
The History of Iodine in Medicine Part II: The Search for and the Discovery of Thyroid Hormones

by Guy E. Abraham, MD

In 1874, Sir William W. Gull, MD, published his observations in five women suffering from hypothyroidism, which he called myxedema associated with a “cretinoid state.”¹ Hypothyroidism was for a short time afterward called Gull’s disease. This condition of unknown etiology was considered incurable then. Excerpts from the detailed description of one patient with myxedema and cretinoid state by Gull follow.

“Miss B, after the cessation of the catamenial period, became insensibly more and more languid, with general increase of bulk. This change went from year to year, her face altering from oval to round, much like the full moon at rising ... Had one not proof that such a patient had been previously fine-featured, well-formed, and active, it would be natural to suppose that it was an original defect such as is common in mild cretinism ... The mind, which had previously been active and inquisitive, assumed a gentle, placid indifference, corresponding to the muscular languor, but the intellect was unimpaired ... I am not able to give my explanation of the cause which leads to the state I have described. It is unassociated with any visceral disease, and having begun appears to continue uninfluenced by remedies.”

Not long after Gull’s publication, similar signs were reported in patients following thyroidectomy. It was then proposed that myxedema was due to loss of function of the thyroid gland. Some 16 years after Gull’s report, a successful attempt was made to implant a sheep thyroid gland under the skin of the inframammary area of a woman suffering from myxedema. The operation was followed by immediate improvement. This case was reported by Betancourt from Lisbon, Portugal in the journal *La Semaine Medicale* on August 18, 1890.²

“The operation was followed by an immediate improvement. Movements became more easy and the

speech more natural. The number of red corpuscles in the blood steadily increased till it nearly reached the normal standard in a month. The temperature was raised. The subcutaneous swelling diminished, and the patient began to perspire once more. The period of menstruation, which before had lasted for two and sometimes three weeks, was reduced to four days.”

Since the improvement was observed immediately after implantation of the sheep thyroid gland, it became obvious that the beneficial clinical effect observed was due to a biological active compound released by the implanted sheep thyroid gland into the peripheral circulation of the patient. One year later in 1891, based on a review of the literature, including successful implant of the thyroid gland in a hypothyroid patient in Lisbon, British physician George R. Murray² postulated that extracts of thyroid glands should be effective in hypothyroidism. He presented in July 1891, at the Annual Meeting of the British Medical Association his observation of a female patient with hypothyroidism (myxedema) treated successfully with hypodermic injections of extract from the thyroid glands of sheep. “It is now three months since the treatment was commenced; it has not, however, been carried out continuously all the time, and at first a weaker preparation than that described was used. Extracts of five lobes of sheep’s thyroid have been injected, that is altogether equal to the extract of two and a half thyroid glands. The patient has steadily improved since the treatment commenced, and, though three weeks were allowed to elapse between the injections of the last two extracts, she did not lose any of the ground she had previously gained.”²

One year after Murray’s publication, physicians MacKenzie³ and Fox⁴ reported respectively that oral administration of fresh sheep thyroid glands³ and thyroid extract⁴ were effective in reversing the signs and symptoms of hypothyroidism in a female patient. MacKenzie’s and Fox’s reports were published back to back in the October 1892 issue of the *British Medical Journal*.^{3,4} Following Murray’s, MacKenzie’s, and Fox’s publications, oral preparations of thyroid extracts became available and were widely used to treat hypothyroidism. Their publications reported the effect of thyroid gland administration on a single case of hypothyroidism each. The Lisbon experiment with implantation of a sheep thyroid gland under the breast was also on a single patient. All of the patients were women.

Prior to 1895, thyroid extracts were not standardized based on iodine content because the presence of iodine
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in the active principle of the thyroid gland was not yet reported. Following Baumans' publication in 1895⁵ reporting high concentrations of iodine tightly bound to proteins in extracts of the thyroid gland, thyroid extracts were standardized to contain 0.2% iodine in order to maintain equal potency of different preparations.

The popularity of thyroid extracts was not adversely affected by the introduction of thyroid hormones in the 1930s. Thyroid extracts continued to be prescribed by the majority of US physicians who claimed better response than with the use of the pure preparation of thyroxine. This trend was to change following a hoax perpetrated in 1963 with the goal of discouraging the use of thyroid extracts and therefore, making thyroxine the only eligible thyroid preparation for hypothyroidism. To quote Derry:⁶ "By 1976 about half (52%) of the prescriptions written for thyroid hormone in the United States were for desiccated thyroid or other natural products. The best pharmacological authorities confirmed desiccated thyroid remains a remarkably clinically predictable and effective preparation which is well absorbed. The medical letter in 1973 maintained that desiccated thyroid had never been unreliable. The slight variations in the T₃ levels mentioned by some are of little clinical significance. A large shipment to distributors in Europe and the United States in 1963 of what was supposed to be desiccated thyroid turned out to be tablets that contained iodine but no thyroid hormone. This was a hoax. Goodman and Gilman stated, 'This episode gave thyroid a bad name because several publications about the unreliability of thyroid appeared before the hoax was uncovered.' (1970) This hoax is the only record of desiccated thyroid being unreliable."

Timing and synchronization of iodophobic misinformation about iodine were evident in this situation. In 1969, Dr. Wolff from the National Institute of Health published his iodophobic misinformation titled, "Iodide goiter and the pharmacologic effects of excess iodide."⁶ A year later, Goodman and Gillman (1970) publicized the fictitious so-called "several publications" confirming the unreliability of thyroid extracts. By the 1970s, thyroxine was the only acceptable treatment modality for hypothyroidism because, of course, the iodophobic domino effect of the 1948 Wolff-Chaikoff publication prevented physicians from supplementing their patients with iodine.^{7,8} Keep in mind that the administration of thyroxine does not lift the brain fog of iodine deprivation.

In the late 1800s, the data available suggested that hypothyroidism was due to a deficiency of a substance secreted by the thyroid gland, and this biologically active substance was orally bioavailable. As previously men-

tioned, the iodine involvement in this thyroidal compound was not suspected until 1895, when Bauman reported large concentrations of protein-bound iodine in the thyroid gland.⁵ Based on his research, Bauman concluded that the active substance in the thyroid gland contains iodine. Afterward, the general medical consensus was that the active principle of the thyroid gland contains iodine, and as a consequence, the thyroid preparations were standardized to contain 0.2% iodine in order to obtain the same concentrations of the active thyroid principle, and therefore the same potency between different batches.

Bauman attempted unsuccessfully to hydrolyze thyroid proteins in order to isolate the active compound. It remained for Kendall,⁹ from the Mayo Clinic, 19 years later to successfully hydrolyze thyroidal proteins with sodium hydroxide in alcohol. The hydrolysate could be separated into two groups — the first group contained compounds that were insoluble in acid, and the second group substances were soluble in acid. Further hydrolysis of the first group yielded a compound containing iodine that was further purified in a crystalline form containing 65% iodine. Clinical trials with these crystals in hypothyroid patients proved that it was the active principle. Kendall wrote: "In brief, the compound containing iodine, the presence of which, as a normal constituent of the thyroid, as foretold by Baumann 19 years ago, has been isolated in pure crystalline form, and further, it has been shown that this compound is the substance in the thyroid which is responsible for the physiologic activity of the gland."

Kendall called it "thyroxin", which became thyroxine in the 1930s at the same time "iodin" became iodine. Unfortunately, Kendall assigned the wrong structure: an indol with three atoms of iodine. "This work shows that it is the iodized indol that produces the physiologic activity. The actual amount of the crystalline iodine compound necessary to produce marked effect is exceedingly small."

In spite of the fact that Kendall assigned the wrong structure for L-thyroxine, his crystals possessed the correct structure and full biological activity. In the 1920s, Kendall's thyroxin became available to clinicians, but it was extremely expensive because of the labor involved. As an example, Kendall stated that three tons of thyroid glands yielded only 33 g of thyroxin, equivalent to approximately 100,000 daily doses.

In 1926, Harrington¹⁰ from the University Medical School in London, England confirmed Kendall's find-

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ings and assigned the correct structure: thyronine with four atoms of iodine. Harrington did not have a high opinion of Kendall's chemical knowledge and his impossible formula: "Contained in this formula are several inherent chemical improbabilities, if not impossibilities, but it is perhaps not necessary to enter into the questions further here, since a careful study of Kendall's paper reveals that very slender nature of the evidence from which the formula is deduced."¹⁰

Thyroxine exists in two isomers: L-thyroxine, the naturally occurring form, and D-thyroxine. A racemic mixture is a preparation containing 50% L-thyroxine and 50% D-thyroxine. Harrington proceeded to synthesize thyroxine from iodinated thyrosine. Because of racemization, his preparation contains a mixture of L- and D-thyroxine. Since D-thyroxine possessed one-tenth the biological activity of the naturally occurring isomer, L-thyroxine,¹¹ Harrington's D,L-thyroxine possessed half the potency of Kendall's L-thyroxine crystals.

In the late 1920s and early 1930s, both preparations became available to clinicians, Kendall's L-thyroxine crystallized from thyroid glands obtained at slaughter houses; and Harrington synthetic racemic mixture. Both preparations were called "thyroxin". No distinction was

made between the two preparations. This is a quote from a textbook of thyroidology published in 1932, making no distinction between the two forms of available thyroxine: "The treatment of hypothyroidism of any type consists merely in the substitution of thyroid extract for the deficient secretion. Any form of prepared gland or the active principle, thyroxin, may be used."¹²

The basal metabolic rate (BMR), developed by German physician Magnus-Levi in 1895,¹³ was the gold standard for the first half of the 20th century for assessing clinical response of hypothyroid patients to thyroid therapy. Regarding the dose of "thyroxin" needed to raise the BMR and alleviate the signs and symptoms of hypothyroidism, physicians using the racemic mixture reported an effective dosage twice as high as the dosages reported by those physicians using the L-thyroxine.

Another factor involved in the relatively high requirements of racemic and pure thyroxine — thyroidologists in the 1930s were unaware that the free-acid form of the thyroid hormone was not efficiently absorbed by the gastrointestinal tract. Because of low bioavailability, the free-acid form of thyroxine became clinically effective only with relatively high dosage, requiring up to 1

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Table 1

The Chronological Sequence of Events during the Search for and the Discovery of Iodine-Containing Thyroid Hormones

1890	Hypothyroidism successfully treated with implant of sheep thyroid gland. ²
1891-1892	Hypothyroidism successfully treated with enteral and parenteral administration of thyroid glands and thyroid extracts. ²⁻⁴
1895	Bauman measured large amounts of thyroidal iodine in an organic form firmly held as a constituent of thyroidal proteins. He postulated that the active principle was an iodine-containing substance. He attempted unsuccessfully to hydrolyze thyroidal proteins in order to isolate the active principle. ⁵
Late 1890s	Thyroid extracts standardized to contain 0.2% iodine in order to maintain equal potency between different preparations.
1915	Kendall succeeded in hydrolyzing thyroid proteins into simpler constituents. Further purification yielded a biologically active iodine-containing substance which was crystallized into a pure form. Kendall called this crystallized product thyroxin. Unfortunately, Kendall assigned the wrong structure to this compound. ⁹
1926	Harrington confirmed Kendall's findings. He assigned the correct structure: thyroxine with four atoms of iodine. ¹⁰
1927	Harrington synthesized thyroxine from iodinated thyrosine. The end product was a racemic mixture of D- and L-thyroxine. Since L-thyroxine is 10 times more potent than D-thyroxine, ¹¹ the racemic mixture possessed one-half the potency of L-thyroxine.
1949	Chalmer published a procedure for the synthesis of pure (non-racemic) L-thyroxine from iodinated L-thyrosine with a high yield of 26%. ¹⁴
1952	L-triiodothyronine (L-T ₃), an intermediate in the synthesis of T ₄ from diiodothyronine that is 3-4 times more potent than L-T ₄ (based on bioassays and basal metabolic rate), ¹⁵⁻¹⁸ is isolated. Synthesis of L-T ₃ is also achieved.

mg/day in hypothyroid patients to raise the BMR to the normal range. This resulted in several cases of iatrogenic hyperthyroidism with cardiovascular complications, when the same effective dosage required for the free-acid racemic mixture in hypothyroid patients was used for the more bioavailable and more bioactive disodium salt of L-thyroxine.

The problem of racemization of L-tyrosine during iodination and coupling was solved by Chalmers,¹⁴ *et al* in 1949. To prevent racemization, the amino group of tyrosine was protected by acetylation and the carboxyl group likewise by esterification. An overall yield of 26% L-thyroxine from L-tyrosine was obtained. Mass production of L-thyroxine (L-T₄) using Chalmers procedure increased markedly the availability and lowered drastically the cost of L-T₄.

In the 1940s, a second thyroid hormone was suspected in thyroglobulin. This was due to a discrepancy observed in the bioassay of thyroglobulin and thyroxine. The bioassay of thyroglobulin revealed a greater biological activity than could be accounted for, based on the amount of thyroxine present in thyroglobulin. 1952 was a very good year for L-triiodothyronine (T₃). Four publications appeared during that year from two groups of investigators, a British/Canadian team^{15,16} and a French team.^{17,18} The following achievements were accomplished in 1952:

- Isolation of L-T₃ from thyroglobulin
- Identification of L-T₃ in plasma
- Synthesis of L-T₃

L-T₃ is a precursor of L-T₄ from diiodothyronine, and its biopotency revealed that it was 3-4 times more potent than L-T₄.

The chronological sequence of events during the search for and the discovery of iodine-containing thyroid hormones is summarized in Table 1.

About the Author

Guy E. Abraham, MD, is a former Professor of Obstetrics, Gynecology, and Endocrinology at the UCLA School of Medicine. Some 35 years ago, he pioneered the development of assays to measure minute quantities of steroid hormones in biological fluids. He has been honored as follows: General Diagnostic Award from the Canadian Association of Clinical Chemists, 1974; the Medaille d'Honneur from the University of Liege, Belgium, 1976; the Senior Investigator Award of Pharmacology, Sweden, 1980. The applications of Dr. Abra-

ham's techniques to a variety of female disorders have brought a notable improvement to the understanding and management of these disorders.

Twenty-five years ago, Dr. Abraham developed nutritional programs for women with premenstrual tension syndrome and post-menopausal osteoporosis. They are now the most commonly used dietary programs by American obstetricians and gynecologists. Dr. Abraham's current research interests include the development of assays for the measurement of iodide and the other halides in biological fluids and their applications to the implementation of orthiodosupplementation in medical practice.

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