Scope of the Essay.

Endocrinology may be defined as the science of the ductless glands, and is thus a branch of physiology. I have not attempted, in this essay, to cover the history of endocrine therapy, nor have I searched for early references to diseases such as diabetes mellitus or cretinism, diseases which were described long before they were shown to have any association with the endocrine system. Only those clinical observations which have contributed to our knowledge of the physiological role of the ductless glands, have been mentioned.

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Endocrinology may be defined as the science of the ductless glands, and is thus a branch of physiology. I have not attempted, in this essay, to cover the history of endocrine anatomy, nor have I searched for early references to diseases such as diabetes mellitus or cretinism, diseases which were described long before they were shown to have any association with the endocrine system. Only those clinical observations which have contributed to our knowledge of the physiological role of the ductless glands, have been mentioned.

The work is not intended to be an exhaustive review of the subject, but rather an outline, with comments on a selected number of important pieces of observational and experimental research. It is based upon original articles written in English, French and German. Unfortunatley, some early articles are not available in the libraries to which I have had access, so that occasionally I have had to resort to quoting another author's account of the article in question, the source used has been given in each case.

One standard textbook of physiology states "the subject of endocrinology belongs entirely to the twentieth century". (Lovatt Evans 1947). If this view is
correct, most of the following essay is superfluous, but I believe that the foundations of endocrinology were laid during the nineteenth century and that the discovery of secretin by Bayliss and Starling marked the end of the early history of the subject. It is true that the term "endocrinology" was not used until the present century and that the concept of the ductless glands forming a specialised system with complex inter-relationships, is of very recent origin. Nevertheless, it was during the eighty years from 1827 to 1907 that the function of the endocrine glands was removed from the realms of speculation and placed upon the surer foundation of experimental evidence.

It is not my purpose to deal with the speculations of the early anatomists, which were really working hypotheses, untested by further experiment or observation. I have described the development of our knowledge on each gland separately, because not until the twentieth century were the individual glands recognized as a part of a new system comparable in importance to the older systems such as the cardio-vascular and respiratory systems.

I hope to demonstrate at the end of this essay that progress in endocrine illustrates to some extent an increasing application of the scientific method.
THE THYROID GLAND.

The earliest record that I have found of any published contribution to the physiology of the thyroid gland, is an article by King in the Guy's Hospital Reports (King 1836), with a note added by Sir Astley Cooper. King described how, by compressing the substance of the thyroid he was able to demonstrate the escape of colloid into the draining lymphatics. He seems to have been influenced by the writings of Morgagni, who had suggested that the lymphatics might be the route via which secretions of the thyroid were carried away. The experiment could be criticised on the grounds that colloid was not seen to escape without the application of mechanical force. King maintained that the neighbouring strap muscles, during the process of mastication, performed this squeezing action. He examined the "thyroid juice" chemically but did not discover any iodine. He commented upon the huge blood supply of the thyroid and realised that this was more than would be required for the nourishment alone, hence he suggested that it might one day be possible to show that "a material is formed, partially stored in reserve, and is supplementary to functions in the course of the circulation".

In the note following this article, Cooper showed by chemical analysis that thyroid fluid contained albumin. He noted the anatomy of the thyroid and nature
of the thyroid juice in humans and several species of mammals. He then described how, in 1827, he performed a thyroidectomy in two ten-week old puppies. These animals survived the operation, suffering from what he called "common irritation". It is interesting to note that Astley Cooper was sufficiently modern in his scientific method, to use a control - a puppy of the same litter remained unoperated upon for comparison. Post mortem examination showed that the thyroids had been removed to the author's satisfaction, but he observed that an "absorbent gland" on each side of the neck was enlarged. It seems likely especially in view of the later fatal results following experimental thyroidectomy, that these were, in fact, fragments of accessory thyroid tissue which had hyper-trophied.

An appendix at the end of this first volume of the Guy's Reports, quotes from the lecture notes of one of Cooper's students. Apparently, as early as 1798 he (Cooper) had carried out thyroidectomy on a dog and a donkey with "peculiar results". This is the earliest record of the removal of a ductless gland experimentally.

For several decades after this various experimenters performed thyroidectomies on animals, some with consistently fatal results. No real advance was made and there was no evidence to refute the opinion of several
workers that the thyroid had no function. The clinicians were meanwhile contributing to the subject. Graves had described a disease of the heart in which the thyroid gland was enlarged. In the 1884 edition of his "Clinical lectures in the practice of medicine" (Graves 1884), he gave an account of three young women each presenting with an enlarged thyroid, palpitations and increased force of the heart beat. Graves was amazed to find that in one of these girls, he could hear the first heart sound distinctly at a distance of four feet from the patient. He describes the exophthalmos, the nervous symptoms and the occurrence of dysphagia, which he rightly attributed to the thyroid enlargement, and distinguished it from globus hystericus. Graves observed that the symptoms of the disease varied in severity with the size of the gland, and he maintained that the enlargement was due to hypertrophy of the glandular tissue. It should be remembered, however, that he did not realize that the symptoms were caused by hypersecretion or even by the thyroid at all.

Cretinism had been recognized since ancient times, and was still surrounded by much folk-lore and superstition. (Rolleston 1936). Hilton Fagge in 1871 anticipated that cretinism would be discovered in adults. (Hilton 1871). This rapidly proved correct, for two years
later Gull described 5 cases of the condition in a report to the Clinical Society of London entitled "A cretinoid condition supervening in adult life in women". (Gull 1874) Although Gull's name became attached to this disease, in my opinion the real credit for our understanding of the condition must go to W.M. Ord who re-named the disease "myxoedema" and demonstrated 5 cases with clinical features which were typical. Each case showed similar pathological changes of the thyroid on post mortem examination. It was this correlation of the pathological findings with the clinical condition which was the mark of a great discovery which was to add to our knowledge of thyroid physiology. (Ord 1878).

In the Brown lectures of 1884, Sir Victor Horsley described experiments on Macaque monkeys. (Horsley 1885) Thyroidectomy in these animals was followed by temporary loss of appetite, increasing fibrillary tremors and anaemia. At post mortem examination much mucin was found deposited in the connective tissues, changes similar to those of myxoedema in humans. Horsley presented the symptoms and signs of cretinism, myxoedema, cachexia strumipriva (Kocher 1883), and cachexia after thyroidectomy in animals, in tabular form, so that the striking similarity of the four conditions was revealed for the first time. Horsley concluded the cause of the symptoms in each case was...
identical - namely loss of thyroid function. He did not commit himself far on the physiological role of the gland except to say that he believed that it was intimately concerned with mucin metabolism and haemopoiesis. This work of correlation confirmed that the thyroid performed some important function in the organism's metabolism.

In 1890 Horsley quoted the results of an experiment of von Eiselberg, in which transplants of thyroid tissue had been grafted in the mesentery of thyroidectomised animals. 8 of the 9 animals died, but in the survivor it was noted at a subsequent post mortem examination that the graft had become vascularised, whereas this had not occurred in the (eight) fatal cases. Horsley concluded from this that grafting of glandular tissue was feasible as a therapeutic measure provided that vascularisation took place. He advocated the use of transplants in myxoedema, recommending sheep's thyroid because it was most like human tissue. (Horsley 1890). Horsley was thus the first person to suggest rational medical treatment in endocrinology, although he actually conceived of replacing a tissue rather than an active principle. His suggestion was quickly taken up, with success, by Bettencourt and Serrano (see Murray 1891).

In the following year Murray reported an amazing success in the treatment of a myxoedematous
woman by hypodermic injections of a glycerine extract of sheep's thyroid. (Murray 1891). Murray had noted a very significant point in the results of Bettencourt and Serrano. These authors had observed an improvement in the clinical features as early as the day following operation. Now Murray correctly argued that vascularisation could not have taken place so quickly, hence the beneficial must be due to an active principle in the gland which had escaped into the surrounding tissues and been absorbed.

I consider this to be the outstanding discovery in the history of the thyroid gland for two reasons. An endocrine disorder had been treated for the first time with undoubted success, and secondly, an important principle in replacement therapy was established - namely that the active principle and not the glandular tissue itself was the important factor in treatment. This naturally lead to the realization that the thyroid secreted an active substance without which the body cannot be regulated.

Horsley's great work of correlation and Murray's demonstration of replacement therapy thus clarified the subject of thyroid hyposecretion. Horsley reviewed the theories of the functions of the thyroid at this stage - he contended that the gland had a secretory action but also an action on the blood. (Horsley 1892).
Attention next swung to Graves' disease, the aetiology of which was still quite unknown. Kocher had shown the beneficial effect of thyroidectomy upon this condition. While his results were widely accepted and his technique applied, the idea that the thyroid was the primary cause of the trouble had few supporters. Byrom Bramwell had pointed out the contrasting features of myxoedema and Graves' disease. (Bramwell 1893)

However, in 1893 Murray reported in the Lancet that his original myxoedematous patient now cured, had been experiencing hot flushes and attacks of tachycardia which were abolished by reducing the dose of thyroid extract. Murray remarked upon the similarity between the symptoms of overdosage and those of Graves' disease, mentioned Bramwell's article and put forward the suggestion that thyroidectomy by removing the source of oversecretion was relieving the symptoms. (Murray 1893)

Professor Greenfield of Edinburgh carefully examined the thyroid glands in six cases dying of Graves' disease, and described the pathological changes of hyperplasia, adding that, in his opinion, the gland had an exaggerated but probably perverted secretion. He thus supposed that there was a qualitative as well as a quantitative change in the secretion of the thyroid - a
fairly natural mistake, since it would be hard to realize that a normal substance, even in excess, could produce such toxic effects. (Greenfield 1893). Up to that time the pathology of the thyroid in Graves' disease had been ignored since the disease was thought to be a disorder of the central nervous system. However, Greenfield looked in the right place and was rewarded.

He summarised the evidence in favour of the theory that Graves' disease was associated with an oversecretion of the thyroid. The pathological changes of hyperplasia and the beneficial effects of surgery were very suggestive. The toxic pathological changes in the nervous system and the toxic nature of the signs and symptoms both pointed to the release of some toxin; while the remarkable contrast between Graves' disease and myxoedema noted by Bramwell, the effect of overdosage of thyroid extract in myxoedema and the effect of the extract on normal persons, tended to add further confirmation.

Additional evidence for the theory was provided by Auld who demonstrated that thyroid extract administered to patients in the quiescent stage of Graves' disease caused a flare-up of the symptoms. (Auld 1894).

Little progress had been made with the identification of the active principle in the thyroid
extracts, apart from Astley Cooper's report of the presence of albumin. Gourlay carried out some biochemical investigations and came to the conclusion that the active principle was a nucleoprotein. (Gourlay 1894). Baumann discovered iodine in the extract, and described an organic iodine-containing compound which he called thyreo-iodin, later called iodothyrin. (Baumann 1896). This work led to the isolation of thyroxine and its subsequent synthesis, but discussion of these more recent events falls outside the province of this essay.

During the period which I have outlined great advances were made in our knowledge and understanding of the pathology and physiology of the thyroid. No other ductless gland was understood so completely at the turn of the century and investigations on no other gland provided a wealth of information of such general application to the later development of endocrinology. Progress resulted from a combination of clinical observation, careful post mortem examinations, animal experiments, therapeutic trial and chemical analysis. All these procedures yielded results when applied to other glands, but it was upon the thyroid, for the most part, that their true significance was established, as valuable tools in endocrine research and investigation.
PARATHYROID GLANDS.

The close association of the parathyroids to the larger thyroid gland delayed both their anatomical recognition and the understanding of their entirely separate physiological role. They were long considered to be merely accessory thyroids or portions of undeveloped thyroid tissue. Horsley confirmed their histological appearances and pointed out that there was no evidence to show that they ever developed into thyroid tissue. (Horsley 1885). The first description of the parathyroids as separate entities by Sandström, was corroborated by Welsh. (Welsh 1898).

The varied results of thyroidectomy, both between different workers and between different species of animal, had long been a source of controversy. Studies in comparative anatomy drew attention to the presence, in some species, of "internal" and "external" parathyroids, particularly did this apply to the rabbit, in which the external glands were shown to be quite separate from the thyroid tissue. In the dog on the other hand all the glands were intimately related to the mass of thyroid tissue.

Edmunds showed that removal of both thyroid and parathyroids in rabbits was fatal. If he removed only the thyroid and its enclosed internal parathyroids, leaving
the external parathyroids in situ, many of the animals died, some of a condition resembling human myxoedema. If the external parathyroids only were excised, no effects were seen. (Edmunds 1895). This author also observed that if the parathyroids were left alone they hypertrophied but did not develop into thyroid tissue.

Welsh (1898) after giving an outline of the history of the parathyroids up to date, described the anatomy and histology of the glands in great detail. He summarised the results of a series of experiments performed on cats. From these he concluded that if sufficient parathyroid tissue remained (either one or two glands) the animal survived. He showed that an extract of parathyroid tissue administered orally had no alleviating action on the symptoms of thyroidectomy.

These experiments of Edmunds and Welsh clearly established that the parathyroids had a distinct function in the animal body and were essential to life. They were a long way, however, from any realization of the glands' true role as controllers of calcium metabolism.

Halsted had observed and reported that tetany was minimal when abundant milk was administered to parathyroidectomised animals. This almost chance observation led MacCallum and Voegtlin to investigate the effects of calcium on these animals, since milk contains such a high
percentage of that element. They were amazed to find that on intravenous injection of calcium, the symptoms of tetany ceased immediately, and did not return so long as the administration of calcium continued. It was also shown that oral calcium had a similar but slower beneficial effect. (MacCallum & Voegtlin 1908). These American workers were thus the first to discover the true significance of the parathyroid glands. Following up their discovery, they estimated the blood and urine levels of calcium in parathyroidectomised dogs. The blood was found to contain about half the quantity of normal animals while the urinary calcium was greatly increased.

The history of early research on the parathyroid glands is perhaps less impressive than that on the thyroid. Their relative insignificant appearance as anatomical structures and their close relationship with the much larger thyroid gland, undoubtedly delayed investigations upon their function - they did not impress research workers as likely fruitful lines of study. In addition the eyes of most physiologists interested in endocrinology, were fixed upon the increasing number of exciting reports on other glands of the endocrine system, particularly the thyroid itself.
THE ADRENAL GLANDS.

Addison's paper "On the constitutional and local effects of disease of the suprarenal capsules." was surely the greatest single contribution to endocrinology in the early if not the whole history of the subject. The article was an outstanding example of the supreme value of accurate and keen observation. What could have been a more unlikely place to seek pathology than in those rather insignificant-looking ill-defined structures - the suprarenal capsules? In his article (see Wilks & Daldy 1868), Addison gives an account of eleven patients. He described the general weakness, anaemia, the poor pulse, the gastric upsets and the pigmentation, and remarked upon the absence of any demonstrable clinical lesion to account for these symptoms. Addison was perhaps fortunate that he was studying a rapidly fatal disease, for that gave him the opportunity to carry out post mortem examinations on every case. In each there was disease of one or both suprarenal capsules, and this single pathological feature was the only lesion which the cases showed in common.

Having demonstrated the constant occurrence of a suprarenal lesion in this new disease, Addison was quite satisfied. He did not begin to speculate on possible functions of the adrenal gland. However, he made one rather significant remark in the discussion.
of Case 10, a girl of 28 with tuberculosis. Having demonstrated a large tubercle at the point of exit of the adrenal vein, he comments:— "This case would render it probable that the excess of dark pigment, so characteristic of renal capsular disease, depended rather upon an interruption of some special function than upon the nature of the organic change; for with the exception of the manifestly recent sanguineous effusion into its tissue, the capsule itself did not appear to have undergone any considerable deterioration."

It would seem from this that Addison realised that the adrenals had some important function to perform, but he made no further comment. Addison's work focussed attention, for the first time, on glands which had been little more than recognized anatomically, and certainly were not thought to have any important physiological role.

Shortly after the publication of these clinical observations, Brown-Séquard carried out a number of experimental adrenalectomies on rabbits, cats and dogs. (Brown-Séquard 1856) He concluded that, as bilateral adrenalectomy was invariably fatal, the adrenals were essential to life. He noted that adrenalectomy was more rapidly fatal than renal failure. The symptoms produced in animals were in many ways similar to those of Addison's
Brown-Séquard examined the urine of adrenalectomised animals and stated that it appeared normal in quantity and quality. He did not carry out a detailed chemical analysis. However, even had he carried out such an analysis it is unlikely that with the methods then available, he would have discovered the change in sodium/potassium ratio, which was demonstrated many years later.

By confirming Addison's findings that the adrenal glands were of great importance to the organism, Brown-Séquard set the stage for further research on the subject, for such study seemed likely to be rewarded. Although much experimental work was undertaken (see Rolleston 1895), little further progress was made until 1894.

In that year Oliver and Schäfer published a preliminary communication on the effects of an extract of the adrenals on the blood pressure of the cat, dog, rabbit, and frog (Oliver & Schäfer 1894). In each animal there was a great and rapid rise in blood pressure, accentuated by cutting the vagi and cutting the cervical cord. Persistence of the activity after severing the peripheral nerves showed that the site of action of the active principle was peripheral.
The rise in blood pressure was due to what the authors called "a prodigious effect on the heart and blood vessels".

In a more detailed article the authors concluded that the adrenals were secreting glands, but that the active principle was found only in the medulla. They showed that their new pressor substance was absent in the glands taken from patients dying of Addison's disease. (Oliver & Schäfer 1895).

Abel in the United States made rapid progress with the chemical identification of the pressor substance in adrenal extracts, and quickly established its empirical formula. (Abel 1897, 1898.)

It soon became evident that the adrenals had other functions which were impaired in Addison's disease, but the experiments leading to the unravelling of the mysteries of the adrenal cortex do not come within the scope of this essay.
THE PITUITARY GLAND.

Marie first described acromegaly, but like Gull, he failed to recognize the essential pathological lesion. (Marie 1885). Souza-Leite, shortly afterwards, pointed out that an enlarged pituitary could be demonstrated in all cases of acromegaly coming to post mortem examination. The significance of this finding was not realised by investigators at that time.

Experimentally, little was carried out due to the relative inaccessibility of the gland. Horsley reported experiments in which he hypophysectomised two dogs. (Horsley 1886). Both animals survived for months, the only abnormality detected was an increased susceptibility to epileptic-like convulsions on stimulation of the cerebral cortex. These results seemed to confirm the view that the pituitary had no significant function in the body.

In 1895, following up his discovery of the pressor activity of adrenal extracts, Schafer prepared extracts of the pituitary gland and tested their activity on the blood pressure. (Oliver & Schafer 1895b). Again he demonstrated pressor activity, but of less intensity than that of the adrenal extract though the effect was more prolonged.

Howell, an astute observer and outstanding physiologist, realising that the pituitary was composed
of two separate parts - the anterior and posterior lobes - made separate extracts of the two lobes and compared their activity. He showed that the pressor principle was contained in the posterior lobe and that the anterior lobe had no significant effect on the blood pressure. (Howell 1898).

Thus at the turn of the century only the posterior lobe of the pituitary was recognized to have any activity. Just as the hormones of the adrenal cortex were not discovered until late, so the hormones of the anterior lobe of the pituitary remained undetected. The full significance of that part of the gland as "leader of the endocrine orchestra" was only revealed when extracts were tested upon appropriate tissues, but these experiments fall outside the scope of this essay.
THE ISLETS OF LANGERHANS:

Diabetes mellitus and its associated glycosuria were recognized in early times, but little experimental work was performed upon the subject until Claude Bernard began his work on sugar metabolism. He was fascinated by the problems suggested by the disease, diabetes, and was anxious to explain the cause of the excess sugar. (see Foster 1899). He set out to discover where dextrose was normally destroyed, but discovered instead that it was synthesised by the liver. He used the term "internal secretion" in reference to the glycogenic activity of the liver. This is perhaps his only claim to inclusion in an essay on endocrinology, for the results of his experiments on dextrose metabolism had little direct effect on the advancement of understanding of either diabetes or the internal secretion of the pancreas.

Von Mering and Minkowski while investigating the role of the pancreas in digestive processes noted that dogs from which the pancreas had been removed showed the signs of diabetes. (Minkowski 1893). This observation drew attention to the role of the pancreas in diabetes, for the first time. It had been shown that ligation of the pancreatic duct was followed by destruction of the pancreatic acinar tissue, leaving the islet tissue unharmed. Opie argued that since tying of the pancreatic
duct was not accompanied by diabetes, there was some link between the islet tissue and the diabetic state. He examined several cases of chronic pancreatitis with this in mind. He described two types of chronic pancreatitis, one involving the islet tissue and often accompanied by diabetes, the other leaving the islet tissue normal and showing no clinical signs of diabetes. (Opie 1901a). In a second paper, Opie added confirmatory evidence by the description of hyaline changes in the islet cells of a negress, who had clinically shown all the signs of diabetes. (Opie 1901b). This pathological evidence certainly focussed the attention of subsequent investigators upon the islets as the site of the lesion in diabetes. It was fortunate that Opie approached the problem from that particular direction, for had he looked for lesions of the pancreas in patients with diabetes, he would have failed to find any significant change in many cases; it is now well recognized that diabetes is accompanied by a demonstrable abnormality of the pancreas in only a small percentage of cases.

The administration of pancreatic extracts orally to diabetic patients met with no success, and this was attributed to the presence of proteolytic enzymes in the pancreatic juice. It was suggested that if islet
tissue could be separated in some way from the acinar cells a suitable preparation for the treatment of diabetes could be made. Two workers in Aberdeen, Rennie and Fraser, tried to achieve this by an application of comparative anatomy. A certain species of Teleostei, Lophius piseatorius, was known to have islet tissue quite distinct from any pancreatic acinar tissue and situated separately from it. These investigators made extracts of this islet tissue, and administered it orally to diabetic patients. The therapy was a failure. (Rennie & Fraser 1907).

Since it was well established that extracts of whole pancreas had no place in the treatment of diabetes and since the inactive nature of the material was believed to be due to the action of the pancreatic juice, it is surprising that these Aberdeen workers did not give their extract parenterally, for oral administration was surely subjecting the preparation to the very destructive processes that they were trying to overcome, except that in this case the agent was the pancreatic secretion of the patient and not the enzymes in the extract.

No advance came until parenteral administration was adopted much later by Banting and Best, who used islet tissue obtained by ligation of the pancreatic duct and consequent destruction of the acinar tissue. This great advance falls outside the scope of this essay.
CONCLUSIONS.

The cycle of scientific research begins with an observation or series of observations, from which the investigator formulates a working hypothesis. This hypothesis is then tested by experiment, and further results and observations are thus yielded. So the cycle is completed, the working hypothesis being suitably modified in the light of the new results, for re-testing.

The evolution of endocrinology to some extent illustrates how this scientific method developed. The observations of the early anatomists, such as Galen, were usually followed by rather dogmatic comments on the function of the newly described structure. These pronouncements on the function of organs were really working hypotheses but little if any attempt was ever made to verify them by further experiment.

The early work on the adrenal glands may be taken as an illustration of progress in the scientific method. Addison described the lesions of the suprarenal capsules and concluded that the glands performed some essential function in the body. This was the working hypothesis. Brown-Séquard tested this by performing adrenalectomies on animals, and produced evidence in support of the hypothesis.

A more advanced example of the application
of the scientific method is afforded by research on the thyroid gland. Ord showed the relationship between myxoedema and certain degenerative changes in the thyroid. Horsley compared the effects of experimental thyroidectomy in animals and the symptoms of myxoedema - he put forward the working hypothesis that the cause was identical in each case namely loss of thyroid function. In addition since transplants were beneficial in thyroidectomised animals, he suggested that they would be successful in the treatment of myxoedema. This was tested with good results by other workers, who noted improvements as early as the day after the operation. This led Murray to formulate the working hypothesis that an active substance was responsible for the effects. This he tested by the hypodermic injection of a glandular extract and so confirmed his hypothesis.

These examples reveal that rapidity in scientific progress depends to a great extent upon the use of this cycle in research. Scientific methods are employed to-day, throughout the whole of the research world, and this being so great advances can be anticipated in all branches of medicine, not least in the field of endocrinology, whose birth and early maturation have here been briefly outlined.
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