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The discovery of thyroid replacement therapy.

Part 2: The critical 19th century

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Conceptualizing the link between the thyroid and myxoedema

Up to the middle of the 19th century there appears to have been no knowledge of thyroid biology but much speculation. That the thyroid must have some important function was suggested by its very generous blood supply. Some wondered whether it functioned as a vascular shunt to prevent sudden rushes of blood to the brain – a neat idea! Others thought it was involved in voice production by some facilitating, perhaps lubricating, action on the larynx. Indeed, the two thyroid lobes had originally been called the laryngeal glands. But Frederik Ruysch, anatomist in Leyden around 1690, adopted, according to Albrecht von Haller in 1766, the ‘only possible remaining opinion, namely, that a peculiar fluid was elaborated in the gland and poured into the veins’.^{1,2} The 19th century thus began with thyroidology at best in embryo; but during that century endocrinology was born and the thyroid was its standard bearer.

In 1836, Thomas Wilkinson King of Guys Hospital, regarded by some as the ‘Father of Endocrinology’, anticipated on the basis of observation and experiment the internal secretion of the thyroid. In a meticulous paper on its anatomy, he wondered at the thyroid’s disproportionately large vascular supply in the absence of any evident mechanical or other local function and also at what he described as its ‘peculiar’ fluid.³ He wrote: ‘The most important novel fact concerning the thyroid gland is doubtless this, that its absorbent vessels carry its peculiar secretion to the great veins of the body’. This language is almost identical to that of Ruysch and Haller more than a century earlier. Indeed, King notes that his view ‘has been indirectly surmised by Morgagni [probably in 1761] and others’, usefully acknowledging a

continuum in thinking. He goes on to say: ‘Yet we may one day be able to shew [*sic*], that a particular material principle is slowly formed [in it], and partially kept in reserve [for] important subsequent functions in the course of the circulation’. King’s experiments included squeezing the gland and observing its lymphatics fill. He proposed that the thyroid is naturally subjected to an analogous periodic kneading or compression during chewing and swallowing from movements of the oesophagus and larynx and adjacent neck muscles, and inferred that the thyroid’s secretion must, therefore, vary through the day. He also noted an association between pathological findings and clinical features, describing in one case ‘the site of the gland occupied entirely by condensed cellular tissue, with the exception of two pea-sized portions of true gland situated on one side within this tissue. In this case, the peculiarities of the individual were fully sufficient to indicate the importance of the defective part.’ One can only speculate on the clinical findings because King, frustratingly, gives no information, and nothing further appears to have come of this impressive paper. It is not even cited in any of the following seminal papers – no joined-up thinking for King.

In 1850, at a meeting of the Royal Medical and Chirurgical Society of London, chaired by Thomas Addison, Thomas Blizzard Curling, surgeon at the London Hospital, provided a clear clinicopathological correlate in a paper entitled ‘Two cases of absence of the thyroid body and symmetrical swellings of fat tissue at the sides of the neck, connected with defective cerebral development’.⁴ Curling’s patients were 10 years old and 6 months old and both were regarded as cretins. Postmortem examination in each revealed no trace of thyroid tissue and that the swellings consisted only of fat. Curling concluded that: ‘... it is highly probable,

arranging access to the 1883 manuscript minute books of the Clinical Society of London. I am similarly grateful to Jackie Dunn, liaison assistant at the Robinson Library, Newcastle University, for supplying a copy of the minutes of the meeting of the Northumberland and Durham Medical Society on 12 February 1891. I very much appreciate the advice given on the Chinese contribution by Vivienne Lo, senior lecturer, and Penny Barrett, specialist translator and honorary research associate, at the Wellcome Trust Centre for the History of Medicine. Gesa Walker kindly translated German texts and Janice Webster was a great help with the French material. I warmly thank them both. I am grateful to Iain Milne, librarian of the Royal College of Physicians of Edinburgh, who photographed the illustrative material. Finally, I would like

that this fat was dependent on the absence of those changes which result from the action of the thyroid'.

Curling's important observation was not pursued until 1871 when, at another meeting of the Society, Curling himself then in the chair, Charles Hilton Fagge, a physician at Guy's Hospital, presented a paper on sporadic cretinism.⁵ He described four living cases, aged from 8 to 20 years. He noted particularly that none of them had a goitre and that one had been well up to the age of eight and, although now physically cretinous, aged 16, she remained very intelligent. He referred to Curling's paper and reached essentially the same conclusion from his own observations, that: '... the healthy thyroid body is capable of exerting a counteracting influence [on cretinism]'. Perceptively, he felt that these cases deserved a 'distinct appellation' to distinguish them from endemic cretinism. He also presciently and accurately speculated on what would be the clinical features of this disease were it to arise in adult life and the possibility then of the thyroid being 'wasted'. Interestingly, he mentioned what he regarded as a similar case of arrested physical and mental development brought to his attention by a Dr Langdon

Down (of Down's syndrome). The appearances of Fagge's own four patients in photolithographs do not suggest mongolism.

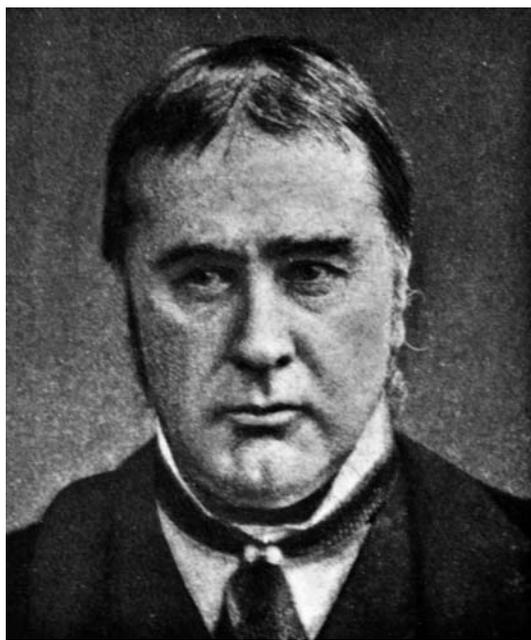
Two years later, in 1873, Fagge's senior colleague at Guy's, Sir William Withey Gull, presented before the Clinical Society of London two of the five cases he had seen of what he called 'A Cretinoid State supervening in Adult Life in Women'.⁶ He described their cretin-like appearance, drawing particular attention to the broad and thick tongue and the guttural voice and its pronunciation 'as if the tongue were too large for the mouth'. He acknowledged his remarks were tentative, hence, he said, his use of the word 'cretinoid', but he had no doubt this was a 'substantive' condition and not one of cardiac or renal origin. In precise, clear language he wrote: 'In the [cases] which I have seen, the thyroid was not enlarged; but from the general fulness of the cutaneous tissues, and from the folds of skin about the neck, I am not able to state what the exact condition of it was'.

Gull was an interesting personality with apparently a remarkable presence, resembling Napoleon in face, form and manner (Figure 1).¹ In the 1970s, 80 years after his death in 1890, he was the subject of a theory, quickly discredited, that he had been 'Jack the Ripper', the killer in the still unsolved murders and mutilations of at least five Whitechapel prostitutes in 1888.⁷ He figured in the 1988 TV film series, *Jack the Ripper*, starring Michael Caine as the detective.

Gull is credited with the first description of hypothyroidism in adults and his paper was important in defining a recognizable clinical syndrome. Yet many doctors must have come across such patients. The Edinburgh physician, Sir Byrom Bramwell, later in 1893, recounted his general practitioner father showing him a typical case in 1869, and a colleague encountering one in 1854 and recognizing it did not conform to any known condition.⁸ Others realized in retrospect they had seen similar cases.⁹

Then, in 1877, William Miller Ord, read his paper before the Royal Medical and Chirurgical Society of London and proposed the term 'myxoedema' for the adult condition.¹⁰ He described the non-pitting, 'mucous oedema'. He also described how the hands of one of his patients went 'dead' when she attempted to sew. This was possibly due to carpal tunnel syndrome, a potential complication of hypothyroidism, but then an

Figure 1
Sir William Withey Gull (1816–1890)¹



to thank Ulrich Tröhler for his helpfully detailed critique. This is the second part of an article previously published in the James Lind Library (www.jameslindlibrary.org), where there are links from the article to illustrative images from the key historical documents and to other relevant texts

unknown entity. Ord ended his paper carefully, stating that: '... the name [myxoedema] is only intended to represent the condition, and does not profess to involve an explanation of its causes'. However, he described the 'practical annihilation' of the thyroid gland he found at autopsy, and went on to discuss the possible relevance of this, attempting a synthesis of the earlier reports by Curling and Fagge. He reached the same conclusion: that destruction of the thyroid might relate in some way to the condition of his patients, although he opined there could be some more ultimate cause. He also presented an engaging theory to explain the lethargy, inertia and slow responses associated with the disease. He suggested that these might result from the sheathing and insulation of the body in a 'jelly-like', mucin-laden integument that interfered with sensory perceptions and stimulation. It is sobering to read his descriptions of the increasingly wretched life endured by these patients, culminating in death in coma or from almost certain cardiac failure.

Ord deserves more credit than just as the originator of a name, but the term 'myxoedema' was certainly an inspired invention. It was a memorable, snappy for the times, single-word label which – notwithstanding some controversy over its appropriateness¹ – must have helped to focus attention on a condition which, despite its frequency and unifying features, had long gone unidentified. Six years later, he chaired the committee set up by the Clinical Society of London to investigate the whole matter. He also later undertook some of the earliest metabolic studies of the effects of treating myxoedema with thyroid extract, showing the rapid weight loss and rise in temperature and in urinary volume and nitrogen excretion that occurred.¹¹

The Swiss key: myxoedème opératoire – precedence and prestige

The key papers, which advanced these English authors observations, were those of the Swiss surgeons, Jaques-Louis Reverdin in Geneva and Emil Theodor Kocher in Bern, Kocher later receiving the Nobel Prize for his work on the thyroid. How fitting it is that it should be two Swiss doctors whose practices unlocked an understanding of the importance of the thyroid. For they each identified

the late effects of total ablation (extirpation) of goitres. Reverdin first presented his findings briefly at a meeting of the Medical Society of Geneva on 13 September 1882¹² and then in an extended paper co-authored with his cousin Auguste Reverdin in June 1883.¹³ In this, they noted the great similarity of Gull's and Ord's myxoedema cases with their affected postoperative patients, referring to the comparison as a '*rapprochement complet*', clearly making the connection. They acknowledged Gull's primacy in describing the clinical manifestations and Ord's 'christening' the condition 'myxoedema', and proposed that surgical cases be known as '*myxoedème opératoire*'. In light of his findings in 1882, Reverdin thereafter sought to conserve a part of the gland during thyroidectomy for goitre, speculating that its complete removal may have been responsible for these late effects. He had noticed that no such problems followed a just unilateral lobectomy.

Kocher, on the other hand, surprisingly appears to have been either unaware of the reports by Gull and Ord, or omitted to refer to them. He first reported his findings to the Congress of the German Surgical Society on 4 April 1883 and they were published later that year.¹⁴ The exact date of publication is unclear, but it was after the Reverdin paper of June 1883.¹⁵ Reverdin had remarked in that paper that he wondered when Kocher would publish his findings. Kocher called the disease picture in his affected cases '*cachexia strumipriva*' – literally, a bad condition due to the removal of a struma (goitre). He ascribed it to a combination of oxygen insufficiency from tracheal atrophy, consequent on operative interference in the neck, and loss of the thyroid's role as a safety valve for both the cerebral circulation – the old theory – and, as he saw it, in breathing. Kocher's biographer, Ulrich Tröhler goes into this in more detail.^{16,17} As Halsted put it in his monumental review of goitre surgery: 'It is interesting to follow the argumentation of a mind so exceptionally keen and sane as Kocher's in its futile efforts to explain insufficiently illuminated phenomena'.¹⁸

In reading Kocher's 1909 Nobel Prize Lecture (in English translation),¹⁹ one gets the impression that Kocher was aware in 1883 of Gull's and Ord's reports, despite not referring to them, and he dismisses Reverdin's contribution. He appears to assert that Reverdin only became aware of the connection between the effects of total thyroidectomy

and the English cases *after* his, Kocher's, oral communication in Berlin, and he firmly refutes Reverdin's 'later claim' to have been the first to discover the ill-effects of total thyroidectomy. In support of his denigration of Reverdin, Kocher fastens on a paper Reverdin had published in April 1883,²⁰ in which, Kocher says, Reverdin made no mention of the findings he had reported the previous year. Indeed, Kocher sarcastically writes, Reverdin 'emphasized and sung the praises of the excellent results of their total excision [of the thyroid]'. But this paper simply described the technical aspects of thyroidectomy and the immediate postoperative period and was the first in a three-part publication over April, May and June, the third part – *Accidents et Résultats* – documenting the longer-term sequelae.¹³ Kocher should have noticed the words '*A suivre*' (to follow) at the end of the paper he was targeting.

This was all intriguing and made more so by Rolleston's comment that: 'A now forgotten controversy arose between J. L. Reverdin and Kocher'.¹ There is no doubt this controversy was an argument over priority and recognition, and this has previously been investigated.^{16,21–23} Reverdin was certainly the first to raise a concern at the Geneva meeting in September 1882, and, by then, he had already modified his surgical approach to one of subtotal thyroidectomy because of the possibility that loss of thyroid function was responsible for the '*non encore décrits*' (not yet described) clinical manifestations.¹² The transcription of his presentation is brief and there is no mention at that point of any awareness of Gull or Ord, and it may be he had not yet made the connection. Kocher was present at that meeting. Indeed, he and Reverdin had had a conversation a few days beforehand – on a steamboat! The nature and direction of that conversation was later the subject of a fascinating correspondence, which is recorded in Henri Reverdin's biography of his father.²³ Kocher claimed he had introduced Reverdin to the ill-effects of total thyroidectomy, whereas Reverdin claimed it was he who had advised Kocher. Reading these letters today, Reverdin's is the more convincing. A full analysis of them is provided by Michler and Benedum.²²

In Reverdin's extended, final part, paper published in June 1883, it seems he was aware of Kocher breathing heavily down his neck, because he refers to the possibility of Kocher publishing

before him. Kocher's paper reported the long-term results in a much larger group of patients and is a superb study, but it was disingenuous of him to dismiss Reverdin in his Nobel Prize Lecture years later. There is every indication that it was Reverdin's prompting in September 1882 that led Kocher to review his thyroidectomised patients. While in his 1883 paper he does acknowledge Reverdin's influence,¹⁴ he concedes it only as having been a spur to investigations allegedly, but unconvincingly, already underway. That Reverdin was the prime mover is the understanding of some latter-day reviewers of the history of thyroid surgery,^{24–26} while others, in paying homage to Kocher, either fail to mention Reverdin or subordinate his contribution in this particular matter to Kocher's.^{27–29}

Kocher, in his Nobel Prize Lecture, also maintains that a letter he wrote to the Clinical Society of London about his findings was the 'impulse' for the Society's subsequent investigation into myxoedema. In fact, that letter, while no doubt of some influence, was itself prompted by a letter from Ord drawing Kocher's attention to his, Ord's, cases of myxoedema, and was accompanied by some photographs of his patients.³⁰ In his reply to Ord, Kocher revealingly wrote he had never seen such a case – presumably because they would be unlikely to come to a surgeon's attention – but, myxoedema having now been brought to his notice, he agreed it was analogous to his cases of *cachexia strumipriva*.³⁰ It is also obvious that Kocher, like many surgeons of the time, cannot have engaged in routine post-operative outpatient follow-up, for otherwise the ensuing problems in his goitre-operated patients would have been detected years earlier.

None of these observations about Kocher should detract from his contributions. They serve rather to show that Reverdin should be recognized more widely. There can be no doubt of the primacy of Reverdin's observations, reported in 1882 and fully published during the first half of 1883; of his speculation then that loss of the thyroid may be to blame; and, perhaps most important, of his decision always to retain a portion of the thyroid in operations for goitre.^{16,17,21–23} In respect of this key moment in the history of the thyroid, Reverdin could be said to hold the intellectual property. The thought has been expressed that perhaps he should have shared the 1909 Nobel Prize with Kocher.^{31,32}

However, despite the self-serving tone in Kocher's Nobel Prize Lecture and his attempts to relegate Reverdin, there is no doubt about his prodigious contribution to the study of the thyroid, which far exceeded Reverdin's, as well as to surgery in general. He was 'A surgical maestro', as one review puts it.²⁸ But it is interesting to read that Kocher was considered 'Very touchy, he hardly overcame setbacks. Likewise, he insisted on the priority of his work and merits, which he aggressively defended ... he had only a few close friends.'³³ Reverdin, in 1927, three days short of his 85th birthday and two years before his death, received a telegram from the International Conference on Goitre in Bern, paying tribute to his pioneering role in myxoedema.²³ It was a nice touch. Kocher, who was from Bern, had died there 10 years earlier, aged 76. By coincidence, the telegram arrived on 25 August, Kocher's birth date.

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