

# Research on Iodine Deficiency and Goiter in the 19th and Early 20th Centuries<sup>1,2</sup>

Michael B. Zimmermann\*

The Human Nutrition Laboratory, Swiss Federal Institute of Technology, 8092 Zürich, Switzerland and the Division of Human Nutrition, Wageningen University, 6700 Wageningen, The Netherlands

## Abstract

In 1811, Courtois noted a violet vapor arising from burning seaweed ash and Gay-Lussac subsequently identified the vapor as iodine, a new element. The Swiss physician Coindet, in 1813, hypothesized the traditional treatment of goiter with seaweed was effective because of its iodine content and successfully treated goitrous patients with iodine. Two decades later, the French chemist Boussingault, working in the Andes Mountains, was the first to advocate prophylaxis with iodine-rich salt to prevent goiter. The French chemist Chatin was the first to publish, in 1851, the hypothesis that iodine deficiency was the cause of goiter. In 1883, Semon suggested myxedema was due to thyroid insufficiency and the link between goiter, myxedema, and iodine was established when, in 1896, Baumann and Roos discovered iodine in the thyroid. In the first 2 decades of the 20th century, pioneering studies by Swiss and American physicians demonstrated the efficacy of iodine prophylaxis in the prevention of goiter and cretinism. Switzerland's iodized salt program has been operating uninterrupted since 1922. Today, control of the iodine deficiency disorders is an integral part of most national nutrition strategies. *J. Nutr.* 138: 2060–2063, 2008.

*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 (1), who subsequently identified it as a new element and named it iodine, from the Greek for violet. Iodine (atomic weight 126.9 g/atom) is an essential component of the hormones produced by the thyroid gland and is therefore essential for mammalian life.

The ancient Greeks, including Galen, used the marine sponge to treat swollen glands, but Italian physicians of the School of Salerno were the first to report the specific use of the sponge and

dried seaweed to treat goiter. In the 13th century, de Villanova (1) cautioned the effect of the sponge on goiter was limited: it could cure goiter of recent origin in young people but had only a modest effect on large, chronic goiters. The sponge remained a 'goiter cure' in the medical armamentarium through the Middle Ages and into the modern era, but it was not until 1819 that Straub demonstrated sponges are rich in iodine. In 1813, learning of the discovery of iodine in seaweed, Coindet (2,3), 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, with a gradual doubling of the dose. 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 (2,3) insisted his treatment was safe when carefully administered, the often acrimonious debate on the safety of iodine would continue into the early 20th century, particularly in central Europe.

## First proposals to use iodized salt

The French chemist Boussingault (4) was the first to advocate prophylaxis with iodine-rich salt to prevent goiter. Working in Bogota, he measured iodine levels in rock and in salt deposits of the Andean region. In 1825, he reported villages in the province of Antioquia treated goiter with 'aceyte de sal,' an acrid, 'marine smelling' fluid from the salt deposits. He demonstrated in 1835 that salt sent from goiter-free Antioquia to neighboring regions reduced goiter endemia. Roulin, who worked with Boussingault

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\* To whom correspondence should be addressed. E-mail: michael.zimmermann@ilw.agrl.ethz.ch.

in the Andes, stated goiters of young people disappeared when they emigrated to goiter-free regions and, conversely, outsiders who immigrated into areas of severe goiter developed goiter within 5–6 y. Boussingault and Roulin were the first to recommend goiter prophylaxis with iodized salt; it would be nearly 100 y before their vision was realized. Nevertheless, they did not believe lack of iodine was the cause of goiter; they suggested goiter was caused by a lack of oxygen in drinking water and was common at high altitudes in the Andes because of the reduced atmospheric pressure (4).

### 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 (5). Chatin, the director of the School of Pharmacy in Paris, had measured iodine in a large number of foodstuffs and water supplies throughout Western Europe and concluded: “Too low a concentration of iodine in the drinking waters of certain areas appears to be the principal cause of goiter. Changing the water source and ... animal foods and above all of eggs are rational treatments against this condition.” However, his estimates of food iodine content were ~10-fold too high (5). Chatin recommended goiter prophylaxis through increased consumption of aquatic plants (e.g. watercress) in which he had detected iodine. Subsequently, referring to Boussingault’s work, Chatin proposed distributing iodized salt in the goitrous zones of France. However, Chatin’s work was greeted with skepticism by the French Academy of Science. Although the Academy recognized the ‘beneficial influence’ of iodine, it felt his theory that goiter and cretinism were due to iodine deficiency was inconclusive: “The facts on which it rests are not yet sufficiently numerous and conclusive to make a final judgment, and he himself admits that general hygienic conditions have an influence in producing the condition” (6).

Despite this, French authorities in 3 Departments where goiter was severe (Bas-Rhin, Seine-Inferieure, and Haute-Savoie) began distributing iodine tablets and salt together with other prophylactic measures. The program was reported in an 1869 *Lancet* article entitled “The stamping-out of goiter” (1). 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, because they were based on Chatin’s original overestimation of the iodine content in food and water, 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). Doctors at the time recognized some goitrous patients reacted adversely to even small doses of iodine; ‘Jodbasedow’ (later termed iodine-induced hyperthyroidism, or IIH) was not uncommon in goitrous adults who received iodine. Thus, whereas French children tolerated the high doses of iodine well, it likely precipitated IIH in some adults. As a result, the program was discredited and discontinued.

### Myxedema and cretinism

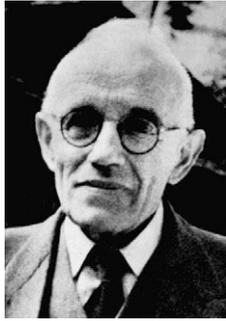
The 1885 edition of Hirsch’s classic pathology text states: “Chatin’s idea of goiter being caused by the absence of iodine in the drinking water and in the air was a short-lived opinion.” Hirsch concludes “goiter and cretinism have to be reckoned among the infective diseases” but still recommends iodine for treatment of the condition (7). Medical authorities recognized cretinism only occurred in areas of 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, was described by Ord in 1877 in London (8). Myxedema resembled cretinism in many ways but was seen only in adults, usually women. It was characterized by a swollen face, slowness in thought and movement, feeling cold, and “spade-like hands with skin resembling dry leather.” As in cretinism, the thyroid was usually atrophic. In 1883, Semon suggested myxedema was due to a lack of activity of the thyroid (9) after reading a report by the Swiss surgeon Kocher describing myxedemic symptoms in patients after total thyroidectomy (10). British physicians began successfully treating myxedema with injections and/or oral doses of animal thyroid extracts; a 1893 review exclaimed “it was one of the greatest therapeutic triumphs of the age” (11). The link between goiter, myxedema, and iodine was established when, in 1896, Baumann and Roos, working in Freiburg, Germany, digested animal thyroid glands and were surprised to isolate a residual insoluble fraction that was ~10% iodine (12). They found this substance, termed thyriodine, 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 (12,13).

### The Swiss experience

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 (1). In 1915, Hunziker, in the canton of Zurich, dismissed the infection theory of goiter and stated it was not a disease but an adaptation to a diet low in iodine. He believed the addition of minute quantities of iodine to the food supply would prevent the condition and gave iodine to cure goiter in children (14). He stated “About a year after iodine medication has been discontinued, the struma, which has meanwhile decreased in size, begins to grow again. The administration of more iodine causes it again to decrease in size.” He believed prophylaxis should start as early as possible, and “any enlargement of the thyroid should be prevented in utero by supplying a goitrous population with ... iodine.”

In 1918, the Swiss physician Bayard (Fig. 1) conducted the first dose-response trial of iodine to treat goiter (15). He did this in Grachen, an isolated village at the base of the famous Matterhorn mountain in the Zermatt valley. The village was reachable only by mule track and >75% of the school children were goitrous. He gave iodized salt for 6 mo to families in the village. The salt had 3 different iodine contents (3, 6, and 15 mg/kg). Iodized at 3 mg/kg, the salt had a modest effect on reducing goiter size. Iodized at 6 mg/kg, the efficacy was greater and even 15 mg/kg was well tolerated. Bayard had established that as little as 30 µg/d of iodine had a clear beneficial effect on goiter and noted ‘soft’ diffuse goiters in children were more responsive than the nodular forms.

During World War I, the exchange of medical literature between the US and Switzerland was interrupted. The results of



**FIGURE 1** In 1915, the rural Swiss general practitioner O. Bayard conducted the first dose-response trial of iodized salt to treat goiter in schoolchildren. Reproduced with permission from (1).

Marine and Kimball's studies of iodine prophylaxis in Akron in 1917 were not announced in Swiss medical literature until 1919 (1). This was after Hunziker and Bayard had carried out their small-scale experiments in Switzerland. In 1919, Klinger, noting the success of the U.S. studies, recommended prophylaxis with iodine tablets at Swiss schools and iodized salt for the general population (1). He suggested the Swiss Federal Government should be responsible for the program and a Swiss Goiter Committee was formed in 1922. The Goiter Committee had no powers of decision but acted in an advisory capacity to the Federal Office of Health. Initially, the committee cautiously advised the introduction of salt iodized at 1.9–3.75 mg/kg nationwide on a voluntary basis, a compromise between the proponents and opponents of iodized salt (16). However, every Swiss canton had its own salt monopoly and each cantonal government or health authority could decide whether to iodize its salt. The first canton in which iodized salt was introduced was Appenzell AR, in 1922, thanks to the efforts of the surgeon Eggenberger (Fig. 2). He pushed the local government to allow the sale of salt iodized at 7.5 mg/kg (17) with spectacular results: newborn goiter disappeared, no new cretins were born, and goiters in children were reduced in size or disappeared.

The iodine in Swiss salt was subsequently increased in a stepwise manner to 7.5 mg/kg (1962), 15 mg/kg (1980), and 20 mg/kg (1998). This gradual increase may have avoided a widespread outbreak of ITH in the chronically iodine-deficient Swiss population (18). In 1980, when the salt iodine content was increased from 7.5 to 15 mg/kg, doubling iodine intakes, the incidence of toxic nodular goiter increased by 12% in the first 2 y following the increase, but then declined to a level only 25% of the initial incidence (19). The Swiss iodized salt program today is a flexible, smooth-running program that involves a minimum of administration. Nearly 94% of household salt and 50–70% of industrial food salt is iodized at 20 mg/kg. Salt producers and retailers must offer both iodized and noniodized salt, as compulsory use would be perceived as unconstitutional. The original Goiter Committee was succeeded by the Fluorine-Iodine-Commission of the Swiss Academy of Medical Sciences, which is still active today (20).

### Iodine supplementation studies in the US

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 US. David Marine (Fig. 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



**FIGURE 2** The birthplace of the Swiss iodized salt program: H. Eggenberger and his family iodizing salt for distribution in the Canton of Appenzell, Switzerland, in 1922. Reproduced with permission from (1).

goiters in the neighborhood and replied without much reflection he would like to work on thyroid disease (21). Marine subsequently confirmed Baumann's finding that large goiters contained less total iodine than healthy glands (22). The American surgeon Halsted had reported when part of the thyroid was resected, the remaining tissue increased in size and called this "compensatory hypertrophy" (23). Marine extended this observation and suggested goiter was "a compensatory reaction to some deficiency" and it appeared "...iodine is the most important single factor..." (22). That iodine deficiency was not the only potential dietary contributor to goiter was confirmed 15 y later when Marine published his work on the goitrogenic action of certain cyanides in animals (24).

Marine realized goiter was a serious public health problem in the Great Lakes region 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 (25,26). The treatment group was girls in the 5th grade and above whose parents gave consent for them to be included in the trial; the controls were those girls whose parents did not consent. Treatment for students in the 5th–8th grades was 200 mg NaI per school day for 10 d, equivalent to a total of 1700 mg iodine; double this amount was given to the older girls. These excessive doses are



**FIGURE 3** In 1916–17, the American physician David Marine conducted the first large-scale trials of iodine supplementation to prevent goiter in children in Akron, Ohio. (From the U.S. National Library of Medicine, Bethesda, MD, and in public domain).

similar to those recommended a century earlier by Coindet (2). The results were unequivocal: in the over 1200 girls in the untreated group at baseline, >25% had goiter at their final examination. In the 900 girls who received iodine who were not goitrous at baseline, only 0.2% showed evidence of enlargement. Marine and Kimball concluded that goiter "...is as easily prevented in man as in fish or in domestic animals" (27). Based on these and other successful experiments, general prophylaxis with iodized salt was introduced in the state of Michigan in 1924. Based on an estimated per capita salt intake of 6.5 g/d, 100 mg/kg potassium iodide was added to table salt to provide 500 µg/d. There were protests and at first the Bureau of Chemistry of the USDA demanded the iodized salt packages be marked with the skull and crossbones used to indicate a poison but then backed down. In Cleveland, Ohio, many households did not adopt iodized salt, and a study in 1936 found 31% of children not receiving iodized salt were goitrous, compared with 7% of children using iodized salt (28). 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 the 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 (29). 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. Universal salt iodization (iodized salt for both human and animal consumption) also improved the viability and quality of livestock (30). 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 iodine deficiency disorders (IDD) was coined and IDD was repositioned as a spectrum of related disorders affecting 1.5 billion individuals (29). It was estimated to be the leading cause of preventable mental retardation around the world. 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. This message was disseminated through high-level political forums to incite attention, commitment, and actions. Since 1990, elimination of IDD has been an integral part of most national nutrition strategies. Today, iodine nutrition continues to be an area of active research, with recent studies focusing on the links between deficient and excess iodine intake and the epidemiology of thyroid diseases, interactions of IDD and other micronutrient deficiencies, as well as molecular mechanisms (31–33).

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