

from new medicines, while elsewhere in the world access to the latest treatments becomes better assured because of reduced protection of patents.

However, pharmaceutical companies are well aware of the problems they need to address in order to restore research productivity and maintain financial viability. In the immediate future major firms can “buy in” promising new molecules from smaller enterprises and extend the use of existing treatments via fresh applications.

Some data indicate the start of a more definitive strategic response to improving research productivity. The number of stage one and two clinical trials has increased by over 50% since the mid-1990s,⁵ although as yet no equivalent rise has occurred in the number of more costly phase three trials. This might indicate that the quality of the overall research pipeline is set to improve through more selective approaches to taking new molecules through development phases.

The future for pharmaceutical industry research is less certain than it seemed during the second half of the 20th century. Nevertheless, new treatments are still being developed. For example, the first of a new class of HIV cell fusion inhibitors is due to be marketed during 2003. In the field of biotechnology, recently introduced monoclonal antibodies are already of proved value in treating conditions such as rheumatoid arthritis and some cancers. Upwards of 100 new products based on monoclonal antibodies are now in trial.

Although the pharmaceutical industry’s new product pipeline is running leaner than in the past, it would be wrong to assume—as yet, at least—that it is running

dry. Critics may welcome the prospect of pharmaceutical companies losing economic power and the opportunities for reform that this might bring.^{6–8} But the value of the industry’s contributions to therapeutic innovation should not be ignored. Those who wish to see as many effective new medicines as possible introduced in the 21st century will hope that the pharmaceutical industry succeeds in strengthening its research performance and is permitted an operating environment in which—in part through adequate protection of intellectual property—it can continue investing in advances that ultimately benefit everyone.

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Zinc deficiency

Has been known of for 40 years but ignored by global health organisations

Although it has been known for more than six decades that zinc is essential for the growth of micro-organisms, plants, and animals, until 1961 it was believed that zinc deficiency in humans could never occur. It is now clear that nutritional deficiency of zinc is widely prevalent and its morbidities are severe. This article describes the history of the study of zinc deficiency from a single case report in 1961 to its current state.

In 1958, a 21 year old male patient in the Iranian city of Shiraz presented with dwarfism, hypogonadism, hepatosplenomegaly, rough and dry skin, mental lethargy, geophagia, and iron deficiency anaemia.¹ This patient had an unusual diet. His intake of animal protein was negligible, and he ate only unleavened bread. In addition, he consumed 0.5 kg of clay daily. His total intake of calories and protein (cereal) was adequate, and except for iron deficiency no other deficiency in micronutrients was documented consistently. In the following three months 10 more patients with a similar illness were seen in the same hospital. The growth retardation and testicular hypofunction in all these patients could not be explained on the basis of iron deficiency—these manifestations are not observed even in iron deficient animals. In animals, among the transi-

tional elements known to have adverse effects on health due to deficiency (Cr, Mn, Co, Cu, and Zn), only zinc deficiency was known to cause growth retardation and testicular hypofunction.

I speculated that some dietary factors responsible for the decreased availability of iron in geophagic patients might also have decreased the availability of zinc.¹ Later it became known that phytate in cereals markedly impairs the absorption of zinc and also iron.² With a well balanced animal protein diet and administration of iron, all the clinical features in the Iranian patients were corrected.

I saw similar patients in Egypt. The evidence for zinc deficiency in these patients was that their concentrations of zinc in plasma, red blood cells, hair, and a 24 hour urine sample were decreased compared with controls;^{6,7} ⁶⁵Zn studies showed that the plasma disappearance curve of zinc was more rapid and the 24 hour exchangeable pool was decreased. Further, the rate of growth in patients who received zinc supplements (average 12.7 cm per year) was much greater compared with those who received iron instead or only an adequate animal protein diet.^{3,4} Gonadal changes were also reversed by zinc supplementation only. Patients who had iron supplementation corrected

their anaemia, but no effect was noted on growth or gonads. In 1973, Barnes and Moynahan noted that acrodermatitis enteropathica, a fatal genetic disorder, was cured by supplementation with zinc.⁵ It is now known that patients with acrodermatitis enteropathica do not absorb dietary zinc normally.

The discovery that zinc is essential for humans made a notable impact. In 1974 the Food and Nutrition Board of the US National Academy of Sciences made a landmark decision, to declare zinc an essential nutrient and establish recommended dietary allowances for humans. Later, including zinc in total parenteral nutrition fluids was made mandatory, which undoubtedly saved many lives. Dietary zinc deficiency is very prevalent in the developing world (affecting nearly two billion people), where mainly cereals are consumed by the population. A meta-analysis of 33 prospective intervention trials of zinc supplementation and its effects on children's growth in many countries showed that zinc supplementation alone had a statistically significant effect on linear growth and body weight gain, indicating that other deficiencies that may have been present were not responsible for growth retardation.⁶ Zinc supplementation has been shown to improve neuropsychological functions in Chinese children with zinc deficiency.⁷ It reduces the incidence and duration of acute and chronic diarrhoea and acute lower respiratory tract infections in children in developing countries, resulting in decreased mortality.⁸ Zinc deficiency in pregnant women causes abnormal labour, retarded fetal growth, and fetal abnormalities.⁹

The immunological effects of zinc deficiency during the early 1960s were not known, although I knew that patients with zinc deficiency in the Middle East died of infection before the age of 25 (personal observation). It has now been shown that in people with zinc deficiency, activity of serum thymulin (a thymus specific hormone involved in T cell function) is decreased, an imbalance between T helper cell (Th1) and Th2 function develops, and lytic activity of natural killer cells and the percentage of precursors of cytolytic T cells is decreased.^{10 11}

Zinc deficiency has now been recognised to be associated with many diseases—for example, malabsorption syndrome, chronic liver disease, chronic renal disease, sickle cell disease, diabetes, malignancy, and other chronic illnesses.⁹ In these conditions, deficiencies of other micronutrients such as vitamins and other trace elements may also be associated. It should be emphasised that nutritional zinc deficiency in the developing countries does not occur in isolation.

Recently the National Institutes of Health's Eye Institute conducted a large double blind clinical trial including 3640 elderly participants, which showed that antioxidants and zinc supplements delayed progression of age related macular degeneration and reduced the risk of loss of vision.¹² Zinc deficiency is also common in elderly people.⁹

Zinc decreases the copper burden in humans; as such it has been used effectively to treat Wilson's disease.⁹ In therapeutic doses, zinc has been shown to

be beneficial in the treatment of hepatic encephalopathy, sickle cell disease, and the common cold.

More than 300 catalytically active zinc metallo-proteins and more than 2000 zinc dependent transcription factors involved in gene expression of various proteins have been recognised.^{13 14}

We have recently shown in cell culture studies that zinc activates nuclear factor-kappa B in T helper cells and in zinc deficiency binding of nuclear factor-kappa B to deoxyribonucleic acid is decreased, leading to decreased gene expression of interleukin 2 and its production.¹⁵

The problem has been known for 40 years and a solution is still outstanding. Despite all the evidence practically no attention has been given to the problem of zinc deficiency by the world's organisations. Growth retardation, increased susceptibility to infectious and cognitive impairment are common in developing countries where nutritional deficiency of zinc is also prevalent. Thus a correction of zinc deficiency is likely to have a great impact on the health of a large population in the developing world and it is imperative that the World Health Organization must include this problem in its top priorities.

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