THE INTEGRATION OF THE ENDOCRINE SYSTEM

I still well remember, almost as if it were yesterday, the thrill of excitement which went through the Physiological Laboratory at Cambridge when on January 30th, 1892, a paper appeared entitled "Remarks on the Function of the Thyroid Gland; a critical and historical review". It was by Victor Horsley, whose name up till then was only known to me by a drawing he made for Schäfer's *Histology*. We eagerly awaited the second part of that paper which appeared a week later. Instinctively we felt that the door was open to a long avenue of discovery. And we were right.

Papers like that do not come out of the blue. Horsley had been working at the subject since 1884. It is perhaps worth while briefly to recall the steps which led up to that paper.

We all know that the story begins with Gull's description of the "cretinoid state" in 1873, which four years later Ord christened myxoedema. In 1882 Kocher and Reverdin independently noted a similar condition following thyroidectomy for

goitre, but attributed it to damage to the trachea. Next year, however, hearing of the English cases of myxoedema, they concluded that the removal of the gland was responsible, but only by damage to nerves. In that year the Clinical Society of London appointed a committee to investigate the subject, and of this committee Horsley was a member. His share was to investigate by experiment, for which his training as a physiologist and a surgeon equipped him admirably. It is of interest to note that his first impression led him to say "the question arises whether we have not to do with the simple case of total removal of an excretory organ". Looking at the bloated appearance of a patient with myxoedema, one can easily understand that impression. A similar idea was enunciated in 1892 by Abelous and Langlois as to the function of the adrenals on slighter grounds. But Rolleston on reviewing the evidence in his Goulstonian Lectures in 1895 suggested that Addison's disease was an atony due to the loss of an internal secretion, a few months before Schäfer and Oliver prepared an active adrenal extract. From all this we can see how slow was Claude

Bernard's conception of internal secretion to permeate physiology and medicine. Even when Schiff in 1884 showed the benefits conferred by transplantation of a thyroid into a thyroidectomised animal, the significance of his observation was missed, though he underlined it with the remarkable sentence "it would be interesting to know whether an emulsion of thyroid gland would not have an analogous effect". We may presume that the effects of transplantation might have been interpreted as the replacement of a missing excretory organ, but the failure to follow up Schiff's further suggestion for six years shows how foreign the idea of internal secretion was to scientific thought of the day. Then in 1890 Vessale gave intravenous injections of thyroid extract to thyroidectomised dogs with beneficial results. The credit for the clinical application of this must be given to G. R. Murray, who had been House Physician at University College Hospital and met Horsley then. Murray wrote to Horsley, making the suggestion that myxoedema might be successfully treated by similar injections, but Horsley was not at first favourable to the idea. Indeed, he

said that the results so far obtained might have been caused by injection from any other tissue. Murray, at a meeting of the Northumberland and Durham Medical Society, showed a patient with myxoedema on whom he proposed to try this treatment. He received a douche of cold water, and later actual opposition. In no way deterred, he carried out his idea, with what success is now common knowledge. Horsley was converted, and a year later Hector Mackenzie and others simplified the treatment by giving thyroid by the mouth, thus establishing the discovery beyond cavil.

In 1894 Horsley was awarded a medal by the Royal Society "for his investigations relating to the physiology of the nervous system, and of the thyroid gland". These were of course two separate lines of enquiry, but my purpose today is to show under the title of "The Integration of the Endocrine System" how much more closely these two subjects are related than was imagined at that time.

It seems to me particularly appropriate to do so in this College, which has played so large a part in elucidating these problems, largely owing to

the work and inspiration of Sir Edward Sharpey-Schäfer, whose recent passing away at a ripe old age, full of honours, leaves a notable gap in our ranks. For it was here that he with Oliver discovered the effects of adrenal and pituitary extracts; it was here that Bayliss and Starling discovered secretin, and it was here that Starling did the work that led him to enunciate the theory of hormones in his Croonian Lectures of 1905. Appropriately enough it was to you that Professor T. R. Elliott came from Cambridge, already distinguished for his researches on adrenalin. And to come down to recent days, it was here that Professor Harington proved the chemical structure of thyroxin. It is a record of which any institution may indeed be proud.

I would stress three recent lines of advance which are leading to a clearer conception of the integration of the endocrine system:

1. The diencephalon (particularly the hypothalamus) has been conclusively shown to be the nervous structure concerned with the expression of the emotions.

2. The pituitary, which is so closely associated

with the diencephalon, has become recognised as the leader of the endocrine orchestra.

3. It is now realised that all nervous impulses have a chemical mediator between the neuron and the tissue cell, and indeed between one neuron and another.

I shall proceed to expatiate on each of these three points in turn, and shall hope to show how they are leading to a new conception of the unity of functioning of the body.

1. From the experiments of Sherrington it has been known that if the higher parts of the brain be severed from the diencephalon in a dog, the animal responds to ordinary stimuli in an exaggerated way by an explosion of what he terms "sham rage". Cushing has reported similar explosions in a patient suffering from a cerebral tumour which similarly destroyed these connections.

The ravages of lethargic encephalitis on this part of the brain may not only damage the statics of the body but may profoundly affect the temperament and behaviour of the victim.

In these instances we are dealing with partial lesions which no doubt have an irritative effect on the remainder. But I will now refer to an extraordinary case under the care of Professor Naish[1] of Sheffield, in which a teratoma involving the whole of the hypothalamus completely blotted out the normal expression of the emotions; in Hughlings Jackson's nomenclature, a destroying rather than a discharging lesion.

A girl aged 10 came under observation with the following history. From birth she had been of an unusual temperament; the contrast being made more manifest to her parents after the birth of the second child who had normal reactions. As an infant she used to sleep considerably longer hours than the average for her age, and during her sleep she would never move. As she grew older it was noticed that she was very undemonstrative in the expression of emotions; she never showed joy or excitement. She never showed fear in the usual way, although she apparently felt fear, especially of loud noises, darkness, solitude, and certain persons. She would tell her parents that she was afraid, but her expression and voice were calm.

What was taken to be anger was shown by sudden refusal to comply with suggestions.

With this absence of expressiveness she yet appeared to have strong feelings, but she displayed none of the usual childish graces and her manners to chance callers were apparently rude. In this respect she appeared to be incorrigible and even unconscious of defect. She was very impenetrable to suggestion, and was what her parents called "strong-willed".

All her life she was liable to frequent sudden rises of temperature followed shortly by sudden falls. Her mental powers were good and she had an excellent memory. Her balance when walking or standing was never very good; when she tripped she seemed to have less than the usual powers of recovery and would fall flat on the floor.

Three years before her death it was noticed that she was drinking heavily and passing large quantities of pale urine both day and night. This was associated with a poor appetite for solid food and wasting; from this time she appeared not to grow at all. The polyuria continued up to about five weeks before her death and then ceased somewhat

abruptly. There was no sugar in the urine. It was noticed that her emotional reactions were further diminished; she never shed a tear. Some three or four weeks before her death she found that she was unable to walk, and spontaneously surmised that she was going to die; she said in an indifferent tone, "Well, we can't help it".

She appeared to feel the cold intensely, and would do all she could to huddle in front of a big fire. This sensation steadily became worse and during the summer of 1933, which was exceptionally hot, she would wear an overcoat at meals. This feeling of cold ceased abruptly some two or three weeks before death. During this same summer it was noticed that she had begun to fall asleep in unusual places. Her powers of vision were lost apparently quite rapidly about five weeks before her death.

On admission she was remarkably drowsy. The pupils were equal and reacted normally. No cranial nerve paralysis was found; the reflexes were normal. There was marked pallor of the central area of each optic disc. She became comatose and died a few days later.

At the post-mortem a firm tumour with a smooth lobulated surface was found projecting from the base of the brain in the hypothalamic region behind the optic chiasma. The body showed no other abnormality except for enlargement of the mesenteric glands with evidence of tuberculous infection. The pituitary gland appeared to be normal.

Microscopically the tumour consisted of irregularly scattered epithelial elements in a connective tissue stroma. Bands of smooth muscle formed a prominent feature. The epithelial elements were frequently in the form of glandular spaces bounded by columnar cells. In one area there was an arrangement of epithelial cells closely resembling foetal glomeruli. In short it was a teratoma.

She therefore had temporary symptoms presumably due to pituitary compression, such as polyuria, disturbances of temperature and much drowsiness, but the most striking feature of the case was the blotting out of nearly all normal emotional expression.

There is then abundant evidence on the first