David Marine and the Problem of Goiter

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David Marine is one of those scientists now largely remembered for the outcome of a single trial rather than for a lifetime of critical, painstaking studies—in his case of the functioning and regulation of the thyroid gland. He is remembered for his trial, with O. P. Kimball as his assistant, of the effect of giving iodide to a large group of schoolgirls in Ohio from 1917 to 1922 and for showing that this greatly reduced their development of goiter (1). It required perseverance to find a school board that would permit such a trial when others had considered it dangerous and irresponsible.

A particular irony here is that the idea was in no way new because, as those with an interest in the history of our subject will know, French chemists and physicians had already demonstrated the value of iodine in the treatment of goiter soon after the discovery of the element in the first half of the previous century. What happened in the meantime for this experience to have become lost or at least ignored? We must consider this before it is possible to put Marine’s work into any kind of perspective.

The historical background

The name “goiter” (or more traditionally “goitre”) had long been given to patients with a greatly swollen thyroid, the ductless gland positioned in the neck in front of the larynx, weighing about 35 g in a healthy adult. The condition had been common from one generation to the next in particular areas, while other areas, sometimes quite close by, had always remained free of the condition. In the former there is said to be “endemic goiter.” The gland had no obvious function and was thought by some just to be providing a wrapping for the larynx and esophagus, and the victims of goiter did not share other characteristic problems.

After the publication of the discovery of iodine in seaweed in 1813, Dr. Coindet, a physician practicing in Switzerland, speculated that the traditional folk treatment of goiter with dried, or ashed, seaweed or sponges might be successful because of its iodine content. He put this to the test by dissolving 48 grains (i.e., 3.11 g) of iodine in a volumetric ounce (28.3 mL) of “spirit of wine” (distilled alcohol) and instructing his goitrous patients to begin by taking 10 drops 3 times per day (totaling ~1.5 mL). This put the initial daily dose at 165 mg iodine, and he recommended gradually doubling this quantity (2). He added that he had already, in 1821, had many successes with this treatment.

Coindet’s paper raised a great deal of interest, as might be expected, with goiter being endemic in many parts of Switzerland. By the time his second paper appeared, a year later, many physicians had told him of the cures that they too had obtained, but some leading citizens of Geneva had complained that the treatment had toxic effects, leading to a public clamor against the use of iodine comparable to that against vaccination when it was first introduced (3). A later reviewer wrote: “It was even rumored that Coindet would not leave his house for fear of being stoned in the street by his poisoned patients, but this was a myth” (4).

In fact, Coindet insisted that under his conditions of treatment, which included a weekly examination of each patient and suspension of the treatment in the very few cases who seemed to show any adverse signs, there was no danger. He recommended that iodine should only be available on prescription and given under medical supervision, and he appealed to the medical societies in Geneva to let him know if even one of his former patients had come to any harm from his treatment, because he knew of none (3). The controversy as to whether iodine was a safe treatment for goiter continued to rage in Europe with attacks appearing in both France and Germany (e.g., 5, 6).

In the largest trial referred to by a reviewer in 1873, 640
boys and girls in the schools in the canton of Albi (south of Lake Geneva in France) were found to have goiter, and 490 (with the permission of their parents) received each school day from their teacher a pill containing 10 mg potassium iodide (equivalent to 7.6 mg iodine) for 75 d, or for a shorter time if the problem disappeared before then (7).

The scheme was kept under medical inspection and 361 children were completely cured, another 129 greatly improved, and none any the worse. Some of those treated redeveloped the condition in the months following, but they again responded to the same treatment in the next school year (7). Another writer has referred to similarly successful trials carried out in the 1860s in 2 other areas of France, but again without giving a primary reference (8).

Toxic or exophthalmic goiter

By at least 1860 it was well accepted that some patients with an enlarged thyroid had a different condition from ordinary, endemic goiter. This included protruding eyeballs, weight loss, palpitation of the heart, and signs of nervousness (9). The condition was given a variety of names including Graves’ or Basedow’s disease, after physicians who were among the first to describe it. It was generally agreed at that time that treatment with iodine was not suitable for such patients and often made things worse.

Early ideas of the cause of endemic goiter

Meanwhile there was a quite separate controversy as to the cause of ordinary, endemic goiter. Jean Baptiste Boussingault, famous later in life as a nutritional chemist, was conducting geological surveys in Central America in the 1820s and, in collaboration with a French physician, concluded that goiter was occurring wherever the salt being consumed was low in iodine, but was absent where salt was naturally richer in this element (10). From this basis he went on to recommend that naturally iodized salt should be distributed by the government in place of more purified material. However, he made no suggestion that lack of iodine was the cause of the disease, any more perhaps than he would have suggested that malaria, which had been treated successfully using quinine, was caused by a lack of that drug.

Boussingault’s hypothesis was, in fact, that the disease was caused by a lack of dissolved oxygen in drinking water, in the high altitudes by reason of the reduced atmospheric pressure and in the lower areas where the disease was endemic, because rotting vegetation in ponds had taken up much of the dissolved oxygen (10).

The French chemist A. Chatin was at least one of the first to claim, in 1851, that a deficiency of iodine was the actual cause of goiter (11). After reporting extensive analyses of water supplies and foods in different parts of France and Italy, he 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 at least some use of wine, of animal foods and above all of eggs are rational treatments against this condition.”

Several other French scientists essentially confirmed Chatin’s findings and the Academy of Sciences appointed a commission to investigate and report on the idea. While they praised Chatin’s industry and were satisfied that he had established the wide distribution of the element, they could not accept his theory: “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” (12).

The commission’s conclusions seemed to put an end to the idea for the next 50 years. A comprehensive French review of the subject in 1879 refers to “multiple causes” and states that someone moving from a healthy area to one where there is endemic goiter will encounter “the toxic principle responsible for the condition” (13). In the 1885 edition of A. Hirsch’s classic Handbook of Historical and Geographical Pathology, we read: “Chatin’s idea of goitre being caused by the absence of iodine in the drinking water and in the air was a short-lived opinion.” Hirsch goes on to refer to other analyses that seem to refute Chatin’s theory and concludes that “goiter and cretinism have to be reckoned among the infectious diseases” although he accepts the value of iodine for treatment of the condition (14). By this date so many diseases had come to be explained in terms of microbial infection that one can understand that this should have become the “fall back” explanation for almost any disease of unknown origin.

Cretinism and myxedema

Hirsch linked the conditions of cretinism and goiter because by the time of his review it had been realized that cretinism, the sad condition in which children were born with organic and intellectual degeneration, only occurred, and in smaller numbers, where goiter itself was endemic (14). However,CRETINS typically had only a shrunken thyroid gland—the exact opposite of goiter.

Another disease with some resemblance to cretinism, but appearing in adulthood, was named “myxedema” (or “myxedema” in the United States) by William Ord in 1877, from his experiences in a London teaching hospital (15). It was characterized by the patient, usually a woman, having become slow in mind and body, although the muscles were not wasted, and always feeling cold. The face was swollen and the hands “spade-like with skin resembling dry leather.” The thyroid gland in these patients was also typically shrunken to one fourth or less of its normal size. Many more physicians in both Europe and the United States then published similar descriptions of the condition (16).

In 1883 at another discussion of the disease in London, Felix Semon suggested that the cause could be insufficient activity of the thyroid gland because the Swiss surgeon Theodore Kocher (who would later receive a Nobel prize for his work) had recently told a conference that several of the patients on whom he had performed a total thyroidectomy had over time developed a condition with all the characteristics of myxedema (17).

Given this idea that the naturally occurring disease might also be the result of a lack of thyroid gland activity, British physicians tried treating the condition first with injections of extracts made from animal thyroid glands and then just by feeding whole glands (18). By 1893 a review of the successful results from 100 published cases treated in this way concluded: “it was one of the greatest therapeutic triumphs of the age” (19). Incidentally, for the first time, this was evidence that the thyroid gland really had a function (16).

Also, since the signs of exophthalmic goiter were the opposite of myxedema, it was apparent that the first condition could reflect an excessive secretion of the natural thyroid hormone(s) rather than secretion of an abnormal toxin, as had been previously supposed, and the standard treatment became the surgical removal of most, but not all, of the overactive gland (20).

Later in the 1890s E.A.G. Baumann and E. Roos, working
in Freiburg, Germany, were able to obtain from peptic digestion of animal thyroid glands a residual insoluble fraction that they called “thyroidea” (later “iodothyronin”) that contained nearly 10% iodine. They found this to be active by mouth in the treatment of both myxedema and goiter and in stimulating metabolism, and they suggested that iodine as such was not therapeutically active, but that it had first to be combined into an organic molecule present in their iodothyronin. Others then confirmed the value of such materials and showed that the material came from the breakdown of an iodine-containing thyroglobulin protein that was readily extractable from the gland.

Baumann’s finding of iodine in the thyroid gland apparently came to him as a surprise. In hindsight, it seems more surprising that no one earlier had thought of looking for it there.

As to the cause of goiter, one standard text in the early 1900s, edited by William Osler, wrote simply: “the cause is unknown” (24) and another that “given lack of discovery of a chemical cause, it may have a microbial causation” (25).

David Marine’s background

We are now almost at the point at which David Marine entered the field (Fig. 1). Born in 1880, he grew up on a farm in Maryland and attended a liberal arts college for 4 years to the age of 20. He then entered Johns Hopkins University to study zoology, but switched to medicine after 1 year, studying under distinguished faculty and graduating high in his class in 1905 (25). He was then appointed to a residency in pathology at Lakeside Hospital (linked to Western Reserve University) in Cleveland, Ohio, and was surprised to be asked immediately on his arrival what research problem he wished to tackle to supplement his clinical duties. According to legend at least, Marine had noticed several dogs with obvious goiters on his walk to the hospital, and he replied that he would like to work on the thyroid gland; this he continued to do for many years (26).

Work with dogs and fish

After 2 years’ work on his new subject, Marine had a paper published in the Johns Hopkins Bulletin. Here he wrote that, because of the complexity of the human disorder, he had begun work on goiter as seen in dogs and farm animals in the Cleveland area. He attributed the recent reduction in what was then considered the serious problem for local sheep farmers to their increased use of iodized salt for their flocks. He himself had been giving iodine to goitrous dogs and seen them change from “wizened and listless” to “active and robust.” The treatment resulted in the thyroid shrinking but greatly increasing in total iodine content. He realized that his work “does not exclude the possibility that iodine may be a specific remedy for an infecting agent,” but he saw that it had an important role in metabolism and there was need to understand whether a deficiency resulted from lack of it in the diet or inefficient absorption (27).

By the following year Marine had collaborated with a colleague in pharmacology and they were able to show, in confirmation of Baumann’s work with humans, that large goitrous thyroids from dogs actually contained less total iodine than was present in the glands from healthy dogs (28). The authors also referred to a term that had been introduced by W. S. Halsted, a surgeon who had been one of his teachers at Johns Hopkins. Having found that, when part of a thyroid gland was removed, the remaining tissue increased in size, Halsted described this as “compensatory hypertrophy” (29).

Marine, referring back to Halsted, went further and suggested that endemic goiter also was “a compensatory reaction to some deficiency.” He was careful not to say dogmatically that this was solely a deficiency of iodine, only “That iodine is the most important single factor is suggested…” (28).

In 1909 Marine was called in to advise on a problem in a trout hatchery that had been described as “thyroid carcinoma.” He was able to show that the fish were suffering from goiter and that it could be prevented either by adding iodine to the water in which they were living or by changing their food from chopped up pigs’ hearts and livers to fresh sea fish. He concluded that “there is not the slightest evidence that it [the disease] is contagious or infectious,” but that their original food “lacked something normally needed by the developing fish…” The beneficial effects of feeding fish may be due to the iodothyroglobulin that it contains… but the conclusion that goitre is due to a deficiency of iodine is not justified… much careful work is still to be done” (30).

Goitrogens

Marine’s caution as to goiter perhaps not always being induced by iodine deficiency was justified some 10 years later when workers at Johns Hopkins saw enlarged thyroids in rabbits that they were using for a study related to syphilis (31). Marine, by then one of the school’s eminent alumni, was asked to examine the thyroids and he confirmed that it was goiter that had been produced, that it had been induced by the cabbage that had been their sole food; and also that it could be prevented by a higher intake of iodine (32). This finding stimulated further work in many parts of the world, but is not the main concern of the present paper.

Treatment of human goiter

We now return to Marine’s main interest. After demonstrating in his clinic that sodium iodide could be used to relieve children suffering from simple goiter and realizing that goiter was a serious problem in the Great Lakes Basin, he set out to organize a large “public health” trial (or demonstration) in Cleveland’s school district. However, the chairman of the school board, himself a physician, vetoed it on the old ground that iodine was poisonous. In 1916 with the help of O. P. Kimball, who had attended his lectures on the subject, he was able to obtain the consent of the board in Akron, Ohio (33).

They planned to use only schoolgirls in the trial because goiter was at least twice as common among girls as boys and to use pupils in the 5th grade and above whose parents had given permission for them to be included in the trial. Those for whom permission had not been obtained would serve as controls. The dosage chosen was 200 mg sodium iodide (in aqueous solution) per school day for 10 d, equivalent to a total of 1700 mg iodine, for pupils in the 5th to 8th grades and double this amount for the older girls. The dosing would be repeated every 6 mo for the next 2 1/2 y. The authors appreciated that these doses “offered a great excess over the amounts needed to saturate even the largest thyroids, and probably much smaller amounts would suffice,” but they did not expect them to be toxic (34). Interestingly, the dosage levels were similar to those recommended by Coindet 100 years earlier (2).

In their final report the authors summarized the findings obtained from over 2000 girls who had received iodide (some of them entering after the project had started) and a further 2000 who had received none. They particularly noted that there had been no indication of “iodine poisoning.” Some of their data are summarized in Table 1.
TABLE 1

Proportions of school girls in Marine and Kimball's trial in Akron whose thyroids changed in size according to whether they received iodine during the period of observation (1)

<table>
<thead>
<tr>
<th>Size of the thyroid</th>
<th>Iodine group</th>
<th>Untreated group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Of those initially normal, n</td>
<td>(908)</td>
<td>(1257)</td>
</tr>
<tr>
<td>Unchanged, %</td>
<td>99.8</td>
<td>72.4</td>
</tr>
<tr>
<td>Increased, %</td>
<td>0.2</td>
<td>27.6</td>
</tr>
<tr>
<td>Of those initially enlarged, n</td>
<td>(1282)</td>
<td>(1048)</td>
</tr>
<tr>
<td>Unchanged, %</td>
<td>39.5</td>
<td>72.0</td>
</tr>
<tr>
<td>Increased, %</td>
<td>0.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Decreased, %</td>
<td>60.3</td>
<td>13.8</td>
</tr>
</tbody>
</table>

The authors drew particular attention to the value of the treatment in preventing the appearance of goiter. Of over 1200 controls who were judged "normal" at entry, >25% showed an enlargement of the thyroid at their final examination. But of 900 normals at entry who then received iodide, only 2 (i.e., 0.2%) showed enlargement, and of these I had recurrent tonsillitis and the other neglected congenital syphilis (1).

For girls who began with enlarged thyroids the effects of treatment were equally dramatic. There were over 1000 in each group; 14% of the untreated girls and only 3 (i.e., 0.2%) of the treated ones showed a worsened condition. The corresponding numbers showing improvement were 14 and 56%, respectively, i.e., more than 3 times as many among those treated (1).

The modern reader will appreciate, of course, that the controls were not chosen by randomization. However, we can understand the authors concluding (given that the term "man" at that period carried no gender implication): "The disease is as easily prevented in man as in fish or in domestic animals" (1).

The Harvey lecture

Marine was invited to give one of the series of Harvey lectures in 1924 (35). This was, of course, an honor and recognition that he was now an accepted authority in his field. The work in Akron, once the fear of iodine poisoning had been lost, had quickly been followed by at least 7 similarly successful studies with schoolchildren in goitrous regions of Switzerland and Italy, to which he could refer (35).

Marine began by placing thyroid diseases into 2 groups. Under "thyroid insufficiencies" or "hypothyroidism" he placed either normal or sick thyroids. One could equally well remove everyone's appendix" (40).

Itself a physician reported that, since iodized salt had become available, he was seeing a considerable increase in cases of hyperthyroidism among adults who had used it, starting with weight loss or marked weakness and progressing to nervous and cardiac signs, but often without either thyroid enlargement or exophthalmos (41).

Kimball responded that the general and continued use of iodized salt had not induced a rise in the incidence of hyperthyroidism, and he used the statistics for goiter surgery at Henry Ford Hospital in Detroit, Michigan, to justify this (42). Strangely, these values (reproduced in Fig. 2) seem to show the opposite, i.e., a considerable increase in operations shortly after iodized salt was introduced in 1924 and for the next year or 2. This is confirmed by a surgeon at the hospital who also reported that annual deaths in Detroit from goiter had increased from about 20 before iodized salt was introduced to a peak of 122 in 1926 (43). However, both operations and deaths had returned to the preiodination rates by 1930, and the incidence of goiter among schoolchildren in Detroit, Michigan, to justify this (42). Strangely, these values (reproduced in Fig. 2) seem to show the opposite, i.e., a considerable increase in operations shortly after iodized salt was introduced in 1924 and for the next year or 2. This is confirmed by a surgeon at the hospital who also reported that annual deaths in Detroit from goiter had increased from about 20 before iodized salt was introduced to a peak of 122 in 1926 (43). However, both operations and deaths had returned to the preiodination rates by 1930, and the incidence of goiter among schoolchildren was by then only about 1/20 of its earlier rate (44,45).

Since that time there have been studies of the effects of introducing some form of iodine supplement in many communities. One of the best documented was in Tasmania where sodium iodate was introduced as a partial replacement for the bromide that was then being added to flour to improve the texture of baked loaves. The introduction was sufficient to increase average iodine intake by some 0.2 mg/d. The number of cases of toxicosis seen at Tasmania's Launceston General Hospital in 1966, when iodate use began in May, and in the surrounding years is given (Fig. 2) (46).

It seems clear that in both Detroit, where iodination of salt began in 1924, and Tasmania there was a considerable increase in the number of cases of thyrotoxicosis when supple-

Possible dangers of iodine supplements

However, concern was expressed in some quarters as to the possible overstimulation of sufferers from marginal exophthalmic goiter. A Swiss goiter surgeon wrote in 1922; "From reading home magazines one could come to believe that the golden goiter-free age had begun and that all the goiters of the world would melt away under the triumphant banner of iodine, like butter in the Sun. One support for the iodine mischief has been the studies of the American physicians in Ohio who claim to have prevented goiter in schoolchildren, but the evidence is as little compelling as similar trials in Switzerland. It has to be proved that they remain without goiter all their lives: we need observation of at least 30 y. We are not opponents of iodine treatment of goiter if correctly carried out. However, we are enemies of today's uncontrolled spread of iodine treatment. It seems like a dangerous experiment to administer this metallic poison to all and sundry with either normal or sick thyroids. One could equally well remove everyone's appendix" (40).

It was certainly true that the trials so far had only tested the effect of iodine supplements on children. And in Cleveland itself a physician reported that, since iodized salt had become available, he was seeing a considerable increase in cases of hyperthyroidism among adults who had used it, starting with weight loss or marked weakness and progressing to nervous and cardiac signs, but often without either thyroid enlargement or exophthalmos (41).

Yoshida, who was attending a medical meeting in Cleveland, could present Marine with evidence that iodine had been used to treat a wide variety of other conditions which might also be considered as manifestations of underfunction of the thyroid gland. He reported that annual deaths in Detroit from goiter had increased from about 20 before iodized salt was introduced to a peak of 122 in 1926 (43). However, both operations and deaths had returned to the preiodination rates by 1930, and the incidence of goiter among schoolchildren was by then only about 1/20 of its earlier rate (44,45).

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The publication of the Akron results stimulated renewed interest in Boussingault’s idea from the 1830s that crude salt naturally rich in iodide or purified table salt deliberately fortified with iodide would be a convenient way for the public to increase their iodine intake in areas where it was otherwise inadequate and so prevent the appearance of endemic goiter.

In the United States 100 mg/kg potassium iodide was added to table salt from 1924 on, on the basis that people consume an average of 6.5 g/d and that this would provide 0.5 mg iodine, in moderate excess of the assumed requirements ranging from 0.15 to 0.3 mg/d (36). Some other countries have adopted lower levels, and in Switzerland, for example, a level of iodide that contributed only 15 mg iodine/kg of salt has proved adequate to eliminate the previously serious problem of cretinism as well as goiter (37). The use of iodized salt across the globe has continued to expand with the active encouragement of the World Health Organization (38). However, in some less developed areas it has proved more practical, and equally effective, to use a “once-a-year” dose of an iodized oil from which the covalently bound iodine is slowly released (39).
mentation was first introduced, but this then died away after about 2 years. In the Tasmanian hospital it was also recorded that the increase was confined almost entirely to patients over the age of 50 years (46).

In more recent years, the same phenomenon of a short-term increase in cases of thyrotoxicosis following the introduction of iodine supplements into an area where there had previously been a long-term shortage of iodine and consequential endemic goiter has been seen repeatedly, whether in Europe (47), South America (48) or Central Africa (49).

It now seems agreed that the problem occurs typically in people whose goiter, over long years of relative iodine deficiency, has become nodular and that this tissue is “out of control” so that as more iodine becomes available to it, the output of hormone(s) climbs to toxic levels.

Current teaching is that, because this is a short-term problem associated with correction of a community's supply of iodine, it should not deter the adoption of a long-term program to eliminate cretinism and endemic goiter although it requires recognition and care of those who are adversely affected in the first years, as a result of earlier deficiency (50,51).

**David Marine's contribution**

It is not easy to summarize Marine's contribution. The first state to set up a well-accepted iodized salt program was Michigan, and the driving force behind this was David Cowie, Professor of Pediatrics at the University of Michigan (36). Marine's former assistant, O. P. Kimball, led the team measuring the incidence of goiter among Detroit school children at different dates; he also worked at attempts to introduce the same system in Ohio but with less collaboration from the authorities in the early years, and later went on to work with the World Health Organization to encourage anti-goiter programs in the Third World (38,50).

It was also Kimball himself who wrote many years later: “Goiter prevention as practiced today is based entirely on the teachings of David Marine” (52). Now that the value of iodine supplements is universally accepted, it is difficult for us to appreciate the weight of authority that had been attached to Kocher's dictum that “iodine is dangerous,” and it was only David Marine's reputation as a moderate and careful scholar that enabled him to present opposing evidence that carried sufficient weight for it to be put to the test.

Nestor is a figure from Greek mythology symbolizing a wise and experienced counselor, and Marine has been called “The Nestor of thyroidology”; “he was one of that noble group who carried the light and handed it to others” (26).

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