Derbyshire Neck and Iodine Deficiency

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Abstract. Goitre and the associated neurological deficits of cretinism and deaf mutism due to iodine deficiency were common in Derbyshire, giving rise to the term *Derbyshire Neck*. These diseases were most prevalent in the 19th century and earlier, when they had devastating effects in the rural population. Since then they have declined in frequency. However, iodine deficiency disorders are still prevalent worldwide, and iodine deficiency is the single most common cause of mental retardation and brain damage. Globally, 2.2 billion people, ~38% of the world population, live in risk areas of iodine deficiency. Dietary iodine deficiency and environmental goitrogens block the synthesis of thyroid hormones. Iodine deficiency disorders are common in areas of low environmental iodine. But the iodine geochemical cycle is complex, and iodine deficiency disorders may develop in areas where iodine is present in the environment but is not bioavailable; this is because it is chemically bound in the soils, or because other dietary components inhibit the synthesis of thyroid hormones. In 19th century Derbyshire iodine deficiency diseases were likely to have been multifactorial. Goitres occurred principally in limestone areas and were due to the binding of iodine in the alkaline soils, with impaired uptake into local farm produce. Supplementary mechanisms may have included genetic susceptibility and dietary goitrogens. The decline of iodine deficiency diseases began with the increased standard of living and a wider range of dietary products from areas outside Derbyshire.

Goitres are clinically discernable enlargements of the thyroid gland in the neck and may arise from many diseases, from inflammation and tumours as well as compensatory enlargement of the gland. They occur sporadically, reflecting particular diseases of the thyroid in individuals, but also endemically, when a large proportion of a population is affected. In such areas, the high prevalence suggests causal environmental factors. Importantly, endemic goitre is accompanied in the population by a spectrum of catastrophic neurological defects including deaf mutism and cretinism. Endemic goitre is an ancient and world wide disease (Langer, 1960). The aphorism "*quis tumidum guttur miratur in Alpibus*" (who wonders at a swelling of the neck in the Alps?) is attributed to the poet Juvenal. Pliny the Elder (23-79AD), who died in the eruption of Vesuvius described goitres as occurring often in certain districts of Switzerland, and gave an early account of the belief, which persisted until the twentieth century, that this was due to water: *Guttur homini tantum et suibus intumescit, aquarum quae potantor plerumque vitio* (Swelling of the throat occurs only in men and swine, caused mainly by the water they drink). Mediaeval clinical descriptions of cretinism which emphasized the association with endemic goitre were those of Paracelsus (c.1527) and Platter (c.1562), who practiced in the Swiss or Austrian Alps (Sawin, 2001).

Goitre in Derbyshire

Derbyshire was an area of endemic goitre in the 18th and 19th Centuries. This gave rise, somewhat unfairly, to the term Derby(shire) Neck (Fig. 1), for there were other areas of Britain such as Yorkshire where it was similarly or more common. Indeed, Inglis (1838) commented that goitre in the Yorkshire Dales was as frequent as in the Swiss Alps. Early medical descriptions in Derbyshire give a flavour of the time both of social conditions and medical practice.

Prosser (1741) describes the lesion as observed and its frequency in one village: *The Bronchocele, or Derby-neck is a tumor arising on the fore part of the neck (Figure1). It generally first appears sometime betwixt the age of eight and twelve years, and continues gradually to increase for three, four or five*

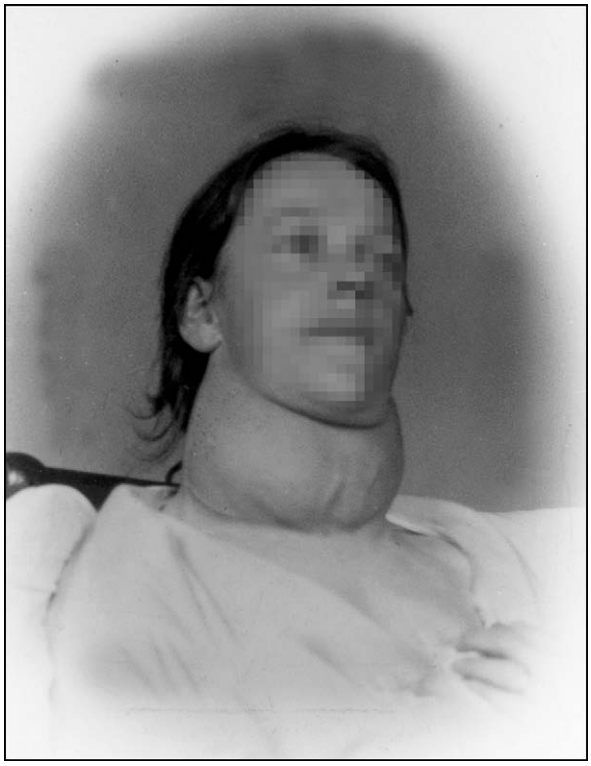

Figure 1. *Diffuse enlargement of thyroid producing "Derbyshire Neck" in a female (from the archives of Derbyshire County Council).*

years; and often the last half year of this time it grows more than it had for a year or two before. It generally occupies the whole front of the neck, as the whole thyroid gland is here generally enlarged, ... but is rather in the pendulous form, not unlike, as Albucasis says, the flap or dew-cap of a turkey-cocks neck, the bottom being generally the bigger part of the tumor and going gradually less upwards.... By the situation and nature of the complaint it occasions a difficult breathing, and very much so upon the patient`s taking cold, or attempting to run or walk fast. In some the tumor is so large , and so much affects their breathing as to occasion a loud wheezing.... .It is very common in many counties in England, Derbyshire especially, where from its frequency, it has the name Derby-neck .... .I have been informed by a gentleman of the faculty, from Duffield in Derbyshire, that there were near fifty poor girls afflicted with it in that small village.

Erasmus Darwin (1796), working as a medical practitioner in Lichfield, drew attention to water supplies as a possible cause of goitre: *Bronchocele. Swelled throat. An enlargement of the thyroid gland said to be frequent in mountainous countries, where river water is drank, which has its source from dissolving snows. This idea is a very ancient one ...The inferior people of Derby are much subject to this disease, but whether more so than other populous towns I can not determine; certain it is that they chiefly drink the water of the Derwent, which arises in a mountainous country, and is very frequently blackened as it passes through the morasses near its source; and is generally of a darker colour, and attended with whiter foam, than the Trent.*

A more vivid and compelling account of the disease and its disastrous social effects on affected families is given by Rev. D. Vawdrey, Rector of Darley Dale and vice-chairman of Bakewell Union in evidence to Parliament (British Parliamentary Papers 1968) and he made the important link between goitre and neurological deficits. *Goitre is an evil incident to this locality, so extensive and so mischievous that no report of the districts of Derbyshire would be complete without some reference to it. There is a great deal of it in this parish. In one family six daughters were deaf and dumb, one son a maniac, and another imbecile. In another family four daughters were deaf and dumb. There are many other cases of imbecility and imperfect development either of bodily or mental power or both, all in this parish. Yet this parish is well drained, has admirable water all flowing from gritstone and is spread over a wide and very open valley. Goitre chiefly prevails among the aboriginal inhabitants. I know but of one instance where any strangers coming to live here (and there are many) have shown any symptoms of it. Among the aborigines the system of intermarrying has been carried on for generations to an extent which I have never met with out of Derbyshire and to this fact more than any other, I attribute the prevalence of this disease* (in fact the western half of the parish is underlain by limestone, and much more has calcareous soils on the limestone-rich till). At the same hearing, Mr C. Evans (British Parliamentary Papers 1968) noted significantly that *Cases of 'Derbyshire neck' are diminishing though still hanging about the districts in which it used to prevail*.

Dr William Webb (1886), a physician and surgeon of Wirksworth for thirty years, emphasized the association of goitre and cretinism (Fig. 2), but gave further insight into the changing frequency of the disease and into life for working women then. He had an eye for the rocks and water sources as possible aetiological factors: *goitre is a true hypertrophy of the thyroid gland from the excessive performance of functional duty. This theory explains to some extent the occurrence of bronchocele when the girl is approaching womanhood; and also those cases which happen in women who get their bread as workers in the cotton mills of Derbyshire and who have frequently to walk two, three or even four miles, over steep hills to their work before six-o-clock in the morning; then to live in a flocculent atmosphere, working all the time, for ten hours a day and afterwards to tramp over the same ground at night. .... Enlargement of the thyroid gland is for the most part seen in women belonging to the working classes, although not altogether confined to them. It is also common in those whose ancestors have intermarried. .... It is found equally amongst the Yoredale rocks and limestone formations, and does not appear to be confined to those who drink any special character of water. .... It is much less prevalent now than it was thirty years ago and yet women drink the same waters. They get better wages, which means better and more nutritious food. The railway communication which did not then connect the goitrous districts with the county town has now given the people opportunities and means to pay visits to other parts of which they constantly avail themselves;*

Figure 2. *Two 19th century cretins from Derbyshire. "I have a family in my recollection at this moment, consisting of a man and his wife (since dead) having a large fibrous goitre. Both are of average mental capacity. They have some sharp children and also two cretin women their offspring. These latter, in age between 20 and 35, are stunted in growth and have but limited powers of understanding or even of going to and fro, except in the shuffling gait of the paralytic. They sit from morning till night, nursing a doll, or other toy and comporting themselves as very little children do, but with only a fractional part of their intelligence". (from Webb, 1886).*

consequently there has been less intermarriage and less breeding in-and-in; and I am decidedly of the opinion that, if the decrease of bronchocele take place in the same ratio as it has done in the last generation, ere another has passed away, endemic goiter will, so far as Derbyshire is concerned, have almost disappeared.

Goitre was, thus, widely recognized in Derbyshire in the 18th and 19th centuries in anecdotal accounts, but the wider pattern of associated diseases was also seen as a problem by physicians and politicians alike.

Towards an understanding

The first systematic study of goitre in England and Wales (Berry, 1891) delineated a high frequency goitre belt extending from Cornwall, through Somerset, Oxfordshire and the Midlands to Derbyshire and the northern Pennines, with offshoots into North and South Wales (Fig. 3). Berry described the Carboniferous limestone areas of England as the very hot bed of goitre, and recorded particularly numerous sufferers in Cromford, Matlock, Youlgreave, Bakewell, Baslow and Stoney Middleton. Stocks (1927) surveyed the prevalence of goitre in 375,000 schoolchildren throughout England and Wales, confirming the distribution of goitre and the high rates in limestone areas. Turton (1933) studied the prevalence of goitre in Derbyshire, and noted that it was not confined to but was much more prevalent in limestone areas. Significantly, he noted that by then cretins had become a rarity.

The Goitre Subcommittee of the Medical Research Council (1944) estimated that in England and Wales there were 500,000 cases of thyroid enlargement in persons between the ages of 5 and 20 years. Kelly and Snedden (1958, 1960) commented that there was no reason to suppose any lessening of the figure in the intervening years. However, a survey by general practitioners of thyroid abnormalities in the Peak District (West Derbyshire Medical Society, 1966) showed a large decrease in thyroid abnormalities in younger people but without a comparable decrease in adults; this provoked them to write that the time had not yet come to forecast the imminent passing of Derbyshire neck and led to the increased recommendation of iodised salt to younger families in their care. Nevertheless they observed: *a lower consumption of locally grown produce began with the railway penetration of the Derbyshire valleys near the turn of the last century and one of the older practitioners used to say this coincided with a fall in the local prevalence of goitre even then.*

In conclusion, the natural history of goitre and its associated disorders in Derbyshire was that its prevalence in the 19th was severe, affecting whole communities, but that it slowly declined in severity. This decline preceded any specific treatment for iodine deficiency, with the opening of rural areas to the wider world by better communications, importation of dietary products from outside Derbyshire and improved living standards. Goitre persisted until the middle years of the 20th century, despite the introduction of iodine prophylaxis. A similar progression in other limestone districts has been observed, as at Hooke Norton in Oxfordshire (on Jurassic limestone), where iodine deficiency persisted in school children until the 1950s (Hughes *et al*, 1959).

Iodine deficiency in goitre

Numerous ancient treatments for goitre included seaweed extracts, and iodine was discovered in burnt seaweed residues by the French chemist Courtois in 1811. Coindet, an Edinburgh-trained physician, gave potassium iodide to goitrous patients in Geneva in 1820 with great success. However, others gave iodide in a grossly high dosage; the induced side effect of thyrotoxicosis caused fatalities, and the treatment largely fell into disrepute (Langer, 1960). At the end of the 19th century, fried sheep thyroid or dried thyroid extract was used successfully in the therapy of hypothyroidism, and in the search for the active principal, iodine was found in the gland. The active hormone thyroxin was identified and named by Kendall in 1919. It was synthetised by Harrington and renamed thyroxine (T4), a more chemically correct name, for it is an amino-acid derivative with four iodine atoms rather than an indole structure as Kendall believed. Subsequently a second hormone triiodothyronine (T3) was found.

Marine (1920) re-established the therapeutic and prophylactic use of iodine in a report on the prevention

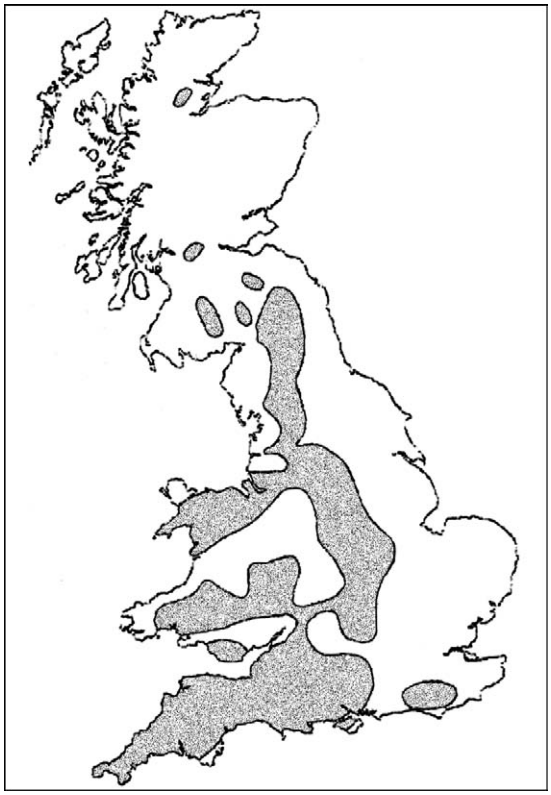

Figure 3. *Goitre distribution in Great Britain, recognized by Berry (1891), with much of the main goitre belt (shaded), underlain by carbonates.*

of simple goitre in schoolgirls in Akron, Ohio. However, his view of endemic goitre as an iodine deficiency disease was not without opposition. The long-established view was that endemic goitre was due to something in the water supplies - toxins, bacteria or parasites (McCarrison, 1906; Berry, 1891) rather than iodine deficiency; this view prevailed for some time and with contention. Turton (1933), working in Derbyshire, produced experimental evidence purporting to show that endemic goitre was not related to iodine deficiency and concluded there was no case for the *promiscuous administration of iodine amongst either the children or adults of this county*.

Nevertheless, opinion changed, and following Stocks` survey (1927), a recommendation was made for the prophylactic administration of iodine to girls in endemic areas of England and Wales, but was never implemented. During the 1939-45 war, concern at the prevalence of goitre in women munitions workers prompted the Medical Research Council to appoint a Goitre Subcommittee (1944). They recommended the general adoption of iodised salt throughout the country, but no government action followed, except that iodide was added to the vitamin tablets issued to expectant and nursing mothers. Iodised salt became commercially available in Britain in the immediate post-war years through the initiative of Cerebos. Iodised salt was custom-packed for various Cooperative Society stores, but the last supplied were in the Derbyshire area.

Sources of iodine in the diet

The recommended adult daily intake of iodine is about 100-150 µg/day (Hetzl, 2000). Fish and seafood is a major source of dietary iodine, and is forty times richer than most other foodstuffs (Johnson *et al*, 2003). Arable crops and vegetables are not rich in iodine, and inland areas far from the marine source may provide only low amounts of iodine. Leafy vegetables and grass concentrate iodine by adsorption on the leaves from the atmosphere. Iodine may then enter the diet through animal products, especially those of grazing animals; these secondarily concentrate iodine, by ingesting not only grass and leaves but also soil, which includes soil-bound iodine not bioavailable through plants. In today's developed countries, a major source of iodine lies in dairy products because of the addition of iodine to cattle feed and the use of iodine containing disinfectants in cattle sheds. Iodised salt is a potentially important source, but its use is not mandatory and much on our shops is not iodinated.

In the past, surface water supplies were emphasized as an important source of dietary iodine, but water sources are likely to supply less than 10% of daily dietary requirements. Inhalation of atmospheric iodine is possible but with a minor input of only 0.5 µg/day.

Pathophysiology of the thyroid

The thyroid gland lies in front of the trachea in the neck. Its principal function is to secrete iodine-containing hormones. This depends on an adequate iodine supply and uptake by the thyroid, on hormone synthesis and release from the gland. Geochemical or dietary agents may interfere at different stages, producing a primary lack of iodine in the diet, inhibition of hormone synthesis or alterations in hormone usage.

- *Iodine concentration in the thyroid*. Iodide is absorbed from the gut and circulates by the blood to the thyroid where it is concentrated to maintain an iodine gradient of 100:1 between the thyroid cell and the blood. In iodine deficient conditions the gradient may rise to > 400:1 to keep the required daily intake.
- *Synthesis and release of thyroid hormones*. Iodide is oxidized to either nascent iodine or I_3 which combine rapidly with tyrosine, to form mono- and di-iodotyrosine and these are coupled to form the thyroid hormones, thyroxine containing 4 iodine atoms (T4) and tri-iodothyronine containing 3 iodine atoms (T3).
- *Peripheral action of thyroid hormones*. T4 and T3 are released into the blood and carried to the tissues. There they maintain cellular metabolism at a basal rate. In addition to these actions, the hormones have important effects on the growth and development of the brain in the foetus and new-born. Therein lies the major importance of iodine deficiency disorders.

Foetal and neonatal brain development is characterized by two main periods of growth. The first is between the third and fifth months of pregnancy when there is nerve cell proliferation and initial organization of the nervous system. The second occurs in the third trimester and continues into the second and third years of post-natal life. Thyroid hormones co-ordinate and regulate growth through binding of T3 to nerve cells in different parts of the brain. During the initial phase of growth the supply of thyroid hormones to the foetus is almost entirely maternal. T3 bound to foetal nerve cells is produced by the foetus from circulating maternal T4. Foetal synthesis of T3 from maternal T4 is of particular importance in those areas where there is a combined deficiency of selenium and iodine (see below), when it is a factor in determining the clinical type of cretinism (Delange, 2000).

Control of thyroid function

The activity of the thyroid gland is controlled by a feedback mechanism: low levels of thyroid hormones induce secretion of thyroid stimulating hormone (TSH) from the pituitary gland. There is then an increase in the number, size and functional capacity of thyroid cells with increased synthesis and release of thyroid hormones from an enlarged thyroid - a goitre.

Enhanced physiological TSH secretion occurs at particular times of need such as adolescence, in girls at the menarche and in pregnancy. In these groups, even on an adequate diet, slight thyroid enlargement may be seen. In some cultures, mild thyroid enlargement and enhanced delicate curve of the neck in young women is seen as a sign of beauty. During the Renaissance, goitre was a common feature in Italian paintings of the

Madonna. In the context of endemic goitre, any environmental factor interfering with thyroid hormone synthesis or function results in thyroid stimulation from the pituitary and pathological enlargement.

Clinical effects of iodine lack

Thyroid enlargement in an individual may cause symptoms (Fig. 1), but this is rarely a major public health problem. However, endemic goitre is a marker for important associated syndromes arising from maternal thyroid hormone deficiency in pregnancy, including infertility, abortions and stillbirths, endemic cretinism and impaired mental capacities in children and adults. The whole spectrum of disorders is better termed iodine deficiency disorders (IDD).

There are two polar forms of endemic cretinism - the neurological and the myxoedematous types (McCarrison, 1908) though many are intermediate in presentation. These forms relate to the timing of the maximal hormonal deficiency insult to the child`s development, whether early in pregnancy or in the neonatal period (Stewart & Pharoah, 1996). Neurologic cretinism is characterized by severe mental deficiency, deaf mutism and spastic paralysis. The myxoedematous form shows mental deficiency with short stature and markedly delayed sexual and bone maturation. The skin and other tissues may be thickened by a mucinous deposit which gives rise to the term "myxoedematous" An associated deficiency of selenium in a geographical area is a factor in the predominance of myxoedematous cretinism in that location (Delange, 2000).

Importantly, studies in at-risk populations indicate that cretinism is not an all-or-none phenomenon and that iodine deficiency has wider neural effects than the classical forms. Associated with endemic cretinism, increased numbers in the "normal" population have motor and cognitive deficits. Any neural damage to the brain is permanent, and eradication of iodine deficiency is therefore a critical public health matter.

Selenium deficiency

A new development in the understanding of iodine deficiency diseases is the recognition of combined iodine and selenium deficiencies (Delange, 2000). Selenium is an element closely allied in chemical and physical properties with sulphur, and occurs as a trace element with a concentration of ~0.05 ppm in continental crust. In the thyroid it is a component of enzymes that scavenge free radicals. These are chemical species that are continuously produced in cell metabolism and are chemically active, with great potential to damage the cell by oxidation. unless constrained by antioxidant mechanisms.

In Zaire, myxoedematous cretinism is the predominant form rather than the neurological form and is found in areas that are severely iodine deficient but which are also deficient in selenium. The selenium deficiency may act in two ways:

• Iodine deficiency produces thyroid stimulation through pituitary feedback with increased synthesis of free radicals in thyroid cells. An associated selenium deficiency causes a lack of scavenging enzymes within the thyroid, which is then more sensitive to oxidative stress and thyroid function is further impaired.

• Selenium is also a component of enzymes responsible for the conversion of T4 to T3 in tissues and deficiency of this enzyme produces decreased breakdown of T4. In a pregnant woman, the selenium deficiency prevents the development of neurologic cretinism by increasing the availability of maternal T4 to the foetus during the first trimester. The myxoedematous form develops due to iodine deficiency in later pregnancy and the neonatal period when the child depends on its own deficient production of thyroid hormones.

Genetic factors

Genetic susceptibility plays a role in the development of IDD. In the western Sudan, family studies show a significantly higher incidence of endemic goitre among the offspring of affected parents than among those of normal parents (Bayouni *et al*, 1988). Held *et al* (1990) studied 70 families afflicted with endemic cretinism in highland Ecuador where an autosomal recessive genetic predisposition is a major factor. In each of three iodine-deficient areas in central China, where neurologic cretinism is common, Wang *et al* (2000) studied the expression of genes which affect thyroid hormone binding to nerve cells, and altering their effects on growing nerve cells. In each area, the genes were significantly more common in affected children than in normal controls.

Goitrogens

Iodine and selenium are geochemical goitrogens whose effect on thyroid function is produced by deficient intake. There are other naturally occurring vegetable goitrogens which produce an effect through positive interference with thyroid function either by inhibiting iodine uptake or hormonal synthesis. They have an additive effect to iodine deficiency, and this is seen if the iodine intake is marginally limited and/or the goitrogen intake is prolonged. Their effects may be severe and their influence is seen in endemic areas.

Thiocyanates and isothiocyanates are goitrogenic and act by blocking transport of iodine into the thyroid. They or their precursors are found in staple foods such as cassava, maize, and bamboo shoots in Third World countries. Cassava, a staple in Zaire, is thought to be an adjunct in the cause of endemic goitre and cretinism due to the release of thiocyanate from a cyanogenic precursor in the tuberose root. Thiocyanates occur in pearl millet a staple food in endemic goitre areas of western Sudan. Pearl millet is rich in flavenoids, a group of polyhydroxyphenols, that are metabolized by intestinal bacteria to compounds which inhibit not only enzymes involved in thyroid hormone synthesis but also those involved in their peripheral metabolism (Engel & Lamm, 2003).

Geological contexts of IDD

At present, iodine deficiency diseases affect more than 740 million people, 13% of the world population, and another 30% are at risk. Nearly 50 million people suffer from some degree of IDD-related brain damage, ranging from cretinism to a lowered intellectual ability (WHO, 2003)

Areas with a high prevalence of goitre show no single unifying geographical or geological feature but certain patterns of distribution occur. Many are in high mountains, including the Alps, Himalayas and Andes and their subsidiary chains. Other areas are at sea level, such as the Netherlands, the Indo-Gangetic plain and coastal Sri Lanka. Areas with water supplies percolating through a limestone source are also at risk; these include the Appalachians, Ecuador and the limestone areas of Britain (Kelly & Snedden, 1958).

In Zaire, there is a significant contrast in goitre prevalence on Idjwi Island in Lake Kivu (Delange *et al*, 1972). The northern part of the island, with a high goitre rate, has granitic and gneiss bedrock; the southern part is non-goitrous and has a basaltic bedrock. The difference in goitre rates may in part be due to dietary goitrogens, but similar contrasts over corresponding bed rocks have been described from Nigeria (Wilson, 1954). An increase in goitre over the granite batholith was formerly seen in S.W. England, but the iodine deficiency was ascribed to iodine binding by the overlying peaty soil (Fuge, 1996).

A large contrast in goitre prevalence has been noted between populations living on either side of the main Karakorum thrust, the western continuation of the Indus-Tsangpo suture line in northeastern Pakistan (Stewart, 1990; Stewart & Pharaoh, 1996). Though both areas were iodine deficient, goitre was more prevalent on the northern Asian plate than on the southern Indian plate. Similar goitre endemias occur in other convergent zones in Indonesia, New Guinea, the Andes, Alps and Pyrenees. Stewart initially speculated that subduction of the Indian plate concentrated metallic goitrogens such as lithium, boron and molybdate in the Asian plate through melting and metamorphism. Subsequently, Huh and Stewart (2003) found significant differences in the iodine concentrations between streams draining the Karakoram metamorphic complex north of the thrust and those draining the Kohistan-Ladakh island arc south of the thrust. They concluded that, in this area, lithology and tectonic processes were more important than atmospheric transport and deposition of iodine.

Almost no country is free from the risk of iodine deficiency disorders, but some are now goitre free due to prophylactic iodination measures. The risk of these disorders is now chiefly, but not entirely (Nohr *et al*, 1993), in poor, isolated and underdeveloped areas of the world, especially if they are dependant for their diet on local produce.

Goitre in calcium-rich environments

Goitre, long recognized in limestone areas suggested a direct role for calcium as a goitrogen (McCarrison, R., 1926). In experimental studies this was ascribed to water hardness (Taylor,1954) but Harrison et al (1967) showed no effect of calcium on iodine metabolism in man. In Nepal, Day and Powell Jackson, (1972) found that goitre prevalence correlated not only with the hardness of the water but also with its fluoride content. In limestone areas, rather than calcium acting on the thyroid directly, its presence alters the chemical environment of the soil, and therefore acts indirectly on the mobility and distribution of other elements.

Environmental sources of iodine

A traditional explanation for dietary iodine deficiency is that it is due to soil depletion following intense glaciation, where iodine is stripped from the soils, then carried by rivers to the sea with failure of replenishment, leaving a low iodine environment and consequent dietary deficiency (Goldschmidt, 1954; Kelley & Snedden, 1958). There is little evidence to support this. There is no major difference between the iodine content of soils in areas of recent glaciation and

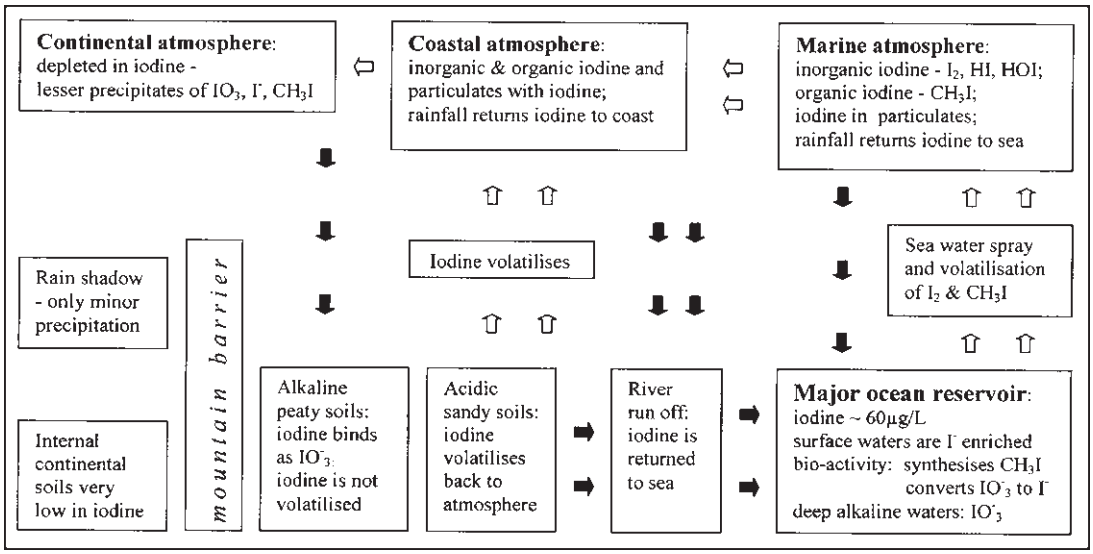

Figure 4. *Migration of iodine between the marine and terrestrial environments.*

those in non-glaciated but similar geographical locations (Fuge, 1987). Young glacial soils re-equilibrate with their surrounds rapidly rather than in thousands of years (Fuge and Johnson, 1986; Johnson *et al* 2002). Persistent low iodine contents of soil in glaciated areas reflect either their geographical location with a low iodine input at altitude and in rain shadows, or an inability of the soil to bind iodine.

Nevertheless, at least in much medical literature, there is an implicit assumption that iodine deficiency diseases are primarily due to low levels of environmental iodine producing a low iodine dietary intake; the assumption is buttressed by the apparent success of iodisation programmes. This emphasises the dietary deficiency of iodine, but it underestimates the complexity of the geochemical cycle of iodine and its interactions with biological processes that produce the deficiency. There is little recognition that soil iodine may not be bioavailable or that geochemical as well as dietary factors may act as goitrogens (Stewart, 1990, Stewart & Pharoah, 1996).

Lack of iodine in surface waters is sometimes a marker of a goitrogenic risk due to low levels of iodine in the environment, as in the Himalayas and rain shadow areas of British Columbia. Here iodine levels in surface waters are less than 1.0 µg/l (Day & Powell-Jackson, 1972; Fuge, 1987) and both are areas of severe endemic goitre. Water supplies have been classed as goitrogenic if they contain less than 3-5 µg/l iodine (McClendon & Williams, 1923). However, iodine levels in surface waters do not always correlate with the presence or absence of goitre. In an analysis of surface waters, the highest values occurred in Missouri and Derbyshire, both areas of endemic goitre and both draining limestones (Fuge,1989). Mean iodine level for surface waters in an area without history of IDD in mid-Wales are ~2.11 µg/l, and this is lower than the ~3.94 µg/l in affected areas of Derbyshire (Fuge, 1989). The iodine content of surface waters is very variable, but is usually less than 15 µg/l. The variability depends not only on the nearness to the seawater source and on precipitation, but also on run-off from recent marine sediments. Effluent contamination from mines and agriculture may also affect levels, as does recycling of domestic supplies, as in London which has high iodine levels (Fuge, 1989).

There is no consistent relationship between levels of environmental iodine and endemic goitre. In a study of the distribution of environmental iodine (atmospheric deposition, soil and surface water content) in England and Wales, related to the goitre belt delineated by Stocks (1927) there was no correlation between the distribution of iodine and the presence or absence of endemic goitre (Stewart *et al*., 2003). Similarly in Sri Lanka iodine contents of soil and water do not correlate strongly with goitre endemicity (Dissanayake & Chandrajith, 1996). Besides absolute low levels of environmental iodine, other mechanisms which inhibit iodine bioavailability have to be sought and the solution to this lies in the iodine geochemical cycle.

Geochemical cycle of iodine

Iodide has a large ionic radius (220 pm), so does not fit easily into crystal lattices and is therefore not generally found in rock-forming minerals. Its concentration in igneous and metamorphic rocks is ~0.25 ppm. There is a greater range in sedimentary rocks, with a higher content in claystones than sandstones; highest values occur in organic-rich shales, with concentrations in bituminous shales up to 44 ppm. The content in limestones is variable and correlates with organic content (Fuge, 2005).

Seawater is the principal reservoir of iodine, where it exists in several forms. Inorganic iodine is present as iodide and iodate anions, with an increased proportion of iodide present in near-coastal waters due to bio-conversion of iodate to iodide. Organic iodine compounds include the volatile methyl iodide, which may be formed biologically by seaweeds and phytoplankton. Organic compounds may constitute nearly half the iodine content in coastal waters.

Iodine is transferred from the ocean to the atmosphere, some as spray and aerosols, but most by volatilization of iodine species. Seawater iodide anions are converted to elemental iodine and volatilized by photochemical oxidation. Volatile organic iodine compounds have been identified as the predominant source of atmospheric iodine in Japan and Europe, and methyl iodide is suggested as a long distance atmospheric iodine transporter (Heumann *et al*, 1990)

Iodine is transferred from the atmosphere to the terrestrial environment by precipitation, with iodine deposition decreasing with distance from the sea. Iodide anions are the principal deposit, with prior conversion of atmospheric iodate to iodide and organic iodines to iodine by photolysis. Fuge (1996) envisaged that marine derived iodine is deposited in a near coastal environment and that it is revolatilised secondarily from the soils and carried in the atmosphere to more inland areas in a series of repeated migratory steps. These steps are subject to blocking at any stage by geochemical barriers such as organic-rich or alkaline soils that increase iodide binding and inhibit further inland migration (Fig. 4).

The iodine content of soils varies over a range of <0.1 to >100 ppm. Soils in coastal areas are enriched in iodine compared to those more distant from the sea; soils in continental interiors and in mountain rain shadows may have very low levels. Variability depends not only on the supply rate of iodine but also on the ability of the soil to fix and retain iodine. Soils are generally richer in iodine than their subjacent parent rocks because most iodine in soils is derived through the ocean-atmosphere link, and relatively little is added by weathering of bedrocks that are low in iodine. However, the parent material may control the amount of iodine in the overlying soil by its ability to bind iodine. The large number of interrelated soil characteristics that affect binding contribute to a simple model (Fig. 5) of the iodine fixation potential of soils (Fuge & Johnson, 1986; Fuge,2005).

Iodine is added to soils by precipitation as iodide and iodate anions. There they are primarily absorbed by clays, iron and aluminium oxides and especially by organic matter such as peat. If some of the iodine remains unbound because of a paucity of binding sites, it persists in a mobile form and is available for revolatilisation, but the amount available also depends on the Eh-pH balance in the soil. In acid soils with oxidizing conditions, the iodate anion is converted to iodide, and all the unbound iodine is then available to be converted to volatile iodine. Importantly, soils overlying carbonate rocks usually have neutral or alkaline pH, and added iodide is converted to iodate with reduced volatilisation and therefore enhanced retention of iodine in the soil.

Iodine in the terrestrial biosphere

The major pathway of inorganic elements into plants is through the root system, followed by translocation to the upper aerial parts of the plant. For iodine, the translocation is minor; root uptake from the soil is therefore unimportant for the overall content of the plant. Gaseous iodine may be absorbed through leaf stomata or iodide may be precipitated on leaf or grass surfaces. Much of this is likely to be iodine that has been re-volatilised from iodide in the soil reservoir, and this is therefore inversely related to the amounts fixed in the soil as iodate and unable to re-enter the gas phase. Arable crops contain less than 0.05 ppm iodine. Grazing animals concentrate iodine by grazing large area of pasture, and they provide entry to the human food chain through dairy products. It is noteworthy that iodine is not mobile in plants and is not concentrated in seeds (Johnson *et al*, 2003). Grain crops such as wheat and oats are therefore a poor dietary source of iodine.

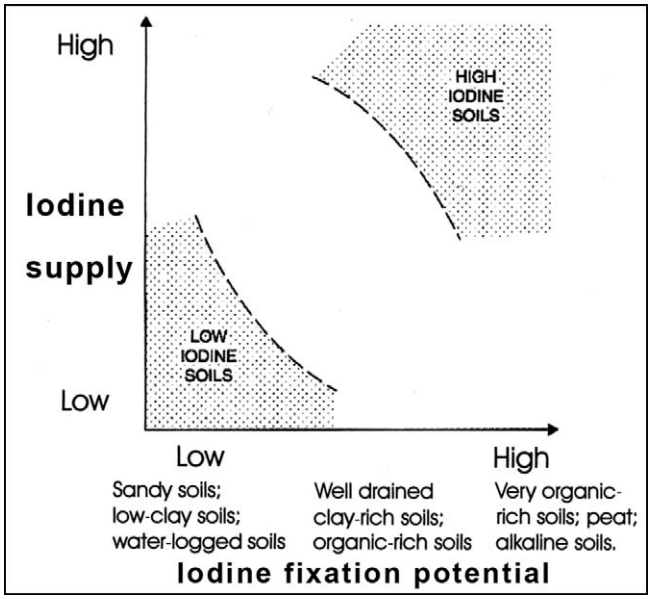

Figure 5. *Iodine and soils' fixation potential (their ability to retain iodine). Soils rich in organics, aluminum and iron oxides have high fixation potential, as do alkaline soils over carbonate rocks (after Fuge & Johnson, 1986; Fuge, 2005).*

Iodine deficiency diseases in Derbyshire

Iodine supply from soil and water

Iodine supply to the environment depends essentially on rainfall and is affected by distance from the sea and prevailing winds. Iodine content of rainfall decreases with increasing distance from the Welsh coast (Fuge, 1996). Samples of rain taken from upland areas of Wales within 12 km of the coast contained 0.005-0.006 ppm iodine, compared to 0.002 ppm from samples taken 84 km east of the coast. Similarly, the mean iodine level in the topsoils of north Derbyshire is only 5.44 ppm, compared to 14.7 ppm in soil samples from within 20 km of the Welsh coast; Derbyshire may thus be described as a relatively low-iodine environment (Fuge & Long, 1989).

Nevertheless, mean iodine levels in top soils are higher in Derbyshire, than in some non-goitrous areas of Britain (Table 1). Furthermore, the distribution of iodine in topsoils is not uniform; iodine content in topsoils overlying limestone bedrock in north Derbyshire, the area of goitre endemia, is greater than that in topsoils of adjacent non-goitrous areas where the underlying lithology is sandstone or shale. This implies that soil iodine in the limestone area is bound, and is therefore not bio-available. Soils in limestone areas are generally well drained and neutral to alkaline, and it is suggested that iodine is present predominantly as the non-volatile iodate rather than the iodide anion. Reduced re-volatilisation permits less deposition on leaves and plants for consumption by humans, either directly, or secondarily after concentration within grazing cattle. There is no need to invoke the action of vegetable goitrogens, because the Eh-pH values in limestone areas produce less mobile iodine (Johnson *et al*, 2003) and uptake by plant roots of iodate is also lower than that of iodide. There are often multiple factors that produce disease.

Dietary factors and possible goitrogens

In the 19th century, prior to the coming of the railways, the diet of poor people in rural limestone districts of Derbyshire was dependant on restricted local produce from soil in which iodine was not bio-available. Oatcakes, low in iodine, were a dietary staple (Farey, 1813) and a predeliction for them was considered responsible for goitre in Matlock (Kelly & Snedden, 1958). The dietary intake of iodine was marginal, and each person`s thyroid status, was liable to be tipped into negative balance by dietary goitrogens. There is no remaining direct evidence for dietary goitrogens in 19th century Derbyshire, but brassica vegetables (including cabbage, brussel sprouts, kale and yellow turnips) featured in the restricted diet of the rural poor; these are rich in goitrin, a thiourea-like compound that inhibits thyroid hormone synthesis. A modern parallel exists: there was a significant increase of goitre, particularly in the age group of 15-25 years in Belgium, during the German Occupation in WWII which was related to the increased consumption of cabbage and related goitrin rich vegetables during a

time of overall food shortage and restricted diet (Kelly & Snedden, 1960).

Genetic factors

There may have been an increased genetic susceptibility to iodine deficiency diseases in the isolated communities of rural Derbyshire in the 19th and earlier centuries. Goitre and cretinism in Derbyshire were commonly familial, and the frequency of close intermarriage within families in an impoverished community with poor communications was emphasized (Farey, 1813; BPP, 1968; Webb, 1886). However, not all those at risk developed goitre or cretinism. Familial aggregations with the sparing of some members suggest that genetic as well as environmental factors are involved.

There is evidence for possible genetic predisposition to IDD in Derbyshire. The ability to taste the bitterness of thiourea chemicals is genetically controlled, and is linked to blood group inheritance (Mourant et al, 1978). About 30% of adult Caucasians are "taste-blind" and cannot recognize thioureas placed on their tongues; about 70% are "tasters". Taste aversion may have an advantage, in avoidance of bitter tasting (to "tasters") brassica vegetables containing thioureas, which eaten in large amounts are goitrogenic. Thyroid deficiency diseases are relatively uncommon among "tasters", which may be attributed to avoidance of brassica vegetables (Tepper, 1998). A higher incidence of "taste-blind" people in Derbyshire than in the Lancaster area is correlated with the higher frequency of goitre in Derbyshire (Cartwright & Sunderland, 1967, Sunderland & Cartwright, 1968). Moreover, the frequency of "taste-blind" females is significantly higher among the descendents of patients with goitre than in the control population.

Soil type related to bedrock	**Iodine range, ppm (mean)**	**Source**
N. Derbyshire, limestone ~80-100 km from coast	2.58 - 26.0 (8.2) (6.58 ex.1*)	Fuge & Long, 1989
Derbyshire, shale, sandstone & dolomite ~80-100 km from coast	1.88 - 8.53 (3.44)	Fuge & Long, 1989
Derbyshire, limestone ~80-100 km from coast	0.56 - 4.6 (2.4)	Saikat et al, 2004
Derbyshire, all samples ~ 80-100 km from coast	1.88 - 26.0 (5.44) (4.68 ex.1*)	Fuge & Long, 1989
Great Britain, clay parent material	2.1 - 8.9 (5.2)	Whitehead, 1984
Great Britain, sandstone	1.7 - 5.4 (3.7)	Whitehead, 1984
Midlands & Welsh Borders >70 km from coast	< 5	Fuge, 1996
Coastal & Mid-Wales	10 - 25	Fuge, 1996

Table 1. *Iodine content of soils and underlying bedrock;* ***** *mean values excluding single outlying high value.*

Conclusion

Iodine deficiency diseases are due to an inadequate intake of dietary iodine or metabolic interference with the hormone synthesis. The dietary deficiency may reflect absolutely low levels of environmental iodine or environmental conditions which retain iodine in the soil making it non-bio-available. On limestones, a key factor is the Eh-pH soil environment that ensures that most soil iodine is bound as the iodate anion. This form of iodine is less volatile and therefore effectively non-available, as it cannot re-volatilise to be absorbed into leaves and precipitated onto grasses, where it can enter the human food chain through the critical link of grazing cattle. The limestone areas of Derbyshire have these soil conditions. However, iodine deficiencies are clearly polygenetic. In by-gone Derbyshire, the basic environmental deficiency was amplified by a restricted diet, possibly containing vegetable goitrogens and expressed in genetically predisposed members of the community. In other parts of the world the distribution of IDD is due to regionally low levels of iodine in areas of low rainfall and great distances from the oceans again with augmentation by goitrogens and genetic factors but intriguingly there now appears to be evidence that the local bedrock and the tectonic environment may be important factors.

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