The Thyroid and Osler

SIR RAYMOND HOFFENBERG, KBE, MD, PRCP, William Withering Professor of Medicine, University of Birmingham Medical School, Birmingham

Osler made no major contribution to the study of the thyroid but he was at the peak of his career at the most exciting time of thyroid, indeed endocrine, conceptual development and he was characteristically quick off the mark in recognising the importance of contemporary work and in adding his own observations to the burgeoning literature of the time.

The scene has to be set roughly 150 years ago. In 1835 Robert Graves[1] described the condition of hyperthyroidism which still bears his name, despite the fact that, as with so many diseases, Parry’s description had preceded his by 10 years. Caleb Hillier Parry[2] was of Welsh descent, the name being derived from ap Harry, and incidentally a lifelong friend of Edward Jenner with whom he was at school in Cirencester. Both were members of the Gloucestershire Medical Society which met in the parlour of the Fleece Inn, Rodborough, and became known as the Fleece Medical Society. It was before this society in July 1788 that Parry presented his famous paper entitled ‘An Inquiry into the Symptoms and Causes of the Syncope Anginos, commonly called Angina Pectoris’ in which he clearly stated the coronary origin of the symptom. He failed to publish his observations until 11 years later (1799), a delay that also characterised his publication on exophthalmic goitre, for he had seen his first case in 1786 and correctly recognised it to be a new and distinct syndrome; publication did not take place until 1825, three years after his death, but still well in advance of Graves’ description of the disease. The first edition of Osler’s textbook of 1892 discusses exophthalmic goitre under the eponyms of Graves and von Basedow, whose description followed in 1840. The third edition of 1898 refers to it as Parry’s disease and contains a defence of Parry’s right to the eponym.

Both Parry and Graves recognised the important triad of the disease—exophthalmos, palpitations and goitre—but they failed completely to appreciate the role of the thyroid in its genesis. The goitre was regarded as a swelling or diverticulum designed to siphon off the superfluous blood in the circulation, thereby preventing a serious flooding of the brain. Graves, in fact, referred to the thyroid as ‘analogous to those tissues properly called erectile’. At the time there was no comprehension of the role of endocrine glands as organs which secreted materials into the circulation and certainly not of disease which might follow excessive secretion. The fact that these organs were known to be ductless must have contributed to this lack of comprehension. I should like to review how the light gradually dawned.

The story is sometimes said to have started with John Hunter, but his experiments on transplantation of a cock’s testis appear to have been carried out as experiments in transplantation rather than studies of the organ’s function and there is nothing to suggest that he comprehended their endocrine significance. Arnold Adolf Berthold published in 1849 the results of similar experiments[3] in which he removed the testes from four young cocks, transplanted them to another site in two of the birds, keeping two as controls in the best scientific mode. He showed that the cock’s comb developed normally in the transplanted birds but did not do so in the non-transplanted pair. To us, today, it would seem incomprehensible in the face of this evidence that the role of the testes as secreting organs was not immediately understood. Yet Berthold did not directly express this opinion. Indeed, he favoured the view that they functioned by extracting matter from the bloodstream.

In the same year (1849) Addison[4], somewhat imperfectly, described the features of the hypoadrenal state that now bears his name. In 1855 he produced a more accurate, less confused and still pertinent clinical description of the consequences of adrenal failure[5]. He, too, failed to appreciate the significance of his findings although he recognised that destruction of the adrenal glands constituted an integral part of the disease. Brown-Sequard, the eminent neurophysiologist, followed up Addison’s report with a superb set of experiments, analogous to those of Berthold, in which he showed that removal of the adrenal glands was followed by severe disease and death, and that this could be prevented by transplantation of the adrenals to another site[6]. Both he and Addison attributed to the adrenals a role in detoxifying substances which, in the absence of adrenal function, led to severe or fatal consequences.

Brown-Sequard, of course, later achieved notoriety through his publication of ‘The Pentacle of Rejuvenescence’, in which he ascribed his own youthful exuberance at the age of 72 years to regular injections of testicular extract, a practice which rapidly became fashionable and may be seen as the beginning of the organotherapy movement.

It was through the thyroid that a proper appreciation was gained of the role of endocrine glands and their secretions and Brown-Sequard’s organotherapy was given more acceptable scientific support. The story really starts with the clinical descriptions of hypothyroidism. Cretinism was one of the earliest diseases ever to be delineated, and its endemic nature was fully appreciated.
in the Middle Ages. But endemic cretinism had largely died out in Britain by 1850, the year in which Thomas Blizzard Curling read a paper before the Royal Medical and Chirurgical Society, with Thomas Addison in the chair, on ‘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’[7]. He noted the absence of the thyroid gland at postmortem examination and said: ‘I am not acquainted with any case on record in which a deficiency of the thyroid gland has been observed in the human body.’ Again, he and others might previously have been misled by the association of the cretinoid condition with goitrous enlargement, not absence of the thyroid gland. It would have required great perspicacity, indeed clairvoyance, to have appreciated at the time that an enlarged gland was functioning too little, not too much. In 1874 Sir William Gull[8] presented to the Clinical Society of London five cases of ‘A cretinoid condition supervening in adult life in women’, to which four years later Ord[9] applied the name ‘myxoedema’ in recognition of the characteristically mucoid oedema shown by the patients. This led to separation of the well-known endemic cretinism with goitre from a sporadic disorder of similar clinical presentation but characterised by absence of the thyroid gland. Hilton Fagge could claim priority in clearly recognising this distinction in a paper he wrote in 1871[10].

At about this time, through improvements in anaesthesia and advances in aseptic technique, European surgeons were beginning to carry out thyroidectomy for large endemic goitres. The Reeverdin cousins in 1883 noted the postoperative sequel of a myxoedematous syndrome in many of their patients [11] and in the same year Theodor Kocher, the Swiss surgeon, presented the results of his operations to a Berlin conference; 30 of his first 100 thyroidectomised patients developed a similar syndrome, to which he gave the name cachexia thyropriva[12]. Kocher attributed this syndrome to operative damage to the trachea with consequential disturbance of cerebral oxygenation. In the same year at a clinical presentation of a case of myxoedema to the London Clinical Society, Sir Felix Semon[13], aware of Kocher’s publication, suggested that his postoperative cachexia thyropriva, Curling’s cretinism and Gull’s adult myxoedema might all be related and he established a committee to investigate this. Ord was chairman of this committee and Victor Horsley, about whom more will be said, was a member. The famous report of the London Clinical Society in 1888[14] concluded that all three diseases were in fact related and due to deficiency of the thyroid gland. This was a stupendous conceptual advance—that a gland which was known not to possess a duct was able to secrete something into the circulation, and that this secretion was necessary for health. But, the committee concluded, there was no hope of cure; its recommended treatment included a warm room, a warm climate, tonics and so on. In 1890 Victor Horsley proposed transplantation of the thyroid gland from a sheep as a means of arresting the progress of myxoedema[15] but this idea was superseded by the far simpler solution of George Murray of Newcastle, a pupil of Horsley’s, who in 1891[15] reported the successful treatment of a patient by injection of an extract of sheep’s thyroid. Brown-Sequard’s organotherapy was on its way.

Within a very short time it was appreciated that Graves’ disease was the antithesis of sporadic myxoedema. In the latter the thyroid was usually absent; in Graves’ it was enlarged. In myxoedema there was torpor, slow pulse, dry skin, coldness, etc.; in Graves’ hyperacti-
vity, tachycardia, heat intolerance and sweating. And, most convincingly, over-enthusiastic treatment of myxoedema with thyroid extract was soon shown to reproduce the clinical picture of Graves’ disease. It was then generally accepted that the disease resulted from excessive secretion by the thyroid gland. Again, this was a remarkable conceptual breakthrough—the recognition that secretion from a gland was not only necessary for health but, if excessive, could lead to disease.

Osler included a section on ophthalmic goitre in the first edition of The Principles and Practice of Medicine. He accepted that worry, fright and depressing emotions preceded the disease in some cases but admitted that its true nature was unexplained. He lent some support to the nervous hypothesis of its cause, originally propounded in 1860 by Trouseau, and discussed the possibility of sympathetic paralysis or ‘affection of the medulla oblongata’. In retaining this view he lagged behind the growing acceptance that the thyroid gland was the primary seat of trouble. In the third edition of 1898 he cites Moebius and Greenfield who regarded Graves’ disease as a primary thyroidal disturbance (hyperthyreosis as opposed to the athyreosis of myxoedema). Osler’s reluctance to accept this view may have been influenced by statements such as those of the pathologist McCullum, who held that ‘organs hypertrophy only to meet the needs of the body, not to insulin it’[16].

Excluding chapters for textbooks, I have counted ten contributions by Osler, which are related to the thyroid[16-25]; three of these are unsigned editorials in Medical News[16-18]; there are a few case reports and clinical notes[19-23], and two substantive publications on sporadic cretinism in America, that of 1893 presented to the American Association of Physicians[24] and of 1897 to the Washington Congress of American Physicians and Surgeons[25]. It is to the earliest of his unsigned editorials that I wish to turn. Headed ‘The Thyroid Gland and Myxoedema’ it refers to the work of Professor Victor Horsley, a man with whom Osler formed a close association, about whom he was later to contribute an obituary for the British Medical Journal, and of whose biography by Stephen Paget[26] he was to write a review from his bed during his last illness in 1919.

Victor Horsley was a remarkable man, probably the best experimentalist of his time. He was, regrettably, a surgeon, but would have endeared himself to present-day Fellows of the Royal College of Physicians by the article he wrote for the Students’ Medical Society in 1883 (the year he was admitted FRCS) ‘on the evil effects of tobacco’. His later crusade against alcohol might have been less well received. The following year (1884) he was appointed Professor-Superintendent of the Brown Institute which had been established in 1871 as a result of a legacy from Mr Thomas Brown of Dublin ‘for investigating, studying and, without charge beyond immediate expenses, endeavouring to cure maladies, distemper and injuries, any quadripod or birds useful to man may be found subject to’. The Brown Institute preceded the Lister and, at that time, there were no research departments in our medical schools. It was thus an important new venture and, through a succession of distinguished investigator-supervisors (Burdon Sanderson, Greenfield, Roy, Horsley, Sherrington, Rose Bradford and Brodie), it came to exert great influence and authority on British medicine. Horsley stayed there from 1884 to 1890 and pursued three lines of research—localisation of function within the brain, protection against rashes, and the relation of myxoedema and cretinism to thyroid function. He was a member of the London Clinical Society’s Committee on Myxoeprhema and was asked by the Committee to study the function of the thyroid gland by experiment. It was through these studies that he developed the idea of treating myxoedema by thyroid gland transplantation that I referred to earlier; despite the success of injections of thyroid extract and later oral therapy for myxoedema, Horsley held on to his idea of transplantation for over 20 years.

In his obituary[27] on Horsley, who died in 1916, Osler refers to a meeting that had taken place one summer evening in 1878 with ‘two young students (of University College) whose bright eyes held the light of high promise’; one of these was Victor Horsley, whose ‘upward path’, Osler says he followed ‘from afar with an affectionate interest’.

In 1885 Osler came to London to give his Goulstonian Lectures and he visited Horsley at the Brown Institute. It is an analysis of Horsley’s work as Osler must have seen it that is presented in the first of his unsigned editorials on the thyroid. In it he says—and this precedes the report of the London Clinical Society by three years—it seems reasonable to attribute ... cretinism, myxoeprhema . . . and cachexia strumipriva—to disturbance or arrest of the functions of this gland, and the possibility of the supervision of this state will make the operation of thyroidectomy almost unjustifiable’. Osler’s dismissal of thyroid surgery was, to say the least, a trifle hasty.

Horsley and Osler met several times thereafter and remained excellent friends. In 1892 Osler attended the annual meeting of the British Medical Association in Nottingham. Horsley was then President of the Section of Pathology and with his pupil, Murray, provided what was generally regarded as the outstanding contribution of the meeting on ‘The Pathology and Treatment of Myxoeprhema’ which included a report of the first four cases cured by the juice of thyroid glands. When Sir John Burdon Sanderson later approached Osler to come to Oxford, he mentioned in his letter, presumably in an attempt to influence Osler’s decision, that Sir Victor Horsley would approve. Osler, in his obituary on Horsley, equated his technical skill as a surgeon to the brilliant diagnostic skill of Gowers. The two men clearly shared great liking and respect for one another.

Osler’s two papers on sporadic cretinism in America contained characteristically clear clinical descriptions of the disease: ‘The stunted stature, the semi-bestial aspect, the blubber lips, retroussé nose, sunken at the root, the wide-open mouth, the lolling tongue, the small eyes, half closed with swollen lids, the stolid, expressionless face, the squat figure, the muddy, dry skin, combine to make the picture of what has been well termed the “pariah of nature”’. In the first paper he quotes extensively from Horsley, provides a detailed review of the history of
cretinism and criticises the confusion of cretinism with other forms of idiocy. He attempted a survey of both endemic and sporadic forms of the disease based on the literature, inquiries made of superintendents of asylums for the insane throughout the country, 'as well as of many friends'. He found 11 cases but on the basis of such a limited and selective survey wisely avoided any firm statistics about its prevalence in America. By 1897 he had collected 60 cases and reported on the results of treatment: 'not the magic wand of Prospero, or the brave kiss of the daughter of Hippocrates ever effected such a change as that which we are now enabled to make in these unfortunate victims, doomed heretofore to live in hopeless imbecility, an unspeakable affliction to their parents and to their relatives'. How excited he would have been by the modern approach to the diagnosis of cretinism by neonatal screening and measurement of TSH on the Guthrie filter paper strips used for the detection of phenylketonuria. Neonatal hypothyroidism affects about one in 3,500 births and, it seems, this 'unspeakable affliction' may now be prevented by early detection and treatment.

Two of his case reports are of interest. The first[20] concerns an acute myxoedematous condition with goitre affecting a 23-year-old man possibly, in retrospect, a case of autoimmune thyroiditis of rather rapid onset and short duration; the history of 3½ months and lack of mention of thyroidal tenderness make a viral subacute thyroiditis less likely. Osler treated this myxoedematous patient with ergot but wisely refrains from commitment about its efficacy. Followers of Osler might have been a little confused in that year because the concurrent first edition of his textbook offers ergot as a treatment for exophal- mic goitre.

The second report[23] is entitled 'An acute myxoedematous condition, with tachycardia, glycosuria, melaena, mania and death'. He starts this report by referring to the patient of his first report who, he now says, had 'for a period of five or six months a myxoedematous condition of the hands and face, which disappeared completely'. Not a word about ergot.

The subject of the second report was a 31-year-old male who six months earlier had rapidly increased in size, to the extent that he had to get 'a completely new outfit of underclothes and outer garments'. His weight went up from 145 to 182 pounds in four months. 'Everyone remarked on the extraordinary increase in his size, and a personal friend asked him if he had been drinking as he looked so bloated'. There was a stage when he got 'queer in his head' and developed delusions, some paranoid. His face became almost purple. When Osler saw him he noted large supraclavicular pads but could not feel the thyroid. The abdomen was large and full and 'the skin presented in concentric lines on either side on the flanks and in the iliac regions the most extraordinary atrophic lineae, six on either side'. The largest 'was fully three-fourths of an inch in breadth at its widest part'. 'All were curved and presented a purplish red colour'. Osler does say 'while he was bloated and puffy, the general appearance was not at all that of a case of myxoedema'. And, of course, Osler was right, for the combination of rapidly increasing truncal obesity, supraclavicular fat pads, a swollen purple face, purplish-red abdominal striae, mania and (as later described) severe muscular weakness and glycosuria makes the diagnosis of Cushing's Syndrome ineluctable. Did Harvey Cushing, his pupil and later biographer, know of Osler's early recognition of his syndrome, more than 30 years before his classical report?

We all know of Osler's great gift of firing the enthusiasm and imagination of colleagues and students. He influenced many physicians, some of whom were later to become eminent endocrinologists—Harvey Cushing, William S. Halsted, James H. Means.

David Marine was another of these[28]. He entered Johns Hopkins Medical School in 1900 to study zoology and chemistry, and the Hospital in 1901 as a medical student. Here he fell under Osler's spell. Dr Josip Matovinovic, of Ann Arbor, writes that David Marine confided to him that he was influenced by Osler's brilliant education, general and professional, his kindness and his dignity[29]. Osler suggested to Marine that he should institute a study of pregnant women and treat them with iodine or dessicated thyroid. This early interest in the thyroid burgeoned when Marine was appointed to Cleveland, a famous epicentre of endemic goitre. Writing about this to Matovinovic in 1968, Marine, then 88 years old, described how on the morning he arrived in Cleveland from Baltimore, walking from his hotel to the hospital he saw many dogs with swollen necks; he stopped three or four of them and found that the swelling was due to enlargement of the thyroid gland. This decided him to follow up the early interest in goitre induced by Osler's influence, and to make this his major research. Iodine treatment of goitre had long been practised in Europe (Switzerland, Germany, France) but had fallen into disrepute because of the high incidence of iodism and, especially, of hyperthyroidism due to excessive iodine intake (Jod Basedow). Marine spent six months in 1913-14 with Theodor Kocher who strongly opposed the use of iodine in goitre therapy and whose prestige at that time was such that the practice was all but abandoned. Despite this Marine remained convinced as a result of his own experiments that endemic goitre was due to absolute iodine deficiency.

Marine initiated the first proper goitre prevention trial in Akron, Ohio, from 1917 to 1920, and showed conclusively that iodine was able to prevent endemic goitre and, indeed, cure many of those that had already developed. By using small doses of iodine he minimised the incidence of iodism and obviated the hazard of hyperthyroidism. It has been estimated that 200 million people throughout the world currently suffer from endemic goitre, often with cretinism or the neurological syndrome of iodine deficiency. Through the use of injections of slowly-released organic iodide-containing oils much of this is now being prevented, a benefit we can attribute directly to David Marine, in whose early work we may discern the guiding hand of Osler.

In his writings on the thyroid, Osler showed all of his familiar characteristics. He was quick to spot the importance of research that was going on in the field, especially in Horsley's laboratory; he was able to place it in its
historical perspective and to discern the connection with cretinism, his clinical descriptions of which could not be bettered today; he spoke and wrote about it only after his own reading, observation and surveys had provided a sound and thoughtful basis for speculation. His contribution to the field was not large but it exemplified his oft-quoted statement: ‘That man can interrogate as well as observe nature, was a lesson slowly learned in his evolution’.

This article is based on the Oslerian Oration delivered to the Osler Club of London in July 1984.

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Book Review

Advanced Medicine 20. Edited by Anne Ferguson. Pitman Publishing, London, 1984. Price £20.

I enjoyed reading this book. The Advanced Medicine Conferences organised by the College are an important part of its educational activities, particularly so since there is now a tradition of rapid publication in book form. Advanced Medicine 20 contains papers presented at the meeting held in London in February 1984, and has been edited by Dr Anne Ferguson of the Western General Hospital, Edinburgh. The eight sections cover inflammatory bowel disease, general gastroenterology, the prevention of cardiovascular disease, chronic disease in adolescence, clinical immunology, an assessment of four ‘new’ diseases, four papers on cancer management and finally two papers on breast cancer.

In trying to assess the value of this book for the general physician I found myself looking for discussions on controversial or difficult areas of current practice; for articles which encourage ‘lateral thought’ (by discussing a topic in a field outside my own interests but leading me to new thoughts about my own patients); for comprehensible reviews of the ‘state of the art’ in current research fields; and for ‘interface’ articles exploring the fascinating ways in which different fields within medicine interact with each other.

From these standpoints this volume has much to commend it. Clearly, the comments that follow are personal reflections, but I have tried to give a flavour of the contributions.

Of the two sections on gastroenterology, I particularly enjoyed firstly the paper on the varied presentations of coeliac disease which illustrates neatly how textbook descriptions of disease can become out of date, and secondly the chapter on the oesophagus as a cause of chest pain which one might characterise as a new explanation for an old symptom. There is a comprehensive review by Misckiewicz of H2 antagonist treatment for peptic ulceration, and the general points made by Lennard-Jones in his discussion of corticosteroid and immunosuppressant treatment in inflammatory bowel disease are sure to be of interest to physicians in other specialties.

From a total of five papers discussing the epidemiological evidence for the value of preventive measures in cardiovascular disease, one would have hoped that a clear picture would emerge of the pathological processes which it is hoped to prevent, and of the ‘best buys’ from the candidates for programmes. However, this is not the case and one has instead a thought-provoking article about pathogenesis, and two somewhat opposing views about coronary heart disease screening from Professor Oliver and Professor Marmot. I think the article upon mild

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