Zinc deficiency associated with nutritional dwarfism was reported from Egypt in 1963. The conclusions drawn from that study were based on biochemical changes in zinc metabolism plus zinc supplementation studies. The dwarfs were of varying ages and were affected in varying degrees of severity.

This syndrome, which is common in the Middle East, has been extensively investigated in Iran where its clinical features were reported in detail in 1961. Our study was designed prospectively to give oral zinc supplementation under controlled conditions. A major factor in the etiology of this syndrome is the village diet which consists largely, and sometimes exclusively, of whole meal wheat bread. This contains a high level of phytate which binds zinc and makes it unavailable. Geophagia, which was present in all subjects, may be a factor in the pathogenesis.

The subjects of this report are fifteen men who were rejected at the Iranian Army induction center because of "malnutrition," and two women. A unique feature was that all were nineteen or twenty years of age. They were studied for six to twelve months. One group was given a well-balanced nutritious diet containing ample animal protein plus a placebo capsule. A second group was given the same diet plus a capsule of zinc sulfate daily containing 27 mg of elemental zinc. A third group was given the diet alone without additional medication for six months, followed by the diet plus the administration of zinc sulfate. Assignment to groups was by random selection.

Although the development in subjects receiving the diet alone was slow, the effect on height increment and onset of sexual function was strikingly enhanced in those receiving zinc capsules as a supplement. The differences were significant statistically (p < 0.01 for height increment and p < 0.001 for time of onset of sexual function).

In 1961 the clinical features of nutritional dwarfism studied in Iran were reported in detail [1]. The salient features were growth retardation, absent sexual development, iron deficiency anemia and geophagia. Other prominent aspects were a rough skin with hyperpigmentation, spoon nails and open epiphyses.
Growth retardation is a conspicuous feature of zinc deficiency in animals and this, together with other similarities, led Prasad and associates [1] to suggest that zinc deficiency in man might explain the failure to grow and to develop sexually. In 1963 biochemical abnormalities of zinc metabolism consistent with that hypothesis were demonstrated [2]. In 1967 the results of a zinc supplementation program which was carried out in Egypt in twenty-two nutritional dwarfs during 1961–1963 were reported [3]. This provided data which indicated a beneficial effect of zinc on growth and sexual development.

The etiologic factors in nutritional dwarfism associated with zinc deficiency, which has been observed in several other countries in addition to Iran and Egypt (Turkey, Morocco, Tunisia, Portugal, Panama), comprise the following:

1. **Unavailability of zinc.** Zinc is ubiquitous and thus is rarely lacking in food intake. However, all cereals contain phytate (inositol hexaphosphate) which binds zinc, making an unabsorbable complex. The zinc contained in animal protein, on the other hand, is readily available. The complex action of phytate in cereals is the most important etiologic factor in zinc deficiency in Iran.

2. **Loss of zinc.** Red blood cells contain approximately 12 μg of zinc/ml of red cells (about twelve times the concentration in plasma). Thus chronic blood loss such as occurs in schistosomiasis (S. hematobium, especially) and hookworm disease, conditions which are prevalent in tropical, moist areas such as the Nile delta of Egypt, probably plays a significant role in zinc deficiency in that region. Sweat also contains zinc and iron. Villagers working in the sun may lose significant amounts of both minerals [4].

3. **Theoretic factors.** Infectious diseases such as pneumonia, active tuberculosis and chronic sepsis are usually associated with low plasma zinc concentrations, as are chronic active liver disease, decubitus ulcers, uremia, pregnancy and malabsorption syndromes [5]. Although a low plasma zinc level is not necessarily an indication of deficiency, it is nevertheless suggestive and makes further investigation of zinc metabolism desirable. In the nephrotic syndrome an excessively large amount of zinc is lost in the urine [6]. Geophagia appears to be closely linked historically to the dwarfism syndrome in Iran but not to the cases reported from Egypt. The role of geophagia in human nutrition has recently been reviewed [7].

The high arid plateau of Iran is unique in that hookworm and schistosome infestations do not occur and thus the patients do not have chronic blood loss. This is in contrast to the Egyptian patients who inhabit the Nile delta where both parasites are prevalent. In Iranian villages the diet consists largely of unleavened whole wheat bread which has a high phytate content.

The work in Egypt indicated for the first time that zinc deficiency might occur in man. The importance of this observation made it mandatory that there be investigation and confirmation in another area. Such a study, which began in 1969, has been completed at Pahlavi University in Shiraz, Iran. This study shows that a key factor in this syndrome in respect to growth and sexual retardation is, indeed, zinc deficiency and that supplementation with zinc results in sexual maturatation and a growth spurt. Zinc, essential for growth, appears to be a basic limiting nutrient. Our purpose is to report results obtained in seventeen nutritional dwarfs, aged nineteen or twenty years, observed under controlled conditions for six to twelve months.

**MATERIAL AND METHODS**

In the villages of Iran the syndrome of nutritional dwarfism is common but not clustered geographically or by family. With the cooperation of the personnel at the Iranian Army induction centers, an excellent source of cases became available. Since all men are called up for the draft at ages nineteen to twenty and since nutritional dwarfs were always rejected, it was possible to identify over 100 of them from the induction center in Shiraz, all of about the same age. Excluded from consideration for the study were dwarfs representing the syndrome described who also had other chronic organic disease, such as liver cirrhosis, tuberculosis, nephritis, heart disease, uro lithiasis with pyelonephritis and malabsorption associated with diarrhea and steatorrhea. From the remainder, those willing to undergo a long period of observation were admitted to the Nemazee Hospital research ward where they received a well-balanced diet with ample animal protein containing 2,500 calories (calculated). After a two or three week stay for clinical and laboratory examinations, including roentgenograms of the left hand, they were transferred to a nearby house or annex. Twelve subjects could be accommodated at a time, and they received the same hospital diet. Analyses of the food consumed by the dwarfs in the annex on an average day showed it to contain from 20 to 30 mg of zinc. The availability of zinc is not known, but because the phytate content in this diet was low and because the diet contained an abundance of meat, fish and milk, availability was high.

*One of us (H.A.H.) found that 3 per cent of all draftees who lived in villages were rejected because they had the syndrome of nutritional dwarfism.
TABLE I Clinical Findings in Nutritional Dwarfs on Admission to Hospital

<table>
<thead>
<tr>
<th>Data</th>
<th>Height</th>
<th>Weight</th>
<th>Hemoglobin (gm%)</th>
<th>Serum Protein (gm%)</th>
<th>Serum Albumin (gm%)</th>
<th>Serum Iron (μg/100 ml)</th>
<th>Plasma Zinc (μg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>141</td>
<td>35</td>
<td>10.3</td>
<td>7.06</td>
<td>5.35</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>Standard deviation (SD)</td>
<td>8</td>
<td>5</td>
<td>4.0</td>
<td>0.69</td>
<td>0.40</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Range</td>
<td>130-150</td>
<td>24-44</td>
<td>4.3-16.2</td>
<td>5.8-8.2</td>
<td>2.8-4.1</td>
<td>17-81</td>
<td>29-83</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>17</td>
<td>16</td>
<td>17</td>
<td>15</td>
<td>15</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Normal values</td>
<td>174.5*</td>
<td>61*</td>
<td>13-16†</td>
<td>6-23.9†</td>
<td>3.7-5.0†</td>
<td>50-150†</td>
<td>95 ± 12§</td>
</tr>
</tbody>
</table>

* From Nelson [8].
† Values obtained in control subjects by research laboratory. Nemazee Hospital.
§ From Halsted and Smith [5].

doubtless equal to that of a western diet. Suitable supervision, entertainment and occupational therapy were provided. The patients stayed in the annex for six months to one year. Of the seventeen subjects studied, eight were observed for twelve months, three for nine months and six for six months.

Two of the seventeen subjects were female, one of whom was found in a village; the other was admitted to the hospital because of severe malnutrition. They were aged nineteen and twenty, respectively, and were transferred, after hospital studies, to the home of one of us (H.A.R.) where they lived during the study, one for six months, the other for one year.

The dwarfs were divided into three treatment groups: Group I received a well-balanced hospital diet plus a placebo capsule from the start. Group II received the hospital diet plus one capsule daily of 120 mg zinc sulfate from the start. This was ZnSO₄.7H₂O, containing 27 mg of elemental zinc. Group III received the hospital diet plus a placebo capsule for six months at which time the zinc sulfate capsule was substituted for the placebo. Selection of subjects for groups I and II was by the method of lottery with replacements. The three members of group III (Cases 8, 9 and 10) were drawn from group I at the end of six months. One of the two female subjects (Case 10) was in group I, the other (Case 16) was in group II. The capsules were given seven days a week between the noon and evening meals by an attendant who made sure that they were swallowed. A physician (H.A.R.) or a senior medical student who had a special interest in the investigation visited the annex daily. The only one who knew which subjects received the zinc capsule and which received the placebo capsule was the supervising physician (H.A.R.). Those who administered the capsules did not know which subjects received which capsule. Iron in doses of 100 mg ferrous fumarate (Toleron®)* was given once daily only to those dwarfs whose hemoglobin value on admission was 7.0 gm per cent or less (four in all). Two of these (Cases 7 and 8) were in group I and two (Cases 13 and 10) were in group II. It was administered only until the hemoglobin level had risen to between 8.0 and 10.0 gm per cent. The Toleron used was found to contain a negligible amount of contaminating zinc. Each three months the subjects were transferred back to the hospital for a few days to undergo clinical and laboratory tests.

RESULTS

The significant clinical findings on admission to the hospital are listed in Table I. Heights were about 20 per cent and weights about 45 per cent below the average values reported for a similar age group in the Iowa Growth Study [8]. The patients were moderately anemic. Serum protein and albumin levels were essentially normal. Plasma zinc levels in groups I and II are given in Table II. The mean value was markedly reduced from the normal. Over a six month treatment period the increase in plasma zinc was similar in each group.

* Kindly supplied by Mallinckrodt Chemical Works, St. Louis, Missouri (Mr. M. L. Bandle).

TABLE II Plasma Zinc Concentration on Admission and After Six Months of Therapy (Rx) (μg/100 ml)

<table>
<thead>
<tr>
<th>Data</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On Admission</td>
<td>After Six Months Rx</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>51 ± 18</td>
<td>75 ± 9</td>
</tr>
<tr>
<td>Range</td>
<td>29-83</td>
<td>65-93</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>

NOTE: Normal concentration in Iranian medical students was 95 ± 12μg/100 ml.

*Preliminary analyses of the phytate content of unleavened bread in Iranian villages showed an amount approximately 40 per cent greater than that found in leavened bread used by urban dwellers. It was also far greater than that found in western whole wheat or rye breads, presumably because it is not subjected to fermentation which destroys phy tate. (Unpublished observations by one of us, J.G.R.)
Roentgenograms of the left hand revealed the average bone age on admission of fourteen of the subjects (eight in group I and six in group II) to be 10.6 years. In twelve of these fourteen there was no significant change in bone age during the period of study. In one (Case 4, group I), there was a change from nine and a half to eleven and a half years in six months of treatment (diet alone). In another (Case 12, group II), there was a change from eleven and a half to thirteen years in six months of treatment (diet plus zinc sulfate).*

Three cases representative of each group are depicted in Figures 1, 2 and 3. Figure 1 shows a twenty year old man who was 150 cm tall, weighed 44 kg and had little sexual development. The plasma zinc level was 44 \( \mu g/100 \text{ ml} \) and the hemoglobin value 8.2 gm per cent. Serum iron was 20 \( \mu g/100 \text{ ml} \) with a total iron-binding capacity of 430 \( \mu g/100 \text{ ml} \). Serum total protein was 8.2 gm per cent with serum albumin of 3.8 gm per cent. This subject was given a hospital diet containing adequate animal protein and thus plenty of available zinc. After six months he had grown 5 cm and gained 12 kg in weight, but only a slight amount of pubic hair had appeared. Little increase in sexual development occurred over the subsequent six months, and his height and weight remained unchanged during that period. Plasma zinc and hemoglobin levels had both risen to normal.

Figure 2 is that of a twenty year old man who

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*We wish to thank Dr. Harry Israel of the Fels Research Institute, Yellow Springs, Ohio for analysis of bone ages.
ZINC DEFICIENCY IN MAN—HALSTED ET AL.

was 136 cm in height, weighed 33 kg and had incipient sexual development. His plasma zinc level was 70 μg/100 ml and hemoglobin value 10.5 gm per cent. The serum total protein was 7.3 gm per cent with serum albumin of 3.3 gm per cent. After six months on a hospital diet, with the addition of 120 mg of zinc sulfate daily, he had grown 10 cm in height and gained 8 kg in weight. The plasma zinc level increased to 83 and the hemoglobin value rose to 13.3 gm per cent. After twelve months on the same therapy his height was 150 cm, a gain of 14 cm. The body weight was essentially unchanged over that at six months. However, sexual development was entirely normal. The plasma zinc level after twelve months of therapy was slightly lower than that at six months. Figure 3 is that of a nineteen year old girl who entered the hospital in quite an emaciated condition. The picture in the first frame was taken one month after admission when her condition had improved considerably and at which time she was admitted to the study. Her height was 134 cm and her weight 27 kg. The plasma zinc level was 29 μg/100 ml and hemoglobin value 7.7 gm per cent. The serum iron was 60 μg/100 ml with a total iron-binding capacity of 320. Serum total protein was 5.8 gm per cent with serum albumin of 2.8 gm per cent. After six months, during which time a well-balanced diet was the only therapy, there was a weight gain from 27 to 41 kg, but there was only a 1 cm increase in height and only minimal signs of sexual development. At this time the plasma zinc level had risen to 78 and the hemoglobin value was 15.3. Zinc sulfate (120 mg) was then added to the treatment regimen. Her first menstrual period occurred thirty-three days after admission when her condition had improved considerably and at which time she was admitted to the study. Her height was 134 cm and her weight 27 kg. The plasma zinc level was 29 μg/100 ml and hemoglobin value 7.7 gm per cent. The serum iron was 60 μg/100 ml with a total iron-binding capacity of 320. Serum total protein was 5.8 gm per cent with serum albumin of 2.8 gm per cent. After six months, during which time a well-balanced diet was the only therapy, there was a weight gain from 27 to 41 kg, but there was only a 1 cm increase in height and only minimal signs of sexual development. At this time the plasma zinc level had risen to 78 and the hemoglobin value was 15.3. Zinc sulfate (120 mg) was then added to the treatment regimen. Her first menstrual period occurred thirty-three days later. Six months after starting zinc therapy pronounced signs of sexual development occurred consisting of growth of breast tissue and pubic hair. Between the sixth and twelfth months there was a 9 cm increase in height.

Analysis of the growth increment (height increase) for the seventeen cases studied is depicted in Figure 4. Eleven subjects in group 1 (Cases 1–11) were given only a well-balanced diet plus one placebo capsule daily for six months. Four of these (Cases 4–6 and 7) then left the study at thirty-two, thirty-nine, twenty-six and twenty-six weeks, respectively. Five subjects in group II (Cases 12–17) were given the same diet plus one zinc capsule daily for the same six month period. In those receiving the diet alone (group I) there was an average increase in height of 3.5 cm ± 2.6 SD, whereas in those receiving the zinc sulfate capsule in addition to the diet (group II) there was an average increase of 10.9 cm ± 4.3 SD. These differences are statistically significant (p <0.01).

During the following six months four subjects (Cases 1–3 and 7) continued to receive the diet without supplementary zinc therapy. In three others (Cases 8–10) a zinc capsule was substituted for the placebo. (These three subjects constituted group III.) During this second six month period there was an increase in height of 2.4 ± 1.4 SD in those continuing on diet alone (Cases 1–3 and 7) and an increase of 8.7 cm ± 0.6 SD in those receiving the diet plus the zinc capsule (Cases 8–10). The difference in these two groups was also highly significant statistically (p <0.001).

Sexual development was evaluated by noting the first sign of sexual function, i.e., nocturnal emission in men and the first menstrual period in the two women. Using these end points the results in number of weeks following admission to the hospital are shown in Figure 5. There was a strikingly longer period of time before sexual function occurred in the subjects who received only a well-balanced diet than in those who received the diet plus the zinc capsule daily. The average time interval before emission or menstruation occurred was thirty-five weeks in the former and ten weeks in the latter. These differences are statistically highly significant (p <0.001).

In one subject (Case 1) no sexual function occurred after fifty-two weeks of treatment with diet alone. One subject (Case 5) was lost to observation at thirty-nine weeks and another (Case 11) at twenty-six weeks; no sexual function occurred in either. If these three subjects are included in the statistical analysis as if sexual function had developed at or shortly after the times they left the study, the statistical differences are still highly significant (p <0.001).

The three subjects in group III who received the diet alone for six months had no evidence of sexual function up to that time. With the addition of zinc sulfate daily, sexual function occurred within four, six and six weeks, respectively.

It thus appears that a well-balanced nutritious diet with ample animal protein resulted in slow but gradual growth, and eventual onset of sexual function. However, with the addition of zinc sulfate daily, growth was greatly enhanced and the onset of sexual function was greatly hastened.

The subjects were more cooperative and docile before sexual development occurred than after sexual function took place. Then they complained more and asked to be discharged. Two left against advice.
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**Figure 4.** Cases 1–11 constituted group I. Cases 12–17 constituted group II. During the second six months (period II) Cases 1, 2, 3 and 7 remained in group I, Cases 4, 5, 6 and 11 having left the study. During period II Cases 8, 9 and 10 constituted group III.

**Figure 5.** Onset of sexual function noted at end of bar of each patient (exceptions are Cases 1, 5 and 11. See text).

**COMMENTS**

Evidence reported in this study makes it clear that zinc can be a limiting essential nutrient in determining both growth and onset of puberty in man. In planning food supplementation programs in underdeveloped countries this factor should be considered. For example, if lysine is added to wheat, from which unleavened village bread is made, zinc, an essential nutrient which is probably necessary for protein synthesis, will still be unavailable. As a consequence fortification of wheat to produce an optimum amino acid composition is not likely to provide an increased benefit in respect to protein nutrition unless zinc is made available.

The syndrome as described from Iran in 1961 comprised eleven male dwarfs, whose degree of anemia, weakness and other debilitating factors was considerably more severe than in the seventeen subjects of this study. The reason for this is not so much that rural conditions respecting food supplies may have improved but that the fifteen male subjects were selected from rejectees of an army induction center whereas in the first report all patients had come to the hospital because they were too weak to survive without seeking medical attention. A follow-up study of the original dwarfs described in 1961 showed that all remained well and developed normally provided that they maintained a regular intake of animal protein. One subject is known to have married and had children. If they reverted to the same dietary pattern and again practiced geophagia relapse occurred [9]. One of the subjects of the present study, upon attaining normal growth and sexual development, was drafted and served in the army.
The two women described herein represent the first cases of nutritional dwarfism in females caused by zinc deficiency. It had been believed that the syndrome was limited to males perhaps because the zinc content of the testis, as measured in rats, is about four times greater than that of the ovary. However, a more likely reason for the absence of females in the previous reports from Iran and Egypt [1-3] is that in Moslem villages females are less likely to receive medical attention.

A report from Iran in 1968 indicated that zinc supplementation was effective in hastening sexual development in growth-retarded but outwardly healthy school boys with delayed puberty and low plasma zinc levels [10]. Those observations coupled with these suggest that a spectrum of zinc deficiency may occur with "full-blown" dwarfism as defined by the features of this syndrome at one end and but moderate growth retardation with late puberty at the other. The mild end of the "zinc deficiency" spectrum may be very widespread in underdeveloped areas of the world where the chief food supplies are of cereal origin with a high phytate content and thus probably lesser amounts of available zinc. One may rightly ask whether this is important from an individual or public health viewpoint. Only further study can answer such questions, but there are suggestions that zinc deficiency may lead to greater susceptibility to infection [5,11]. It is likely that other subtle signs of subnormal health may be traced to mild zinc deficiency when it is studied more extensively and when physicians become more attuned to this possibility.

Investigation in depth in man of the problem of mineral availability related to the role of complexants deserves a high priority in nutritional research. In addition to more detailed study of etiologic factors in zinc deficiency, knowledge of the results, especially endocrine dysfunction, is needed. This aspect has not been extensively studied, although two reports have been published from NAMRU-3* in Egypt [3,12].

A low plasma zinc concentration is prevalent among Iranian villagers [5]. The meaning of this is not entirely clear and can only be considered suggestive but not diagnostic of zinc deficiency. The only certain criterion for zinc deficiency is a clinical response to administration of zinc under controlled conditions, which was the objective of this investigation.

Suboptimal intake of zinc in rats results in an immediate depression of the plasma level, followed by growth impairment [13]. Undoubtedly the priority for zinc must be for metabolic function so that if a shortage of zinc occurs the plasma may serve as a reservoir to be drawn upon for immediate needs. Conversely if tissue zinc deficiency exists, as reflected not only by abnormal function but also by a low plasma level, and zinc is added to rectify this deficiency the plasma level may return to normal at varying rates. This could explain the continued lowered plasma levels in some of these patients who were receiving adequate amounts of zinc, even after growth and sexual function had developed. In other words the rate of return to a normal plasma level seems to be a reflection of the degree of tissue zinc deficiency with resulting metabolic deficits.

Geophagia must be considered as a possibly important factor in nutritional dwarfism in view of the fact that every subject in this investigation and all but one of the eleven Iranian dwarfs originally described admitted to eating large amounts of clay. This might explain the fact that nutritional dwarfism is not clustered geographically and that with occasional exceptions only one member of a family was affected even though all members ate the same diet. In Turkey the problem of geophagia has been studied by Minnich et al. [14] who found that clay fed to both normal and iron-deficient subjects inhibited the absorption of radioactive iron. On the other hand Prasad and his coworkers [2] did not mention that the Egyptian dwarfs admitted to the practice of geophagia. Moreover an experimental study in zinc-deficient rats given clay obtained from Shiraz from the same source as eaten by one of the dwarfs indicated that this clay was beneficial to the rats by providing a source of zinc otherwise lacking in the experimental zinc deficient diet [13]. Thus it is possible that zinc deficiency results in clay eating in an attempt to obtain zinc. The problem of nutritional effects of geophagia obviously requires further study.

The functions of zinc are beginning to unfold. For thirty years it has been known to be a part of enzyme molecules, carbonic anhydrase being the first to be described [15]. Since then many zinc metalloenzymes have been documented [16]. It is probably essential for nucleic acid and protein synthesis [17,18].

This syndrome (which Prasad and one of us [J.A.H.] erroneously believed to be the first to document) was well described for the first time in 1910 by Lemann in New Orleans [19] associated with chronic blood loss from hookworm infestation. It seems possible that many people in the...
developing nations who survive the ravages of infantile malnutrition and infection may have varying degrees of zinc deficiency associated with a primarily cereal diet. Moreover, zinc deficiency as manifested by the syndrome under discussion undoubtedly occurs in western countries secondary to other diseases [20]. It should be considered as a possible factor in growth retardation secondary to disorders of absorption, such as childhood regional enteritis, cystic fibrosis and celiac disease.

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