



The discovery of thyroid replacement therapy.

Part 1: In the beginning

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There is a poignant before and after photolithograph of a Victorian lady in the 1878 transactions of the Royal Medical and Chirurgical Society of London (Figure 1).¹

This is not the usual celebratory image before and after successful treatment. It is a picture of the woman, aged 21 in 1870, and then seven years later, unrecognizably aged by the effects of undiagnosed and untreated thyroid deficiency. It is poignant because she probably dies of the disease, the introduction in 1891 of effective treatment with subcutaneous injections of thyroid extract by George Murray of Newcastle-upon-Tyne coming too late.²

The images are from a paper by William Ord, physician at St Thomas's Hospital, entitled 'On Myxoedema, a term proposed to be applied to an essential condition in the "Cretinoid" Affection occasionally observed in Middle-Aged Women'. In this he described a 'mucous oedema' of the skin,

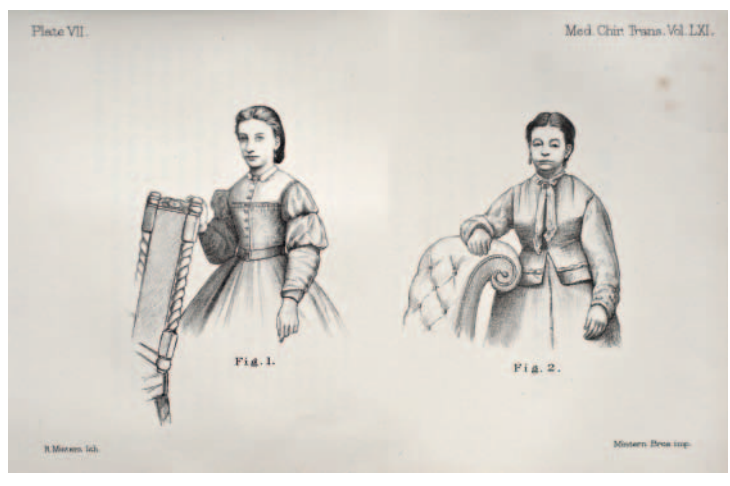
finding in it an excess of mucin on microscopy and chemical analysis. From this description he coined the term 'myxoedema', a name lastingly synonymous with thyroid deficiency.

A number of steps led to the discovery of thyroid replacement therapy: the slow understanding that this debilitating disease, myxoedema, was in some way linked to the thyroid; the acceptance of the notion that the thyroid elaborated some important factor with an endocrine function; the emergence of the principle of replacement therapy; and the introduction of replacement therapy in practice. But, contrary to general belief, Murray was not the first to treat myxoedema effectively.

In the beginning: endemic goitre and iodine

The history of the thyroid gland goes back millennia. Its name derives from the Greek *θυρπιος*, a shield, because of the shield-like shape of the tracheal cartilage there. Its long history is inseparable from that of goitre – Latin *guttur*, neck or throat – for there must always have been people with goitrous swollen necks. August Hirsch in his monumental three-volume work, *Handbook of Geographical and Historical Pathology*,³ provides many past references worldwide to endemic goitre and endemic cretinism, notably prevalent in mountain valley regions but absent in coastal regions. Among these – and suggestive evidence of a general public awareness of goitre – is Juvenal in the early second century CE asking rhetorically: '*Quis tumidum guttur miratur in Alpibus*', 'Who wonders at a swollen neck in the Alps'. Rolleston⁴ quotes a source in 1775 describing an incident involving an English traveller in the Tyrol of whom it was remarked that he would have been quite

Figure 1
Before (left), aged 21 years in 1870, and seven years later with myxoedema¹



indispensable and tireless help of Estela Dukan, library assistant at the Royal College of Physicians in Edinburgh, and Valerie McClure, assistant librarian at the Royal College of Physicians and Surgeons in Glasgow. I am grateful to Mira Gogova, archivist/conservator at the Royal Society of Medicine, for arranging access to the 1883 manuscript minute books of the Clinical Society in 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

handsome if only he had had a goitre, such was the almost universal presence of goitre in that region (presumably a longstanding feature). In Britain, we had our own, colloquial, 'Derbyshire neck'.

Goitres did not escape artistic or literary attention, being painted by Leonardo Da Vinci – *A Grottesque Head* or *Scaramuccia*⁵ – among others, and referred to by Shakespeare in *The Tempest*:

Faith, sir, you need not fear. When we were boys, Who would believe that there were mountaineers Dew-lapp'd like bulls, whose throats had hanging at 'em Wallets of flesh? (Gonzalo, Act III, Scene 3)

Mark Twain in *A Tramp Abroad* writes in 1880 of a fellow traveller laconically remarking: 'Well, I am satisfied, I have seen the principal features of Swiss scenery – Mont Blanc and the goiter – now for home!'⁶

Hirsch, in his forensic analysis of the possible cause of endemic goitre, touches on a 'short-lived opinion' that absence of iodine in the drinking water and in the air was responsible. However, he concludes that while iodine 'in the most minimal quantities [in] air and food' may protect against endemic goitre and endemic cretinism, these conditions were probably infective in origin. Tantalisingly close to the truth, while he refers to the 'curative power' of iodine – though, surprisingly, provides no reference – he thought it 'very doubtful' whether giving iodine would have any prophylactic value. It was Jean Francois Coindet in Geneva who, in 1820, reported iodine's efficacy in treating goitre.^{7,8} He also, astutely, in light of things to come, recommended it preoperatively to diminish goitre size and vascularity. At the time, he did not know he was treating iodine deficiency, just 'suspected, from analogy' that iodine might be the active principle in burnt sponge, which he knew to have been a long-time remedy. He encountered opposition, opponents claiming iodine was poisonous, and it has been suggested that 'Coindet would not leave his house for fear of being stoned in the street!'⁹ Coindet is regarded as the first to try iodine but, in fact, William Prout in London had done so earlier in 1816, five years after iodine was discovered.¹⁰ However, he appears to have treated only one case and did not publish until 1834, and then only in a short, but informative, footnote, saying he was instrumental in St Thomas' Hospital adopting the remedy in 1819.

Further historical detail on this aspect is provided by Rolleston⁴ and more recently by Medvei¹¹ in their extensive monographs and by Zimmermann.⁹ It is sobering to reflect that, as recounted by Medvei and in particular detail by Zimmermann, it took 100 years after Coindet's successful treatment of goitre for the safe prophylactic value of iodine to be convincingly established by Marine and Kimball in a controlled trial in schoolgirls in Akron, Ohio.^{12,13} One of the grounds for earlier antagonism was that a goitre exempted young men from military service in the French army!⁹ Yet, challenges in the delivery and uptake of iodine prophylaxis remain.¹⁴

The Chinese contribution

One thing missing in Hirsch's 1883 account is the Chinese contribution. Missing, because China was then largely a closed book to the West, otherwise it is likely there would have been earlier progress on the thyroid and in several other scientific and technical matters. For the Chinese were not just well aware of an environmental influence on goitre, they looked on it as an anomaly and were treating it. In a work dating from 239 BCE – *Master Lu's Spring and Autumn Annals* – it is recorded that: 'In places where there is too much light water there is much baldness and goitre'.^{15,16} In 610 CE, Chao Yuan Fang, in *Discussion of the Origin of Symptoms in Diseases*, observed: 'Do not live long in mountainous regions with black earth and spring water. Drinking such water for a long time may cause goitre'.¹⁷ There is reference to treating goitre with burnt sponge and seaweed in 1600 BCE.¹⁸ But any possibility of the use of algae dating from around 2700 BCE, as has been hinted at^{4,19} – many traditional Chinese medicines being attributed to the cultural hero and divine, Shen Nong, who is supposed to have lived then – is based on mythology. Powdered shells of molluscs are reported to have been used in the fifth century CE from the *Goitre Prescriptions of the Abbot Shen*.¹⁵

Even more remarkable is that the Chinese are said to have been treating cretins with sheep's thyroid in the sixth century CE.²⁰ This is presumably insofar as they distinguished cretinism – by whatever name they called it – from other forms of childhood mal-development. It is also most likely to have been in the context of goitrous cretinism,

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for there is reference to this as well as to the treatment of goitre *per se* with sheep or deer thyroid in the wonderfully titled *Thousand Gold Remedies* or *Thousand Golden Ducats Prescriptions*.^{17,21} This is the *Beiji qianjin yaofang* by Sun Simiao, literally translated as *Essential Prescriptions worth a Thousand Gold Pieces for Every Emergency*, completed around 652 CE.²² Although Chinese medicine did not really have a theory of thyroid problems without goitre, and what we know as myxoedema may have corresponded to 'exhaustion' or 'oedema' and been treated differently,¹⁷ the Chinese are bound to have come across non-goitrous cretinism and may have treated it, too, with animal thyroid. The Chinese also recognized then that there were different kinds of goitre: solid neck swellings – malignant tumours – that could not be cured, and movable ones that could.¹⁵ The extent to which they distinguished and how they managed thyrotoxic goitres is not clear. Remarks in a recent paper on traditional Chinese medicine suggest they may have been aware of a difference and a difficulty in treatment with seaweed.²³

Robert Temple, in *The Genius of China*,¹⁶ a useful distillation of Joseph Needham's monumental, multivolume work, *Science and Civilisation in China*, lists a number of thyroid prescriptions for goitre in the seventh century CE. One of these recommended taking 100 thyroid glands from gelded rams, washing them in warm water, removing the fat, then drying them and chopping them up and mixing with jujubes (Chinese dates) – no doubt to try to disguise the taste – to make into pills. Another advised a single thyroid gland be removed from a sheep, the fat taken off, and the raw gland sucked by the patient until all the juice had been extracted and swallowed and the gland itself then eaten. Yet another involved air-drying various animal thyroids to powder, to be taken every night in cold wine. Two of these prescriptions are from *Old and New Tried and Tested Prescriptions* (*Gujin lu yanfang*), attributed to Zhen Quan, written about 640 CE. *Medical Secrets of an Official* (*Waitai Miyao*) by Wang Tao, 752 CE, recommended steeping sheep's thyroids in wine and afterwards roasting them to take one daily.²¹ It seemed not to matter which animal was used, whether pigs, sheep, water buffalo or deer; all seem to have been judged effective. One seaweed prescription may have consisted of baking seaweed and sea grass to dryness, then grinding the

mixture into a powder that was to be taken in warm water daily.²⁴

It seems improbable that these apparently routine therapeutic interventions of long ago were not the result of astute observation and experience. While their origin may have lain in serendipity or in some instinctive idea of treating like with like, a diseased thyroid with a healthy one – the Chinese *thung lei* (identity of categories) principle¹⁵ – their firm incorporation into Chinese pharmacopoeic texts is most likely to have been because they were seen to work. These texts included *The Great Pharmacopoeia* – the *Pen-ts'ao kang mu* or *Bencao gangmu* (*Systematic compendium of materia medica*) – by Li Shizhen, published in 1593 or 1596.^{16,25} It has not proved possible to consult directly any of the original Chinese writings mentioned, but several references to the use of thyroid (*ye*) and of seaweed (*haizao*) – or both together – in treating goitre (*ying*) have been located in modern edited editions.^{26–29}

China might not have been the only ancient civilization to use seaweed for goitre. For in a paper on the role of algae as a food in antiquity in Central and South America, evidence is presented that dried seaweed was imported into the Andean highlands, an endemic goitrous area.³⁰

The discovery of iodine in 1811, millennia after the Chinese and perhaps other ancient civilizations were using seaweed empirically, was serendipitous and the circumstances are interesting. A French chemist, Bernard Courtois, noticed violet fumes while washing seaweed ash with sulphuric acid in the manufacture of saltpetre. The gas was condensed into crystalline flakes and its properties investigated by Louis Gay-Lussac and Sir Humphry Davy who proposed the name *iodine* for the new substance, from the Greek *ιωδης*, violaceous.³¹ Davy, assisted by Michael Faraday, worked on it in Paris, visiting the city in 1813 under special permission from Napoleon, having gone there to collect a prize and medal Napoleon had awarded him in 1807 for his electro-chemical work.^{32–34} Napoleon's own affairs had by then taken a fateful turn, but the circumstance of honouring an enemy alien in this way must be very unusual, if not unique. Indeed, French chemists calling on Davy for help in identifying a new substance connected with saltpetre (potassium nitrate), a key component of gunpowder, is also remarkable for it might have proven of military importance. It is evident from Davy's account that

they were already aware it formed a detonating compound with ammonia!

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