ENDOCRINES IN THEORY AND PRACTICE

This article concludes the series on Endocrinology contributed by invitation

THE HISTORY OF ENDOCRINOLOGY

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Nomenclature

The term "ductless glands" was used by the encyclopaedic Haller in the eighteenth century, that of "internal secretion" by Claude Bernard in 1855; "endocrine" and "endocrinology" (ἐνδον = within, κρίνω = I separate) came into use in this century. In 1905 Starling, on the look out for a synonym for "chemical messengers," adopted the suggestion of hormones (ὁρμάω = I excite) made by the late Sir W. B. Hardy and his classical colleague W. T. Vesey of Gonville and Caius College, Cambridge. Jayle (1937) argued that the word ὁρμῶντα of similar derivation, in the book of the *Epidemic Diseases* of Hippocrates should be translated as "secretions," not as "movements," and from the context included internal as well as external secretions. The word "hormone" fitted secretin—discovered in the duodenum by Bayliss and Starling in 1902—a substance which stimulates the pancreas to secrete; but for chemical messengers which exerted the opposite, a depressing or inhibitory, effect the word chalones (χαλάω = I relax) was suggested in 1913 by Schäfer, who also proposed autacoids (αὐτός = self, ἄκος = drug) to include both forms. The words dysfunction, dysthyroidism, and dyspituitarism have been used in two slightly different senses: for an abnormal secretion of a gland—such as a thyroxine differing in its composition from that normally secreted in being incompletely oxidized, as was suggested by H. S. Plummer in toxic goitre; and for irregular or overlapping syndromes—such as cases of toxic goitre with some features of myxoedema or, with regard to dyspituitarism, combinations of hyper- and hypo-pituitarism, as Cushing pointed out in 1910.

The conception and the name of anti-hormones have recently been brought forward by Loeb, Aron, and Collip to explain the diminution of reaction which may follow long-continued injections of hormones. Collip and Anderson (1934) found that repeated experimental injection of the pituitary thyrotropic hormone was followed by the production of an anti-thyrotropic principle in the blood, which when injected into normal animals rendered them non-reacting. This mechanism would appear to tend to preserve the endocrine balance. The synonyms given by independent workers to the same hormone, especially those of the gonads and pituitary, may be puzzling and confusing; it is therefore to be hoped that a standardized nomenclature will be adhered to in the interests of clarity and precision.

Organotherapy

The use of animal and human substances with medical intent is an ancient and widespread custom among primitive races, the origin of which has been ascribed to various superstitions, especially to totemism, but has also come about in a somewhat capricious manner. Sometimes, however, the underlying idea appears quite obvious—namely, that when a disease was thought to involve an organ—for example, the heart or the lungs—that organ was employed as the remedy. Incidentally it must be admitted

that in the recent past a similar train of thought was suggested by some advertisements of glandular extracts. Evidence that organotherapy has long been practised is obvious from the contents of the early pharmacopoeias issued by the Royal College of Physicians of London, those between 1618 and 1746 containing a large number of nauseous substances which have often been compared to the contents of the witches' cauldron in *Macbeth* (1606).

Pre-scientific Suggestions

The conception of internal secretions has been read into a remark of Théophile de Bordeu in 1775 to the effect that each organ gives off "emanations" which are necessary for the well-being of other parts of the body. Like some of his contemporaries, he also laid stress on the tonic effects of the secretions of the testes and ovaries. Legallois (1801) has been thought to have a more solid claim to be considered the forerunner of the conception of internal secretions. An important experimental proof of the internal secretion of the testes was published in 1849 by A. A. Berthold of Göttingen, who showed that transplantation of a cock's testes to another part of the body prevented the atrophy of the comb, which otherwise follows castration. This result he ascribed to the influence exerted by the testes on the blood and thus on the whole body. This observation, although the same, was shown to be true for the ovaries in 1900 by Knauer and by Halben, was forgotten until Biedl exhumed it in 1910, the year that Steinach published his conclusion that sexual desire and the secondary sex characters are controlled by the internal secretions of the gonads.

Claude Bernard, Addison, and Brown-Séquard

Scientific activity in endocrinology otherwise dates from 1855, when two important events took place. On January 9, in a lecture at the Collège de France, Claude Bernard, who was much in advance of his time, pointed out that the liver had two secretions—an external one of bile into the intestine and an internal one of sugar directly into the blood. In the same year Thomas Addison of Guy's Hospital brought out his monograph *On the Constitutional and Local Effects of Disease of Supra-Renal Capsules*. In it he explained, more fully than in his address in 1849 entitled "On Anaemia: Disease of the Suprarenal Capsules," that in searching for the cause of "idiopathic" (afterwards called pernicious and later Addisonian) anaemia he "stumbled" (his own word) on the association of disease of the adrenals with the definite train of symptoms to which his name was attached by Trousseau in 1856. This stimulated Brown-Séquard in Paris to physiological research on the adrenals, and Sir Jonathan Hutchinson in London to collect clinical cases and post-mortem specimens. Brown-Séquard was a remarkable pioneer in endocrinology; probably quite unconscious of de Bordeu's speculative views, he expanded the conception of an internal secretion of the ductless glands to include all the organs and tissues of the body, thus anticipating the modern neuro-humoralism, though mainly on a basis of keen imagination. Further, when a septuagenarian, his enthusiastic advocacy of the rejuvenating effects of testicular emulsions, though naturally arousing adverse criticism, yet focused attention on the

hormonal effects of the gonads. In 1856 he found that removal of the adrenals was fatal, and ascribed this to toxæmia, poisons normally produced being no longer neutralized or removed by the adrenals. In the discussion which followed it was suggested that the results were due to the operative damage to the sympathetic. But the hypothesis that the ductless glands exerted a detoxicating effect was widely accepted, and in the case of the adrenals was not abandoned until after 1894, when Oliver and Schäfer, by experimental injection of extracts of adrenals, discovered in the adrenal medulla the pressor substance adrenaline. This, the first hormone to be thus established, was isolated in 1901 by Takamine and by Aldrich, and was synthesized in 1904 by Stolz. The active principle of the cortex, called "cortin" by Hartman (1928) and "eschatin" by Swingle and Pfiffner (1930), has been proved to be the hormone absence of which is responsible for the symptoms of Addison's disease, thus reversing the previous belief that these symptoms were due to absence or deficiency of adrenaline.

The Thyroid

The knowledge that the symptoms of endocrine inadequacy are due to the absence or diminution of an internal secretion present in, and necessary for, health was first established in the case of the thyroid.

Attention may be directed to two early but little-known anticipations of an internal secretion of the thyroid. In 1836 Wilkinson King, lecturer on pathology at Guy's Hospital in succession to Thomas Hodgkin, described the passage of the secretion of the thyroid into its lymphatics and so into the great veins, and clearly foresaw the internal secretion of the thyroid. In 1850 T. B. Curling, surgeon to the London Hospital, in reporting "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," wrote: "I am not acquainted with any case on record in which a deficiency of the thyroid body has been observed in the human body," and added, "It is highly probable that this abnormal secretion of fat was dependent on the absence of those changes which result from action of the thyroid."

In 1871, when the endemic form of cretinism, recognized in the sixteenth century in the Duchy of Salzburg by Paracelsus, had practically died out in this country, Hilton Fagge described sporadic cretinism. He then prophesied that this condition might occur in adult life. Two years later his senior at Guy's Hospital, Sir William Gull, described "a cretinoid condition supervening in adult life in women," which in 1877 W. M. Ord named myxoedema. This was followed by active research into the physiology of the thyroid; the effects of thyroidectomy performed in 1858 were republished by Moritz Schiff in 1884, and repeated by Sir Victor Horsley in 1885, and by others. Clinical observations were widely reported, and in 1883 Sir Felix Semon put forward the view, at first derided but subsequently confirmed, that cretinism, myxoedema, and post-operative myxoedema (cachexia strumipriva) were all due to insufficiency of the thyroid gland.

Other diseases due to diminished endocrine activity or its suppression are parathyroid tetany, eunuchoidism, and disorders due to hypopituitarism—for example, adiposogenital dystrophy, described by Babinski in 1900 and more fully by Fröhlich in the following year, and Simmonds's pituitary cachexia (1914), of which progeria (πρόγρησις = prematurely old), described by Sir Jonathan Hutchinson (1886) and given that name by Hastings Gilford in 1904, appears to be the juvenile form.

An interesting historical point in therapeutics is the alternating association and neglect of iodine in connexion with (a) the occurrence of goitre in districts poor in iodine, (b) the prophylactic treatment of simple goitre, and (c) the treatment of toxic goitre. Seaweed and sponge had been empirically used in the treatment of simple goitre centuries before iodine was isolated in 1814. In the first quarter of the last century it was employed with such enthusiasm that the resulting iodism led to its almost complete abandonment. In the middle of the last century Chatin's inquiries suggested that iodine want was responsible for goitre; but the prophylactic use of iodine was not widely established until after the success obtained in 1916 by Marine and Kimball in North America. Toxic goitre was treated in the middle of the last century by iodine, for example, by W. B. Cheadle in 1869; but this method went completely out of fashion until about 1921.

Diseases Due to Excess of Endocrine Secretion

After it was established that absence or deficiency of the internal secretion of the thyroid caused symptoms which could be relieved by substitution treatment—namely, by the injection of an emulsion of the gland, as was done by G. R. Murray in 1891 or later by an extract by the mouth (Hector Mackenzie; E. L. Fox, 1892)—a further question excited interest. This was whether an excess of the normal secretion or an altered secretion produced morbid symptoms the reverse of those due to absence or deficiency of the secretion. This possibility had in fact been suggested earlier, before the introduction of the successful treatment of myxoedema by thyroid extract: Rehn in 1884 regarded toxic goitre as due to excessive thyroid secretion, and Möbius two years later argued that the disease was caused by an abnormal activity of the thyroid which poisoned the body. Much later, in 1923, H. S. Plummer and Boothby stated that exophthalmic (or toxic) goitre was due to two factors—namely, an excess of normal thyroxine and an abnormal thyroxine—whereas toxic adenoma was caused by an excess of normal thyroxine alone. Harington (1933) strongly criticized the idea of an abnormal internal secretion in toxic goitre, and the general principle that pathological states of endocrine glands may produce too much or too little of their internal secretion but do not manufacture abnormal compounds has recently been emphasized by Cameron (1936). Hyperplasia, adenomas, and, less often, carcinomas of the endocrine glands may, for this is not constantly the case, secrete the hormones proper to the glands, but their altered histological structure logically suggests that their secretion would also be abnormal.

Diseases other than toxic goitre ascribed to excessive endocrine secretions are: (i) acromegaly, at first confused clinically with myxoedema, due to adenomatous growth and overactivity of the eosinophil cells in the anterior pituitary, the anterior lobe being incriminated by Tamburini in 1894 and the responsibility of the eosinophilic adenomas established in 1901 by Benda. (ii) Small adenomas composed of basophil cells in the anterior lobe ("pituitary basophilism") were described as responsible for a remarkable train of symptoms by Harvey Cushing in 1932—deservedly called "Cushing's syndrome"; much discussion has been excited about its relation to, or identity with, the adrenogenital syndrome. (iii) Although Addison's disease in 1855 was the first endocrine disease to be described, it was half a century later that Bulloch and Sequeira (1905) correlated the adrenogenital syndrome of virilism with tumours of the adrenal cortex. The association of tumours of the chromaffin cells (chromaffinomas or pheochromocytomas) of the adrenal medulla with

paroxysmal crises of hypertension has been quite recently established. This condition contrasts with the persistent hypertension seen in some tumours of the adrenal cortex. (iv) Adenomas of the parathyroid glands were associated in 1904 by Askanasy with von Recklinghausen's generalized osteitis fibrosa cystica, but this was not definitely recognized until 1926. (v) Adenomas or hyperplasia of the islands of Langerhans (hyperinsulinism) give rise to spontaneous hypoglycaemia, a morbid state which was not recognized until 1924 by Seale Harris, after it had been produced by the administration of insulin to animals and described early in 1923 by Banting, Campbell, and Fletcher before insulin was available in this country.

Parathyroids

Though described in man and animals in 1880 by I. V. Sandström of Upsala University, the parathyroid glands did not attract any attention until 1891, when Eugène Gley of Paris independently described them in animals. At first they were regarded as accessory thyroids, but Kohn (1895) stated that they are anatomically and physiologically distinct from the thyroid, and in 1909 MacCallum and Voegtlin proved that they control calcium metabolism and that their removal is followed by tetany. Before the recognition of the parathyroids some of the symptoms following total thyroidectomy, which were really due to simultaneous removal of the parathyroids, were ascribed to removal of the thyroid. The isolation and standardization of a powerful parathyroid extract by Collip (1925) and the association of hyperparathyroidism, due to adenomatous change in the parathyroids, with generalized osteitis fibrosa cystica (1926) are milestones in the physiology and pathology of the parathyroids.

Multiglandular Syndromes

The conception of inadequacy of several endocrine glands was initiated in 1907 by Claude and Gougerot, and was followed in 1908 by that of the interaction and interdependence of the endocrine glands or the endocrine balance, brought forward by Eppinger, Falta, and Rudinger. The idea of multiglandular syndromes—namely, co-existent primary disturbance of more than one endocrine gland—met with considerable criticism. The position has been altered and clarified by the discovery of the controlling influence of the anterior pituitary over the other endocrine glands, by means of its thyrotropic, adrenotropic, gonadotropic, and other hormones.

The Pituitary

The pituitary, now the predominant endocrine gland, was later than the adrenals and the thyroid in attracting modern investigation; for in 1889, in a review of nervous physiology, it was dismissed as having little if any use in the organism of the higher vertebrates, and in the same year Alexander Macalister, professor of anatomy at Cambridge, described it as "probably the rudiment of an archaic sense organ." Like the thyroid and pineal, it was known to Galen; Vesalius (1543), believing that it collected waste material (*pituita* = phlegm, slime) from the brain and in some way conducted it into the nasopharynx, gave it what is still its familiar name, although a century later C. V. Schneider and Richard Lower destroyed the basis for such a title. Soemmerring (1778) called it the hypophysis. Like the pineal or epiphysis, it was thought to be concerned in the regulation of the cerebro-spinal fluid by Sylvius of Leyden and Vieussens in the seventeenth century, and even as late as 1842 by Magendie.

Pierre Marie in 1886 gave the clinical account of acromegaly which in the following year was connected with the pituitary by Minkowski, and thus directed attention to the gland; but it was not until this century, especially since 1905, that its physiology and pathology were exhaustively investigated, particularly by Harvey Cushing, whose epoch-making work *The Pituitary Body and its Disorders* appeared in 1912. The pituitary now bears much the same relation to the other ductless glands that the brain does to the remainder of the nervous system. Unlike the thyroid, parathyroids, and adrenal medulla, which each secrete one hormone only, the pituitary has been thought to manufacture an increasing number of active principles or hormones—the anterior pituitary as many as fourteen and the posterior seven—but doubt has been expressed, especially by Abel (1924), whether each different action of pituitary extracts is necessarily due to a separate hormone. The pituitary hormones chiefly, if not entirely, act by stimulating other endocrine glands, the thyroid, adrenals, gonads.

Thus hyperpituitarism—hyperplasia and correspondingly increased secretion of eosinophil or of basophil cells in the anterior pituitary—may be followed by similar reactions in the adrenals, gonads, and thyroid. It has been suggested, but not proved, that the thyroid changes in exophthalmic (or toxic) goitre are primarily due to excessive secretion of the thyrotropic hormone by the anterior pituitary. On the other hand hypopituitarism due to disease, for example, by infarction as in pituitary cachexia (Simmonds's disease, 1914), or to experimental hypophysectomy, is followed by atrophy not only of the dependent endocrine glands but of the body generally. The interrelations between the anterior pituitary and other endocrine glands are, at any rate in some instances, reciprocal; thus castration gives rise to the cellular changes known as "castration cells," and the corpus luteum of pregnancy causes the formation of "pregnancy cells" in the anterior lobe of the pituitary.

The Islands of Langerhans

The islands in the pancreas, described in 1869 by P. Langerhans, were in 1893 named after him by Laguesse, who with Hédon in that year concluded that the islands provided the internal secretion of which the experimental production of fatal diabetes mellitus by excision of the pancreas in 1889 by von Mering and Minkowski had shown the existence. In 1902 Opie described hyaline degeneration of the islands in diabetes mellitus. In the next twenty years there were several attempts to treat diabetes mellitus by pancreatic extracts, especially by Zuelzer in 1908; but these preparations produced such severe reactions from the contained proteins that they were abandoned. The hormone was named "insuline" in advance (before it was obtained protein-free in 1922 at Toronto) by de Meyer in 1910 and independently by Schäfer in 1916. After first calling their hormone "iletin," Macleod, Banting, and Best in 1922 adopted the slightly modified name insulin.

The Gonads

Though from the eighteenth century the gonads were vaguely thought to exert what is now recognized as an endocrine influence, and although the first experimental evidence of a testicular, and indeed of any, hormonal function dates back to Berthold in 1849, further scientific advance in this direction is of quite recent origin. During the last few years the output of scientific investigation

has been enormous, so much so that the practical application of this new physiological knowledge has not had time to keep abreast. The sex hormones and their relations to the anterior pituitary have thus been recognized, and their extreme complexity, especially of the female hormones, has become manifest. Probably the services of organic chemistry are now more important here than in any other branch of endocrinology.

Methods of Endocrine Research

These comprise: (1) Correlation and comparison of the clinical features with the morbid changes in the endocrine glands, the method employed by Addison. With this may be associated observation of substitution treatment—namely, the clinical effect of (a) administration of an extract of the gland, damaged or rendered inadequate by atrophy or disease; or (b) removal of a gland considered to be over-active, such as the thyroid in exophthalmic goitre, or of an adrenal in the adrenogenital syndrome. (2) Experimental removal of normal glands and, when symptoms have been thus produced, grafting the same gland into the animal or by giving extracts of the gland parenterally. (3) The new method of extending over successive generations of animals either (a) excision of the endocrine organ or (b) administration of its extract. Employing this technique Rowntree, Hanson, and their co-workers have brought forward evidence to show that the thymus (1934) and the pineal (1936) are endocrine glands controlling growth and sexual development. (4) The isolation, crystallization, and synthesis of hormones by organic chemists, a comparatively recent and most important line of advance.

Neuro-humoralism

The vegetative portions of the animal body appear to be controlled by a double or alternative mechanism—namely, by nervous and by chemical messages. In 1904 T. R. Elliott suggested that nervous impulses of the sympathetic may act on the effector cells at the periphery by the liberation of adrenaline. In 1906 W. E. Dixon found that a heart submitted to vagal stimulation liberated a body which inhibited the frog's heart; this hypothesis was followed up by Loewi (1921), Dale (1929), and Cannon (1933), and Dixon's "inhibitor" has been called "vagal substance," acetylcholine, and parasympathin. Acetylcholine therefore stands in much the same relation to the parasympathetic as adrenaline does to the sympathetic division of the autonomic system.

In this short essay on the history of endocrinology it was inevitable that reference should be made to what is happening to-day. The future historian of the subject, indeed, may look upon "to-day" as the most important and fruitful period in the development of a science to which the clinician has made such valuable contributions. What these are is plain to the reader of the previous articles in the series, which fill the many large gaps in this survey and bring the story of endocrinology up to the present moment.

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Nova et Vetera

THE CORONATION AND A DISUSED RITUAL

[FROM A CORRESPONDENT]

The practice of touching for the king's evil is no doubt as dead as Queen Anne, the last of our monarchs to essay the therapeutic art. Yet for all those who decline to regard history as "bunk" any matter which was for centuries closely connected with the sovereignty of England cannot in this year of the King's crowning be without interest.

In 1911, the year of the Coronation of King George V, a scholarly series of lectures was delivered by Sir Raymond Crawford before the Royal College of Physicians, and subsequently published by the Clarendon Press under the title of *The King's Evil*. Since the publication of this volume there appears to have been no further detailed investigation of the subject. It seems opportune, therefore, to gather up and supplement the result of these earlier researches.

History of the Practice

In England the beginning of the practice may be reckoned as dating from the reign of Edward the Confessor, who died in the year 1066, though in France the ceremony is referred back to the Coronation of Clovis in A.D. 496. It began soon to be debated by the chronicler William of Malmesbury and the monks whether the Confessor had cured by virtue of his own holiness or whether the power had been transmitted to him by his royal ancestors. These healings seem at first to have been of many diseases—leprosy, plague, jaundice, and possibly tubercle—and from the large numbers touched at later dates it must surely be inferred that the term "scrofula" was extended to cover not only glandular swellings of the neck, but swellings of any kind in any part of the body. Evidence of the practice is lacking during the reigns of William II, Henry I, and Stephen. It was revived by Henry II, but there is no evidence that John or Richard I ever touched—the latter King being very little in England. With Edward I we are on firmer ground, for the Household accounts (1277–8) of that monarch show "for 17 sick persons signed by the King 17d.," and in one month he touched 533 persons. During the fifteenth century there are few cases recorded, but Henry VII restored the practice and added a new ceremony, giving to each person an angel—a gold coin with the figure of St. Michael on the obverse. The service employed, together with others, has been preserved, and there was little alteration in the forms until the rite was finally discontinued after the death of Queen Anne, except that after the Reformation the office was said in English and some few markedly Roman Catholic characteristics, such as the invocation of the Virgin Mary and the Saints, were omitted. The words of the first Gospel, "They shall lay their hands on the sick and they shall recover," were repeated by the chaplain so long as the King was handling the sick persons. The concluding words of the second Gospel, "That was the true Light, which lighteth every man that cometh into the world," were similarly repeated "as long as the King shall be crossing the sore of the sick person with an Angel Noble, and the sick person is to have the same Angel hanged about his neck and to wear it until he be full whole." The dissolution of the monasteries by Henry VIII led to a large increase in the numbers of the sick poor, for whom there was now no provision; and—though there is no certainty that Edward VI touched—this led to a great number attending the court both of Mary and of Elizabeth to obtain relief. Queen Mary's Manual, formerly in the possession of Cardinal Manning, contains three miniatures, (1) showing the Queen blessing cramp rings, (2) a crucifixion, (3) the Queen clasping the swollen neck of a boy with both hands.