# Myxoedema: some early reports and contributions by British authors, 1873–1898

**L Doyle** MB FRCPI *Wythenshawe Hospital, Manchester M23 9LT*

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This paper discusses some selected early reports on myxoedema by British authors, a memorable meeting of the Clinical Society of London in 1883, the report of a committee set up to investigate myxoedema and some subsequent developments. In the period under review, myxoedema was the term used to denote one specific malady; nowadays, it is applied more often to one feature of the florid cases of hypothyroidism.

In 1871, Fagge read a paper 'On Sporadic cretinism, occurring in England'[1]. Of the four cases described, one was probably a case of juvenile myxoedema which had developed in a girl aged 8 years, after a measles-like illness. A plate is included in the report. The thyroid gland was impalpable.

In 1873, Sir William Gull, in a paper entitled 'On a Cretinoid State supervening in Adult Life in Women'[2], gave details of two such cases. The first, in middle age, 'became insensibly more and more languid, with general increase in bulk. This change went on from year to year, her face altering from oval to round, much like the full moon at rising . . . the cheeks tinted of a delicate rose-purple, the cellular tissue under the eyes being loose and folded . . . the whole expression of the face remarkably placid . . . voice guttural . . .' The second case was similar. Gull could offer no explanation for the cause of this condition. The thyroid was not enlarged; however, he was 'not able to state what the exact condition of it was'. These two cases were the first recorded accounts of some of the clinical features of hypothyroidism with myxoedema, in adults.

In 1877, Ord (Figure 1) read a paper on two cases, similar to Gull's[3]. The first, a woman of 54, who '. . . noticed that her hand became "dead" when she used a needle . . . [and] she had become weaker . . . could walk only slowly, and the knees often gave way suddenly . . . the eyelids, the lower in particular, were swollen and ridged, so as almost to hide the eyeball, and at the same time to hang down flaccidly on the cheek; they were remarkably translucent . . . [there was] a delicate flush on the cheeks . . . the complexion was pale yellow, and in the flush on the cheek were many enlarged vessels . . . She died by breathlessness and exhaustion'. Some points made after the post-mortem examination were: 'The apparent oedema, so well marked in the face . . . [was due to] the presence in the skin of a jelly-like interstitial material or of tissue in a jelly-like state . . . in the thyroid gland, the alveoli were compressed and almost annihilated by this substance', considered by Ord, to be chiefly mucin. Thus, the changes noted in the thyroid gland were just part of a generalized, connective tissue, mucin-deposition disorder. Ord, well versed in the Classics, gave the name myxoedema to this affection.

*Figure 1. William Miller Ord (1834-1902); reprinted with the kind permission of the Wellcome Institute Library, London*

Ord then published a 'Clinical Lecture on Myxoedema' in 1878[4], based on two further cases. He again stressed the facial features, the liability to sudden falls, the voice 'leathery' in intonation and 'little or no trace of the thyroid'. The body temperature in both was below the average by 1°F. Again, he asserted that there existed 'a substantive affection in which a gelatinous dropsy [was present] without albuminuria'.

In 1879, Duckworth and Ord[5,6] each, at the same meeting, read a paper on one of his own cases of myxoedema. Duckworth's patient 'thought her hands were more clumsy then formerly and "sleepy and dead" in the mornings, they also tingled . . .'. Ord's patient, a woman aged 52 years, died from hypothermia, in the month of February.

*Progrès Médical* in 1880, published in two parts an article by Hadden (Ancien 'Medical Registrar' de St Thomas's Hospital)[7], entitled: Du Myxoedème. Cachexie Pachydermique (Myxoedème, des auteurs anglais) was the title of the article[8] which followed immediately after Hadden's first contribution. In the introduction, Ballet, interne des hôpitaux à la Salpêtière (M Charcot), noted: 'M Hadden (de Londres), fait paraître ici même une revue générale sur les faits

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de myxoedème étudiés en Angleterre, et dont il a pu observer personnellment plusieurs . . .' Charcot himself (1881)[9], wrote on the subject and referred to the writings of Gull, Ord and Hadden (un élève de M Ord).

On 9 December 1881, five further cases of myxoedema were presented at a meeting of the Clinical Society of London (Lunn, two cases; Cavafy, two cases; and Ord, one case)[10]. Towards the end of the meeting, Mohamed threw down the gauntlet, asking 'were they not really cases of chronic Bright's disease?'. In the account in the *Lancet* of this meeting, it was announced that Mohamed's paper would be published in its next issue, 24 December 1881. It was entitled: 'The Pathology and Etiology of Myxoedema'[11]. He made his case, in full, ending: '. . . I must venture to express a fear that we may be led to regard as a disease what may only be a symptom . . .' - falsely true!. On 13 January 1882, the discussion was resumed[12]. First, two further cases of myxoedema were reported; then, in the general discussion Marcet doubted whether mucin was the characteristic 'jelly-like' substance. He suggested that it 'might be due to Dickinson's altered fibrin or waxy material'. (In 1869-1871, both Marcet and Dickinson had been members of a committee set up to study the nature of the deposit in lardaceous disease)[13]. Ord reported that the iodine test on the 'jelly-like' material was negative. Ord, himself, replied to Mohamed's question. A week later, 21 January, the whole debate was reviewed in a ***British Medical Journal*** Editorial[14]. It implied some criticism of Mohamed's conduct: '[He] ventured to call into question the nosographical entity of the disease . . . this gentleman gave a more detailed exposition in a contemporary journal . . .'. None the less, Mohamed's role in the debate was of value. A strong persistent challenge always helps to establish and refine a new idea.

In 1882, Gowans read a fine case report on myxoedema to The Northumberland and Durham Pathological Society[15] and later, Oliver (1883) delivered a lecture on the subject at The Infirmary, Newcastle upon Tyne[16]. In 1883, Coxwell reported a case of myxoedema in a girl aged 13 years[17,18] who 'until 8 years of age, she differed in no way from other children, and could read a chapter out of The Bible, or a story, as well as her mother; could write and learnt arithmetic. A great change came over her . . . her memory became defective . . . her speech became thick and indistinct, her head drooped forward unto her chest, her legs became weak and her gait unsteady. The skin [of her face] became translucent with a circumscribed patch of redness, the lower eyelids were swollen . . . temperature was frequently below 95.6°F [35°C] . . . her power of speech became worse, she could hardly utter a single word . . .' This description must certainly be one of the earliest detailed accounts of the clinical features of florid juvenile myxoedema.

## The turning point

At a meeting of the Clinical Society of London in November 1883[19] Drewitt presented a case of myxoedema. Then, Semon, who had studied medicine at Heidelberg and Berlin, 'said he ventured to acquaint the Society with a most important contribution from a very unexpected source . . .' In the previous April, in Berlin, Professor Kocher of Berne, had read a paper (later published)[20] on results of thyroidectomy. Kocher's attention had been drawn to the changed state of health in one patient who, previously, had had a total thyroidectomy. Subsequently, Kocher was able to review 34 cases (out of 101) who had had a prior thyroidectomy. The 16 patients with a partial thyroidectomy were in good health. '. . . matters, however, were different with regard to the eighteen patients on whom total extirpation of the thyroid body had been performed. Of these, two only showed an undeteriorated or even improved, state of health; but it was remarkable that, in one of these cases, a small accessory thyroid gland had undergone a hypertrophic change, and that, in the other, a recurrence of the goitre had taken place. All the remaining sixteen showed more or less considerable derangements of their health (cachexia strumipriva) . . . not one symptom was present in myxoedema which was not met with in the cases of total extirpation . . .'

Sometime before the meeting of The Clinical Society of London (November 1883), Semon discussed Kocher's findings with Ord. On Semon's suggestion, Ord wrote to Kocher, sending details and photographs of some cases of myxoedema. Kocher replied promptly. In the discussion at this meeting of The Clinical Society of London (November 1883), Ord read out a long extract from Kocher's letter, part of which ran: '. . . there cannot be the slightest doubt of the analogy of myxoedema and cachexia strumipriva. I was not aware of it before . . . I think you will agree with me that, by my observations, the atrophy of the thyroid body which you have found in your cases, gets much greater importance . . .'

So in December, 1883, The Clinical Society of London, nominated the members of a Committee set up to investigate myxoedema.

In the next 4 years, further case reports and notes on this topic were published. Three of special interest were:

(i) A commentary by Sir William MacCormack (1884) on Kocher's paper[21]. He also pointed out: 'In the preceding year M. Reverdin of Geneva had independently described [*Journal de la Suisse Romande* 1882: p 529] results following complete ablation of the gland, which also resemble myxoedema . . .'

(ii) The Brown Lectures by Horsley (1885)[22]. In the introduction, he wrote: 'I am prepared in my first two lectures to support the dictum (first completely enunciated by my friend, Dr Felix Semon) that cretinism, congenital or acquired myxoedema and cachexia strumipriva are merely phases of one and the same state, namely, arrest of the function of the thyroid gland'. Horsley induced myxoedema in monkeys by total extirpation of the thyroid gland, with enlargement of the salivary glands, as a conspicuous feature. Recently, attention has been drawn by Fulop (1989)[23], to enlargement of the salivary glands in some cases of human myxoedema.

(iii) Three reports: Suckling (1885[24] and 1886[25]) and Barling (1886)[26] on the clinical history, death in coma and hypothermia, and the postmortem findings, with special reference to the changes in the thyroid gland, in a myxoedematous woman aged 76 years.

In 1888, The Report of the Committee, set up in 1883, to investigate myxoedema, was published[27]. It was impressive in its size (about 200 pages), analyses,

14. That a general review of symptoms and pathology leads to the belief that the disease described under the name of myxœdema, as observed in adults, is practically the same disease as that named sporadic cretinism when affecting children; that myxœdema is probably identical with cachexia strumipriva; and that a very close affinity exists between myxœdema and endemic cretinism.

15. That while these several conditions appear, in the main, to depend on, or to be associated with, destruction or loss of the function of the thyroid gland, the ultimate cause of such destruction or loss is at present not evident.

WILLIAM M. ORD, *Chairman.*

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|---|---|
| JOHN CAVAFY. | VICTOR HORSLEY. |
| ARTHUR E. DURHAM. | SYDNEY JONES. |
| RICKMAN J. GODLEE. | STEPHEN MACKENZIE. |
| JAMES F. GOODHART. | FELIX SEMON. |
| W. D. HALLIBURTON. | W. PUGIN THORNTON. |
| WARRINGTON HAWARD. | W. B. HADDEN, *Hon. Secretary.* |

*Figure 2. Committee set up to investigate myxoedema: membership and last two conclusions (1888)*

## THYROIDEUM SICCUM.

### Dry Thyroid.

A powder prepared from the fresh and healthy thyroid gland of the sheep. Remove the external fat and connective tissue from thyroid glands taken from sheep immediately after killing. Cut the glands across, and reject any which contain cysts, are hypertrophied, or otherwise abnormal. Mince finely the healthy glands, and dry at a temperature of 90° to 100° F. (32·2° to 37·8° C.); powder the dried product; remove all fat from it by treatment with *petroleum spirit*; and again dry the residue.

*Characters.*—A light dull-brown powder, with a very faint meat-like odour and taste, and free from any flavour of putrescence. It is liable to become damp on exposure to the air, and then deteriorates.

*Dose.*—3 to 10 grains.

*Figure 3. Entry in the British Pharmacopoeia*

bibliography and in the clarity of its 15 conclusions (Figure 2). It had a favourable review (1889)[28]. Then in 1890, Bettencourt and Serrano reported definite clinical improvement in a case of myxoedema by implanting a sheep's thyroid under the skin[29]. Aware of this, Murray (1891) suggested that extracts from sheep's thyroid glands might be injected hypodermically, in the treatment of myxoedema[30]. Five months later (1891), he was able to report on the excellent result achieved, in one case, using a glycerine extract, injected once every 2 or 3 weeks[31]. He again reported (1896) on this woman's continued good health (then, on oral thyroid treatment)[32]. Beatty (1892)[33] and Carter (1892)[34] each reported an excellent result in the treatment of myxoedema in one case of his own, using Murray's method or a modification. Murray (1892) reported (with good 'before and after treatment' photographs) on further cases of myxoedema, treated by his method[35]. A few months later, MacKenzie (1892) (by feeding with fresh sheep's thyroid gland)[36] and Fox (1892) (by taking extract from sheep's thyroid by the mouth)[37] introduced a simplification in treatment. A relevant annotation in the *British Medical Journal* stated: '. . . By an interesting coincidence we received, after Dr MacKenzie's paper was in type, the note from Dr Fox which is also published in this issue . . .'[38]. During the next year, a spate of good results in the oral treatment of myxoedema, was published in several British journals. Three of these, of special note, appeared in early 1893. First, a clinical lecture by MacKenzie[39]. Secondly, the presentation of some treated cases of myxoedema (of long-standing) at a meeting of the Clinical Society of London[40]. The *Lancet*, in an Editorial, summed up the mood of the time: 'Those who were fortunate enough to be present at the last meeting of the Clinical Society of London had the advantage of seeing living examples of what cannot but be considered as one of the greatest therapeutic triumphs of the age . . .'[41]. Thirdly, a well attended meeting (with guest speakers) held by the Edinburgh Medico-Chirurgical Society[42,43]. Byrom Bramwell, one of the main speakers, gave a masterly account of the clinical features of myxoedema (the record of his account covered nine pages of *The Transactions of the Medico-Chirurgical Society of Edinburgh*). Four points, worthy of recall, were:

(i) '. . . the upper lid in many cases droops over the eyeball; and in order to prevent the loss of sight which is occasioned by this drooping of the upper lid, there is often a compensatory elevation of the eyebrows due to a permanent contraction of the occipito-frontalis muscle'.

(ii) '. . . The skin [of the face] has a yellow, tawny tinge . . .' yellow, tawny is probably a more accurate detail of the change than just yellow alone.

(iii) '. . . The temperature in myxoedema is subnormal, and the temperature variations are much less marked than normal . . . the diurnal rises and falls which occur in health may be almost entirely absent . . .'.

(iv) '. . . Pituitary body enlarged . . . (1×1½ cms.), and very firm; its fossa unusually deep . . .' (p 164), was one finding at the postmortem examination of a 51-year-old woman who died suddenly and had suffered from myxoedema for over 10 years.

Ord (1898) in his Bradshaw Lecture[44], reviewed in full the clinical features and treatment of myxoedema. He twice referred to cases of myxoedema which had followed, after a lapse of time, Graves' disease (Williams, 1893, had noted this sequence, previously)[45].

Also, in 1898, Liquor Thyroidei and Thyroideum Siccum, (each with its method of preparation) were included, for the first time, in the British Pharmacopoeia (Figure 3).

In the 25-year period between Gull's paper and Ord's Bradshaw Lecture, significant advances were made both in understanding the nature of myxoedema and in its treatment. In these, the British contribution was a major one and Ord's, a substantial part of it. His original view that mucin (a mixture of highly glycosylated glycoproteins) was the major constituent of the myxoedema, was near the mark. An extracellular accumulation of hyaluronic acid (with its strong water binding capacity) is one important change, noted in the dermis, in myxoedema[46].

Perhaps, the meeting of the Clinical Society of London, held on Friday 23 November 1883, was the crucial point in this fascinating unfolding.

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