THE HISTORY OF THE DEVELOPMENT OF OUR KNOWLEDGE REGARDING INTERNAL SECRETIONS.

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BEING

AN ESSAY PRESENTED IN COMPETITION FOR ONE OF THE WELLCOME (HISTORY OF MEDICINE) PRIZES & MEDALS.

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BY

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{SHOWING SYNOPSIS OR GENERAL OUTLINE OF ESSAY}

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THE ESSAY:

FOREWORD.

Endocrinology is indeed a very romantic offshoot of that basal science, physiology. Comparatively young in age — for it first saw the light barely seventy-five years ago — it has now attained such a gigantic stature as almost to relegate its mighty ancestor into a dignified, if perhaps lugubrious, second place! The seed that was planted by BERTHOLD in 1849, and assiduously watered and tended by Claude Bernard, Brown-Sequard, the Reverdins of Geneva, Oliver, Sharpey-Schafer, Horsley, Schiff, Kocher, Popielski, von Mering, Minkowski, Starling, Bayliss, Vincent, Gley, Biedl, Marshall, Jolly, and a host of many other endocrinologists no less distinguished, has since germinated; it has now grown to such a virile and luxuriant tree that the stalwart branches thereof afford a glorious haven of rest and a fertile source of inspiration, fame, and honour to innumerable biologists from all the four corners of the earth!

The literature that has grown around this young but nevertheless highly organised and vastly important science is so extensive and complicated, that no attempt has been made to include the substance of it all within the circumscribed compass of this essay. Reference has therefore been omitted in several places to many unimportant or minor points which further careful experimentations have failed to establish; to

matters of little or no clinical or physiological significance; and to most of the many recent findings, the importance of which can only be assayed and their correlation established in the light of future observations. The discussion of the more important recent findings has however been carried, where practicable, as far as the last few months, as in the case of insulin. References to important findings up to the last few days of presenting this essay are made in some of the footnotes.

The history of the clinical aspects of certain internal secretions (e.g. Addison's disease, under suprarenals, and Diabetes, in the section on the internal secretion of the pancreas) has been referred to at some length with the idea that, although it is perhaps of little direct scientific import, it may, nevertheless, add some more interest to a lengthy and perhaps dry account of purely physiological findings. The physiological, biochemical, and pharmacological history of most of the internal secretions has also received due attention. A more lengthy account than is perhaps merited in the present state of our biochemical and therapeutic knowledge has been given of insulin, the discovery of which is, however, one of the most important landmarks in the annals of endocrinology.

For the purpose of convenience and easy reference, the essay has been divided into three parts. PART I endeavours to set forth a general review of the history of the subject from the ancient

times to the present day. In PART II., the respective internal secretions are dealt with in some more detail; whilst PART III. represents an attempt at a general and speculative discussion on the past, present, and future aspects of the subject. The PARTS are further subdivided into sections. An appendix of references is also added, as well as a chronological table of the landmarks or principal dates in the history of our knowledge.

Lavish use has been made of the numerous text books on the subject. These are: Sir Sharpey-Schafer's Endocrine Organs, 1st & 2nd Editions; Cammidge's Insulin Treatment of Diabetes, Livingstone, Edinburgh, 1924; Allbutt and Rolleston's, Osler and Macrae's, Gibson's, and Tagge's text-books and "Systems" of Medicine; Buck's Handbook of the Biological Sciences; Howell's, Burton-Opitz's, Halliburton's, and Starling's text books of physiology; Marshall's Physiology of Reproduction; Macallum's Pathology; Professor Cushny's Pharmacology; and Thomas' Series of Classics of Scientific Methods. (These books are acknowledged in the text in the appropriate places.) The material on which the references to the history of the glands of external secretion are based is obtained from Dr. Comrie's History of Medicine Lecture Notes of Oct. 1923 - Jan. 1924, which have been found to be particularly helpful. Ample use has also been made of material in the various scientific periodicals and journals on the subject.

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University Union, Edinburgh.
May 1, 1924.

PART I

GENERAL INTRODUCTORY DISCUSSION OF THE HISTORY OF OUR KNOWLEDGE FROM ANCIENT TIMES TO ~ THE PRESENT DAY. ~

SECTION I.

GENERAL INTRODUCTORY DISCUSSION.

Although the real history of our scientific knowledge regarding the internal secretions, as we know them in modern times, cannot be dated farther back than the middle of the 19th century (1849), yet, that certain kinds of fluids which are essential to life circulate in the body was not an altogether unknown entity to the ancients.

Ancient Theories up to 500 A.D.

Plato (circa B.C. 400) was the first who, in certain of his medico-philosophic works, gave articulate expression to the idea of the circulation of hypothetical "humours" in the body. Before this, Pythagoras (circa 1000 B.C.) had attributed the cause of diseases to pathological conditions in these "humours". Aristotle[1] (circa 342 B.C.) taught that "there are four 'humours' in a man's body, whereof every one hath its proper place. The first is 'choler', called by the physicians 'flava bilis', which is placed in the liver. The second is 'melancholy', called 'astra vellis', the seat whereof is in the spleen. The third is 'phlegm', whose place is in the head. The fourth is 'blood', whose place is in the heart." Again, "Man's body is full of many 'humours';..... the watery and grosse 'humours' are purged by the eyes, 'melancholy' by

the ears, 'choler' by the nose, and 'phlegm' by the hair." These theories seem to have been widely held right up till the time of Galen (circa 200 AD) who elaborated them, and further taught that an imaginary essence, viz., the "natural spirits", was elaborated by the liver (which organ Hippocrates – circa 400 BC – had regarded as the seat of primitive sensations), and thence passed to the blood. The presence of these imaginary "natural spirits" was supposed by Galen to be necessary for the continuance of even the lowest forms of life. A second kind of "spirits", viz., the "vital spirits", were supposed to be derived from the heart; whilst a third variety, viz., the "animal spirits", Galen believed, functioned through the intermediary of the brain. These animal spirits were supposed to be separated from the blood and sent out to the body as a sort of nervous fluid which was distributed through the nerves, which were at that time supposed to be merely hollow, tubular organs.

The 7th – 15th Centuries: The Middle Ages; The Renaissance.

No further elaboration of these "humors" and "spirit" theories seems to have been attempted in the post-Alexandrian or Arabian period (600–1200 A.D.), the Anglo-Saxon period, or during the Dark Ages. The 13th to the 15th centuries were entirely devoted to mere translations — frequently erroneous — of the works of the ancient masters. Even

During the Middle Ages and the Renaissance, the writings of the physiologists tend to indicate that their mental horizon was still befogged with the crude biological philosophies of Aristotle, and the imaginative physiological suppositions of Galen. The learned Vesalius in his classic, "The Fabric of the Human Body" in 1543 enunciated no new idea, although he appeared to doubt the truth of the fundamental basis of Galen's and Aristotle's physiology. The erudite Servetus (1511 – 1553 A.D.) in his half-physiological, half-theological work, "The Restitution of Christianity", showed ~~only~~ but a minor departure from Aristotle's and Galen's teachings by ~~denying~~ questioning the existence of the "humours" and "natural spirits". The great teachers, Realdus Columbus, Gabriel Fallopius, Jerome Fabricius of Aquapendente, Ambroise Paré, Bacon, Boralle, and even that master-experimenter Harvey, professed no new theory.

Our Knowledge in the 16th, 17th & 18th Centuries.

The revival of the experimental method in the 16th., and the introduction of the microscope by Malpighi (1628 – 1694) in the 17th. century, gave an extraordinary impetus to the development of the study of the microscopic structures and physiological functions of the secretory glands.* Thus the lymphatic glands, formerly described by Herophilus of Alexandria, were rediscovered and studied in greater detail by Rudbeck in 1653; but their functions were not explained till the time of Alexander Monro secundus of

* from Dr. Comrie's History of Medicine Lecture Notes, Oct 1923 – Jan. 1924.

Edinburgh in 1757. Asselli and Bartholini discovered and described certain other glands. Pecquet discovered the thoracic duct. In 1654, Glisson in his "De Hepatae" gave a complete account of the liver; but the physiological functions of this organ remained obscure to him. Of course, all the secretory glands like the pancreas, spleen, etc., were well known to the ancients; but nothing except fanciful explanations were given regarding their physiological significance. However, Francis Sylvius (1614 – 1672) was the first to differentiate between the "lymphatic" glands and what he called the "conglomerate" (i.e. free secreting) glands*. Vieussens (1640 – 1673) in 1654 discovered the pancreatic duct, and, somewhat later, gave a full description of the thymus. De Graaf (1641 – 1673) was the first to give a complete account of the ovary and of the changes it undergoes during gestation. He also showed the digestive nature of the pancreatic juice, the chemical analysis of which was investigated later by Claude Bernard. Conrad Brünner (? 1772) of Heidelberg in 1672 discovered the duodenal glands which he called "pancreas secondarium", and he also observed that pancreatectomy in dogs produced "a ravenous appetite, thirst, and wasting". Reamur (1683), Spallanzani (1729 – 99) Prout of Edinburgh (1834), Schwann (1836), John Hunter (1876), Claude Bernard, Pavlov, and Ludwig also made extensive researches on the chemical nature of the digestive and lymphatic secretions.

* Malpighi in his "Excercitationes de structura viscerum" in 1665 referred to them as "conglomerated follicular glands."

Thus it is seen that, whilst the development of our knowledge of the functions of glands that possess ducts and secrete externally has made giant strides since the 16th century — and the function of a gland with a duct is a comparatively simple physiological proposition — yet the use of the ductless or internally secreting glands was for long a puzzle to scientific investigators. The difficulty of investigating this subject was no doubt increased by the fact that it was impossible to obtain the internal secretion in a state of comparative purity for scientific examination, like the gastric and pancreatic juices. It was found to be always mixed with or masked by the lymph or blood into which it is normally shed directly in the body (Halliburton). The diseases of the internally secreting or ductless glands were well known at this period as they were to the ancients, as shall be indicated when the history of our knowledge with regard to the individual secretion is reviewed. For example, diabetes was well known to the ancient Celsus; but no exact relationship between clinical symptoms (arising from glandular disease) and endocrinological function was ever demonstrated.

The Beginning of Our Modern Knowledge: The 19th Century.

Although, according to Berman[2], Borden sometime in the 18th century promulgated the idea of an internal secretion, yet the ~~beginning of the scientific~~ scientific study of the

** Addendum I, from reference on opposite page :-

Théophile de Borden did in fact promulgate in 1775 certain views which have been supposed to indicate a clear conception of internal secretion. (Borden : " Analyse médicinale du sang". Oeuvres complètes, ed. Richerand, t. ii, pp 942-3, Paris, 1818.) That this statement is historically correct is maintained by such eminent authorities as M. Neuburger ("Theophile de Borden — 1722-76 — als Vorläufer der Lehre von der inneren sekretion", Wien. klin. Woch., 1911, 24, 1367) and A. Biedl (Innere Sekretion, 2te Aufl., Berl. u. Wien., 1913, 1, 5.). E. Gley however at the 17th Internat. Congr. of Med., London, 1913, Sect ii Trans., p 3 denied that Borden gave a clear expression of what he regarded as internal secretion. Nevertheless, there is no question but that the idea was sufficiently clear to Borden himself at least, as he regarded each organ as a "humeur particulière" which exerts its influence upon the body generally. C. Legallois in 1801 (Dissertat. inaugurale soutenu à l'Ecole de Med. de Paris, en sept., 1801), Johannes Muller in 1838 (Elements of Physiology, Trans. Baly, 1838), & W.B. Carpenter 14 years later (Article on Secretion, Cyclop. of Anat. & Physiol., ed. R.B. Todd, London, 1852, vol. 4 p 440) expressed the same belief and credited several organs including the spleen, lymph glands, and even adipose tissue with internally secreting (ie. "endocrine") function.

** Addendum II, also from reference on opposite page.

The conclusion which Berthold drew was that the correlation of different organs and tissues of the body (the "consensus partium" of the older writers) depends on the fact that the testes affect the blood which in turn affects the whole organism. The nervous system, he believed, plays a prominent part in the sequence of events :-

> "..... der fragliche Consensus durch das productive Verhältniss der Hoden, d.h., durch die Einwirkung auf das Blut, und dann durch entsprechende Einwirkung des Blutes auf den allgemeinen Organismus überhaupt, wovon allerdings das Nervensystem einen sehr wesentlichen Theil ausmacht, bedingt wird" (Biedl, Innere Sekretion, 2te Aufl., Berl. u. Wien, 1913, i, 5.).

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ductless glands did not begin till 1849 when Berthold[3] of Göttingen enunciated his theory that the testis represented an organ of internal secretion which was transferred by it directly into the blood stream and was responsible for the development of the secondary sexual characters.** He removed these organs from cocks and grafted them upon some other part of the body. "These animals", said Berthold, "remained male in regard to voice, reproductive instinct, fighting spirit, and growth of comb and wattles".†† (Please see addendum II on opposite page)

In 1850, Harling, of Switzerland, suggested that cretinism might be due to a deficiency in the secretion of the thyroid gland which he observed was not infrequently absent in that disease. In 1855, Claude Bernard[4] gave a more elaborate presentation of the subject, and stated that "glands may form a 'sécrétion externe' by withdrawing substances from the blood, and also a 'sécrétion interne' which, instead of being carried off to the exterior by a duct, is passed directly into the blood or lymph stream". The name "internal secretion" was specifically employed by Bernard in 1857 when he illustrated his conception of the functions of the ductless glands by referring especially to the liver which, in addition to its external secretion, the bile, he maintained also furnished an internal agent which was directly concerned in the mobilization of glycogen and the formation of sugar.

In the succeeding years, the interest of the

** Please see addendum I on opposite page. Also †† Addendum II

physiological world was especially centred on observing the effects of total and partial enucleation of these glands, the clinical symptoms following their diseases, the effects of the injection of their extracts and of their transplantation from one animal to another from which the gland has been removed, and the chemical examination of the glands or their extracts. Schiff, in 1856, (and later Kocher, 1883) showed that extirpation of the thyroids (with parathyroids) in the dog was followed by death in from 1–4 weeks, after exhibiting a characteristic symptom-complex, termed later by Kocher "cachexia strumipriva or thyreopriva": muscular tremors, convulsions, cachexia, emaciation, etc. This was later confirmed, and in some cases denied, by subsequent observers. In 1873, Sir Wm. Gull (and later, Ord, 1877) described "myxoedema" — a "cretinoid change in women"; and, in the same year, Sir Victor Horsley and Sir Felix Semon pointed out that myxoedema, (Kocher's) cachexia strumipriva, and sporadic cretinism were all due to a deficiency in, or loss of the secretion of, the thyroid. In 1886, Marie described acromegaly, and showed that this disease was due to a hypersecretion of the pituitary. In 1889, Brown-Sequard, then 72 years of age, announced to the Societé de Biologie de Paris that he had carried out upon himself a series of experiments with extracts of the testicle, proving that this therapy had "given him much physical strength, an invigoration of cerebral function, and a good appetite and digestion, and a restoration

of the fire and vigour of youth". It is not unlikely, however, that some of the effects which Brown-Sequard attributed to the use of the extract were, in reality, due to autosuggestion!

Bernard at this period appears to have amplified the conception of an internal secretion by assuming that all tissues in the body gave off something which was essential for nutrition, to the blood. This idea led to a revival of the old notions regarding the treatment of diseases of different organs by extracts of the corresponding tissues; and thereafter followed a period of organotherapy, (or opotherapy, substitution therapy, hormone therapy or auto therapy, as it has been called), during which every organ of the body was tested as to its remedial qualities in diseases supposedly produced by a deficiency of some internal secretion. However, much of this material was rendered scientifically valueless because it was much aggrandized for purposes of commercial gain. Indeed, one may perhaps herewith parenthetically quote the sapient words of Harvey Cushing who, some three years ago, declared, with regard to this aspect of the subject, as follows: "We find ourselves embarked on the fog-bound and poorly charted sea of endocrinology. It is easy to lose our bearing, for we have, most of us, little knowledge of sea-faring and only a vague idea of our destination. Our motives are varied: some unquestionably follow the love of discovery; some are earnest colonizers; some have the spirit of the missionaries and would spread the gospel; some are attracted merely by the prospect of gain and are [illegible] running ... P.T.O.

~~insufficient observations, stand pre-eminent~~ However, ~~much~~ running full sail before the trade winds ....."
~~of this organotherapy was rendered scientifically valueless because~~
~~it was much aggrandized for purposes of commercial gain.~~

Brown-Sequard in 1889 added to the conception of Bernard the new idea that certain glands not only secreted certain specific substances into the blood stream, but also tended to produce a definite correlation of function between different secretory organs; and in the same year, this was illustrated by von Mering and Minkowski who showed that removal of the pancreas was followed by hyperglycaemia and other general metabolic disturbances, affecting various other ductless glands & other organs, and resulting in death (from diabetes). Several years later, Schiff compiled additional data pertaining to the effects following the removal of the thyroid, these being mainly based on the clinical observations of the brothers Reverdin of Geneva (1882-3) and of Kocher (1883) on post-operative myxoedema, further confirming Brown-Sequard's view. This new theory really formed the basis of a conception unknown till that time regarding the effects of internal secretions on each other and on general metabolism, as shall be discussed afterwards.

In 1890, Horsley showed that post-operative myxoedema (which was at that time sometimes associated with spasms and tetanic convulsions owing to simultaneous excision of the parathyroids followed by apathy and coma) could be prevented in thyroidectomised monkeys if the thyroid was

successfully transplanted to the abdominal cavity. In 1891, George Murray, Horsley's pupil, employed the method of subcutaneous injection of thyroid extract in myxoedema; and Hector Mackenzie in London, and Howitz in Copenhagen, introduced the method of oral administration in 1892. It is of some historical interest to note that the first patient successfully treated by Murray in London in 1891 died of heart disease in 1919, aged 74 (Osler & Macrae). Medical science has, in fact, made no more brilliant advance in organo-therapeusis than in the cure of the ~~diseases~~ disorders due to ~~the~~ disturbed function of the thyroid gland by means of this form of "extract" treatment. It constitutes, indeed, a marvellous triumph in the annals of ~~med~~ experimental medicine; and for it, we are deeply indebted to Sir Victor Horsley and his pupil, George Murray.

In the succeeding years, Sir Sharpey-Schafer and Dr. Oliver (1895), Cybulski (1895), Biedl (1898), and Dreyer (1899) carefully studied the action of suprarenal extracts upon the cardio-vascular system.

By the end of the 19th century, then, we see that it was indubitably shown that our body contains certain aggregates of cells which possess an altruistic function, because they supply the organism as a whole with substances which have to do with its general welfare; and the mediums through which these internally secreting organs are able to exert their influence was

thus clearly demonstrated to be the blood, or more particularly, the blood plasma.

The 20th Century — up to 1924.

(a) Researches up to 1906. This century has witnessed the most remarkable advances in our knowledge of the internal secretions. To Blum is due the credit of shewing, in 1901, that subcutaneous injection of adrenalin (obtained from suprarenals by Takamine in this year) produced glycosuria. Italban[5], in the same year, shewed that removal of the ovaries in apes was followed by cessation of menstruation which, however, was afterwards restored by the successful grafting of another ovary. Morris and Glass[6] obtained similar results also in human beings. Frolich in this year also described the syndrome known by his name and named by Bartels "dystrophia adiposogenitalis"; and he showed its connexion with hypophitiotarism. Schulze and Szbolew[7] in 1902 proved that ligature of the pancreatic duct was followed by a complete atrophy of the pancreatic acini, whilst the cells of the islands of Langerhans were unaffected. These observations once more drew renewed attention to the internal secretion of the pancreas islets named by Sir Sharpey-Schäfer "insulin" two years previously, and they thus laid the direct trail that was eventually to lead to its isolation by Banting and Best of Toronto in 1922. The year 1902 also witnessed the discovery of Sir Wm. Bayliss and Professor Starling that a substance, "secretin", which was derived from the duodenal mucosa, could evoke the flow of the pancreatic juice. At about the same time, Professor Starling

and Miss Lane-Claypon demonstrated the existence in the female generative organs of a similar stimulant which could induce the growth of the mammary glands. Starling[8] therefore in 1906 proposed to apply to all these internal principles or "chemical messengers" (as he originally and more wisely termed them four years previously (Journ. Physiol 28, 1902)) the name "hormone" (Verhandl d. Naturforscher-Versammlung, Stuttgart, 1906), from the Greek ὁρμάω, to stir up, or excite, or arouse. But, inasmuch as some of these cellular products had been shown to retard a function, (e.g., the extract of the interstitial cells of the ovary tends to inhibit the uterus (Itagaki)), and as the term "hormone" is, etymologically considered, manifestly not applicable to such products, therefore, Sir Sharpey-Schafer[9] at the International Congress of Medicine in 1913. advised to include all these principles under the general term "autacoid substances", or, shortly, "autacoids", from the Greek ἄκος, a remedy, and αὐτος, natural. Thus, an "autacoid" was proposed by Sir Sharpey to represent any drug-like principle which was produced in internally secreting tissues and organs. He pointed out that these substances might then be grouped as "hormones" or "chalones" (from the Greek χαλάω, to make slack), according as they are excitatory or inhibitory in their action, respectively.*

It is perhaps of historical interest to note herewith

* An alternative word which might be used instead of "hormone" to indicate a "chemical messenger" (the term originally employed by Baylis & Starling) is "Hermone" from Greek Ἑρμης = Mercury (Sharpey-Schäfer).

that Starling's latest (1914) definition of the term "hormone" is much wider now than that he originally applied to organic principles of an endocrine nature (v.: Schafer's Endocrine Organs, 1924). "By the term 'hormone'", he said, "I understand any substance normally produced in the cells of some part of the body and carried to the blood stream to distant parts, which it affects for the good of the organism as a whole" (Proc. Roy. Soc. Med. vol 7, 1914, Therap. and Pharmacol. Sect., p 29). He gave as examples secretin, adrenalin, and carbon-dioxide, the latter a product of tissue metabolism which stimulates the respiratory centre to further activity. "Obviously", Sir Sharpey-Schafer points out, "this definition would include many substances normally present in the blood such as water, urea, glucose and inorganic salts, which are produced in various parts of the body and affect distant organs such as the kidneys: indeed, it may be supposed that most circulating materials will, when we know about their history, come into this definition." Sir Sharpey continues, "The expression 'hormone' has not hitherto been employed by physiologists and clinicians in this extended sense; the term has usually been restricted to the active organic principles of the internal secretions". Several terms notably "exciting and inhibiting hormones" (Biedl) and "incretion" were recently introduced to denote internal secretion; but they are so philologically incorrect or crude (e.g. Biedl's "exciting hormones" which is, etymologically, a tautology, and "inhibiting hormones" which, for

the same reason, is a contradiction) that an unbiased judgment would proclaim the term "autacoid" (Schäfer) as the correct one to apply to these principles.

(b) Recent researches, to 1924. Of the innumerable but nevertheless highly important researches of recent years, mention must be made

(1) of the discovery by Edkins in 1906 of "gastrin" – an autacoid produced by the gastric mucosa and influencing the secretion of gastric juice;

(2) of the fact recorded in the same year by Basch[10] that the removal of thymus in young dogs retarded their growth;

(3) that foetal extracts injected into a virgin rabbit caused a development of the mammary glands and promoted the flow of the gastric juice (Starling & Lane-Claypon, 1906)[11] (The "Foetal Hormone Theory").

(4) of the brilliant researches of Marshall and Jolly (1907), Carmichael & Jolly (1907), Steinach (1912 & 1920–22), Marshall and Runciman (1914), and H. Walker (1923–24) on the internal secretion of the reproductive organs; and of the works of Basch (1910), Mackenzie (1911), Healy and Kastle (1911), and Ott and Scott (1912) on the hormone of the mammary gland;

(5) of the observations of Erdheim (1906), Bing (1908), Macallum and Voegtlin (1908), Thomson (1910),

F. Mursk (1913); Cannon, du Bois, Cattell, Aschen, and Levy (1916), Reid Hunt (1923 + 1909), Paton, Findlay, and their co-workers (1917), Dyerre (1923), and Sutherland Simpson (1923) and many others on the pathological chemistry of the thyroid and parathyroids; and of the isolation of thyroxin from thyroid extracts by Kendall[12] in 1918;

(6) of the researches of Madelung (1904), Sir Sharpey-Schafer and Herring (1906), Harvey Cushing (1910), Oliver and Mackenzie (1911), and Sir Byrom-Bramwell (1915) on the pituitary body;

(7) of the work of Goodall (1905), Basch (1906), Klose and Vogt (1910), Gudernatsch (1912), and McClure and Park (1919) on the thymus;

(8) of the observations of Crowe and Wislocki (1914-17), Hopkins, Cunning, and Berry (1916), and Sharpey-Schafer and Lim (1919) with regard to the suprarenal extract (the active principle of which, viz: adrenalin, was obtained by Takamine in 1901 and since synthesised from catechol by the biochemists Stolz and Dakin);

and (9) — of the last and perhaps most important of all, — the pioneer biochemical work on pancreatic extracts of Rennie and Fraser (1904), Lydia de Witt (1906), Zuelzer (1908)[13], Forschbach, and Lefine (1909), Starling and Knowlton (1912)[14], E.L. Scott (1912)[15], Merlin and Kramer (1913)[16], Kleiner (1919)[17], and Clarke (1920)[18], — all of which anticipated and inspired those most brilliant

researches at Toronto of Banting and Best that culminated in the epoch-making discovery of insulin two years ago (Dec. 1922)

Conclusion.

In most instances, these internal agents are as yet wholly unknown to us chemically; and their presence can only be demonstrated by physiological experimental procedures. However, in some cases, some of which are briefly indicated above, they have been isolated and have been dealt with as definite chemical entities. Carbon-dioxide (Gley, and Starling) is a substance of this kind, because it plays the part of a hormone in stimulating the respiratory centre whenever it is produced in excess. Another one is "iodothyrin" (Baumann and Roos, 1896) or "thyroxin" (Kendall, 1918), which is the active principle of the thyroid, and has been demonstrated to contain iodine and to exert a peculiar action on the neuromuscular mechanism. Still another is "adrenalin" which, as mentioned above, was isolated from the suprarenal extract (medullary) by Takamine[19] in 1901 and has since been synthesised by Stolz and Dakin (v.: Professor Barger's "The Simpler Natural Bases", 1914). As a fourth might also be mentioned (Burton-Opitz) the hydrochloric acid of the gastric juice, which liberates "secretin" (Bayliss + Starling 1902) and "gastrin" (Edkins 1906) from the duodenal mucosa. By far the greatest number of these antacoids, however, are of still unknown composition (e.g. insulin), and their

presence has only been proved physiologically, for example, by injecting extracts of the tissues in which they are supposed to exist into the blood stream. Much work however as to the general chemical nature of these active principles has been done by Professor E. H. Starling, who emphasizes the fact that they are all of a simpler chemical nature than the enzymes, and that they partake of the nature of the crystalloids rather than of the colloids. Thus, they are dialysable and are, relatively, thermostable bodies, and are not rendered inactive ~~inactive~~ by prolonged boiling: a fact which sharply differentiates them from the ferments and enzymes. Further, many of these autacoids act instantly, their action, as Starling has shewn, resembling that produced by the active chemical principles of drugs, especially those of organic or vegetable origin (v.: Schafer's Endocr. Org., 1924). Some of them affect the tissues immediately they escape into the blood stream, whilst others have been shewn to operate more slowly, exerting their influence upon the growth and nutrition of special organs or of the body generally. The name "hormozones" (from the Greek ὁρμοζω, I govern) has accordingly been suggested for these "morphogenetic" autacoids by *Gley[20]. An example par excellence of this is the thyroid secretion which, as will be shewn ~~later~~ below, has been demonstrated to have a vast influence upon general metabolism and on various other functions of the body. Other internal secretions have

* Gley: Revue scientific, 4 mars, 1911, 48, 257-265; p 262.

been reported to have a similar "morphogenetic" influence; but Cramb and M. Taylor recently pointed out (Endocrinology, 6, 1922) that these act more or less through the thyroid. (Schäfer's Endoc. Organs 1924).

We have found that the expression "internal secretions" now embraces a far wider signification than that was originally meant by Claude Bernard (v.: Starling's definition, supra, p 13). Although it is said that the term is not now usually extended, as it used to be, to lymphatic glands, "of which the material production is merely of a morphological character" (Schafer), yet it has now come to denote, according to Gley, all materials contributed to the blood both by the tissues ~~and~~ as well as by the true "endocrine organs" (so named by Prof. Sharpey-Schafer from the Greek ἔνδον, within, and κρίνω, to separate), such like:

(1) carbon dioxide and urea (Gley, and Starling), and other products of metabolism;

(2) the secretions of the thyroids and of the parathyroids; of the thymus: (the inclusion of thymus among the true endocrines has been condemned by Sir Sharpey Schafer on the strength of the recent careful work of McLure and Park: — v.: Schäfer's Endoc. Org. 1924); of the liver (Gley)[20], the gastric, duodenal, and intestinal mucosa, and of the pancreas; of the spleen (Gley)[20]; of the suprarenals; of the pineal gland, and of the pituitary body; of the placenta, the

choroid (?) plexus (Baston-Opitz), the testes, and the ovaries; and of the uterus, the mammary gland, and the foetus. Gley*, in his "The Internal Secretions" (translated by Fishberg, Hober, New York 1917)[20], suggests the following classification (the comprehensiveness and correctness of which is however a matter of much debate), viz:-

A. Nutritive.
- glucose : liver.
- fat : intestinal mucosa.
- albumins of blood : intestinal mucosa and blood.

B. Harmozones.
1. Substances affecting nutritive changes
   - Sugar metabolism : pancreas
   - sugar mobilization : adrenals.
2. Substances helping to maintain int. medium
   - antithrombin : liver.
3. Morphogenetic.
   - testicles,
   - ovaries,
   - thyroid,
   - hypophysis (pituitary)
   - thymus.

C. Hormones.
- Chemical
  - activating the trypsin : spleen.
  - catabolic : thyroid.
- Physiological
  - secretin : duodenum.
  - adrenalin : suprarenals.
  - galactogogue : placenta.

D. Parhormones
- Carbon dioxide : muscles and glands.
- Urea : Liver.

Every one of these organs may be regarded as presenting at least three of the characteristics ordinarily assigned, in the state of our present knowledge, to internally secreting

* Also: Revue scientific, 4 mars, 1911, 49, 257-265; p 262.

structures, namely (Burton-Opitz):-

(a) that "the cells comprising them are usually arranged in the form of acini and embrace a certain amount of granular and other material from which the secretion may be derived";

(b) that "whilst not in possession of true ducts, they lie in close relation with definite efferent and afferent blood vessels and lymphatic channels";

(c) that "their product can be isolated chemically from their venous blood or lymph";

(d) that "their substance or the blood or lymph returned from them may be shown to possess a specific physiological action"; and

(e) that "their removal or disease is followed by a loss of definite function which is absolutely essential to the health and very existence of the animal" (from Burton-Opitz's Physiology).

* * * * * * * * * * * * * *

Having thus briefly indicated the general channels through which our present knowledge of the internal secretions were and are still being derived, we may now proceed to review in more detail the history of the development of our knowledge regarding the ~~individual~~ individual endocrine organ and of its specific internal secretion‡.

‡ A very instructive general survey of the subject is given by Dr. A. E. Gow in a B.M.A. lecture delivered before the Hereford Division of the Brit. Med. Assoc. on Feb 25/1924 (reported in Brit. Med. Journ., April 19/1924).

PART II

THE HISTORY OF THE DEVELOPMENT OF OUR KNOWLEDGE REGARDING THE ~ INDIVIDUAL INTERNAL SECRETION ~

SECTION II

A. The THYROID and ACCESSORY THYROID GLANDS.

The thyroid (Greek, thyreos, shield) is a very vascular gland on the anterior aspect of the neck, and consists of a right and left lobe which are connected with one another by a bridge or isthmus of the same tissue extending transversely across the trachea. Its tissue is composed of a large number of "vesicles", which are lined by a single row of cuboidal, or low-columnar, epithelium, and which contain a peculiar colloid material. "Aberrant" and "accessory" thyroidal tissues viz: the lingual, mediastinal and "cystic" thyroids, have been described (J. W. Packard).

Earliest Theories regarding the Thyroid Secretion

Although Kuig, in 1835, had described the colloidal structure of the thyroid vesicles and had demonstrated that their contents could be made to flow into the surrounding lymphatics by gentle massage of the lobes of the gland (Albutt, Rolleston), yet it was not till many years later, i.e. the last quarter of the 19th century, that the real physiological functions of the thyroid began to be understood. Of the numerous hypotheses until then framed to account for the presence of this organ, some few showed a glimmering perception of the truth; but most of them, if ingenious were fanciful and

altogether far-fetched. The gland was until then regarded as absolutely functionless by a number of eminent scientific men of that time, like Sir John Simon. Some authorities surmised that the gland was seated in the neck simply to give a shapely roundness to its contour (Wharton); some looked on it as providing a mechanical protection covering for the numerous important vessels and nerves underlying it; others thought that it was in some way connected with the mechanism of voice production; others, again, impressed by the number, size, and perplexing meanderings of its blood vessels, concluded that it acted as a safety valve regulating the blood supply to the brain (Cyon). Still another thesis was made that each lobe had a special nutritive relationship with the corresponding cerebral hemisphere, manufacturing some substance needed for cerebral activity (Sir John Simon). Another hypothesis assured us that the gland swells during sleep, over which phenomenon it was supposed to exercise control. It was alleged by others that there was a close relationship between the thyroid gland and the female sexual organs, in support of which argument was urged the variation in size it underwent at the menstrual periods or under the influence of strong sexual excitement*, and the greater frequency of thyroid disease in the female sex. Others, again, supposed that the gland had special relations with the central nervous

* Heindenreich, 1844. (Vide also E. Couland, Ann. de Med., Dec. 1923, p. 516 & B. M. J. Ap. 12, 1924, Supp., p. 58.; also footnote on page 99 of this essay.)

system, swelling or throbbing under such influences as joy, anger or sorrow.

Early Observations and Conclusions:

Grave's Disease and Cretinism — 1786-1850

Wagner was the first at this period to show that in young animals the removal of one lobe was followed by hypertrophy of the other; and that after complete removal of the gland proper, the accessory thyroids, which are present in some animals, sometimes hypertrophy and function vicariously for the excised gland.

Diseases of the thyroid were at this time quite well known*; but little was known of their physiological significance. Thus, in the posthumous writings of Caleb Hillier Parry (1825) was a description of 8 cases of "Enlargement of the Thyroid Gland in Connexion with Enlargement or Palpitation of the Heart" (Osler & Macrae). In the first of these cases seen by Parry in 1786, the exophthalmos was also described: "the eyes were protruded from their sockets, and the countenance exhibited an appearance of agitation and distress, especially in any muscular movement." (The Italians, however, claim that Flajani was the first to describe the disease, though, according to Moebius, his account of the disease, published in 1800 — some authorities give the date as 1798 — "was meagre and inaccurate, and bore no comparison with that of Parry") Soon after, Adelmann, in Germany, reported 2 cases, with an autopsy. (1828) R. Graves

* References to suspected cases can be found in the 18th Century, as in Morgagni (Dock: Osler's System of Medicine, vol. vi, p. 415)

also described the disease in 1835, and Basedow gave a fuller account in his original paper "Exophthalmus durch Hypertrophie des Zellgewebes in de Augenhöhle", in "Wochf. d. ges Heilk", in 1840. Basedow's three cardinal symptoms of this condition were "a rapid and irregular heart; a raising of the temperature usually 1° – 2° above the normal; prominent, staring eyes, with the thyroid gland somewhat enlarged." To these have since been added many other secondary symptoms like increased appetite, insomnia, restlessness, intensified sensations, mental excitement accompanied by hallucinations, muscular tremors, anaemia, asthenia, loss of weight, and many others. Ordinary endemic goitre (struma or bronchocele – "Derbyshire neck") had, of course, been long known, and its aetiological relationship with drinking certain forms of water which was rich in lime and magnesia (and with a high degree of radioactivity (Ridin) but poor in iodine, had been acknowledged to be a proved fact; and it had been further demonstrated that the vesicles contained much colloidal material during this condition.

Reference has ~~also~~ been made above (page 6) to the observation of Hasling who, in 1850, in Switzerland, noticed that the thyroid gland was usually absent in cretins. However, it was not until several years later that it was shown that all these conditions were due to hypersecretion

of the thyroid and their operative measures (Kocher, 1883) for their cure was established.

The Beginning of Scientific Experimentation and careful Clinical Observations — 1856, et seq.

(a) Schiff[21] — 1856. The real significance of the thyroid was uninvestigated till the middle of the 19th. century when, as in the case of most ductless glands, clinical observations of surgeons began to contribute materially to our knowledge of its internal secretion. Schiff[21] was the first to shew in 1856 (and again in 1859) that the removal of the entire thyroid in dogs induced certain pathologic conditions which invariably proved fatal in the course of 3 - 4 weeks. Previous to this, we have similar experiments by Sir Astley Cooper, Rapp, and Bardeleben, which at the time led to no definite results. Subsequently, however, in all these cases, thyroidectomy was found to be followed by alarming symptoms which presented themselves chiefly as metabolic disorders like marked asthenia followed by motor and sensory paralysis, emaciation, apathy, tremors and usually clonic, tetanic, and spastic convulsions, followed by death in from 9 - 12 days (Reverdin; Kocher; and Billroth[22]). This was confirmed by subsequent observers, though many exceptions were noted, especially amongst the herbivora.

(b) Gull, Semon, Ord, Horsley, Kocher, etc.: 1873 - 1891. The study of the thyroid seems to have been left in abeyance after

Schiff's observations of 1856, until the attention of physiologists and clinicians was again especially directed to the importance of this organ by the clinical findings of Gull, Horsley, Felix Semon (1873), and Ord (1877) on myxoedema and cretinism, and by the researches of the brothers Reverdin of Geneva (1882), Kocher (1883), and Schiff (1884) on thyroidectomy. Gull, in 1873, described "a cretinoid change affecting women", and he was the first to point out a well-defined pathological entity which he termed "myxoedema adultorum" — "a condition in which the features are swollen and imperfectly outlined, the skin thickened, swollen, dry and oedematous, from accumulation of mucin in the subcutaneous tissue; the hair is coarse and scanty and the patient is mentally apathetic, idiotic, easily fatigued, and has a tendency to abnormal deposition of fat" (Buxton-Opitz). Gull also pointed out that myxoedema and cretinism (or infantilism) were due to hypothyroidism. Horsley and Felix Semon showed in 1873 that the changes following complete removal of the gland ("cachexia thyreopriva" or "strumipriva") and myxoedema and sporadic cretinism were all due to a loss of function of the thyroid gland. In 1884, Schiff operated upon his 2nd series of sixty dogs of which fifty-nine died within 3 weeks. Schiff's study drew renewed attention to the thyroid, and spirited efforts were made henceforth to unravel the mystery of its function. Then, it was

soon discovered by Eiselberg[23] in 1892 that the serious symptoms — named by Kocher "cachexia thyreopriva (strumipriva)" — following its total extirpation could be prevented by permitting a portion, say, of its lower extremity, (or one-sixth, (Beresofsky)), to remain in the body. Likewise, Schiff and Horsley showed that the successful transplantation of the thyroid to some other part of the body, such as the peritoneal cavity, protected the animal against the consequences of thyroidectomy; and this knowledge was immediately applied to human beings in cases of cretinism and myxoedema with astonishingly successful results. Vassale[24], Mackenzie, and Fox, Murray (London), and Howitz (Copenhagen) in 1891 proved that the alarming effects of thyroidectomy could also be obviated by the feeding of thyroid substance, or the injection of thyroid extract. Brilliant results in myxoedema and cretinism were obtained by these observers. Lastly, Kocher succeeded in showing that Graves's disease was due to a hypersecretion of the thyroid and[25] a flooding of the system with an excessive amount of its secretion. He demonstrated

(1) that symptoms of Graves's disease could be produced in the normal animal (rabbit), either by continued feeding with thyroid substance, or by intravenous injection of thyroid extract; and

(2) that in 90% of his cases of Graves's disease, partial extirpation of the thyroid, or, in fact, in many of his cases, mere reduction of its vascularity by ligaturing one of its main arteries, gave rise to an almost immediate

amelioration of the symptoms.

[Mention may herewith be made also of the fact that thyroidectomy was found by Professor Lorrain Smith in 1894 to lower the body temperature and to lessen the heat regulating power (Journ. Physiol. 16, 1894).]

(c) Baumann ("Thyroidin"), Reid Hunt, Kendall ("Thyroxin"), etc.: 1891–1918. The years following 1891 were mainly devoted to the pursuit of the problem of the biochemical nature of the thyroid secretion, and to the further application of the facts of experimental physiology to the problems of clinical therapeutics. Even now, much uncertainty still prevails regarding the chemical nature of the active agent contained in the secretion of this gland.

Baumann[25] (with Roos) was the 1st to isolate from the thyroid extract a substance to which he gave the name "iodothyrin" or "thyroidin", and which he found contained some 9·3% iodine. This discovery of iodine in the extract of the gland no doubt directly suggested the treatment of certain diseases of that gland by iodine compounds — a treatment which has been found to be eminently successful (v.: D. Marine, Arch. Intern. Med. Dec. 1923, p. 811). Whilst the exact action of Baumann's iodothyrin has not yet been definitely ascertained, nevertheless there is no question that it is at least closely associated with the activity of the thyroid, inasmuch as it has been shown that its activity is much connected with the metabolism of iodine. Further, no demonstrable quantities of iodine are ever present

in extreme conditions of goitre, and the administration of thyroidin in cases of bronchocele or struma (endemic goitre) and of myxoedema has been found to be attended with beneficial results.

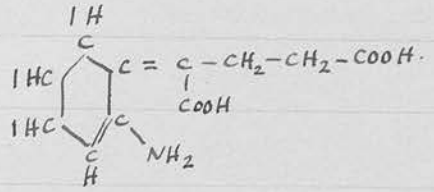
Reid Hunt[26] in 1905 showed that mice fed with thyroid substance were very resistant to poisonous doses of acetonitrile*; and four years later[27] he demonstrated also that the physiological effects of thyroid extracts were proportional to the amount of iodine contained in them, and that the minimum amount of iodine necessary to maintain the usual histological picture of thyroid tissue did not fluctuate materially in any given species.

Gudernatch[28], in 1913, Graham[29], in 1916, and Rogoff and Marine[30], in 1917 & 1919, showed that tadpoles exposed to the influence of iodine-free sheep thyroid were retarded in growth, whilst their differentiation (metamorphosis) took place at a much faster rate.

Kendall[31] in 1918 isolated a similar to, but less complex than, Baumann's thyroidin of 1896. With body Osterberg in 1919, (Journ. Biolog. Chem. 40, 1919; also Harvey Lectures, (1919-20), he succeeded in identifying this substance chemically as tri-iodo-oxyindol-propionic-acid, (or "thyroxin", as he

* this acetonitrile phenomen was recently found to be positive for the blood of patients affected with exophthalmic goitre & is thus a valuable diagnostic test (v.: Hunt: American J. of Physiol, 63, 1923.)

originally termed it). This substance has been shewn to be related to tyrosine, adrenalin, and tryptophane, and to occur in the "open-ring" form in the natural thyroid secretion in the body. Kendall gave the formula ("open-ring" form) as:



Kendall maintains that this compound is responsible for all the characteristic physiological and therapeutic effects produced by the thyroid juice or extract, the only exception being that it does not cause an increased contraction of the suspended intestinal muscular strip which is actively excited by thyroid extract (Schafer). We may infer, then, that the active principle of the thyroid internal secretion is an iodine-containing hormone (the efficacy of which has been proved to depend not so much on the iodine as on the character of its combination with other substances). (Burton-Opitz)

Recent Physiological Researches.

(a) to 1920. A further development of our modern knowledge of this organ is furnished by various researches recently made to shew the functional correlation between the thyroid secretion and other organs (cp. Brown-Sequard's thesis of 1889, p 9). Thus, Asher and Lusty[32] have proved that the thyroid and suprarenal secretions augment the activity of each other. Du Bois, Cannon, and Cattell[33] recently proved that the thyroid possessed secretory autonomic nerves, and are thus closely related to all tissues and organs in the body similarly supplied. Chalmers Watson recently shewed that there is a close relationship between the size and

and structure of the gland and the general nutrition of the animal (Schafer's Endocr. Organs). Krause and Cramer found that in the cat and rat fed with thyroid, glycogen disappeared from the liver. F. Munk (1917) demonstrated a diminution of lipoids in the cortex of the suprarenals in similarly treated animals, whilst the same procedure was found to increase the mitosis in pancreatic cells (Kojima) and cutaneous glands of the salamander tadpole (Lin: Quart. J. Exp. Physiol., 11, 1920).

(b) 1920 — 1924. Of the very numerous findings of the last four years, mention may be made of the following important ones.

A: 1920. (i) McCarrison, working in India, (Ind. Journ. Med. 1920) found that vitamine-poor diets caused a decrease in the size and weight of thyroid; whilst vitamine-rich ones had the opposite effect. He also has demonstrated water-borne microörganisms as the causative factor of endemic goitre.

B: 1921. (i) E. Mellanby found that vitamines occuring in butter accentuated the symptoms of hyperthyroidism, and he recommended that butter be excluded from the diets of patients afflicted with exophthalmic goitre (Journ. Phy. 60, 1921, Proc. Physiol. Soc.).

(ii) G. W. Crile (New York. Med. J. 1921) found that the administration of adrenalin excited the thyroid to activity (cp. Asher & Levy's observations, p 30), probably acting, as has been suggested by Sir Sharpey-Schafer (End. Org. 1924)

through its sympathetic supply.

C: 1922. (i) The immense importance of the thyroid secretion on general metabolism was further demonstrated by Professor J. C. Meakins and Dr. Davies in a series of valuable observations which they reported to the Edinburgh Medical Journal, 1922.

(ii) Cannon and Smith adduced further evidence of the nervous control of the thyroid secretion (Am. J. of Phys., 60, 1922); and C. Hart found that ~~the thyroid~~ it was increased by external cold and by morphine, quinine, and strychnine, the action in all probability being produced through the sympathetic nervous system (Schafer) (Arch. f. d. ges. Physiol., 191, 1922) (iii) The cells of the thyroid were found by Cowland (C. r. soc. biol., 87, 1922) to be very sensitive to X rays which ~~found~~ observed caused them to undergo degeneration changes and a diminution of activity. Treatment by X rays has since been proved to be of some success in certain cases of exophthalmic goitre (G. R. Murray).

D: 1923. (i) Sir Sharpey-Schafer (Quart. J. Exp. Phys., 13, 1923) found that the blood or serum of patients suffering from Graves's disease excited the contraction of a muscular strip of intestinal muscle to a far greater extent than the same amount of blood or serum from normal persons — a finding of vast diagnostic importance.

(ii) Sutherland Simpson found that thyroidectomised sheep took far longer to learn to find

their way to food through a maze than controls (Quart. J. Exp. Phys., 13, 1923).

(iii) B. Romeis determined by the tadpole test that the activity of Kendall's thyroxin was considerably diminished if it was allowed to stand with blood in vitro, and was rapidly abolished if introduced into the circulating blood (Biol. Zeitschr., 140, 1923).

(iv) N. M. Dott (Quart. J. Exp. Phys. Nov 1923) showed that the pituitary and thyroid were inter-correlated with regard to influence on growth of the body.

E: 1924. (i) Dr. Alice White, in her article in the Brit. Med. Journal of Feb 2/1924 on "The Effect of Thyroid and Ovarian gland Extracts in Cases of previous Miscarriage and Stillbirth" showed that in 100% of her cases of previous still-births and miscarriages, 90% was found to bear healthy children after administration of thyroid combined with ovarian extract; 30% had children above normal weight; and those of the rest who had subnormal children successfully improved their weight after birth by similar extracts.

Conclusion

The discovery of the relationship between thyroid and those morbid conditions caused by its disease is specially interesting, because important practical results in their treatment have followed close on the heels of experimental investigation. The outcome of the best of recent

researches on the thyroid has been the recognition of the enormous influence that its internal secretion exercises on normal growth in childhood, and on metabolism: increasing the output of carbon-dioxide, nitrogen, and phosphoric acid, and the consumption of oxygen, — thus stimulating both the vegetative and the nervous system. It is upon this finding that the therapeutic value of thyroid feeding in obesity has been shown to rest.

The importance of thyroid medication has of recent years been more and more established. This therapy has been found beneficial, not only in cases of endemic goitre and myxoedema (Hale-White) and the mental disorders accompanying them, but also in a few cases of climacteric insanity and in epilepsy (Easterbrook). Its beneficial therapeutic effect has been satisfactorily demonstrated in cases of dry chronic eczema and chronic psoriasis (G. R. Murray); sometimes in chronic exophthalmic goitre (Mackenzie); in acromegaly (Gibson); in "backwardness" in children, and in adenoids associated with thyroid inadequacy (Waller & Cobb; New York Med. Journ., Jan 1922); for nocturnal enuresis (Williams); for obesity and adiposis dolorosa (Hutchison); for delayed union of fractured bones and in articular and muscular rheumatism (Halsey: Barker's Endocrinology, 1922); in various affections of the skin, hair, and nails, in derangement of the nervous system associated with thyroid deficiency, and in certain forms of infantilism (Horsley; Leopold-Levi & de Rothschild) [from Sir Shorey-Schäfer's Endoc. Org., 1924]

SECTION III

B. THE PARATHYROIDS.

The parathyroids are four small ovoid masses, different wholly in structure from the thyroid, and embedded in the substance of that gland on either side of its lateral lobes. They vary somewhat in position in different animals and individuals (Thomson)[34]. They may also appear in the form of accessory masses along the trachea.

The Development of our Knowledge regarding the Parathyroid Internal Secretion: 1880–1896.

We have seen that definite and emphatic results were obtained with work on the internal secretion of the thyroid. Further and more careful experimental work however made it necessary for the physiologists to distinguish between thyroid and parathyroid secretion. Most of the symptoms of thyroidectomy were described before the parathyroids were recognised as a definite and different anatomical entity, late during the period of thyroid experimentation. We have noted above that notable deviations from the effects of thyroidectomy described by Schiff in 1856 were observed, especially amongst the herbivora. In fact, many of the symptoms that were ascribed to the loss of thyroid, e.g. the muscular tremors and tetany, were undoubtedly caused by simultaneous excision of the parathyroids.

To Sandström[35] the Swedish anatomist is due the credit of having discovered these bodies in 1880 (although some authorities state that

they were first noticed in the rhinoceros by Owen in 1862 (albutt and Rolleston), by Remak in 1855, & by Virchow in 1863 (Dock: in Osler's System, Vol vi, p382)). Kohn[36] described their microscopic features fully in 1895. Not long after Sandström's discovery, Gley (in 1891) proved that the symptoms following thyroidectomy were marked by different from those produced by removal of the parathyroids. A re examination of the symptoms by Gley showed that these arranged themselves in two groups, one of which was characterised by disorders of metabolism such as malnutrition and cachexia, the other, by defects of nervous function such as muscular tremors and tetany (the term "tetany" having been first employed by Corsivat in 1852 (Schafer)). The subsequent investigations of Vassale and Generali in 1896 fully confirmed Gley's deduction — although it is even yet not now accepted by some present authorities like Forsyth, Swale Vincent, Jolly, etc. Nevertheless, it may now be regarded as certain that "pure" thyroidectomy produces a state of malnutrition, terminating in the condition of cachexia strumipriva (Kocher), whilst parathyroidectomy alone results in muscular tremors, spasms, continuous flexing of the hand, tetany, stiffness and rigor of the entire body, and loss of muscular coördination & strength, exaggerated irritability of the autonomic and central nervous system — the symptoms constituting the acutely toxic clinical picture of what has been termed "cachexia parathyreopriva" (Bing, & Biedl)[37]

Modern Findings: 1906-1923.

(a) 1906-1910. The problem of the parathyroid secretion

does not appear to have been actively pursued from 1896 till the researches of Erdheim in 1906 again directed attention to its pathological chemistry. Fleischmann and Erdheim[38] in 1906 led evidence in favour of the conception that the parathyroids preside in some way over calcium metabolism, and the latter authority drew attention to the fact that in children, and in parathyroidectomised rats suffering from chronic tetany, calcium failed to be deposited in the constantly growing teeth which, as a result, became soft and fragile. Edmunds and Biedl[39] in 1907 recorded the development of colloid staining vesicles in the parathyroids in a case of thyroid atrophy in man. Forsyth[40] described an altered condition of these organs also in a case of myxoedema in the same year. In 1908, Macallum and Voegtlin[41] found that post-operative parathyroid tetany could be mitigated or even abolished by the administration of parathyroid extracts, sodium bicarbonate, alkalies, and especially Calcium salts, the latter fact confirming Erdheim's original suggestion that tetany results from calcium deficiency*. During the next year, Macallum also showed that bleeding and infusion of saline solution caused tetany to disappear, and that injection of the blood serum of animals afflicted with tetany produced the symptoms of cachexia

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* This observation of Erdheim, and of Voegtlin & Macallum, was recently confirmed (in 1920) by Luckhardt & Goldberg (Journ. Amer. Med. Assoc., 20, 1920) who found that the symptoms of tetany in dogs could be absolutely controlled by oral administration of 1·5 grammes of calcium lactate per kilo daily.

parathyreopriva in other (normal) animals.

(b) 1911 – 1923. In 1911, W. H. Brown[42] showed that the results of parathyroidectomy could be obviated by grafting parathyroid tissue from the same species — a definite proof of its endocrine nature. The ophthalmologists in 1916 reported that chronic tetany was often associated with cataract[43]; and in 1917 Twiddy and Prof. Paton[44] of Glasgow advanced a new hypothesis that the parathyroids influence the activity of the muscles and possess certain powers of detoxication by neutralising and thus preventing the accumulation of certain protein metabolic products, especially guanidine, which they showed is formed in large numbers after parathyroidectomy and found gave rise to fatal tetany similar to tetania parathyreopriva or idiopathic tetany when injected intravenously. These observations were recently confirmed (1922) by Yoshimoto (Quart. J. Exp. Phys. 12, 1922) and (1923) by Drogstedt and Peacock (Am. J. Phys., 64, 1923)

Conclusion

A considerable divergence of opinion still exists as to the significance of the parathyroids. Some authorities still sponsor the view that these organs are just immature thyroid tissue, and they point out that thyroidectomy is not infrequently followed by hypertrophy of, & formation of colloidal thyroid-like cysts in, the parathyroids. The apparent contradictoriness of the results that are from time to time still being obtained in parathyroid experimentation has been shown to

result from the variations ~~of~~ in the morphological distribution of the organ in different animals (v.: Thomson, p. 35). The matter ~~of the internal secretion~~ of the parathyroids does not seem definitely settled yet by the physiologists, though they are agreed that they furnish an internal secretion which supplements that of the thyroid gland and controls calcium metabolism. Even this latter calcium theory, they assure us, requires further confirmation!

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SECTION IV.

C. The INTERNAL PRINCIPLE OF THE THYMUS.

The thymus is a glandular mass situated in the ~~antero-posterior~~ superior recess of the mediastinum, and it covers the great vessels.

Vieussens was the first to give a complete account of the thymus in about 1660; and the introduction of the microscopic study of this organ has led to a long dispute as to the nature and origin of its component cells.

The Development of our Knowledge Regarding its Secretion — 1905-1919

Aside from the demonstration of the fact that the thymus reaches its maximal development coincidentally with the maturation of the sexual organs and then gradually atrophies ("involution"), nothing appears to have been for long done experimentally with a view to unravelling its function till Goodall[45] and Paton[46], in 1905, shewed that its removal gave rise to a more rapid development of the testes and that, correspondingly, the removal of the testes (castration) delayed its atrophy or involution. Basch, in 1906, shewed that thymusectomy in young dogs was followed by such developmental anomalies as retardation of growth and rachitic changes in bones. In 1910, Klose and Vogt[47] discovered that the organ was especially concerned with the process of nucleic acid synthesis. Haroland

and Vincent[48] in their researches on thymusectomy in 1911 observed that the thymus was not essential to adult life, and that its complete removal in young animals did not prove fatal, as was formerly supposed. They found, nevertheless, that it resulted in retardation of the growth of bones, mental deterioration, and a marked tendency to adiposity. Attention may be called also to the experiments of Gudernatch[49] in 1912 which showed that young tadpoles fed on the thymus gland were stimulated to excessive growth, whilst the changes of metamorphosis to the frog stage were correspondingly delayed (v.: the same observer on thyroid feeding, p 29). Many observers[50] recently pointed out that hyperthymisation was not infrequently associated with acromegaly, genital hyperplasia, eunuchoidism, Addison's disease, and especially Graves disease; and that pieces of the thymus of rabbits, when transplanted to other regions of the body, were affected in precisely the same way as the intact organism, by castration and sexual stimulation (1917). Ruhräh showed that the gland was congenitally atrophied in marasmus and in many chronic wasting disorders of children; and Symmers recently ~~found~~ demonstrated ~~not~~ thymus hyperplasia in status lymphaticus (Osler and Macrae).

Conclusion.

The state of our present knowledge of the internal secretion of the thymus, the physiologists tell us, is at present so obscure and indefinite that we can only say that whilst this organ is not absolutely essential to life, it is,

by wholly chemical means, concerned with growth; that it furnishes a chalone which exercises a restraining influence on the development of the reproductive organs (especially in the male); and that it exercises a metabolic influence which attains its greatest importance at about the time of maturation. However, careful experiments made in 1919 by Park and McLure (Am. J. Dis. Ch., 18, 1919) on dogs showed that no appreciable result was obtained by removal of the thymus; and the evidence for its endocrine function is therefore no greater than that for any other of the lymphoid structures like the tonsils, haemolymph glands, and spleen (Schäfer). Indeed, the thymus has been expelled from authoritative text books of endocrinology like the new edition of Sir Shafey-Schäfer's work!

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SECTION V.

THE INTERNAL SECRETION OF THE LIVER, THE GASTRIC & DUODENAL MUCOSA —.

D. THE INTERNAL SECRETORY PRODUCTS OF THE LIVER.

Historical Survey.

Reference has been made above to the views of the ancients (Pythagoras and Plato) regarding the function of the liver (p. 2), and to the full description of this organ by Glisson in his monograph "De Hepatae" — the first medical book of that nature — in 1654 (p. 4). The products of its external secretion, viz: bile, has been since Glisson's time thoroughly investigated, but nothing was known regarding its internally secreting power till Bernard, in 1857, taught that it also furnished an intra hepatic principle (in connexion with which Bernard first used the term "internal secretion" ("secretion interne")), which he called "glycogenase" and shewed to be "concerned with carbohydrate metabolism: synthesising sugar and mobilizing glycogen, and reconverting the latter substance to sugar when necessary." (Bernard). Bernard's view was, not long after, confirmed by Boek, Hoffmann, and Sieger, who found that the removal of the liver or ligaturing of its blood vessels caused the sugar in the blood to disappear.

The liver has also been found to have an influence on protein metabolism in that it secretes various internal principles*, like arginase etc., (Kossel and Dakin, 1904)[51] which make the production of urea possible. Schrödder, Mellanby, Folin, Schaffer, Hopkins, and many other biochemists have recently contributed much to our knowledge of these various intrahepatic principles; and Howell[52] some years ago (1911) promulgated a new thesis in affirming the presence of an internal principle, "antithrombin" which, he tells us, prevents coagulation of blood in the body of the normal animal.

E. THE INTERNAL SECRETION OF THE GASTRIC & PYLORO-DUODENAL MUCOSA.

Historical Survey.

An examination of the accounts of the preliminary experiments of Claude Bernard, Popielski, Wertheim, and Lepage reveals the fact that these observers (rightly, in the light of modern knowledge) supposed that the gastric and intestinal (duodenal) mucosae produced an internal secretion of a true endocrine nature. In the elaboration of these original experiments, Sir

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* These various intrahepatic principles come properly under the category of "ferments" or "enzymes", like pepsin or trypsin, and are not usually classed with internal secretions of an endocrine nature. (v. Supra, p 17)

Wm. Bayliss and Prof. E. H. Starling in 1902 found that the duodenal mucosa contained a "chemical messenger" or "hormone" which they named "prosecretin" and which, whenever the reaction of the adjoining medium became acidified by the hydrochloric acid of the gastric juice, was liberated as "secretin". They shewed that this "hormone", "secretin", was absorbed into the blood and carried to the pancreas, liver, and intestine, where it excited a flow of the corresponding digestive secretions. They found that the injection of the neutralised hydrochloric-acid-extract (= "secretin") of the duodenal mucosa produced a rapid flow of the pancreatic juice, whilst the watery-extract (= "prosecretin") did not.

A similar hormone, viz: "gastrin" (derived from the inert "pro-gastrin") was demonstrated four years later (1906) by Edkins to reside in the pyloric mucosa; and of late years, similar experiments on the gastric mucosa have been carried on by Dr R. K. S. Lim of the Histology Department of Edinburgh University under Prof. Sir Edward Sharpey-Schafer.

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SECTION VI.

F. THE INTERNAL SECRETION OF THE PANCREAS : INSULIN.

The Pancreas is a club-shaped, tubulo racemose gland, about 5½" long and 1½" broad, situated transversely across the posterior wall of the abdomen, behind the stomach, and in front of the great vessels at the level of the 1st lumbar Vertebra

Ancient Knowledge of Pancreatic Diseases; Diabetes*.

Although the diseases of the pancreas have been longest known of ~~any~~ all ~~other~~ internally secreting glands, yet the mystery of its internal secretion* was almost the most late to be unravelled;— but the process of that unravelling is ~~the~~ most certainly unique in the history of science.

(a) 1500 B.C (Egyptian Medicine) — 1679 A.D. (Willis). In the papyrus Ebers (which is a copy of an Egyptian medical encyclopaedia already old in the time of the lawgiver Moses), there is mention of polyuria (1500 B.C). Indeed, it is hard to conceive that such a marked pathological departure from health could at any time, however primitive, have escaped observation. The disease was known to Celsus (50 A.D.); yet no notice of it is to be found in Greek writings earlier than those of Aretaeus of Cappadocia (circa 150 A.D) who was Galen's contemporary,

* Much of the subject matter for this section is obtained from the "System of Medicine" by Allbutt and Rolleston.

and was probably a Roman physician. Aretaeus was the first to use the term "diabetes" (from the Greek word διαβήτης, signifying a syphon) which he described as "a wonderful affection melting down the flesh and limbs into urine". His description, like that of Galen (131 – 210 A.D.) who wrote at great length on the disease, laid stress on the polyuria and thirst. However, the important fact that the urine contains sugar escaped the notice of all the writers of the Egyptian as well as the Greek and Roman periods. Nevertheless, if we may trust some passages of the Indian writer Ayur Veda (circa 500 A.D.), this fact was already at that time known to the Hindus. (Hirsch)

No further observation on the disease was made during the Dark Ages: and in this respect, this period hardly belies its name! During the 15th century, however, a Cingalese writer undoubtedly referred to diabetes as "madu mehe (= "honey urine"), and, in this respect, Eastern Medicine was far ahead of Western knowledge, for it was not until fully two centuries later that Willis the English physician in 1679 (some authorities give the date as 1674) mentioned that the diabetic urine had a sweet taste, "as if there has been sugar and honey in it." Willis was also the first to recognise the distinction between a saccharine and a non-saccharine form of diabetes. (Willis: "Pharmaceutice Rationalis", 1674)

(6) P.T.O.

(b) 1776 - 1797. It was not till the last quarter of the 18th century that fresh contributions began again to be made to our knowledge of this condition. Dobson of Liverpool in 1776 chemically demonstrated the presence of sugar, and this discovery so impressed the learned Cullen that he would hardly allow that this was not true of all ~~cases~~ cases of diabetes. Indeed, it was not till the last century that the distinction was firmly established which we now recognise in the names diabetes insipidus and diabetes mellitus.

Rollo, writing in 1797, gave an admirable account of the disease and recommended the use of a protein diet.

References to other pancreatic diseases in ancient writings.

References to other disorders of the pancreas may be found in comparatively ancient literature. Thus Alberti in 1578; and Heurnius in 1599 wrote of diseases of the pancreas along with those of the mesentery. Tulpius, in 1641, wrote on the suppuration of the gland; and in 1682, Regnerus de Graaf showed that excessive salivation (sialorrhoea) was a pancreatic disease, and hinted that there was a sympathetic connexion between the pancreas and the salivary glands. In not a single one of these cases, however, was a connexion established between pathological symptoms and endocrinological function. ~~pancreatic disease~~.

The Search... P.T.O.

The Search for the Pancreatic Antacoid.

Early clinical investigations: 1788–1877.

Cowley was the first in 1788 to draw attention to the co-existence of pancreatic disease with diabetes. More interest became focussed on the pathology of this condition when Claude Bernard in 1849 shewed that the liver after death contained sugar, and when he further demonstrated the glycogenic function of this organ in 1857. Previous to this, Gmelin and Tiedemann in 1823 had shewed that sugar was formed by digestion of the carbohydrates; and Ambrosiani in 1835 had again demonstrated the presence of sugar in the blood, thus confirming Dobson's finding of 1775 & 1776 that the blood serum of diabetics "had a sweet taste". In 1874, Külz discovered that diabetics could assimilate laevulose and inulin, but not other forms of sugar. During this year also, Hüsnall described the features of diabetic coma, and suggested acetone poisoning as its cause; and Sir Walter Forster, in a paper read before the British Medical Association at Manchester in 1877, further focussed attention to this phenomenon. In the same year, Lancereaux drew the attention of the French Academy of Medicine to certain changes in the pancreas which he believed were constantly present in severe cases of diabetes, the importance of this being verified in experimental diabetes in dogs. However, the precise physiological significance of diabetes remained unknown.

Early Experimental Investigations: 1889-1904.

Although Conrad Brünner is said to be the 1st, in 1672, (? 1772) to have observed that pancreatectomy in dogs produced "a ravenous appetite, thirst, and wasting", yet it was not till the time of Fitz, whose work, coinciding as it did with the classical experiments of von Mering and Minkowski[53] in 1889, began an epoch in the history of our recent advances not only in pancreatic, but also in general, endocrinology. These investigators found that the total extirpation of the pancreas gave rise not only to digestive disturbances (owing to loss of the pancreatic juice) but also to a complex syndrome commonly associated with diabetes mellitus. This syndrome terminated fatally in the course of 2-6 weeks, after the animal had shown symptoms of hyperglycaemia, glycosuria, polyuria, polyphagia, loss of weight and strength (in spite of a voracious appetite), thirst, emaciation, and asthenia. On the contrary, they found that these symptoms were not manifested if the gland was incompletely removed, or if a part of it was transplanted to other parts of the body, e.g., grafting its processus uncinatus with the corresponding blood vessels under the skin of the abdominal wall. These experiments thus demonstrated the importance of the pancreas in carbohydrate metabolism, and directly suggested that it possesses an internal secretion. Indeed, it was concluded at the time that the cause of diabetes had been discovered, and high hopes were entertained that

the disease might be successfully treated by the administration of fresh pancreas or of extracts of the gland by the mouth in much the same way as it had been found possible to control the symptoms of myxoedema and sporadic cretinism with preparations of the thyroid. Unfortunately, these hopes were not fulfilled, experience showing that, although improvement might occur, the glycosuria and other symptoms of the diabetic condition were not favourably influenced.

In 1890, Robert Saundby in his Bradshaw lecture pointed out that varying degrees of interstitial inflammation, with formation of connective tissue and new duct, occurred in diabetes.

Schulze, Opie[54], and others, in 1901, found that the islands of Langerhans (described by Langerhans in 1869) showed signs of hyaline degeneration and atrophy at autopsies in dead diabetics (although the correctness of this finding was questioned in 1906 by Vincent and Thompson[55]). In 1902, Szobolew[56] confirmed Hering and Minkowski's observations of 1889, and found further that ligation of the pancreatic duct was followed by a complete atrophy of the pancreatic acini, whilst the cells of the islands of Langerhans were unaffected.

The succeeding years were marked by the brilliant researches of Flexner and Opie[57] who, in America, did for our theoretical knowledge what the surgical skill

of Mayo Robson, following in the footsteps of Senn Körte and others, accomplished in the domain of practical therapeutics; and, in 1904, Sir Byrom-Bramwell gave an altogether ~~new contribution~~ new contribution to our knowledge when, in his "Clinical Studies" (1904), he described a pancreatic form of infantilism which he showed was a result of deficient pancreatic internal secretion.

Early Researches to extract INSULIN:

1904 – 1920.

Lepine[59] was the first to suggest definitely that the condition of diabetes mellitus, which von Mering and Minkowski had discovered in 1889 to follow pancreatectomy, might be due to the withdrawal of an internal autacoid which is necessary in the normal animal for the complete metabolism of sugar. (Prof. J. MacLeod) Previous to this, vague notions were already in existence regarding the internally secreting power of the pancreas on the strength of Mering and Minkowski's and other experiments and observations, and, indeed, Professor Sir Edward Sharpey-Schafer in 1900 suggested the islands of Langerhans as the source of this internal secretion, to which he gave the name "insulin" (= "island secretion", from the Latin "insula", an island). Further, it had for a much longer time been recognised that injections of the fresh extract of the pancreas reduced the sugar content of the blood, and temporarily improved the glycosuria and hyperglycaemia following pancreatectomy in animals. In fact, discoveries that extracts

of other endocrine organs, such as the suprarenals, could induce pharmacological actions, and that the extracts of other endocrine organs, such as the thyroid, could relieve the symptoms associated with the atrophy of such organs, gave strong though indirect support for the view that the pancreas must also yield an internal secretion. Numerous attempts to apply this knowledge clinically to the treatment of human diabetes however ultimately ended in failure, in spite of ephemeral success in some instances. The most satisfactory results were first obtained by Rennie and Fraser in 1904 who, taking advantage of the fact that cell islets visible to the naked eye are met with in certain teleostean fishes, prepared extracts from them, and found that they were of some success in several cases of diabetes on which they were tested; but owing to the difficulties they had in obtaining material, these investigations were not further pursued. Two years later (1906), Lydia de Witt, basing her experiments upon the previous observations of Schulze, Szobolew and others in 1902, viz: that complete atrophy of the glandular structure of the pancreas was caused by ligaturing the pancreatic duct whilst the islets of Langerhans remained unaffected (v. p. 51), made extracts of the islet tissue of cats and found that, whilst these had no proteoclastic powers, yet they possessed well-marked glycolytic properties (from Cammidge, "Insulin Treatment of Diabetes", Livingstone, Edinburgh, 1924). In 1908, Luelzer[60] and his associates employed an expressed

alcoholic extract of the gland, the injections of which gave quite satisfactory results in the 6 cases of diabetes which they recorded. The success attending Zuelzer's experiments was so positive at the time that his method was patented by the Schering Co. of Berlin, who undertook the preparation of his extract on a commercial scale. The results, however, proved unsatisfactory, as the therapeutic effects of the commercial preparation were variable; and the project was therefore ultimately abandoned. During the next year (1909), Forchbach[61], employing the same method, obtained good results in depancreatised dogs, but he was not so fortunate with human diabetes.

In 1910, Eppinger, Falta, and Rudinger pointed out the correlation of the endocrine organs — the pancreas, thyroid and suprarenal in particular — with regard to the production of glycaemia and glycosuria; and de Meyer in his Sécrétion Interne du Pancréas in 1910 further demonstrated the relation of the internal secretion of the pancreas with the glycogenic function of the liver. No attempt was however made during this year to find out what this internal agent was. Further, the extracts prepared by Starling and Knowlton[62] in 1912, by E. L. Scott[63] (1912), by Merkin and Cramer[64] in 1913, and by Kleiner[65] in 1919 did not yield results that were considered convincing enough to justify a further development of their investigations with a view to employing them in clinical therapeutics in human

diabetes.

We may here refer to certain other observations published at this period, because of their historic interest and of the bearing they have on a fuller appreciation of the development of the researches on the successful isolation of this antacoid. Thus, Pratt[66], towards the end of 1910, reported several cases of diabetes in which the islands of Langerhans were not affected, and several observers put forward the view that the islands represent mere stages in the development of the ordinary parenchyma of the pancreas. Bensley[67] however in 1915 showed conclusively by intra-vitam staining methods that the islets were permanent structures, and that the contention of Pratt and others of 1910, viz: that the islands were "developing reserve cells of the acini", was wrong*. Further, Carlson and Drennan[68] in the same year (1915) found that if the extirpation of the pancreas was effected in a pregnant dog near term, the animal did not exhibit the symptoms of diabetes till the pups were born or removed by Caesarean section — the internal secretion of the foetal pancreas being sufficient to protect the mother. Again, in 1920, Clarke[69] discovered that the isolated mammalian heart (which had been kept alive by perfusing its blood vessels with Locke's solution containing glucose) removed sugar from perfusing fluids much more rapidly when the fluids used had first of all been perfused through the blood vessels of the pancreas

* Prof. H. Oertel of McGuill, basing his observations on the work of his pupils L.S. Milne & H. Le B. Peters, has also a few weeks ago challenged the independence of / P.T.O.

than it did those the fresh fluid. (Locke's solution) — thus further clearly demonstrating the existence of a pancreatic antacid which has great glycolytic properties.

The Researches of Howard, Forsyth, and Cammidge; Banting and Best & their co-workers: 1921 — 1922.

It had baffled the endocrinologists to isolate insulin from pancreatic extracts hitherto made owing to the destruction influence of trypsin and other proteoclastic enzymes. Howard, Forsyth, and Cammidge in the B.M.J of 15th Oct 1921 p 686, and Thomson in the same journal of 11th Nov 1922 p 948, reported certain experiments they made with certain extracts of the pancreas; but these were not proved to give satisfactory results. However, Banting and Best[70] and their co-workers, working in Professor Macleod's laboratory in Toronto University, were the first who found in December 1922 that the offending enzymes could be circumvented by allowing the secreting acini to degenerate (for 10 weeks) by ligaturing the pancreatic ducts (as had been done by Schulze and Szbolew and others in 1902, and by Lydia de Witt in 1906) before the extracts were made. They observed that continual injections of such extracts into depancreatised dogs permanently and definitely diminished blood and urine sugar, and prolonged their lives. Later, taking advantage of Abrahim's finding some years before that the foetal pancreas is almost free from proteoclastic

(Contd from last footnote on last page) of the acini (parenchyma) and the islets; and claims that the endocrinological function of the pancreas is not a monopoly of the islets only, i.e., is what he terms a "general cell action" — Prof Oertel; Transac. B. 1905; and W. Langdon Brown, "The Pancreas & Diabetic Metabolism" Lancet April 5, 1924, page 695. (Also H.H. Dale, Phil. Lancet April 19, 1924, p 823.)

enzymes, they obtained satisfactory alcoholic extracts from this organ, as well as from adult of pancreas. Banting and Best having now found that their extract was at least experimentally quite perfect, proceeded to apply it clinically. The first clinical test was made at Toronto General Hospital in 1922 on a diabetic boy of 14 years, in whom an almost immediate reduction of about 25% in blood sugar was recorded. Subcutaneous injection of Banting and Best's extract has since been shown both in Europe and America to give brilliant clinical results which are most spectacular especially in cases of advanced diabetic coma. The injection are said to need daily repetition; and an overdose has been shown to produce convulsions, which are however controllable by injections of dextrose. (V.: Professor Macleod, 11th Intern. Congress of Physiol., Edin., 1923; also Dale, Lancet, May 19, 1923, p 989).

*Recent Work and Reports, 1922-1924.

Although the discovery of insulin was only announced in 1922, a considerable volume of literature has grown up around it. Indeed, no sooner had Banting and Best and their Toronto collaborators ploughed the first furrow in the field of insulin research than the active cultivation of this substance was commenced by many other workers in all parts of the world. Some devoted their attention

*sed, for the most part, on Cammidge; "The Insulin Treatment of Diabetes"; Livingstone, Edinburgh: 1924.

solely to the therapeutic effects of the remedy; some investigated its physiological properties; whilst others probed the depths of its exact chemistry.

The active principle of the substance has not yet been isolated in even approximate purity; but Cushny suggests that it may be a complex molecule nearly approaching the simpler proteins in size, since it is destroyed by pepsin and trypsin (v.: Cushny's Pharmacology 8th Edition 1924). Collip, on the other hand, has expressed the belief that it is really a fairly simple substance of a non-protein nature, and suggests that it is possibly a guanidin compound.

A new method of biological assay has recently been devised to control the doses and therapeutic effects of insulin. The original unit of insulin employed by Banting and Best was "the amount which, on subcutaneous injection, lowers a rabbit's blood sugar by 50% in 1–3 hours". However, the discovery of the convulsive effect of an overdose of insulin together with recent clinical work with preparations standardised by the original Toronto method has led to the abandonment of this unit for a new one, which is defined as "one-third of the amount of insulin in cubic centimetres required to lower the blood sugar below 0·045% and cause convulsions in a rabbit weighing 2 kilos which had been previously fasted for 24 hours". Cammidge and Howard however a few weeks ago (Lancet March 1st 1924, p. 465) called attention

to the fact that, from a series of careful experiments they carried out, they found that the potency of insulin units would be likely to vary with the different types of rabbits against which they are standardised.

Insulin-like bodies have of late been reported to be found in various substances. Banting and Best found that whilst preparations from the liver and spleen gave no appreciable effect on blood-sugar level of diabetics, extracts prepared (by the same method by which they originally obtained insulin) from thyroid and thymus caused distinct though temporary lowering of the sugar %. Later, Best and Scott prepared similar extracts from liver, spleen, submaxillary gland, muscular tissue, and normal blood. It would therefore appear that insulin occurs in practically all the tissues of the body, and is probably carried to them from the pancreas by the blood (Cammidge)

Professor MacLeod recently confirmed Rennie and Fraser's observations of 1904 (v. page 53) and found that an antidiabetic substance could be isolated from the cell islets of certain fishes which are rich in insulin. Various practical difficulties have however prevented extracts from being commercially produced. The Toronto workers have also recently found that extracts of several forms of lower life yield insulin. Thus, Collip has succeeded in extracting it from clam tissue; Winter and Smith (confirmed later by Collip) demonstrated an insulin-like substance in the commercial yeast;

and Collip also found a similar substance in the higher plants such as the green tops of sprouting onions, lettuce, sprouting wheat, and even the common lawn grass! For these substances — the exact chemical nature of which is unknown to the biochemists —, Collip recently suggested the name "Glucokinin". Cammidge however is of opinion that "it seems unlikely that vegetable or animal extracts other than those prepared from the islands of Langerhans will prove of value in the treatment of diabetes, partly because their effects are uncertain and difficult to predict; and partly because they give rise to intensive and wasteful metabolic changes with progressive loss of weight and emaciation" (Cammidge: "The insulin treatment of diabetes", 1924)

Of the numerous clinical observations made last year, reference may be made to the findings of L. Blum, Carlier and H. Schwab reported in Bull. et. Mém. Soc. Méd. des. Hop. des. Paris, Dec. 27/1923 p. 1789 (v.:B.M.J. Feb 2/1924). These observers found that patients who had received insulin treatment became more prone to acidosis and very suddenly die of diabetic coma if the treatment was stopped. This has since been confirmed by Marcel Labbé, who further found that there was no evidence that insulin produced a regeneration of pancreatic tissue in adults, though there might be some restoration of glandular function in very young children so treated. He further found also that, for insulin treatment to be successful, it

must be continuous and combined with an antidiabetic dietary (v. also: F. Fischler, Muench. med. Woch., Nov 23, 1923, p. 1407). Also, several efforts have recently been made with a view to a cheaper and less complicated process of manufacture, ~~production~~ of insulin. In this connection, we may note that certain workers at the Westminster Hospital Laboratory recently obtained potent watery extracts of the substance; & H.W. Dudley and W.W. Starling, working in the Department of Biochemistry and Pharmacology of the National Institute for Medical Research, also reported (1924) a new and simpler method of preparation, the technical details of which will be found in Bioch. J., vol. 18 No. 1, 1924. (An admirable account on insulin up-to-date is given by Professor Milroy in the new edition of Encyclopaedia Medica edited by Dr. Goodall)

A notable experimental fact discovered of late is that experimental hyperglycaemia with Bernard's puncture or with adrenalin is entirely prevented by insulin. However, the ~~they~~ endocrinologists are not yet quite agreed as to what the essential action of this substance consists of. It is clear, however, that it restores the power of utilising sugar which is wholly or partly lost in diabetes. Several views have been advanced to explain the way in which ~~the sugar~~ it accelerates the sugar combustion; but these are at present hardly beyond the speculative stage. Professor Cushny is of opinion however that "there is every reason to believe that the action

is on the general tissues and not on any special organ, that the normal pancreas secretes insulin into the blood, and that its presence in the muscles and other organs enables them to utilize glucose" (Cushny: Pharmacology 8th Ed., 1924.)

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SECTION VII.

THE INTERNAL SECRETION OF THE SPLEEN & OTHER TISSUES.

G. THE INTERNAL SECRETORY POWER OF THE SPLEEN.

The spleen, with other lymphoid structures, is not now classed among internally secreting glands (Schäfer); but the development of our knowledge with regard to its endocrinological nature is of historic interest, because an internal secretion was formerly attached to it.

Ancient Theories of its function.

The ancients regarded this organ as the seat of anger, and Aristotle and later Galen taught that it was the seat of the "melancholic humours". These ancient sages were aware that it was quite inessential to life, and splenectomy was frequently practised by them without serious results in the belief that such a surgical procedure improved the "wind" of runners (Osler). No further record of the conception of its physiology appears to have been made till after the middle of the 19th Century, when Griesinger (1866), H. C. Wood (1871), and Bonti (1882) attributed certain forms of anaemia to an enlargement of the spleen ("splenomegaly"); but no evidence was ever adduced regarding the presence of an intrasplenic ~~of the relation between~~ antacoid.

Modern theories regarding its supposed Internal Secretion.

The spleen has of late years (Gley 1917)[20] been described as furnishing an internal secretion which activates the proteoclastic ferment, viz: trypsin, of the pancreatic juice. Also, Vincent and Sheen (1903), J. L. and E.M. Miller (1911), Stern and Rothlin (1919) and some other authorities have obtained from splenic extracts effects indicating that these either cause contraction, or produce relaxation if contracted, of the plain muscle of the blood vessels, intestine, uterus, etc.: and this has been ascribed by them to the presence of an intra-splenic autacoid. These effects, however, resemble those of certain bodies such as histamine and choline which have been found in many tissues and organs, and their presence, Sir. Sharpey-Schäfer points out, cannot be regarded as sufficient reason for ascribing to the organs which yield them an internally secreting function. Moreover, as stated above, it has been known from time immemorial that surgical removal of the spleen is attended with no appreciable symptoms: which is not the case with any of the true endocrine organs.

Conclusion.

We may infer, then, that the proof of the existence of an internally secreting function in connexion with the spleen is so inferior to that which we now possess regarding for instance, the thyroid, pancreas or suprarenal, that such an hypothesis — for it cannot be raised to the dignity of

a theory — finds little or no favour with most endocrinologists.

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H. Internal Secretion of the Tissues.

Historical Survey

The amplification by Bernard in 1889 of the idea of an internal secretion to include the secretions of all the tissues in the body has already been referred to (p. 8). Traube and Rosenthal shortly after Bernard shewed that Carbon dioxide, a product of metabolism in all tissues, stimulated the respiratory centre if it was produced in excess in the blood. The hypothetical ferment "thrombokinase" was shewn first by Schmidt (1895), then by Morawitz (1903) to be resident in the tissues, leucocytes and platelets, and it was demonstrated that its liberation from these structures conditioned the phenomenon of blood coagulation. Glycogenase, arginase, and similar internal agents* which regulate carbohydrate and protein metabolism, were also shewn to be present in the tissues, especially muscles and embryonal tissue.

Conclusion.

Thus, all tissues in the body have been regarded as furnishing an internal principle. It has even been shewn that the extracts of many structures in the body, on injection, cause a specific fall in blood pressure; and it has

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* all these bodies do not come under the modern conception of "internal secretions" of an endocrinological nature.

therefore been hastily assumed that such extracts represent true internal secretions of an endocrinological nature. However, Popielski and Penek in 1909 (Arch f. d. ges Physiol., 128, 1909) and more recently J. J. Abel, Kubota, and D. I. Macht in 1919 (J. Pharm. and Exp. Therap., 13 & 14, 1919) have shewn that such lowering of blood pressure was due to substances which are quite common to all animal tissues, viz: vasodilatin, histamine, and, in a few cases, choline. The blood pressure finding is not therefore a proof of true endocrine function* (Schafer).

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* F. G. Hopkins (Lancet, June 23/1923) has recently discovered a substance "glutathione", a dipeptide containing the amino acids cystein and glutamic acid. It brings about oxidation in muscle and is regarded by Swale Vincent as an internal secretion of this organ (Swale Vincent, Introd. to study of Secretion, Arnold, London, 1924, p. 98.)

SECTION VIII.

J: THE AUTACOID OF THE SUPRARENALS AND OF THE CHROMAPHIL BODIES OR PARAGANGLIA.

The suprarenal glands are situated, in man, in the epigastric region, one on each side of the vertebral column and in the immediate neighbourhood of the upper pole of each kidney. Each gland consists of two portions, viz: an outer cortex, and an inner medulla.

The glands were first recognised by Bartholomeus Eustachius Sanctoseverinatus in 1563. Winslow, in 1756, fully described them, and later Meckel (1806), Eckes (1846), Leydig (1851), and Kölliker (1854) dealt with their structural peculiarities, and demonstrated that the suprarenals were intimately related to many other similar bodies which were scattered chiefly along the course of the chains of the sympathetic ganglia and which were consequently called the "paraganglia". They have also been termed "chromaphil-" or "chromaffine-bodies".

The History of systemmatic Clinical Studies of the function of the Gland: Bright, Addisson, &c., 1846 et seq.

The physiological significance of the suprarenal glands remained for long a matter of much speculation. The first clinical case of what is now known to be produced by a pathological lesion of the suprarenal glands (Addison's disease) (Trousseau, 1856) appears in Lobstein's treatise: "De nervi sympathici

humani fabrica et morbis", Paris, 1823, from which is the following (translated) extract (Pancoast's)*:

"..... I have myself observed the nerves forming the supra-renal plexus much thicker in disease where the capsulares renales, which were more than twice as large as usual, had degenerated into tuberculous substance ....."

Lobstein's patient was an unmarried woman, 25 years of age, who died "in convulsive spasms analogous to the epileptic"; and at the autopsy, "nothing unusual was discovered in the body of the woman but the aforesaid change in the suprarenals, and the enlargement of the nerves" Notwithstanding the fact that there is no record of any darkening of the complexion, this account by Lobstein was undoubtedly a typical case of what would now be called "Addison's disease" in which, moreover, death from convulsions, as recorded by Lobstein, is not uncommon. The observation regarding the thickening of the nerves in this, the first recorded instance of this disease, is indeed of remarkable interest. The second case was recorded in the "Halle Hospital Reports" by Dr. Schotte in October 1823, and was later published in vol. vii of the Deutsches Archiv. f. Klin. Med. by Risel in the course of his article: "Zur Pathologie des Morbus Addissonii". The third case came under the observation of Dr. Richard Bright of Guy's Hospital, London, in July 1829. This case is contained in

* from Buck: "Handbook of the Biological Sciences"

Bright's classical "Reports of Medical Cases" and also figures as Case v. in Addison's original memoir. The lesions of the glands were characteristic; there was no other affection of any consequence besides those described by Lobstein 6 years before, but for the first time in the history of this disease, Bright recorded that "the complexion was very dark". A few other cases were reported by Arran and others in 1846; but it was reserved for the sagacity of Thomas Addison*, a physician of Guy's Hospital, London, to demonstrate in 1849 to the South London Medical Society the relationship between lesions of the suprarenals and the train of the well-marked constitutional symptoms of the affection, which now bears his name. (Trousseau, 1856).

The attention of the clinicians and physiologists does not however appear to have been attracted until 1855 (some authorities give the date as 1853), when Addison published a nine-page monograph: "On the Constitutional and local Effects of Disease of the Suprarenal Capsules". Addison gave the symptoms as "a progressive idiopathic anaemia, digestive disorder, diarrhoea, general langour or debility, tremors, convulsions, apathy, ... feebleness of the heart, irritability of the stomach, ... and a peculiar change of colour (bronzing) of the skin ...". Even at this time, Addison's discovery was slow to receive general recognition, for, in the prefatory remarks appended to the reprint of that monograph in Addison's collected writings published by the New Sydenham Society in 1868 — i.e. eight

* That Addison is intimately associated with the disease is proved by the fact that his name is invariably employed to describe the disease in the medical literature of all civilised countries. Thus, French: "asthénie surrénale, mélanodermie asthénique, maladie bronzée, maladie d'Addison"; German: "Addison'sche Krankheit"; Italian "morbo di Addison, malattia di addison"; Spanish: "enfermedad de Addison ó Bronceada", &c. [Latin: Melasma Addisonii seu suprarenale morbus Addisonii.]

years after Addison's death — we read that "even it (i.e. Addison's disease) does not find a place in the nosology of some writers". In fact, although Greenhow, in his Croonian lectures before the Royal College of Physicians of London in 1875 gave a complete review of the subject, yet, Addison's account of the pathology and clinical features of the disease was so perfect that comparatively little has been since this time added to our knowledge of the ~~clinical aspect~~ pathology and symptomatology of the disease besides the fact that the anaemia, a symptom specially regarded as pathognomonic by Addison, is by no means common.

Addison's account of this disease led Brown-Sequard[71] in 1857 to investigate the effect of the removal of the suprarenals in animals. He found that this procedure proved fatal within 2 or 3 days, accompanied with the development of Addison's symptoms (but without the bronzing). Brown-Sequard's results were confirmed by Nothnagel[72] (1879), Stilling[73] (1888), Tizzoni[74] (1889), and others. Stilling in 1888, and later Horsley, established the additional facts —

(1) that extirpation of only one gland was compensated for by hypertrophy of the ~~other~~ other, and did not prove fatal under strict aseptic precautions;

(2) that some of Brown-Sequards findings of 1857 were in no inconsiderable measure the consequences of surgical shock and especially Sepsis;

and (3) that animals (e.g. rabbits) which possess

accessory suprarenals ("chromaphil bodies") did not die after removal of the capsules.

The experiments of Cannalis (1887) and of Imbert (1899) in suprarenal transplantation produced negative results, though Biedl[75] in 1897 succeeded in growing the glands extraperitoneally. Many years later (in 1908), Haberer and Stoerk[76] demonstrated that they could be transplanted within the kidney substance, provided their blood supply remained intact.

We may parenthetically note here that feeding of extract of suprarenal gland to suprarenalectomised animals or to humans in Addison's disease have led to abortive results. Indeed, our present condition in therapeutics regarding the suprarenals is the exact opposite of our knowledge of thyroid organotherapy. Sir Wm. Osler (in his text book on Medicine, 1901) stated that of the large series of Addison's disease treated by him with various suprarenal preparations, only 3 showed marked improvement. It was early shown that the tuberculous nature of the lesions (v. Lobstein's account, p 68) in most cases of the disease and the attendant widespread involvement of the sympathetic system were a formidable obstacle in treatment. Some cases, however, are marked by benefited by administration of suprarenal extract per os or hypodermically. O. Grünbaum (Journ. Physiol., 24, 1899) obtained a rise of blood pressure on enteral administration of the extract in cases of Addison's disease, though this was not

observable in normal individuals. As we have noted above, negative results were mostly obtained from suprarenal transplantation, as the transplanted gland almost invariably underwent necrosis. Two years ago, however, some successes were attained by implantation of foetal suprarenal by A. F. Hurst (B.M.J., Feb 18, 1922) into the testicle of a patient dying from Addison's disease, a steady and lasting improvement being obtained without the pigmentation of the skin being however affected. It may be said, therefore, that with the progress of surgery, the possibility of successful implantation is now much less hopeless than it was a few years ago.

Researches on the Suprarenal Extract: OLIVER & SHARPEY-SCHAFER:

1895.

The experiments of Brown-Sequard and others attracted much attention at the time they were performed (1857) (page 70), but they were almost forgotten for many years. Whilst Brown-Sequard's experiments clearly proved that the suprarenals furnished an antacoid which was absolutely essential to the life of the organism, and whilst, in fact, Vulpian[77] had a year before Bernard's experiment isolated from these glands a substance which he found, to exert remarkable colour reactions with various chemical reagents (C. r. acad. sci, 43, 1856), yet the precise nature of the active internal principle of the glands remained unrevealed until the time of Sharpey-Schafer and Oliver (1895)[78]. These two investigators

found that when an extract of the medulla of the suprarenal was injected intravenously into the living animal, a rise in blood pressure (which was correctly referred by them to a vaso-constriction of the blood vessels through stimulation of their sympathetic endings (myo-neural junction)) occurred. This effect, they found, was not produced by cortical extracts. Nothing definite could be learned regarding the obscure antacoid of the cortex, although they found that its loss resulted in marked asthenia, coma, convulsions, and rapid death.

Further Physiological Researches: 1897 et. seq.

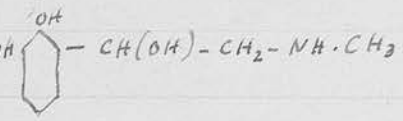
The experiments that followed Oliver and Sharpey-Schafer's brilliant results were chiefly concerned with investigating the nervous mechanism of the secretion of the suprarenals. Biedl[79] in 1897, and Dreyer[80] two years after (1899), shewed that stimulation of the splanchnic nerves produced two rises in blood pressure, the first owing to direct effect of the stimulation, and the second, to a discharge of the suprarenal antacoid, presumably derived from the medulla. Frend and Blanchard some years later produced hyperglycaemia by piqûre or by stimulation of the splanchnics after suprarenalectomy, proving that other structures, i.e. the chromaphil bodies, could produce the internal secretion of the suprarenals. Cannon[81] also shewed that emotions, like anger and fright, caused a reflex discharge of this antacoid which he found was responsible for the peculiar vascular and sensations usually experienced during these reactions

conditions, and ~~for~~ a rapid depolymerisation of glycogen resulting in the so-called emotional glycosuria or hyperglycaemia.

Biochemical Researches: 1898–1901:

ADRENALIN.

The production of the Schafer-Oliver suprarenal extract of 1895 immediately led to a spirited investigation of the biochemistry of this substance; and to Abel[82] is due the credit of being the the first* to isolate from the medullary extract in 1898 (some authorities give the date as 1894) a somewhat impure chemical substance which he found was an epinephrin hydrate of the formula $C_{10}H_{13}NO_3, \frac{1}{2}H_2O$. The substance was also demonstrated to be present in the external neck glands of a tropical toad. Abel's epinephrin was later proved to be but a benzoylated compound of the pure extract. Later (1901) Aldrich[83] and Takamine[84] isolated its free base (laevorotatory), adrenalin, to which biochemists have given the formula $C_9H_{13}NO_3$, or, structurally –



(with an asymmetric carbon atom) and have since synthesised (Dakin and Stolz) from catechol.

Recent .... PT.O.

* The chemical active principle ("sphygmogenin") has been claimed to have been obtained by S. Fraenkel in 1896 (Wien. med Bl., 19, 1896) and by v. Furth (who gave to it the name "Suprarenin") in 1897 (Zeit. f. Physiol. Chem., 24, 1897). These preparations were however very crude and chemically impure.

Recent physiological and other researches on ADRENALIN : 1901 — 1916.

The characteristic action of the natural or synthesised adrenalin, [the laevorotatory variety of which Professor Cushny (Journ. Phys. 37 + 38, 1908) showed to be considerably stronger than the dextro-rotatory compound] has by recent work been shown to consist in a general excitation of the sympathetic division of the autonomic system (Langley). It was found

(1) that its action was a very general one involving the activation of the structures innervated by these autonomic sympathetic nerves;

and (2) that the function of these structures could be augmented or inhibited according to the structural features of the effector elements so affected — a reaction which was found to be identical with that induced by stimulation of the sympathetic nerve fibres themselves. Thus it was found that, whilst adrenalin produced an abrupt rise in blood pressure by direct action on the cardiac musculature and on the "myoneural junction" (Langley) of the sympathetic nerve endings in the arterioles (and even in ~~lessened~~ very excessively minute quantities as $\frac{1}{400}^{th}$ of a milligram per kilo body weight (Burton-Opitz)), it lessened the cardiac frequency through vagal inhibition (if the vagus is intact), or, characteristically, accelerated the heart (if the vagus is cut). On the contrary, Dale[85] proved that small quantities could produce a vaso-dilator effect (capillary) and a consequent fall in blood pressure.

Blum, in 1901, shewed that its subcutaneous injection was invariably followed by hyperglycaemia and glycosuria. Meltzer[86] in 1903 shewed that intravenous injections dilated the pupil (especially if the sympathetic ganglia were removed), arrested peristalsis, & caused a loss of tone of the walls of the stomach, intestine, gall bladder, urinary bladder, the bronchioles, and the non-pregnant uterus, whilst the gravid uterus, the pyloric-, ileo-colic-, and internal-anal-sphincters, the muscularis mucosæ of the intestines, the bile duct, vas deferens, seminal vesicles, the salivary and lacrimal glands & kidneys were stimulated to further activity. Thus, it was further demonstrated that the action of adrenalin consists in a general stimulation of the sympathetic autonomic fibres — the effect on the tissues varying according as their sympathetic supply is either excitatory or inhibitory. In 1906, Underhill and Closson[87] shewed that it stimulated hepatic cells through activating the sympathetic fibres regulating the formation of dextrose from glycogen (thus producing "adrenalin glycosuria") and that, in addition to these effects on the neuromuscular and neuroglandular substance, it also influenced the metabolism of the different foodstuffs, especially the carbohydrates. Cannon, Nice, and Gruber[88] in 1913 demonstrated that intravenous injection of adrenalin was followed by a temporary improvement in the contracting power of fatigued muscles, especially in cases of Addison's disease. Cannon[89] in 1914 shewed that the intravenous injection of this agent in amounts of 0·0001 mgr. per kilo. of body weight shortened the coagulation time of the

blood. Gunn (1913), and later Hoskins, Gunning, and Berry[90] (1916) found that the blood vessels of the heart and of skeletal muscles were dilated by doses of adrenalin which would cause constriction in the arteries of the skin or intestine. Stewart and Rogoff[91] showed recently (1916) :—

(1) that the amount of adrenalin "spontaneously" liberated in the body is at a definite rate of about 0·001 G. per min.;

(2) that, normally, in the body, adrenalin aids in keeping the vascular system in a state of tonus;

and (3) that it is only in consequence of definite stimuli, for instance, during strong emotions, that larger amounts than are normally passed into the blood are discharged thereinto and actually constrict the blood vessels, producing a definite but temporary rise of blood pressure.

Miscellaneous Researches: to 1919.

Various attempts have of late years been made in order to find out the exact relationships between the internal secretion of the suprarenal and that of the other endocrine organs; but the matter is not yet entirely cleared up. Herring found that the suprarenal gland (especially the cortex) and adrenalin secretion was increased by continuous feeding of animals with thyroid substance. Further, adrenalin glycosuria has been shown to be less easy to produce in the absence of thyroid, although pancreatectomy still produces it. Again, it was found that glycosuria was often associated with Graves's disease. Thus it would appear that

these two organs, suprarenals and thyroid, are much closely related, the correlation been effected possibly through the autonomic system (Cole)

Reference has been made above to Cannon's observations (p.73) on emotional hyperglycaemia. This was shewn to represent a phenomenon of protective mechanism on the part of nature, whereby the animal could use its muscles violently without fatigue (owing to their being abundantly supplied with dextrose under these emotional conditions), and could thus fight for its existence or run for its life to the best advantage. (Bainbridge & Menzies).

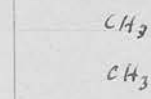
In 1917, Stewart and Rogoff[92] shewed, in a careful experimental study, that, by extirpating one suprarenal and cutting the nerves to the other, the liberation of adrenalin into the blood was stopped. This, they shewed, did not however affect the health of the animal, and they found that all the procedures such as asphyxia, fright, etc., by which hyperglycaemia could be produced still produced that effect. They noted however that there was no definite production of hyperglycaemia by fright or by other emotional disturbances, and could find no evidence of an increase in adrenalin output under these conditions.

It is of some interest to note here with that Sir Sharpey-Schafer and Dr. R.K.S. Lim in 1919 (Quart. J. Exp. Phys., 12, 1919) definitely proved that the pulmonary vessels are constricted by adrenalin: a point which was up to that time fiercely debated by the endocrinologists.

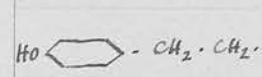
Miscellaneous Researches in ADRENAL Biochemistry and Pharmacology: to 1917.

Our recent advances in adrenalin biochemistry are so many, and their interpretation so complex, that reference may with propriety be made to only a very few of them.

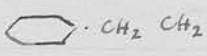
Dr. Dale and Professor Barger[93] have described certain principles which they called "sympatho-mimetic" amines, which occur in in infusions of putrid meat and are biochemically related to adrenalin. An examination of the structural formulae of these amines will reveal their close relationship to adrenalin – thus:



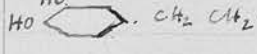
Isoamylamine.



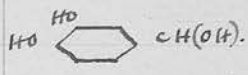
p. hydroxyphenylethylamine (= tyramine)



phenylethylamine.



Epinine (an artificial amine, (Cushny).)



ADRENALIN.

Also, in 1917, Hartmann and Fraser[94] found that, although adrenalin could be successfully administered in cases of congestion or bleeding like post-partum haemorrhage, yet fairly safe doses could produce poisoning, intestinal haemorrhage, oedema of blood vessels, and paralysis of the respiratory centre through rupture of its blood vessels. These investigators also clinically confirmed Dale's finding that minute quantities of adrenalin not infrequently produce vasodilatation and a fall of blood pressure.

Sergent has also shown that favourable results were obtained on administration of suprarenal extract in cases of ordinary adrenalin insufficiency (hypoepinephrinaemia). (Osler)

The Internal Secretion of the CORTEX:

Modern Findings: to 1922

Whilst the embryonic development of the medulla from neuroblasts is enough by itself to suggest that its internal secretion may have some influence over the nervous system, the mesodermal development of the cortex (from the Wolffian body) gives no clue whatever as to its own active principle. The endocrinologists tell us comparatively little about it. Abelous, Soulei, and Toujan in 1904 (C.r. Soc. biol., 57, 1905) claimed to have obtained from it what they found gave adrenalin reactions after incubation for 24 hours and therefore regarded as a precursor of adrenalin. This has been denied by several authorities like Voegtlin and Macht. The Italian worker Austoni in 1911 (Arch. ital. de biol. 56, 1911) obtained effects from extracts of the cortex antagonistic to those yielded by extracts of the medulla, whilst Voegtlin and Macht in 1913 (Journ. Americ. Med. Assoc., 61, 1913) claimed to have isolated a vasoconstrictor principle from chloroform extracts of the dessicated cortex. Further, Crowe and Wislocki in 1914, and Swale Vincent in 1917, observed that "there is little doubt that the rapidly fatal effects of extirpation of both suprarenals is to be ascribed rather to the removal of the cortex than of the medulla" (Starling?) And this, it would appear

that the cortex is the more vitally important of the two!

*Clinical evidence has of late years been accumulating to shew that the internal principle of the cortex influences the secondary sexual characters, which undergo remarkable changes in tumours and other lesions associated with the cortex — the so-called "suprarenal genital syndrome" (Osler). Pseudo hermaphroditism has been observed in hyperplasia of the foetal gland. Thus, Tuffier recently described a case in which an old lady who developed a suprarenal cortical tumour after the menopause assumed male characters: a heavy beard, baldness, ability to perform heavy labour without fatigue etc. (="virilismus" or "hirsutismus"). This was followed in later years by emaciation, pigmentation, and mental deficiency. Again, such tumours have also been shewn to lead to very precocious sexual development in children (Bullock and Sequeira), and this affords the ground for the suggestion that has since been persistently made that the adrenal cortex furnishes an autacoid which influences sexual development especially in the female sex. Robert Hutchison has also described a remarkable syndrome, in children, of adrenal tumours associated with exophthalmos and cranial tumours; and Wm. Pepper (Tertius) has described a form characterised by rapid growth in conjunction with diffuse involvement of the liver unaccompanied however with jaundice (Osler). Further,

the cortex has been noticed to become enlarged during pregnancy and in many sexual disturbances, and to undergo hyperplastic changes during the oestrous cycle and lactation (Verdozzi). The suggestion that there is some relationship, direct or indirect, between the functions of the cortex and the female generative organs was further referred to in 1921 (Journ. Obstr. and Gynaecol., 1921) ~~also~~ by Professor E. E. Glynn, who put forward the view that the cortical secretion is concerned with a differentiation and growth of the sex cells.

Of recent observations, mention may be made of Adler's finding of 1922 (Munch. med. Woch. (1922)) that tadpoles fed with suprarenal cortex grew more rapidly than controls, thus suggesting that the internal secretion of this portion yet gained influences the metabolic processes.

Recently, several authorities like Elliott, Tuckett, Leignel-Lavastine, Rosenheim, Tebb and others have inclined to the view, suggested by various careful experiments, that the main function of the cortex is the manufacture, storage, and metabolism of the lipoids and cholesterol esters, thus playing "a role of vital importance" (Macallum). And, it has also been demonstrated that the primary cause of death on removal or disease of the cortex (involving necessarily the medulla) consists in the deprivation of the body of these substances. These authorities have also shown that removal of the cortex ~~is~~ is followed invariably by degenerative changes in the myelin

sheaths of nerves, and have therefore concluded that the cortex furnishes an antacid which is especially concerned with the formation and development of the myelin (lipoid) of nerve fibres and of the central nervous system. (Schäfer's Endoc. Org., (914).

General Conclusion.

We see, then, that quite successful results have attended experimental work on the suprarenal glands; but it still remains to explain why the bronzing that usually accompanies Addison's disease has not so far been obtained in experimental lesions of these glands. It has been suggested that Addison's pigmentation may be due to the very slow and universally destructive process of the disease. At present, however, it is but only by a process of exclusion that we may guess at an aetiological relationship between the destruction of the cortex and the Addisonian bronzing. No doubt, as Starling has pointed out, it is possible that future investigations may show some connexion between this part of the gland and the general destruction of pigment in the body.

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SECTION IX.

K: THE PITUITARY AUTACOID.

The pituitary autacoid is produced by the pituitary body or hypophysis cerebri, a small structure which, in human beings, lies at the base of the brain as an infero-posterior relation of the optic chiasma. It occupies the hypophyseal recess in the sella turcica of the sphenoidal bone and consists of an anterior and a posterior lobe, separated from each other by a cleft; the posterior lobe consisting of a pars intermedia and a pars nervosa. A pars tuberans has also been described (Herring).

1885–1886: Early investigations (and their recent confirmation: up to 1918).

The study of the internal secretion of this organ is a comparatively modern development. Paulesco, and later Horsley in 1885, showed that the total removal of the pituitary body was accompanied by symptoms not unlike cachexia thyreopriva, followed by death in a few days. But it was left. to Pierre Marie to demonstrate definitely the physiological significance of this secretion. Marie (associated later with Marinesco) in 1886 described 2 cases of the disease now known by his name, & which he observed in Charcot's clinique at La Salpêtrière and to which he gave the expressive name "acromegaly". From these, and from 5 other cases which he rescued from oblivion in the older literature, he was able to put on record the essential

and most important clinical characteristics of the malady. He showed that hyperfunction of the pituitary was responsible for this "acromegaly" and "gigantism", his description of the malady aptly expressing its most prominent sign, viz: "hypertrophie singulière non-congénitale des extrémités supérieures, inférieures et congénitale" — i.e., a marked non-congenital enlargement of the limbs and head. Shortly after Marie's discovery, Rogowitsch showed that pituitary enlargement followed the removal of the thyroid. In 1888 and 1889, Marie gave a more complete description of his disease; and the following year (1890) Souza-Leitz, his pupil, published a monograph on the subject with accounts of 35 cases collected from diverse sources, showing their intimate connexion with hyperpituitarism.

Poulesco's and Horsley's 1885 observations on the removal of the pituitary were confirmed by Bastre in 1889, by Clay in 1891, by Casseli in 1900, by Gaglio in 1902, by Fischera in 1905, by Aschner in 1912, by Cushing in 1912, by Biedl in 1913, and by Houssay in 1918 (Burton-Opitz). These observers found that the 2 lobes of the organ possessed different functions: that the extirpation of the anterior lobe was immediately fatal, whilst that of the posterior lobe did not produce any decisive symptoms. Partial removal, they found, was followed by obesity and infantilism.

The Researches on the Nature of the Autacoid:

1895 — 1923.

The

The physiological and chemical nature of the internal principle produced by this organ did not start to be immediately investigated till after some years after Marie's discovery of 1886.

(a) 1895 – 1899. In 1895, Oliver and Schafer[95] found that the extract of the pituitary body produced a marked rise in blood pressure and a great increase in force of heart beats; and three years later, Howell demonstrated that ~~only~~ extracts of the posterior lobe only (especially the pars intermedia) were responsible for this action. In 1899, Vincent and Schäfer[96] found that the successive injections of the extract caused increasingly lower rises in the blood pressure. ~~followed~~

(b) 1901 – 1909. In 1901, Frölich demonstrated the relationship between hypopituitarism and what Barbels afterwards called "dystrophia adiposogenitalis" (= "Frölich's disease). Benda, in 1904, shewed that hyperplasia of the glandular elements of the anterior lobe occurred in acromegaly, and that the pituitary was rudimentary in true dwarfs; and Madelung in the same year also described obesity in a girl of 9 years, whose hypophysis had been destroyed by a bullet lodged in the Sella turcica. In 1906, Schafer and Herring[97] shewed that the extract augmented the flow of urine. Cramer[98] in 1908 demonstrated that the action of the pituitary extract was different from that of adrenalin in that it (i.e. the former) acted directly on the muscular elements, and not upon the nervous terminals like adrenalin. In 1909, Frankl-Hochwarth[99] and Frölich found

that the first injection of an extract of the posterior lobe induced a powerful contraction of the pregnant uterus and bladder more than subsequent injections did.

(c) 1910 – 1923 The recent experimental work and clinical studies of Dr. Harvey Cushing and others do well mark an epoch in the study of the internal secretion of the pituitary. Cushing in 1910 shewed a large number of clinical conditions which he grouped together under the term "dyspituitarism", the causation part which the pituitary plays in these conditions being brought well to the fore. (v.: Cushing: "The Pituitary Body and its Disorders, J. B. Lippincott Co., 1912). Oliver and Mackenzie[100], and Ott and Scott[101], in 1911 demonstrated the galactogogue effect of the pituitary extract on pregnant or parturient animals. This same year also marked the brilliant researches of Engeland and Kutscher[102], who isolated "pituitrin" or "hypophysin" – as they termed it – from the posterior lobe. Sharpey-Schafer in 1912 obtained favourable results on growth by feeding preparations of the anterior lobe to young rats. In 1915, Simpson and Hill[103] found that pituitrin had the same galactogogue effect that had been demonstrated for pituitary extract by Oliver Mackenzie and others four years previously (1911), and shewed that it also induced a copious flow of the cerebro-spinal fluid and urine, and its glycosuria-producing faculty was also demonstrated by Sir Byrom-Bramwell (Bramwell: "Intracranial Tumours", 1915). Robertson[104] in 1916 succeeded in isolating

from the anterior lobe a substance which he called "tethelin", containing nitrogen and phosphorous and stimulating the growth of young mice. Magnus, Levy, and Falta also reported that the administration of such pituitary extracts increased protein metabolism; and, in this connexion, we may note also the admirable experimental work done by N. M. Dott and reported in the Quart. Journ. Exp. Physiol. of Nov 1923, p 241. This investigator found

(1) that the secretion of the anterior lobe had a marked influence on cell activity, especially on embryonal tissues like epiphyses etc.;

(2) that the pars nervosa had no effect on metabolism;

(3) that hypophyseal (pituitary) polyuria was due to increased secretion of the pars intermedia; and

(4) that the pituitary and thyroid in conjunction had a vast influence on growth of young animals*.

Conclusion.

In the light of our present knowledge, we may briefly conclude that the endocrinologists regard the anterior lobe as influencing growth and development, and as being necessary to life; whilst the posterior lobe possibly helps to maintain normal blood pressure, and influences the metabolism of the carbohydrates, proteins, and perhaps, fat (Burton-Opitz.)

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* Recent work by J. Camus and G. Roussy (La Presse Méd, July 8/1914, p 517-521) and by P. Bailey and F. Brewer, (Endoc. 1921, 5, 761; Also Bailey, Exptl. J. Physiol, 1922, 20, 162) indicate that many if not all of the results usually attributed to lesions of the pituitary body are really due to lesions of the brain in the opto-peduncular region. This finding is, perhaps happily, as yet unconfirmed.

SECTION X.

THE INTERNAL SECRETION OF THE PINEAL GLAND.

THE CAROTID & COCCYGEAL GLANDS.

I: THE PINEAL AUTACOID.

The pineal gland is a small structure that lies in the posterior aspect of the brain between the anterior corpora quadrigemina. It is pyramidal in shape, its base being directed forwards across the roof of the 3rd ventricle.

The pineal internal secretion: Ancient and Modern Theories.

That "there is a small gland in the brain in which the soul exercises its function more than in the other parts" was the opinion of the ancient, Descartes (1596–1650 AD); and for more than 2½ centuries, this was the type of our knowledge of the functions of this gland. (Osler). It was in fact for very long regarded as representing but a vestigial remnant of the eye of an ~~ext~~ antediluvian vertebrate ancestor of mankind. (Bucke).

What we now know regarding this gland is derived chiefly from clinical cases. Thus, Virchow[105] in 1909 called attention to the fact that cystic growths and tumors of the gland presented a clinical picture not dissimilar to that of diseases of the pituitary body, except that sexual infantilism was absent. It also showed that lesions

of the organ were associated with cachexia, obesity and trophic disturbances.

Recent papers on the nature of the internal secretion of the gland increasingly show that the gland plays a no mean rôle in the process of growth; but ~~W~~what particular place this rôle occupies, the endocrinologists are by no means agreed, and their findings have been, moreover, very contradictory. Thus McCord, in 1914, showed that feeding of pineal to young guinea pigs hastened their sexual maturity and growth; whilst, on the contrary, Horrax in his papers of 1916 demonstrated that the removal of this gland in male guinea pigs favoured the development of the sexual organs and hastened the sexual maturity and breeding power of the female (Burton-Opitz): it would thus appear that hypo-~~pinitarism~~pinealism and hyper-pinealism produce identical results! Further, Foa showed that removal of the pineal gland also produced, in cockerels, not only a more rapid growth of the body but also an earlier development of the testicles and of the secondary sexual characteristics: these findings have been confirmed by Sartoschi. Intravenous injections of an alcoholic extract of the gland have been shown also to produce a marked but temporary fall in blood pressure; and plethysmographic observations have further demonstrated a diminution in kidney volume (v.: Sharpey-Schafer, Endoc. Org., 1916). A galactogogue effect has also been recorded (? Starling)

Conclusion

In the state of our present knowledge, then, we may conclude that the active principle of the pineal contains a chalone as well as a hormone which undoubtedly acts on growth. Our notions of the function of the gland are however still nebulous, and they require further clarification by the endocrinologists

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M: The Carotid and Coccygeal Glands.

These are minute ductless glands lying respectively of the bifurcation of the carotids and in front of the apex of the coccyx.

Our knowledge of their Endocrine Function.

Absolutely nothing is known of the function or the internal secretion of these glands, if they have any at all. The histologists inform us that they show a relationship to the medulla of the suprarenal glands in that their cells are of a chromaphil nature*. (Schäfer's Essentials of Histology, 11th Ed., p254)

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* George Dock, M.D., in Osler's System of Medicine Vol. VI, Part II, page 353 states that Biedl, Wiessel, & Mulon have succeeded in producing an adrenalin-like glycosuria with extracts of these organs obtained from the horse.

*SECTION XI.

THE INTERNAL SECRETION OF THE SEX ORGANS: THE TESTIS & OVARY.

N: THE TESTICULAR HORMONE.

It was known from time immemorial, e.g. in Oriental countries, that removal of the male generative organs in young animals usually prevented the development of the accessory generative organs and of the features which characterise the male sex generally. There are numerous references to in ancient Eastern literature to the effects of castration in the eunuchs of royal harems. These individuals were described to retain most infantile characteristics, viz: "the pelvis, very small; the amount of axillary and pubic hair, extremely scanty. The growth of the larynx is arrested and the voice, soprano-like in character..... They are prone to become phlegmatic and to develop a heavy panniculus adiposus which smoothens their contours and gives them a feminine appearance ....." (Burton-Opitz). The testes, then, were quite known in ancient times to influence growth and to control the development of the sexual characteristics. However, the precise mechanism or the nature of this influence was in those times an insoluble proposition.

Early Developments: to 1849.

According to Berman,[106] the idea of a testicular hormone

* This section is based principally on F.H.A. Marshall's "Physiology of Reproduction", 2nd Ed., 1922.

was expressed by Cowden in the 18th Century. In fact, John Hunter (according to Professor K.N. Walker in his Hunterian Lecture on "Testicular Grafts" delivered before the Roy. Coll. of Surgeons of England on Feb 4/1924 — reported in Lancet of 16th Feb 1924) as long ago as 1780 succeeded in transplanting the testicle of a dog. The full import of this experiment was however unappreciated till Berthold[3] in 1849 definitely affirmed the existence of a testicular autacoid (and incidentally founded endocrinology as an organised and a coherent science). Berthold based his belief on the results of testicular transplantation in fowls in which the testes, after removal, were attached to new positions (v. General Introduction, p 6). These transplants, he found, still sufficed for the development of the sexual characters. Indeed, in attributing this role to the testes, Berthold was undoubtedly the first to assign an endocrine function to any bodily organ soever, thus anticipating Claude Bernard (1855) and the numerous eminent endocrinologists who succeeded him.

Later Developments: 1850–1896.

Although Leydig a year after Berthold's experiments had described the interstitial cells of the testis (1850), and although the first scientifically detailed description of sexual infantilism had been given by Lorraine some years later (1871) in the preface to the thesis of his pupil Tarnean de la Cour (Allbutt and Rolleston), yet, it was not till some 40 years after that renewed

interest was taken in the subject. Brown-Sequard[107] in 1889 (v. General Introd.: p 7) found that subcutaneous or intravenous injections of testicular extracts produced invigorating qualities which manifested themselves in improvement of mental and physical vigour, not only in cases of general prostration, neurasthenia, deficiency of normal testicular functional activity, but also in old age (Brown-Sequard was 72 years old at this time). Later work has however not corrobated Brown-Sequard's findings, which were perhaps the result of perverted enthusiasm and auto-suggestion rather than of accurate, scientific observation. Two years after Brown-Sequard's observations, Poehl (1891)[108] claimed to have extracted a substance which he believed to be the active principle of the testicular extract. To this substance he gave the name "Spermine", with the formula $C_5H_{14}N_2$, which he found three years later (1894)[109] "acted as a 'physiological catalytic' which increased the action of the heart and of the digestive organs". In 1896, Loth and Pregel[110] ergographically recorded that testicular extracts augmented the muscular power by as much as 50%, and diminished muscular fatigue.

20th Century Findings: 1900-1924.

The experiments that have been performed on this subject since 1900 to the present day are so numerous, and their literature is so extensive, that justice could hardly been done to them by quoting them all here.

Only very brief reference may therefore be made to the names of many investigators whose work has advanced our knowledge of the testicular hormone. A very few of these are: Dixon and G. Walker (1900); Ancel and Bouin (1903); Shattock and Seligmann (1904); ..... Coincy (1907); Marshall (1911); Steinach ("Pubertal Gland", 1912); Holzknecht (1913); Boring & Pearl (1917); Pezard (1918); Rasmussen and Lipschütz (1919); Hyrle, Kohn, Fiedje, and Sand (1921); Prof. T.H. Morgan (1922); Otto, Wagner, and Bormann (1922) — to mention but a very few .....

Perhaps the most remarkable development regarding our modern knowledge is the finding of Steinach[111] 4 years ago (1920) (confirmed by Sand[112] in 1921) that vasectomy produced hypertrophy of the "interstitial" (Leydig) or "pubertal" (Steinach) gland, and restored aged men and senile animals to their former state of physical and mental vigour (v.: Marshall's Physiol. of Reprod., 2nd Ed., pp. 327 and 328)*. Recent experiments by Prof. L.N. Walker (1924) (v: "Internal Secretion of the Testes", Lancet, Jan 5/1924) have however failed to confirm Steinach's observations. Walker's additional findings may be summarised as follows:

(1) that the sex characters are stimulated rather than originated by the internal secretion of the testes; and

(2) that this internal secretion is formed, not by the interstitial cells (whose function, he believes, is trophic rather than secretory

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* Some authorities state that this had already been noticed by Tandler in 1908 and again in 1910 (Burton-Opitz) (Tandler, Wiener Klin. Woch. 1908 & 1910)

in character), but by the cells of the tubules .... The matter is as yet unsettled.

Conclusion.

All the experiments by modern investigators, coupled with our ancient knowledge, seem to show that the testes give an internal secretion generally believed to be furnished by the interstitial cells of Leydig, having a considerable influence on growth and on the development of sexual characters, ~~and~~ especially sexual desire (Steinach)*

— " — " — " — " — " —

O: THE OVARIAN AUTACOID.

The structure of the ovary was described by Von Graafe (1641-1673) who ~~described~~ discovered what are now known as the Graafian follicles.

Early Observations:

That women gain in weight after artificial or natural menopause was well known to the ancients; but nothing specific was understood regarding the causative factor of this phenomenon. Subsequent clinical observations that were made, viz: that adult women in whom the ovaries had been removed for the cure of ~~tumours~~ ovarian or cystic growths showed retrogressive changes in their genitalia, such as atrophy of the uterus and vagina, ~~and~~ with peculiar vasomotor and psychoneurotic conditions, led attention to the endocrinological function of this organ. Subsequent to this, the successful results of the administration of ovarian extracts in these cases

* Eminently successful results have been obtained from grafts of monkey testes to human beings by Dr. Voronoff — British Medical Journal, March 22/1924.

confirmed the theory that the ovary furnishes an internal secretion. Lastly, this conclusion was upheld later by the observation that young females castrated before puberty showed no signs of menstruation or of other sexual characteristics — which result did not occur if a portion of the ovarian tissue was left or transplanted to other regions of the body (v: Meredith, B.M.J. 1904)*.

Modern Experimentations: 1889–1915.

Loewy and Ritchie[113] in 1889 showed that the internal secretion of the ovaries exerted a remarkable effect on general nutrition; and they demonstrated that removal of the ovaries could exert a favourable influence upon the course of the disease "osteomalacia". Glass in 1899 and Halban and Morris in 1901[114] found that the cessation of menstrual flow produced by ovariotomy did not occur if the ovaries were transplanted into the uterus or elsewhere in the abdominal cavity. In 1905, Marshall and Jolly found that a temporary condition of oestrus (="heat") could be incited in mature animals by the injection of ovarian extract from an animal in heat, and that this condition could also be produced in castrated (ovariotomised) animals by grafting ovarian tissue (v: Phil. Trans. Roy. Soc. Lond., 1905). In 1904, Bouin[115] found that extracts of the entire ovary were more beneficial than those of the corpus luteum or Graafian follicle alone. He therefore referred the ovarian endocrine function to the peculiar stroma cells, which he designated as the

* Removal of the ovary for cystic growths or other tumours to which reference was made on the last page was first deliberately performed ("ovariotomy") by Ephraim McDowell in 1809, when a woman aged 47 — A.H. Southam, Brit. Med. Journ. Mar 22/1924, page 513.

"glande interstitielle l'ovaire" (interstitial cells of the ovary). Carmichael and Tolly[116] and Marshall and Tolly[117] during the year found also that removal of the ovaries in very young people prevented the normal development of the uterus, whilst removal in adults caused a degeneration of this organ. — which could be averted by a successful transplantation of ovarian tissue.

Vague notions were already existing by this time (1907) that the phenomenon of menstruation was dependent upon a periodically discharged autacoid furnished by the ovaries. Fränkel[118] was the first to confirm these views in 1910, proving that the corpus luteum, which controls the blood supply of the ovary, furnished this secretion. This knowledge was instantly applied to clinical therapeutics by the employment of dried extracts of the cow's corpora lutea in cases of suppressed menstruation and artificial menopause, brilliant results being obtained.

Miscellaneous Researches: up to 1916.

Numerous experiments have of late years been made to determine the effect of the ovarian secretion on other organs. Thus, in 1915, Sir Byrom-Bramwell reported a case of acromegaly and gigantism in whom castration had been carried out before puberty (Byrom-Bramwell: "Clinical Studies", Edin. Med. Journ., June 1915). Further, castration has been proved to be associated with increase in weight of the hypophysis, thymus, and suprarenal glands (Bustan-Opitz), and to intensify the symptoms of hyperthyroidism. Recent investigations

by Crew (?) has also shown that the grafting of an ovary from a female rat or guinea pig into a young castrated male of the same species produces a pseudo-hermaphrodite, with persistent male generative organs and female secondary characteristics.

Dr. M. Itagaki of Kyushu University, working recently in Prof. Sir. Sharpey-Schafer's laboratory in Edinburgh, found that the extracts of the interstitial cells invariably inhibited, whilst those of the Graafian follicle or corpus luteum increased, uterine contraction. It would thus appear that the ovarian secretion is a typical antacoid which comprises a hormone or well as a ~~hormone~~ chalone (V.: Schäfer's Endoc. Org., 1916, p 141)‡.

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‡ E. Cowland (Ann. de Med., Dec. 1923 p 516 & "Ovarian Therapy in enlarged thyroid", B. M. J., 12th Ap 1924 Supp., p 53) has recently carefully investigated the exact relationship between the thyroid and ovary. This observer found that every stage in the feminine sexual life is marked by some degree of thyroid hyperdrophy (c.f. p. 22 of essay, text & footnote). He also demonstrated that successful results could be obtained in all forms of goitre by treatment with ovarian extracts.

* SECTION XII.

THE INTERNAL SECRETION OF THE SEX ORGANS (CONTD):

THE UTERUS, MAMMARY GLAND, &c.

P: THE INTERNAL SECRETION OF THE UTERUS.

Despite the fact that the uterine functions fall into abeyance after complete ovariotomy, yet some eminent surgeons and gynecologists have adopted the view that the uterus possesses an independent internal secretion on which the functional activity of the ovary depends. Lowenthal was the first who, in 1884 (Arch. f. Gynekol., vol 24, 1884), suggested the theory that the uterus has a distinct endocrine function.

Experimental & Clinical Observations etc. 1898–1917.

Bond[119] in 1898 reported an experiment upon a rabbit in which one of the ovaries after transplantation in an abnormal position was found to contain somewhat aberrant "corpus luteum of pregnancy" in association with a gravid uterus. He interpreted these observations as supplying evidence of internal uterine secretion acting on the ovaries and so exciting a growth of luteal tissue; and he further supposed that this secretion was quite different from the saline extract elaborated from the quiescent uterus. ~~Sometime~~ ~~previously by~~ Zweifel and Abel[120] during the next year (1899) demonstrated that atrophy of the ovaries with menopause symptoms followed complete hysterectomy, the symptoms being obviated if a portion of the uterine mucosa was left. Mandl and Burger,[121] in their monograph of 1905, expressed the belief that the ovaries,

* This section is based in part on J. H. A. Marshall's "Physiology of Reproduction", 2nd Ed.

after complete hysterectomy, showed a gradual cessation of function, whilst Doran[122], in his careful clinical observations on sub-total hysterectomy in the November of that year, confirmed Zweifel and Abel's findings of 1899 (v. last page). In 1906, Holzbach[123], on the contrary, stated that the ovaries did not usually atrophy after hysterectomy and that if this condition did occur, it was due to interference with nervous connections consequent upon the operation rather than with the endocrine function, if any, of the uterus. During the same year, Bard[124] put forward the views

(1) that the ovarian secretion is influenced by a colloid secretion from the ancestrous uterus;

(2) that the 2 secretions, ovarian and uterine, act antagonistically to one another; and

(3) that the removal of the uterine secretion by hysterectomy favours the hypertrophy rather than the atrophy of the ovaries. (cp. Holzbach).

In 1907, Boston (Lancet Jan 1907) recorded that in 4 cases of women in whom the uterus was congenitally absent, the development of the breasts and other changes relating to puberty (excepting menstruation) were present; thus casting some doubts on the theory that the supposed internal secretion of the uterus influences secondary sexual characters. Blair Bell, in 1916, made the suggestion that ovulation and menstruation were produced by a uterine internal secretion which he termed "Uterine", (Blair Bell: "The Sex Complex", London, 1916). and which has since been found to comprise a galactogogue hormone. In 1917, Graves[125] showed that vasomotor disturbances after

hysterectomy occurred with approximately equal frequency, whether the ovaries be retained in situ, or totally ablated, or transplanted ~~(Marshall)~~

Recent Scientific Researches: 1918-1922.

Of modern researches, those of Marshall and Carmichael are perhaps the most important in that they mark an epoch in the history of the systematic investigation of the nature of the internal secretion. The experiments of these observers showed that the clinical evidence regarding the endocrinological function of the uterus by no means agreed with careful scientific investigation; and that the growth and development of the ovaries was* in no way whatever dependent on the presence of the uterus, as has been previously supposed by Zweifel, Abel, Doran, and others (pages 100 & 101; also cp. Holzbach, & Bond, page 101)

Conclusion.

We see, then, that our knowledge of the internal secretion of the uterus is by no means clear; the question has been, and will perhaps for some time be, a matter for polemical debate. The clinical evidence for the endocrinological ~~function~~ function of the uterus, especially the mucosa (v: Zweifel and Abel, p. 100), acting on the sex characteristics and the various phenomena attending thereto is by no means unconvincing; how much careful experimental work remains to be done before the problem could be regarded as being incontrovertibly settled.

Q: THE MAMMARY—

P.T.O.

Q: THE MAMMARY GLAND: ITS INTERNAL SECRETION & THE INFLUENCE OF OTHER INTERNAL SECRETIONS ON ITS (GALACTOGOGUE) ACTIVITY.

Its Internal Secretion.

The state of our knowledge of the internal secretion of this gland is rather poor. The only reference to it which one finds in the literature is the observations of Healy and Kastle in 1912 (Bulletin 160, Ky. Agric Exp. Station, 1912). These investigators found that the mammary glands furnished an internal hormone for the contraction of the gravid uterus during parturition.

Researches on the Influence of Other Internal Secretions on its (galactogogue) activity:

(a) 1895 - 1905. It was early shown that the factors involved in the external secretory activity of this gland involve certain closely related and very complex nervous and chemical mechanisms. The idea that a chemical rather than a nervous process is involved in its activity began with Goltz and Ewald[126] who, in 1896, found that bitches in whom the spinal cord had been completely dissected became pregnant and lactated. Ribbert[127] two years later (1898) confirmed these experiments, and further demonstrated that mammary tissue transplanted to the neighbourhood of the ears and severed from all its nervous connexion enlarged and secreted milk during a subsequent pregnancy — thus showing that a purely chemical process was involved in lactation.

These findings were subsequently confirmed, directly or indirectly, by various other observers especially Halban who, in 1905, expressed the opinion that the specific internal (hormonic) stimulus arose mainly in the chorionic villi and placenta.

(b) 1906 – 1909: The "Foetal Hormone" Theory. The specific nature of this hormone was not conclusively demonstrated till the time of Miss Lane-Claypon and Prof. E.H. Starling[128] who, in 1906, advanced their "Foetal Hormone Theory". They found that foetal extracts injected into a virgin rabbit produced a genuine development of the mammary gland, closely simulating the growth that normally occurs during pregnancy; and that similar extracts from the ovaries, placenta, or uterus had no such effect. Foa, two years later (1908), found that this hormone was not specific for any given species and that its physiological action was destroyed if heated to 110° C. (Marshall's Phys. of Reprod., 2nd Ed., p. 612)

(c) 1910 – 1922: This period was devoted chiefly to further observations on the influence of ovarian, placental and other antacoids on mammary secretion, and to various clinical observations; Basch[129] in 1910 described the case of the hygopagus twins – the Blazek sisters – in whom pregnancy and parturition in one was followed by lactation in both. This observation, with the fact that instances of secretion of milk have been known to occur in males and in virgin animals, led to a very acrimonious controversy regarding the Lane Claypon – Starling "foetal hormone theory". It must in justice be remarked, however, that it was not of any

time contended by Miss Lane Claypon or by Professor Starling that the foetus was the sole source of the stimulus for mammary development; indeed, these observers specially demonstrated that the mammary growth that occurred at puberty, for instance, could only be attributed to ovarian influence, since this growth did not take place if the ovary had been removed before puberty. However, since that time, it has been definitely experimentally proved by Ott and Scott (1910), Schafer and Mackenzie (1911), Ancel and Bouin and Schil (1912), Fraenkel and Blercier (1913), Gavin (1913), Hill and O'Donoghue (1913), Hammond and Marshall (1914), Simpson and Hill (1915), Athias (1916), Halban (1917), Hesselberg (1917), Loeb and Kuramitsu (1921), Woodman (1922) and various other investigators, that extracts of the ovary (Corpus luteum), posterior lobe of pituitary, placenta, involuting uterus, the so-called "myometrial gland" of the uterus (Ancel and Bouin), lactating mammary gland itself, and of the pineal gland as well as those of foetal tissue, have a marked galactogue effect.

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PART III

GENERAL CONCLUSION.

SECTION XIII

GENERAL CONCLUSION.

"Science is the great antidote to the poison of enthusiasm and superstition" — ADAM SMITH (1723-1790): The Wealth of Nations, Book 5, part 3, art. 3.

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THERE is perhaps no other branch of science which more aptly illustrates these eminently significant words of the great Adam Smith than the science of endocrinology.

In the foregoing chapters, we have endeavoured to trace how the human mind has triumphed over the many difficulties it has encountered in its manifold activities to comprehend the universe, to discover the truth, to conquer disease, and to wrest from Nature her jealously guarded secrets. We have observed the vicissitudes of the fortune and the ultimate success that have attended the slow but sure steps by which Man passed from an age of fanciful theoretication to an epoch of scientific experimentation. We have seen the manner of process by which he freed himself from the trammels of conservative superstition to enjoy the freedom of liberal enlightenment; how he has, indeed, emerged from the darkness of chaotic ignorance into the light of ordered knowledge. —— And such is our glorious heritage!

"Human beings are queer and incomprehensible mixtures," we are assured by a great philosopher, "and great scientific discoverers are no less so than other

men". — And so we have been weightily impressed with regard to the history of the development of our knowledge of the internal secretions. We have seen from our study of the many researches on this great subject that, in scientific research, there exists quite as many methods as there are ~~many~~ endocrinologists, though, doubtless, many of these methods claim a common source of inspiration. We have observed that the task of these physiological investigators is "to correct old creeds" (Emerson), to observe the appearances which Nature presents, to ascertain what lies behind these appearances, to unify them in a faith commensurate with the grander orbits and universal laws which they disclose, and, lastly, to employ them in the alleviation of human suffering. We have seen that the methods by which these observers of nature arrive at their conclusions are not of much consequence, so long as these methods are sufficiently scientific; nor need they, as mighty men of science, ~~concern~~ pre-occupy themselves over-much with the "ultimate" truths of Nature. But the point that does vitally affect the course of the history of science is not the channels whereby they derive their ideas, but how they prove or verify their statements and apply their knowledge. Indeed, we have seen how the vague analogies of an Aristotle and the nebulous theories of a Galen may derive a common origin or aim at a common goal as the precise conclusions of a Claude Bernard, the brilliant findings

of a Banting, or, indeed, the immense depth of the profundities of a Sir Sharpey-Schafer. But we have seen, on the other hand, that a fathomless chasm exists between these two types of investigators: between superstition and ignorance on the one hand, and enlightenment and knowledge on the other. Thus, we find that whilst an Aristotle or a Galen was satisfied with "subtleties and mere fanciful conjectures"[130] based on totally unscientific methods, a Bernard or a Banting or a Sharpey-Schafer passed ~~cautiously~~ cautiously from observation to inference, from inference to verification, and from verification to application, in an orderly and stately sequence.

The organs of internal secretion represent but an infinitesimal fraction of the whole weight of the body: it has even been cynically said by an eminent authority (Keith) that the whole series of them could be safely and almost unobtrusively stowed away in a man's vest-pocket; — and yet, it is on these very organs that most, if not all, of the vital processes of life, and, incidentally the theories thereon, depend. Endocrinology offers indeed a most fascinating field for speculation and theorisation! Psychologists have already ~~descried~~ descried in it a solution of some of their most acute problems! (v: H. Crichton Miller in his paper on the influence of the thyroids, sex glands, and suprarenals on emotions, read before the Section of Psychiatry of the Royal Med. Soc. on Feb 12/1924 and reported in Lancet 23rd Feb/1924). Eminent anthropologists have even begun to

assume us that racial characteristics are dependent on the relative development of the several endocrine organs! Thus, in his Presidential address on "The Differentiation of Mankind into Racial Types", delivered before the Anthropological Section of the British Association for the Advancement of Science in 1919, Sir Arthur Keith pronounced, especially with regard to the pituitary, as follows:—

> "..... We are justified in regarding the pituitary body as one of the principal agents in the body machinery which ..... is directly concerned in determining ..... the marks of race ..... The characteristic delineation of the Caucasean face, the tendency to strong eyebrow ridges ..... the bulk and height of stature ..... are best explained in terms of pituitary function....."

Again, "..... The pigmentation characteristic of the different races is directly proportional to the relative activity of their suprarenal glands ....."

and so on, ad libitum! The various other theories, psychological, anthropological, phylogenetical, sexological, and so forth hardly has any limit to their expansion! However, by far the most fruitful source of speculation consists in the employment of various tissue extracts in therapeutics; though one fears that the theoretical views on which most of these are based have often outrun the established data and encouraged methods of therapeusis which are sometimes more profitable to the manufacturing chemist than to the patient! Further,

the theories on which such are evolved "ahew", as one eminent authority (Cushny) puts it, "very little advance upon the belief of the savage that the courage of the lion may be acquired by the simple process of eating that animal's heart"; and the clinical observations which are generally cited to support the use of these commercialised tissue extracts are usually of an equally primitive order. Indeed, no more fruitful source of quackery exists, even at the present day, than in the exploitation of these so-called "remedies", and, amongst these, all the extracts of the testes and ovaries which were originally introduced, as we have noted above (v.: General Introd.: p 7), by Brown-Sequard in 1889 on quite insufficient observations, stand pre-eminent. One may perhaps pause here to say that further advance is to be looked for in the use of these so-called Extracts; but this can only be accomplished through careful observation and experiment which alone has given to mankind the useful remedies of this class which are now available after many years of patient research. The indiscriminate and haphazard use of these organic extracts in every sort of disease did not, as we have seen, lead to any progress in the past, and will perhaps hardly be more successful in the future! *

However, there can be no question that, of the numerous vaunted tissue extracts, four, namely: those of the thyroid, pituitary, suprarenals, and islets of the pancreas, are assured of a permanent place in therapeutics. The first, thyroid, has, as has been indicated, been employed in cases of deficiency of the thyroid gland with brilliant results. The second, pituitary, is chiefly employed in obstetrics. The third, adrenalin, obtained from the suprarenal medulla, has been found most useful in controlling haemorrhage in operations in general surgery, in heart failure or shock, in asthma, and in post-partum haemorrhage; though no success has attended its use in Addison's lesion of that organ. Insulin, the fourth and latest arrival in organotherapeutics is, as has been noted,

* The subject of modern organotherapy is very instructively dealt with by J.T. Harley: Endocrinology and Metabolism, 1922

obtained from the islet tissue of the pancreas. It has opened up a new source of hope to the sufferers afflicted with that dread disease, diabetes mellitus; but whether, as has been pointed out by Prof. Macleod, this hope will be fully justified will be a matter of a few more years of careful observations.

Despite our many advances, further researches remain to be done to add to the symposium and armamentarium of our knowledge of the internal secretions. The endocrinological function of the carotid and coccygeal bodies and of the pineal gland and uterus yet has to be unravelled. The exact significance of the internal secretion, if any, of the thymus has yet to be made clear. We still yet have to make further advance in the therapeutic treatment of Addison's disease. Further developments still have to be made with regard to the methods of the cheap commercial production of insulin; and a new method has yet to be found to prevent its alleged deterioration in tropical countries. We may confidently hope, however, that, with time, these problems will be elucidated.

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THE END.

APPENDICES

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APPENDICES :

I : TABLE OF LANDMARKS OR PRINCIPAL DATES.

II : REFERENCES.

APPENDIX I:

A TABLE OF THE LANDMARKS OR PRINCIPAL DATES IN THE HISTORY OF INTERNAL SECRETIONS.

A.D 50 Celzus described diabetes.

150 Aretaeus of Cappadocia first used the word "diabetes". (from the Greek Διαβήτης = a syphon.)

1563. Suprarenals first recognised by Eustachius Sanctoseverinatus.

1614–74 Sylvius differentiated between true secreting glands and lymph glands.

1640–1673 Vieussens discovered the pancreatic and other ducts, and described certain ductless glands

1641–1673 De Graaf described the ovarian (Graafian) follicles.

1654. Glisson fully described the liver in "De Hepatae"

1660 Vieussens gave the first complete account of the thymus.

? 1672 Brünner of Heidelberg discovered the duodenal glands (Brunner's) and found that pancreatectomy produced "a ravenous appetite, thirst and wasting." (? 1772)

1679 Willis differentiated between saccharine and non-saccharine forms of diabetes. (mellitus and insipidus)

1775 Théophile de Bordeu promulgated certain views which have been supposed to indicate a clear conception of internal secretion. (This fact is denied by some authorities)

1776 Dobson first chemically demonstrated sugar in diabetic urine.

1780 The first successful testicular graft was obtained by John Hunter.

1788 Cowley first discovered the connexion of diabetes with disease of pancreas

1809 First operation of ovariotomy performed by Ephraim McDowell.

1823 Lobstein 1st described what is now known as Addison's Disease.

1825 Parry described "Enlargement of thyroid with Enlargement ~~and~~ or Palpitation of the heart"

1835. Graves described this disease (exophthalmic goitre) more fully. King first demonstrated the colloid contents of the thyroid vesicles.

1849 THE FIRST IDEA OF INTERNAL SECRETIONS WAS FIRST DEFINITELY ADVANCED BY BERTHOLD.

Addison shewed the relationship of this disease with lesions of the suprarenals.

1850 Leydig 1st described interstitial cells of testicle.

Harling in ~~New Zeal~~ Switzerland first observed that thyroid was absent in cretins.

1856 Schiff first studied the fatal effects of thyroidectomy.

Vulpian obtained certain suprarenal extracts giving marked colour reactions with chemical reagents.

1857 Brown Sequard first investigated effects of removal of suprarenals.

The name "internal secretion" was first employed by Claude Bernard who in this year also discovered the glycogenic function of liver.

1864 Langerhans described the islet tissue of the pancreas.

1873. Sir Wm Gull described myxoedema adultorum; and Horsley and Semon shewed that it, ~~and~~ cretinism, and post operative myxoedema were related to hypothyroidism.

1880 Sandström discovered the parathyroids.

1883 Kocher first employed the term cachexia strumipriva for the ~~the~~ effects of thyroidectomy.

1884 Lowenthal first suggested that the uterus furnishes an internal secretion.

1885 Paulesco and Horsley first studied the effect of removal of pituitary.

1886 Marie described acromegaly and gigantism, shewing their relation to hyperpituitarism.

1889 ~~B~~ The effects of testicular extracts were first studied by

Brown-Sequard.

von Mering and Minkowski ~~first discovered~~ proved that experimental pancreatectomy produced diabetic symptoms.

1891 "Spermine" was isolated from testicular extract by Poehl.

Gley differentiated between cachexia strumipriva and tetania parathyreopriva.

Thyroid extracts were first successfully employed in therapeutics by George Murray.

1895. Schafer and Oliver first demonstrated the action of suprarenal and pituitary extracts on the cardio-vascular system.

1896 Thyroidin was isolated from thyroid extract by Baumann.

1897 The first successful suprarenal transplantation was recorded by Biedl.

1898 Bond first ~~experimentally suggested~~ proved the endocrinological function of the uterus.

1900 Sir Sharpey-Schafer suggested the islands of Langerhans as the source of the pancreatic intestinal secretion which he termed "insulin".

1901 Schulze and Ofie first found that the islets of Langerhans showed atrophy and hyalin degeneration in diabetes.

Adrenalin was first ~~obtained~~ isolated by Aldrich and Takamine from suprarenal extract.

Halban first studied the amenorrhoeal effects of ovariotomy.

The connexion of hypopituitarism with adiposogenitalis was demonstrated by Frölich.

1902 Szbolew demonstrated that atrophy of pancreas parenchyma only
and not of the islets followed ligation of the pancreatic duct.

Bayliss and Starling discovered "secretin"

1904 Rennie and Fraser obtained the first satisfactory extract
from pancreas of fishes.

1905. Goodall and Paton first studied the effects of thymusectomy.

1906 Edkins discovered "gastrin".

Fleischmann and Erdheim showed the effect of the
parathyroid over Calcium metabolism.

Lane-Claypon and Starling promulgated their foetal
hormone theory

1908 Macallum and Voegtlin found that parathyroid extracts and
especially calcium salts abolished the effect of tetania
parathyreopriva and that the parathyroid presides over
Calcium metabolism.

Satisfactory clinical results in 6 cases of diabetes
treated with pancreatic extracts (which were patented
by Schering Co. of Berlin) were obtained by Zuelzer
and his co-workers.

1909 Virchow first called attention to symptoms following pineal enlargement.

1911 Kutscher and Engeland isolated pituitrin from pituitary extract

1913. Schäfer advised the name "autacoid" for all internal
secretions, and "endocrine organs" for the organs which
furnish them.

The influence of thyroid on growth was demonstrated
by Gudernatch.

1914 McCord first demonstrated the effect of the pineal on growth.

1916 Robertson isolated "tethelin" from the anterior pituitary lobe, demonstrating its influence on growth.

Blair Bell first employed the term "uterine" for the internal secretion of the uterus.

1917 Findlay and Paton conclusively demonstrated the relation of the parathyroid to protein metabolism, especially guanidine.

1918 Kendall isolated "thyroxin" from thyroid extract.

1919 The first patient treated by Murray with thyroid extract in 1891 died from heart disease.

Park and McClure found that the thymus has no true endocrinological function.

1920 The beneficial effects of vasectomy in old age were demonstrated by Steinach.

1922 "Insulin" was obtained by Banting and Best of Toronto University.

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APPENDIX II

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