The Heritage of Dr. Hakaru Hashimoto (1881–1934)

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Goiter of one type or another has been a problem for centuries. Often associated with iodine deficiency in mountainous areas, such as Switzerland, some goiters were quite disfiguring. Eventually, by the end of the 19th century, surgeons perfected the operative cure of this disorder, later followed by the possibility of its prevention by supplying sufficient iodine.

However, some goiters seem not to be related to iodine deficiency. One of these is the disease extensively described by Hakaru Hashimoto in 1912. Hashimoto, then finishing his surgical training at Fukuoka, wrote an article that established his name as the eponym for goitrous lymphocytic thyroiditis, an entity that many years later was realized to be an autoimmune disease of the thyroid gland. Hashimoto’s article, entitled, “Notes on lymphomatous in the thyroid gland (struma lymphomatosa)” was essentially a monograph [1]; he wrote in German in a German journal because that was the scientific language of the time and he probably thought that writing in German would make his work more available around the world. Curiously, as his career led not to academia but to the practice of medicine in his hometown, this article was his only publication on the thyroid gland.

To define Hashimoto’s heritage, this paper first describes what Hashimoto found and then shows the effect of Hashimoto’s description on others’ subsequent thinking about thyroid disease over the following ninety years.

Hashimoto’s description

What did Hashimoto actually find? He studied the thyroid histology and clinical findings of four women, all over age 40 years, who had been seen in the clinic where he had studied over the course of seven years. These patients were seen by him and his chief from 1905 to 1909; all had goiter and all were treated by partial thyroidectomy. The goiters were unusual: instead of the colloid goiter so commonly found, these goiters had a preponderance of lymphoid cells: “lymphomatous goiter ... is characterized histologically by a massive growth of lymphatic elements, primarily lymphoid follicles, and by ... parenchymal [and] interstitial changes.” Further, at least one of the four women, and perhaps two others, had hypothyroidism, one of whom he treated with a thyroid preparation. He recognized the similarity between this histology and that of Graves’ disease, but ruled out Graves’ disease clinically. He discussed the possibility of chronic infection—note that goiter was then regarded by many as an infectious disease—but found nothing to support that idea.

He carefully compared these patients to those with Riedel’s thyroiditis but found that there was no real resemblance, either clinically or histologically. He then went on to compare this disease to Mikulicz’ disease, a disorder of the salivary and lacrimal glands that histologically closely resembled the histology of the goiters in his patients. Both disorders had a lymphocytic infiltrate and lymphoid follicles. Hashimoto speculated that the same disease affected the thyroid gland in some patients and the salivary and lacrimal glands in others. Curiously, Mikulicz’ disease has since been “downgraded” to a syndrome or lumped together with Sjögren’s syndrome; although discussed in textbooks of medicine in the first half of the 20th century, it disappeared after 1980. The relationship speculated by Hashimoto remains uncertain to this day.

After an extensive review of the world’s literature, mainly in German, Hashimoto speculated that there was some factor that stimulated the lymphocytic expansion of the thyroid’s size (“we can assume that ... the lymphocytic elements are stimulated by a certain factor”) but explicitly stated that “at present we
cannot say anything definite about the cause.” He therefore named the disorder after its histologic characteristics—“lymphomatous goiter”—mainly because there was no known cause.

Hashimoto’s influence in the international community

What then happened? How was his contribution regarded by others? It is said that there was only limited recognition in his own country, Japan, because many could not read German. I will emphasize how his work was recognized in Europe and America.

In the first few years after publication, that is, in the 1910s, there was, as one might expect, some recognition in Germany. The year following his paper, 1913, Simmonds, a German pathologist, mentioned Hashimoto’s paper but was unsure whether it was really separate and distinct from other thyroid diseases [2]. In 1914, a German surgeon, Heineke, thought it a peculiar form of chronic thyroiditis [3]. However, major texts written late in the decade by McCarrison, a British physician working in India, and Crotti, an American surgeon trained by Theodor Kocher himself, did not mention Hashimoto at all even though they discussed inflammatory disorders of the thyroid gland; one must conclude that they were simply unaware of Hashimoto’s work.

Thus, by the end of the 1910s, Hashimoto’s work had not been ignored as some in the 1930s suggested. It had been noticed but not widely so. Most likely, this was because of the rarity of the disease compared to endemic goiter, because of the need to translate from the German, because no one quite knew what to do with it, and because the First World War completely changed the way Germany was regarded as a scientific mecca. Note also that Japan came into that War against the German side.

In the 1920s, we see more German references to Hashimoto’s paper but mainly in pathology rather than in clinical journals. For example, Reist in a comprehensive review of chronic thyroiditis in 1922 noted Hashimoto’s work but did not think there was anything special about it [4]. But recognition of Hashimoto was erratic: the very next year, 1923, Simmonds, who had at least mentioned Hashimoto 10 years before, now omitted all reference to Hashimoto in a review of chronic thyroiditis and fibrotic atrophy of the thyroid gland [5].

Major surgical texts—one should remember that goiter was then primarily a surgical disease—also continued to make no mention of Hashimoto. For example, neither George Crile nor Arthur Hertzler, both well-known American thyroid surgeons, noted Hashimoto’s description even though they discussed inflammation of the thyroid gland and did mention Riedel’s disease; the same was true in 1924 for Felix de Quervain, the Bernese surgeon who succeeded Theodor Kocher.

By the mid-1920s, a British pathologist, Williamson, described what was for him a new disease; he called it “lymphadenoid goiter.” He wrote it up as his M.D. thesis and noted that this disorder was associated with hypothyroidism. He seems to have missed completely Hashimoto’s description of the same disease. His review of the literature was not very complete, in contrast to Hashimoto’s own extensive literature review [6]. Even by the end of the 1920s, Williamson still had not heard of Hashimoto [7]. By 1929, only E. M. Eberts, a Canadian surgeon in Montreal, found and noted Hashimoto’s description in his textbook on surgery of the thyroid gland.

There was also confusion of Hashimoto’s disease with Riedel’s thyroiditis despite Hashimoto’s careful distinction between the two disorders. In 1929, for example, J. Howard Means at Boston’s Massachusetts General Hospital thought that what Hashimoto described was simply the early stage of Riedel’s thyroiditis [8] (as did Williamson in England and Eberts in Canada).

So, by the end of the 1920s, the Germans may or may not have remembered Hashimoto. One should remember that German medical and biological science was seriously disrupted by the War. The British and the Americans, on the other hand, appeared mostly ignorant of Hashimoto’s description or paid it little attention. Two major factors to account for this are the fact the many English speakers did not care to read German in the 1920s and the influence of David Marine and his work with iodine prevention of goiter. Marine’s work then dominated thinking about the cause of goiter and little effort seems to have gone into other possibilities. Still, cases of what Hashimoto described were reported, though without reference to him, and the disease was con-
nected to the occurrence of hypothyroidism.

Hashimoto's obscurity clearly changed in the 1930s when two papers by Allen Graham, a surgeon in Cleveland, Ohio, pointed out what Hashimoto had said all along: lymphomatous goiter was not Riedel's thyroiditis and it is a separate disease [9, 10]. Note that Graham made a clear connection between Hashimoto's disease with goiter and the same kind of thyroid disease with thyroid atrophy, a prescient connection when one considered the events of the 1950s below. Soon after Graham's papers, the surgeons, who had not mentioned Hashimoto in the 1920s, now included his work in their textbooks. This included both George Crile, also from Cleveland, Ohio, who had now become world-famous as a thyroid surgeon, and Arthur Hertzler.

By the mid-1930s, Hashimoto's name was routinely attached to his disease, at least in America. Hertzler was quite outspoken on this point, and noted that disease was "first accurately described by Hashimoto and commonly designated by his name." Hertzler also pointed out once again that hypothyroidism is an expected outcome ("most ... terminate in spontaneous myxedema") [11].

The British were not as quick. Joll, a British surgeon with an international reputation, in 1932 followed his fellow Englishman, Williamson, in recognizing lymphomatous goiter as a discrete disorder and in not recognizing Hashimoto [12]. But he later realized his error and admitted in print that he had simply not read the literature carefully. He then wrote an entire paper entitled, "The pathology, diagnosis, and treatment of Hashimoto's disease (struma lymphomatosa)," in 1939 [13]. Howard Means in Boston also changed his mind from 1929; by 1937 he recognized that Hashimoto's disease was in fact a distinct entity, that it was not Riedel's disease, and that Williamson was not the original describer but rather that honor belonged to Hashimoto [14].

So, by the end of the 1930s, Hashimoto's disease was recognized as an entity on its own. For example, an entire session was devoted to it at the Third International Thyroid Conference held in Washington, DC, in 1938. However, the disorder was still regarded as an uncommon disease, was considered a histological curiosity, and no one thought it related to most patients with hypothyroidism. The treatment was still surgical even though this treatment increased the likelihood of consequent hypothyroidism.

There was little discussion of Hashimoto's disease in the 1940s; the textbooks of the time changed little in their discussions of thyroid disease from the 1930s. Most of the world was occupied with the Second World War. But even after the war nothing much changed over the next decade. Hashimoto's disease remained in most minds a strange variant of goiter. In the early 1950s, for example, McGavack's textbook noted the rarity of Hashimoto's disease and our complete ignorance about it: "any real knowledge of the origin of Hashimoto's disease seems to be completely lacking" [15]. Yet the same textbook goes on to point out that most cases of spontaneous hypothyroidism have a lymphocytic infiltrate! Most investigators simply failed to make the connection between common hypothyroidism and Hashimoto's disease. One pathologist wrote in 1953 that the "irritant responsible ... is probably a chemical one" - in truth, the conceptual basis of the disease was no further along than Hashimoto's own speculations more than 40 years before. The stumbling block to making the connection between Hashimoto's disease and most cases of hypothyroidism was the lack of a recognized etiology.

But then, in 1956, there was a revolution in how to think about Hashimoto's disease. That year, two landmark papers came out. The first was a paper by Witebsky and Rose, immunologists in Buffalo, New York. They were studying the organ specificity of certain natural compounds with the idea that at least some compounds were specific to an organ and probably to an organ of each species. Thyroglobulin was one of these compounds and they were used to using rabbits in their work. They "knew" that the rabbit does not make antibodies to its own thyroglobulin, because it was the standard teaching at the time. But they found that, when they injected the thyroglobulin with Freund's adjuvant (after learning the technique from Freund himself), the rabbits did indeed make antibodies to their own thyroglobulin. Even more interesting was the thyroid histology: the lymphocytic infiltrate looked like Hashimoto's thyroiditis! So they looked for patients with Hashimoto's disease: it took three years to get 12 serum samples (the classic disease with goiter was indeed uncommon) and found positive antibodies in all samples. Their first draft was rejected because the editor said that the results were impossible. Their 1956 paper included
the rabbit work but not the data in the patients with Hashimoto's disease [16]. What they had done was almost accidentally overthrow the dictum that animals could not make antibodies to their own natural proteins. Once published, this finding brought respectability to the idea of autoimmunity that had been around for awhile but which most did not believe.

Then just a bit later in England, and before Witebsky and Rose published their patient data (that had to wait until the following year [17]), Roitt, Doniach and their colleagues looked at the serum from patients with Hashimoto's disease. They, too, found thyroid antibodies and published a short, one-page preliminary note in the Lancet (which at the time could publish a submitted paper within a week) [18]. At last there was a pointer to the cause of this uncommon form of goiter. One should note that Roitt and Doniach did not find thyroid antibodies in patients with myxedema. It turned out, however, that that was because of the low sensitivity of their original assay and was soon corrected after the English and Americans collaborated [19]. Thyroid antibodies, it turned out, were not specific to Hashimoto's disease but also occurred in patients with spontaneous hypothyroidism and even in those with Graves' disease. Finally, a pathophysiological connection was established between Hashimoto's disease and non-goitrous hypothyroidism. The concept of autoimmune disease was now real.

However, while the idea was real, it took some time for this new idea to sink into medical thought. It was basically too heretical for many. For example, 10 years after thyroid antibodies were found, a major textbook of pathology stated only that there was "some immunologic derangement" in Hashimoto's disease. But sink in it did: autoimmune thyroid disease is now itself a major industry.

"Hashimoto's disease"

What about the eponym, "Hashimoto's disease"? Should we still call it by that name? Or should the eponym be abolished in favor of a pathophysiologic one? Why do we have eponyms in the first place?

There are several opinions on this matter. But I believe that there are several good reasons to retain the eponym. Remembrance is one: the name serves to remember the man who described it. There is also the matter of the honor that is due to an important discovery. Furthermore, an eponym serves a useful purpose when the cause of a disease is unknown: one cannot apply a pathophysiologic name to a disease when the pathophysiology is poorly understood. So, an eponym allows the disease to be recognized while we try to figure out what causes it to begin with. Hashimoto described a goitrous condition; we now know that thyroid antibodies seem related to the causation of both goiter and thyroid atrophy. The fact remains that we really do not know why some patients with autoimmune thyroiditis develop goiter and some do not [20]. Thus, because we do not know the cause of the goiter in this disease, the eponym, Hashimoto's disease, actually has practical value. The retention of an eponym in this circumstance allows for a change in understanding the cause while keeping a constant name for the entity itself. Should the eponym, Hashimoto's disease, be applied to all autoimmune thyroid disease? Certainly, no one would change the name of Graves' disease to Hashimoto's disease even though some patients seem to have characteristics of both. But should the eponym be used for all patients without hyperthyroidism? Some say that "Hashimoto's disease" should apply to all such patients and that one should simply recognize two forms of Hashimoto's disease: goitrous and atrophic.

Classification is always a problem when the cause is unknown. There are also biases that affect terminology: clinicians, pathologists, and immunologists simply see things differently and these views in turn affect the names of diseases. Further, whatever one's specialty, some persons are naturally "splitters" and favor more detailed classifications while others are "lumpers" and prefer as few categories as possible. In retrospect, Hashimoto described what we now call goitrous autoimmune thyroiditis and the eponym should at least apply to that disorder. But Hashimoto's real emphasis was on the histologic picture and we now know, of course, that that picture is related to abnormal antibody production and is the same in both the goitrous and non-goitrous disease. I believe a good case can be made for calling both types of autoimmune thyroiditis, goitrous and non-goitrous, "Hashimoto's disease." It might also be worth keeping in mind that the term "Hashimoto's disease" is more commonly used than ever. Over the
last 40 years, the number of references to that term in
the medical literature has gone up more than five-
ofold, from 292 in the 1960s to 1792 in the 1990s.

Our medical colleagues seem to approve of the epo-
nym!

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