RES MEDICA
Journal of the Royal Medical Society

Parry and Parry's Disease

R. I. Legge

Abstract

THE MAN

In 1778 the Charter of Incorporation was granted by George Ill to the presidents and associates of the Medical Society of Edinburgh, confirming Robert Freer, James Melliar, Andrew Wardrop and Caleb Parry in their office as Presidents. Caleb Parry, whose name appears here, became a highly esteemed practitioner at Bath and like Heberden acquired a lifelong habit of taking notes. He described the first recorded case of facial hemiatrophy in 1814, of congenital idiopathic dilatation of the colon in 1825, and in 1786 he left an account of exophthalmic goitre so complete and original that it more justly entitles him to the honour of its discovery than either Flajani in 1800, Graves in 1835, or von Basedow in 1840.

Caleb Hillier Parry was born on October 21st 1755, at Cirencester, near Gloucester, where his father Joshua was a non-conformist minister. His early education was at the grammar school in Cirencester, where he met Edward Jenner: and the latter dedicated his epochal Inquiry in the Causes and Effects of the Variolae Vaccinae" to "C. H. Parry, M.D., at Bath, My Dear Friend." At the age of 18, Parry became a student of medicine at Edinburgh, in the days when William Cullen dominated the scene. Parry spent two of his undergraduate years in London, but when he returned in 1777, he was elected a president of the Medical Society of Edinburgh. And it was during his term of office that the Royal Charter was achieved, an honour which remains unique for an undergraduate society.

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, May 1961, 2(4): 33-37
doi: 10.2218/resmedica.v2i4.363

PARRY AND PARRY'S DISEASE

By R. I. LEGGE

Based on a Dissertation read before the Royal Medical Society on Friday, 18th November, 1960.

THE MAN

In 1778 the Charter of Incorporation was granted by George III to the presidents and associates of the Medical Society of Edinburgh, confirming Robert Freer, James Melliar, Andrew Wardrop and Caleb Parry in their office as Presidents. Caleb Parry, whose name appears here, became a highly esteemed practitioner at Bath and like Heberden acquired a life long habit of taking notes. He described the first recorded case of facial hemiatrophy in 1814, of congenital idiopathic dilatation of the colon in 1825, and in 1786 he left an account of *exophthalmic goitre* so complete and original that it more justly entitles him to the honour of its discovery than either Flajani in 1800, Graves in 1835, or von Basedow in 1840.

Caleb Hillier Parry was born on October 21st 1755, at Cirencester, near Gloucester, where his father Joshua was a non-conformist minister. His early education was at the grammar school in Cirencester, where he met Edward Jenner: and the latter dedicated his epochal "Inquiry in the Causes and Effects of the Variolae Vaccinae" to "C. H. Parry, M.D., at Bath, My Dear Friend." At the age of 18, Parry became a student of medicine at Edinburgh, in the days when William Cullen dominated the scene. Parry spent two of his undergraduate years in London, but when he returned in 1777, he was elected a president of the Medical Society of Edinburgh. And it was during his term of office that the Royal Charter was achieved, an honour which remains unique for an undergraduate society.

At the end of the same year in which he graduated M.D., 1778, Parry settled in Bath, which city he hardly left even for a day.

At the beginning of his career in Bath, Parry found that the practice of medicine did not demand all his time, so he devoted his leisure to the collection of fossils. Gradually, however, he acquired a very large practice and increasing occupation in more human relics prevented further progress in his work on fossils. It would appear appropriate then that Parry, the most prominent physician at that fashionable health resort, should have attended John Hunter when he stayed in Bath in 1785 and suffered some anginoid symptoms; but the great authorities have found no evidence for this.

So Parry must have been a cultivated man with wide interests; an omnivorous reader, no mean metaphysician and keenly interested in natural history and its practical applications. His portrait shows him to have been remarkably handsome; he must have been a charming personality. He died on March 9th, 1822, some five years after being inflicted with a right hemiplegia, and aphasia.

THE DISEASE

Definition: Hyperthyroidism connotes hyperactivity of the thyroid gland and hypersecretion of its hormone; thyrotoxicosis is the clinical synonym. The structural correlate of this excessive secretion is hyperplasia of the thyroid epithelium. Other more or less independent components are the ocular changes and a group of nervous manifestations; and both of these may persist virtually unchanged after the hyperthyroidism has been eradicated. In 1935, Harrington and his co-workers established the fundamental fact that the glandular secretion in hyperthyroidism, though excessive in amount, is not qualitatively different from normal.

The comparative simplicity of the thyroid gland is evidenced by its secreting but one hormone—thyroxine—which regulates the rate of metabolic activity within the cells of the body.

Etiology: Numerous factors have been put forward to explain what is still unknown. Firstly, it is possible to produce all the clinical features of thyrotoxicosis, with the notable exception of exophthalmos, by administration of thyroid extract in excessive amounts. Secondly, partial extirpation of the gland leads to improvement of some or all of the symptoms and signs. But since psychical trauma, sexual maladjustment and infection frequently precede or initiate the symptoms, it seems likely that the normal relationship of the thyroid and the pituitary is disturbed in thyrotoxicosis.

Incidence: Thyrotoxicosis may occur at any age, but is most commonly seen during the third and fourth decades. And there appears to be a general predominance of female patients in all the series.

Clinical Features: These are legion, and perhaps it is not inappropriate to set out first those factors which led Parry and many others to the idea of such a syndrome. He describes his first case of *Enlargement of the Heart in connection with Enlargement of the Thyroid Gland* in 1786, and this includes references to many interesting features: the syndrome followed an infection; it began in the fourth decade; the patient suffered violent palpitations; she had a tachycardia of 156 per minute and the pulse showed an irregularity which to-day would be termed atrial fibrillation; she suffered dyspnoea indicative of pressure symptoms; she subsequently developed increasing goitre and exophthalmos; and the author says that she appeared agitated and distressed. This is surely a remarkable collection of signs and symptoms for the year 1786. But it was some 27 years later that Parry came to a full realisation of the disease, when he stated that his attendance on three similar cases in 1813 suggested to him some connection "between the malady of the heart and the bronchocele." Robert Graves, who was Physician to the Meath Hospital in Dublin, published his findings entitled *Newly Observed Affection of the Thyroid Gland in Females* in 1835; and Carl von Basedow published his findings in what was probably the first autopsy in a case of recognised exopthalmic goitre in 1848. From Basedow's time, until the end of the nineteenth century, attention was concentrated mainly on exophthalmic goitre as such, but some of Parry's cases did not exhibit exophthalmos; so Parry must have realised that there were two types of thyrotoxicosis.

An acute onset with or without an initiating factor is rare. The patient is more likely to complain of some vague indefinite feeling of anxiety, restlessness, or irritability towards the children. It is often held however that the appearance of a vivacity and dynamic spontaneity is but an accentuation of pleasing feminine characteristics, and the slight exophthalmos gives a glint to the eye which is not unattractive. But the fully developed case will present

with thyroid enlargement, exopthalmos, tachycardia with palpitations, tremor of the hands, fatigue and loss of weight. The possibility of thryrotoxicosis without thyroid enlargement raises the question of ectopic thyroid tissue, e.g., in the retrosternal position where it may cause respiratory embarrassment from tracheal compression.

(a) Eye Signs: The numerous ocular abnormalities bring to mind more names from the past. Von Graefe is remembered by the physician for his discovery of lid lag, a separate entity from exophthalmos. The problem of exophthalmos is not fully understood but it does seem certain that the sympathetic nerve sensitivity produced by the excess of thyroxine can lead to contraction of the intraorbital smooth muscle, which will produce exophthalmos and may obstruct the venous return, so giving rise to oedema of the orbital muscles, which would accentuate the position. Jeffroy noticed the inability to contract the occipito-frontalis muscle as evidenced by the absence of wrinkling of the forehead ; whilst Stellwag thought the absence of blinking significant ; and Möbius found inability to sustain convergence a feature of the disease.

(b) Cardoivascular Signs: Parry's inclusion of the heart within the syndrome leads directly to these. The tachycardia which is almost invariably present persists during sleep and is thus differentiated from the functional variety, for in thyrotoxicosis the raised metabolic rate which is inherent in the disease demands more oxygen, and this, together with the direct stimulatory action of thyroxine on the heart, is bound to produce a marked tachycardia. The raised pulse pressure is accounted for by the decrease in the diastolic pressure with a comparatively normal systolic pressure. The young patient will compensate for this, but in the older patient it will often lead to decompensated cardiac failure, with atrial fibrillation. The ECG will show characteristic changes in 30% of cases and ECG examination must be carried out pre-operatively to assess the state of the myocardium. A systolic bruit will be heard over the gland if the latter is very vascular, and may be possible to palpate this—the feeling of a bag of worms.

(c) Locomotor Signs: The patient may notice the tremor when pouring out the tea, but the clinician may best elicit the tremor by placing a sheet of paper on the patient's outstretched hand. There may be weakness of the skeletal muscles, and a true myasthenic element responsive to neostigmine has been reported. This weakness may of course be due to the marked loss of weight which often occurs as a result of an excess of catabolism over anabolism. This accounts for the patient's voracious appetite, which is often insatiable.

(d) Endocrine Signs: Disturbances of mentstruation and pregnancy are to be expected in any endocrine upset which involves the whole of the body's metabolism. Though menstruation may be normal, it is often suppressed partially or completely. It is physiological for the thyroid to enlarge during pregnancy, and pregnanacy has been named as a precipitating factor ; but when pregnanacy supervenes in an established case of hyperthyroidism, the condition may be unaltered or even ameliorated.

(e) Other manifestations: Excessive perspiration may be troublesome, and on shaking hands with the patient, it may be possible to reach a diagnosis at the first consultation ; for in thyrotoxicosis the palms are warm, as distinct from the cold sweat of the anxiety state.

(f) Laboratory Investigations: The essential action of the thyroid gland is to increase the metabolic rate of the cells throughout the body. Thus an increase in the Basal Metabolic Rate is inherent in the diagnosis ; but efforts to achieve the basal state are so seldom fruitful that this procedure is not adopted nowadays. The degree of lowering of the serum cholesterol is significant : the normal

range of 150-220 mg% is usually lowered to 80 mg%. Signs of demineralisation may be seen on skeletal x-rays, and this negative calcium balance is confirmed by the finding of excessive calcium loss in the faeces with normal levels of serum calcium and phosphorus, but the serum phosphatase values are often raised. Since thyroidectomy alleviates this, and the reverse is found in myxoedema, it must be assumed that thyroxine exerts a direct effect upon the metabolism of calcium and phosphorus. Most cases of thyrotoxicosis can be confirmed by the finding of a raised serum protein-bound iodine, but it is not every laboratory that has the facilities for this determination. A small diagnostic dose of radio-active iodine—5 microcuries—will show whether the gland is hyperactive, and there is no real hazard in such a small dose.

Treatment: Experience has shown that the course of thyrotoxicosis, which untreated is a series of exacerbations and remissions, may be favourably modified by the use of small doses of iodine, and be interrupted temporarily or permanently by the administration or thiourea or its derivatives, or of the salts of radio-active iodine, or by subtotal thyroidectomy. In the last decade wide practical experience has been gained in the use of antithyroid drugs and radio-active iodine, and more adequate medical preparation has improved the results of surgery. Consequently each case can now be considered on its own merits, and one therapeutic route tailored to it.

(a) *Antithyroid drugs*: It has been shown that drugs of the thiouracil series inhibit the combination of iodine with tyrosine. Carbimazole was introduced as producing fewer side-effects than methylthiouracil, particularly to combat the production of agranulocytosis by the latter. Carbimazole is, however, slower in action and is usually given in one tenth the dosage of methylthiouracil as it has been reported to be ten times as effective. Potassium perchlorate on the other hand is a rival and more recent antithyroid preparation which inhibits the iodine-trapping mechanism of the thyroid gland. It is a simple inorganic compound and is therefore unlikely to sensitise the haemopoietic system. A full investigation into these various drugs has been carried out by Crookes in Glasgow. One of his series involved the following four daily drug dosages — (1) 600 mg methylthiouracil; (2) 600 mg potassium perchlorate; (3) 1000 mg potassium perchlorate; (4) 60 mg carbimazole. The results of this showed that the higher dosage of potassium perchlorate was the most effective and was attended by the least side-effects; whilst carbimazole was not as effective in one tenth dosage as methylthiouracil. In addition, no evidence could be found that potassium chlorate increases the vascularity of the gland at surgery. It would seem then that potassium perchlorate may replace carbimazole as the antithyroid drug of choice, even in those cases which undergo a course of medical therapy prior to surgery.

(b) *Surgery*: The surgical approach is chosen on certain definite indications. The patient may choose it in preference to 12 months' drug therapy which cannot guarantee success; or she may be considered unlikely to persist with the prolonged regimen of medical treatment. Signs and symptoms of pressure are an indication for surgical intervention, and operation may be a suitable alternative when sensitivity to the drugs arises. Cases of secondary thyrotoxicosis are less likely to respond to drugs, and these together with those who do not respond to a prolonged medical regimen are candidates for surgery. Subtotal thyroidectomy, removing 7/8 of the gland, is not a hazardous procedure in experienced hands, but its few dangers should be borne in mind, particularly if a repeat operation is being considered. The possibility of interference with the recurrent laryngeal nerve necessitates direct laryngoscopy both before and after operation. A careful dissection to leave a posterior layer

of the gland covering the parathyroids will obviate any disturbance of the blood supply to the latter. Severe haemorrhage and thyroid crises are distinct rarities nowadays. The specific response of the thyrotoxic patient to iodine as a pre-operative measure is a remarkable phenomenon. For 5 - 10 minims of Lugol's iodine three times a day will produce a rapid decline in symptoms, slowing the pulse, increasing the body weight, and decreasing the metabolic rate. But its benefit is only felt for about two weeks. Thus iodine has no effect on the duration or progress of the disease, and there is now experimental evidence to show that iodine merely prevents the thyroid from giving a maximal response to the stimulus of thyrotrophin.

(c) *Radio-active Iodine:* Deep x-ray therapy is no longer recommended, but good results are now being achieved with I-131 ; for the hyperplastic gland shows such an avidity for the radio-active iodine that a therapeutic concentration is more than easily obtained without damage to the rest of the body. Gene mutation and carcinogenesis are theoretical possibilities which have not yet been seen in man, but are factors which usually preclude the use of radio-active iodine during the reproductive years of life.

Hyperthyroidism is one of the key problems of internal medicine, for in one direction it overlaps toxic nodular goitre, and the relationship of primary to secondary thyrotoxicosis is still not understood. It also merges into the anxiety states, autonomic imbalance and neurocirculatory asthenia. Exophthalmos is still an unsolved problem. And perhaps there may even be some inkling of truth in the contention that hyperthyroidism should be called *Parry's disease.*