Research on iodine deficiency and goiter in the 19th and early 20th century

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I am satisfied. I have seen the principal features of Swiss scenery – Mount Blanc and the goiter – and now for home.
Mark Twain, 1880

Introduction
In 1811, France was at war, and Bernard Courtois was producing saltpeter for gunpowder for Napoleon’s army. He was burning seaweed to isolate sodium bicarbonate, and when he added sulfuric acid to the ash he produced an intense violet vapor that crystallized on cold surfaces. He sent the crystals to Gay-Lussac, who subsequently identified it as a new element, and named it iodine, from the Greek for ‘violet’.

The ancient Greeks, including Galen, used the marine sponge to treat swollen glands. The sponge and dried seaweed remained a ‘goiter cure’ in the medical armamentarium through the Middle Ages. In 1813, learning of the discovery of iodine in seaweed, Coindet, a physician in Geneva, Switzerland, hypothesized the traditional treatment of goiter with seaweed or sponges was effective because of their iodine content. He began giving oral iodine tincture to goitrous patients at an initial daily dose at 165 mg. This provoked strong opposition among the medical profession; opponents claimed it was poisonous, and it was suggested “…Coindet would not leave his house for fear of being stoned in the street by his poisoned patients…” Although Coindet insisted his treatment was safe, the often acrimonious debate on the safety of iodine would continue into the early 20th century.

First proposals to use iodized salt
The French chemist Boussingault, was the first to advocate prophylaxis with iodine-rich salt to prevent goiter. He measured iodine levels in rock and in salt deposits of the Andean region, and, in 1825, he reported villages in the province of Antioquia treated goiter with ‘aceye de sal’, an acidic, ‘marine smelling’ fluid from the salt deposits. He demonstrated in 1835 that salt sent from goiter-free Antioquia to neighboring regions reduced goiter endemia.
Boussingault was the first to recommend goiter prophylaxis with iodized salt; it would be nearly 100 years before their vision was realized!

Chatin and goiter prophylaxis in France
The French chemist Chatin was the first to publish, in 1851, the hypothesis that iodine deficiency was the cause of goiter. Chatin, the director of the School of Pharmacy in Paris concluded: “Too low a concentration of iodine in the drinking waters of certain areas appears to be the principal cause of goiter.” However, his estimates of food iodine content were about 10-fold too high and Chatin’s work was greeted with great skepticism by the French Academy of Science.

Despite this, French authorities, in three Departments where goiter was severe – Bas-Rhin, Seine-Inférieure and Haute-Savoie, began distributing iodine tablets and salt together with other prophylactic measures. In the prefect of Haute-Savoie, the cause of goiter was attributed by local physicians to drunkenness, dampness, poor hygiene and contaminated drinking water. Various measures were taken: large trees that prevented the entry of fresh air to villages were felled, wet streets were drained, the water tested for potability and school hygiene improved. In addition, iodized salt was distributed and schoolchildren were given iodine tablets daily. The program was clearly effective: in a survey of 5000 goitrous children, 80% were cured or improved by the iodine treatment.
However, because goiter exempted young men from unpopular military service in the French army, many parents, fearing their sons would be enlisted, were against iodine prophylaxis. Also, the doses of iodine administered both in table salt and tablets were too high: a concentration of 100-500 mg/kg was chosen for salt iodization, and the tablets, which were to be taken daily, contained 100 mg KI. This high dose of iodine was consistent with the enormous doses of iodine used to treat many diseases at the time (scrofula, syphilis, arthritis). While many people tolerated the high doses of iodine well, it likely precipitated iodine-induced hyperthyroidism in some individuals, and as a result, the program was discredited and discontinued.

**Myxedema and cretinism**

Medical authorities recognized cretinism only occurred in areas endemic goiter, but were puzzled by the fact that many cretins had an atrophic or absent thyroid gland, the opposite of goiter. A clue to this apparent paradox appeared when a related disease, myxedema, that resembled cretinism, was described by Ord in 1877 in London. In 1883, Semon suggested myxedema was due to a lack of activity of the thyroid after reading a report by the Swiss surgeon Kocher (Figure 1) describing myxedemal symptoms in patients after total thyroidectomy. British physicians began successfully treating myxedema with injections and/or oral doses of animal thyroid extracts; a 1893 review explained "it was one of the greatest therapeutic triumphs of the age".

The link between goiter, myxedema and iodine was established when, in 1896, Baumann and Röss, working in Freiburg, Germany, digested animal thyroid glands and were surprised to isolate a residual insoluble fraction that was ca. 10% iodine. They found this substance, termed "thyroidine", to be effective in the treatment of both myxedema and goiter. They correctly surmised iodine itself was not therapeutically active, but had to be first incorporated into an organic molecule.

**The Swiss introduce iodized salt**

Switzerland’s iodized salt program has been operating uninterrupted since 1922. Before its introduction, Switzerland was severely iodine deficient. For example, in 1800, a census ordered by Napoleon reported 4000 cretins among the 70,000 inhabitants of the Canton Valais, in the Swiss Alps. In 1918, the Swiss physician Bayard (Figure 2) did the first dose-response trial of iodine to treat goiter. He did this in Grachen, an isolated village at the base of the famous Matterhorn mountain in the Zermatt valley, reachable only by mule track. He gave iodized salt for six months to families in the village with 3 different iodine contents (3, 6 and 15 mg/kg). Bayard established that as little as 30 mg of iodine daily had a clear beneficial effect on goiter, and noted 'soft' diffuse goiters in children were more responsive than the nodular forms.

The Swiss Goiter Committee was formed in 1922. Initially, the committee cautiously advised the introduction of salt iodized at 1.9 to 3.75 mg/kg nationwide on a voluntary basis, a compromise between the proponents and opponents of iodized salt. The first canton in which iodized salt was introduced was Appenzell AR, in 1922, where salt was iodized at 7.5 mg/kg with spectacular results: newborn goiter disappeared, no new cretins were born, and goiters in children were reduced in size or disappeared.

**Iodine supplementation studies in the USA**

At about the same time as the first Swiss iodine studies in 1915-1919, Marine and Kimball were introducing iodine prophylaxis in the Midwest region of the U.S. David Marine (Figure 3) trained at Johns Hopkins was appointed to a residency in pathology at Lakeside Hospital in Cleveland, Ohio. According to legend, he was surprised when asked on his first day what research problem he would like to work on. He had noticed several dogs with large goiters in the neighborhood and replied without much reflection he would like to work on thyroid disease. Marine subsequently confirmed Baumann’s finding that large goiters contained less total iodine than in healthy glands. The American surgeon Halsted had reported when part of the thyroid was resected, the remaining tissue increased in size. Marine extended this observation and suggested goiter was "a compensatory reaction to some deficiency" and it appeared "...iodine is the most important single factor...".

Marine realized goiter was a serious public health problem and in 1916 he planned to do an intervention with iodine in schoolchildren in Cleveland. However, the school board refused, concerned iodine could be poisonous. With the help of Kimball he received permission to do the study in neighboring Akron, Ohio. The treatment group of girls received 200-400 mg NaI per school day for 10 d. The treatment was clearly effective and Marine and Kimball concluded goiter: "...is as easily prevented in man as in fish or in domestic animals".
Based on these studies, general prophylaxis with iodized salt was introduced in the state of Michigan in 1924. There were protests, and at first the Bureau of Chemistry of the Department of Agriculture demanded the iodized salt packages be marked with the skull and crossbones used to indicate a poison, but then backed down. In 1948, the U.S. Endemic Goiter Committee tried to introduce iodized salt to all the states by federal law, but the bill failed.

The modern era: 1930 to the present
In 1980, the first global estimate from WHO on the prevalence of goiter was reported: it estimated 20-60% of the world’s population was iodine deficient and/or goitrous, with most of the burden in developing countries. But although it was recognized many countries were affected by goiter, little attention was paid to iodine deficiency in public health programs. Goiter was considered a lump in the neck primarily of cosmetic concern; it generated little political attention or action and few resources were allocated for its control.

This changed during the period of 1970-90. Controlled studies in iodine-deficient regions showed that iodine supplementation not only eliminated the incidence of cretinism but also improved cognitive function in the remaining population. Iodine deficiency was thus shown to have social and economic consequences far greater than previously appreciated, that could slow country development. This changing view allowed iodine deficiency and goiter to be repositioned in the development perspective. The term ‘the iodine deficiency disorders (IDD)’ was coined, and IDD was repositioned as a spectrum of related disorders affecting 1.5 billion individuals. Programs against IDD had obvious political appeal because its human, economic and social consequences could be averted by a low-cost intervention, universal salt iodization. Since 1990, elimination of IDD has been an integral part of many national nutrition strategies.