THE MIDWESTERN AMERICAN "EPIDEMIC" OF IODINE-INDUCED HYPERTHYROIDISM IN THE 1920s*

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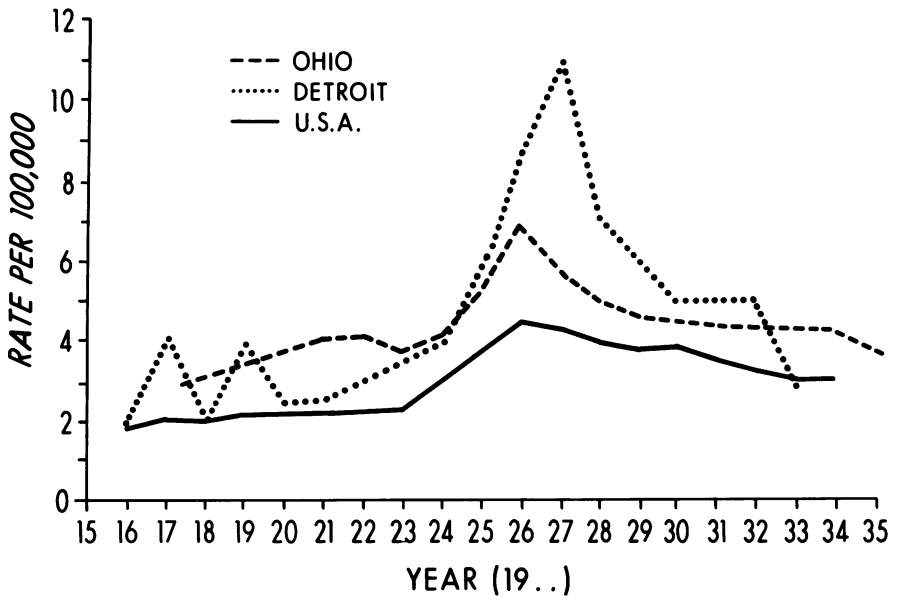
IN 1926, 1927, and 1928 there was a sharp rise in the incidence of hyperthyroidism in the United States, notably in the midwestern "goiter belt." The first warning came from surgical centers frequented by thyrotoxic patients and the uniformity predicted a crisis, not merely a scare. At Henry Ford Hospital in Detroit McClure[1] saw a marked increase, especially in toxic nodular glands; he later[2] found that this had been true for six other local institutions. Similar observations were made[3] at the University of Michigan in Ann Arbor and at the Jackson Clinic,[4] a major Wisconsin center. In Cleveland Dr. George Crile, Jr., recalls[5] that 2,700 thyroidectomies were done at his father's famous clinic in 1927, compared with 400 to 500 in the years before and after this period. At the Mayo Clinic, Plummer,[6] whose opinions warrant further comment, observed that not only were there slightly more patients with adenomatous goiters but also that they were somewhat older, with a higher proportion of males.

Mortality data confirmed these impressions. Statistics for the city of Detroit,[7] for the state of Ohio,[8] and for the states of the entire United States for which statistics were reported[9] were consistent: from 1926 to 1929 more people than previously died of hyperthyroidism. It is improbable that this was due solely to improved diagnosis or altered terminology. Nor was the trend limited to the United States. In the Canadian province of Ontario there was a similar rise in the death rate from exophthalmic goiter.[10] From 1915 to 1923 this had averaged less than 3.1 deaths per 100,000 inhabitants. It doubled in 1926 and fell to 4.3 by 1930.

*Supported in part by Grant No. 6429 from the Penrose Fund of the American Philosophical Society, Philadelphia.



Mortality from exophthalmic goiter, 1915 to 1935.

This apparent "epidemic" appeared a few years after a great increase in the use of iodine—attributable in large part to David Marine and his associates. This work began in animals, in the field, and in the laboratory and culminated in a bold and successful experiment on man.

In June 1905 Marine graduated from Johns Hopkins Medical School. (In the same class at Baltimore were George H. Whipple and F. Peyton Rous, who were subsequently to be awarded Nobel prizes for medicine and physiology. To students of goiter Marine's claim to fame is equally valid.) Having been refused a surgical internship by Halsted,[11] he chose a residency in pathology at Lakeside Hospital in Cleveland. Two years later he joined the H. K. Cushing Laboratory of Experimental Pathology at Case Western Reserve Medical School, where he taught and worked until 1920; his co-worker was chiefly C. H. Lenhart, who eventually transferred his interest to surgery and later became chairman of that department. What led them to focus on the thyroid remains conjectural, but Marine mentioned in 1907[12] that "90% of the dogs brought to the laboratory (presumably for experimental use) were strumatous." He also was intrigued by the frequency of goiter in Michigan sheep and in carcasses in the Chicago stockyards. Studies were soon begun on goiter and iodine deficiency, not only in mammals but in several species

of fish. This phase developed from an invitation to investigate, in a Pennsylvania brook-trout stream, an outbreak of what had been mistaken for cancer of the thyroid[13] but proved to be simple goiter. Study in the laboratory led to formulation of what has since been called the "Marine cycle":[14] hypertrophy, hyperplasia, and exhaustion atrophy with deposition of colloid, all from a lack of iodine. This in turn established the proposition: deprivation of iodine in animals leads to goiter; adequate dietary iodine will avert or arrest it. The same should be true in man.

Perhaps more often than is recognized, a student is influenced by a lecture or a lecturer. One student who listened in 1916 while Marine was talking of ductless glands in general and in particular of what had been done with iodine in animals, was O. P. Kimball, then in his second year. He had had difficulty getting to medical school;[15] mild tuberculosis and family poverty had forced him to alternate periods of study with stretches of teaching mathematics in the public schools of Akron, Ohio, which eventually financed a B.S. degree at the University of Chicago and the medical course at Cleveland. "If all you say is true, something ought to be done about human endemic goiter,"[16] he said to his professor. "I know the school system and the political system [in Akron] from A to Z having taught there for eight years." Marine's previous attempts in Cleveland and some of its suburbs had failed, but the next week the professor and his student were meeting the Akron school board. Adroit maneuvering must have been necessary (plus invaluable help from H. V. Hotchkiss, the superintendent) to persuade this group and the local (Summit County) medical society that the proposal was sound. These efforts succeeded, and later in 1916 the test was organized. For 10 school sessions, twice yearly, 0.2 to 0.4 gm. of sodium iodide in solution were administered by the teacher or nurse to a large number of youngsters. It is probable that much of the iodine was excreted rapidly, but the total annual dose averaged 9 mg. daily for the younger students and 18 mg. for high school students, quantities which today we might think excessive but which had been chosen by the investigators in order to be certain of adequacy. The results were dramatic and unequivocal; no treated child developed struma, and many of those already affected had remissions, compared with the unaltered course of the controls (children whose parents had refused participation).[17] Fully aware of the danger of inducing hyperthyroidism, even at levels which

they felt were safe, the investigators could happily report two and four years later[18] that no child had so suffered.

From 1917 to 1925 the results of this study appeared in a dozen papers by Marine, by Kimball (now M.D.), or by the two together. The news was momentous. Along with plaudits, there naturally were expressions of disbelief and scare stories, but the word spread: goiter had been and could be prevented readily.

In those early 1920s public interest was further stirred by news of the studies of McClendon and his co-workers[19] on the relation of the presence of iodine in local water supplies to the rejection rate for goiter among draftees in World War I. The charts were convincing: low levels of iodine were predictive of more struma, confirming for the United States the findings of Chatin[20] in France and Boussingault[21] in Columbia and the data established for Switzerland by von Fellenberg.[22] The general interpretation was naturally that iodine was a necessity. "The public has adopted iodine,"[23] said Hartsock, somewhat sourly. Iodized salt appeared on grocery shelves, as did so-called "sea salt" (still available in 1975 in health-food stores), although analysis showed that of the medicated brands some had less than their stated content of iodine and others none at all.[24] A few cities—Rochester, N. Y., was a notable example[25]—dosed the public water supply with iodides. In other locations this was projected or begun but was blocked by citizens' groups heavily recruited from Christian Scientists. In Michigan in 1924, after confirmation of McClendon's findings by the state health authorities and the pediatric section of the state medical society,[26] the manufacturers of salt cooperated with the Wholesale Grocers' Association in a voluntary program of exhortation, example, and advertising, whereby in some localities 95% of the retail sales were soon of iodized salt (potassium iodide 1:10,000, yielding nearly 1 mg. of iodine daily). In several of the worst affected counties this was highly successful in reducing the number of childhood goiters,[27] even though a short-sighted federal policy in the depths of the depression of 1929 curtailed the project in the name of economy.

Another increase in the use of iodine followed Plummer's 1923 announcement[28] that, contrary to previous opinion, iodine in small doses induced temporary remission in hyperthyroidism; during this period surgical operation was easier and safer. While this effect had been described earlier by Cheadle,[29] by Trousseau[30] (who had missed its signi-

ficance), and by several observers[31] who reported its value before Plummer, almost all "sound" medicine followed the rule laid down by Kocher[32] or Müller:[33] "No iodine in hyperthyroidism." Plummer's prestige, backed by that of the Mayo Clinic, had a revolutionary effect and led both to the wide use and also the misuse of iodine as a definitive treatment, as well as to its trial in many unrelated disorders. Physicians had not previously shunned the drug; besides its established value in gummata and its probable worth in bronchopulmonary disease, it held a considerable reputation (*faute de mieux*) in many vascular disorders. After Marine, Kimball, McClendon, and Plummer it is improbable that the nonspecific use of iodine declined; it is more likely to have multiplied. "*Wenn man nicht weiss Wieso und, Warum Dann gibt man iodkalium.*"[34]

Not unexpectedly, as in Geneva a century earlier, there came a brisk increase in the over-the-counter sale of iodine, which at times was extravagantly advertised, often in doubtful mixtures. As late as 1955 some popular brands of vitamin-mineral capsules contained up to 0.5 mg. of iodine. For a time, in some areas of the midwest, avoidance of iodine might have been difficult. (It might be noted that in 1975 in at least some of these products the iodine content has been reduced to 0.1 mg.).

Returning to the epidemic of 1926-1929, was the proliferation of iodine in the early 1920s responsible? Physicians at first not only answered "yes" but picked iodized salt as the chief culprit. Jackson and Freeman[35] invoked Breuer's 1900 "iod-Basedow" warning[38] against even minute amounts in adenomatous goiters, although a decade later they reduced the charge to "injudicious use." In Boston, which was only slightly affected, Frank Lahey joined the chorus,[37] qualifying his disapproval to allow "small preventive doses." But by 1929 Coller and Potter at Ann Arbor[38] were ready to absolve salt. McClure, who had dealt with the great outbreak in Detroit, declared[39] that it had ended and that it had left a population less goitrous and containing no cases of salt-induced toxicity. At the Cleveland Clinic opinion was divided. Hartsock's early warning[40] was refuted by Kimball,[41] now a staff member, who, naturally not unprejudiced, found in a larger series of patients that iodized salt as the sole precipitating factor in hyperthyroidism was rare (4.1%), whereas 55% of the patients denied any exposure to iodine whatsoever. A few years later, George Crile, Jr., writing in his father's well-known text,[42] dismissed iod-Basedow as "not a danger." Charles

Mayo[43] was at first severe. He feared "lurking adenomas," even in children with normal or colloid glands, and continued[44] to prefer individualizing their treatment. In contrast, Henry Plummer,[45] his opposite number at the clinic, while admitting that the great wave of 1927-1928 followed the popularization of iodized salt, was uncertain of its guilt. He pointed out that in Olmstead County, the area surrounding the clinic, besides a slight steady rise in thyrotoxicosis for many years, there had been noticeable increases following the influenza pandemics both of 1898 and 1918. While the Mayo Clinic drew patients from far and wide, Pummer's judgment on local disease can never be rejected lightly. His impressions approach morbidity statistics. For, while it is possible that some Baltimoreans prefer Cape Cod oysters to their native Chesapeake varieties or that there are Dijonnais who send for claret in preference to local burgundies, it is implausible that any goitrous person within driving distance of Rochester, Minn., would fail to go there for an opinion.

The Mayo Clinic experienced the predictable rise in toxic goiters, beginning in 1926, with the familiar distribution in age and sex ratio, but by 1931 iodized salt was here to stay, the epidemic was over, and Plummer dismissed the risks of prophylaxis as negligible. In many of the so-called "salt-induced cases" he thought that hyperthyroidism had been present for years. In 1970[46] the clinic reported that the incidence of hyperthyroidism had not changed materially in 40 years. In summary, our medical men were quick to blame iodine for their troubles, and in particular its spread via iodized salt, but as the epidemic waned many of them had the grace to retract.

What of their colleagues overseas? Europe's initial judgment of the results in Akron was cautious but not overcritical. The apparent "accidents" which had occurred ever since iodine first was used for goiter had been interpreted variously.[47] Some investigators believed that minute amounts were highly if not most dangerous—Kocher, for example, had cited[48] an instance of iod-Basedow which followed painting of the gums for dental surgery—whereas others thought that untoward results only followed excessive dosage. Still another group, probably those dealing with nonstrumatous disease such as syphilis, found that, at worst, large quantities produced rashes and indigestion. But in Alpine regions—despite cretinism, deaf-mutism, and huge masses in the neck—goiter was easier to accept than iod-Basedow, which was a threat to survival. In

the United States, although cretinism was infrequent, large goiters apparently were less acceptable than abroad. Here iodine-induced hyperthyroidism seems to have been less common, less terrifying, and certainly less publicized. More than a little iodine seems to have been used for goiter by otherwise conservative American physicians.[49-51]

In the early 1920s several Swiss investigators announced that they had repeated or even anticipated the Akron experiment.[52, 53] By 1922 a few highly goitrous Swiss cantons had approved the sale of lightly iodized salt, providing about 50 μgm. of iodine daily.[54] Even de Quervain, who now spoke with the authority of the surgical chair at the University of Bern, formerly held by Kocher, approved prophylaxis with a safety ceiling of 80 mg. of iodine yearly.[55] However, there were cries of warning, as from Bircher,[56] who even denied the validity of the Akron experiment. Then, in 1929, when Europe imagined that toxic nodular goiters were crowding the midwestern surgical clinics, the Continental attitude stiffened from tolerance to *Schadenfreude*.[57] European experience and judgment, after all, should have been respected; if we dared, as in Michigan, to allow 20 times the needed dose, we were due to pay the penalty. Rumblings against their own *vollsalz* (iodized salt) were heard from far-off Berlin.[58] At a distance of a half century, the anti-iodine cause had some of the features—unimplemented—of our ill-fated prohibition crusade.

However, the epidemic receded. It was acknowledged to have been a wave, possibly of great size but not a thyrotoxic deluge, and attention, at least in Switzerland, refocussed on local problems. By 1938 Fluck,[59] Eggenberger,[60] and de Quervain[61] agreed that while iod-Basedow existed, it was less likely to be due to the expanding prophylactic salt program than to pre-existing nodular goiter in persons given large doses of iodine. By the 1950s Swiss hyperthyroidism was thought to be declining.[62] Even the existence of iod-Basedow was occasionally attacked:[63] these might be "naturally" occurring cases, although the excellent review of Mach[64] sums up evidence that heavy diagnostic or therapeutic administration remains risky.

Through many decades there had been a solid European minority which was unconvinced of iodine toxicity. Here stood the impressive figure of Julius Wagner-Jauregg, professor of psychiatry at the University of Vienna. His abhorrence of cretinism had led him as early as 1898[65] to urge resumption of prophylactic iodine, which had been suc-

cessful in Austria and Savoy 50 years earlier but largely abandoned as dangerous. When *vollsalz* was placed on sale in Austria after the Kaiser's war and was attacked as a cause of hyperthyroidism, he defended its value and rebuked many of its accusers. He went further. Dr. Jacob Adler[66] recalls that in the early 1930s, when Wagner-Jauregg's authority was further enhanced by the award of a Nobel prize for the recognition and promotion of the value of malarial paroxysms in general panesis, he recommended that medical students take one drop of tincture of iodine at breakfast to ward off the common cold.

If iodine is to be absolved of blame for the epidemic or let off with a Scotch verdict, what are the alternatives? Several other outbreaks of hyperthyroidism have remained unexplained. In Breslau in 1931 the cases were of classical exophthalmic goiter, with an unusually high proportion of affected males.[67] Wagner was forced to fall back for cause to "the strain of chronic unemployment." The large Danish outbreak of 1942-1944, reported by Meulengracht[68] and in greater detail by Ivesen,[69] could not be associated with iodine or any other discernible factor. Almost simultaneously, Grelland observed[70] a considerable rise in case frequency in Oslo; this also subsided in two years. Among his subjects toxic adenomata were less frequent. His final explanation was "war strain." Neighboring Sweden, which had remained neutral, was unaffected.

The shapes of these outbreaks and the populations most often attacked are strikingly similar to our own; thus, we might consider Plummer's postinfection hypothesis and other hypotheses which did not blame iodine. Prolonged latencies after infection are often irregular and are not novel. For example, recall the variability of the sequence of lethargic encephalitis to the 1918 influenza pandemic. Invasion and production of disease by slow viruses apparently do not depend on cannabalism alone. As for pathological findings, neither of the better-known American reports on influenza[71, 72] even mentions the thyroid gland; both focus on the bronchopulmonary tree. The autopsies in these series, moreover, were done on young individuals under war conditions. The recent burst of attention[72] to *Yersinnia enterocolitica*, especially in Scandinavian countries, as a possible precursor of hyperthyroidism needs further study.

From other angles, current interest in hormonal and immunological abnormalities has added vastly to our knowledge of the mechanisms but

not the etiology of thyroid disease. Our psychosomatically oriented colleagues have shown that not infrequently personality and situational profiles may be uncovered[74] but so far they have failed to be convincing. There may be multiple causes of hyperthyroidism; it took millenia to differentiate the fevers and to substitute plasmodia for miasma as the cause of malaria.

In summary, there is no doubt that in 1926, 1927, and 1928 the morbidity and mortality of hyperthyroidism increased sharply in the American midwest and probably in other sections of the continent. The patients affected were usually more than 30 years of age, with an unusually high proportion of males, and many had long-standing nodular goiters. The wave appeared about a year after a great increase in the use of iodine, contributed by individuals, physicians, and health authorities. By 1929 sickness and deaths from hyperthyroidism were no more frequent than in 1920, although iodinization was maintained. The incidence of simple goiter, both in children and adults, had dropped significantly. This was certainly coincident with and probably attributable to iodized-salt prophylaxis, although questions remain—ably summarized by Greenwald[75]—which throw doubt on this interpretation. The benefits associated with this treatment must be weighed against a definite loss of lives, possibly induced by iodine, in a disease whose origin remains ill defined.

Acknowledgments

Many people have cooperated by furnishing material for this study. For invaluable help over several years I record special thanks to Mrs. Norma Somers, librarian of the Rochester Academy of Medicine, to Miss Sandra L. Markus and Mrs. Lucretia W. McClure of the Edward G. Miner Library of the University of Rochester Medical School and Mr. Philip J. Weimerskirch, chief of its History of Medicine Section, and to Miss Marian M. Allen, formerly chief of reference at the university's Rush Rhees Library. I am indebted to Dr. Robert J. Biggar of the U.S. Public Health Service, formerly attached to the Monroe County Health Department, for the graph of mortality from hyperthyroidism.

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