ROLE OF ZINC IN HEPATIC ENCEPHALOPATHY

THESIS

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To My Parents,

To Whom I Owe Every Thing.

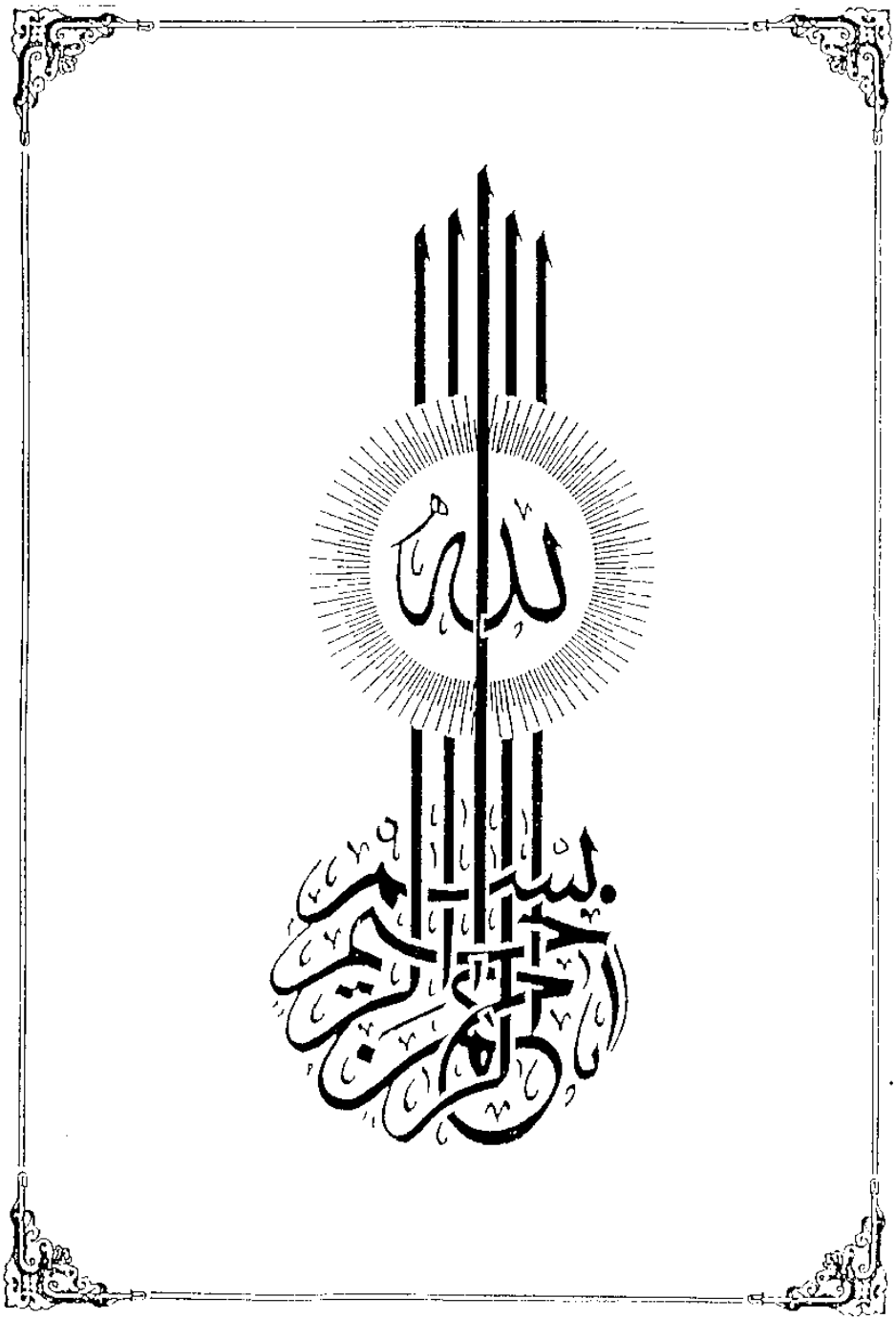
To My Brother,

Who Gave A Lot.

To My Husband and My Dear Son,

Who Paved The Way For The Existence

Of This Work .



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AIM OF THE WORK

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Chronic spontaneous nitrogenous encephalopathy is a well known complication of advanced cirrhosis ,of all the postulated cerebral toxins in hepatic encephalopathy ammonia has received most attention and currently effective treatments of hepatic encephalopathy act either on the production or the clearance of intestinal ammonia.

This is achieved by altering the diet and reducing intestinal ammonia production and absorption , generally by neomycin or lactuolose . Despite of protien restricted diet and lactuolose treatment ,some patients still experience intellectual deterioration . In some respects zinc deficient states resemble liver cirrhosis, beside the raised blood ammonia, there is low blood urea nitrogen which reflects the depressed capacity of the liver to sythesis urea .

Zinc deficiency is common in cirrhosis and many factors were postulated for this. Furthermore it was found that serum zinc is inversily related to fasting ammonia level.

One of the factors responsible for this low serum zinc

is the extent of porto-systemic shunting which is always associated with chronic porto-systemic encephalopathy.

The aim of our work is to correct the low serum zinc in our patients who suffer from hepatic encephalopathy. This is achieved by giving the patients 200 mg. Zinc acetate t.d.s., The score of trail making test, BUN., Zinc level, SGOT, SGPT, alkaline phosphatase, serum albumin, and serum bilirubin level are studied before and after the trial to demonstrate any valuable effect of zinc supplement. Blood Urea Nitrogen BUN reflects the capacity of the liver to synthesise urea from ammonia . SGOT, SGPT, alkaline-phosphatase, serum albumin and serum bilirubin level assess the severity of liver cell damage.

Trail making test is a psychological test that has been used to evaluate organic brain damage.

REVIEW OF LITERATURE

HUMAN ZINC METABOLISM

HISTORICAL REVIEW:

In the fall of 1958, at Saadi Hospital, Shiraz,came a 21-year-old patient who looked like a 10-year-old boy. In addition to dwarfism,he had severe anemia, hypogonadism, hepatosplenomegaly, rough and dry skin,mental lethargy, and geophagia (Prasad et al,1961). He ate only bread made of wheat flour, and his intake of animal protein was negligible. He also consumed nearly one pound of clay daily. The habit of geophagia (clay eating) is common in the villages around Shiraz. Ten additional similar cases came .

The anemia was due to iron deficiency and was corrected by oral iron therapy. It was not possible to explain all the clinical features solely on the basis of tissue iron deficiency,since growth retardation, testicular atrophy, and skin changes in animals are not seen in iron-deficient animals.

In Egypt, patients were later encountered(Prasad et al,1963a ,1963b) with similar dietary history,except that

geophagia was not documented, and they were proven to have zinc deficiency. This conclusion was based on the following findings: (a) the zinc concentrations in plasma, red cells, and hair were decreased, and (b) radioactive zinc-65 studies revealed that the plasma-zinc turnover rate was greater, the 24-hour exchangeable pool was smaller, and the excretion of zinc-65 in stool and urine was less in the patients than in the control subjects.

Further studies in Egypt showed that the rate of growth was greater in patients who received supplemental zinc compared with those who received an animal-protein diet consisting of bread, beans, lamb, chicken, eggs, and vegetables (Prasad et al, 1976 & Prasad, 1966). Pubic hair appeared in all cases within 7 to 12 weeks after zinc supplementation was initiated. Genitalia size became normal, and secondary sexual characteristics developed within 12 to 24 weeks in all subjects receiving zinc. On the other hand, no such changes were observed in a comparable length of time in the iron-

supplemented group or in the group on an animal-protein diet alone. Thus, the growth retardation and gonadal hypofunction in these subjects were related to zinc deficiency.

Later studies in Iran demonstrated that zinc is a principal limiting factor in the nutrition of children (Halsted et al, 1972). It was also evident that the requirement of zinc under different dietary conditions varied widely in the Middle East. For instance, in the studies reported by Prasad (Prasad, 1966) and Sandstead (Sandstead et al, 1967), 18mg supplemental zinc with adequate animal protein and calorie intake was sufficient to produce a definite response with respect to growth and gonads, but in other studies, when the subjects continued to eat the village diet, up to 40 mg zinc supplement was required to show some growth effect (Ronaghy et al, 1974).

METABOLISM

The zinc content of a normal 70 kg male has been estimated to be 1.5 to 2.0g . Liver, kidney, bone,retina, prostate, and muscle appear to be rich in zinc (Widdow son et al,1951) . In man, the zinc content of testes and skin has not been determined accurately, although clinically it appears that these tissues are sensitive to zinc depletion (Prasad et al,1970).

Zinc in the plasma is bound mainly to albumin, but other proteins such as alpha-2 macroglobulin, transferrin, ceruloplasmin, haptoglobin, and gamma globulins also bind significant amounts of zinc (Prasad et al,1970).
Besides the protein-bound fraction, a smaller portion of zinc 2-3% of total zinc in the plasma exists as an ultra-filtrable fraction mostly bound to amino acids, but a smaller fraction as ionic form . Histidine, glutamine, threonine, cystine, and lysine appear to have significant zinc-binding ability (Parisi et al, 1970) .
Whereas amino acids competed effectively with albumin, haptoglobin, transferrin, and IgG for binding of zinc ,

a similar phenomenon was not observed with respect to ceruloplasmin and alpha-2 macroglobulin, suggesting that the latter two proteins exhibited a stronger binding affinity for zinc .

Approximately 20 to 30 % of ingested dietary zinc is absorbed. Data are meager on both the site(s) of absorption in man and on the mechanism(s) of absorption, whether active , passive , or facultative transport . Recently, a model attempting to explain the data on the mechanism of zinc absorption at the level of intestinal mucosal cell has been proposed (Cousins,1979). A portion of the dietary zinc entering the lumen of the small-intestine is transported across the mucosal brush border membrane by a process probably requiring A.T.P within the intestinal cells,newly acquired cytoplasmic zinc, equilibrates with zinc pool and is either transferred to high molecular weight proteins,to low molecular weight proteins (metallothioneine) or to the plasma .(Cousins,1979) Zinc absorption is variable and is highly dependent upon a variety of factors. Zinc is more available for absorption from animal proteins. Among other factors that might affect