subjects were collected. The samples were washed sequentially in hexane, ethanol and finally three times with deionized water. The hair were then dried in an oven at 110° and allowed to cool. 1 g hair of each sample was ashed in muffle-furnace and chromium estimated as per method detailed in Chapter II.
IV.3: RESULTS AND DISCUSSION:

Data on concentration of zinc and chromium in the whole blood of 15 diabetics have been presented in Table 24 while concentration of zinc and cadmium as estimated in the whole blood of 15 hypertensive subjects have been shown in Table 25. Concentration of zinc, cadmium and chromium in the whole blood of 15 normal subjects have been tabulated in Table 23. Chromium has been estimated in the hair of 10 diabetics and 10 normal subjects. The results are presented in Table 26.

The literature contains few references to the quantitative determination of trace metals in human blood. It is difficult to compare the scant data which are available because of the divergence of the methods used and of the units in which different authors chose to express their results ⁴⁷-⁵¹.

Valley and Gibson ⁵² determined the zinc-content of normal human whole blood and the values reported by them are 9.1 ± 0.9 μg/ml. Valley ¹¹ in his later studies has reported whole blood zinc as 880 ± 200 μg/100 ml. In the present studies, the estimated zinc content in the whole blood is 866 ± 40.84 μg/100 ml which agrees well with the observations of Valley.
Kumar and Rao\textsuperscript{19} have studied the blood and urinary zinc levels in diabetes mellitus and they reported significant reduction in the concentration of zinc in plasma, leucocytes and erythrocytes. Low levels of zinc in blood have been observed in diabetics. In the present studies, the mean value for zinc in diabetics is $686.66 \pm 49.80 \, \mu \text{g}/100 \, \text{ml}$. Thus, a significant reduction in zinc level of diabetics is clearly observed.

The chromium level in the whole blood of normal subjects reported by various earlier workers are: Grushko\textsuperscript{53} (USSR) - 35 ppb; Urone and Anders\textsuperscript{54} (USA) - 50 ppb; Imbus\textsuperscript{55} (USA) - 27.6 ppb; Medenedeva\textsuperscript{56} (USSR) - 60 ppb; Tiwari\textsuperscript{57} - $40 \pm 3.89 \, \text{ng}/\text{ml}$. These values as reported by different authors show wide variations. The difference can be attributed to geographical variation, dietary factors, etc. Tiwari has reported mean values of $30.24 \pm 4.78 \, \mu \text{g}/\text{ml}$ for maturity-onset diabetics. In the present study the mean values obtained for the normals are: $10.8 \pm 1.74 \, \mu \text{g}/100 \, \text{ml}$ and $6.4 \pm 1.12 \, \mu \text{g}/100 \, \text{ml}$ for the diabetics. Thus, a decline in chromium level is observed in diabetics as compared to normals.

Willden and Hyne\textsuperscript{58} have estimated cadmium in the whole blood of normal adults and the mean values reported by them are $2.38 \pm 0.32 \, \mu \text{g}/100 \, \text{ml}$ (smokers)
and $2.02 \pm 0.37 \, \mu g/100 \, ml$ (non-smokers). Dalley et al. have determined blood-cadmium level in nontreated hypertensives and normotensives. The mean values reported by them are $2.6 \pm 0.4 \, \mu g/ml$ for controls and $3.3 \pm 0.4$ for the hypertensives. Thus, an elevated cadmium level has been observed by them. In the present investigations, the mean values obtained for cadmium content are $1.30 \pm 0.259 \, \mu g/100 \, ml$ for the normals and $2.473 \pm 0.162 \, \mu g/100 \, ml$ for the hypertensives. A rise in the cadmium level is, thus, observed in our findings also.

Analysis of hair has been successfully employed as a means of detecting both deficiency and excess of trace elements in the body. A characteristic of many trace elements including chromium is that normally they are concentrated in hair at least ten times that of ambient blood levels. The problem of analytical sensitivity is therefore obviated. Hambidge et al. have determined the chromium content in the hair of normal children and children with juvenile diabetes mellitus. Hair-chromium concentration in the adults appear to be influenced both by sex and parity but the mean levels of all adult groups are lower than those of normal children. The mean values reported by Hambidge are $0.85 \pm 2 \, \mu g/g$ for the normal children and $0.56 \pm 2 \, \mu g/g$ for juvenile diabetic
children. A reduction in chromium level in hair is thus seen. In the present studies the mean values obtained are $0.451 \pm 0.44 \mu g/g$ for the normals and $0.354 \pm 0.034 \mu g/g$ for the diabetics. A reduction in the hair-chromium concentration is, thus observed in case of diabetics (Table 26).

The observations reported above do indicate a possible correlation between trace-elements and disease-states but the involvement of other elements in the two disease states studied cannot be excluded. It is, however, difficult to comprehend the functional significance of the trace elements due to a number of variables and experimental difficulties.


<table>
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<th>S.No.</th>
<th>Initials</th>
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<th>Sex</th>
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<th>Cadmium</th>
<th>Chromium</th>
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<td>1.4</td>
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<tr>
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<td>830</td>
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**Mean**

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<tr>
<th></th>
<th>866.00</th>
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**S.D.**

|       | 40.848 | 0.259 | 1.740 |

The values are shown in μg/100 ml. of whole Blood.
ESTIMATION OF ZINC AND CHROMIUM IN BLOOD OF DIABETIC PATIENTS

<table>
<thead>
<tr>
<th>No.</th>
<th>Initials</th>
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<th>Chromium (μg)</th>
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<td>760</td>
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**MEAN**

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<tr>
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**S.D.**

<table>
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<tbody>
<tr>
<td>49.809</td>
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The values are shown in μg/100 ml. of whole Blood.
### Table 1: Estimation of Zinc and Cadmium in Blood of Hypertensive Patients

<table>
<thead>
<tr>
<th>S.N.O.</th>
<th>Initials</th>
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<td>A.C.</td>
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</tbody>
</table>

**Mean**

- Zinc: 676.666
- Cadmium: 2.473

**S.D.**

- Zinc: 50.802
- Cadmium: 0.162

The values are shown in μg/100 ml. of whole blood.
**Table 26**

**Estimation of Chlorium in Hair of Normal and Diabetics**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Initials</th>
<th>Age</th>
<th>Sex</th>
<th>Normal Subject</th>
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<th>Age</th>
<th>Sex</th>
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<td>G.A.</td>
<td>50</td>
<td>M</td>
<td>0.35</td>
</tr>
<tr>
<td>2.</td>
<td>R.P.</td>
<td>48</td>
<td>M</td>
<td>0.45</td>
<td>S.S.</td>
<td>34</td>
<td>M</td>
<td>0.35</td>
</tr>
<tr>
<td>3.</td>
<td>L.R.</td>
<td>50</td>
<td>M</td>
<td>0.40</td>
<td>N.K.</td>
<td>35</td>
<td>M</td>
<td>0.40</td>
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<tr>
<td>4.</td>
<td>A.S.</td>
<td>45</td>
<td>M</td>
<td>0.50</td>
<td>S.S.</td>
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<td>M</td>
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<tr>
<td>5.</td>
<td>K.S.</td>
<td>48</td>
<td>M</td>
<td>0.42</td>
<td>A.K.</td>
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<td>M</td>
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<td>6.</td>
<td>C.K.</td>
<td>44</td>
<td>M</td>
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<td>S.S.</td>
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<td>M</td>
<td>0.37</td>
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<td>7.</td>
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<td>32</td>
<td>M</td>
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<td>K.K.</td>
<td>40</td>
<td>M</td>
<td>0.30</td>
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<td>8.</td>
<td>P.K.</td>
<td>35</td>
<td>M</td>
<td>0.48</td>
<td>D.K.</td>
<td>35</td>
<td>M</td>
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<tr>
<td>9.</td>
<td>C.L.</td>
<td>30</td>
<td>M</td>
<td>0.50</td>
<td>R.K.</td>
<td>33</td>
<td>M</td>
<td>0.40</td>
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<td>10.</td>
<td>N.D.</td>
<td>30</td>
<td>M</td>
<td>0.51</td>
<td>R.P.</td>
<td>50</td>
<td>M</td>
<td>0.30</td>
</tr>
</tbody>
</table>

**Mean**

| Normal Subjects | 0.451 |
| Diabetics      | 0.354 |

| S.D. | Normal Subjects | 0.044 |
|      | Diabetics      | 0.334 |

The values are shown in mg/l.
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