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Hypothyroidism in Switzerland

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Introduction

Hypothyroidism is a condition of mild to severe impairment of physical and mental development due to an untreated deficiency of thyroid hormones, and can be endemic, genetic, or sporadic. Endemic hypothyroidism arises from a diet deficient in iodine. The most common iodine deficiency disorders are goiter (enlarged thyroid gland) and hypothyroidism at all ages, as well as endemic cretinism,[1] mental impairment, delayed physical development in growing children (Iglesias and Diez 2008; Zimmermann, Jooste, and Pandav 2008; Zimmermann 2009, 2010).

Populations living in iodine deprived areas such as the Himalayas, the Andes, and the European Alps, are most at risk. In the Alpine region of Switzerland endemic hypothyroidism was very common until the beginning of the twentieth century. The aim of this study is to present the theme from three different, but complementary perspectives. The medical perspective lays the groundwork regarding the pathophysiology, the clinical picture, and the differential diagnosis of the condition. The historical perspective presents contemporary scientific studies on conscription and published data on goiter and cretinism as endemic manifestations of hypothyroidism (since 1900) and the archaeo-anthropological perspective reports one of the first documentations of the condition in an archaeological population from Switzerland (11th–15th century AD). Together, they offer insights into a significant health problem and contribute significantly to the biological history of the Alpine regions.

The interdisciplinary approach of this contribution brings together different fields with different methods and sources of information. This is necessary, since medical, historical, and anthropological sources for the period before 1900 are extremely limited and, in some cases, completely absent. By comparing medical background, skeletal manifestations

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1 The use of the term cretinism and cretin—referring to severely stunted physical and mental development due to lack of thyroid hormones—is made for the sake of medical, historical, and social facets that the disease shaped during the beginning of the twentieth century and by no means entails a negative connotation.

in the Swiss population past and present, and historic and modern survey data, we gained new insights into a highly complicated, but also significant, health and social problem, namely hypothyroidism. The overlap between the three disciplines both in terms of actual data—e.g., variation in stature between hypothyroid and non-hypothyroid individuals—and also in terms of theoretical background underlines the need for interdisciplinary studies such as this. To our knowledge, this is the first time that hypothyroidism in Switzerland has been the subject of a multidisciplinary study, and we hope that this paper will offer insights and motivation for the study of the condition in the neighboring Alpine regions of Germany, Italy, and Austria.

Frank Rühli

Hypothyroidism: A Medical (Bone) Perspective

The aim of this first, medically oriented section is not only to list the clinical classification of various types or etiologies of hypothyroidism, but also to present specifically selected cases of hypothyroidism as found in the so called "Galler collection," a bone pathology reference series from the University Hospital, Zurich, mostly circa 1940–1970 (for some general information on this, see Rühli, Hotz, and Böni 2003).

Within the thyrotrophin cycle, hypothyroidism is defined as a lack of lack of triiodothyronine (T3) and thyroxine (T4), and can severely affect tissue development and remodeling. The main skeletal manifestation of hypothyroidism is delayed epiphyseal fusion (affecting the axial skeleton and long bones), resulting in short hands, limb asymmetries, changes in skull form such as sella turcica, or osteoporosis. Other manifestations (psychological, soft tissue) are: fatigue, decreased heart rate, weight gain, problems with memory and concentration, depression, goiter (enlarged thyroid gland), muscle pain, dry swollen skin, and irregular menstrual periods (in women).

Thyrotrophin-releasing hormone (TRH) is released from the hypothalamus via specific vessels to the hypophysis (pituitary gland), and, in turn, thyrotrophin or thyroid-stimulating hormone (TSH) from the hypophysis regulates the thyroid function. Iodine is needed (ca. 200 µg/day) in order to correctly synthesize the hormones T3 and T4 produced by the thyroid. T3 and T4 increase the general metabolism, sensitivity to

catecholamines (organic compounds that act upon the heart among other organs); or calcium, and phosphate metabolism. Inborn variants of hypothyroidism (thyroid hypofunction) are aplasia (absence of an organ), dysplasia (alteration of cells or of a structure), and hormone resistance (receptor defects), and acquired variants are iatrogenic (i.e., resulting from medical treatment, such as through iodine exposition or following an operation). Primary variants are a lack of iodine or autoimmune thyroiditis (inflammation of thyroid gland; "Morbus Hashimoto"); a secondary variant is a lack of TSH (hypopituitarism); tertiary variants are a lack of TRH or disruption of the portal system (Pickardt syndrome, or interruption of the vein system connecting hypothalamus and pituitary, e.g. due to tumors). In Switzerland, 757 cases of hypothyroidism in newborns have been reported since 1977 (ca. 1:3500). There is regular screening of infants at day four or five after birth. Severity grades are: latent/compensated (only TSH is elevated); subclinical (T3 and T4 lowered, but no symptoms); and manifest (symptoms).

An exemplary case of "cretinism" from the Galler pathological bone-reference series from the nineteenth and twentieth centuries in Switzerland (Rühli, Hotz, and Böni 2003) is presented here, together with clinical case reports, as well as autopsy findings. One 79-year-old male individual in the Galler series, who was 160 cm tall, had particularly strong signs of hypothyroidism. The autopsy findings reported, among other indications, a cretinoid habitus as well as a struma diffusa on the x-rays.

In general, skeletal manifestations of hypothyroidism (thyroid hypofunction) in the Galler cases are: kyphoscoliosis, large cranium, proportional dwarfism, cretinoid habitus, renal osteopathy (fibro-osteoclasia), hyperostosis frontalis interna (thickening of the inner table of the frontal bone), coxarthritis, osteoporosis (mild/severe), and club foot. Causes of death were: subdural hematoma (cerebral hemorrhage) from a fall, pneumonia, heart failure, and uterus corpus carcinoma.

Kaspar Staub

Historical Perspectives on Hypothyroidism in Switzerland: Endemic Iodine Deficiency, Goiter, and Cretinism since the Late Nineteenth Century

Switzerland was one of the few countries to become completely iodine sufficient before 1990 (together with some of the Scandinavian countries, Australia, USA, and Canada), and was a world pioneer, introducing its iodized salt program in 1922 (first in Canton Appenzell AR, then subsequently all over Switzerland, operating uninterrupted since then). The consensus among researchers is that iodine prophylaxis was the decisive factor in eradicating substantial risks of iodine deficiency and preventing endemic goiter and cretinism during the first half of the twentieth century (Bürgi, Supersaxo, and Selz 1990; Zimmermann 2008). This section will summarize this process since its inception in the late nineteenth century.

Prior to the introduction of the iodized salt program, Switzerland was severely iodine deficient. Goiter and "cretinism" were widespread in alpine areas and the foothills of the Alps. Surveys have been made since the beginning of the nineteenth century. For example, a census ordered by Napoleon reported four thousand cretins among the 70,000 inhabitants of Canton Valais in 1800. Many travelers to Switzerland reported the devastating endemic of goiter and cretinism; for example, Mark Twain, who stated in 1884: "I am satisfied. I have seen the principal features of Swiss scenery—Mount Blanc and the goiter—and now for home." Goiters appeared also in numerous illustrations and chronicles (Bürgi, Supersaxo, and Selz 1990; Zimmermann 2008; Merke 1971).

Since the 1880s, scientific studies and surveys based on data from schoolchildren and military conscripts showed the degree and regional spread of goiter and cretinism. In 1889, Theodor Kocher showed in his goiter survey of around 80,000 schoolchildren in the Canton of Bern that 20 to 100 percent of the seven to sixteen-year-old children had goiters. In 1883, Heinrich Bircher had already demonstrated the regional prevalence of military service exclusion due to large goiters in Swiss conscript data for the period 1875–1880, mapped down to village level. The enormous variation from one village to another was explained by differences in soil geology and water supply (the presence of some kind of goitrogenic agent). These early researchers failed to consider iodine deficiency as the cause, even though the relationship between iodine deficient

soil/water and goiter had already been established by Chatin in 1850/1860 (Bircher 1883; Bürgi, Supersaxo, and Selz 1990; Zimmermann 2008; Merke 1971).

For the period 1884–1891, the Swiss Army published the percentage of 19-year-old conscripts found unfit for service because of large goiters (N≈170,000), mapped down to district level.[2] Various contemporary studies mapped the prevalence of goiter across districts, highlighting the comparative rarity of large goiters causing military unfitness (less than 4 percent) in the western part of Switzerland (Cantons Jura, Neuchatel, Vaud, and Geneva), whereas the Alps, the foothills, and the midlands from southwest to northeast were areas of high prevalence (greater than 7 percent). For the conscription years 1920/21, Otto Stiner drew a new district map, including not only large goiters leading to unfitness in his calculations, but also smaller goiters of conscripts fit for service (fig. 1). Stiner's map consolidated the findings on regional goiter prevalence, but this had now risen to 30 percent of young men in certain regions. In the literature, the low goiter prevalence in western Switzerland is explained by the fact that the Jura was not covered by ice during the last two ice ages, so iodine in the soil had not been washed out. Furthermore, the marked contrast in goiter prevalence between the two Cantons of Vaud (low) and Fribourg (high) can be explained by the fact that, in contrast to Fribourg and other Cantons, Vaud had its own salt mine at Bex, which was rich in iodine. In 1924/25, new exact instructions on the grading of palpable goiters were implemented. The goiters did not have to be large enough (e.g. leading to unfitness) to be recorded. Now, the district-wide prevalence increased to a range from 5 to 82 percent of young men having goiter, with 29 of the 136 districts reporting a prevalence of over 50 percent (Bürgi, Supersaxo, and Selz 1990; Eggenberger 1923; Stiner 1924; Stiner 1928).

Between 1900 and 1920, iodine deficiency became accepted as the main causative factor for endemic goiter and cretinism in Switzerland. Between 1910 and 1920, Theodor Fellenberg, a federal chemist, measured iodine levels and confirmed that in goitrous regions soil, rock, water, milk, and other locally produced food contained little iodine. He stated that large areas of Switzerland were grossly iodine-deficient (Solca et al. 1999). Around 1920, the idea of iodine prophylaxis in schools was put into practice in the cities of Zurich and Bern, with great success. Medical examination by the

2 According to the instructions, a large goiter that caused breathing problems or which was strongly disfiguring was a reason for unfitness to serve. Medical examination during conscription was standardized and compulsory from 1875 onwards.

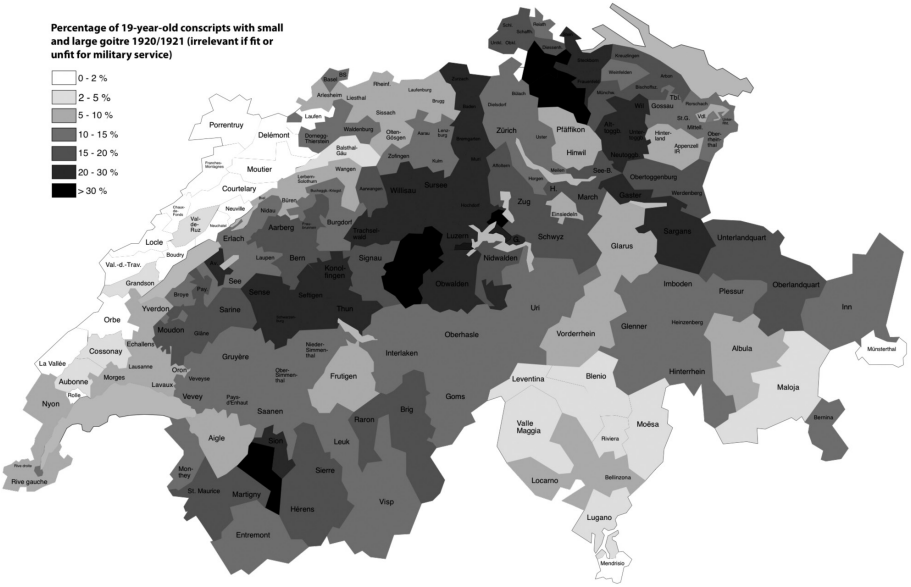

Figure 1: Percentage of small and large goiters in Swiss conscripts 1920/21 (Stiner 1924, 1928).

school medic in the City of Bern showed that 60 percent of all fifth graders had at least a visibly enlarged thyroid. Gradually, beginning in 1921, all first graders, and then every subsequent year all children of other grades, were supplied with one tablet of 0.003 g iodine each week. The fifth graders first received the tablets primarily in 1926, and the prevalence of enlarged thyroids immediately decreased (Bürgi, Supersaxo, and Selz 1990; Lauener 1936; Zimmermann et al. 2008; Staub 2010).

Final steps towards the introduction of iodized salt were made by successful *in situ* tests by H. Hunziker and O. Bayard around 1920 (Bürgi et al. 1979). Hans Eggenberger, a surgeon in Herisau (Canton Appenzell AR), started a campaign and petition to the government, which in 1922 allowed the distribution of salt containing 7.5 mg iodine per kg. The salt was first iodized by Eggenberger himself and his family. The results were spectacular: within a year, existing goiters had shrunk in 66 percent of the schoolchildren whose families used iodized salt on a regular basis, and the average surface area of the thyroid shrank to an invisible and normal level after four years of prophylaxis. Furthermore, newborn goiter disappeared; no babies showed physical signs of hypothyroidism (Bürgi, Supersaxo, and Selz 1990; Zimmermann 2008; Eggenberger 1922).

In 1922, the Swiss Federal Office of Public Health appointed most of the people engaged in goiter research as members of the Swiss Goiter Commission in an advisory function. In June 1922, the committee cautiously recommended that the twenty-five Cantons commence sale on a voluntary basis of salt containing 1.9 to 3.75 mg iodine per kg; non-iodized salt remained available. Every Swiss Canton had its own salt monopoly, and each cantonal government could decide whether to iodize its salt. After the breakthrough in Appenzell AR, other Cantons complied with the recommendations with varying degrees of zeal; by 1930, iodized salt had reached 50 percent of all salt sales in only thirteen of the twenty-five Cantons. Opposition came from ignorance of the iodine deficiency theory and from fear of a massive outbreak of hyperthyroidism (Bürgi 2010). Iodine prophylaxis did not attain full acceptance in all Cantons until the 1950s (Bürgi, Supersaxo, and Selz 1990; Zimmermann 2008).

Thus, iodized salt was the decisive factor in eradicating endemic goiter and cretinism in Switzerland, and also in preventing other iodine deficiency disorders (fig. 2). The percentage of conscripts unfit for duty due to large goiters, severe mental deficiency, and height of under 156 cm decreased markedly as the use of iodized salt increased between 1920 and 1950. Large goiters in recruits had disappeared by 1950 (except in two Cantons, which had not introduced iodized salt: Basel-Land and Aargau).

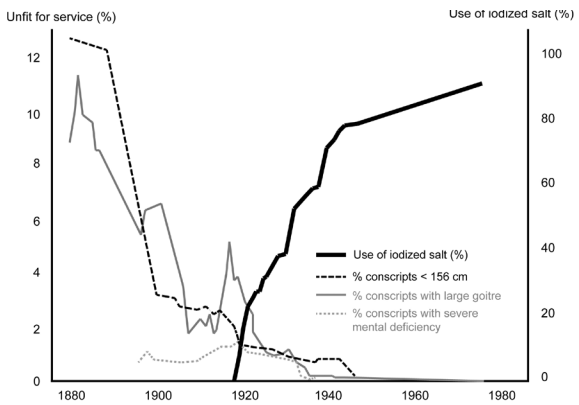

Figure 2: The results of the Swiss iodized salt program since the 1920s (Bürgi, Supersaxo and Selz 1990).

In the 1980s, only 5.2 percent of conscripts had a palpable but not visible goiter, 0.26 percent a slightly visible goiter, and 0.04 percent a visible goiter, but not one single conscript was found unfit because of goiter (Schmid et al. 1980). Although it has clearly declined, goiter may still occur today; but only at a clinically irrelevant level (Bürgi, Supersaxo, and Selz 1990; Zimmermann 2008). Iodized salt has without any doubt been the most cost-effective preventive health measure ever applied in Switzerland (Bürgi, Supersaxo and Selz 1990; Bürgi 1986; Steck et al. 1999).

Christina Papageorgopoulou

Hypothyroidism in Alpine Medieval Switzerland

Hypothyroidism has practically never been described in a historic or prehistoric population, except in clinically documented case studies (Ortner and Hotz 2005). This section reports one of the first documentations of hypothyroidism due to iodine deficiency in archaeological populations, in this case the presence of endemic hypothyroidism in a medieval Swiss Alpine community, thus contributing significantly to the biological history of the Alpine regions. Furthermore, the large sample number adequately describes the variability of the skeletal manifestations and the epidemiological pattern of the disease.

The skeletal sample consists of 404 adult and subadult individuals, originating from the archaeological site of Tomils/Sogn Murezi and dating from the eleventh to fifteenth centuries AD. Tomils is located in the Alpine region of the canton Grisons, Switzerland, a thousand meters above sea level. The skeletal material was examined for all standard anthropological variables (e.g., age and sex determination, cranial and postcranial metrics, pathological conditions; Papageorgopoulou 2008). Where necessary, the bones were x-rayed at the University Clinic Balgrist (Zurich, Switzerland).

For the diagnosis of hypothyroidism, a list of observed pathological features characteristic for the condition were examined and statistically tested based on related literature (e.g., Borg, Fitzer, and Young 1975; Guggenbühl 1853; Evans 1952; Reilly and Smyth 1937; Scholz 1906) and clinical studies from the region of Switzerland (e.g., De Quervain and Wegelin 1936; König 1968; Weygand 1904; Wieland 1940). We also performed macroscopic and radiological comparisons of diagnosed cases of hypothyroidism from Switzerland in the nineteenth and twentieth centuries (Galler pathological reference series, University of Zurich). The epidemiological pattern of the disease was analyzed, and further pathological (dental condition, degenerative joint disease, trauma) and archaeological parameters (interment within the cemetery) were tested.

A high frequency of delayed epiphyseal fusion, in both the axial skeleton and the long bones; hip and shoulder epiphyseal dysplasias; limb asymmetries and/or abnormal length of the long bones; and epiphyseal growth plate problems (osteochondritis dissecans) were present in the skeletal material (table 1). Additionally, cranial characteristics such as short

face; large piriform aperture; wide nasal root; brachycephalisation; prognathism; and anomalies in tooth position and eruption were observed in hypothyroid individuals. Statistically significant differences have been noted between hypothyroid and non-hypothyroid skulls, mainly concerning facial cranial measurements (M7, M9, M10, M11, M16, M40, M42, M45, M61, M63, M66, M79 after Martin 1914).

Skeletal Manifestations of Hypothyroidism in Tomils	
Vertebra column: delayed apophyseal fusion, unfused odontoid	20.3%
Sternum: delay in ossification	10%
Extremities: delayed epiphyseal fusion, asymmetry	15.2%
Hip and shoulder unilateral and/or bilateral dysplasias	2.2%
Epiphyseal growth plate problems (osteochondritis dissecans)	3.2%

Table 1: Frequencies of single growth disturbances in hypothyroidism from Tomils (calculated per skeleton).

Most of the above manifestations appear in combination in the same skeleton. Of 404 individuals, 7.4 percent show two of the above diagnostic criteria; 3.5 percent three diagnostic criteria; 2 percent four diagnostic criteria; and 0.7 percent five diagnostic criteria. The individuals showing only one diagnostic criterion were excluded from further analysis, since they do not provide enough evidence for a univocal hypothyroidism diagnosis. Individuals exhibiting more than two diagnostic criteria (13.6%) were grouped together. The rate of hypothyroidism in Tomils, although high, is similar to modern (nineteenth and twentieth century) clinical data for this region (Lorenz 1895), which is considered one of the most affected regions in Switzerland.

No statistically significant differences were found between males and females. Juveniles and young adults were more affected than older adults; the difference was significant. This is associated with the lower life expectancy of juvenile individual, with hypothyroidism (life expectancy of a juvenile e_{juv}= 39.0 years) compared to non-hypothyroid individuals (life expectancy of a juvenile e_{juv}= 45.6 years). Hypothyroidism was not observed in children. We interpret this more as a problem of diagnosis in immature individuals than as the absence of the condition.

Hypothyroid male individuals were 2 to 3 cm shorter than non-hypothyroid individuals (statistically significant, Mann-Whitney non-parametric test). Hypothyroid females were

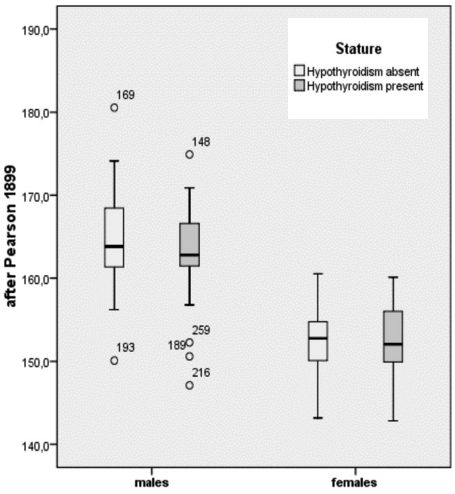

Figure 3:
Hypothyroid male individuals are 2 cm shorter (shorter hypothyroid individual 145 cm) compared to non-hypothyroid individuals; statistically significant differences for males, Mann-Whitney non-parametric test.

0.5 to 1 cm shorter, but in this case there was no statistical significance (fig. 3). Hypothyroid individuals exhibited a higher frequency of caries, calculus, dental wear, and linear enamel hypoplasia than non-hypothyroid individuals, and the differences are statistically significant. No statistically significant differences between hypothyroid and non-hypothyroid individuals were observed regarding the frequency of Harris lines, fractures/traumas, and degenerative joint diseases of the spine and the long bones. No differences were found between the two groups in terms of grave goods, place of interment, and type of burial.

A differential diagnosis for the single bone elements may include, for example Perthes for hip dysplasias, bilateral humerus varus for shoulder dysplasias, or multiple epiphyseal dysplasias. However, in the presence of a combination of delayed ossification, long bone asymmetries, and the characteristic features of the skull, a diagnosis of hypothyroidism is more probable. A differential diagnosis for the combined skeletal manifestations may include achondroplasia, although the stature of the individuals, within normal limits, does not support a diagnosis of achondroplastic dwarfism.

Conclusion

In our contribution, we presented hypothyroidism in Switzerland from three different, but complementary, perspectives: medical, historical, and archaeological. The medical perspective lays the non-time-specific and scientific groundwork regarding definition, anatomy, variants, pathophysiology, severity grades, clinical picture, and differential diagnosis of hypothyroidism. It also presents some cases from the Galler pathological bone-reference series (twentieth century), particularly the case of a seventy-nine-year-old individual whose clinical case report, autopsy findings, and remaining bones indicate clear signs of hypothyroidism.

The historical perspective takes other sources of information about the past into consideration: contemporary scientific studies on conscription, as well as published data on goiter and cretinism as endemic manifestations of hypothyroidism due to iodine deficiency since the late nineteenth century. In certain regions of Switzerland, 0.5 percent of inhabitants suffered from hypothyroidism (cretinism), circa 100 percent of schoolchildren had large goiters, and up to 30 percent of young men were unfit for military service before the implementation of iodine in salt (Bürgi, Supersaxo, and Selz 1990).

The anthropological perspective reports one of the first documentations of hypothyroidism due to iodine deficiency in archaeological populations, contributing significantly to the biological history of the Alpine regions. The large size of the skeletal sample (404 adult and subadult individuals) originating from the archaeological site of Tomils/Sogn Murezi and dating to the eleventh to fifteenth centuries AD, adequately describes the presence and variability of the skeletal manifestations and the epidemiological pattern of endemic hypothyroidism in a medieval Swiss Alpine population. This can be used as the basis for diagnosis of skeletal material originating from high-risk regions, which, until now, was absent in the palaeopathological literature. From an archaeo-anthropological point of view, the medical and the historical perspectives contribute significantly to the identification and positive diagnosis of the condition, since they both provide the necessary evidence. Both the presentation of the Galler hypothyroid cases and the historical documentation reinforce the anthropological and the archaeological data.

Furthermore, the historical perspective bridges medieval times with the present, when the implementation of the pioneering iodized salt program eradicated endemic goiter and cretinism in Switzerland. Iodized salt has with any doubt been the most cost-effective preventive health measure ever applied in Switzerland. Looking back, the prolonged administration of iodine or of thyroid hormone has been found highly effective in reducing the size of endemic iodine deficiency, and thus hypothyroidism. Switzerland was one of the few countries to be completely iodine sufficient before 1990 (together with some of the Scandinavian countries, Australia, USA, and Canada), and iodine intake in schoolchildren can be assumed to have been constant since 1980. We demonstrate that this was not the case in medieval times or in the nineteenth century: iodine deficiency, goiter, and hypothyroidism were major problems for the local populations.

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