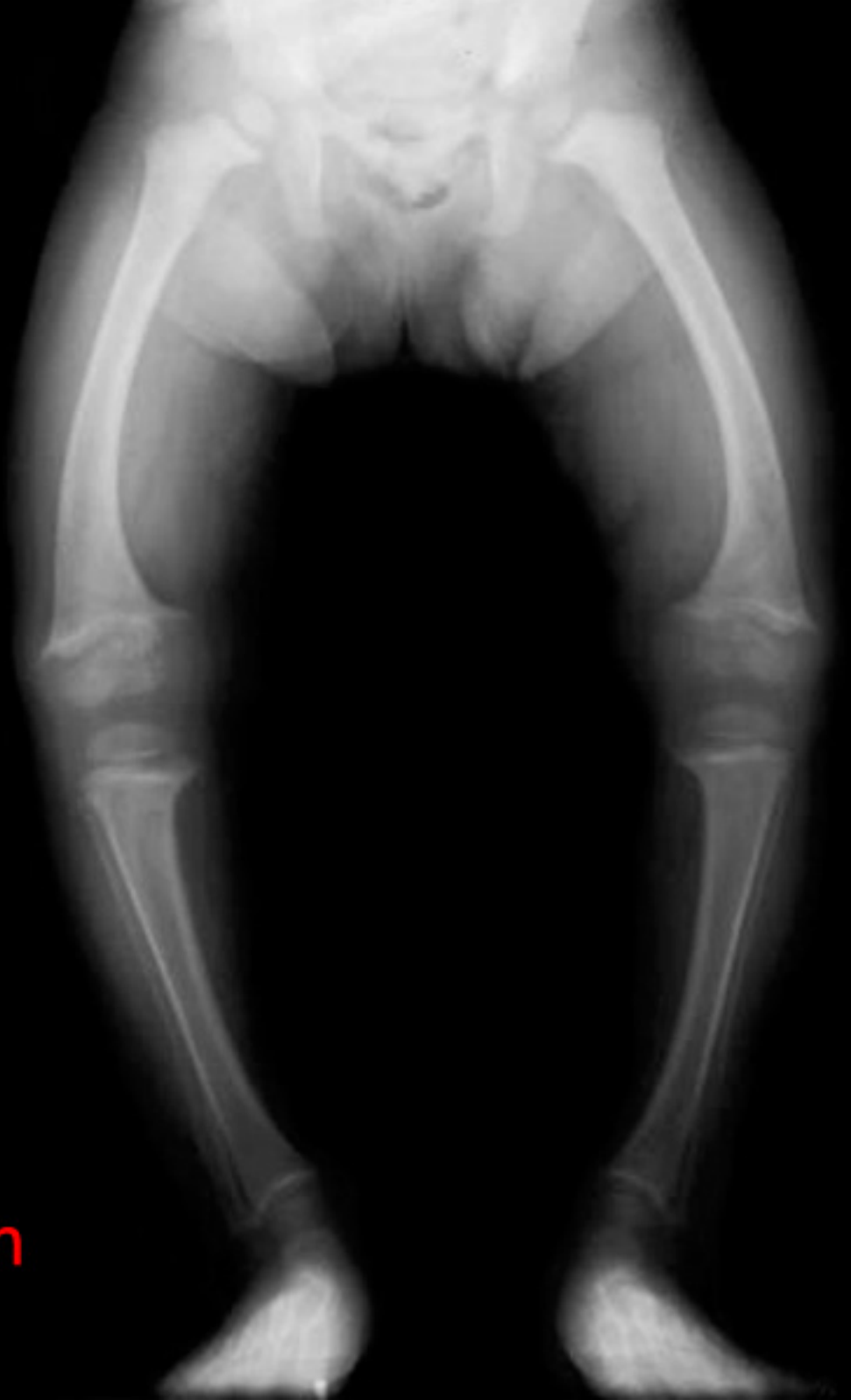
Nutrition Deficiency Disorders



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Introduction

Nutrition disorder

MeSH D009748

Nutritional Diseases are diseases in humans that are directly or indirectly caused by a lack of essential nutrients in the diet. Nutritional diseases are commonly associated with chronic malnutrition. Additionally, conditions such as obesity from overeating can also cause, or contribute to, serious health problems. Excessive intake of some nutrients can cause acute poisoning.

Overnutrition

Metabolic

Obesity is caused by consuming too many calories compared to the amount of exercise the body is performing, causing a distorted energy balance. It can lead to diseases such as cardiovascular disease and diabetes. Obesity is a condition in which the natural energy reserve, stored in the fatty tissue of humans and other mammals, is increased to a point where it is associated with certain health conditions or increased mortality.

The low-cost food that is generally affordable to the poor in affluent nations is low in nutritional value and high in fats, sugars and additives. In rich countries, therefore, obesity is oftentimes a sign of poverty and malnutrition while in poorer countries obesity is more associated with wealth and good nutrition. Other non-nutritional causes for unhealthy obesity included: sleep deprivation, stress, lack of exercise, and heredity.

Acute overeating can also be a symptom of an eating disorder.

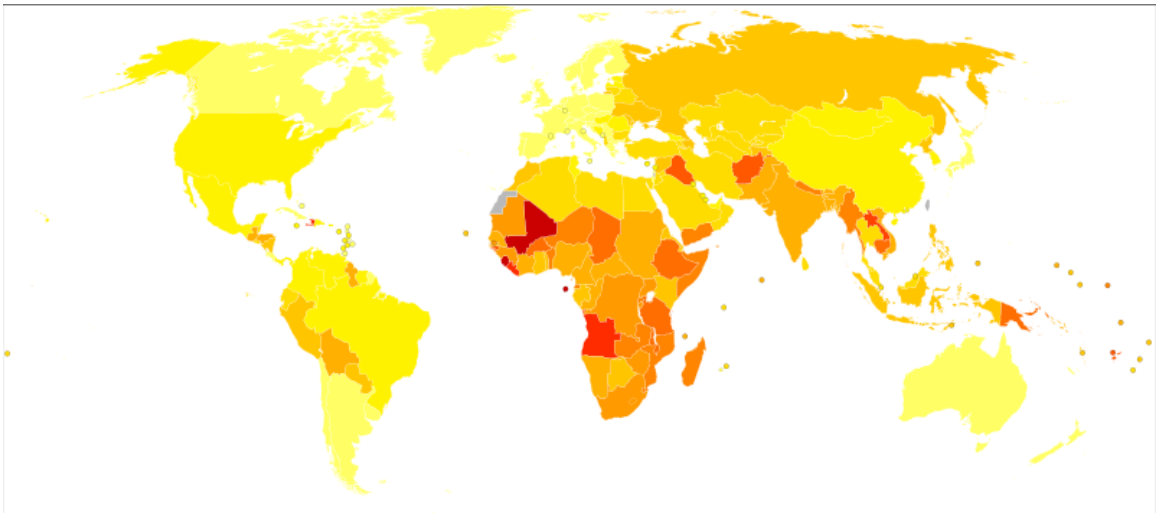
Goitrogenic foods can cause goitres by interfering with iodine uptake.

Vitamins and micronutrients

Vitamin poisoning is the condition of overly high storage levels of vitamins, which can lead to toxic symptoms. The medical names of the different conditions are derived from the vitamin involved: an excess of vitamin A, for example, is called "hypervitaminosis A".

Iron overload disorders are diseases caused by the overaccumulation of iron in the body. Organs commonly affected are the liver, heart and endocrine glands.

Deficiencies



Disability-adjusted life year for nutritional deficiencies per 100,000 inhabitants in 2002. Nutritional deficiencies included: protein-energy malnutrition, iodine deficiency, vitamin A deficiency, and iron deficiency anaemia.

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- 150-300
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- 450-600
- 600-750
- 750-900
- 900-1050
- 1050-1200
- 1200-1350
- 1350-1500
- 1500-1750
- more than 1750

Proteins/fats/carbohydrates

- Protein-energy malnutrition
  - Kwashiorkor
  - Marasmus
  - Mental retardation

Dietary vitamins and minerals

- Calcium
  - Osteoporosis
  - Rickets
  - Tetany
- Iodine deficiency
  - Goiter
- Selenium deficiency
  - Keshan disease
- Iron deficiency
  - Iron deficiency anemia
- Zinc
  - Growth retardation
- Thiamine (Vitamin B_1)
  - Beriberi
- Niacin (Vitamin B_3)
  - Pellagra
- Vitamin C
  - Scurvy
- Vitamin D
  - Osteoporosis
  - Rickets

Complex disorders

In some cases, eating too much of one thing can induce an apparent deficiency of something else. A common example occurs when livestock eat locoweed: locoweed contains a toxin that inhibits enzymes, simulating a deficiency of the enzymes.

Chapter 1

Malnutrition

Malnutrition

The orange ribbon—an awareness ribbon for malnutrition.

ICD-9	263.9
eMedicine	ped/1360
MeSH	D044342

Malnutrition is the condition that results from taking an unbalanced diet in which certain nutrients are lacking, in excess (too high an intake), or in the wrong proportions. A number of different nutrition disorders may arise, depending on which nutrients are under or overabundant in the diet.

The World Health Organization cites malnutrition as the gravest single threat to the world's public health. Improving nutrition is widely regarded as the most effective form of aid. Emergency measures include providing deficient micronutrients through fortified

sachet powders, such as peanut butter, or directly through supplements. The famine relief model increasingly used by aid groups calls for giving cash or cash vouchers to the hungry to pay local farmers instead of buying food from donor countries, often required by law, as it wastes money on transport costs.

Long term measures include investing in modern agriculture in places that lack them, such as fertilizers and irrigation, which largely eradicated hunger in the developed world. However, World Bank strictures restrict government subsidies for farmers and the spread of fertilizer use is hampered by some environmental groups.

Effects

Mortality

According to Jean Ziegler (the United Nations Special Rapporteur on the Right to Food for 2000 to March 2008), mortality due to malnutrition accounted for 58% of the total mortality in 2006: "In the world, approximately 62 million people, all causes of death combined, die each year. One in twelve people worldwide is malnourished. In 2006, more than 36 million died of hunger or diseases due to deficiencies in micronutrients".

According to the World Health Organization, malnutrition is by far the biggest contributor to child mortality, present in half of all cases. Underweight births and inter-uterine growth restrictions cause 2.2 million child deaths a year. Poor or non-existent breastfeeding causes another 1.4 million. Other deficiencies, such as lack of vitamin A or zinc, for example, account for 1 million. Malnutrition in the first two years is irreversible. Malnourished children grow up with worse health and lower educational achievements. Their own children also tend to be smaller. Malnutrition was previously seen as something that exacerbates the problems of diseases as measles, pneumonia and diarrhea. But malnutrition actually causes diseases as well, and can be fatal in its own right.

Illness

Malnutrition increases the risk of infection and infectious disease; for example, it is a major risk factor in the onset of active tuberculosis. In communities or areas that lack access to safe drinking water, these additional health risks present a critical problem. Lower energy and impaired function of the brain also represent the downward spiral of malnutrition as victims are less able to perform the tasks they need to in order to acquire food, earn an income, or gain an education.

Nutrients	Deficiency	Excess
Food energy	Starvation, Marasmus	Obesity, diabetes mellitus, Cardiovascular disease
Simple carbohydrates	none	diabetes mellitus, Obesity

Complex carbohydrates	none	Obesity
Saturated fat	low sex hormone levels	Cardiovascular disease
Trans fat	none	Cardiovascular Disease
Unsaturated fat	none	Obesity
Fat	Malabsorption of Fat-soluble vitamins, Rabbit Starvation (If protein intake is high)	Cardiovascular Disease (claimed by some)
Omega 3 Fats	Cardiovascular Disease	Bleeding, Haemorrhages
Omega 6 Fats	none	Cardiovascular Disease, Cancer
Cholesterol	none	Cardiovascular disease
Protein	kwashiorkor	Rabbit starvation
Sodium	hyponatremia	Hypernatremia, hypertension
Iron	Anemia	Cirrhosis, heart disease
Iodine	Goiter, hypothyroidism	Iodine Toxicity (goiter, hypothyroidism)
Vitamin A	Xerophthalmia and Night Blindness, low testosterone levels	Hypervitaminosis A (cirrhosis, hair loss)
Vitamin B_1	Beri-Beri	
Vitamin B_2	Cracking of skin and Corneal Ulceration	
Vitamin B_3 (Niacin)	Pellagra	dyspepsia, cardiac arrhythmias, birth defects
Vitamin B_{12}	Pernicious anemia	
Vitamin C	Scurvy	diarrhea causing dehydration
Vitamin D	Rickets	Hypervitaminosis D (dehydration, vomiting, constipation)
Vitamin E	nervous disorders	Hypervitaminosis E (anticoagulant: excessive bleeding)
Vitamin K	Haemorrhage	
Calcium	Osteoporosis, tetany, carpopedal spasm, laryngospasm, cardiac arrhythmias	Fatigue, depression, confusion, anorexia, nausea, vomiting, constipation, pancreatitis, increased urination
Magnesium	Hypertension	Weakness, nausea, vomiting, impaired breathing, and hypotension

Potassium	Hypokalemia, cardiac arrhythmias	Hyperkalemia, palpitations

Psychological

Malnutrition, in the form of iodine deficiency, is "the most common preventable cause of mental impairment worldwide." Even moderate iodine deficiency, especially in pregnant women and infants, lowers intelligence by 10 to 15 I.Q. points, shaving incalculable potential off a nation's development. The most visible and severe effects — disabling goiters, cretinism and dwarfism — affect a tiny minority, usually in mountain villages. But 16 percent of the world's people have at least mild goiter, a swollen thyroid gland in the neck.

Research indicates that improving the awareness of nutritious meal choices and establishing long-term habits of healthy eating has a positive effect on a cognitive and spatial memory capacity, potentially increasing a student's potential to process and retain academic information.

Some organizations have begun working with teachers, policymakers, and managed foodservice contractors to mandate improved nutritional content and increased nutritional resources in school cafeterias from primary to university level institutions. Health and nutrition have been proven to have close links with overall educational success. Currently less than 10% of American college students report that they eat the recommended five servings of fruit and vegetables daily. Better nutrition has been shown to have an impact on both cognitive and spatial memory performance; a study showed those with higher blood sugar levels performed better on certain memory tests. In another study, those who consumed yogurt performed better on thinking tasks when compared to those who consumed caffeine free diet soda or confections. Nutritional deficiencies have been shown to have a negative effect on learning behavior in mice as far back as 1951.

"Better learning performance is associated with diet induced effects on learning and memory ability".

The "nutrition-learning nexus" demonstrates the correlation between diet and learning and has application in a higher education setting.

"We find that better nourished children perform significantly better in school, partly because they enter school earlier and thus have more time to learn but mostly because of greater learning productivity per year of schooling."
91% of college students feel that they are in good health while only 7% eat their recommended daily allowance of fruits and vegetables.
Nutritional education is an effective and workable model in a higher education setting.
More "engaged" learning models that encompass nutrition is an idea that is picking up steam at all levels of the learning cycle.

There is limited research available that directly links a student's Grade Point Average (G.P.A.) to their overall nutritional health. Additional substantive data is needed to prove that overall intellectual health is closely linked to a person's diet, rather than just another correlation fallacy.

Nutritional supplement treatment may be appropriate for major depression, bipolar disorder, schizophrenia, and obsessive compulsive disorder, the four most common mental disorders in developed countries. Supplements that have been studied most for mood elevation and stabilization include eicosapentaenoic acid and docosahexaenoic acid (each of which are an omega-3 fatty acid contained in fish oil, but not in flaxseed oil), vitamin B12, folic acid, and inositol.

Cancer

Cancer is now common in developing countries. According a study by the International Agency for Research on Cancer, "In the developing world, cancers of the liver, stomach and esophagus were more common, often linked to consumption of carcinogenic preserved foods, such as smoked or salted food, and parasitic infections that attack organs." Lung cancer rates are rising rapidly in poorer nations because of increased use of tobacco. Developed countries "tended to have cancers linked to affluence or a 'Western lifestyle' — cancers of the colon, rectum, breast and prostate — that can be caused by obesity, lack of exercise, diet and age."

Metabolic syndrome

Several lines of evidence indicate lifestyle-induced hyperinsulinemia and reduced insulin function (i.e. insulin resistance) as a decisive factor in many disease states. For example, hyperinsulinemia and insulin resistance are strongly linked to chronic inflammation, which in turn is strongly linked to a variety of adverse developments such as arterial microinjuries and clot formation (i.e. heart disease) and exaggerated cell division (i.e. cancer). Hyperinsulinemia and insulin resistance (the so-called metabolic syndrome) are characterized by a combination of abdominal obesity, elevated blood sugar, elevated blood pressure, elevated blood triglycerides, and reduced HDL cholesterol. The negative impact of hyperinsulinemia on prostaglandin PGE1/PGE2 balance may be significant.

The state of obesity clearly contributes to insulin resistance, which in turn can cause type 2 diabetes. Virtually all obese and most type 2 diabetic individuals have marked insulin resistance. Although the association between overweight and insulin resistance is clear, the exact (likely multifarious) causes of insulin resistance remain less clear. Importantly, it has been demonstrated that appropriate exercise, more regular food intake and reducing glycemic load all can reverse insulin resistance in overweight individuals (and thereby lower blood sugar levels in those who have type 2 diabetes).

Obesity can unfavourably alter hormonal and metabolic status via resistance to the hormone leptin, and a vicious cycle may occur in which insulin/leptin resistance and obesity aggravate one another. The vicious cycle is putatively fuelled by continuously

high insulin/leptin stimulation and fat storage, as a result of high intake of strongly insulin/leptin stimulating foods and energy. Both insulin and leptin normally function as satiety signals to the hypothalamus in the brain; however, insulin/leptin resistance may reduce this signal and therefore allow continued overfeeding despite large body fat stores. In addition, reduced leptin signalling to the brain may reduce leptin's normal effect to maintain an appropriately high metabolic rate.

There is a debate about how and to what extent different dietary factors— such as intake of processed carbohydrates, total protein, fat, and carbohydrate intake, intake of saturated and trans fatty acids, and low intake of vitamins/minerals—contribute to the development of insulin and leptin resistance. In any case, analogous to the way modern man-made pollution may potentially overwhelm the environment's ability to maintain homeostasis, the recent explosive introduction of high glycemic index and processed foods into the human diet may potentially overwhelm the body's ability to maintain homeostasis and health (as evidenced by the metabolic syndrome epidemic).

Hyponatremia

Excess water intake, without replenishment of sodium and potassium salts, leads to hyponatremia, which can further lead to water intoxication at more dangerous levels. A well-publicized case occurred in 2007, when Jennifer Strange died while participating in a water-drinking contest. More usually, the condition occurs in long-distance endurance events (such as marathon or triathlon competition and training) and causes gradual mental dulling, headache, drowsiness, weakness, and confusion; extreme cases may result in coma, convulsions, and death. The primary damage comes from swelling of the brain, caused by increased osmosis as blood salinity decreases. Effective fluid replacement techniques include Water aid stations during running/cycling races, trainers providing water during team games such as Soccer and devices such as Camel Baks which can provide water for a person without making it too hard to drink the water.

Causes

Major causes of malnutrition include poverty and food prices, dietary practices and agricultural productivity, with many individual cases being a mixture of several factors. Malnutrition can also be a consequence of other health issues such as diarrheal disease or chronic illness, especially the HIV/AIDS pandemic Clinical malnutrition, such as in cachexia, is a major burden also in developed countries.

Poverty and food prices

As much as food shortages may be a contributing factor to malnutrition in countries with lack of technology, the FAO (Food and Agriculture Organization) has estimated that eighty percent of malnourished children living in the developing world live in countries that produce food surpluses. The economist Amartya Sen observed that, in recent decades, famine has always a problem of food distribution and/or poverty, as there has

been sufficient food to feed the whole population of the world. He states that malnutrition and famine were more related to problems of food distribution and purchasing power.

It is argued that commodity speculators are increasing the cost of food. As the real estate bubble in the United States was collapsing, it is said that trillions of dollars moved to invest in food and primary commodities, causing the 2007-2008 food price crisis.

The use of biofuels as a replacement for traditional fuels may leave less supply of food for nutrition and raises the price of food. The United Nations special rapporteur on the right to food, Jean Ziegler proposes that agricultural waste, such as corn cobs and banana leaves, rather than crops themselves be used as fuel.

Dietary practices

A lack of breastfeeding can lead to malnutrition in infants and children. Possible reasons for the lack in the developing world may be that the average family thinks bottle feeding is better. The WHO says mothers abandon it because they do not know how to get their baby to latch on properly or suffer pain and discomfort.

Deriving too much of one's diet from a single source, such as eating almost exclusively corn or rice, can cause malnutrition. This may either be from a lack of education about proper nutrition, or from only having access to a single food source.

Many tend to think malnutrition only in terms of hunger, however, overeating is also a contributing factor as well. Many parts of the world have access to a surplus of non-nutritious food, in addition to increased sedentary lifestyles. In turn, this has created a universal epidemic of obesity. Yale psychologist Kelly Brownell calls this a "toxic food environment" where fat and sugar laden foods have taken precedent over healthy nutritious foods. Not only does obesity occur in developed countries, problems are also occurring in developing countries in areas where income is on the rise.

Agricultural productivity

Food shortages can be caused by a lack of farming skills such as crop rotation, or by a lack of technology or resources needed for the higher yields found in modern agriculture, such as nitrogen fertilizers, pesticides and irrigation. As a result of widespread poverty, farmers cannot afford or governments cannot provide the technology. The World Bank and some wealthy donor countries also press nations that depend on aid to cut or eliminate subsidized agricultural inputs such as fertilizer, in the name of free market policies even as the United States and Europe extensively subsidized their own farmers. Many, if not most, farmers cannot afford fertilizer at market prices, leading to low agricultural production and wages and high, unaffordable food prices.

An 18-month old Afghan girl, weighing approximately 14 pounds, is treated by a US Army medical team in Paktya province.

Reasons for the unavailability of fertilizer include moves to stop supplying fertilizer on environmental grounds, cited as the obstacle to feeding Africa by the Green Revolution pioneer Norman Borlaug.

Future threats

There are a number of potential disruptions to global food supply that could cause widespread malnutrition.

Climate change is of great importance to food security. With 95% of all malnourished peoples living in the relatively stable climate region of the sub-tropics and tropics. According to the latest IPCC reports, temperature increases in these regions are "very likely." Even small changes in temperatures can lead to increased frequency of extreme weather conditions. Many of these have great impact on agricultural production and hence nutrition. For example, the 1998-2001 central Asian drought brought about an 80% livestock loss and 50% reduction in wheat and barley crops in Iran. Similar figures were present in other nations. An increase in extreme weather such as drought in regions such as Sub-Saharan would have even greater consequences in terms of malnutrition. Even without an increase of extreme weather events, a simple increase in temperature reduces the productiveness of many crop species, also decreasing food security in these regions.

Colony collapse disorder is a phenomenon where bees are dying in large numbers. Since many agricultural crops worldwide are pollinated by bees, this represents a serious threat to the supply of food.

An epidemic of stem rust on wheat caused by race Ug99 is currently spreading across Africa and into Asia and, it is feared, could wipe out more than 80% of the world's wheat crops.

Management

Fighting malnutrition, mostly through fortifying foods with micronutrients (vitamins and minerals), improves lives at a lower cost and shorter time than other forms of aid, according to the World Bank. The Copenhagen Consensus, which look at a variety of development proposals, ranked micronutrient supplements as number one. However, roughly $300m of aid goes to basic nutrition each year, less than $2 for each child below two in the 20 worst affected countries. In contrast, HIV/AIDS, which causes fewer deaths than child malnutrition, received $2.2 billion—$67 per person with HIV in all countries.

Emergency measures

Micronutrients can be obtained through fortifying foods. Fortifying foods such as peanut butter sachets and Spirulina have revolutionized emergency feeding in humanitarian emergencies because they can be eaten directly from the packet, do not require refrigeration or mixing with scarce clean water, can be stored for years and ,vitally, can be absorbed by extremely ill children. The United Nations World Food Conference of 1974 declared Spirulina as 'the best food for the future' and its ready harvest every 24 hours make it a potent tool to eradicate malnutrition. Additionally, supplements, such as Vitamin A capsules or Zinc tablets to cure diarrhea in children, are used.

There is a growing realization among aid groups that giving cash or cash vouchers instead of food is a cheaper, faster, and more efficient way to deliver help to the hungry, particularly in areas where food is available but unaffordable. The UN's World Food Program, the biggest non-governmental distributor of food, announced that it will begin distributing cash and vouchers instead of food in some areas, which Josette Sheeran, the WFP's executive director, described as a "revolution" in food aid. The aid agency Concern Worldwide is piloting an method through a mobile phone operator, Safaricom, which runs a money transfer program that allows cash to be sent from one part of the country to another.

However, for people in a drought living a long way from and with limited access to markets, delivering food may be the most appropriate way to help. Fred Cuny stated that "the chances of saving lives at the outset of a relief operation are greatly reduced when food is imported. By the time it arrives in the country and gets to people, many will have died." US Law, which requires buying food at home rather than where the hungry live, is inefficient because approximately half of what is spent goes for transport. Fred Cuny further pointed out "studies of every recent famine have shown that food was available

in-country — though not always in the immediate food deficit area" and "even though by local standards the prices are too high for the poor to purchase it, it would usually be cheaper for a donor to buy the hoarded food at the inflated price than to import it from abroad." Ethiopia has been pioneering a program that has now become part of the World Bank's prescribed recipe for coping with a food crisis and had been seen by aid organizations as a model of how to best help hungry nations. Through the country's main food assistance program, the Productive Safety Net Program, Ethiopia has been giving rural residents who are chronically short of food, a chance to work for food or cash. Foreign aid organizations like the World Food Program were then able to buy food locally from surplus areas to distribute in areas with a shortage of food. Not only has Ethiopia been pioneering a program but Brazil has also established a recycling program for organic waste that benefits farmers, urban poor, and the city in general. City residents separate organic waste from their garbage, bag it, and then exchange it for fresh fruit and vegetables from local farmers. As a result, this reduces its countries waste and the urban poor get a steady supply of nutritious food.

Long term measures

The effort to bring modern agricultural techniques found in the West, such as nitrogen fertilizers and pesticides, to Asia, called the Green Revolution, resulted in decreases in malnutrition similar to those seen earlier in Western nations. This was possible because of existing infrastructure and institutions that are in short supply in Africa, such as a system of roads or public seed companies that made seeds available. Investments in agriculture, such as subsidized fertilizers and seeds, increases food harvest and reduces food prices. For example, in the case of Malawi, almost five million of its 13 million people used to need emergency food aid. However, after the government changed policy and subsidies for fertilizer and seed were introduced against World Bank strictures, farmers produced record-breaking corn harvests as production leaped to 3.4 million in 2007 from 1.2 million in 2005, making Malawi a major food exporter. This lowered food prices and increased wages for farm workers. Proponents for investing in agriculture include Jeffrey Sachs, who has championed the idea that wealthy countries should invest in fertilizer and seed for Africa’s farmers.

Breast-feeding education helps. Breastfeeding in the first two years and exclusive breastfeeding in the first six months could save 1.3 million children’s lives. In the longer term, firms are trying to fortify everyday foods with micronutrients that can be sold to consumers such as wheat flour for Beladi bread in Egypt or fish sauce in Vietnam and the iodization of salt.

Restricting population size is a proposed solution. Thomas Malthus argued that population growth could be controlled by natural disasters and voluntary limits through “moral restraint.” Robert Chapman suggests that an intervention through government policies is a necessary ingredient of curtailing global population growth. Garret Hardin takes an anti-immigration, isolationist approach arguing that “…all sovereign states must accept the responsibility of solving their population problems in their own territories" and that immigration acts as a sort of pressure release valve which allows countries to

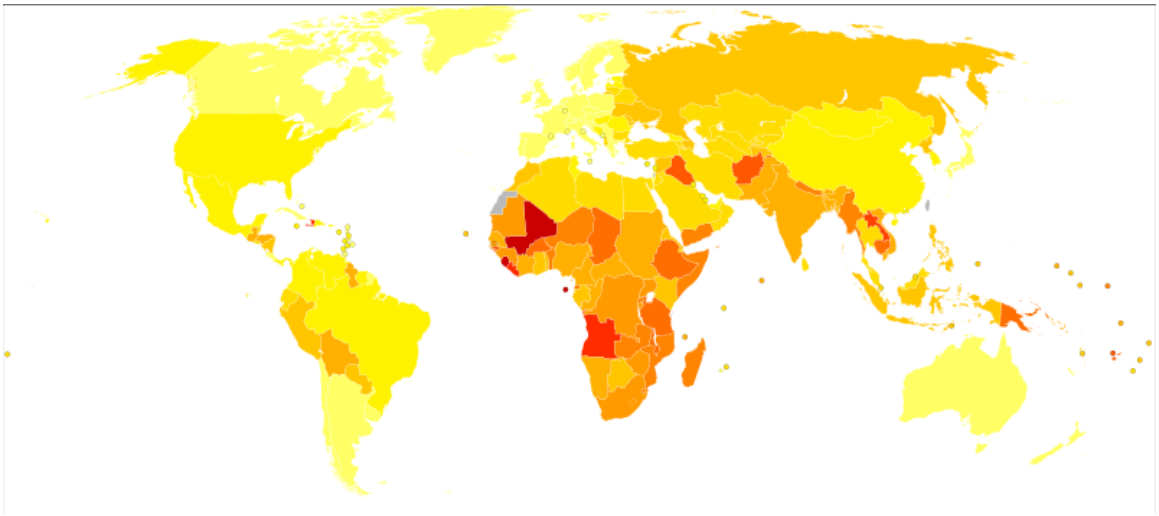
continue to ignore solving their population problems. For Amaryta Sen, “no matter how a famine is caused, methods of breaking it call for a large supply of food in the public distribution system. This applies not only to organizing rationing and control, but also to undertaking work programmes and other methods of increasing purchasing power for those hit by shifts in exchange entitlements in a general inflationary situation.” One suggested policy framework to resolve access issues is termed food sovereignty, the right of peoples to define their own food, agriculture, livestock, and fisheries systems in contrast to having food largely subjected to international market forces. Food First is one of the primary think tanks working to build support for food sovereignty. Neoliberals advocate for an increasing role of the free market. The World Bank itself claims to be part of the solution to malnutrition, asserting that the best way for countries to succeed in breaking the cycle of poverty and malnutrition is to build export-led economies that will give them the financial means to buy foodstuffs on the world market.

When aiming to prevent rather than treat overeating, which is also a form of malnutrition, starting in the school environment would be the perfect place as this is where the education children receive today will help them choose healthier foods during childhood, as well as into adulthood. As seen in Singapore, if we increase nutrition in school lunch programs and physical activity for children and teachers, obesity can be reduced by almost 30-50%.

Some initiatives have been done to reduce malnutrition, especially hunger. A great example has been done by Muhammad Yunus called The Grameen Bank to combat hunger. It provides small loans to help very poor women generate income and those loans can lift women out of poverty, and yet yield nutritional benefits. Some studies show when a woman is provided with an income, she will spend nearly all of it on household needs, especially food. Therefore, by focusing on women empowerment, poverty can be reduced, and also malnutrition, especially hunger can be fought.

Micro-credit initiatives focus predominantly on women because hunger disproportionately affects females more so than males. By targeting women, micro-credit initiatives strive to reduce malnutrition by promoting both employment and educational opportunities. If women are able to receive employment, they can then earn enough money to feed themselves and their families. Furthermore, if we allow girls the chance to become educated they can hopefully achieve a more equal status with men, and therefore, reduce a gender bias that men require more food than women. Ultimately, with the presence of micro-credit initiatives we can hopefully reduce the number of women who are malnourished throughout the world.

Epidemiology



Disability-adjusted life year for nutritional deficiencies per 100,000 inhabitants in 2002. Nutritional deficiencies included: protein-energy malnutrition, iodine deficiency, vitamin A deficiency, and iron deficiency anaemia.

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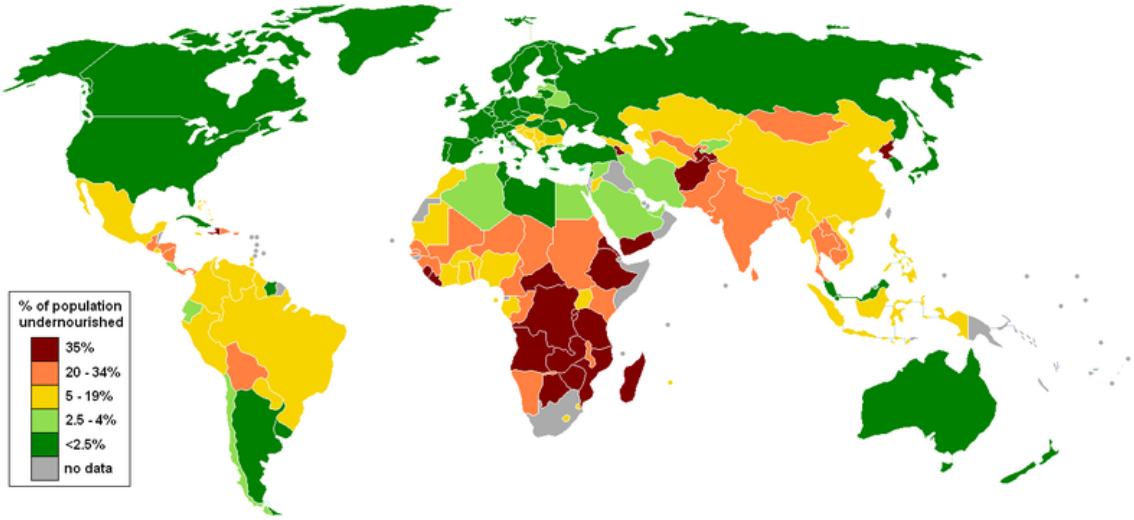
There were 925 million malnourished people in the world in 2010, an increase of 80 million since 1990, despite the fact that the world already produces enough food to feed everyone - 6 billion people - and could feed the double - 12 billion people.

Year	**1990**	**1995**	**2005**	**2008**
Malnourished people in the world (millions)	843	788	848	923

Year	**1970**	**1980**	**1990**	**2005**	**2007**
Share of malnourished people in the developing world	37 %	28 %	20 %	16 %	17 %



Percentage of population affected by undernutrition by country, according to United Nations statistics.

Number of undernourished people (million) in 2001-2003, according to the FAO, the following countries had 5 million or more undernourished people :

Country	Number of Undernourished (million)
India	217.05
China	154.0
Bangladesh	43.45
Democratic Republic of Congo	37.0
Pakistan	35.2
Ethiopia	31.5
Tanzania	16.1
Philippines	15.2
Brazil	14.4
Indonesia	13.8
Vietnam	13.8
Thailand	13.4
Nigeria	11.5
Kenya	9.7
Sudan	8.8
Mozambique	8.3
North Korea	7.9

Yemen	7.1
Madagascar	7.1
Colombia	5.9
Zimbabwe	5.7
Mexico	5.1
Zambia	5.1
Angola	5.0

Note: This table measures "undernourishment", as defined by FAO, and represents the number of people consuming (on average for years 2001 to 2003) less than the minimum amount of food energy (measured in kilocalories per capita per day) necessary for the average person to stay in good health while performing light physical activity. It is a conservative indicator that does not take into account the extra needs of people performing extraneous physical activity, nor seasonal variations in food consumption or other sources of variability such as inter-individual differences in energy requirements.

Malnutrition and undernourishment are cumulative or average situations, and not the work of a single day's food intake (or lack thereof). This table does not represent the number of people who "went to bed hungry today."

Various scales of analysis also have to be considered in order to determine the sociopolitical causes of malnutrition. For example, the population of a community may be at risk if it lacks health-related services, but on a smaller scale certain households or individuals may be at even higher risk due to differences in income levels, access to land, or levels of education. Also within the household, there may be differences in levels of malnutrition between men and women, and these differences have been shown to vary significantly from one region to another with problem areas showing relative deprivation of women. Children and the elderly tend to be especially susceptible. Approximately 27 percent of children under 5 in developing world are malnourished, and in these developing countries, malnutrition claims about half of the 10 million deaths each year of children under 5.

Middle East

Malnutrition rates in Iraq had risen from 19% before the US-led invasion to a national average of 28% four years later.

South Asia

According to the Global Hunger Index, South Asia has the highest child malnutrition rate of world's regions. India contributes to about 5.6 million child deaths every year, more than half the world's total. The 2006 report mentioned that "the low status of women in South Asian countries and their lack of nutritional knowledge are important determinants of high prevalence of underweight children in the region" and was concerned that South Asia has "inadequate feeding and caring practices for young children".

Half of children in India are underweight, one of the highest rates in the world and nearly double the rate of Sub-Saharan Africa.

Research on overcoming persistent under-nutrition published by the Institute of Development Studies, argues that the co-existence of India as an 'economic powerhouse' and home to one-third of the world's under-nourished children reflects a failure of the governance of nutrition: "A poor capacity to deliver the right services at the right time to the right populations, an inability to respond to citizens' needs and weak accountability are all features of weak nutrition governance." The research suggests that to make under-nutrition history in India the governance of nutrition needs to be strengthened and new research needs to focus on the politics and governance of nutrition. At the current rate of progress the MDG1 target for nutrition will only be reached in 2042 with severe consequences for human wellbeing and economic growth.

United States

Childhood malnutrition is generally thought of as being limited to developing countries, but although most malnutrition occurs there, it is also an ongoing presence in developed nations. For example, in the United States of America, one out of every six children is at risk of hunger. A study, based on 2005-2007 data from the U.S. Census Bureau and the Agriculture Department, shows that an estimated 3.5 million children under the age of five are at risk of hunger in the United States. In developed countries, this persistent hunger problem is not due to lack of food or food programs, but is largely due to an underutilization of existing programs designed to address the issue, such as food stamps or school meals. Many citizens of rich countries such as the United States of America attach stigmas to food programs or otherwise discourage their use. In the USA, only 60% of those eligible for the food stamp program actually receive benefits. The U.S. Department of Agriculture reported that in 2003, only 1 out of 200 U.S. households with children became so severely food insecure that any of the children went hungry even once during the year. A substantially larger proportion of these same households (3.8 percent) had adult members who were hungry at least one day during the year because of their households' inability to afford enough food.

Overeating vs. Hunger

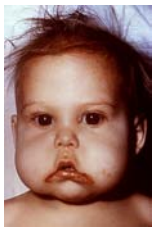
Although a lot of the focus regarding malnutrition centers around undernourishment, overeating is also a form of malnutrition. Overeating is much more common in the United States, where for the majority of people, access to food is not an issue. The issue in these developed countries is choosing the right kind of food. Fast food is consumed more per capita in the United States than in any other country. The reason for this mass consumption of food is the affordability and accessibility. Oftentimes the fast food, low in cost and nutrition, are high in calories and heavily promoted. When these eating habits are combined with increasingly urbanized, automated, and more sedentary lifestyles, it becomes clear why gaining weight is difficult to avoid. However, overeating is also a problem in countries where hunger and poverty persist. In China consumption of high-fat foods have increased while consumption of rice and other goods have decreased.

Overeating and hunger are equally serious issues depending on what part of the world you live in. Overeating leads to many diseases such as, heart disease and diabetes, that result in death. To aid in fixing this issue of overeating, health care could recognize obesity as a disease and cover weight-loss and other nutritional interventions. An encouraging first step in this direction is Mutual of Omaha's decision to cover intensive dietary and lifestyle modification program of patients with heart disease, an initiative they hope will eliminate costly prescriptions and prevent surgeries months or years down the road. A logical next step for the industry might be to cover regular nutrition checkups, akin to dental check-ups, as part of a basic insurance coverage.

Chapter 2

Kwashiorkor

Kwashiorkor



Kwashiorkor

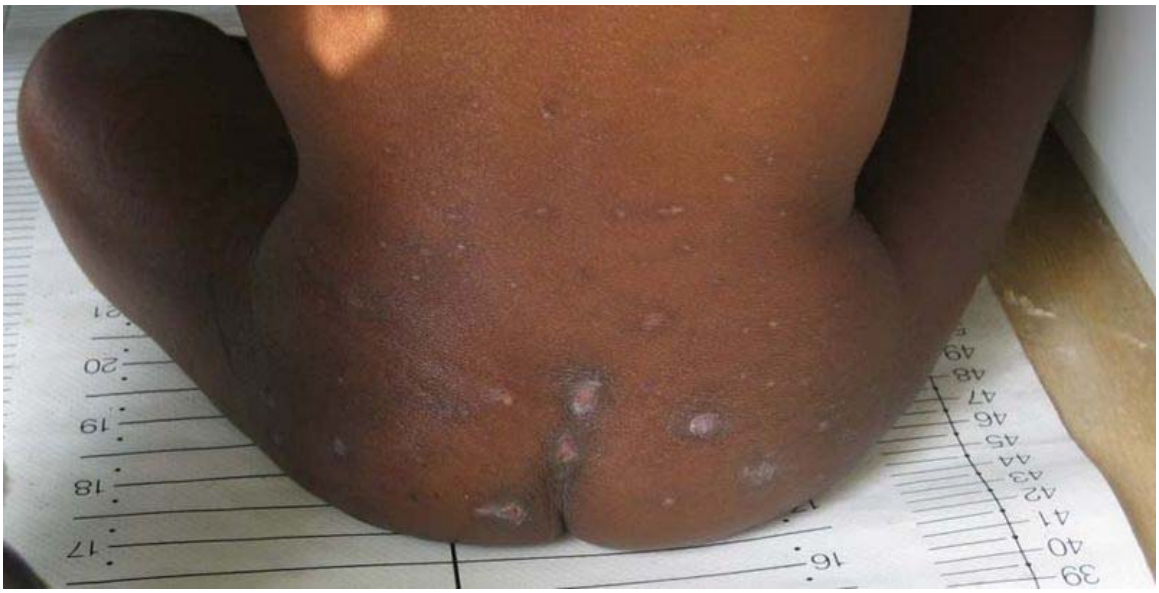
ICD-10	E40., E42.
ICD-9	260
DiseasesDB	7211
MeSH	*D007732*

Kwashiorkor is an acute form of childhood protein-energy malnutrition characterized by edema, irritability, anorexia, ulcerating dermatoses, and an enlarged liver with fatty infiltrates. The presence of edema caused by poor nutrition defines kwashiorkor. Kwashiorkor was thought to be caused by insufficient protein consumption but with sufficient calorie intake, distinguishing it from marasmus. More recently, micronutrient and antioxidant deficiencies have come to be recognized as contributory. Cases in the developed world are rare.

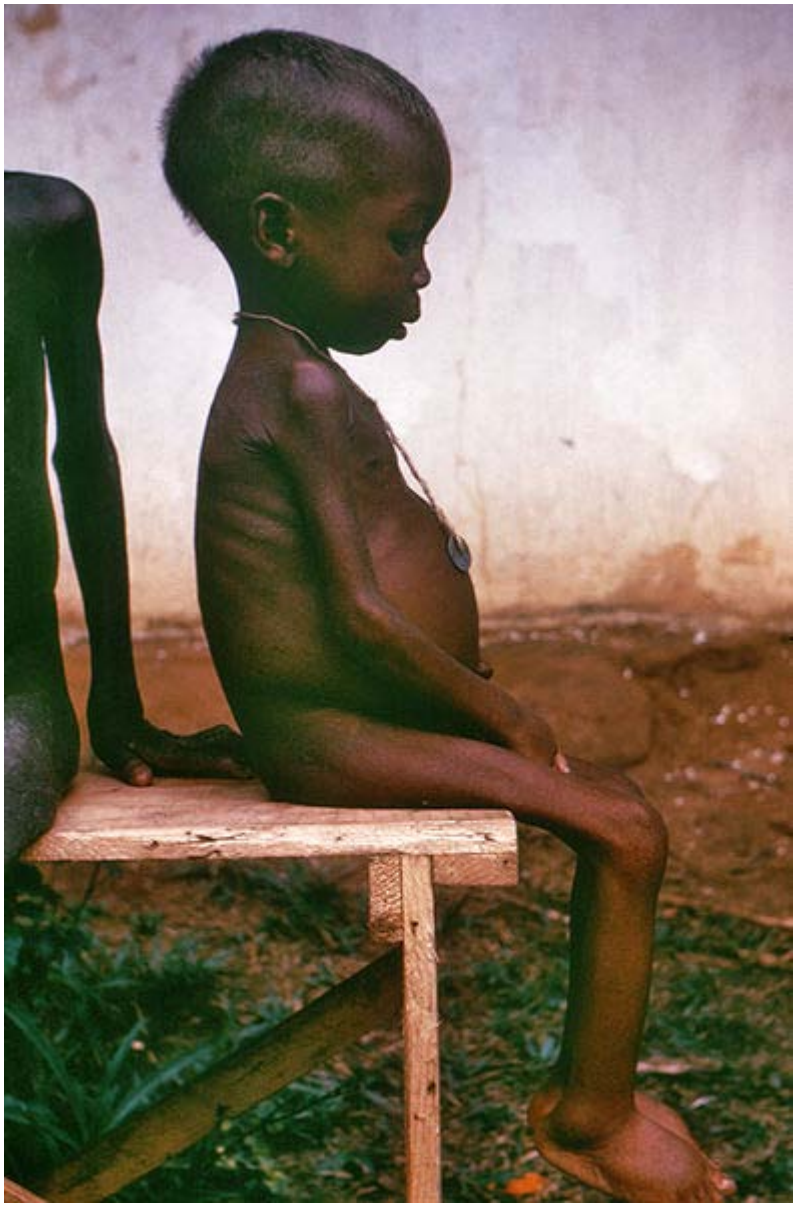
Jamaican pediatrician Dr. Cicely D. Williams introduced the name into the medical community in her 1935 Lancet article. The name is derived from the Ga language of coastal Ghana, translated "the sickness the baby gets when the new baby comes", and reflecting the development of the condition in an older child who has been weaned from the breast when a younger sibling comes. Breast milk contains proteins and amino acids vital to a child's growth. In at-risk populations, kwashiorkor may develop after a mother

weans her child from breast milk, replacing it with a diet high in carbohydrates, especially starches, but deficient in protein.

Signs and symptoms



Typical ulcerating dermatosis seen on a Malawian patient with kwashiorkor.



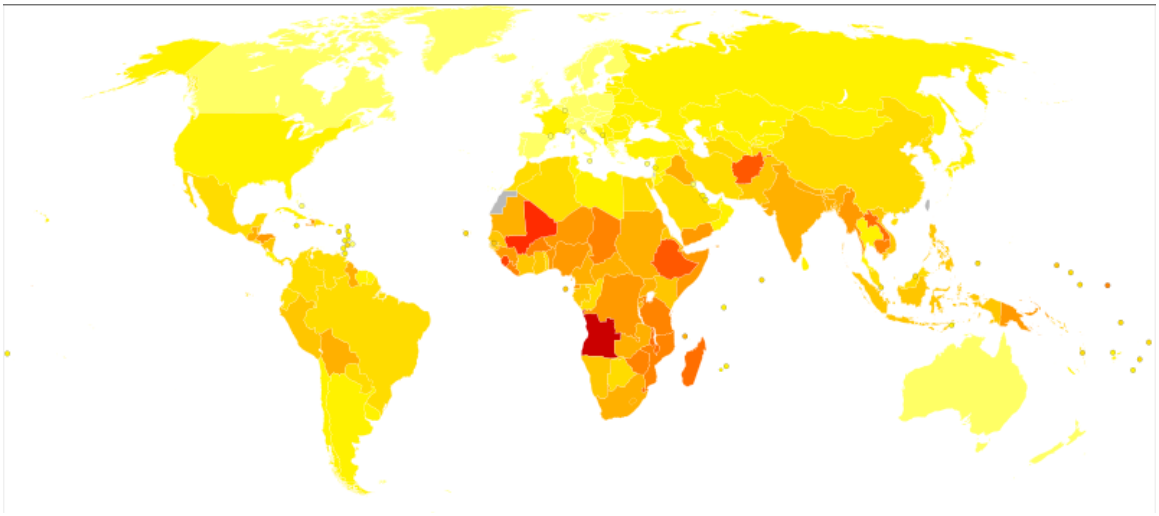
One of many kwashiorkor cases in relief camps during the Nigerian–Biafran War.

The defining sign of kwashiorkor in a malnourished child is pedal edema (swelling of the feet). Other signs include a distended abdomen, an enlarged liver with fatty infiltrates, thinning hair, loss of teeth, skin depigmentation and dermatitis. Children with kwashiorkor often develop irritability and anorexia.

Victims of kwashiorkor fail to produce antibodies following vaccination against diseases, including diphtheria and typhoid. Generally, the disease can be treated by adding food energy and protein to the diet; however, it can have a long-term impact on a child's physical and mental development, and in severe cases may lead to death.

In dry climates, marasmus is the more frequent disease associated with malnutrition. Another malnutrition syndrome includes cachexia, although it is often caused by underlying illnesses. These are important considerations in the treatment of the patients. Kwashiorkor can lead to death. People can recover from the illness by having a gradual build up of nutrients, but they will not grow properly and will probably be quite small.

Possible causes



Disability-adjusted life year for protein-energy malnutrition per 100,000 inhabitants in 2002.

- no data
- less than 10
- 10-100
- 100-200
- 200-300
- 300-400
- 400-500
- 500-600
- 600-700
- 700-800
- 800-1000
- 1000-1350
- more than 1350

There are various explanations for the development of kwashiorkor and the topic remains controversial. It is now accepted that protein deficiency, in combination with energy and micronutrient deficiency, is necessary but not sufficient to cause kwashiorkor. The condition is likely due to deficiency of one of several types of nutrients (e.g., iron, folic acid, iodine, selenium, vitamin C), particularly those involved with anti-oxidant protection. Important anti-oxidants in the body that are reduced in children with kwashiorkor include glutathione, albumin, vitamin E and polyunsaturated fatty acids.

Therefore, if a child with reduced type one nutrients or anti-oxidants is exposed to stress (e.g. an infection or toxin) he/she is more liable to develop kwashiorkor.

Ignorance of nutrition can be a cause. Dr. Latham, director of the Program in International Nutrition at Cornell University cited a case where parents who fed their child cassava failed to recognize malnutrition because of the edema caused by the syndrome and insisted the child was well-nourished despite the lack of dietary protein.

One important factor in the development of kwashiorkor is aflatoxin poisoning. Aflatoxins are produced by molds and ingested with moldy foods. They are toxified by the cytochrome P450 system in the liver, the resulting epoxides damage liver DNA. Since many serum proteins, in particular albumin, are produced in the liver, the symptoms of kwashiorkor are easily explained. It is noteworthy that kwashiorkor occurs mostly in warm, humid climates that encourage mold growth.

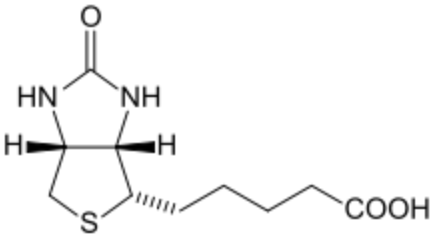
Protein should be supplied only for anabolic purposes. The catabolic needs should be satisfied with carbohydrate and fat. Protein catabolism involves the urea cycle, which is located in the liver and can easily overwhelm the capacity of an already damaged organ. The resulting liver failure can be fatal.

Chapter 3

Biotin Deficiency and Folate Deficiency

Biotin deficiency

Biotin deficiency



Biotin

ICD-10	E53.8
ICD-9	266.2
eMedicine	ped/238

Biotin deficiency is a rare nutritional disorder which can become serious, even fatal, if allowed to progress untreated. It can occur in people of any age, ancestry, or gender.

Biotin deficiency rarely occurs among healthy people, since the daily requirement of biotin is low, many foods provide adequate amounts of it, intestinal bacteria synthesize small amounts of it, and the body effectively scavenges and recycles it from bodily waste. However, deficiencies can be caused by consuming raw egg whites over a period of months to years. Egg whites contain high levels of avidin, a protein that binds biotin strongly. When cooked, avidin is denatured and becomes entirely non-toxic.

Causes

Causes of biotin deficiency include the following:

1. Eating raw egg whites: Some mistakenly believe that raw egg-white consumption is the only cause of biotin deficiency. Nonetheless, a diet that contains raw egg whites quickly and almost invariably leads to biotin deficiency.
2. Total parenteral nutrition without biotin supplementation: Several cases of biotin deficiency in patients receiving prolonged total parenteral nutrition (TPN) therapy without added biotin have been reported. Therefore, all patients receiving TPN must also receive biotin at the recommended daily dose, especially if TPN therapy is expected to last more than 1 week. All hospital pharmacies currently include biotin in TPN preparations.
3. Anticonvulsant therapy: Prolonged use of certain drugs, especially phenytoin, primidone, and carbamazepine, may lead to biotin deficiency; however, valproic acid therapy does not cause this condition. Some anticonvulsants inhibit biotin transport across the intestinal mucosa. Evidence suggests that these anticonvulsants accelerate biotin catabolism. Therefore, supplemental biotin, in addition to the usual minimum daily requirements, has been suggested for patients who are treated with anticonvulsants that have been linked to biotin deficiency.
4. Prolonged oral antibiotic therapy: Prolonged use of oral antibiotics has been associated with biotin deficiency. Alterations in the intestinal flora caused by the prolonged administration of antibiotics are presumed to be the basis for biotin deficiency.
5. Genetic mutation: Mikati et al (2006) reported a case of partial biotinidase deficiency (plasma biotinidase level of 1.3 nm/min/mL) in a 7-month-old boy.8 The boy presented with perinatal distress followed by developmental delay, hypotonia, seizures, and infantile spasms without alopecia or dermatitis. The child's neurologic symptoms abated following biotin supplementation and antiepileptic drug therapy. DNA mutational analysis revealed that the child was homozygous for a novel E64K mutation and that his mother and father were heterozygous for the novel E64K mutation.

Symptoms

Initial symptoms of biotin deficiency include:

1. Dry skin
2. Seborrheic dermatitis
3. Fungal infections
4. Rashes including red, patchy ones near the mouth (erythematous periorofacial macular rash)
5. Fine and brittle hair
6. Hair loss or total baldness (alopecia)

If left untreated, neurological symptoms can develop, including:

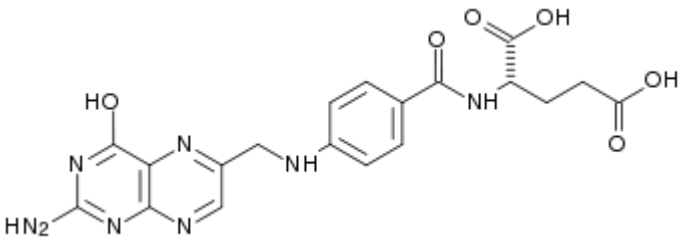
1. Mild depression, which may progress to profound lassitude and, eventually, to somnolence
2. Changes in mental status
3. Generalized muscular pains (myalgias)
4. Hyperesthesias and paresthesias

Treatment

Biotin deficiency is easily corrected by biotin tablets, which are inexpensive and readily available. If overconsumption of raw egg whites is responsible, a change in diet may be appropriate.

Folate deficiency

Folate deficiency



Folic acid (B_9)

ICD-10	D52. E53.8
ICD-9	266.2
DiseasesDB	4894
MedlinePlus	000354
eMedicine	med/802
MeSH	D005494

Folate deficiency is a lack of folic acid in the diet and the signs are often subtle. **Folate deficiency anemia** is the medical name given for the condition.

Symptoms

Loss of appetite, and weight loss can occur. Additional signs are weakness, sore tongue, headaches, heart palpitations, irritability, and behavioral disorders.

Women with folate deficiency who become pregnant are more likely to give birth to low birth weight and premature infants, and infants with neural tube defects. In adults, anemia (macrocytic, megaloblastic anemia) can be a sign of advanced folate deficiency. In infants and children, folate deficiency can slow growth rate.

Late studies suggested an involvement in tumorogenesis (especially in colon) through demethylation/hypomethylation of fast replicating tissues.

Some of the symptoms can also result from a variety of medical conditions other than folate deficiency. It is important to have a physician evaluate these symptoms so that appropriate medical care can be given.

Depression

Studies have shown that folate and vitamin B_{12} status play a role in depression. The role of vitamin B_{12} and folate in depression is due to their role in transmethylation reactions, which are crucial for the formation of neurotransmitters (e.g. serotonin, epinephrine, nicotinamides, purines, phospholipids).

Low levels of folate or vitamin B_{12} can disrupt transmethylation reaction, leading to an accumulation of homocysteine (hyperhomocisteinemia) and to impaired metabolism of neurotransmitters (especially the hydroxylation of dopamine and serotonin from tyrosine and tryptophan), phospholipids, myelin, and receptors. Hyperhomocysteinemia could also lead to vascular injuries by oxidative mechanisms which can contribute to cerebral dysfunction. All of these can lead to the development of various disorders, including depression.

Low plasma B_{12} and low plasma folate has been found in studies of depressive patients. Furthermore, some studies have shown that low folate levels are linked to a poor response of antidepressant treatment, and other studies also suggest that a high vitamin B_{12} status may be associated with better treatment outcomes. Therefore, not only does adequate consumption of these two vitamins help decrease the risks of developing depression, but they can also help in the treatment of depression when antidepressant drugs are used.

Causes

A deficiency of folate can occur when the body's need for folate is increased, when dietary intake of folate is inadequate, or when the body excretes (or loses) more folate than usual. Medications that interfere with the body's ability to use folate may also

increase the need for this vitamin. Some research indicates that exposure to ultraviolet light, including the use of tanning beds, can lead to a folic acid deficiency.

Situational

Some situations that increase the need for folate include:

- pregnancy and lactation (breastfeeding)
- tobacco smoking
- malabsorption, including celiac disease
- kidney dialysis
- liver disease
- certain anemias

Pharmacological

Medications can interfere with folate utilization, including:

- anticonvulsant medications (such as phenytoin, and primidone)
- metformin (sometimes prescribed to control blood sugar in type 2 diabetes)
- sulfasalazine (used to control inflammation associated with Crohn's disease, ulcerative colitis and rheumatoid arthritis)
- triamterene (a diuretic)
- methotrexate, an anti-cancer drug also used to control inflammation associated with Crohn's disease, ulcerative colitis and rheumatoid arthritis.

When sulfasalazine is prescribed, folic acid supplements are normally given with the sulfasalazine. The purpose of methotrexate is to inhibit dihydrofolate reductase and thereby reduce the rate *de novo* purine and pyrimidine synthesis and cell division. It may therefore be counter-productive to take a folic acid supplement with methotrexate. Although the folic acid inhibition of sulfasalazine is normally seen as a side effect, it is possible that it is a part of the therapeutic effect of the drug, given that methotrexate, a frank folic acid inhibitor, is often given if sulfasalazine fails. It would therefore be wise to consult with a physician before taking a folic acid supplement along with sulfasalazine or methotrexate.

Prevention and treatment

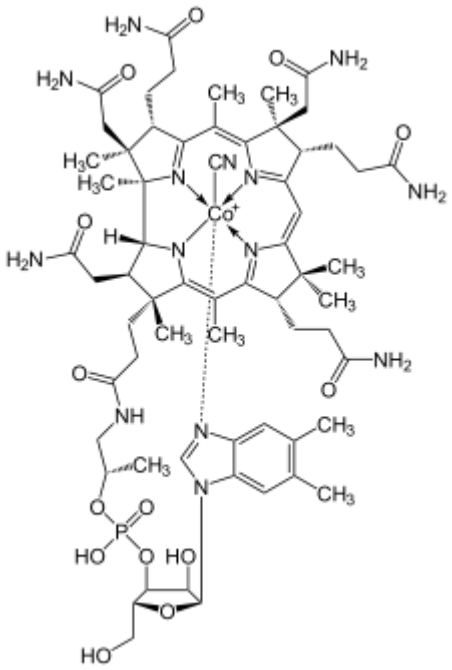
When cooking, use of steaming or of a food steamer can help keep more folate content in the cooked foods, thus helping to prevent folate deficiency.

Folate deficiency during human pregnancy has been associated with an increased risk of infant neural tube defects. Such deficiency during the first four weeks of gestation can result in structural and developmental problems. NIH guidelines recommend oral B vitamin supplements to decrease these risks near the time of conception and during the first month of pregnancy.

Chapter 4

Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency



Cyanocobalamin

ICD-10	E53.8
ICD-9	266.2
DiseasesDB	13905

Vitamin B_{12} was discovered from its relationship to the disease pernicious anemia, which is an autoimmune disease that destroys parietal cells in the stomach that secrete intrinsic factor. Pernicious anemia, untreated, is usually fatal within three years. Once identified,

however, it can be treated successfully and with relative ease (although it cannot be cured and continued treatment is required). Intrinsic factor is crucial for the normal absorption of B_{12} in amounts that occur in foods, and thus a lack of intrinsic factor, as seen in pernicious anemia, causes a vitamin B_{12} deficiency. Pernicious anemia can cause permanent damage to nervous tissue if it has been symptomatic and has gone without treatment for sufficient time. Many other subtler kinds of vitamin B_{12} deficiency and their biochemical effects have since been elucidated.

Deficiency of B_{12} due to low amounts of intake alone, is quite rare, and generally limited to vegan children, who are at risk due to higher needs of the vitamin, no intake of animal products that contain it, and low body stores. Vegans are generally encouraged to ingest B_{12} supplements, which are vegan since all commercial B_{12} is produced directly by bacteria.

The total amount of vitamin B_{12} stored in the body is about 2–5 mg in adults. Around 50% of this is stored in the liver. Approximately 0.1% of this is lost per day by secretions into the gut, as not all these secretions are reabsorbed. Bile is the main form of B_{12} excretion; however, most of the B_{12} secreted in the bile is recycled via enterohepatic circulation. Due to the extremely efficient enterohepatic circulation of B_{12}, the liver can store several years' worth of vitamin B_{12}. How quickly B_{12} levels may change when dietary intake is low, depends on the balance between how much B_{12} is obtained from the diet, how much is secreted, and how much is absorbed. B_{12} deficiency may arise in a year if initial stores are low and genetic factors unfavourable, or may not appear for decades. In infants and children, B_{12} deficiency appears much more quickly when the diet becomes poor in the vitamin.

Symptoms and pathomorphology

Vitamin B_{12} deficiency has the following pathomorphology and symptoms:

Pathomorphology: A spongiform state of neural tissue along with edema of fibers and deficiency of tissue. The myelin decays, along with axial fiber. In later phases, fibric sclerosis of nervous tissues occurs. Those changes apply to dorsal parts of the spinal cord and to pyramidal tracts in lateral cords. The pathophysiologic state of the spinal cord is called subacute combined degeneration of spinal cord.

In the brain itself, changes are less severe: They occur as small sources of nervous fibers decay and accumulation of astrocytes, usually subcortically located, and also round hemorrhages with a torus of glial cells. Pathological changes can be noticed as well in the posterior roots of the cord and, to lesser extent, in peripheral nerves.

Clinical symptoms: The main syndrome of vitamin B_{12} deficiency is Biermer's disease (pernicious anemia). It is characterized by a triad of symptoms:

1. Anemia with bone marrow promegaloblastosis (megaloblastic anemia)
2. Gastrointestinal symptoms

3. Neurological symptoms

Each of those symptoms can occur either alone or along with others. The neurological complex, defined as *myelosis funicularis*, consists of the following symptoms:

1. Impaired perception of deep touch, pressure and vibration, abolishment of sense of touch, very annoying and persistent paresthesias
2. Ataxia of dorsal cord type
3. Decrease or abolishment of deep muscle-tendon reflexes
4. Pathological reflexes — Babinski, Rossolimo and others, also severe paresis

Vitamin B_{12} deficiency can potentially cause severe and irreversible damage, especially to the brain and nervous system. These symptoms of neuronal damage may not reverse after correction of hematological abnormalities, and the chance of complete reversal decreases with the length of time the neurological symptoms have been present.

Psychological symptoms and mental disorders

During the course of disease, mental disorders can occur. These include irritability, focus/concentration problems, depressive state with suicidal tendencies, and paraphrenia complex.

At levels only slightly lower than normal, a range of symptoms such as fatigue, depression, and poor memory may be experienced. However, these symptoms by themselves are too nonspecific to diagnose deficiency of the vitamin.

Vitamin B_{12} deficiency can also cause symptoms of mania and psychosis, fatigue, memory impairment, irritability, depression and personality changes.

In general psychiatric symptoms referable to deficiency of B_{12} are thought to be reversible when vitamin B_{12} has been repleted. However, mental symptoms which do not reverse may be attributed to other causes, and are difficult to prove were as a direct result of vitamin deficiency.

Association of low B_{12} with diseases not classically due to vitamin deficiency

A number of diseases not classically thought to be caused by B_{12} deficiency are epidemiologically associated with it, raising questions of whether B_{12} status is an independent risk-factor, or a partial causal agent in these states. None of these causal connections have been proved, and all are under active investigation. These diseases are listed not as symptoms of B_{12} deficiency, but as investigational candidates where B_{12} deficiency has been investigated as having a role.

B_{12} status may be associated with the onset and cause of Alzheimer's disease. Some studies have found no relationship, while several recent studies indicate a relationship

between B_{12}, homocysteine, and Alzheimer's. B_{12} status is routinely measured at the time of Alzheimer's diagnosis, and there is some indication that ongoing measurements may be useful to detect the development of a severe deficiency. In addition to checking serum B_{12}, checking the levels of other compounds (particularly methylmalonic acid) may be necessary to accurately detect a deficiency state, because serum levels do not necessarily correlate with efficient utilization of B_{12}.

Studies showing a relationship between clinical depression levels and deficient B_{12} blood levels in elderly people are documented in the clinical literature.

Bipolar disorder appears to genetically co-segregate with the hereditary B_{12}-deficiency disorder pernicious anemia.

Science Daily reported that "a deficiency of B-vitamins may cause vascular cognitive impairment, according to a new study by the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University." Aron Troen, PhD, said that: "The vascular changes occurred in the absence of neurotoxic or degenerative changes. Metabolic impairments induced by a diet deficient in three B-vitamins — folate, B_{12} and B_6 — caused cognitive dysfunction and reductions in brain capillary length and density in our mouse model."

Causes

- Inadequate dietary intake of vitamin B_{12}. As the vitamin B_{12} occurs naturally only in animal products (eggs, meat, milk); a vegan diet can produce a deficiency unless one uses supplements or eats enriched food. Children are at primary risk for dietary deficiency, since they have fewer vitamin stores and a relatively larger vitamin need per calorie of intake.

- Selective impaired absorption of vitamin B_{12} due to intrinsic factor deficiency. This may depend on loss of gastric parietal cells in chronic atrophic gastritis (in which case, the resulting megaloblastic anemia takes the name of "pernicious anemia"), or may result from wide surgical resection of stomach (for any reason), or from rare hereditary causes of impaired synthesis of intrinsic factor.

- Impaired absorption of vitamin B_{12} in the setting of a more generalized malabsorption or maldigestion syndrome. This includes any form of structural damage or wide surgical resection of the terminal ileum (the principal site of vitamin B_{12} absorption).

- Forms of achlorhydria (including that artificially induced by drugs such as proton pump inhibitors) can cause B_{12} malabsorption from foods, since acid is needed to split B_{12} from food proteins and salivary binding proteins. This process is thought to be the most common cause of low B_{12} in the elderly, who often have some degree of achlorhydria without being formally low in intrinsic factor. This process

does not affect absorption of small amounts of B_{12} in supplements such as multivitamins, since it is not bound to proteins, as is the B_{12} in foods.

- Surgical removal of the small bowel (for example in Crohn's disease) such that the patient presents with short bowel syndrome and is unable to produce vitamin B_{12}. This can be treated with regular injections of vitamin B_{12}.

- Celiac disease may also cause impaired absorption of this vitamin, but this is due not to loss of intrinsic factor, but damage to the small bowel so that it cannot be absorbed.

- Some bariatric surgical procedures, especially those that involve removal of part of the stomach, such as Roux-en-Y gastric bypass surgery. (Procedures such as the adjustable gastric band type do not appear to affect B_{12} metabolism significantly).

- Chronic intestinal infestation by the fish tapeworm *Diphyllobothrium*, that competes for vitamin B_{12}, seizing it for its own use and therefore leaving insufficient amount for the host organism. This is mostly confined to Scandinavia and parts of Eastern Europe (for example, in preparers of gefilte fish, who would acquire the tapeworm by nibbling bits of fish before it was cooked while making the Eastern European delicacy).

- Bacterial overgrowth in parts of the small bowel are thought to be able to absorb B_{12}. An example occurs in so-called blind loop syndrome. This absorption by a different organism in the bowel before the body can absorb the vitamin somewhat resembles that from fish tapeworm disease.

- The diabetes medication metformin may interfere with B_{12} dietary absorption.

- Hereditary causes such as severe MTHFR deficiency, homocystinuria, and transcobalamin deficiency.

- Some studies have shown that giardiasis, or similar parasite should be considered as a cause of Vitamin B_{12} deficiency, this a result of the problems caused within the intestinal absorption system.

- Chronic alcohol abuse. However the mild macrocytosis of chronic alcoholism is usually not due to vitamin deficiency, but is due to a direct toxic effect of alcohol on red cell formation.

- Nitrous oxide abuse

Diagnosis

Serum B_{12} levels are often low in B_{12} deficiency, but if other features of B_{12} deficiency are present with normal B_{12} then the diagnosis must not be discounted. One possible explanation for normal B_{12} levels in B_{12} deficiency is antibody interference in people with high titres of intrinsic factor antibody. Some researchers propose that the current standard norms of vitamin B_{12} levels are too low. In Japan, the lowest acceptable level for vitamin B_{12} in blood has been raised from about 200 pg/ml (145 pM) to 550 pg/ml (400 pM).

There is confusion in units of B_{12} deficiency when given by various labs in various countries. Where units are presented as pg/liter, or pg/L, they are likely in error. Where they are presented as pg/mL or pmol/L, they are likely correct. The ranges for these two units are similar, since the molecular weight of B_{12} is approximately 1000, the difference between mL and L. Thus: 550 pg/mL = 400 pmol/L.

Serum Homocysteine and Methylmalonic acid levels are considered more reliable indicators of B_{12} deficiency than the concentration of B_{12} in blood. The levels of these substances are high in B_{12} deficiency and can be helpful if the diagnosis is unclear. Approximately 10% of patients with vitamin B_{12} levels between 200–400pg/l will have a vitamin B_{12} deficiency on the basis of elevated levels of homocysteine and methylmalonic acid.

Routine monitoring of methylmalonic acid levels in urine is an option for people who may not be getting enough dietary B_{12}, as a rise in methylmalonic acid levels may be an early indication of deficiency.

If nervous system damage is suspected, B_{12} analysis in cerebrospinal fluid can also be helpful, though such an invasive test would be applicable only after unrevealing blood testing.

The Schilling test can play a role in the diagnosis.

Treatment

B_{12} can be supplemented in healthy subjects by oral pill; sublingual pill, liquid, or strip; intranasal spray; transdermal patch or by injection. B_{12} is available singly or in combination with other supplements. B_{12} supplements are available in forms including cyanocobalamin, hydroxocobalamin, methylcobalamin, and adenosylcobalamin (sometimes called "cobamamide" or "dibencozide"). Oral treatments involve giving 250 μg to 1 mg of B_{12} daily.

Vitamin B_{12} can be given as intramuscular or subcutaneous injections of hydroxycobalamin, methylcobalamin, or cyanocobalamin. Body stores (in the liver) are partly repleted with half a dozen injections in the first couple of weeks (full repletion of liver stores requires about 20 injections) and then maintenance with monthly injections

throughout the life of the patient. Vitamin B_{12} can also be easily self-administered by injection by the patient, using the same fine-gauge needles and syringes used for self-administration of insulin.

B_{12} has traditionally been given parenterally (by injection) to ensure absorption. However, oral replacement is now an accepted route, as it has become increasingly appreciated that sufficient quantities of B_{12} are absorbed when large doses are given. This absorption does not rely on the presence of intrinsic factor or an intact ileum. Generally 1 to 2 mg daily is required as a large dose . By contrast, the typical Western diet contains 5–7 μg of B_{12} (Food and Drug Administration (FDA) Daily Value). It has been appreciated since the 1960s that B_{12} deficiency in adults resulting from malabsorption (including loss of intrinsic factor) can be treated with oral B_{12} supplements when given in sufficient doses. When given in oral doses ranging from 0.1–2 mg daily, B_{12} can be absorbed in a pathway that does not require an intact ileum or intrinsic factor. In two studies, oral treatment with 2 mg per day was as effective as monthly 1 mg injections.

Hypokalemia, an excessive low potassium level in the blood, is anecdotally reported as a complication of vitamin B_{12} repletion after deficiency. Excessive quantities of potassium are used by newly growing and dividing hematopoeitic cells, depleting circulating stores of the mineral.

Recently, claims have been made that other routes of B_{12} administration, such as intranasal and sublingual routes of administration, are superior to the simple swallowed pill. Although the intranasal route is are effective at increasing B_{12} levels, there have been no direct comparisons to show that they are any more effective than simple swallowed megadose tablets (1 to 2 mg). In particular, the sublingual route, in which B_{12} is presumably or supposedly absorbed more directly under the tongue, has not proven to be necessary, though there are a number of lozenges, pills, and even a lollipop designed for sublingual absorption. A 2003 study found no significant difference in absorption for serum levels from oral vs. sublingual delivery of 500 μg (micrograms) of cobalamin, although the study measured only serum levels as opposed to tissue levels, which is more reflective of B_{12} levels. Sublingual methods of replacement may be effective only because of the typically high doses (500 micrograms), which are swallowed, not because of placement of the tablet. As noted below, such very high doses of oral B_{12} may be effective as treatments, even if gastro-intestinal tract absorption is impaired by gastric atrophy (pernicious anemia).

Natural food sources of B_{12}

Vitamin B_{12} can be found in animal products, including fish, meat, poultry, eggs, milk, and milk products and fortified breakfast cereals. However, B_{12} is first made by yeasts and microorganisms and thus, animal products are not the only reliable source. One half chicken breast, provides some 0.3 μg per serving or 6% of your daily value (DV), 3 ounces of beef, 2.4 μg, or 40% of your DV, one slice of liver 47.9 μg or 780% of your DV, and 3 ounces of molluscs 84.1 μg, or 1,400% of your DV, while one egg provides

0.6 µg or 10% of your DV. Other sources include fortified nutritional yeast, fortified soy milks, and fortified energy bars.

Epidemiology

Recent research indicates that B_{12} deficiency is far more widespread than formerly believed. A large study in the US found that 39 percent of studied group of 3,000 had low values. This study at Tufts University used the B_{12} concentration 258 pmol/l (= 350 pg/mL) as a criterion of "low level". However, a recent research has found that B_{12} deficiency may occur at a much higher B_{12} concentration (500–600 pg/mL). On this basis Mitsuyama and Kogoh proposed 550 pg/mL, and Tiggelen et al. proposed 600 pg/mL. Against this background, there are reasons to believe that B_{12} deficiency is present in a far greater proportion of the population than 39% as reported by Tufts University.

In the developing world the deficiency is very widespread, with significant levels of deficiency in Africa, India, and South and Central America. This is due to low intakes of animal products, particularly among the poor. The increased bacterial load due to poor sanitation, unprocessed/unsterilized food, or other sources of dietary contamination could also lead to pathogen-related malabsorption issues.

B_{12} deficiency is even more common in the elderly. This is because B_{12} absorption decreases greatly in the presence of atrophic gastritis, which is common in the elderly.

B_{12} deficiency is common among vegetarians and vegans who do not take B_{12} supplements. In vegans the risk is very high because none of their natural food sources contain B_{12}. One American study found blood levels below normal in 92 % of vegans, 64 % of lactovegetarians, 47 % of lacto-ovo vegetarians who did not supplement their diet with B_{12}. The study applied the old normal values, so in reality a considerably greater proportion may have been deficient. On the other hand, one must take into account that the study was conducted in 1982 with a group taking no vitamin supplements: today soy drinks are often fortified with vitamin B_{12}.

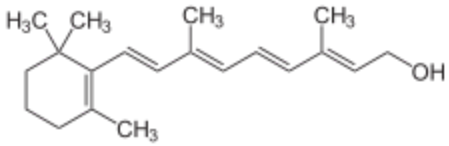
Masking effect of Folic acid

The National Institutes of Health has found that "Large amounts of folic acid can mask the damaging effects of vitamin B_{12} deficiency by correcting the megaloblastic anemia caused by vitamin B_{12} deficiency without correcting the neurological damage that also occurs", there are also indications that "high serum folate levels might not only mask vitamin B_{12} deficiency, but could also exacerbate the anemia and worsen the cognitive symptoms associated with vitamin B_{12} deficiency". Due to the fact that in the United States legislation has required enriched flour to contain folic acid to reduce cases of fetal neural-tube defects, consumers may be ingesting more than they realize. To counter the masking effect of B_{12} deficiency the NIH recommends "folic acid intake from fortified food and supplements should not exceed 1,000 mcg daily in healthy adults."

Chapter 5

Vitamin A Deficiency

Vitamin A deficiency



Retinol

ICD-10	E50.9
ICD-9	264.9
DiseasesDB	13902
eMedicine	med/2381
MeSH	D014802

Vitamin A deficiency is a lack of vitamin A in humans. It is common in developing countries but rarely seen in developed countries. Night blindness is one of the first signs of vitamin A deficiency. Xerophthalmia and complete blindness can also occur since Vitamin A has a major role in phototransduction. Approximately 250,000 to 500,000 malnourished children in the developing world go blind each year from a deficiency of vitamin A, approximately half of which die within a year of becoming blind. The United Nations Special Session on Children in 2002 set the elimination of vitamin A deficiency by 2010. The prevalence of night blindness due to vitamin A deficiency is also high among pregnant women in many developing countries. Vitamin A deficiency also contributes to maternal mortality and other poor outcomes in pregnancy and lactation.

Vitamin A deficiency also diminishes the ability to fight infections. In countries where children are not immunized, infectious disease like measles have higher fatality rates. As elucidated by Dr. Alfred Sommer, even mild, subclinical deficiency can also be a

problem, as it may increase children's risk of developing respiratory and diarrheal infections, decrease growth rate, slow bone development, and decrease likelihood of survival from serious illness.

Vitamin A deficiency is estimated to affect approximately one third of children under the age of five around the world. It is estimated to claim the lives of 670,000 children under five annually. Approximately 250,000-500,000 children in developing countries become blind each year owing to vitamin A deficiency, with the highest prevalence in Southeast Asia and Africa. According to the World Health Organization (WHO), vitamin A deficiency is under control in the United States, but in developing countries vitamin A deficiency is a significant concern.

Signs and symptoms

The most common cause of blindness in developing countries is vitamin A deficiency (VAD). The World Health Organization (WHO) estimates 13.8 million children to have some degree of visual loss related to VAD. Night blindness and its worsened condition, xerophthalmia, are markers of VAD, as VAD can also lead to impaired immune function, cancer, and birth defects.

Night blindness is the difficulty for the eyes to adjust to dim light. Affected individuals are unable to distinguish images in low levels of illumination. People with night blindness have poor vision in the darkness, but see normally when adequate light is present.

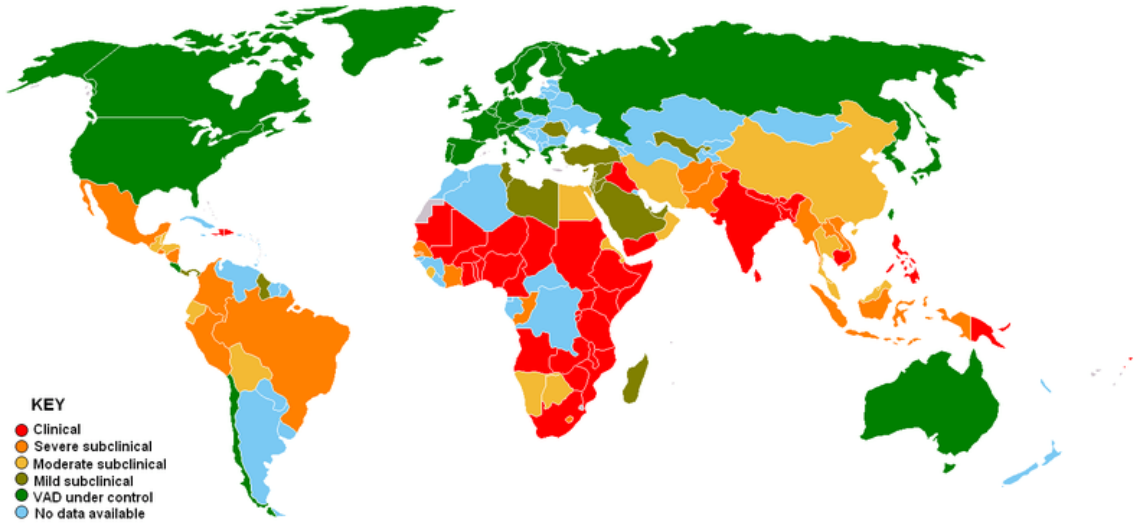
VAD affects vision by inhibiting the production of rhodopsin, the eye pigment responsible for sensing low light situations. Rhodopsin is found in the retina and is composed of retinal (an active form of vitamin A) and opsin (a protein). Because the body cannot create retinal in sufficient amounts, a diet low in vitamin A will lead to a decreased amount of rhodopsin in the eye, as there is inadequate retinal to bind with opsin. Night blindness results.

Night blindness caused by VAD has been associated with the loss of goblet cells in the conjunctiva, a membrane covering the outer surface of the eye. Goblet cells are responsible for secretion of mucus, and their absence results in xerophthalmia, a condition where the eyes fail to produce tears. Dead epithelial and microbial cells accumulate on the conjunctiva and form debris that can lead to infection and possibly blindness.

Decreasing night blindness requires the improvement of vitamin A status in at risk populations. Supplements and fortification of food have been shown to be effective interventions. Supplement treatment for night blindness includes high doses of vitamin A (200,000 IU) in the form of retinyl palmitate to be taken by mouth, which is administered two to four times a year. Intramuscular injections are poorly absorbed and are ineffective in delivering sufficient bio-available vitamin A. Fortification of food with vitamin A is costly, but can be done in wheat, sugar, and milk. Households may circumvent expensive

fortified food by altering dietary habits. Consumption of yellow-orange fruits and vegetables rich in carotenoids, specifically beta carotene, provides pro-vitamin A precursors that will prevent VAD related night blindness.

Causes



Prevalence of vitamin A deficiency. Source: WHO

The major cause is diets which include few animal sources of pre-formed vitamin A. Breast milk of a lactating mother with vitamin A deficiency contains little vitamin A, which provides a breast-fed child with too little vitamin A.

In addition to dietary problems, there are other causes of vitamin A deficiency. Iron deficiency can affect vitamin A uptake. Excess alcohol consumption can deplete vitamin A, and a stressed liver may be more susceptible to vitamin A toxicity. People who consume large amounts of alcohol should seek medical advice before taking vitamin A supplements. In general, people should also seek medical advice before taking vitamin A supplements if they have any condition associated with fat malabsorption such as pancreatitis, cystic fibrosis, tropical sprue & biliary obstruction.

Treatment

Treatment of vitamin A deficiency can be undertaken with both oral and injectable forms, generally as vitamin A palmitate.

- As an oral form, the supplementation of vitamin A is effective for lowering the risk of morbidity, especially from severe diarrhea, and reducing mortality from measles and all-cause mortality. Studies have shown that vitamin A supplementation of children under five who are at risk of vitamin A deficiency can reduce all‐cause mortality by 23 per cent. Some countries where vitamin A deficiency is a public health problem address its elimination by including vitamin

A supplements available in capsule form with National Immunization Days (NIDs) for polio eradication or measles. Vitamin A capsules cost about US$0.02. The capsules are easy to handle; they don't need to be stored in a refrigerator or vaccine carrier. When the correct dosage is given, vitamin A is safe and has no negative effect on seroconversion rates for Oral Polio Vaccine or measles vaccine. However, because the benefit of vitamin A supplements is transient, children need them regularly every four to six months. Since NIDs provide only one dose per year, NIDs-linked vitamin A distribution must be complemented by other dose programs to maintain vitamin A in children Maternal high supplementation benefits both mother and breast-fed infant: high dose vitamin A supplementation of the lactating mother in the first month postpartum can provide the breast-fed infant with an appropriate amount of vitamin A through breast milk. However, high-dose supplementation of pregnant women should be avoided because it can cause miscarriage and birth defects.

- Food fortification is also useful for improving vitamin A deficiency. A variety of oily and dry forms of the retinol esters, retinyl acetates and retinyl palmitate are available for food fortification of vitamin A. Margarine and oil are the ideal food vehicles for vitamin A fortification. They protect vitamin A from oxidation during storage and prompt absorption of vitamin A. β-carotene and retinyl acetate or retinyl palmitate are used as a form of vitamin A for vitamin A fortification of fat-based foods. Fortification of sugar with retinyl palmitate as a form of vitamin A has been used extensively throughout Central America. Cereal flours, milk powder, and liquid milk are also used as food vehicles for vitamin A fortification.

- Dietary diversification can also control vitamin A deficiency. Non-animal sources of vitamin A which contain pre-formed vitamin A account for greater than 80% of intake for most individuals in the developing world. The increase in consumption of vitamin A-rich foods of animal origin in addition to fruits and vegetables has beneficial effects on vitamin A deficiency. Researchers at the Agricultural Research Service have been able to identify genetic sequences in corn that are associated with higher levels of beta-carotene, the precursor to vitamin A. They found that breeders can cross certain variations of corn to produce a crop with an 18-fold increase in beta-carotene. Such advancements in nutritional plant breeding could one day aid in the illnesses related to vitamin A deficiency in developing countries.

Global Initiatives

Global efforts to support national governments in addressing vitamin a deficiency are led by the Global Alliance for Vitamin A (GAVA), which is an informal partnership between A2Z, the Canadian International Development Agency, Helen Keller International, Micronutrient Initiative, UNICEF, USAID, and the World Bank. Joint GAVA activity is coordinated by the Micronutrient Initiative.

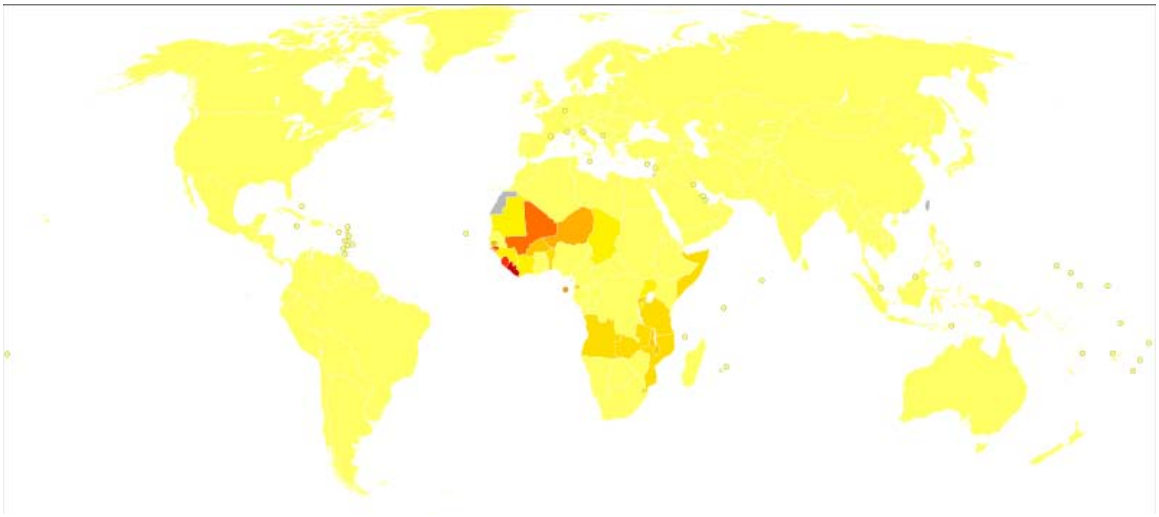
Vitamin Angels has committed itself to eradicating childhood blindness due to Vitamin A deficiency on the planet by the year 2020. Operation 20/20 was launched in 2007 and will cover 18 countries. The program gives children two high dose vitamin A and anti-parasitic supplements (twice a year for four years), which provides children with enough of the nutrient during their most vulnerable years in order to prevent them from going blind and suffering from other life-threatening diseases caused by Vitamin A Deficiency.

About 75 per cent of the vitamin A required for supplementation activity by developing countries is supplied by the Micronutrient Initiative with support from the Canadian International Development Agency.

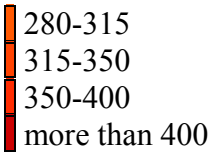
An estimated 1.25 million deaths due to vitamin A deficiency have been averted in 40 countries since 1998.

In 2008 it was estimated that an annual investment of US$60 million in vitamin A and zinc supplementation combined would yield benefits of more than US$1 billion per year, with every dollar spent generating benefits of more than US$17. These combined interventions were ranked by the Copenhagen Consensus 2008 as the world's best development investment.

Epidemiology



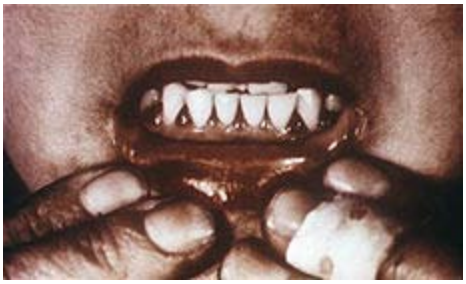
Disability-adjusted life year for vitamin A deficiency per 100,000 inhabitants in 2002.
- no data
- less than 35
- 35-70
- 70-105
- 105-140
- 140-175
- 175-210
- 210-245
- 245-280


280-315
315-350
350-400
more than 400

Chapter 6

Scurvy

Scurvy



Scorbutic gums, a symptom of scurvy. Note gingival redness in the triangle shaped interdental papillae between teeth

ICD-10	E54.
ICD-9	267
OMIM	240400
DiseasesDB	13930
MedlinePlus	000355
eMedicine	med/2086 derm/521 ped/2073 radio/628
MeSH	D012614

Scurvy is a disease resulting from a deficiency of vitamin C, which is required for the synthesis of collagen in humans. The chemical name for vitamin C, ascorbic acid, is

derived from the Latin name of scurvy, *scorbutus*, which also provides the adjective **scorbutic** ("of, characterized by or having to do with scurvy"). Scurvy leads to the formation of spots on the skin, spongy gums, and bleeding from the mucous membranes. The spots are most abundant on the thighs and legs, and a person with the ailment looks pale, feels depressed, and is partially immobilized. In advanced scurvy there are open, suppurating wounds and loss of teeth.

Scurvy was at one time common among sailors, pirates and others aboard ships at sea longer than perishable fruits and vegetables could be stored (subsisting instead only on cured and salted meats and dried grains) and by soldiers similarly separated from these foods for extended periods. It was described by Hippocrates (c. 460 BC–c. 380 BC), and herbal cures for scurvy have been known in many native cultures since prehistory. Scurvy was one of the limiting factors of marine travel, often killing large numbers of the passengers and crew on long-distance voyages. This became a significant issue in Europe from the beginning of the modern era in the Age of Discovery in the 15th century, continuing to play a significant role through World War I in the 20th century.

Today scurvy is known to be caused by a nutritional deficiency, but until the isolation of vitamin C and its direct link to scurvy in 1932, numerous theories and treatments were proposed, often on little or no experimental data. This inconsistency is attributed to the lack of vitamin C as a distinct concept, the varying vitamin C content of different foods (notably present in fresh citrus, watercress, and organ meat), and how vitamin C can be destroyed by exposure to air and copper.

Treatment by fresh food, particularly citrus fruit, was periodically implemented, as it had been since antiquity, but the ultimate cause of scurvy was not known until 1932, and treatment was inconsistent, with many ineffective treatments used into the 20th century. It was a Scottish surgeon in the British Royal Navy, James Lind who first proved it could be treated with citrus fruit in experiments he described in his 1753 book, *A Treatise of the Scurvy,* though his advice was not implemented by the Royal Navy for several decades.

In infants, scurvy is sometimes referred to as **Barlow's disease,** named after Sir Thomas Barlow, a British physician who described it. (N.B. Barlow's disease may also refer to mitral valve prolapse.) Other eponyms include **Moeller's disease** and **Cheadle's disease**.

Scurvy does not occur in most animals because they can synthesize their own vitamin C. However, humans and other higher primates (the simians and tarsiers), guinea pigs, most or all bats, and some species of birds and fish lack an enzyme necessary for such synthesis and must obtain vitamin C through their diet. Vitamin C is widespread in plant tissues, with particularly high concentrations occurring in citrus fruits (oranges, lemons, limes, grapefruits), tomatoes, potatoes, cabbages, and green peppers.

Cause

Scurvy or subclinical scurvy is caused by the lack of vitamin C. In modern Western societies, scurvy is rarely present in adults, although infants and elderly people are

affected. Vitamin C is destroyed by the process of pasteurization, so babies fed with ordinary bottled milk sometimes suffer from scurvy if they are not provided with adequate vitamin supplements. Virtually all commercially available baby formulas contain added vitamin C for this reason, but heat and storage destroy vitamin C. Human breast milk contains sufficient vitamin C, if the mother has an adequate intake.

Scurvy is one of the accompanying diseases of malnutrition (other such micronutrient deficiencies are beriberi or pellagra) and thus is still widespread in areas of the world depending on external food aid. Though rare, there are also documented cases of scurvy due to poor dietary choices by people living in industrialized nations.

Pathogenesis

Ascorbic acid is needed for a variety of biosynthetic pathways, by accelerating hydroxylation and amidation reactions. In the synthesis of collagen, ascorbic acid is required as a cofactor for prolyl hydroxylase and lysyl hydroxylase. These two enzymes are responsible for the hydroxylation of the proline and lysine amino acids in collagen. Hydroxyproline and hydroxylysine are important for stabilizing collagen by cross-linking the propeptides in collagen. Defective collagen fibrillogenesis impairs wound healing. Collagen is also an important part of bone, so bone formation is also affected. Defective connective tissue also leads to fragile capillaries, resulting in abnormal bleeding.

Prevention

Scurvy can be prevented by a diet that includes certain citrus fruits such as oranges or lemons. Other sources rich in vitamin C are fruits such as blackcurrants, guava, kiwifruit, papaya, tomatoes, bell peppers, and strawberries. It can also be found in some vegetables, such as carrots, broccoli, potatoes, cabbage, spinach and paprika. Some fruits and vegetables not high in vitamin C may be pickled in lemon juice, which is high in vitamin C. Many animal products, including liver, Muktuk (whale skin), and oysters, contain vitamin C. Though redundant in the presence of a balanced diet, various nutritional supplements are available that provide ascorbic acid well in excess of that required to prevent scurvy, and even some candies and most soft drinks contain vitamin C as a preservative.

Treatment

Scurvy is treated with vitamin C.

Prognosis

Untreated scurvy is invariably fatal. However, death from scurvy is rare in modern times. Since all that is required for a full recovery is the resumption of normal vitamin C intake, it is easy to treat if identified correctly. Consumption of dietary supplements and/or citrus fruits are means by which to accomplish this.

History

Herbal cures for scurvy have been known in many native cultures since prehistory. Scurvy was documented as a disease by Hippocrates, and Egyptians have recorded its symptoms as early as 1550 BC. The knowledge that consuming foods containing vitamin C is a cure for scurvy has been repeatedly rediscovered and reforgotten into the early 20th century.

Early modern era

In the 13th century, the Crusaders frequently suffered from scurvy. In the 1497 expedition of Vasco de Gama, the curative effects of citrus fruit were known. In 1536, the French explorer Jacques Cartier, exploring the St. Lawrence River, used the local natives' knowledge to save his men who were dying of scurvy. He boiled the needles of the arbor vitae tree (Eastern White Cedar) to make a tea that was later shown to contain 50 mg of vitamin C per 100 grams. Such treatments were not available aboard ship, where the disease was most common.

Between 1500 and 1800, it has been estimated that scurvy killed at least two million sailors. According to Jonathan Lamb, "In 1499, Vasco da Gama lost 116 of his crew of 170; In 1520, Magellan lost 208 out of 230;...all mainly to scurvy."

In 1593 Admiral Sir Richard Hawkins advocated drinking orange and lemon juice as a means of preventing scurvy.

The British civilian medical profession of 1614 believed that it was the acidic principle of citrus fruit which was lacking, although they considered any acid acceptable when ascorbic acid (Vitamin C) was unavailable. In 1614 John Woodall, Surgeon General of the East India Company, published "The Surgion's Mate" as a handbook for apprentice surgeons aboard the company's ships. In it he described scurvy as resulting from a dietary deficiency. His recommendation for its cure was fresh food or, if not available, oranges, lemons, limes and tamarinds, or as a last resort, Oil of Vitriol (sulfuric acid).

18th century

A 1707 handwritten book by Mrs Ebot Mitchell discovered in a house in Hasfield, Gloucestershire contains a "Recp.t for the Scurvy" that consisted of extracts from various plants mixed with a plentiful supply of orange juice, white wine or beer.

In 1734, the Leiden-based physician Johann Bachstrom published a book on scurvy in which he stated that "scurvy is solely owing to a total abstinence from fresh vegetable food, and greens; which is alone the primary cause of the disease" and urged the use of fresh fruit and vegetables as a cure. In 1740, citrus juice (usually lemon or lime juice) was added to the recipe of the traditional daily ration of watered-down rum known as grog to cut down on the water's foulness. Although they did not know the reason at the time, Admiral Edward Vernon's sailors were healthier than the rest of the navy, due to the

daily doses of vitamin C the sailors received. However, it was not until 1747 that James Lind formally proved that scurvy could be treated and prevented by supplementing the diet with citrus fruit such as limes or lemons, though not by other acids, in one of the earliest European clinical trials. This solution was not adopted by the Royal Navy until the 1790s, and the idea that any acid would suffice continued in Britain into the late 19th century.

During the 18th century, scurvy killed more British sailors than enemy action. It was mainly by scurvy that George Anson, in his celebrated voyage of 1740–2, lost within the first ten months nearly two-thirds of his crew (1300 out of 2000). During the Seven Years War, the Royal Navy reported that it conscripted 184,899 sailors, of whom 133,708 died of disease or were 'missing', and scurvy was the principal disease.

James Cook succeeded in circumnavigating the world (1768–71) in HM Bark *Endeavour* without losing a single man to scurvy, but his suggested methods, including a diet of sauerkraut and wort of malt, were of limited value. Sauerkraut was the only vegetable food that retained a reasonable amount of ascorbic acid in a pickled state, but it was boiled to reduce it for preservation and much of the vitamin C content was lost. In Cook's time it was impractical to preserve citrus fruit for long sea voyages. More important was Cook's regime of shipboard cleanliness, enforced by strict discipline, as well as frequent replenishing of fresh food. The most effective regime implemented by Cook was his prohibition against the consumption of fat scrubbed from the ship's copper pans, then a common practice in the Navy. In contact with the hot copper, this fat acquired substances which possibly irritated the gut and prevented proper absorption of vitamins.

The first major long distance expedition that experienced virtually no scurvy was that of Alessandro Malaspina, 1789–1794. Malaspina's medical officer, Pedro González, was convinced that fresh oranges and lemons were essential for preventing scurvy. Only one outbreak occurred, during a 56-day trip across the open sea. Five sailors came down with symptoms, one seriously. After three days at Guam all five were healthy again. Spain's large empire and many ports of call made it easier to acquire fresh fruit.

Despite advances, British sailors throughout the American Revolutionary period continued to suffer from scurvy, particularly in the Channel Fleet. The eradication of scurvy from the Royal Navy in the 1790s was finally due to the chairman of the Navy's Sick and Hurt Board, Gilbert Blane, who finally put Bachstrom and Lind's long-ignored prescription of fresh lemons to use during the Napoleonic Wars. Other navies soon adopted this successful solution.

19th century

The surgeon-in-chief of Napoleon's army at the Siege of Alexandria (1801), Baron Dominique-Jean Larrey, wrote in his memoirs that the consumption of horse meat helped the French to curb an epidemic of scurvy. This started the 19th-century tradition of horse meat consumption in France.

Lauchlin Rose patented a method used to preserve citrus juice without alcohol in 1867, creating a concentrated drink known as Rose's lime juice. The Merchant Shipping Act of that same year required all ships of the Royal Navy and Merchant Navy to provide a daily lime ration to sailors to prevent scurvy. The product became nearly ubiquitous, hence the term "limey", first for British sailors, then an English immigrant in the former British colonies (particularly America, New Zealand and South Africa), and finally, in old American slang, all British people.

The plant *Cochlearia officinalis*, also known as "Common Scurvygrass", acquired its common name from the observation that it cured scurvy, and it was taken on board ships in dried bundles or distilled extracts. Its very bitter taste was usually disguised with herbs and spices; however, this didn't prevent scurvygrass drinks and sandwiches becoming a popular fad in the UK until the middle of the nineteenth century, when citrus fruits became more readily available.

West Indian limes replaced lemons because they were more easily obtained from Britain's Caribbean colonies, and were believed to be more effective because they were more acidic, and it was the acid, not the (then-unknown) Vitamin C that was believed to cure scurvy. This was mistaken – the West Indian limes were significantly lower in Vitamin C than the previous lemons (having only ¼ the Vitamin C content), and further were not served fresh, but rather as lime juice, which had been exposed to air and piped through copper tubing, both of which significantly reduced the Vitamin C. Indeed, an 1918 animal experiment using representative samples of the Navy and Merchant Marine's lime juice showed that it had virtually no antiscorbutic power at all.

The belief that scurvy was fundamentally a nutritional deficiency, best treated by consumption of fresh food, particularly fresh citrus or fresh meat, was not universal in Britain in the 19th and early 20th centuries, and thus British sailors and explorers continued to suffer from scurvy into the 20th century.

In the Royal Navy's Arctic expeditions in the 19th century it was widely believed that scurvy was prevented by good hygiene on board ship, regular exercise, and maintaining the morale of the crew, rather than by a diet of fresh food, so that Navy expeditions continued to be plagued by scurvy even while fresh meat was well-known as a practical antiscorbutic among civilian whalers and explorers in the Arctic.

The confusion is attributed to a number of factors:

- while *fresh* citrus (particularly lemons) cured scurvy, lime *juice* that had been exposed to air and copper tubing did not – thus undermining the theory that citrus cured scurvy;
- fresh meat (especially organ meat, consumed in arctic exploration) also cured scurvy, undermining the theory that fresh produce was essential to preventing and curing scurvy;

- increased marine speed via steam shipping, and improved nutrition on land, reduced the incidence of scurvy – and thus the ineffectiveness of copper-piped lime juice compared to fresh lemons was not immediately revealed.

In the resulting confusion, a new hypothesis was floated, following the new germ theory of disease – that scurvy was caused by **ptomaine**, a waste product of bacteria, particularly in tainted tinned meat.

Infantile scurvy emerged in the late 19th century due to children being fed pasteurized cow's milk, particularly in the urban upper class – the pasteurization killed bacteria, but also destroyed vitamin C. This was eventually resolved by supplementing with onion juice or cooked potatoes.

20th century

At the time Robert Falcon Scott made his two expeditions (1903 and 1911) to the Antarctic in the early 20th century, the prevailing theory was that scurvy was caused by "tainted" meat, particularly tinned meat. Accordingly, Scott's expeditions suffered from scurvy, though he initially did not record this in his notes on his 1903 expedition, due to stigma associated with scurvy.

Vilhjalmur Stefansson, an arctic explorer who lived among the Eskimos, proved that the all meat diet they consumed did not lead to vitamin deficiencies. He participated in a study in New York's Bellevue Hospital in 1935, where he and a companion ate nothing but meat for a year while under close medical observation, yet remained in good health. Some Antarctic expeditions, such as Scott's two expeditions and Shackleton's Ross Sea party, suffered from scurvy, mainly during inland sledge journeys when the men had access to very limited range of food, virtually none of it fresh. Scurvy was rare or absent when they had access to a wider range of stored food or relied on seal meat.

Refined carbohydrates seem to accelerate the process of depleting vitamin C. Insulin in the bloodstream causes all amino acids, except for tryptophan, to be stored as fat. Tryptophan competes to enter the bloodstream, causing less vitamin C to be available to the body. This could be one reason sailors and explorers, with their rations heavy with hard tack biscuits and refined carbohydrates, were so prone to scurvy.

In 1907, the needed biological-assay model to isolate and identify the antiscorbutic factor was discovered. Axel Holst and Theodor Frølich, two Norwegian physicians studying shipboard beriberi contracted aboard ship's crews in the Norwegian Fishing Fleet, wanted a small test mammal to substitute for the pigeons then used in beriberi research. They fed guinea pigs their test diet of grains and flour, which had earlier produced beriberi in their pigeons, and were surprised when classic scurvy resulted instead. This was a serendipitous choice of model. Until that time, scurvy had not been observed in any organism apart from humans, and had been considered an exclusively human disease. (Pigeons, as seed-eating birds, were also later found to make their own vitamin C.) Holst and Frølich found they could cure the disease in guinea pigs with the addition of various

fresh foods and extracts. This discovery of a clean animal experimental model for scurvy, made even before the essential idea of "vitamins" in foods had even been put forward, has been called the single most important piece of vitamin C research.

In 1927, Hungarian biochemist Szent-Györgyi (who won the 1937 Nobel Prize for Medicine) for his studies in the biological functions of the compound "hexuronic acid" while working with antioxidant compounds in the adrenal cortex. Szent-Györgyi suspected hexuronic acid, which he had isolated from adrenal glands, might be the antiscorbutic agent, but could not prove it without an animal-deficiency model.

It was not until 1932 that the connection between hexuronic acid and scurvy was finally proven by American researcher Charles Glen King of the University of Pittsburgh. King's laboratory was given some hexuronic acid by Szent-Györgyi and soon established that it was "vitamin C". In honor of its antiscorbutic properties, hexuronic acid was named "ascorbic acid" by Szent-Györgyi.

Experimental human trials

Notable human dietary studies of experimentally-induced scurvy have been conducted on conscientious objectors during WW II in Britain, and on Iowa state prisoner "volunteers" in the late 1960s. These studies both found that all obvious symptoms of scurvy previously induced by an experimental scorbutic diet with extremely low vitamin C content, could be completely reversed by additional vitamin C supplementation of only 10 mg a day. In these experiments, there was no clinical difference noted between men given 70 mg vitamin C per day (which produced blood levels of vitamin C of about 0.55 mg/dl, about 1/3 of tissue saturation levels), and those given 10 mg per day (which produced lower blood levels). Men in the prison study developed the first signs of scurvy about 4 weeks after starting the vitamin C free diet, whereas in the British study, six to eight months were required, possibly due to the pre-loading of this group with a 70 mg/day supplement for six weeks before the scorbutic diet was fed. Men in both studies on a diet devoid or nearly devoid of vitamin C had blood levels of vitamin C too low to be accurately measured when they developed signs of scurvy, and in the Iowa study, at this time were estimated (by labeled vitamin C dilution) to have a body pool of less than 300 mg, with daily turnover of only 2.5 mg/day.

In other animals

Most plant and animal species synthesize vitamin C. Notable mammalian group exceptions include most or all of the order chiroptera (bats), and one of the two major primate suborders, the "Anthropoidea" (Haplorrhini) (tarsiers, monkeys and apes, including human beings). The Strepsirrhini (non-tarsier prosimians) can make their own vitamin C (these include lemurs, the Aye-aye, lorises, pottos, and galagos). Ascorbic acid is also not synthesized by at least two species of Caviidae, the capybara and the guinea pig. There are known species of birds and fish that do not synthesize their own Vitamin C. All species that do not synthesize ascorbate require it in the diet. Deficiency causes scurvy in humans, and somewhat similar symptoms in other animals.

Chapter 7

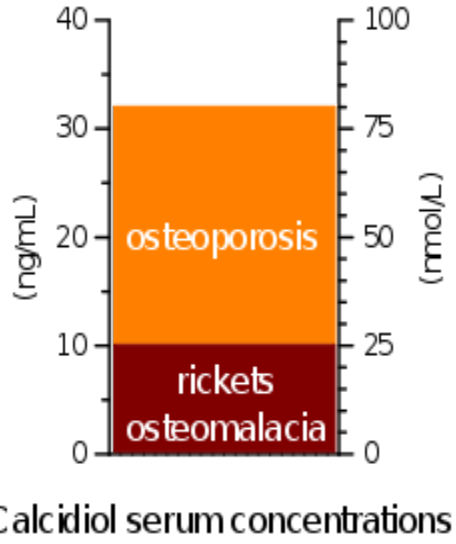
Hypovitaminosis D

Hypovitaminosis D

ICD-10	E55.
ICD-9	268
DiseasesDB	13942
MeSH	D014808

Hypovitaminosis D is a **deficiency of Vitamin D**. It can result from: inadequate nutritional intake of vitamin D coupled with inadequate sunlight exposure (in particular sunlight with adequate ultra violet B rays), disorders that limit vitamin D absorption, and conditions that impair the conversion of vitamin D into active metabolites including certain liver, kidney, and hereditary disorders. Deficiency results in impaired bone mineralization and leads to bone softening diseases including rickets in children and osteomalacia and osteoporosis in adults.

Classification



Mapping of several bone diseases onto levels of vitamin D (calcidiol) in the blood.

Hypovitaminosis D is typically diagnosed by measuring the concentration in blood of the compound 25-hydroxyvitamin D (calcidiol), which is a precursor to the active form 1,25-dihydroxyvitamin D (calcitriol). One 2008 review has proposed the following four categories for hypovitaminosis D:

- Insufficient 50-100 nmol/L (20-40 ng/mL)
- Mild 25-50 nmol/L (10-20 ng/mL)
- Moderate 12.5-25.0 nmol/L (5-10 ng/mL)
- Severe < 12.5 nmol/L (< 5 ng/mL)

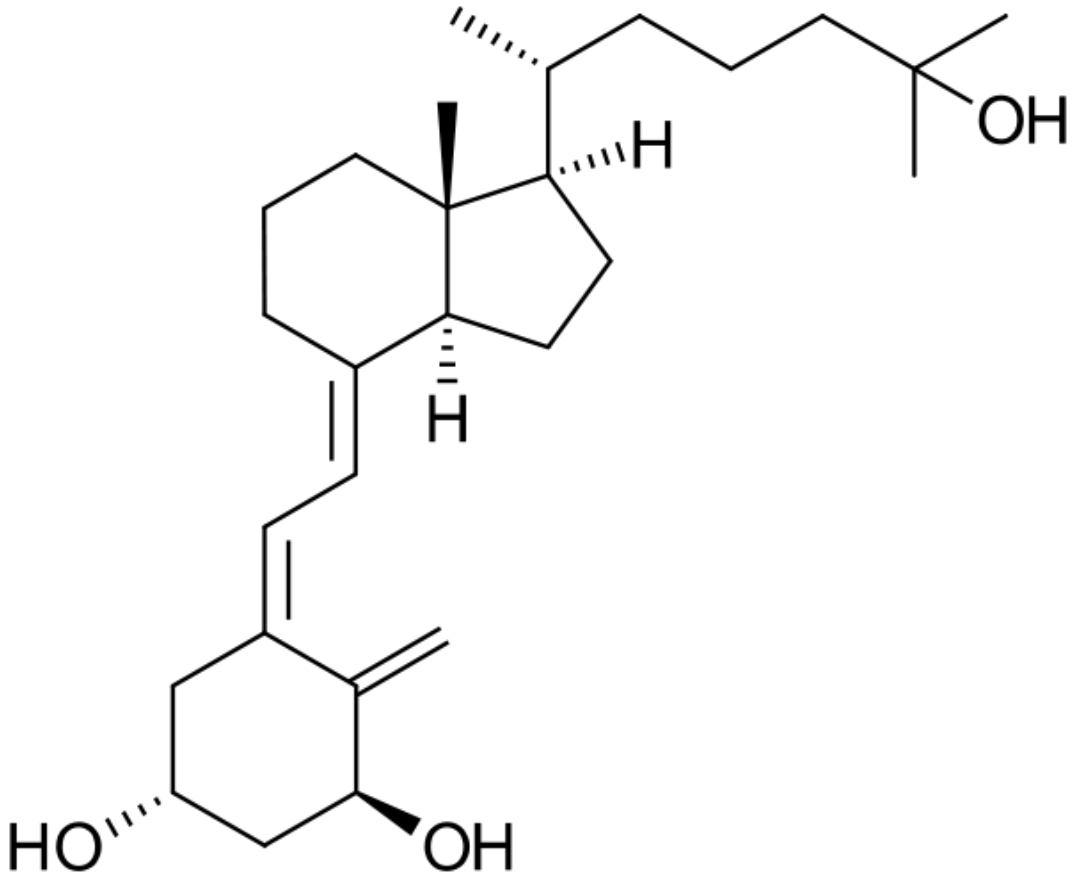
Note that 1.0 nmol/L = 0.4 ng/mL for this compound. Other authors have suggested that a 25-hydroxyvitamin D level of 75-80 nmol/L (30-32 ng/mL) may be sufficient although a majority of healthy young people with comparatively extreme sun exposure did not reach this level in a study done in Hawaii.

Vitamin D status and supplementation

The increased risk of vascular events in healthy older women receiving calcium supplementation found in a controlled trial has led to some specialists questioning the use of vitamin D supplementation to attaining the relatively high serum concentrations of vitamin D now being promoted as 'sufficient'. The putative benefits of higher levels were not borne out in a 2010 study which found that women with a seasonally adjusted 25(OH)D concentration under 50 nmol/L or 20 ng/ml, (a level considered 'deficient' by

some researchers) were not at an increased risk of adverse consequences for any musculoskeletal outcome, including fracture, falls, bone density, grip strength or any nonskeletal outcomes, including death, myocardial infarction, cancer, heart failure, diabetes, or adverse changes in blood pressure, weight, body composition, cholesterol, or glucose.

Signs and symptoms



Calcitriol (1,25-dihydroxycholecalciferol). Active form. Note extra OH groups at upper right and lower right.

Vitamin D deficiency is known to cause several bone diseases including:

- Rickets, a childhood disease characterized by impeded growth, and deformity, of the long bones. The earliest sign of subclinical vitamin D deficiency is Craniotabes, abnormal softening or thinning of the skull.
- Osteomalacia, a bone-thinning disorder that occurs exclusively in adults and is characterized by proximal muscle weakness and bone fragility.
- Osteoporosis, a condition characterized by reduced bone mineral density and increased bone fragility.
- Muscle aches and weakness (in particular proximal limb girdle)

- Muscle twitching (Fasciculations)

The role of diet in the development of rickets was determined by Edward Mellanby between 1918–1920. In 1921 Elmer McCollum identified an anti-rachitic substance found in certain fats that could prevent rickets. Because the newly discovered substance was the fourth vitamin identified, it was called vitamin D. The 1928 Nobel Prize in Chemistry was awarded to Adolf Windaus, who discovered the steroid 7-dehydrocholesterol, the precursor of vitamin D.

Prior to the fortification of milk products with vitamin D, rickets was a major public health problem. In the United States, milk has been fortified with 10 micrograms (400 IU) of vitamin D per quart since the 1930s, leading to a dramatic decline in the number of rickets cases.

Risk factors

Age

The amount of vitamin D recommended for all infants, children, and adolescents has recently doubled—from 200 to 400 IU per day. As of October 2008, the American Pediatric Association advises vitamin D supplementation of 400 IU/day (10µg/d) from birth onwards. (1 IU Vitamin D is the biological equivalent of 0.025 µg cholecalciferol/ergocalciferol). The daily dose of 400 IU is required to prevent rickets and possibly also a wide range of chronic nonskeletal diseases. The Canadian Paediatric Society recommends that pregnant or breastfeeding women consider taking 2000 IU/day, that all babies who are exclusively breastfed receive a supplement of 400 IU/day, and that babies living above 55 degrees latitude get 800 IU/day from October to April. Health Canada recommends 400IU/day (10µg/d). Infant formula is generally fortified with vitamin D.

Malnutrition

Although rickets and osteomalacia are now rare in Britain, there have been outbreaks in some immigrant communities in which osteomalacia sufferers included women with seemingly adequate daylight outdoor exposure wearing Western clothing. Having darker skin and reduced exposure to sunshine did not produce rickets unless the diet deviated from a Western omnivore pattern characterized by high intakes of meat, fish and eggs, and low intakes of high-extraction cereals. The dietary risk factors for rickets include abstaining from animal foods . Vitamin D deficiency remains the main cause of rickets among young infants in most countries, because breast milk is low in vitamin D and social customs and climatic conditions can prevent adequate UVB exposure. In sunny countries such as Nigeria, South Africa, and Bangladesh where the disease occurs among older toddlers and children it has been attributed to low dietary calcium intakes, which are characteristic of cereal-based diets with limited access to dairy products. Rickets was formerly a major public health problem among the US population; in Denver where ultraviolet rays are approximately 20% stronger than at sea level on the same latitude

almost two thirds of 500 children had mild rickets in the late 1920s. An increase in the proportion of animal protein in the 20th century American diet coupled with increased consumption of milk fortified with relatively small quantities of vitamin D coincided with a dramatic decline in the number of rickets cases.

Obesity

Obese individuals have lower levels of the circulating form of vitamin D, probably because of reduced bioavailability, and are at higher risk of deficiency. To maintain blood levels of calcium, therapeutic vitamin D doses are sometimes administered (up to 100,000 IU or 2.5 mg daily) to patients who have had their parathyroid glands removed (most commonly renal dialysis patients who have had tertiary hyperparathyroidism, but also to patients with primary hyperparathyroidism) or with hypoparathyroidism. Patients with chronic liver disease or intestinal malabsorption disorders may also require larger doses of vitamin D (up to 40,000 IU or 1 mg (1000 micrograms) daily).

It has been argued that there is little evidence to support the use of high dose therapy to attain thresholds for vitamin D deficiency that greatly exceed widely used definitions of vitamin D deficiency (25OHD <10 ng/ml or 25 nmol/L), and for vitamin D insufficiency (25OHD < 20 ng/ml or 50 nmol/L). Studies are potentially subject to confounding by frailty as people with poorer health are likely to remain indoors, receive less sun exposure, and have low 25OHD levels compared to their healthy peers (rather than low vitamin D levels causing ill health). Those leading sedentary lives are at increased risk of obesity, and increased fat mass is inversely associated with 25OHD levels. This association may confound the reported relationships between low vitamin D status and conditions such as diabetes, ischaemic heart disease, hypertension, and cancer that occur more commonly in obesity. Confounding by health status can be powerful, as evidenced by the disparate results of randomised controlled trials and observational studies of postmenopausal hormone replacement therapy. Obesity remains a likely confounding factor for the associations between low 25(OH)D levels and poor health. Some continue to argue the reverse — that obese and sedentary people are at high risk of many diseases specifically because they have low serum 25(OH)D levels

Sun exposure

The use of sunscreen with a sun protection factor (SPF) of 8 can theoretically inhibit more than 95% of vitamin D production in the skin. In practice, however, sunscreen is applied so as to have a negligible effect on vitamin D status. The vitamin D status of those in Australia and New Zealand is unlikely to have been affected by campaigns advocating sunscreen. Instead, wearing clothing is more effective at reducing the amount of skin exposed to UVB and reducing natural vitamin D synthesis.

Darker skin color

It has been suggested the reduced pigmentation of light-skinned individuals results in higher vitamin D levels and that, because melanin acts like a sun-block, dark-skinned

individuals, in particular, may require extra vitamin D to avoid deficiency at higher latitudes. The natural selection hypothesis suggests that lighter skin color evolved to optimise vitamin D production in extreme northern and southern latitudes.

Rickets is sometimes due to genetic disorders such as autosomal dominant hypophosphatemic rickets or X-linked hypophosphatemia and associated with consanguineous marriage, and possibly founder effect. In Kashmir, India patients with pseudovitamin D deficiency rickets had grossly raised 25-hydroxyvitamin D concentrations. Skin colour has also been associated with low 25(OH)D, especially in Africans living in countries with a temperate climate. For example 25-OHD under 10 ng/mL (25 nmol/l) in 44% of asymptomatic East African children living in Melbourne However a study of healthy young Ethiopians living in Addis Ababa (10 degrees N) found average 25(OH)D levels of 23.5nmol/L. A review of Vitamin D in Africa gives the median levels for equatorial countries: Kenya 65.5 nmol/L and Congo-Kinshasa 65nmol/L, concluding that it remains to be established if associations between vitamin D status and health outcomes identified in Western countries can be replicated in African countries.

Vitamin D levels are approximately 30% higher in northern Europe than in central and southern Europe; higher vitamin D concentrations in northern countries may have a genetic basis. In a meta-analysis of cross-sectional studies on serum 25(OH)D concentrations globally the levels averaged 54 nmol/l and were higher in women than men, and higher in Caucasians than in non-Caucasians. There was no trend in serum 25(OH)D level with latitude. African Americans often have a very low circulating 25(OH)D level. However, those of African descent have higher parathyroid hormone and 1,25-Dihydroxycholecalciferol associated with lower 25-hydroxyvitamin D than other ethnic groups; moreover, they have the greatest bone density and lowest risk of fragility fractures compared to other populations. Deficiency results in impaired bone mineralization, and leads to bone softening diseases

Nutritional factors

Cancer

A US National Cancer Institute study analyzed data from the third national Health and Nutrition Examination Survey (NHANES) to examine the relationship between levels of circulating vitamin D in the blood and cancer mortality in a group of 16,818 participants aged 17 and older. It found no support for an association between 25(OH)D and total cancer mortality. Unlike other studies, this one was carried out prospectively — meaning that participants were followed looking forward — and the researchers used actual blood tests to measure the amount of vitamin D in blood, rather than trying to infer vitamin D levels from potentially inaccurate predictive models.

The molecular basis for thinking vitamin D has the potential to prevent cancer lies in its role as a nuclear transcription factor that regulates cell growth, differentiation, apoptosis and a wide range of cellular mechanisms central to the development of cancer. These

effects may be mediated through vitamin D receptors expressed in cancer cells. Polymorphisms of the vitamin D receptor (VDR) gene have been associated with an increased risk of breast cancer, although a study of 78 Turkish breast cancer patients showed that the prevalence of the VDR Taq I and Bsm I alleles and the genotype frequencies in patients with breast cancer was similar to that in the normal population. Impairment of the VDR-mediated gene expression is thought to alter mammary gland development or function and may predispose cells to malignant transformation. Women with homozygous FOK1 mutations in the VDR gene had an increased risk of breast cancer compared with the women who did not. FOK1 mutation has also been associated with decreasing bone mineral density which in turn may be associated with an increase in the risk of breast cancer. Research is also being done on the use of calcitriol in the medical treatment of patients with advanced prostate cancer.

Research has also suggested that cancer patients who have surgery or treatment in the summer — and therefore make more endogenous vitamin D — have a better chance of surviving their cancer than those who undergo treatment in the winter when they are exposed to less sunlight.

Correlation of the vitamin D levels of a population with the solar irradiance to which they are exposed can be confounded by other factors such as age, gender, skin pigmentation, latitude, sunscreen use, and clothing. Moreover, there are genetic factors involved with cancer incidence and mortality which are more common in northern latitudes.

A 2005 metastudy found correlations between serum levels of vitamin D and cancer, drawing from a meta-analysis of 63 observational studies of vitamin D status. The authors suggested that intake of an additional 1,000 international units (IU) (or 25 micrograms) of vitamin D daily reduced an individual's colon cancer risk by 50%, and breast and ovarian cancer risks by 30%. Low levels of vitamin D in serum have been correlated with breast cancer disease progression and bone metastases.

Another 2006 study found that taking the U.S. RDA of vitamin D (400 IU per day) cut the risk of pancreatic cancer by 43% in a sample of more than 120,000 people from two long-term health surveys. However, in male smokers, a 3-fold increased risk for pancreatic cancer in the highest compared to lowest quintile of serum 25-hydroxyvitamin D concentration has been found.

A randomized intervention study involving 1,200 women, published in June 2007, reports that vitamin D supplementation (1,100 international units (IU)/day) resulted in a 60% reduction in cancer incidence, during a four-year clinical trial, rising to a 77% reduction for cancers diagnosed *after* the first year (and therefore excluding those cancers more likely to have originated prior to the vitamin D intervention). The study was criticized on several grounds including lack of data, use of statistical techniques and comparison with a self-selected (i.e. non-randomized) observational study that found long term convergence of breast cancer incidence The author's response provided the required data, explained their statistical usage and commented that even if the vitamin D merely

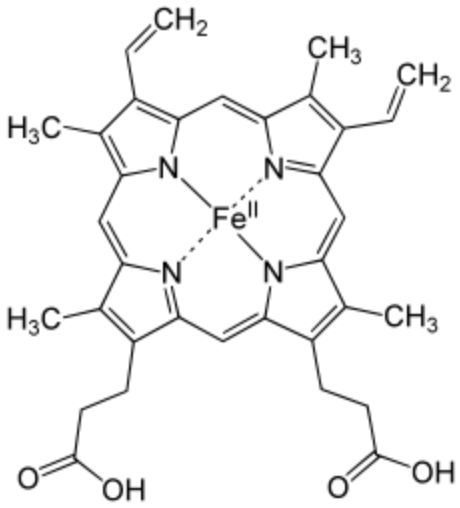
delayed the appearance of cancer (which they did not believe, based on other studies), that that was still a considerable benefit.

A study by Cedric F. Garland and Frank C. Garland of the University of California, San Diego analyzed the blood from 25,000 volunteers from Washington County, Maryland, finding that those with the highest levels of levels of Calcifediol had one-fifth the risk of colon cancer compared to typical rates.

Chapter 8

Iron Deficiency (Medicine)

Iron deficiency



Iron in heme

ICD-10	E61.1
ICD-9	280.9
DiseasesDB	6947
MedlinePlus	000584
eMedicine	med/1188

Iron deficiency (**sideropenia** or **hypoferremia**) is one of the most commonly known forms of nutritional deficiencies. In the human body, iron is present in all cells and has several vital functions—as a carrier of oxygen to the tissues from the lungs in the form of

hemoglobin, as a transport medium for electrons within the cells in the form of cytochromes, and as an integral part of enzyme reactions in various tissues. Too little iron can interfere with these vital functions and lead to morbidity and death.

The direct consequence of iron deficiency is iron deficiency anemia. Groups that are most prone to developing this disease are children and pre-menopausal women.

Total body iron averages approximately 3.8 g in men and 2.3 g in women. In blood plasma, iron is carried tightly bound to the protein transferrin. Bacteria, like human cells, require iron for growth, and restricting its bioavailability in this way prevents their infectious growth. Indeed, during fever, one way of controlling bacterial growth is through temporary hypoferremia.

There are several mechanisms that control human iron metabolism and safeguard against iron deficiency. The main regulatory mechanism is situated in the gastrointestinal tract. When loss of iron is not sufficiently compensated by adequate intake after some time that is determined by the state of body iron storage, iron deficiency develops.

Causes

- chronic bleeding (hemoglobin contains iron)
    - excessive menstrual bleeding
    - non-menstrual bleeding
    - bleeding from the gastrointestinal tract (ulcers, hemorrhoids, etc.)
    - rarely, laryngological bleeding or from the respiratory tract
- inadequate intake (special diets low in dietary iron)
- substances (in diet or drugs) interfering with iron absorption
- malabsorption syndromes
- fever where it is adaptive to control bacterial infection
- blood donation

Though genetic defects causing iron deficiency have been studied in rodents, there are no known genetic disorders of human iron metabolism that directly cause iron deficiency.

Symptoms

Symptoms of iron deficiency can occur even before the condition has progressed to iron deficiency anaemia.

Symptoms of iron deficiency are not unique to iron deficiency (i.e. not pathognomonic). Iron is needed for many enzymes to function normally, so a wide range of symptoms may eventually emerge, either as the secondary result of the anemia, or as other primary results of iron deficiency. Symptoms of iron deficiency include:

- fatigue
- pallor

- hair loss
- irritability
- weakness
- pica
- brittle or grooved nails
- Plummer-Vinson syndrome: painful atrophy of the mucous membrane covering the tongue, the pharynx and the oesophagus
- Impaired immune function
- Pagophagia

Likely lab test results in people with iron deficiency

- A full blood count would likely reveal microcytic anemia

- Low serum ferritin *
- Low serum iron
- High TIBC (total iron binding capacity)
- It is possible that the fecal occult blood test might be positive, if iron deficiency is the result of gastrointestinal bleeding.

As always, laboratory values have to be interpreted with the lab's reference values in mind and considering all aspects of the individual clinical situation.

Serum ferritin can be elevated in inflammatory conditions and so a normal serum ferritin may not always exclude iron deficiency.

Consequences

Continued iron deficiency may progress to anemia and worsening fatigue. Thrombocytosis, or an elevated platelet count, can also result. A lack of sufficient iron levels in the blood is a reason that some people cannot donate blood.

Treatment

Before any treatment is commenced there should be definitive diagnosis of the underlying cause for iron deficiency, particularly in older patients who are most susceptible to colorectal cancer and the gastrointestinal bleeding it often causes. In adults, 60% of patients with iron deficiency anemia may have underlying gastrointestinal disorders leading to chronic blood loss. It is likely that the cause of the iron deficiency will need treatment as well.

When iron deficiency has been diagnosed the condition can be treated with iron supplements, e.g. in the form of ferrous sulfate, ferrous gluconate, or amino acid chelate tablets. Recent research suggests the replacement dose of iron, at least in the elderly with iron deficiency, may be as little as 15 mg per day of elemental iron.

Food sources of iron

Mild iron deficiency can be prevented or corrected by eating iron-rich foods. Because iron is a requirement for most plants and animals, a wide range of foods provide iron. Good sources of dietary iron include red meat, poultry, lentils, beans, leaf vegetables, tofu, chickpeas, black-eyed peas, fortified bread, and fortified breakfast cereals. Iron in low amounts is found in molasses, teff and farina.

Iron from different foods is absorbed and processed differently by the body; for instance, iron in meat (heme iron source) is more easily broken down and absorbed than iron in grains and vegetables ("non-heme" iron source), but heme/hemoglobin from red meat has effects which may increase the likelihood of colorectal cancer. Minerals and chemicals in one type of food may inhibit absorption of iron from another type of food eaten at the same time. For example, oxalates and phytic acid form insoluble complexes which bind iron in the gut before it can be absorbed.

Because iron from plant sources is less easily absorbed than the heme-bound iron of animal sources, vegetarians and vegans should have a somewhat higher total daily iron intake than those who eat meat, fish or poultry. Legumes and dark-green leafy vegetables like broccoli, kale and oriental greens are especially good sources of iron for vegetarians and vegans. However, spinach and Swiss chard contain oxalates which bind iron making it almost entirely unavailable for absorption. Iron from nonheme sources is more readily absorbed if consumed with foods that contain either heme-bound iron or vitamin C. This is due to a hypothesised "meat factor" which enhances iron absorption.

Iron deficiency can have serious health consequences that diet may not be able to quickly correct, and iron supplementation is often necessary if the iron deficiency has become symptomatic.

Bioavailability and bacterial infection

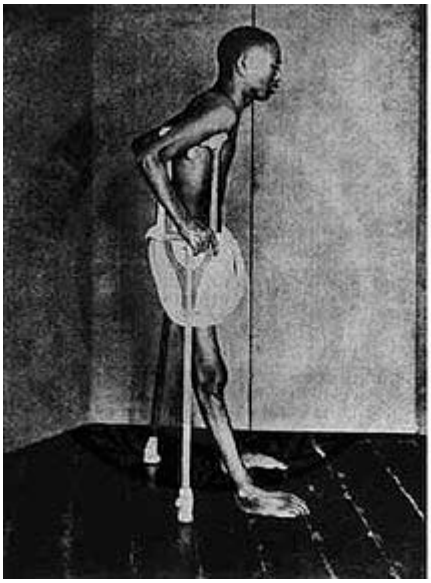
Iron is needed for bacterial growth making its bioavailability an important factor in controlling infection. Blood plasma as a result carries iron tightly bound to transferrin, and only releases it to cells with appropriate cell markers thus preventing its access to bacteria. Between 15 and 20 percent of the protein content in human milk consists of lactoferrin that binds iron. As a comparison, in cow's milk, this is only 2 percent. As a result, breast fed babies have fewer infections. Lactoferrin is also concentrated in tears, saliva and at wounds to bind iron to limit bacterial growth. Egg white contains 12% conalbumin to withhold it from bacteria that get through the egg shell (for this reason prior to antibiotics, egg white was used to treat infections).

To reduce bacterial growth, plasma concentrations of iron are lowered in fever, and following surgery after open wounds where it acts as a protection against infection. Reflecting this link between iron bioavailability and bacterial growth, the taking of iron supplements can increase the risk of infection. A moderate iron deficiency, in contrast, can provide protection against acute infection.

Chapter 9

Beriberi

Beriberi



A sufferer – turn of the 20th century in southeast Asia

ICD-10	E51.1
ICD-9	265.0
DiseasesDB	14107
eMedicine	ped/229 med/221
MeSH	D001602

Beriberi is a nervous system ailment caused by a **thiamine deficiency** (deficiency of vitamin B_1) in the diet. Thiamine is involved in the breakdown of energy molecules such

as glucose and is also found on the membranes of neurons. Symptoms of beriberi include severe lethargy and fatigue, together with complications affecting the cardiovascular, nervous, muscular, and gastrointestinal systems.

Etymology

The origin of the term is obscure. One hypothesis is that it comes from a Sinhalese phrase meaning "I cannot, I cannot", the word being reduplicated for emphasis. Another hypothesis is that it is from the Arabic "bhur-bhari", meaning "sailor's asthma."

History

In Asia, where polished white rice was the common staple food of the middle class, beriberi resulting from lack of vitamin B_1 was endemic. In 1884, Takaki Kanehiro, a British-trained Japanese medical doctor of the Japanese Navy, observed that beriberi was endemic among low-ranking crew who often ate nothing but rice, but not among crews of Western navies and officers who consumed a Western-style diet.

In 1883, Kanehiro learned of a very high incidence of beriberi among cadets on a training mission from Japan to Hawaii, via New Zealand and South America that lasted for 9 months. On board, 169 men out of 376 developed the disease and 25 died. With the support of the Japanese Navy, he conducted an experiment in which another ship was deployed on the same route and under identical conditions, except that its crew was fed a diet of meat, fish, barley, rice, and beans. At the end of the voyage, this crew had suffered only 14 cases of beriberi and no deaths. This convinced Kanehiro and the Japanese Navy that diet was the cause of beriberi.

This was confirmed in 1897, when Dr. Christiaan Eijkman, a Dutch physician and pathologist, demonstrated that beriberi is caused by poor diet. He discovered that feeding unpolished rice instead of the polished variety to chickens helped to prevent beriberi in the chickens.

The following year, Sir Frederick Hopkins postulated that some foods contained "accessory factors"—in addition to proteins, carbohydrates, fats, and salt—that were necessary for the functions of the human body.

In 1901, Gerrit Grijns (May 28, 1865 – November 11, 1944), Dutch physician and assistant to Christiaan Eijkman in Netherlands Indies, correctly interpreted the disease as a deficiency syndrome. Indeed, it was later shown that beriberi results from the deficiency of thiamine (vitamin B_1).

Dr. Edward Bright Vedder established (1910–13) an extract of rice bran as a treatment for beriberi.

Eijkman and Hopkins were awarded the 1929 Nobel Prize for Physiology or Medicine for the discovery.

Prevalence

Beriberi is rare in developed countries because most foods are now vitamin-enriched. Excluding the presence of arsenic in the environment (e.g. well water) one can get enough thiamine by eating a normal, healthy diet. Today, beriberi occurs mostly in patients who abuse alcohol. Drinking heavily can lead to poor nutrition, and excess alcohol makes it harder for the body to absorb and store thiamine.

General symptoms and effects

Its symptoms include weight loss, emotional disturbances, impaired sensory perception (Wernicke's encephalopathy), weakness and pain in the limbs, and periods of irregular heart rate. Edema (swelling of bodily tissues) is common. It may increase the amount of lactic acid and pyruvic acid within the blood. In advanced cases, the disease may cause heart failure and death.

Types

The main types of beriberi are:

- *Wet beriberi* affects the cardiovascular system.
- *Dry beriberi* and *Wernicke-Korsakoff syndrome* affect the nervous system.
- *Infantile beriberi* affects mostly children in countries that are developing.

Dry beriberi

Dry beriberi causes wasting and partial paralysis resulting from damaged peripheral nerves. It is also referred to as *endemic neuritis*. It is characterized by:

- Difficulty walking
- Tingling or loss of feeling (sensation) in hands and feet
- Loss of muscle function or paralysis of the lower legs
- Mental confusion/speech difficulties
- Pain
- Involuntary eye movements (nystagmus)
- Vomiting

Wet beriberi

Wet beriberi affects the heart; it is sometimes fatal, as it causes a combination of heart failure and weakening of the capillary walls, which causes the peripheral tissues to become edematous. It is also characterized by:

- Vasodilation leading to increased arteriovenous shunt
- Peripheral edema
- Awakening at night short of breath

- Increased heart rate
- Shortness of breath with activity
- Swelling of the lower legs

Infantile beriberi

This type of beriberi is commonly found in children in developing countries. Obvious signs and symptoms are crying, but not loudly and without tears. Untreated, it can prove fatal within 24 hours.

Exams and tests

A physical examination may show signs of congestive heart failure, which include:

- Difficulty breathing with neck veins that stick out
- Enlarged heart
- Fluid in the lungs
- Rapid heartbeat
- Swelling in both lower legs
- Confusion, memory loss, delusions, and lost sensitivity to vibrations may be witnessed on late-stage patients.

A neurological exam may show signs of:

- Changes in the gait
- Coordination problems
- Decreased reflexes
- Drooping of the eyelids

Blood tests will measure the amount of thiamine in the blood while urine tests will determine if thiamine is passing through the urine.

Treatment

The goal of treatment is to provide the thiamine the body is lacking. This is done with thiamine supplements which are given by injection or taken by mouth.

Other vitamins may also be recommended.

Subsequent blood tests will determine if the thiamine supplements are being effective.

Treatment for beriberi is with thiamine hydrochloride, either in tablet form or injection. A rapid and dramatic recovery within hours can be made when this is administered to patients, and their health can be improved within an hour of starting treatment. In emergency situations where concentrated thiamin supplements are unavailable, feeding

the patient with a thiamin-rich diet (e.g. whole grain brown bread) will lead to recovery, though at a much slower rate.

Causes

Beriberi is caused by a lack of thiamine (vitamin B_1). Thiamine occurs naturally in unrefined cereals and fresh foods, particularly whole grain bread, fresh meat, legumes, green vegetables, fruit, milk, etc. Beriberi is therefore common in people whose diet excludes these particular types of nutrition e.g. as a result of famine.

Beriberi may be found in people whose diet consists mainly of polished white rice, which is very low in thiamine because the thiamin-bearing husk has been removed. It can also be seen in chronic alcoholics (Wernicke-Korsakoff syndrome), Arsenic poisoning causes alterations in cellular metabolism resulting in blockage of thiamine use which results in thiamine deficiency without any dietary shortfall. The mechanism of arsenic neuropathy may be similar to the neuropathy of thiamine deficiency [Sexton and Gowdy 1963], whereby arsenic inhibits the conversion of pyruvate to acetyl coenzyme A and thus blocks the Krebs cycle.

The disease was often found in Asian countries (especially in the 19th century and before), due to those countries' reliance on white rice as a staple food.

Thiamine deficiency causes neuropathy through neuron death due to its effects upon astrocytes. This causes alterations in their glutamate uptake, through changes in the levels of the astrocytic glutamate transporters EAAT1 and EAAT2 creating excitotoxicity. Other changes include those to the GABA transporter subtype GAT-3, GFAP, glutamine synthetase, the water channel protein Aquaporin 4. These create lactic acidosis, brain edema, oxidative stress, inflammation, and white matter impairment.

A rare condition known as genetic beriberi is passed down through families. People with genetic beriberi lose the ability to absorb thiamine from foods. This can happen slowly over time and symptoms occur when the person is an adult. However, because doctors may not consider beriberi in non-alcoholics, this diagnosis is often missed.

Beriberi can occur in breast-fed infants when the mother's body is lacking in thiamine. The condition can also affect infants who are fed unusual formulas that don't have enough thiamine.

Chapter 10

Pellagra

Pellagra

Pellagra sufferer with skin lesions

ICD-10	E52.
DiseasesDB	9730
MedlinePlus	000342
eMedicine	ped/1755
MeSH	*C18.654.521.500.133.699.529*

Pellagra is a vitamin deficiency disease most commonly caused by a chronic lack of niacin (vitamin B_3) in the diet. It can be caused by decreased intake of niacin or

tryptophan, and possibly by excessive intake of leucine. It may also result from alterations in protein metabolism in disorders such as carcinoid syndrome. A deficiency of the amino acid lysine can lead to a deficiency of niacin as well.

History

The traditional food preparation method of corn (maize), nixtamalization, by native New World cultivators who had domesticated corn required treatment of the grain with lime, an alkali. It has now been shown that the lime treatment makes niacin nutritionally available and reduces the chance of developing pellagra. When corn cultivation was adopted worldwide, this preparation method was not accepted because the benefit was not understood. The original cultivators, often heavily dependent on corn, did not suffer from pellagra. Pellagra became common only when corn became a staple that was eaten without the traditional treatment.

Pellagra was first described in Spain in 1735 by Gaspar Casal, who published a first clinical description in his posthumous "Natural and Medical History of the Asturian Principality" (1762). This led to the disease being known as "Asturian leprosy", and it is recognized as the first modern pathological description of a syndrome. It was an endemic disease in northern Italy, where it was named "pelle agra" (pelle = skin; agra = sour) by Francesco Frapoli of Milan. Because pellagra outbreaks occurred in regions where maize was a dominant food crop, the belief for centuries was that the maize either carried a toxic substance or was a carrier of disease, people also believed it was carried by insects. It was not until later that the lack of pellagra outbreaks in Mesoamerica, where maize is a major food crop (and is processed), was noted and the idea was considered that the causes of pellagra may be due to factors other than toxins.

Dr. Joseph Goldberger

In the early 1900s, pellagra reached epidemic proportions in the American South. There were 1,306 reported pellagra deaths in South Carolina during the first ten months of 1915; 100,000 Southerners were affected in 1916. At this time, the scientific community held that pellagra was probably caused by a germ or some unknown toxin in corn. The Spartanburg Pellagra Hospital in Spartanburg, South Carolina, was the nation's first facility dedicated to discovering the cause of pellagra. It was established in 1914 with a special congressional appropriation to the U.S. Public Health Service (PHS) and set up primarily for research. In 1915, Joseph Goldberger, assigned to study pellagra by the Surgeon General of the United States, showed that pellagra was linked to diet by inducing the disease in prisoners, using the Spartanburg Pellagra Hospital as his clinic.

By 1926, Goldberger established that a balanced diet or a small amount of brewer's yeast prevented pellagra.

Goldberger performed an experiment using 11 volunteers from a prison, giving them clean clothes and keeping them in a house that was cleaned every day. Before the experiment, the prisoners were eating fruits and vegetables from the garden. Goldberger started feeding them only corn. About 2 weeks into the experiment the prisoners complained of headaches, confusion, and loss of appetite. In the third week, 7 of the 11 broke out in pellegra, and the prisoners begged for release. Goldberger cured them, feeding them fruits and vegetables again, and gave them their freedom. However, he failed to identify which element, the lack of which caused the pellagra. Goldberger continued his work but made no further progress.

Elvehjem showed that the vitamin niacin cured pellagra (manifested as black tongue) in dogs. Later studies by Tom Spies, Marion Blankenhorn, and Clark Cooper established that niacin also cured pellagra in humans, for which *Time* Magazine dubbed them its 1938 Men of the Year in comprehensive science.

In the research conducted between 1900 and 1950, it was found that the number of cases of women with pellagra was consistently double the number of cases of afflicted men. This is thought to be due to the inhibitory effect of estrogen on the conversion of the amino acid tryptophan to niacin. It is also thought to be due to the differential and unequal access to quality foods within the household. Some researchers of the time gave a few explanations regarding the difference. As primary wage earners, men were given consideration and preference at the dinner table. They also had pocket money to buy food outside the household. Women gave protein quality foods to their children first. Women also would eat after everyone else had a chance to eat. Women also upheld the triad of maize, molasses and fat back pork which combine to contribute to cause pellagra.

Gillman and Gillman related skeletal tissue and pellagra in their research in South African Blacks. They provide some of the best evidence for skeletal manifestations of pellagra and the reaction of bone in malnutrition. They claimed radiological studies of adult pellagrins demonstrated marked osteoporosis. A negative mineral balance in pellagrins was noted which indicated active mobilization and excretion of endogenous mineral substances, and undoubtedly impacted the turnover of bone. Extensive dental caries were present in over half of pellagra patients. In most cases caries were associated with "severe gingival retraction, sepsis, exposure of cementum, and loosening of teeth". Pellegra is no longer common in the United States, as niacin is now a required addition to certain foods.

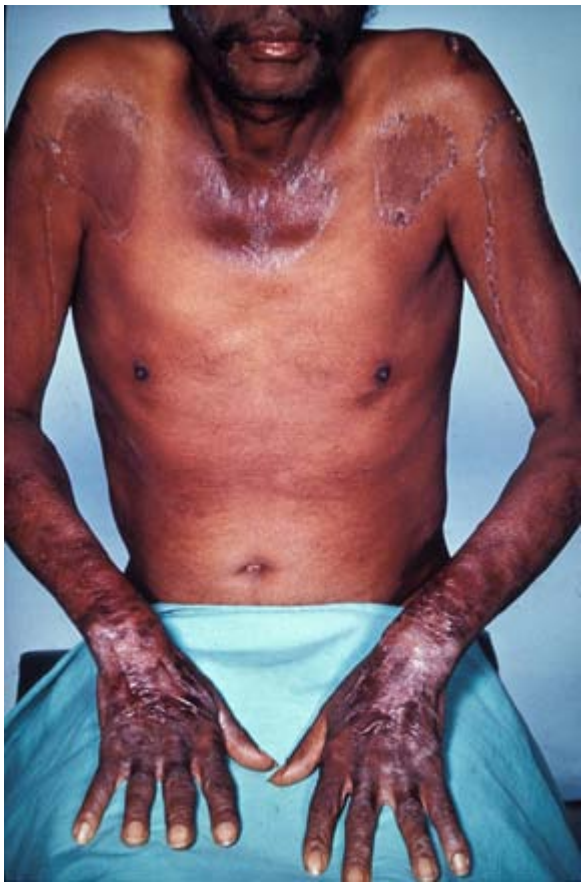
Epidemiology

Pellagra can be common in people who obtain most of their food energy from maize (often called "corn"), notably rural South America where maize is a staple food. Maize is a poor source of tryptophan as well as niacin if it is not nixtamalized. Nixtamalization of the corn corrects the niacin deficiency, and is a common practice in Native American

cultures that grow corn. Following the corn cycle, the symptoms usually appear during spring, increase in the summer due to greater sun exposure, and return the following spring. Indeed, pellagra was once endemic in the poorer states of the U.S. South, like Mississippi and Alabama, as well as among the inmates of jails and orphanages as studied by Dr. Joseph Goldberger.

Pellagra is common in Africa, Indonesia, and China. In affluent societies, a majority of patients with clinical pellagra are poor, homeless, alcohol dependent, or psychiatric patients who refuse food. It was common amongst prisoners of Soviet labor camps, the Gulag. It can be found in cases of chronic alcoholism. In addition, pellagra is a micronutrient deficiency disease that frequently affects populations of refugees and other displaced people due to their unique, long-term residential circumstances and dependence on food aid. Refugees typically rely on limited sources of niacin provided to them, such as groundnuts; the instability in the nutritional content and distribution of food aid can be the cause of pellagra in displaced populations.

Symptoms



The dermatologic features of this disorder include desquamation, erythema, scaling, and keratosis of sun-exposed areas, all of which this patient had.

Pellagra is classically described by "the four D's": diarrhea, dermatitis, dementia and death. A more comprehensive list of symptoms includes:

- High sensitivity to sunlight
- Aggression
- Dermatitis, alopecia, oedema
- Smooth, beefy red glossitis
- Red skin lesions
- Insomnia
- Weakness
- Mental confusion
- Ataxia, paralysis of extremities, peripheral neuritis
- Diarrhea
- Dilated cardiomyopathy
- Eventually dementia

Frostig and Spies (acc. to Cleary and Cleary) described more specific psychological symptoms of pellagra as:

- Psycho-sensory disturbances (impressions as being painful, annoying bright lights, odours intolerance causing nausea and vomiting, dizziness after sudden movements)

- Psycho-motor disturbances (restlessness, tense and a desire to quarrel, increased preparedness for motor action)

- Emotional disturbances

Pathophysiology

Pellagra can develop according to several mechanisms, all of which ultimately revolve around niacin deficiency. The first is simple dietary lack of niacin. Second, it may result from deficiency of tryptophan, an essential amino acid found in soybeans, meat, poultry, fish, and eggs that the body converts into niacin. Third, it may be caused by excess leucine, though the relationship is unclear.

Alterations in protein metabolism may also produce pellagra-like symptoms. An example of this is carcinoid syndrome, a disease in which carcinoid tumors produce excessive serotonin. In normal patients, only one percent of dietary tryptophan is converted to serotonin; however, in patients with carcinoid syndrome this value may increase to 70 percent. The diversion of tryptophan to making serotonin in patients with metastatic tumors can result in tryptophan deficiency. Carcinoid syndrome thus may produce decreased protein synthesis, niacin deficiency, and clinical manifestations of pellagra.

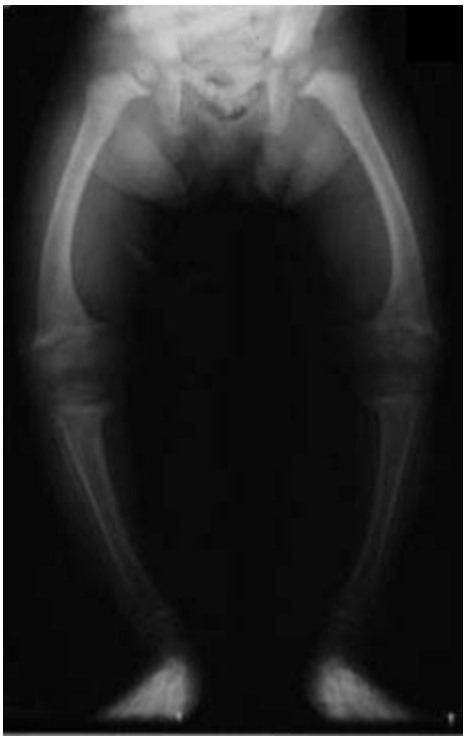
Prognosis

Untreated, the disease can kill within four or five years. Treatment is with nicotinamide, a chemical related to niacin. The frequency and amount of nicotinamide administered depends on the degree to which the condition has progressed.

Chapter 11

Rickets

Rickets



Radiograph of a two-year old rickets sufferer, with a marked genu varum (bowing of the femurs) and decreased bone opacity, suggesting poor bone mineralization.

ICD-10	E55.
ICD-9	268
DiseasesDB	9351

MedlinePlus	000344
eMedicine	ped/2014
MeSH	*D012279*

Rickets is a softening of bones in children due to deficiency or impaired metabolism of vitamin D, phosphorus or calcium, potentially leading to fractures and deformity. Rickets is among the most frequent childhood diseases in many developing countries. The predominant cause is a vitamin D deficiency, but lack of adequate calcium in the diet may also lead to rickets (cases of severe diarrhea and vomiting may be the cause of the deficiency). Although it can occur in adults, the majority of cases occur in children suffering from severe malnutrition, usually resulting from famine or starvation during the early stages of childhood. Osteomalacia is the term used to describe a similar condition occurring in adults, generally due to a deficiency of vitamin D. The origin of the word "rickets" is probably from the Old English dialect word 'wrickken', to twist. The Greek derived word "rachitis" (ραχίτις, meaning "inflammation of the spine") was later adopted as the scientific term for rickets, due chiefly to the words' similarity in sound.

Signs and symptoms

Signs and symptoms of rickets include:

- Bone pain or tenderness
- dental problems
- muscle weakness (rickety myopathy or "floppy baby syndrome" or "slinky baby" (where the baby is floppy or slinky-like)
- increased tendency for fractures (easily broken bones), especially greenstick fractures
- Skeletal deformity
    - Toddlers: Bowed legs (genu varum)
    - Older children: Knock-knees (genu valgum) or "windswept knees"
    - Cranial, spinal, and pelvic deformities
- Growth disturbance
- Hypocalcemia (low level of calcium in the blood), and
- Tetany (uncontrolled muscle spasms all over the body).
- Craniotabes (soft skull)
- Costochondral swelling (aka "rickety rosary" or "rachitic rosary")
- Harrison's groove
- Double malleoli sign due to metaphyseal hyperplasia
- Widening of wrist raises early suspicion, it is due to metaphysial cartilage hyperplasia.

An X-ray or radiograph of an advanced sufferer from rickets tends to present in a classic way: bow legs (outward curve of long bone of the legs) and a deformed chest. Changes in the skull also occur causing a distinctive "square headed" appearance. These deformities

persist into adult life if not treated. Long-term consequences include permanent bends or disfiguration of the long bones, and a curved back.

Types

- Nutritional Rickets
- Vitamin D Resistant Rickets
- Vitamin D Dependant Rickets
  - Type I
  - Type II
- Congenital Rickets

Cause

The primary cause of rickets is a vitamin D deficiency. Vitamin D is required for proper calcium absorption from the gut. Sunlight, especially ultraviolet light, lets human skin cells convert Vitamin D from an inactive to active state. In the absence of vitamin D, dietary calcium is not properly absorbed, resulting in hypocalcaemia, leading to skeletal and dental deformities and neuromuscular symptoms, e.g. hyperexcitability. Foods that contain vitamin D include butter, eggs, fish liver oils, margarine, fortified milk and juice, and oily fishes such as tuna, herring, and salmon. A rare X-linked dominant form exists called Vitamin D resistant rickets.

Cases have been reported in Britain in recent years of rickets in children of many social backgrounds caused by inability to make vitamin D because the sun's ultravoilet light was not reaching the skin because of persistent use of strong sunblock, or too much "covering up" in sunlight, or spending too much time indoors playing computer games; the *British Medical Journal* reported in 2010 that doctors in Newcastle on Tyne saw 20 cases of rickets per year.

Diagnosis

Rickets may be diagnosed with the help of:

- Blood tests:
  - Serum calcium may show low levels of calcium, serum phosphorus may be low, and serum alkaline phosphatase may be high.
- Arterial blood gases may reveal metabolic acidosis
- X-rays of affected bones may show loss of calcium from bones or changes in the shape or structure of the bones.
- Bone biopsy is rarely performed but will confirm rickets.

Treatment and prevention

ultraviolet light therapy and medicine.

Recommendations are for 400 international units (IU) of vitamin D a day for infants and children. Children who do not get adequate amounts of vitamin D are at increased risk of rickets. Vitamin D is essential for allowing the body to uptake calcium for use in proper bone calcification and maintenance.

Supplementation

Sufficient vitamin D levels can also be achieved through dietary supplementation and/or exposure to sunlight. Vitamin D_3 (cholecalciferol) is the preferred form since it is more readily absorbed than vitamin D_2. Most dermatologists recommend vitamin D supplementation as an alternative to unprotected ultraviolet exposure due to the increased risk of skin cancer associated with sun exposure. Endogenous production with full body exposure to sunlight is approximately 250 μg (10,000 IU) per day.

According to the American Academy of Pediatrics (AAP), infants who are breast-fed may not get enough vitamin D from breast milk alone. For this reason, the AAP recommends that infants who are exclusively breast-fed receive daily supplements of vitamin D from age 2 months until they start drinking at least 17 ounces of vitamin D-fortified milk or formula a day.

Epidemiology

In developed countries, rickets is a rare disease (incidence of less than 1 in 200,000).

Those at higher risk for developing rickets include:

- Breast-fed infants whose mothers are not exposed to sunlight
- Breast-fed infants who are not exposed to sunlight
- Babies with dark complexions (e.g. brown skin, South African), particularly when breastfed and exposed to little sunlight
- Individuals not consuming milk, such as those who are lactose intolerant

Individuals with red hair have been speculated to have a decreased risk for rickets due to their greater production of vitamin D in sunlight.

Children ages 6 months to 24 months are at highest risk, because their bones are rapidly growing. Long-term consequences include permanent bends or disfiguration of the long bones, and a curved back.

Chapter 12

Vitamin K Deficiency and Vitamin E Deficiency

Vitamin K deficiency

Vitamin K deficiency	
ICD-10	E56.1
ICD-9	269.0
eMedicine	med/2385
MeSH	D014813

Vitamin K deficiency is a form of avitaminosis resulting from insufficient vitamin K.

Causes

Vitamin K-deficiency may occur by disturbed intestinal uptake (such as would occur in a bile duct obstruction), by therapeutic or accidental intake of vitamin K-antagonists or, very rarely, by nutritional vitamin K deficiency. As a result, Gla-residues are inadequately formed and the Gla-proteins are insufficiently active.

Symptoms

Symptoms include ecchymosis, petechiae, hematomas, oozing of blood at surgical or puncture sites, stomach pains; risk of massive uncontrolled bleeding; cartilage calcification; and severe malformation of developing bone or deposition of insoluble calcium salts in the walls of arteries.

In infants, it can cause some birth defects such as underdeveloped face, nose, bones, and fingers.

Condition	Prothrombin time	Partial thromboplastin time	Bleeding time	Platelet count
Vitamin K deficiency or warfarin	prolonged	prolonged	unaffected	unaffected
Disseminated intravascular coagulation	prolonged	prolonged	prolonged	decreased
Von Willebrand disease	unaffected	prolonged	prolonged	unaffected
Haemophilia	unaffected	prolonged	unaffected	unaffected
Aspirin	unaffected	unaffected	prolonged	unaffected
Thrombocytopenia	unaffected	unaffected	prolonged	decreased
Early Liver failure	prolonged	unaffected	unaffected	unaffected
End-stage Liver failure	prolonged	prolonged	prolonged	decreased
Uremia	unaffected	unaffected	prolonged	unaffected
Congenital afibrinogenemia	prolonged	prolonged	prolonged	unaffected
Factor V deficiency	prolonged	prolonged	unaffected	unaffected
Factor X deficiency as seen in amyloid purpura	prolonged	prolonged	unaffected	unaffected
Glanzmann's thrombasthenia	unaffected	unaffected	prolonged	unaffected
Bernard-Soulier syndrome	unaffected	unaffected	prolonged	decreased

Vitamin supplementation

According to a study published in the October 14, 2008 edition of PLoS Medicine, Vitamin K (5mg of K_1/day) does not protect against age-related decreasing bone density, but may protect against fractures and cancers, in postmenopausal women taking calcium and vitamin D supplements.

Menaquinone (vitamin K_2), but not phylloquinone (vitamin K_1), intake is associated with reduced risk of CHD mortality, all-cause mortality and severe aortic calcification.

In a cohort study in Germany (11319 men, mean follow-up time 8.6y), Menaquinone intake was associated with decreased incidence of advanced prostate cancer.

Prevalence

The prevalence of vitamin K deficiency varies by geographic region.

For infants in the United States, vitamin K deficiency without bleeding may occur in as many as 50% of infants younger than 5 days old. Therefore, the Committee on Nutrition of the American Academy of Pediatrics recommends that 0.5 to 1.0 mg Vitamin K_1 be administered to all newborns shortly after birth.

Postmenopausal and elderly women in Thailand have high risk of Vitamin K_2 deficiency, compared with the normal value of young, reproductive females. Current dosage recommendations for Vitamin K may be too low.

The deposition of calcium in soft tissues, including arterial walls, is quite common, especially in those suffering from atherosclerosis, suggesting that Vitamin K deficiency is more common than previously thought.

Vitamin E deficiency

Vitamin E deficiency	
ICD-10	E56.0
ICD-9	269.1
DiseasesDB	13950
eMedicine	article/126187
MeSH	D014811

Vitamin E deficiency causes neurological problems due to poor nerve conduction. These include neuromuscular problems such as spinocerebellar ataxia and myopathies. Deficiency can also cause anemia, due to oxidative damage to red blood cells.

Vitamin E deficiency is rare in humans and is almost never caused by a poor diet. Instead, there are three specific situations when a vitamin E deficiency is likely to occur. It is seen in persons who cannot absorb dietary fat, has been found in premature, very low birth weight infants (birth weights less than 1500 grams, or 3.5 pounds), and is seen in individuals with rare disorders of fat metabolism.

Individuals who cannot absorb fat may require a vitamin E supplement because some dietary fat is needed for the absorption of vitamin E from the gastrointestinal tract. Anyone diagnosed with cystic fibrosis, individuals who have had part or all of their stomach removed, and individuals with malabsorptive problems such as Crohn's disease, liver disease or pancreatic insufficiency may not absorb fat and should discuss the need for supplemental vitamin E with their physician. People who cannot absorb fat often pass greasy stools or have chronic diarrhea and bloating.

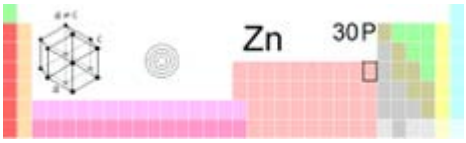
Very low birth weight infants may be deficient in vitamin E. A neonatologist, a pediatrician specializing in the care of newborns, typically evaluates the nutritional needs of premature infants.

Abetalipoproteinemia is a rare inherited disorder of fat metabolism that results in poor absorption of dietary fat and vitamin E. The vitamin E deficiency associated with this disease causes problems such as poor transmission of nerve impulses, muscle weakness, and degeneration of the retina that can cause blindness. Individuals with abetalipoproteinemia may be prescribed special vitamin E supplements by a physician to treat this disorder. In addition, there is a rare genetic condition termed isolated vitamin E deficiency or ataxia with isolated with vitamin E deficiency, caused by mutations in the gene for the tocopherol transfer protein. These individuals have an extremely poor capacity to absorb vitamin E and develop neurological complications that are reversed by high doses of vitamin E.

Chapter 13

Zinc Deficiency

Zinc deficiency	



Zinc

ICD-10	E60.
ICD-9	269.3
DiseasesDB	14272

Zinc deficiency is a lack of sufficient zinc to meet the needs of biological organisms. It can occur in both plants and animals. Zinc deficient soil is soil in which there is insufficient zinc to allow plants to grow normally.

Animals

Description

Hypozincemia is a condition where insufficient zinc is available for metabolic needs.

Prevalence

In fact, one-third of the world population is at risk of zinc deficiency, ranging from 4 to 73% depending on the country. Zinc deficiency is the fifth leading risk factor for disease in the developing world. Providing micronutrients, including zinc, to humans is one of

the four quick-win solutions to major global problems identified in the Copenhagen Consensus from an international panel of distinguished economists.

Conservative estimates suggest that 25% of the world's population is at risk of zinc deficiency.

Causes

Hypozincemia is usually a nutritional deficiency, but can also be associated with malabsorption, diarrhea, acrodermatitis enteropathica, chronic liver disease, chronic renal disease, sickle-cell disease, diabetes, malignancy, and other chronic illnesses. It can also occur after bariatric surgery.

Zinc deficiency is typically the result of inadequate dietary intake of zinc, disease states that promote zinc losses, or physiological states that require increased zinc. Populations that consume primarily plant based diets that are low in bioavailable zinc often have zinc deficiencies. Diseases or conditions that involve intestinal malabsorption promote zinc losses. Fecal losses of zinc caused by diarrhea are one contributing factor., often common in developing countries. Changes in intestinal tract absorbability and permeability due, in part, to viral, protozoal, and bacteria pathogens may also encourage fecal losses of zinc. Physiological states that require increased zinc include periods of growth in infants and children as well as in mothers during pregnancy.

Signs and symptoms

Signs of zinc deficiency include hair loss, skin lesions, diarrhea, and wasting of body tissues. A lack of zinc can contribute to acne. Eyesight, taste, smell and memory are also connected with zinc. A deficiency in zinc can cause malfunctions of these organs and functions. Congenital abnormalities causing zinc deficiency may lead to a disease called acrodermatitis enteropathica.

One easily recognized sign which may be caused by zinc deficiency is white spots, bands, or lines on fingernails (leukonychia). An occasional white spot is usually evidence that the immune system overcame a bacterial or some other systemic infection, and is a positive, not negative sign. Some women may have multiple parallel white bands or lines on the fingernails marking menstrual cycles when marginal zinc deficiency was present.

Anorexia

Zinc deficiency may cause a decrease in appetite which can degenerate into anorexia or anorexia nervosa. Appetite disorders, in turn, cause malnutrition and, notably, inadequate zinc intake. Anorexia itself is a cause of zinc deficiency, thus leading to a vicious cycle: the worsening of anorexia worsens the zinc deficiency. The use of zinc in the treatment of anorexia has been advocated since 1979 by Bakan. At least 15 trials showed that zinc improved weight gain in anorexia. A 1994 randomized, double-blind, placebo-controlled trial showed that zinc (14 mg per day) doubled the rate of body mass increase in the

treatment of anorexia nervosa (AN). Deficiency of other nutrients such as tyrosine and tryptophan (precursors of the monoamine neurotransmitters norepinephrine and serotonin, respectively), as well as vitamin B_1 (thiamine) could contribute to this phenomenon of malnutrition-induced malnutrition.

Cognitive and motor function impairment

Cognitive and motor function may also be impaired in zinc deficient children. Zinc deficiency can interfere with many organ systems especially when it occurs during a time of rapid growth and development when nutritional needs are high, such as during infancy. In animal studies, rats who were deprived of zinc during early fetal development exhibited increased emotionality, poor memory, and abnormal response to stress which interfered with performance in learning situations. Zinc deprivation in monkeys showed that zinc deficient animals were emotionally less mature, and also had cognitive deficits indicated by their difficulty in retaining previously learned problems and in learning new problems. Human observational studies show weaker results. Low maternal zinc status has been associated with less attention during the neonatal period and worse motor functioning. In some studies, supplementation has been associated with motor development in very low birth weight infants and more vigorous and functional activity in infants and toddlers.

Diarrhea and pneumonia

Zinc deficiency contributes to an increased incidence and severity of diarrhea and pneumonia. Studies have shown that zinc treatment results in a 25 percent reduction in duration of acute diarrhea and a 40 percent reduction in treatment failure or death in persistent diarrhea. The studies determined that a ten-day therapy of zinc treatment can considerably reduce the duration and severity of diarrheal episodes, decrease stool output, and lessen the need for hospitalization. Zinc may also prevent future diarrhea episodes for up to three months. The current World Health Organization recommendation for diarrhea control includes the use of 20 mg per day of zinc supplementation for 10 to 14 days (10 mg per day for infants under the age of six months). A zinc taste test may have potential for diagnosing deficiency.

Dysmenorrhea

High dose of zinc, 30 mg 1-3 times a day, prevents dysmenorrhea.

Pregnancy

Zinc deficiency during pregnancy can negatively affect both the mother and fetus. Animal studies indicate that maternal zinc deficiency can upset both the sequencing and efficiency of the birth process. An increased incidence of difficult and prolonged labor, hemorrhage, uterine dystocia and placental abruption has been documented in zinc deficient animals. These effects may be mediated by the defective functioning of estrogen via the estrogen receptor, which contains a zinc finger protein. A review of pregnancy

outcomes in women with acrodermatitis enteropathica, reported that out of every seven pregnancies, there was one abortion and two malfunctions, suggesting the human fetus is also susceptible to the teratogenic effects of severe zinc deficiency. However, a review on zinc supplementation trials during pregnancy did not report a significant effect of zinc supplementation on neonatal survival.

Vitamins A and D

Plasma zinc levels have been found to be dependent upon vitamins A and D. This suggests that a Vitamin A or D deficiency could cause a secondary zinc deficiency and that for treatment of zinc deficiency one should ensure adequate vitamin A and D intake.

Hunger

The influence of zinc on hunger is complex and likely depends upon the status of other nutrients, the developmental stage of the animal, and percentage body fat. Some research groups have argued for a role of zinc deficiency decreasing appetite, while others have shown zinc ingestion can reduce feelings of hunger by increasing leptin levels. There is evidence that the way zinc influences hunger depends on the sodium/osmotic status of the organism, with low sodium/low zinc levels increasing hunger and high sodium/low zinc levels decreasing it. An organism with a low level of zinc has an increased susceptibility to hypoosmotic stress and cell rupture. Thus if the osmotic pressure is too low the organism may be inclined to eat to raise osmolality and prevent osmotic shock. It should be noted that zinc is known to affect osmolality by increasing sodium retention.

In rats, the "first visible sign" of zinc deficiency is a decreased appetite.

Treatment

Zinc supplementation has been shown to reduce diarrhea prevalence and mortality in children younger than 5 years of age.

To combat zinc deficiency, five intervention strategies can be used:

- Supplementation using medicines
- Food fortification through the incorporation of zinc additives in food
- Dietary modification/diversification
- Genetic biofortification through plant breeding
- Agronomic biofortification through zinc fertilization.

These five intervention strategies may be used individually or in combination, depending on the setting, target group and degree of zinc deficiency.

The amount of zinc absorbed by the human body is a function of dietary intake of both zinc and phytate (a phosphate storage compound that chelates zinc), because the ratio between these two substances affects the bioavailability of zinc. Meeting the needs for

absorbed zinc requires an increase in the zinc content and/or a decrease in the phytate content.

Plants, crops, and soils

Zinc is an essential micronutrient needed not only by people but also by crops. Almost half of the world's cereal crops are deficient in zinc, leading to poor crop yields. Many agricultural countries around the world are affected by zinc deficiencies. In China, zinc deficiency occurs on around half of the agricultural soils, affecting mainly rice and maize.

In India, zinc-deficient soils occupy almost 50% of the agricultural area and are a critical constraint on yield, but crops are highly responsive to zinc fertilization.

In Turkey, major yield and quality benefits in wheat have been obtained with the widespread use of zinc fertilizers, where half of the cereal growing land is zinc-deficient.

Research has shown that areas with zinc-deficient soils are often regions with widespread zinc deficiency in humans.

A basic knowledge of the dynamics of Zn in soils, understanding of the uptake and transport of Zn in plant systems and characterizing the response of plants to Zn deficiency are essential steps in achieving sustainable solutions to the problem of Zn deficiency in plants and humans (Zinc in soils and crop nutrition), International Fertilizer Industry Association (IFA)and International Zinc Association (IZA).)

Fertilization

Experiments show that soil and foliar application of zinc fertilizer can effectively reduce the phytate:zinc ratio in grain. People who eat bread prepared from zinc enriched wheat show a significant increase in serum zinc, suggesting that the zinc fertilizer strategy may be a viable commercial approach to address zinc deficiencies in humans.

Where zinc deficiency is a limiting factor, zinc fertilization can increase crop yields. Balanced crop nutrition supplying all essential nutrients, including zinc, is a cost effective management strategy. Even with zinc-efficient varieties, zinc fertilizers are needed when the available zinc in the topsoil becomes depleted.

Plant breeding, including modern biotechnology, can improve:

Zinc uptake capacity of plants under soil conditions with low chemical availability of zinc; Zinc translocation, thus elevating zinc content in edible crop parts rather than the rest of the plant; Zinc bioavailability. For optimal efficiency, zinc-efficient genotypes should be associated with complementary soil crop management (including fertilization) to ensure adequate zinc uptake by roots and thus enhance zinc nutrition of crops and humans

Turkey

Central Anatolia, in Turkey, was a region with zinc-deficient soils and widespread zinc deficiency in humans. In 1993, a research project found that yields could be increased by 6 to 8-fold and children nutrition dramatically increased through zinc fertilization.

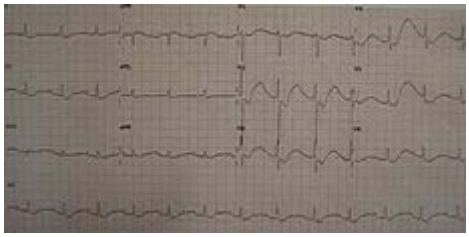
Through a partnership with Cukurova University, the State and the private company TOROS Agri Industry Group, zinc was added to fertilizers. While the product was initially made available at the same cost, the results were so convincing that Turkish farmers significantly increased the use of the zinc-fortified fertilizer (1 per cent of zinc) within a few short years, despite the repricing of the products to reflect the added value of the content.

Today, nearly 10 years after the identification of the zinc deficiency problem, the total amount of zinc-containing compound fertilizers produced and applied in Turkey reached a record level of 300,000 tonnes per annum. It is estimated that the economic benefits associated with the application of Zn-fertilizers on Zn deficient soils in Turkey is around US$ 100 million per year. Zinc deficiency in children has been dramatically reduced.

Chapter 14

Hypokalemia

Hypokalemia



An ECG in a person with a potassium level of 1.1 showing the classical ECG changes of ST segment depression, inverted T waves, large U waves, and a slightly prolonged PR interval.

ICD-10	E87.6
ICD-9	276.8
DiseasesDB	6445
MedlinePlus	000479
eMedicine	emerg/273
MeSH	D007008

Hypokalaemia (British English), **hypopotassemia** (ICD-9) or **Hypokalemia** (American English) refers to the condition in which the concentration of potassium (K^+) in the blood

is low. The prefix *hypo-* means "under" (contrast with *hyper-*, meaning "over"); *kal-* refers to *kalium*, the Neo-Latin for potassium, and *-emia* means "condition of the blood."

Normal serum potassium levels are between 3.5 to 5.0 mEq/L; at least 95% of the body's potassium is found inside cells, with the remainder in the blood. This concentration gradient is maintained principally by the Na+/K+ pump.

Signs and symptoms

Mild hypokalemia is often without symptoms, although it may cause a small elevation of blood pressure, and can occasionally provoke cardiac arrhythmias. Moderate hypokalemia, with serum potassium concentrations of 2.5-3 mEq/L, may cause muscular weakness, myalgia, and muscle cramps (owing to disturbed function of the skeletal muscles), and constipation (from disturbed function of smooth muscles). With more severe hypokalemia, flaccid paralysis and hyporeflexia may result. There are reports of rhabdomyolysis occurring with profound hypokalemia with serum potassium levels less than 2 mEq/L. Respiratory depression from severe impairment of skeletal muscle function is found in many patients.

Some electrocardiographic (ECG) findings associated with hypokalemia include flattened or inverted T waves, a U wave, ST depression and a wide QT interval.

Causes

Hypokalemia can result from one or more of the following medical conditions:

Inadequate potassium intake

- Perhaps the most obvious cause is insufficient consumption of potassium (that is, a low-potassium diet) or starvation. However, without excessive potassium loss from the body, this is a rare cause of hypokalemia.

Gastrointestinal/integument loss

- A more common cause is excessive loss of potassium, often associated with heavy fluid losses that "flush" potassium out of the body. Typically, this is a consequence of diarrhea, excessive perspiration, or losses associated with surgical procedures. Vomiting can also cause hypokalemia, although not much potassium is lost from the vomitus. Rather, there are heavy urinary losses of K^+ in the setting of post-emetic bicarbonaturia that force urinary potassium excretion. Other GI causes include pancreatic fistulae and the presence of adenoma.

Urinary loss

- Certain medications can cause excess potassium loss in the urine. Diuretics, including thiazide diuretics (e.g. hydrochlorothiazide) and loop diuretics (e.g.

furosemide) are a common cause of hypokalemia. Other medications such as the antifungal, amphotericin B, or the cancer drug, cisplatin, can also cause long-term hypokalemia.

- A special case of potassium loss occurs with diabetic ketoacidosis. In addition to urinary losses from polyuria and volume contraction, there is also obligate loss of potassium from kidney tubules as a cationic partner to the negatively charged ketone, β-hydroxybutyrate.
- Hypomagnesemia can cause hypokalemia. Magnesium is required for adequate processing of potassium. This may become evident when hypokalemia persists despite potassium supplementation. Other electrolyte abnormalities may also be present.
- Alkalosis can cause transient hypokalemia by two mechanisms. First, the alkalosis causes a shift of potassium from the plasma and interstitial fluids into cells; perhaps mediated by stimulation of Na^+-H^+ exchange and a subsequent activation of Na^+/K^+-ATPase activity. Second, an acute rise of plasma HCO_3^- concentration (caused by vomiting, for example) will exceed the capacity of the renal proximal tubule to reabsorb this anion, and potassium will be excreted as an obligate cation partner to the bicarbonate. Metabolic alkalosis is often present in states of volume depletion, so potassium is also lost via aldosterone-mediated mechanisms.
- Disease states that lead to abnormally high aldosterone levels can cause hypertension and excessive urinary losses of potassium. These include renal artery stenosis and tumors (generally non-malignant) of the adrenal glands. Cushing's syndrome can also lead to hypokalaemia due to excess cortisol binding the Na+/K+ pump and acting like aldosterone. Hypertension and hypokalemia can also be seen with a deficiency of the 11-beta-hydroxysteroid dehydrogenase type 2 enzyme which allows cortisols to stimulate aldosterone receptors. This deficiency—known as apparent mineralocorticoid excess syndrome -- can either be congenital or caused by consumption of glycyrrhizin, which is contained in extract of licorice, sometimes found in herbal supplements, candies and chewing tobacco.
- Rare hereditary defects of renal salt transporters, such as Bartter syndrome or Gitelman syndrome, can cause hypokalemia, in a manner similar to that of diuretics. As opposed to disease states of primary excesses of aldosterone, blood pressure is either normal or low in Bartter's or Gitelman's.

Distribution away from ECF

- In addition to alkalosis, other factors can cause transient shifting of potassium into cells, presumably by stimulation of the Na-K-ATPase. These hormones and medications include insulin, epinephrine, and other beta agonists (e.g. salbutamol or salmeterol), and xanthines (e.g. Theophylline).

- Rare hereditary defects of muscular ion channels and transporters that cause hypokalemic periodic paralysis can precipitate occasional attacks of severe hypokalemia and muscle weakness. These defects cause a heightened sensitivity to the normal changes in potassium produced by catechols and/or insulin and/or

thyroid hormone, which lead to movement of potassium from the extracellular fluid into the muscle cells.

Other/ungrouped

- There have been a handful of published reports describing individuals with severe hypokalemia related to chronic extreme consumption (4-10 L/day) of colas. The hypokalemia is thought to be from the combination of the diuretic effect of caffeine and copious fluid intake, although it may also be related to diarrhea caused by heavy fructose ingestion.

Pseudohypokalemia

- Pseudohypokalemia is a decrease in the amount of potassium that occurs due to excessive uptake of potassium by metabolically active cells after blood has been drawn. It is a laboratory artifact that may occur when blood samples remain in warm conditions for several hours before processing.

Pathophysiology

Potassium is essential for many body functions, including muscle and nerve activity. The electrochemical gradient of potassium between the intracellular and extracellular space is essential for nerve function; in particular, potassium is needed to repolarize the cell membrane to a resting state after an action potential has passed. Decreased potassium levels in the extracellular space will cause hyperpolarization of the resting membrane potential. This hyperpolarization is caused by the effect of the altered potassium gradient on resting membrane potential as defined by the Goldman equation. As a result, a greater than normal stimulus is required for depolarization of the membrane in order to initiate an action potential.

In certain conditions, this will make cells less excitable. However, in the heart, it causes myocytes to become hyperexcitable. Lower membrane potentials in the atrium may cause arrhythmias because of more complete recovery from sodium-channel inactivation, making the triggering of an action potential more likely. In addition, the reduced extracellular potassium (paradoxically) inhibits the activity of the I_{Kr} potassium current and delays ventricular repolarization. This delayed repolarization may promote reentrant arrythmias.

Treatment

The most important treatment in severe hypokalemia is addressing the cause, such as improving the diet, treating diarrhea or stopping an offending medication. Patients without a significant source of potassium loss and who show no symptoms of hypokalemia may not require treatment.

Mild hypokalemia (>3.0 mEq/L) may be treated with oral potassium chloride supplements (Klor-Con, Sando-K, Slow-K). As this is often part of a poor nutritional intake, potassium-containing foods may be recommended, such as leafy green vegetables, tomatoes, citrus fruits, oranges or bananas. Both dietary and pharmaceutical supplements are used for people taking diuretic medications.

Severe hypokalemia (<3.0 mEq/L) may require intravenous (IV) supplementation. Typically, a saline solution is used, with 20-40 mEq KCl per liter over 3–4 hours. Giving IV potassium at faster rates (20-25 mEq/hr) may predispose to ventricular tachycardias and requires intensive monitoring. A generally safe rate is 10 mEq/hr. Even in severe hypokalemia, oral supplementation is preferred given its safety profile. Sustained release formulations should be avoided in acute settings.

Difficult or resistant cases of hypokalemia may be amenable to a potassium-sparing diuretic, such as amiloride, triamterene, or spironolactone. Concomittant hypomagnesiumemia will inhibit potassium replacement as magnesium is a cofactor for potassium uptake.

When replacing potassium intravenously, infusion via a central line is encouraged to avoid the frequent occurrence of a burning sensation at the site of a peripheral IV, or the rare occurrence of damage to the vein. When peripheral infusions are necessary, the burning can be reduced by diluting the potassium in larger amounts of IV fluid, or mixing 3 ml of 1% lidocaine to each 10 meq of KCl per 50 ml of IV fluid. The practice of adding lidocaine, however, raises the likelihood of serious medical errors.

In other animals

Cats can develop hypokalemia, which may be manifested by abnormal gait and an inability to keep the head elevated. Cats respond well to dietary supplementation of potassium chloride. A feline form of hypokalemic periodic paralysis has been described in Burmese kittens, which appears to be related to an autosomal recessive mutation. Although these kittens are not hypokalemic between episodes, regular supplementation of [KCl] seems effective.

Chapter 15

Copper Deficiency

Copper deficiency	
ICD-10	E61.0
ICD-9	275.1

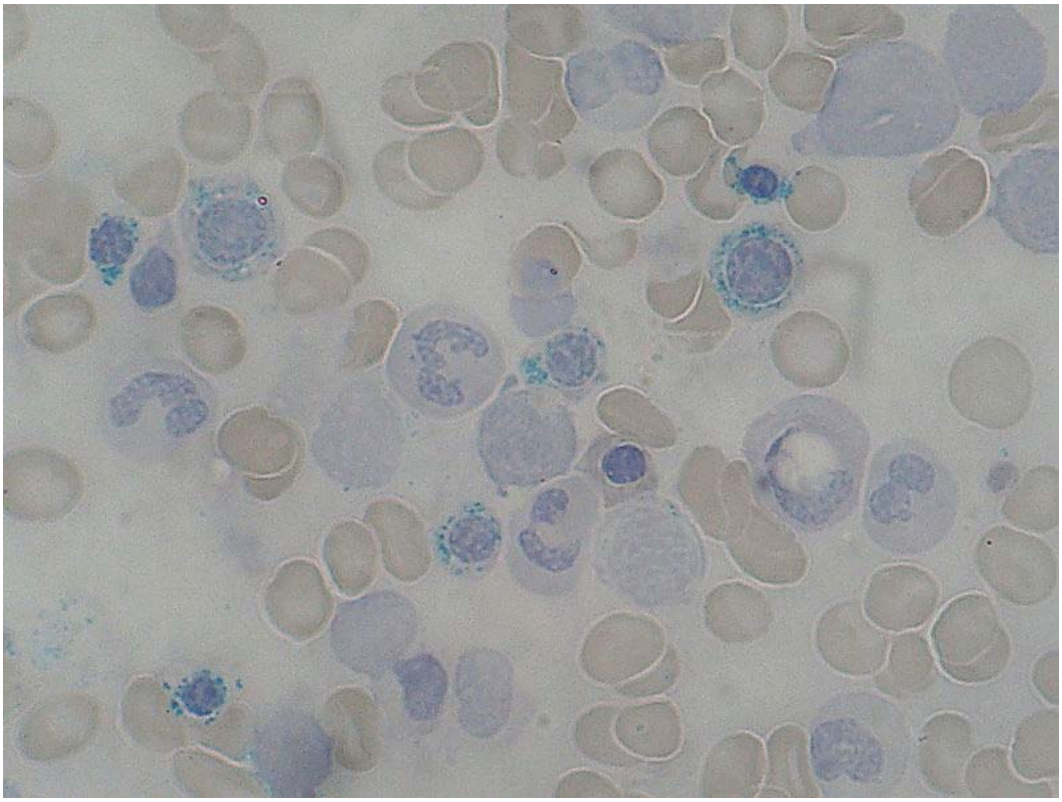
Copper deficiency is a very rare hematological and neurological disorder The neurodegenerative syndrome of copper deficiency has been recognized for some time in ruminant animals, in which it is commonly known as "swayback" The disease involves a nutritional deficiency in the trace element copper. Copper is ubiquitous and daily requirement is low making acquired copper deficiency very rare. Copper deficiency can manifest in parallel with vitamin B12 deficiency and zinc toxicity. The most common cause of copper deficiency is a remote gastrointestinal surgery, such as gastric bypass surgery, due to malabsorption of copper. Menkes disease is a variation of copper deficiency involving a wide variety of symptoms . Menkes disease is a congenital genetic disorder that is often fatal. Copper is involved in normalized function of many enzymes, such as cytochrome c oxidase, which is complex IV in mitochondrial electron transport chain, ceruloplasmin, Cu/Zn superoxide dismutase, and in amine oxidases. These enzyme catalyze reactions for oxidative phosphorylation, iron transportation, antioxidant and free radical scavenging and neutralization, and neurotransmitter synthesis, respectively . A regular diet contains a variable amount of copper, but may provide 5 mg/day , of which only 20-50% are absorbed. . The diet of the elderly have shown to have lower copper amounts than the recommended daily intake . Dietary copper can be found in whole grain cereals, legumes, oysters, organ meats (livers), cherries, dark chocolate, fruits, leafy green vegetables, nuts, poultry, prunes, and soybeans products like tofu . The deficiency in copper can cause many hematological manifestations, such as myelodysplasia, anemia, leukopenia (low white blood cell count) and neutropenia (low count of neutrophils, a type of white blood cell that is often called "the first line of defense" for the immune system). Copper deficiency has long been known for as a cause of myelodysplasia(when a blood profile has indicators of possible future leukemia development), but it was until recently in 2001 that copper deficiency was associated with neurological manifestations. Some

neurological manifestations can be sensory ataxia (irregular muscle coordination), peripheral neuropathy (damage in the peripheral nerves) and myelopathy (disease of the spinal cord) .

Symptoms

Hematological Presentation

Most sufferers generally complain about tiredness, fatigue, and light headedness. These are all common symptoms of anemia. Around half of the patients displayed some kind of anemia with



Ring Sideroblast smear 2010-01-13

markedly reduced leukocytes also known as “leukopenia” . In addition to leukopenia, many patients are deficient in neutrophils (neutropenia) . Neutropenia has become a hematological hallmark, enabling physicians to investigate copper deficiency as a diagnosis . All types of anemia including microcytic (small red blood cells), macrocytic (large red blood cells, leaving insufficient amounts of hemoglobin per unit volume of blood) and normocytic (a deficiency in normal sized red blood cells) manifest . It is very rarely that thrombocytopenia, which is a syndrome of low blood platelets leading to slowed clotting and abnormal bleeding, is observed in patients . Usually prolonged

copper deficiency has to persist to manifest thrombocytopenia . Many times during a bone marrow biopsy, decreased granulocyte (which are granulated white blood cells including neutrophils, eosinophils, and basophils) maturation, vacuolization of red blood cell precursors, and ringed sideroblastic cells are present . Sideroblastic cells have unusual patterns of iron clumping in the mitochondria that is visible when the cell is stained, receiving its name "ringed" sideroblast . Subacute combined degeneration is also a degeneration of the spinal cord, but instead of copper deficiency as the cause of degeneration, vitamin B12 deficiency is the cause. . These bone marrow findings can lead to a diagnosis of myelodysplasia . Myelodysplasia is sometimes referred to "preleukemia." . This disease often later progresses into a form of leukemia. Most of the people who are diagnosed with myelodysplasia will have to undergo a stem cell transplantation. A diagnosis of copper deficiency at the state is crucial to prevent unnecessary painful surgery, such as the bone marrow biopsy.

Neurological Presentation

Copper deficiency can cause a wide variety of neurological problems including, myelopathy, peripheral neuropathy, and optic neuropathy .

Myelopathy

Sufferers typically present difficulty walking (gait difficulty) caused by sensory ataxia (irregular muscle coordination) due to dorsal column dysfunction or degeneration of the spinal chord (myelopathy) . Patients with ataxic gait have problems balancing and display an unstable wide walk. They often feel tremors in their torso, causing side way jerks and lunges . In brain MRI, there is often an increased T2 signalling at the posterior columns of the spinal cord in patients with myelopathy caused by copper deficiency . T2 signalling is often an indicator of some kind of neurodegeneration. There are some changes in the spinal cord MRI involving the thoracic cord, the cervical cord or sometimes both . Copper deficiency myelopathy is often compared to subacute combined degeneration (SCD) . Subacute combined degeneration is also a degeneration of the spinal chord, but instead vitamin B12 deficiency is the cause of the spinal degeneration. SCD also has the same high T2 signalling intensities in the posterior column as copper deficient patient in MRI imaging .

Peripheral Neuropathy

Another common symptom of copper deficiency is peripheral neuropathy, which is numbness or tingling that can start in the extremities and can sometimes progress radially inward towards the torso . In an Advances in Clinical Neuroscience & Rehabilitation (ACNR) published case report, a 69 year old patient had progressively worsened neurological symptoms . These symptoms included diminished upper limb reflexes with abnormal lower limb reflexes, sensation to light touch and pin prick was diminished above the waist, vibration sensation was lost in the sternum, and markedly reduced proprioception or sensation about the self's orientation. Many people suffering from the neurological effects of copper deficiency complain about very similar or identical

symptoms as the patient. This numbness and tingling poses danger for the elderly because it increases their risk of falling and injuring themselves. Peripheral neuropathy can become very disabling leaving some patients dependent on wheel chairs or walking canes for mobility if there is lack of correct diagnosis. Rarely can copper deficiency cause major disabling symptoms. The deficiency will have to be present for an extensive amount of time until such disabling conditions manifest.

Optic Neuropathy

Some patients suffering from copper deficiency have shown signs of vision and color loss. The vision is usually lost in the peripheral views of the eye . The bilateral vision loss is usually very gradual. An optical coherence tomography (OCT) shows some nerve fiber layer loss in most patients, suggesting the vision loss and color vision loss was secondary to optic neuropathy or neurodegeneration.

Causes

Surgery

Bariatric surgery is a common cause of copper deficiency . Bariatric surgery, such as gastric bypass surgery, is often used for weight control of the morbidly obese. The disruption of the intestines and stomach from the surgery can cause absorption difficulties not only in copper, but also in iron and vitamin B12 and many other nutrients . The symptoms of copper deficiency myelopathy may take a long time to develop, sometimes decades before the myelopathy symptoms manifest.

Zinc Toxicity

Increased consumption of zinc is another cause of copper deficiency. Zinc is often used for the prevention or treatment of common colds and sinusitis (inflammation of sinuses due to an infection), ulcers, sickle cell disease, celiac disease, memory impairment and acne . Zinc is found in many common vitamin supplements and is also found in denture creams . Denture cream was recently accused of causing neurological problems, such as numbness, tingling, muscle weakness, and anemia, in their consumers.

Metallic zinc is the core of all United States currency coins, including copper coated pennies. People who ingest massive amount of coins will have elevated zinc levels, leading to zinc toxicity induced copper deficiency and thus displaying neurological symptoms. This is the case for a 57 year old woman who was diagnosed with schizophrenia. This woman consumed over 600 coins, and started to show neurological symptoms such as unsteady gait and mild ataxia .

Heriditary Disorders

Menkes disease showing symptoms of the sparse, steel colored "kinky hair" and paleness

Menkes disease is a congenital disease that is a cause of copper deficiency . Menkes disease is a hereditary condition caused by a defective gene involved with the metabolism of copper in the body . Menkes disease involves a wide variety of symptoms including floppy muscle tone, seizures, abnormally low temperatures, and a peculiar steel color hair that feels very rough . Menkes disease is usually a fatal disease with most children dying within the first ten years of life .

Other

It is rarely suggested that excess iron supplementation causes copper deficiency myelopathy . Another more rare cause of copper deficiency is celiac disease, probably due to malabsorption in the intestines. . Still, a large percentage, around 20%, of cases have unknown causes .

Biochemical Etiology

Copper functions as a prosthetic group, which permits election transfers in key enzymatic pathways like theelectron transport chain . Copper is integrated in the enzymes cytochrome c oxidase, which is involved in cellular respiration and oxidative

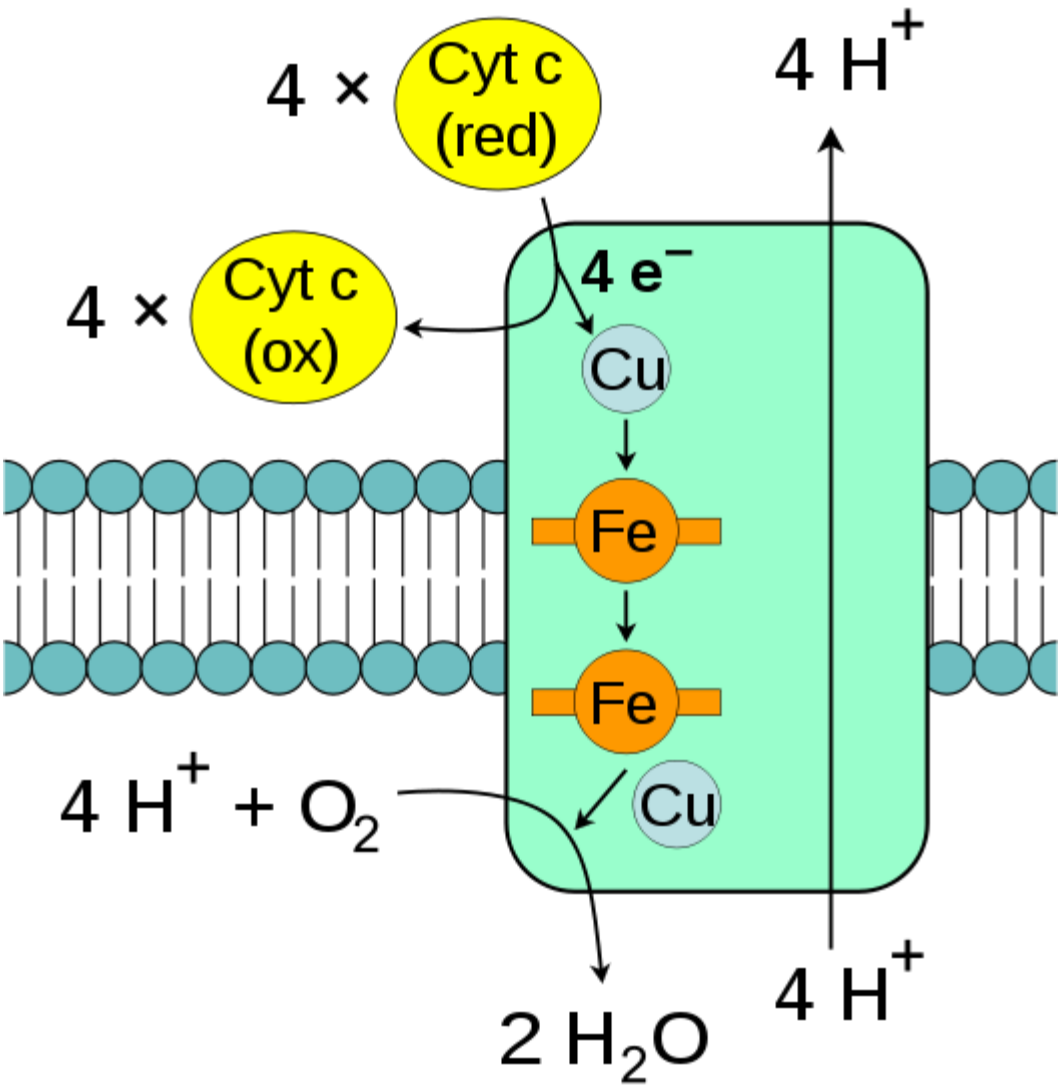
phosphorylation, Cu/Zn dismutase, which is involved in antioxidant defense, and many more listed in the table below.

Several Copper Dependent Enzymes and Their Function

Group	Enzyme	Function
Oxidases	Flavin-containing amine oxidase	Metabolism of neurotransmitters: noradrenaline, dopamine, serotonin and some dietary amines
	Protein-lysine-6-oxidase (lysyl oxidase)	Connective tissue synthesis-cross-linking of collagen and elastin
	Copper-containing amine oxidase	Metabolism of amines-histamines, putrescine, cadaverine
	Cytochrome c oxidase	Oxidative phosphorylation, electron transport in the mitochondrial membrane
	Superoxide dismutase (Cu/Zn dismutase)	Antioxidant and free radical scavenger, oxidizes dangerous superoxides to safer hydrogen peroxide
	Ferroxidase I (ceruloplasmin)	Iron transport-oxidation of Fe2+ to Fe 3+, copper storage and transport, antioxidant and free radical neutralizer
	Hephaestin (ferroxidase)	Iron transport and oxidation of Fe2+ to Fe3+ in intestinal cells to enable iron uptake
Monooxygenases	Dopamine beta-monooxygenase	Conversion of dopamine to norepinephrine
	Peptidylglycine monooxygenase	Peptide hormone maturation-amidation of alpha-terminal carboxylic acid group of glycine
	Monophenol monooxygenase (Tyrosinase)	Melanin synthesis
Methylation Cycle	Methionine synthase	Transfer of methyl group from methyltetrahydrofolate to homocysteine to generate methionine for the methylation cycle and tetrahydrofolate for

		purine synthesis
	Adenosylhomocysteinase (S-Adenosyl-L-homocysteine)	Regeneration of homocysteine from adenosylhomocyesteine (S-Adenosyl-L-homocysteine) in the methylation cycle

Neurological Etiology

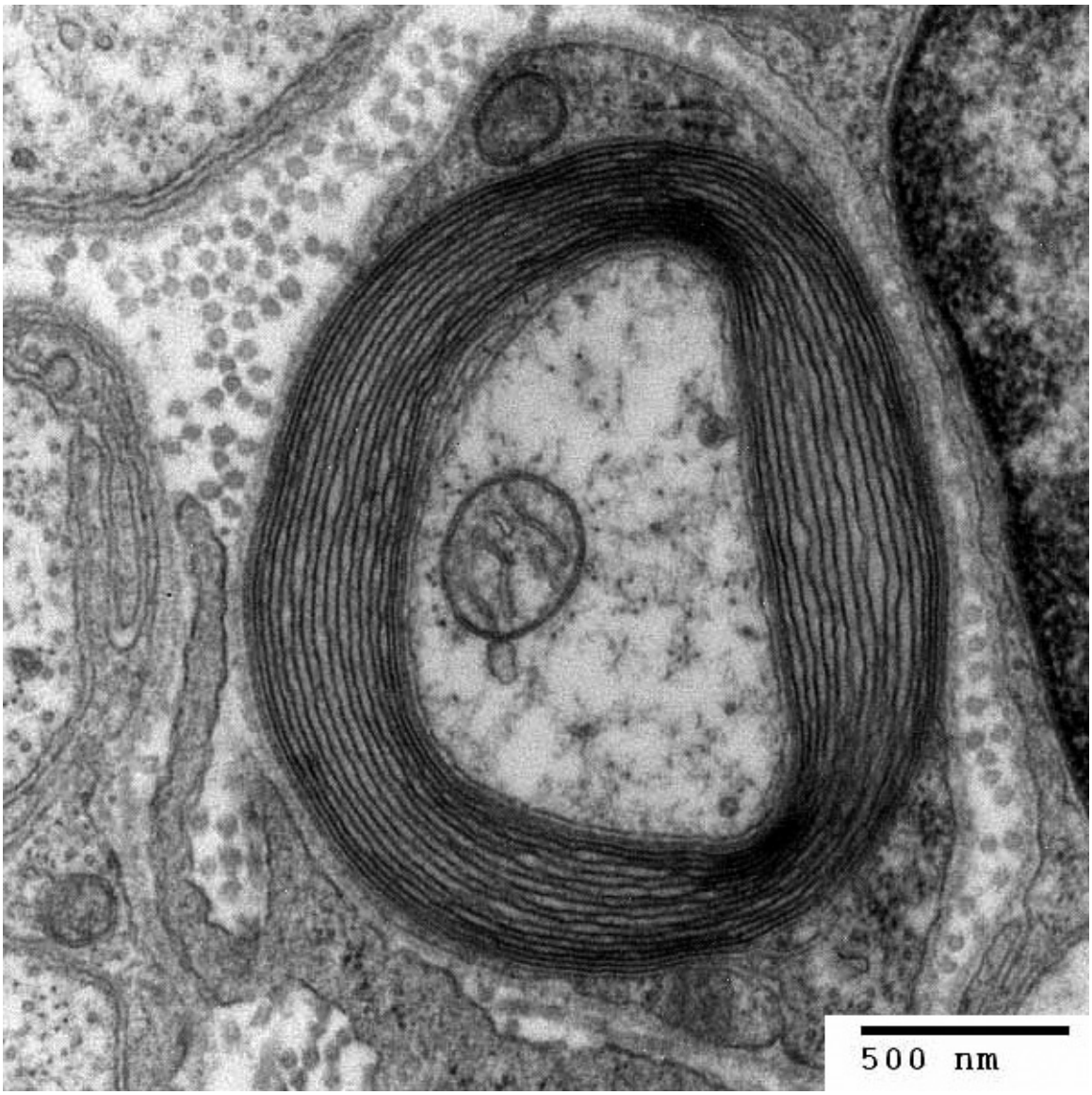


Cytochrome c Oxidase mechanism in mitochondrial membrane

Cytochrome c Oxidase

There have been several hypotheses about the role of copper and some of its neurological manifestations. Some suggest that disruptions in cytochrome c oxidase, also known as Complex IV, of the electron transport chain is responsible for the spinal cord degeneration .

Methylation Cycle



Myelinated neuron

Another hypothesis is that copper deficiency myelopathy is caused by disruptions in the methylation cycle. The methylation cycle causes a transfer of a methyl group (-CH3) from methyltetrahydrofolate to a range of macromolecules by the suspected copper dependent enzyme methionine synthase. This cycle is able to produce purines, which are

a component of DNA nucleotide bases, and also myelin proteins. The spinal cord is surrounded by a layer of protective protein coating called myelin. When this methionine synthase enzyme is disrupted, the methylation decreases and myelination of the spinal cord is impaired. This cycle ultimately causes myelopathy.

Hematological Etiology

Iron Transportation

The anemia caused by copper deficiency is thought to be caused by impaired iron transport. Hephaestin is a copper containing ferroxidase enzyme located in the duodenal muscosa that oxidizes iron and facilitate its transfer across the basolateral membrane into circulation. Another iron transporting enzyme is ceruloplasmin . This enzyme is required to mobilize iron from the reticuloendothelial cell to plasma . Ceruloplasmin also oxidizes iron from its ferrous state to the ferric form that is required for iron binding . Impairment in these copper dependent enzymes that transport iron may cause the secondary iron deficiency anemia . Another speculation for the cause of anemia is involving the mitochondrial enzyme cytochrome c oxidase (complex IV in the electron transport chain). Studies have shown that animal models with impaired cytochrome c oxidase failed to synthesize heme from ferric iron at the normal rate . The lower rate of the enzyme might also cause the excess iron to clump, giving the heme an unusual pattern . This unusual pattern is also knows as ringed sideroblastic anemia cells.

Cell Growth Hault

The cause of neutropenia is still unclear; however, the arrest of maturing myelocytes, or neutrophil precursors, may cause the neutrophil deficiency .

Zinc Intoxification

Zinc intoxication may cause anemia by blocking the absorption of copper from the stomach and duodenum . Zinc also upregulates the expression of chelator metallothionein in enterocytes, which are the majority of cells in the intestinal epithelium. Since copper has a higher affinity for metallothionein than zinc, the copper will remain bound inside the enterocyte, which will be later eliminated through the lumen . This mechanism is exploited therapeutically to achieve negative balance in Wilson's disease, which involves an excess of copper .

Treatment

Copper deficiency is a very rare disease and is often misdiagnosed several times by physicians before concluding the deficiency of copper through differential diagnosis (copper serum test and bone marrow biopsy are usually conclusive in diagnosing copper deficiency). On average, patients are diagnosed with copper deficiency around 1.1 years after their first symptoms are reported to a physician . Copper deficiency can be treated with either oral copper supplementation or intravenous copper. If zinc intoxication is

present, discontinuation of zinc may be sufficient to restore copper levels back to normal, but this usually is a very slow process . People who suffer from zinc intoxication will usually have to take copper supplements in addition to ceasing zinc consumption. Hematological manifestations are often quickly restored back to normal. The neurological symptoms will often cease, but the symptoms are not always restored back to normal.

Chapter 16

Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome

Obesity hypoventilation syndrome often improves with positive airway pressure treatment administered overnight by a machine such as this device

ICD-10	E66.2
ICD-9	278.8
OMIM	257500
DiseasesDB	32243
MedlinePlus	000085
eMedicine	ped/1627 med/3470
MeSH	D010845

Obesity hypoventilation syndrome (also known as **Pickwickian syndrome**) is a condition in which severely overweight people fail to breathe rapidly enough or deeply

enough, resulting in low blood oxygen levels and high blood carbon dioxide (CO_2) levels. Many people with this condition also frequently stop breathing altogether for short periods of time during sleep (obstructive sleep apnea), resulting in many partial awakenings during the night, which leads to continual sleepiness during the day. The disease puts strain on the heart, which eventually may lead to the symptoms of heart failure, such as leg swelling and various other related symptoms. The most effective treatment is weight loss, but it is often possible to relieve the symptoms by nocturnal ventilation with positive airway pressure (CPAP) or related methods.

Obesity hypoventilation syndrome is defined as the combination of obesity (body mass index above 30 kg/m^2), hypoxia (falling oxygen levels in blood) during sleep, and hypercapnia (increased blood carbon dioxide levels) during the day, resulting from hypoventilation (excessively slow or shallow breathing). The disease has been known since the 1950s, initially as "Pickwickian syndrome" in reference to a Dickensian character but currently under a more descriptive name.

Classification

Obesity hypoventilation syndrome is a form of sleep disordered breathing. Two subtypes are recognized, depending on the nature of disordered breathing detected on further investigations. The first is OHS in the context of obstructive sleep apnea; this is confirmed by the occurrence of 5 or more episodes of apnea, hypopnea or respiratory-related arousals per hour (high apnea-hypopnea index) during sleep. The second is OHS primarily due to "sleep hypoventilation syndrome"; this requires a rise of CO_2 levels by 10 mmHg (1.3 kPa) after sleep compared to awake measurements and overnight drops in oxygen levels without simultaneous apnea or hypopnea. Overall, 90% of all people with OHS fall into the first category, and 10% in the second.

Signs and symptoms

Most people with obesity hypoventilation syndrome have concurrent obstructive sleep apnea, a condition characterized by snoring, brief episodes of apnea (cessation of breathing) during the night, interrupted sleep and excessive daytime sleepiness. In OHS, sleepiness may be worsened by elevated blood levels of carbon dioxide, which causes drowsiness ("CO_2 narcosis"). Other symptoms present in both conditions are depression, and hypertension (high blood pressure) that is difficult to control with medication. The high carbon dioxide can also cause headaches, which tend to be worse in the morning.

The low oxygen level leads to excessive strain on the right side of the heart, known as *cor pulmonale*. Symptoms of this disorder occur because the heart has difficulty pumping blood from the body through the lungs. Fluid may therefore accumulate in the skin of the legs in the form of edema (swelling), and in the abdominal cavity in the form of ascites; decreased exercise tolerance and exertional chest pain may occur. On physical examination, characteristic findings are the presence of a raised jugular venous pressure, a palpable parasternal heave, a heart murmur due to blood leaking through the tricuspid

valve, hepatomegaly (an enlarged liver), ascites and leg edema. Cor pulmonale occurs in about a third of all people with OHS.

Mechanism

It is not fully understood why some obese people develop obesity hypoventilation syndrome while others do not. It is likely that it is the result of an interplay of various processes. Firstly, work of breathing is increased as adipose tissue restricts the normal movement of the chest muscles and makes the chest wall less compliant, the diaphragm moves less effectively, respiratory muscles are fatigued more easily, and airflow in and out of the lung is impaired by excessive tissue in the head and neck area. Hence, people with obesity need to expend more energy to breathe effectively. These factors together lead to sleep-disordered breathing and inadequate removal of carbon dioxide from the circulation and hence hypercapnia; given that carbon dioxide in aqueous solution combines with water to form an acid (CO_2[g] + H_2O[l] + excess H_2O[l] --> H_2CO_3[aq]), this causes acidosis (increased acidity of the blood). Under normal circumstances, central chemoreceptors in the brain stem detect the acidity, and respond by increasing the respiratory rate; in OHS, this "ventilatory response" is blunted.

The blunted ventilatory response is attributed to several factors. Obese people tend to have raised levels of the hormone leptin, which is secreted by adipose tissue and under normal circumstances increases ventilation. In OHS, this effect is reduced. Furthermore, episodes of nighttime acidosis (e.g. due to sleep apnea) lead to compensation by the kidneys with retention of the alkali bicarbonate. This normalizes the acidity of the blood. However, bicarbonate stays around in the bloodstream for longer, and further episodes of hypercapnia lead to relatively mild acidosis and reduced ventilatory response in a vicious circle.

Low oxygen levels lead to hypoxic pulmonary vasoconstriction, the tightening of small blood vessels in the lung to create an optimal distribution of blood through the lung. Persistently low oxygen levels causing chronic vasoconstriction leads to increased pressure on the pulmonary artery (pulmonary hypertension), which in turn puts strain on the right ventricle, the part of the heart that pumps blood to the lungs. The right ventricle undergoes remodeling, becomes distended and is less able to remove blood from the veins. When this is the case, raised hydrostatic pressure leads to accumulation of fluid in the skin (edema), and in more severe cases the liver and the abdominal cavity.

The chronically low oxygen levels in the blood also lead to increased release of erythropoietin and the activation of erythropoeisis, the production of red blood cells. This results in polycythemia, abnormally increased numbers of circulating red blood cells and an elevated hematocrit.

Diagnosis

Formal criteria for diagnosis of OHS are:

- Body mass index over 30 kg/m^2 (a measure of obesity, obtained by taking one's weight in kilograms and dividing it by one's height in meters squared)
- Arterial carbon dioxide level over 45 mmHg or 6.0 kPa as determined by arterial blood gas measurement
- No alternative explanation for hypoventilation, such as use of narcotics, severe obstructive or interstitial lung disease, severe chest wall disorders such as kyphoscoliosis, severe hypothyroidism (underactive thyroid), neuromuscular disease or congenital central hypoventilation syndrome

If OHS is suspected, various tests are required for its confirmation. The most important initial test is the demonstration of elevated carbon dioxide in the blood. This requires an arterial blood gas determination, which involves taking a blood sample from an artery, usually the radial artery. Given that it would be complicated to perform this test on every patient with sleep-related breathing problems, some suggest that measuring bicarbonate levels in normal (venous) blood would be a reasonable screening test. If this is elevated (27 mmol/l or higher), further investigations for OHS may be needed.

To distinguish various subtypes, polysomnography is required. This usually requires brief admission to a hospital with a specialized sleep medicine department where a number of different measurements are conducted while the subject is asleep; this includes electroencephalography (electronic registration of electrical activity in the brain), electrocardiography (same for electrical activity in the heart), pulse oximetry (measurement of oxygen levels) and often other modalities. Blood tests are also recommended for the identification of hypothyroidism and polycythemia.

To distinguish between OHS and various other lung diseases that can cause similar symptoms, medical imaging of the lungs (such as a chest X-ray or CT/CAT scan), spirometry, electrocardiography and echocardiography may be performed. Echo- and electrocardiography may also show strain on the right side of the heart caused by OHS, and spirometry may show a restrictive pattern related to obesity.

Treatment

In people with stable OHS, the most important treatment is weight loss—by diet, through exercise, with medication, or sometimes weight loss surgery (bariatric surgery). This has been shown to improve the symptoms of OHS and resolution of the high carbon dioxide levels. Weight loss may take a long time and is not always successful. Bariatric surgery is avoided if possible, given the high rate of complications, but may be considered if other treatment modalities are ineffective in improving oxygen levels and symptoms. If the symptoms are significant, nighttime positive airway pressure (PAP) treatment is tried; this involves the use of a machine to assist with breathing. PAP exists in various forms, and the ideal strategy is uncertain. Some medications have been tried to stimulate breathing or correct underlying abnormalities; their benefit is again uncertain.

While many people with obesity hypoventilation syndrome are cared for on an outpatient basis, some deteriorate suddenly and when admitted to hospital may show severe

abnormalities such as markedly deranged blood acidity (pH<7.25) or depressed level of consciousness due to very high carbon dioxide levels. On occasions, admission to an intensive care unit with intubation and mechanical ventilation is necessary. Otherwise, "bi-level" positive airway pressure is commonly used to stabilize the patient, followed by conventional treatment.

Positive airway pressure

Positive airway pressure, initially in the form of *continuous* positive airway pressure (CPAP), is a useful treatment for obesity hypoventilation syndrome, particularly when obstructive sleep apnea co-exists. CPAP requires the nighttime use of a machine that delivers a continuous positive pressure to the airways and preventing the collapse of soft tissues in the throat during breathing; it is administered through a mask on either the mouth and nose together, or if that is not tolerated on the nose only (nasal CPAP). This relieves the features of obstructive sleep apnea, and is often sufficient to remove the resultant accumulation of carbon dioxide. The pressure is increased until the obstructive symptoms (snoring and periods of apnea) have disappeared. CPAP alone is effective in more than 50% of people with OHS.

In some occasions, the oxygen levels are persistently too low (oxygen saturations below 90%). In that case, the hypoventilation itself may be improved by switching from CPAP treatment to an alternate device that delivers "bi-level" positive pressure: higher pressure during inspiration (breathing in) and a lower pressure during expiration (breathing out). If this too is ineffective in increasing oxygen levels, addition of oxygen therapy may be necessary. As a last resort, tracheostomy may necessary; this involves making a surgical opening in the trachea to bypass obesity-related airway obstruction in the neck. This may be combined with mechanical ventilation with an assisted breathing device through the opening.

Other treatments

Medroxyprogesterone, a form of the hormone progesterone, has been shown to improve the ventilatory response, but this has been poorly studied and is associated with an increased risk of thrombosis. Similarly, the drug acetazolamide can reduce bicarbonate levels, and thereby augment to normal ventilatory response, but this has been researched insufficiently to recommend wide application.

Prognosis

Obesity hypoventilation syndrome is associated with a reduced quality of life, and people with the condition incur increased healthcare costs, largely due to hospital admissions including observation and treatment on intensive care units. OHS often occurs together with several other disabling medical conditions, such as asthma (in 18–24%) and type 2 diabetes (in 30–32%). Its main complication of heart failure affects 21–32% of patients.

Those with abnormalities severe enough to warrant treatment have an increased risk of death, reported to be 23% over 18 months and 46% over 50 months. This risk is reduced to less than 10% in those receiving treatment with PAP. Treatment also reduces the need for hospital admissions and reduces healthcare costs.

Epidemiology

The exact prevalence of obesity hypoventilation syndrome is unknown, and it is thought that many people with symptoms of OHS have not been diagnosed. About a third of all people with morbid obesity (a body mass index exceeding 40 kg/m^2) have elevated carbon dioxide levels in the blood.

When examining groups of people with obstructive sleep apnea, researchers have found that 10–20% of them meet the criteria for OHS as well. The risk of OHS is much higher is those with more severe obesity, i.e. a body mass index (BMI) of 40 kg/m^2 or higher. It is twice as common in men compared to women. The average age at diagnosis is 52. American Black people are more likely to be obese than American whites, and are therefore more likely to develop OHS, but obese Asians are more likely than people of other ethnicities to have OHS at a lower BMI as a result of physical characteristics.

It is anticipated that rates of OHS will rise as the prevalence of obesity rises. This may also explain why OHS is more commonly reported in the United States, where obesity is more common, than in other countries.

History

The discovery of obesity hypoventilation syndrome is generally attributed to the authors of a 1956 report of a professional poker player who, after gaining weight, became somnolent and fatigued and prone to fall asleep during the day, as well as developing edema of the legs suggesting heart failure. The authors coined the condition "Pickwickian syndrome" after the character Joe from Dickens' *The Posthumous Papers of the Pickwick Club* (1837), who was markedly obese and tended to fall asleep uncontrollably during the day. This report, however, was preceded by other descriptions of hypoventilation in obesity. In the 1960s, various further discoveries were made that led to the distinction between obstructive sleep apnea and sleep hypoventilation.

Chapter 17

Magnesium Deficiency (Medicine) , Chromium Deficiency and Selenium Deficiency

Magnesium deficiency (medicine)

Magnesium deficiency

Magnesium

ICD-10	E61.2
MedlinePlus	002423

Magnesium deficiency refers to an intake of dietary magnesium below minimal levels, which can result in numerous symptoms and diseases. These can generally be remedied by an increase of magnesium in diet or oral supplements. However intravenous supplementation is necessary for more severe cases.

Symptoms

Symptoms of magnesium deficiency include: hyperexcitability, muscle weakness and fatigue. Severe magnesium deficiency can cause hypocalcemia, low serum potassium levels (hypokalemia), retention of sodium, low circulating levels of PTH, neurological and muscular symptoms (tremor, muscle spasms, tetany), loss of appetite, nausea,

vomiting, personality changes and death from heart failure. Magnesium plays an important role in carbohydrate metabolism and its deficiency may worsen insulin resistance, a condition that often precedes diabetes, or may be a consequence of insulin resistance.

Incidence/prevalence

61% of the US population does not meet the US RDA for levels of magnesium. The kidneys are very efficient at maintaining body levels, but not in cases where the diet is deficient.

Terminology

"Magnesium depletion" (ICD10 code E83.4) should be distinguished from hypomagnesemia, since the first refers to a disorder of magnesium metabolism, and is much more difficult to treat. However, in the past, the terms have sometimes been used interchangeably. Magnesium deficiency can be present without hypomagnesemia, and hypomagnesemia can be present without magnesium deficiency.

Causes of magnesium deficiency include alcohol abuse, poorly controlled diabetes, excessive or chronic vomiting and/or diarrhea. Certain drugs can also deplete magnesium levels such as osmotic diuretics, cisplatin, ciclosporin, amphetamines, and possibly proton pump inhibitors. Also deficiency may occur in Bartter syndrome and Gitelman syndrome.

Treatments

Magnesium is absorbed orally at about 30% bioavailability from any *water soluble salt,* such as magnesium chloride or magnesium citrate. The citrate is the least expensive soluble (high bioavailability) oral magnesium salt available in supplements, with 100 mg and 200 mg magnesium typically contained per capsule or tablet.

Magnesium aspartate, chloride, lactate, citrate and glycinate each have bioavailability 4 times greater than the oxide form and are equivalent to each other per amount of magnesium, though not in price.

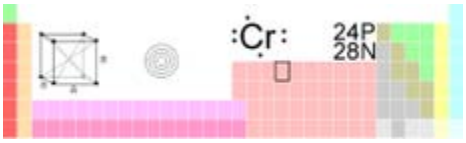
The ligand of choice for large-scale manufacturers of multivitamins and minerals containing magnesium is the magnesium oxide due to its compactness, high magnesium content by weight, low cost, and ease-of-use in manufacturing. However it is insoluble in water. Insoluble magnesium salts such as magnesium oxide or magnesium hydroxide (milk of magnesia) depend on stomach acid for neutralization before they can be absorbed, and thus are relatively poor oral magnesium sources, on average.

Magnesium sulfate (Epsom salts) are soluble in water, but are commonly used as a purgative, due to the poor absorption of the sulfate component. In lower doses, they may be used as an oral magnesium source, however.

Severe hypomagnesemia is often treated medically with intravenous or intramuscular magnesium sulfate solution, which is completely bioavailable, and effective.

Chromium deficiency

Chromium deficiency



Chromium

ICD-10	E61.4
DiseasesDB	2625

Chromium deficiency is a disorder that results from an insufficient dietary intake of chromium. Whether or not such a deficiency ever occurs in people eating a normal diet is debated, and clear cases of deficiency have only been observed in hospital patients who were fed defined liquid diets intravenously for long periods of time. Although chromium is an essential trace element in humans, the basis for this need is not fully understood, since no chromium-containing biomolecules with beneficial effects have been characterized.

Use of chromium in the body

Trivalent chromium is the state that has been discussed as a possible essential trace metal; hexavalent chromium is toxic and mutagenic.

Trivalent chromium was thought to be a constituent in the so-called glucose tolerance factor (GTF). GTF has been hypothesised to be a metalloprotein complex that is formed when the oligopeptide chromodulin, which consists of the four amino acid residues aspartate, cysteine, glutamate, and glycine, is bonded with four (Cr^{3+}) centers. Some studies have suggested that chromodulin could bind to the insulin receptor and stimulate insulin signaling. However, the existence of this glucose tolerance factor remains uncertain, a 2001 academic review concluded that "To date, no chromium-containing glucose tolerance factor has been characterized, the purpose of the low-molecular-weight chromium-binding protein is questionable, and no direct interaction between chromium and insulin has been found."

Dietary guidelines

The US dietary guidelines for adequate daily chromium intake were lowered in 2001 from 50–200 µg for an adult to 30–35 µg (adult male) and to 20–25 µg (adult female). These amounts were set to be the same as the average amounts consumed by healthy individuals. Consequently, it is thought that few Americans are chromium deficient.

Approximately 2% of ingested chromium(III) is absorbed, with the remainder being excreted in the feces. Amino acids, vitamin C and niacin may enhance the uptake of chromium from the intestinal tract. After absorption, this metal accumulates in the liver, bone, and spleen.

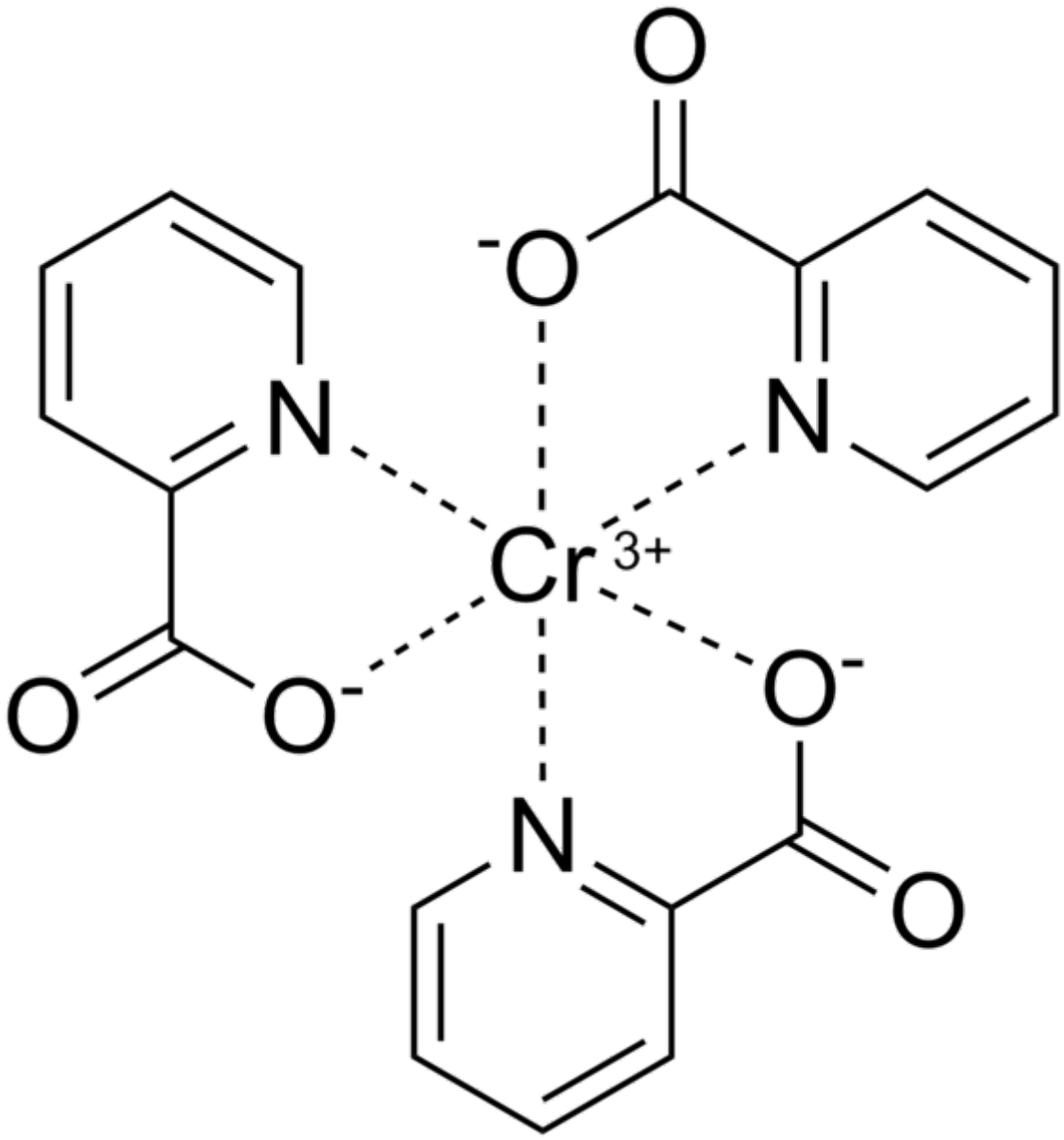
Trivalent chromium is found in a wide range of foods, including: whole-grain products, processed meats, high-bran breakfast cereals, coffee, nuts, green beans, broccoli, spices, and some brands of wine and beer. Most fruits and vegetables and dairy products only contain low amounts. Most of the chromium in people's diet comes from processing or storing food in pans and cans made of stainless steel, which can contain up to 18% chromium.

The amount of chromium in the body can be decreased as a result of a diet high in simple sugars, which increases the excretion of the metal through urine. Because of the high excretion rates and the very low absorption rates of most forms of chromium, acute toxicity is uncommon.

Symptoms

The symptoms of chromium deficiency caused by long-term total parenteral nutrition are severely impaired glucose tolerance, a loss of weight, and confusion. Another patient also developed nerve damage (peripheral neuropathy).

Supplementation



Chromium picolinate

Chromium picolinate is the most commonly used synthetic supplement. However, recent studies "have concluded that such supplements have no demonstrated effects on healthy individuals." A meta-analysis in 2002 found no effect on blood glucose or insulin in healthy people, and the data were inconclusive for diabetics. Subsequent trials gave mixed results, with one finding no effect in people with impaired glucose tolerance, but another seeing a small improvement in glucose resistance. In a 2007 review of these and other clinical trials it was again concluded that chromium supplements had no beneficial effect on healthy people, but that there might be an improvement in glucose metabolism in diabetics, although the authors stated that the evidence for this effect remains weak.

A 2003 pilot trial of 15 patients suggested that chromium picolinate might have antidepressant effects in atypical depression. A larger trial in 2005 set up to test this finding found no effect on depression in its test group, but suggested that the use of chromium supplementation could help to reduce carbohydrate cravings and regulate appetite in these patients. A post-hoc analysis of a subpopulation of patients in this study that experienced high carbohydrate cravings suggested that these patients experienced significant improvements in their depression compared to those treated with a placebo.

This supplement is purported to correct imbalances in glucose metabolism due to chromium deficiency, even though the occurrence of such a deficiency is extremely rare in countries where the supplement is sold. The mechanism by which this complex enters the cells in the body differs from that for the introduction of trivalent chromium found naturally in food does, and for this reason the safety of this supplement is debatable, since chromium is toxic at high levels. For chromium to be used in the cells it must be released from chromium picolinate, in a process in which the chromium becomes reduced. This process can possibly lead to the formation of dangerous reactive oxygen species.

Although it is controversial if supplements should be taken by healthy adults eating a normal diet, chromium is needed as a component of the defined liquid diet that is given to patients receiving total parenteral nutrition (TPN), since deficiency can occur after many months of this highly restricted diet. As a result chromium is added to normal TPN solutions, although the trace amounts from even in supposedly "chromium free" preparations may be enough to prevent deficiency in some individuals. Indeed, a 1992 paper in *The Lancet* suggested that adding chromium to feeding solutions given to children produces excessive levels of this metal in their bodies.

Selenium deficiency

Selenium deficiency

Selenium

ICD-10	E59.
ICD-9	269.3
DiseasesDB	11941

Selenium deficiency is relatively rare in healthy well-nourished individuals. Few cases have been reported.

Causes

It can occur in patients with severely compromised intestinal function, those undergoing total parenteral nutrition, those who have had gastrointestinal bypass surgery, and also on advanced aged people (over 90).

Alternatively, people dependent on food grown from selenium-deficient soil are also at risk.

Reference ranges

In the USA, the Dietary Reference Intake for adults is 55 μg/day. In the UK it is 75 μg/day for adult males and 60 μg/day for adult females. 55 μg/day recommendation is based on full expression of plasma glutathione peroxidase. Selenoprotein P is a better indicator of selenium nutritional status, and full expression of it would require more than 66 μg/day.

Presentation

Selenium deficiency can lead to Keshan disease, which is potentially fatal. Selenium deficiency also contributes (along with iodine deficiency) to Kashin-Beck disease. The primary symptom of Keshan disease is myocardial necrosis, leading to weakening of the heart. Kashin-Beck disease results in atrophy, degeneration and necrosis of cartilage tissue. Keshan disease also makes the body more susceptible to illness caused by other nutritional, biochemical, or infectious diseases.

Selenium is also necessary for the conversion of the thyroid hormone thyroxine (T4) into its more active counterpart, triiodothyronine, and as such a deficiency can cause symptoms of hypothyroidism, including extreme fatigue, mental slowing, goitre, cretinism and recurrent miscarriage.

Epidemiology and prevention

These diseases are most common in certain parts of China where the intake is low because the soil is extremely deficient in selenium. Studies in Jiangsu Province of China have indicated a reduction in the prevalence of these diseases by taking selenium supplements.

Chapter 18

Manganese Deficiency (Medicine), Hypervitaminosis A and Disorders of Calcium Metabolism

Manganese deficiency (medicine)

Manganese deficiency (medicine)

ICD-10 E61.3

Manganese deficiency in humans results in a number of medical problems. Manganese is a vital element of nutrition in very small quantities (adult male daily intake 2.3 milligrams). However, in greater amounts manganese, like most metals, is poisonous when eaten or inhaled.

Function

Manganese is a component of some enzymes and stimulates the development and activity of other enzymes. Manganese superoxide dismutase (MnSOD) is the principal antioxidant in mitochondria. Several enzymes activated by manganese contribute to the metabolism of carbohydrates, amino acids, and cholesterol.

A deficiency of manganese causes skeletal deformation in animals and inhibits the production of collagen in wound healing.

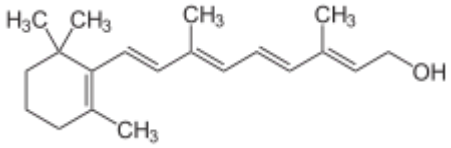
Manganese is found in leafy green vegetables, fruits, nuts and whole grains. The nutritious kernel, called wheat germ, which contains the most minerals and vitamins of the grain, has been removed from most processed grains (such as white bread). The wheat germ is often sold as livestock feed. Many common vitamin and mineral supplement

products fail to include manganese in their compositions. Relatively high dietary intake of other minerals such as iron, magnesium, and calcium may inhibit the proper intake of manganese.

Health

Many nutritionists attribute joint pain, inflammation, arthritis, bursitis, dermatitis, and many diseases including Parkinson's disease, osteoporosis, schizophrenia, diabetes, and epilepsy to manganese deficiency.

Hypervitaminosis A

Hypervitaminosis A	
	
ICD-10	E67.0
ICD-9	278.2
DiseasesDB	13888
eMedicine	med/2382

Hypervitaminosis A refers to the effects of excessive vitamin A (specifically retinoid) intake.

Presentation

Effects include

- Birth defects
- Liver problems
- Reduced bone mineral density that may result in osteoporosis
- Coarse bone growths
- Skin discoloration
- Hair loss

- Excessive skin dryness/peeling (desquamation)
- Angular cheilitis
- Intracranial hypertension

Signs

Signs of acute toxicity include nausea and vomiting, headache, dizziness, blurred vision, and loss of muscular coordination.

Pathophysiology

Hypervitaminosis A occurs when the maximum limit for liver stores of retinoids is exceeded. The excess vitamin A enters the circulation causing systemic toxicity. Betacarotene, a precursor of vitamin A, is selectively converted into retinoids, so it does not cause toxicity.

Although hypervitaminosis A can occur when large amounts of liver are regularly consumed, most cases of vitamin A toxicity result from an excess intake of vitamin A in the form of vitamin supplements. Toxic symptoms can also arise after consuming very large amounts of preformed vitamin A over a short period of time. The U.S. Institute of Medicine says that the Lowest Observed Adverse Effect Level (LOAEL) for vitamin A, when taken over an extended period of time is 21,600 IU. Most multivitamins contain vitamin A doses below 10,000 IU, therefore multi-vitamins are unlikely to cause vitamin A toxicity when taken at their recommended dosages. But in high doses, its central nervous system toxicity can be enhanced by its lipid solubility because it is readily transported across the blood brain barrier and concentrated in the brain.

Vitamin A causes cells to swell with fluid; too much vitamin A causes them to rupture in hyposmotic environments, hence the toxicity. Toxicity has been shown to be mitigated through vitamin E (tocopherol), cholesterol, zinc, taurine, and calcium. Cholesterol has been shown to prevent retinol induced golgi fragmentation.

Recommended supplement limits

The U.S. Institute of Medicine has established Daily Tolerable Upper Levels (UL) of intake for vitamin A from supplements that apply to healthy populations, in order to help prevent the risk of vitamin A toxicity. These levels for preformed vitamin A in micrograms (μg) and International Units (IU) are

- 0–3 years: 600 μg or 2000 IU
- 4–8 years: 900 μg or 3000 IU
- 9–13 years: 1700 μg or 5665 IU
- 14–18 years: 2800 μg or 9335 IU
- 19+ years: 3000 μg or 10,000 IU

The dose over and above the RDA is among the narrowest of the vitamins and minerals. Possible pregnancy, liver disease, high alcohol consumption, and smoking are indications for close monitoring and limitation of vitamin A administration. However, vitamin A has also been repeatedly tested and used therapeutically over several decades in larger amounts. For example, a total dosage of 100,000 - 400,000 IU has been given for treatment of severe pediatric measles, in areas where vitamin A deficiency may be present, in order to reduce childhood mortality.

Toxicity from eating liver

The liver of certain animals — including the polar bear, seal, walrus, and husky — is unsafe to eat because it is extraordinarily high in vitamin A. This danger has long been known to the Inuit and has been recognized by Europeans since at least 1597 when Gerrit de Veer wrote in his diary that, while taking refuge in the winter in Nova Zemlya, he and his men became severely ill after eating polar bear liver. In 1913, Antarctic explorers Douglas Mawson and Xavier Mertz were both poisoned (and Mertz died) from eating the liver of their sled dogs.

Vitamin A itself was not discovered until 1917.

Pathological changes consistent with hypervitaminosis A have been seen in bones of Homo erectus, and have also been attributed to consumption of carnivore liver.

Disorders of calcium metabolism

Disorders of calcium metabolism

Calcium

ICD-10	E83.5
ICD-9	275.4
MeSH	D002128

Disorders of calcium metabolism occur when the body has too little or too much calcium. The serum level of calcium is closely regulated within a fairly limited range in the human body.

The amount of biologically active calcium varies with the level of serum albumin, a protein to which calcium is bound, and therefore levels of *ionized calcium* are better measures than a *total calcium*; however, one can correct a *total calcium* if the albumin level is known.

- A normal *ionized calcium* is 1.12-1.45 mmol/L (4.54-5.61 mg/dL).
- A normal *total calcium* is 2.2-2.6 mmol/L (9-10.5 mg/dl).
    - *Total calcium* of less than 8.0 mg/dL is hypocalcaemia, with levels below 1.59 mmol/L (6 mg/dL) generally fatal.
    - *Total calcium* of more than 10.6 mg/dL is hypercalcaemia, with levels over 3.753 mmol/L (15.12 mg/dL) generally fatal.