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

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

BY
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The Essay:
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 relegiate 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, Broom-Segard, the Reverends of Geneva, Oliver, Sharpey-Schafer, Horley, Schiff, Kocher, Popielaki, von Mering, Minkowski, Starling, Baylis, Vincent, Gley, Marshall, Jolly, and a host of many other endocrinologists no less distinguished, has since germinated; it has now grown to such a vital 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 organized and vastly important science is so extensive and complicated that no attempt has been made to include 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 experimentation have failed to establish.
matters of little or no clinical or physiological significance, and to the many recent findings, the importance of which can only be assessed and their correlation established in the light of future observations. The discussion of the more important findings has therefore 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 foot-notes.

The history of its clinical aspects of certain internal secretions (e.g. Addison's disease, under-supplements, 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 it perhaps merits 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 detail; whilst Part III represents an attempt at a general and speculative discussion of 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 J. Horner-Schofer's 'Endocrine Organs,' 1st and 2nd Editions; Cambridge's Insulin Treatment of Diabetes, Livingstone, Edinburgh, 1924; A. L. Bell and K. W. Koller, 'Oler and Macrae's,' Gebuhr's and Tagg's text books of Medicine; Buck's Handbook of the Biological Sciences; Howell, Burton, Ofstoy's, Halliburton's, and Stirling's text books of physiology; Marshall's Physiology of Reproduction; Macallum's Pathology; Professor Cusack's Pharmacology; and Thomas' Series of Classics of Scientific Methods. The material on the history of the which the references to the English and German secretions 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.

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 the "humours" in the body. Pythagoras (circa 1000 B.C.) attributed the cause of disease to pathological conditions in these "humours". Aristotle (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 sile', which is placed in the liver. The second is 'melancholy', called 'sclara sile', the next 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 gross humours are purged by the eyes, "melancholy" by..."
The era, 'cholera by the nose, and phlegm by the hair.'

These theories seem to have been widely held right up till the time of Galen (circa 150 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 - 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 "spirit," 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 off to the body as a sort of nervous fluid which was distributed through the nerves, which were supposed to be merely hollow, tubular organs.

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

No further elaboration of the "humors" and "spirits" theories seems to have been attempted in the post-Alexandrian or Arabian period (600-1200 AD), 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 ancient masters. Even
during the Middle Ages and the Renaissance, the writings of the physicians tend to indicate that their mental horizon was still befogged with the crude biological philosophies of Aristotle, and the imaginative physiological speculations 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 limits of the fundamental basis of Galen's and Aristotle's physiology. The condit Servetus (1511-1553 A.D.) in his half-physiological, half-theological work, "The Restoration of Christianity," showed a marked departure from Aristotle's and Galen's teachings by questioning the existence of the "humors" and "natural spirits." The great teachers, Realdus Columbus, Gabriele Fallopio, Jerome Fabriaccius of Aquapendente, Ambroise Paré, Bacon, Borello, and even that master-experimenter Harvey, proposed no new theory.

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

The revival of the experimental method in the 16th, and the introduction of the microscope by Halski (1628-1694) in the 17th century, gave an extraordinary impetus to the development of the study of the microscopic structure and physiological functions of the rninary glands.

Thus, the lymphatic glands, formerly described by Herophilus of Alexandria, were rediscovered and studied in greater detail by Rabelo in 1653, but these functions were not explained till the time of Alexander Monro seconds of
Edinburgh in 1757. Acelli and Bacchini discovered and described several other glands. Pequet discovered the biliary duct. In 1654, Glisson in his "De Hepatice" gave a complete account of the liver, but the physiological function of the organ remained obscure to him. Of course, all the secretory glands except the pancreas, spleen, etc., were well known to the ancients; but nothing except fanciful explanations were given regarding their physiological significance. However, Francis Sydenham (1614-1682) was the first to differentiate between the 'lymphatic' glands and what he called the "conglomeratibus" (i.e., free secreting) glands. Virchow (1843-1911) in 1854 discovered the pancreatic duct, and, somewhat later, gave a full description of the pancreas. De Graaf (1661-1673) was the first to give a complete account of the ovary and of the changes it undergoes during gestation. He also observed the digestive nature of the pancreatic juice, the chemical analysis of which was investigated later by Claude Bernard. Brûllen of Heidelberg in 1672 discovered the duodental gland, which he called "pancreas secretum," and he also observed that pancreatectomy in dogs produced "a ravenous appetite, thirst, and weakness." Reamer (1883), Spallanzani (1729-99), Grant of Edinburgh (1834), Schwalbe (1836), John Hunter (1876), Claude Bernard, Pavlov, and Ludwig also made extensive researches on the chemical nature of the digestive and lymphatic secretions.

* Egalpighi in his "Exercitaciones de structura viscerae" in 1665 referred to them as "conglomerated follicular glands."
This it is seen that, whilst the development of our knowledge of the functions of glands that possess ducts and secrete externally has made great strides since the 16th century — and the function of a gland with a duct is a comparatively simple physiological proposition — yet the use of its 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 attain its 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 washed by the lymph or blood into which it is normally shed in the body. The diseases of the internally secreting or ductless glands were well known at this period so they were to the ancients, as shall be indicated when the history of our knowledge will regard to the individual secretion is reviewed. For example, diabetes was well known to the ancient Celts; but no exact relation ship between clinical symptoms (arising from glandular disease) was ever demonstrated.

The Beginning of Our Modern Knowledge:

The 19th Century.

Although, according to Berman, Borden, and others in the 18th century, promulgated the idea of an internal secretion, yet the beginning of scientific study of the
Addendum I, from reference on opposite page:

Theophile de Borda in 1775 certain views which have been supposed to indicate a clear conception of internal secretion. (Borda: "Analyse médicale du sang", Oeuvres complètes, ed. Richerand, t. ii., pp. 942-9, Paris, 1818.) That this statement is historically correct is maintained by such eminent authorities as M. Neuburger ("Theophile de Borda—1722—76—als Vorbote der Lehre von der inneren Sekretion", Welt. klin. Woch., 1913, 24, 567) and A. Biedl ("Innere Sekretion", 2te Aufl., Band. v. Wien, 1913, 1.5). E. Stolz however at the 17th Internat. Congr. of Med., London, 1913, Sect. ii. Trans., p. 3 denied that Borda gave a clear expression of what he regarded as internal secretion. Nevertheless, there is no question that he idea was sufficiently clear to Borda himself or others, as he regarded each organ as a "Humorium particularium" which exerts its influence upon the body, generally. C. Segalbois in 1801 (Dissertat. inaugural. benomm. à l'Ecole de Med. de Paris, en sept. 1801, Johannes Muller in 1838 ("Elementa Physiologiæ", Trans. Baby, 1838), and W. Carpenter 14 years later ("Anatomy of the secretion", Cyclop. of Anat. & Physiol., ed. R. H. Todd, London, 1852, vol. 4, p. 444) expressed the same belief and credited several organs including the spleen, lymph glands, and even adipose tissue with internally secreting ("Glandulaline") functions.

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 latter affect the blood which in turn affects the whole organism. The nervous system, he believed, plays a prominent part in the regulation of events:

"... der fragliche Consensus durch die Einwirkung auf das Blut, und dann durch entsprechende Einwirkung des Blutes auf den übrigen Organismus überhaupt, woron allerdings das Nervensystem einen sehr wesentlichen Theil ausmachet, bedingt wird." (Biedl, Innere Sekretion, 2te Aufl., Band. v. Wien, 1913, 1.5.)
Saussure glands did not begin till 1809 when Berthold of Göttingen announced his theory that the testis represented an organ of internal secretion which was transformed by it directly into the blood stream and was responsible for the development of the secondary sexual character. ** It removed these organs from cocks and grafted them upon some other part of the body. "They animals", said Berthold, "remained male in regard to voice, reproduction instinct, fighting spirit, and growth of comb and wattles."‡‡ (Please see addendum I on opposite page.)

In 1830, Harling of Switzerland, suggested that eczema might be due to a deficiency in the secretion of the thyroid gland which he observed was not infrequently absent in that disease. In 1833, Claude Bernard gave a more elaborate presentation of the subject, and stated that "glands may form a 'secretion externe' by withdrawing substances from the blood, and also a 'secretion internne' which, instead of being carried off to the system by a duct, is passed directly into the blood or lymph stream." The term "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...
physiological world was especially centred on observing the effects of total and partial enucleation of these glands, the clinical symptoms following their excision, the injection of their extracts and of their transplantation from one animal to another from which the gland had 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 (and parathyroids) in the dog was followed by death in from 1-4 weeks, after exhibiting a characteristic symptom—complexfatality, termed later by Kocher “cachexia strumipriva or thyreopriva”: muscular tremor, 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 Simon pointed out that myxoedema, (Kocher’s) cachexia strumipriva, and sporadic cachexia were all due to a deficiency in, or loss of the secretion of the thyroid. In 1886, Marie described acromegaly, and showed that this lesion was due to a hypersecretion of the pituitary. In 1889, Browne, regard, then 72 years of age, announced to the Société 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 Bernard described attributed to the use of the extract were, in reality, due to auto-suggestion.

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 organotherapy, substitution therapy, hormone therapy or autotherapy, 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. The theory on which much was based rested, really, because it was much exaggerated for purposes of commercial gain. Indeed, one school in the light of some present knowledge, very little advance may perhaps beyond philosophical quite the subject. But it should be noted that the view of some three years ago, when I regard this aspect of the subject, as follows:

We find ourselves embarked on the path-bound and poorly charted sea of these animal substances and the clinical observation, in what endocrinology. It is easy to lose our bearing, for we have, most of us, little or no idea to support this view more generally. Our 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 exploitation of these natural remedies, and among these, missionaries and would spread the gospel; some are attracted merely by the prospect of gain and are...
Brown-Séquard 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 secreting 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 or 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 Pecori of Geneva (1882–3) and of Kocher (1883) on post-operative myxedema, further confirming Brown-Séquard’s view. This new theory really formed the basis of a conception unknown till that time regarding the effects of internal members on each other and on general metabolism, as shown to discussed afterwards.

In 1890, Itesbly showed that post-operative myxedema (which was sometimes associated with parathyroid operation) and tetanic convulsions 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 myxedema; and Hector MacKenzie in London, and Horsley 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 (Oller & Macrae). Medical science has, in fact, made no more brilliant advance in organotherapy than in the cure of diseases due to disturbed function of the thyroid gland by means of this form of treatment. It constitutes, indeed, a marvellous triumph in the annals of 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. Alvin (1895), Cybulski (1895), Biedl (1896), and Dreyer (1899) carefully studied the action of supernormal extracts upon the cardiovascular system.

By the end of the 19th century, then, we see that it was ineluctably 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 medium through which these 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. Dr. Blum is due the credit of showing, in 1901, that subcutaneous injection of adrenalin produced glycosuria. Halden, in the same year, showed that removal of the ovaries in ovariectomized rabbits was followed by cessation of menstruation, which, however, was afterwards restored by the successful grafting of ovaries from other rabbits. In 1902, Morris and Glass obtained similar results also in human beings. Of another ovary, which had been removed from a rabbit, the same year also described the syndrome known by his name and named by Bartels, "syndrome adinternitrate," and he showed its connexion with hypophyseitis.

Schulze and Langerhans in 1903 proved that ligation of the pancreatic duct was followed by a complete atrophy of the pancreatic acini, whereas the cells of the islets of Langerhans were unaffected. These observations once more drew renewed attention to the internal secretion of the pancreatic islets, named by Sir Sharpey-Schäfer, "insulin" two years previously, and how, they laid the direct trail that was eventually to lead to its isolation by Banting and Best of Toronto in 1921. The year 1902 also witnessed the discovery of Sir Wm. Bayliss and Starling of 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 S. Claypole demonstrated the existence in the
female generative organs of a similar stimulus which could
induce the growth of the mammary glands. Shearing 8 therefore
in 1906 proposed to apply to all these internal "chemical messengers" (as he originally and more widely termed them four years previously) *Journ. Physiol. 28, 1902*) the
name "hormone" (Verhandl. d. Naturforsch. Versammlung,
Stuttgart, 1906), from the Greek ὅρμος, to urge up, or excite or arouse.

But, inasmuch as none of these cellular products had been
shown to retard a function (e.g., the extract of the intesti-
nal cells of the ovary tends to inhibit the uterus), therefore, Sir
Shearpe - Schafer 9 at the International Congress of Medicine in
1913 advised to exclude all these principles under the
general term "autacoid substances" or, shortly, "autacoids", from the Greek ἀὐτάκος, a remedy, and αὐτός, natural. Thus,
as "autacoids" were proposed by Sir Shearpe to represent
any drug-like principle which was produced in internally
restraining tissues and organs. He pointed out that these
substances might then be grouped as "hormones" or
"chelones" (from the Greek χηλός, a claw, or χέλω, to make black), according
as they are excitatory or inhibitory in their action,
respectively.  

* An alternative word which might be used instead of "hormone" to indicate a
  "chemical messenger" (the term originally employed by Bayliss & Starling) is "Hermone"
  from Greek Ἠρμῆς ὅρμος (Shearpe - Schafer).
that Starling's latest definition of the term "hormone" is much wider now than what he originally applied to organic principles of an endocrine nature (v. Schäfer'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 in the blood stream to distant parts, which is effective for the good of the organism as a whole." (Proc. Roy. Soc. Ed. vol. 1, 1914, Ztschr. und Pharm. Ges. Sect. p. 29). As examples secretin, adrenalin, and carbon dioxide, it 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." "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 "secretion" were recently introduced to denote internal secretion, but they are no 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" as it were one to apply to these principles.

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

1. of the discovery by Tolks 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 that the removal of the thymus in young dogs retarded their growth;

3. that foetal extract injected into a virgin rabbit caused a development of the mammary glands and promoted the flow of gastric juice (Sterling & Law

Blampain, 1906) (The "Foetal Hormone Theory");

4. of the brilliant researches of Marshall and Tolly (1907), Carmichael & Tolly (1907), Steinach (1912—1920—22), Marshall and Parie (1914), and Walker (1923—24) on the internal secretion of the reproductive organs; and of the works of Basch (1910), Hackett (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), Haeman and Voeghlin (1908), Thornton (1910),
F. Huxley (1913); Cannon, du Bois, Cattell, Archer, and Levy (1916); Reid Hunt (1923–1929); Paton, Findlay, and their co-workers (1917); Dayraca (1923); and Sutherland Simpson (1923) and many others in the pathological chemistry of the thyroid and parathyroids; and of the isolation of thyroxin from thyroid extracts by Heberden in 1918.

6) of the researches of Maddelung (1904), Sir Shrapney Schapir and Herree (1906), Harvey Cushing (1910), Oliver and MacKerris (1911), and Sir Byron Bramwell (1915) on the pituitary body; Goodau (1905); 7) of the work of J. Basch (1906), Illoz and Vogt (1910), Sudematsch (1912), and Melvin and Park (1919) on the thymus;

8) of the observations of Crowe and Wieloch (1914–17), Horskins, Gunning, and Barry (1918), and Shrapney-Schapir and Liu (1918) with regard to the pancreatic extract (the active principle of which, viz. adrenaline, was obtained by Takamine in 1901 and nine years thence from catechol by the biochemists Delitz and Takeda); and (9) of the last and perhaps most important of all, the pioneer biochemical work on pancreatic extracts of Hennicke and Morales (1904), Lyde de Witt (1906), Zuelzer (1906), Forschbach and Lefine (1909), Starling and Knowlton (1912), E. S. Scott (1912), Merlin and Kramer (1913), Heumer (1919), and Clarke (1920), all of which anticipated and inspired these most brilliant
Conclusion.

In most instances, these internal agents are as yet wholly unknown to us chemically; and their presence can only be demonstrated by 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 (Pey and Stokely) is a substance of this kind, because it plays the part of a hormone in stimulating the respiratory centre. However, it is produced in excess. Another one is "iodo thyrocin" (Baumann and Roos, 1896) 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 (medulla) by Jakamini 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 (Barton & Ofiz) the hydrochloric acid of the gastric juice, which liberates "secretin" (Baylis & Stokely, 1902) and "gastrin" (Elkins, 1906) from the duodenum mucosa. By far the greatest number of these autacoids, 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. Their work, however, as to the general chemical nature of these active principles has been done by Professor C. H. Stahl, 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 dialyzable and are, relatively, thermolabile bodies, and are not rendered inactive in situ by prolonged boiling; a fact which sharply differentiates them from the ferment and enzymes. Further, many of these antacids act instantly, their action, as Stahl has shown, resembling that produced by the active chemical principles of drugs, especially those of organic or vegetable origin (cf. Schoen’s Ende. Org., 1914). Some of them affect the tissues immediately, they escape into the blood stream, whilst others have been shown to operate more slowly, exciting their influence upon the growth and nutrition of special organs or the body generally. The name “hormones” (from the Greek, ὠρμόζειν, I govern) has accordingly been suggested for these “morphogenetic” antacids by *Heil. An example par excellence of this is the thyroid secretion which, as will be shown later, has been demonstrated to have a vast influence upon general metabolism and in various other functions of the body. Other internal secretions have

been reported to have a similar "morphogenetic" influence, but
Cohn and M. Taylor recently pointed out (Endocrinology, 6, 1922)
that these are more or less through the thyroid, (Schäfer
Endo. Organ 1924).

We have found that the expression "intercellular
receptions" now embraces a far wider signification than
that was originally meant by Claude Bernard (v. Schäfer'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" (Schäfer), yet it has now come
to denote, according to Hiley, all materials contributed
to the blood both by the liver as well as by the true "endocrine
organs" (so named by Prof. Sharpey-Schafer from the
Greek ἐνδοκοίνος, within, and ἐκ, ō, to separate), such as:

1) Carbon dioxide and urea (Giley, and Sharpey), and
other products of metabolism;

2) The secretions of the thyroid and of the parathyroids;

of the thymus: (the inclusion of thymus among the true endocrines
has been condemned by Dr. Sharpey-Schafer on the strength
of the recent careful work of McCune and Park; — v.:
Schäfer's Endo. Org. 1924); of the liver (Giley), the
gas-tro-duodenal, and intestinal mucosa, and of the pancreas;
of the spleen (Giley); of the reproductive; of the sexual
gland, and of the pituitary body; of the placenta; As
A. Nutritive. 
- glucose: liver.
- fat: intestinal mucosa.
- albumins of blood: intestinal mucosa and blood.

B. Hormones. 
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.
- Secretin: duodenum.

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

Every one of these organs may be regarded as possessing at least some of the characteristics ordinarily assigned, in the state of our present knowledge, to internally secreting.
structures, namely (Burton-Offit):

(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 "cells not in possession of true ducts, they lie in close relation with definite different and affrent blood vessels and lymphatic channels";

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

(d) that "their substance in the blood or lymph achieved 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-Offit'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 endocrine organ and of its specific internal secretion.*
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 contain a peculiar colloid material. "Aberrant" and "accessory" thyroidal tissues viz. the lingual, mediastinal and "cystic" thyroids, have been described (T. W. Parker).

Earliest Theories regarding the Thyroid

Secretion

Although King, in 1835, had described the cellular 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 (Alcott's Retention), 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, none few showed a glimmering perception of its 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 supposed that the gland was used in the neck simply to give a shape or roundness to its contours, 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 its 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 has a special intimate relationship with the corresponding cerebral hemisphere, manufacturing some substance needed for cerebral activity (Sir John Simon). Another hypothesis assumed in that the gland swells during sleep, a rich 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 on 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 relation with the central nervous

*Neihardt, 1844. (Vide also E. Couland, Ann. de Med., Dec. 1923, p. 514; & P. M. J., Apr. 12, 1924, Supp. p. 52; also footnote on page 19 of this essay.)
system, swelling or shrinking 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 hyper trophy of the other; and that after complete removal of the gland proper, the accessory thyroid, which are present in some animals, sometimes hypertrophy and function vicariously for the excised gland.

Disease of the thyroid was at this time quite well known*; but little was known of their physiological significance. Thus, in the posthumous writings of Goliath More to Parry (1825) was a description of 8 cases of “Enlargement of the Thyroid Gland in Connection with Enlargement or Paralysis of the Heart” (Osler, Practice). In the front of these cases seen by Parry in 1486, the exophthalmus 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.” (Osler, Practice).

The Italians, however, claim that Hajani was the first to describe the disease, though, according to Morelli, his account of the disease, published in 1800—now authorities—give the date as 1798—“was vague and inaccurate.”

Soon after, Aledemar, in Berne, reported a case, with an autopsy (1828) and from no comparison with that of Parry.”

* References to suspected cases can be found in the 17th century, as in Morgagni (Book: Osler’s System of Medicine, Vol VI, p. 415)
also described the disease in 1835, and Bazex gave a full account in his original paper "Exophthalmus durch Hyperplasie des Zellgewebes in der Augenhöhle", in "Woch. f. d. ges. Heilk." in 1840. Bazex'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, arteria, loss of weight, and many others. Ordinary endemic goitre (stomach or bronchocele—"Derbyshire neck") has, of course, been long known, and its pathological relationship with drinking certain forms of water which was rich in sodium and magnesium (and with a high degree of radioactivity (Radium)) but low in iodine, has been acknowledged to be a proved fact; and it has been further demonstrated that the vesicles contained much colloidal material during this condition.

Reference has also been made above (page 6) to the observations of Kehrling who, in 1845, in Switzerland, noticed that the thyroid gland was unusually active in certain. However, it was not until several years later that it was shown that all these conditions were due to hypersecretion.
of the thyroid and the operative removal (Boeck, 1883) for
their cure was established.

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

(a) Schiff — 1856. The real significance of the thyroid was uninvestigated till the middle of the 19th century when, as in the case of most endocrine glands, clinical observations of surgeons began to contribute materially to our knowledge of its internal secretion. Schiff was the first to show 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. 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, tetany, and usually chronic, ischemic, and apoplectic convulsions, followed by death in from 9–12 days (Reverdin; Kocher; and Billroth). This was confirmed by subsequent observers, though many exceptions were noted, especially amongst the herbivora.

(b) Gold, Semon, Ord, Hotchkiss, etc., 1873–1891. The study of
the thyroid seems to have been left in abeyance after
Schiff's observations of 1856, until the adoption of physiology and clinicians were again especially directed to the importance of the organ by the clinical findings of Bell, Hornby, Felix Simon (1873), and Ord (1877) in myxoedema and cretinism, and by the researchers of the Brothers Revisordin of Geneva (1882), Kocher (1883), and Schiff (1884) in thyroidectomy. Bell, 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 adutorum"—"a condition in which the features are swollen and imperfectly outlined, the skin thickened, swollen, dry, and pendent, with 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" (Bostrom-Flint). Bell also pointed out that both myxoedema and cretinism (of infancy) were due to hypo thyroidism. Hornby and Felix Simon showed in 1873 that the changes following complete removal of the gland ("cachexia thyreoprica" or "strenuoprica") and myxoedema and cretinoid cretinism were all due to a loss of function of the thyroid gland. In 1884, Schiff operated upon his 1st series of sixty days 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. Thus, it was
soon discovered by Eiselsberg in 1892 that the serious symptoms — named by Koch as "cachexia thyreophratica" — following its total extirpation could be prevented by permitting a portion, say, of its lower extremity, to remain in the body. Likewise, Schiff and Horley showed that its successful transplantation of the thyroid to some other part of the body, such as the peritoneal cavity, protected the animal against the consequences of thyroidec- tomy; and this knowledge was immediately applied to human beings in cases of cachexia and myxoeoea with astonishingly successful results. Vasal, Mackenzie, and For, Murray (London), and Hruby (Copenhagen) in 1891 proved that the alarming effects of thyroidec- tomy could also be abated by the feeding of thyroid substance, or the injection of thyroid extract. Brilliant results in myxoedema and cachexia were obtained by these observers. Lastly, Koch succeeded in showing that Graves' disease was due to a hypersecretion of the thyroid and to a flooding of the system with an excessive amount of its secretion. He demonstrated

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

(2) that in 90% of his cases of Graves' 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.

[Note: a further comment is made about the fact that thyroidectomy was found in 1894 to lower the body temperature and to lessen the heat regulating power (Jour. 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 fruits of experimental physiology to the problems of clinical treatment. Even now, much uncertainty still prevails regarding the nature of the active agent contained in the secretion of this gland.

Baumann (with Roos) was the first to isolate from the thyroid extract a substance which he gave the name "Iodothyronin" or "Thyroidin," and which he found contained some 9.3% iodine. This discovery of iodine in an extract of the gland so doubt directly suggested the treatment of certain diseases of the gland by iodine compounds—a treatment which has been found to be eminently successful (v.: D. Marine, Arch. Intern. Med. Dec. 1923, p. 1811). Whilst the exact action of Baumann's iodothyronin 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, 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 myxedema has been found to be attended with beneficial
results.

Reid Hunt in 1905 showed that mice fed with
thyroid substance were very resistant to poisons doses of
acetonitrile; and four years later he demonstrated also
that the physiological effects of thyroid extracts were pro-
portional to the amount of iodine contained in them, and that
the amount of iodine necessary to maintain the usual bio-
llogical picture of thyroid tissue did not fluctuate materially
in any given species.

Kendall, in 1913, Graham, in 1916, and
Rosoff and Ninane, in 1917 and 1919, showed that tadpoles exposed
to the influence of iodine-free bile, thyroid were retarded in
growth, whilst their differentiation (metamorphosis) took place
as a much faster rate.

Hendall, in 1918, isolated a similar to, but
body
lesser complex than, Baumann’s thyroidin of 1896. With
Osterberg, in 1919, (Journ. Biol. Chem. 44, 1919; also Harvey Lectures,
1919-20), he succeeded in identifying this substance chemically
as tri-iodo- oxy in 301-propionic-acid, or “thyroxin,” as he

* This acetonitrile phenomenon was recently found to be positive
for the blood of patients affected with exophthalmic goitre and
is, thus, a valuable diagnostic test (V. : Hunt : American J.
of Physiol., 62, 1923.)
Originally termed it. It has been known to be related to tyrosine, adenalin, and tryptophane, and possess in the "open-ring" form, in the natural thyroid secretion in the body. Kendall gave the formula ("open-ring" form) as:

\[
\begin{align*}
&\text{H} \\
&\text{HC} \\
&\text{C} = \text{C} - \text{CH}_2 - \text{CH}_2 - \text{COOH} \\
&\text{H} \\
&\text{HC} \\
&\text{C} - \text{NH}_2
\end{align*}
\]

Kendall maintains that this compound is responsible for all its 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 suspend.

intestinal muscular strip which is actively excited by thyroid.

We may infer, then, that the active principle of the thyroid internal secretion is an indox-containing hormone (the efficacy of which has been proved in detail not so much on the indox as on the character of its combination with other substances). (Burton-Dick)

Recent Physiological Researches.

1920. A further development of our modern knowledge of this organ is furnished by various researches recently made to show the functional correlation between the thyroid secretion and other organs (e.g. Brown-Sequard's thesis of 1889, p. q.). Thus, Ascher and Drey have proved that the thyroid and suprarenal secretion augment the activity of each other. In Bois, Cannon, and Cattell recently proved that the thyroid possesses secretory autonomic nerves, and are thus closely related to tissues and organs in the body similarly supplied. Chalmers Watson recently stated that there is a close relationship between the thyroidea
and structure of the gland and the general nutrition of the animal (Schaffer: Endocr. Organs). Keane and Cranie found that in the cat and rat fed with thyroxin, glycogen disappeared from the liver. E. Munch (1917) demonstrated a diminution of lipoids in the cells of the suprarenals in similarly treated animals, whilst the same procedure was found to increase the mitotic in pancreatic cells (Kojima) and anterior glands of the pituitary body (Linn: Quart. J. Exp. Physiol. 1, 1920).

1920 - 1924. Of the many 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 vitamin-poor diets caused a decrease in the size and weight of the gland; whilst vitamin-rich ones had the opposite effect. He also had demonstrated water-borne microorganisms as the causative factor of endemic goitre.

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

(ii) J. W. Cole (New York J. Med. 1921) found that the administration of adrenalin excited the thyroid to activity (cf. Archer & Levy's observations, p. 30), probably acting as has been suggested by Si Sharpey-Schafer (Endocr. 1924).
through its sympathetic supply.

C: 1922. 

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

(ii) Cannon and Smith adduced further evidence of the nervous control of the thyroid secretion (Am. J. of Physiol., 60, 1922), and C. Hirst found that it was increased by external cold and by morphine, quinine, and strychnine, the action in all probability being produced through the sympathetic nervous system (Schaper) (Arch. f. d. ges. Physiol., 41, 1922).

(iii) The use of the thyroid was found by Coulomb (C. r. soc. Biol., 87, 1922) to be very resistant to X-rays which he found caused them to undergo degenerative changes and a diminution of activity. Treatment by X-rays has since been found to be of some success in certain cases of exophthalmic goitre (J. R. Murray).

D: 1923. 

(i) Sir Sharpey-Schaefer (Annals. Trop. 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) Saltwell and Simpson found that thyroidectomised sheep took far longer to learn to find
their way to food through a maze than controls (J. Exp. Physiol. 13, 1923).

(iii) B. Rennie determined by the Fedoroff test that the activity of Flinders'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 (Birch, Zeitschr. 140, 1923).

(iv) N. M. Dott (J. Exp. Physiol. 20, 1923) showed that the pituitary and thyroid were inter-correlated with regard to influence on growth of the body.

E. 1924. (i) F. 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 the cases of previous stillbirths 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 malformed 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 host of recent
researches on the thyroid has been the recognition of its enormous influence on normal growth in childhood, and on metabolism: increasing the output of carbon dioxide, nitrogen, and phosphoric acid, and its consumption of oxygen—thus stimulating both the vegetative and 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 myxedema (Hale—White) and the mental disorders accompanying them, but also in a few cases of climacteric virility and in childhood (Easterbrook). Its beneficial therapeutic effect has been satisfactorily demonstrated in cases of dry chronic eczema and chronic psoriasis (F. D. Murray); sometimes in chronic exophthalmic goitre (Stiecken); in acromegaly (Fisher); in "backwardness" in children, and in adrenoids associated with thyroid inadequacy (Wallis & Cobb: New York Med. Journ., Jan. 1921); for nocturnal enuresis (Williams); for obesity and adipsia (Jobee); for delayed union of fractured bones and in articular and muscular rheumatism (Halsey: Bartholomew Endocrinology, 1922); in various affections of the skin, hair, and nails, in degeneration of the nervous system associated with thyroid deficiency, and in certain forms of infantile (Horrey; Leopold-Lewi; de Rothschild) [from Sir Shorley-Scherif's Endoc. Org., 1924]
SECTION III

B. THE PARATHYRIOIDS.

The parathyroids are four small oval masses, different in structure from the thyroid, and embedded in the substance of the gland on either side of its lateral lobes. They vary in position somewhat in different animals and individuals (Thomson). 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. Careful and more 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, later during the period of thyroid experimentation. We have noted above that notable deviations from the effects of thyroidectomy described by Schultze in 1886 were observed, especially amongst the livestock. Many of these 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 Sandstrom 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 1864, by Remak in 1855, and by Koch in 1863 (Dr. K. C. Rouch, 1862). Hahn described their microscopic features fully in 1895. Shortly after Sandstrom's discovery, they (in 1891) proved that the symptoms following thyroidectomy were markedly different from those produced by removal of the parathyroid. A re-examination of the symptoms by Hahn showed that these arranged themselves in two groups, one of which was characterized 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 Corvisart in 1852 (Schatz)). The subsequent investigations of Vissiole and Generali in 1896 fully confirmed Hahn's deduction — although it is even yet not now accepted by some present authorities like Tomiyama, Jolles, Vincent, Jolly, etc.

Nevertheless, it may now be regarded as certain that "pure" thyroidec- tomy produces a state of malnutrition, terminating in the condition of cachexia symptomatica (Hocher), whilst parathyroidec- tomy alone results in muscular tremors, spasms, tetany, paling of the hand, tetany, stiffness and rigidity of the entire body, and loss of muscular coordination or strength, exaggerated irritability of the autonomic and central nervous system — the symptoms constituting the acutely toxic clinical picture of what has been termed "cachexia parathyroide reactiva" (Bing, Biedl).


(a) 1906-1910. The problem of the parathyroid reaction
does not appear to have been actively pursued from 1896 to 1906.
In 1906, the research of Erdheim again directed attention to its pathological chemistry. Fleischmann and Erdheim in 1906
led evidence in favour of the assumption that the parathyroids
produce 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 alkalosis, calcium
fails to be deposited in the constantly growing teeth which,
as a result, become soft and fragile. Edmunds died in 1907
recorded the development of cortical thinning vessels in
the parathyroids in a case of thyroid atrophy in man.
Forrester described an altered condition of these organs also in
a case of myxoedema in the same year. In 1908, Macallum
and Voeghtlin 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 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
inflicted with tetany produced the symptoms of cachexia.

* This observation of Erdheim, and of Voeghtlin & Macallum, was recently
confirmed (1920) by Leach Harter & Goldberg (Journ. Am. Med. Assoc. 62, 221
1920) who found that the symptoms of tetany in dogs could be absolutely
controlled by oral administration of 10 grams of calcium lactate
per kilo daily.
parathyreophsia in other (normal) animals.

(8) 1911 - 1923. In 1911, Dr. E. Brown 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 ophthalmologist reported that chronic tetany was often associated with catarrh, and in 1917 Findlay and Hopkins of Glasgow advanced a new hypothesis that the parathyroids influence the activity of the muscles and possess certain powers of detoxification by neutralizing and thus preventing the accumulation of certain protein metabolite products, especially guanidine, which they viewed is formed in large numbers after parathyroidectomy and found some signs to fatal tetany similar to tetanus parathyreophsia or idiopathic tetany when injected intravenously. These observations were recently confirmed (1922) by Yoshinoto (Proc. J. Phys. 12, 1922) and in 1923 by Dragonstedt and Peacock (Am. J. Phys. 6, 1923).

Conclusion

A considerable divergence of opinion still exists as to the significance of the parathyroids. Some authorities still espouse the view that these organs are just immature thyroid tissue, and that until such time as thyrotoxicosis is not infrequently followed by hypertrophy of the formation of colloidified thyroid-like cysts in the parathyroids. The apparent contradictions of the results that are from time to time still being obtained in parathyroid experiments have been shown to...
result from the variations in the morphological distribution of the organ in different animals (c.f. Johnson, 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 theory, as we see, requires further confirmation!
SECTION IV.

C. THE INTERNAL PRINCIPLE OF THE THYMUS.

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

Vicq d'zea 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 its 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 ("involutive"), nothing appears to have been done for long time experimentally with a view to unravelling its function till Goodall 45 and Paton 46 in 1905, showed 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. Borch in 1906, showed that thymectomy in young dogs was followed by such developmental anomalies as retardation of growth and rachitic changes in bones.

In 1910, Thelix and Vogt 47 discovered that the organ was especially concerned with the process of nuclear acid synthesis.
and Vincent in their researches on thyroectomy 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 literature in 1912 which showed that young rats fed on a thyroxin gland were stimulated to excessive growth, whilst the changes of metamorphosis to the frog stage were correspondingly delayed (cf. the same observer in thyroid feeding, p. 29). Many observers recently pointed out that hyperthyroism was not infrequently associated with acromegaly, genital hyperplasia, myxœdema, Addison's disease, and especially Gravis' disease, and that pieces of the thymus of rabbits, when transplanted to the region of the body, were affected in precisely the same way as the intact organ, by castration and sexual stimulation (1917). Richards showed that the gland was quantitatively atrophic in marasmus and in many chronic wasting disorders of children, demonstrated and Symmers recently found thyromyxoedema in children, symptoms (Oster andoccoae).

**Conclusion.**

The state of our present knowledge of the internal secretion of the thymus, the physiologist tells us, is as possuom 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 substance which exercises a restraining influence on the develop-
ment 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 1914 by Park and St. Louis (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 texts
better of endocrinology like the new edition of Sir Sharpey-
Schäfer's work!

* * * * * * * * * *
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 first description of this organ by Gleason in his monograph "De Hepatce"—its first medical book of that nature—in 1664 (p. 4). The product of its internal secretion, viz. bile, has been since Gleason's time thoroughly investigated, but nothing was known regarding its internally secretory power till Bernard, in 1857, taught that it also furnished an intra-hepatic principle (in commune with which Bernard first used the term "internal secretion" ("secretion interne")), which he called "glycozyma" and claimed to be "concerned with carbohydrate metabolism: synthesising sugar and mobilising glycogen, converting the latter substance to sugar when necessary." (Bernard). Bernard's view was, not long after, confirmed by Bock, Hoffmann, and Siegen, who found that the removal of the liver or ligation 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 "intralobular principles," like erginase et al., (Kossel and Dakin, 1904), which are probably of enea possible. Schröder, Mellanby, Tolkien, Schaffers, Hopkins, and many other biochemists have recently contributed much to our knowledge of these various intralobular principles, and Howell, 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.

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

Historical Survey.

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

* These various intralobular 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)
Dr. Bayliss and Prof. E. H. Starling in 1902 found that the duodenal mucosa contained a "chemical messenger" or "hormone" which they named "secretin" and which, whenever the reaction of the adjoining medium became acidified by the hydrochloric acid of the gastric juice, was liberated as "secretin". They showed 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 secretion. They found that the injection of the neutralized 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 word "pro-gastrin") was demonstrated four years later (1906) by Edelman to reside in the pyloric mucosa; and of late years, similar experiments on the gastric mucosa have been carried on by Dr. R. E. S. Linn of the Histology Department of Edinburgh University under Sir Edward Sharpey-Schafer.

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SECTION VI.

F. THE INTERIOR SECRETION

OF THE PANCREAS: INSULIN.

The pancreas is a club-shaped, tubulo-acinar 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 3rd lumbar vertebra.

Ancient Knowledge of Pancreatic Diseases:

Diabetes.*

Although the disease of the pancreas has been longest known of any other internally secreting gland, yet the mystery of its interior secretion was almost the most late to be unravelled; but the process of this unravelling is most certainly unique in the history of science.

(a) 1500 B.C. (Egyptian Medicine) - 1679 A.D. (Willis). In the papyri, Ebers (which is a copy of an Egyptian medical encyclopedia already old in the time of the lawgiver Moses), there is mention of polyuria. 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 Andreas of Caphadocia (circa 150 A.D.) who was Galen's contemporary,

*Much of the subject matter for this section is obtained from "System of Medicine" by Alburt and Rolleston.
and was probably a Roman physician. Aretaeus was the first to use the term "diabetes" (from the Greek word meaning a syphon) which he described as "a wonderful affection melting down the flesh and turning into urine." His description, like the work of Galen (131-210 A.D.) who wrote at great length on the disease, laid stress only on the polyuria and thirst.

However, the important fact that 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 Agya Veda (circa 500 B.C.), 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 13th century, however, a German writer undoubtedly referred to diabetes as "mudemehe" (a "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 had been sugar and honey in it." Willis was also the first to recognize the distinction between a saccharine and a non-saccharine form of diabetes. (Willis: "Pharmacoeutic Rationalis," 1674)
1776 - 1797. It was not till the last quarter of the 18th century that new 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 improved the learned Cullen that he would hardly allow that this was not true of all cases of diabetes. Indeed, it was not till the last century that the distinction was firmly established which we now recognize 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 rectum. Tulpius in 1641, wrote on the suppuration of the gland, and in 1682, Regenous de Graaf showed that excremum salivatum (sialorrhea) was a pancreatic disease, and hinted that there was a speculative 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.
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 1864 showed that the liver, after death sustained when he sugars, and further demonstrated the glyogenic function of this organ in 1857. Previous to this, Gmelin and Friedemann in 1823 had showed that sugar was formed by dijelion of the carbohydrates, and Lambrrosci and in 1833 had further demonstrated the presence of sugar in the blood, thus confirming Dobene's finding of 1775 and 1776 that the blood serum of diabetics "had a sweet taste". In 1874, Liley discovered that diabetics could assimilate levulose and melon, but not other forms of sugar. During this year also, Harrisall described the features of diabetic coma, and suggested acetone poisoning as its cause, and Sir Walter Todd, in a paper read before the British Medical Association at Manchester in 1877, further focussed attention to this phenomenon. In the same year, Lancereau 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 Brunner is said to be the 1st, in 1672, 34
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 in 1889, began
to check in the history of our recent advances not only in pancreatology, but also in general, endocrinology. These in-
vestigators 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 2-4 weeks, after the animal had shown
symptoms of hyperglycaemia, glycosuria, polyuria, polyphagia,
loss of weight and strength (in spite of a ravenous appetite),
 thirst, evacuation, 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 processes unattached
into corresponding blood vessels under the skin of the
abdominal wall. These experiments demonstrated the
importance of the pancreas in carbohydrate metabolism, and
directly suggested that it possesses an internal secretion.
Indeed, it was concluded at that the cause of diabetes
had been discovered, and high hopes were entertained that
the disease might be successfully treated by an 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 myxedema and acromatia continuum 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 Sandby in his Bradford lecture pointed out that varying degree of interstitial inflammation, with formation of connective tissue and new ducts, occurred in diabetes.

Schulze, Opie, and others, in 1901, found that the islets 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 Unicars and Thompson. In 1902, Zblecki confirmed Hering and Pickwick's observations of 1889, and found further that hyalination 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, who, in America, did for our theoretical knowledge what the surgical skill
of Mayo Robson, following in the footsteps of Senn Hörnli and others, accomplished in the domain of practical therapeutics; and, in 1904, Sir Byron Bramwell gave an altogether new contribution to our knowledge when, in his "Clinical Studies" (1904), he described a pancreatic form of infantilism which he termed was a result of deficient pancreatic internal secretion.

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Early Researches to extract Insulin:

1904–1920.

Lehms was the first to suggest definitely that the condition of diabetes mellitus, which von Mering and Birkbeck had discovered in 1889 to follow pancreatectomy, might be due to the withdrawal of an internal hormone which is necessary in the normal animal for the complete metabolism of sugar. Previous to this, vague notions were already in existence regarding the internally regulating powers of the pancreas on the strength of Mering and Birkbeck's and other experiments and observations, and, indeed, Professor Sir Edward Shorty-Schafer in 1900 suggested the islands of Langerhans as the source of the internal secretion, to which he gave the name "insulin" (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 glycosuria and hyperglycaemia following pancreatectomy in animals. In fact, discoverer 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 those 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 Banting and Best in 1921, who, taking advantage of the fact that all islets visible to the naked eye on the walls of certain fishes, prepared extracts from them, and found that they were of some success in several cases of diabetes on which they were tried; but owing to the difficulties they had in obtaining material, these investigations were not pursued. Two years later (1923), Lydia de Wilt, basing her experiments upon the previous observations of Schulze, Sydow 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 proteolytic power they possessed well-marked glycolytic properties (from Lambridge, “Insulin Treatment of Diabetes”, Livingstone, Edinburgh, 1924). In 1925, Lüdinger 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), Torchbach, employing the same method, obtained good results in depancreatized dogs, but he was not so fortunate with human diabetes.

In 1910, Oppenheimer, Talia, and Huddingger pointed out the correlation of the endocrine organs—the pancreas, thyroid and supramedial in particular—with regard to the production of glyceremia and glycosuria; and de Meyer in L' Sécrétion Interne du Pancreas, 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 extract prepared by Starling and Haldane in 1912, by E. L. Scott (1913), by Merkin and Craner in 1913, and by Klein in 1919, did not yield results that were considered convincing enough to justify a further development of these 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 hormone. Thus, Brattle, towards the end of 1910, reported several cases of diabetes in which the islands of Langerhans were not affected, and several observers have pointed the view that these islands represent mere stages in the development of the ordinary parenchyma of the pancreas. Bensley, however, in 1915, viewed exclusively by intravitam staining methods that the islands were permanent structures, and that the opinion of Brattle and others of 1910, viz.: that the islands were "developing reserve cells of the islets," was wrong.* Further, Carlson and Drennan in the same year found that if the islet of Langerhans was affected in a pregnant dog or a rat, the animal did not exhibit symptoms of diabetes until the pup was born or removed by Caesarean section—the internal seclusion of the foetal pancreas being sufficient to protect the mother. Again, in 1910, Clarke discovered that if 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. W. Catterall of McGill, basing his observations on the work of his pupils L.S. Miller and H. Le D. Peters, has also a few weeks ago challenged the independence of Brattle's views. 
than it did from its fresh fluid. (Rochester solution) — this
further clearly demonstrating the existence of a fermentative antecedent
which has great glycolytic properties.

The researches of Howard, Forsyth,
and Camidge; Banfing and Best & their co-workers;
1921 — 1922.

It had baffled the endocrinologists to isolate insulin from
pancreatic extracts hitherto made owing to its destruction
influence of trypsin and other proteolytic enzymes. Howard,
Forsyth, and Camidge in the B.M. J of 15th Oct. 1921, p. 886,
and Sisson in the same journal of 14th Nov. 1921, p. 948,
reported certain experiments they made with certain extracts of the
pancreas, but these were not proved to give satisfactory results.
However, Banfing and Best and their co-workers, working in
Professor Macleod's laboratory in Toronto University, were the first
found in December 1922 that the offending enzyme was in
February, by the secondary action to the incision (5-10
weeks) by ligaturing the pancreatic ducts (as had been done by
Schulze and Szilbois and others in 1902) and by Hygeia de Witt
in 1906) before the extracts were made. They observed that
continued injection of such extracts into hypophysectomized
dogs permanently and definitely diminished blood and
urine sugar, and prolong the lives. Later, taking
advantage of Abraham's finding nine years before that
enough, they obtained satisfactory extracts from this organ, as well as from adults or 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 12 years, in whom an almost instantaneous reduction of about 25% in blood sugar was noticed. Subsequent injection of Banting and Best's extract has since been shown both in Europe and America to give brilliant results which are most spectacular, especially in cases of diabetic coma. The injection can be given daily with ease; and an overdose has been shown to produce cyanosis, which can however be controllable by injection of eucaine. (See: Professor Haskel, 11th Intern. Congress of Physiol., Edin., 1922; also Dale, Lancet, May 19, 1923; 1929).

*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, so many had Banting and Best and their Toronto collaborators plunged the first furrow in the field of insulin research than the actual cultivation of this substance was commenced by many other workers in all parts of the world. Some devoted their attention...
solely to the therapeutic effects of the remedy, some investigated its physiological properties; whilst others professed the depth of its exact chemistry.

The action principle of the substance has not yet been isolated in even approximate purity; but匙ting suggests that it may be a complex molecule nearly approaching the simplest proteins in size, since it is destroyed by peptic and trypsin (v. Caro in Pharmacology, 11th Edition p.14). Colloïd, 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 quarternary compound.

A new method of biological assay has nearly been devised to control the dose and therapeutic effects of insulin. The original unit of insulin employed by Banting and Best was "the amount which, on subcutaneous injection, lowers the rabbit's blood sugar by 50% in 1-2 hours." However, the discovery of the curative effect of an extract of insulin together with recent clinical work with a preparation standardized 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 0.025% and cause convulsions in a rabbit weighing 2 kilos which had been previously fasted for 24 hours." Howard Brown a few weeks ago (Lancet March 1st, 1924, p.665) called attention
to the fact that, from a series of 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 standardized.

Insulin-like bodies have of late been reported to be found in various substances. Bunting and Best found that whilst preparations from the liver and spleen gave no appreciable effect on blood sugar level of diabetic, 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, muscle, bone, 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 (Cambridge).

Professor Fick has recently confirmed Rennie and Frenès's observations of 1904 (135, page 53) and found that an antidiabetic substance could be isolated from the liver of certain fishes which are rich in insulin. Various practical difficulties have hitherto prevented extracts being commercially produced. The Toronto workers have also recently found that extracts of several forms of liver yield insulin. Thus, Collip has succeeded in extracting it from ham 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 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 stamina." (Cammidge: "The insulin treatment of diabetes", 1924)

"Of the numerous clinical observations made last year, reference may be made to the findings of L. Blohm, Carliis and H. Schwarz reported in Bull. et. Mem. Soc. Med. des. Hop. des. Paris, Dec. 27/1923 p. 1989 (V. O. F. F. T. 73/1924). These observers found that patients who had received insulin treatment became more prone to acidosis and very suddenly de of diabetic coma if the treatment was stopped. This has since been confirmed by Marcel Lelbe, 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 that for insulin treatment to be successful, it
must be continuous and combined with an anti-diabetic therapy (e. g. also: F. Fischler, Münch. med. Wochen., Nov. 23, 1923, p. 1407). Also, several efforts have recently been made with a view to a cheaper and less complicated process of manufacture of insulin. In this connection, we may note that certain workers at the Westminster Hospital Laboratory recently obtained potent reactive extracts of the substance \( \text{insulin} \) by H. W. Bünckley and W. A. Stirling, 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 Birth T., vol. 18, no. 1, 1924. (An admirable account of insulin up to date is given by Professor Maudsley in the new edition of "Encyclopaedia Medicina" edited by Dr. Fostall.)

A notable experimental fact discovered of late is that experimental hyperglycaemia with Bernard's pancreas in vivo is entirely prevented by insulin. However, the old endocrinologists are not yet quite agreed as to what the essential action of this substance consists of. It is clear, however, that is restores the power of utilising sugar which is chiefly or partly lost in diabetes. Several views have been advanced to explain the way in which it accelerates the sugar combustion, but these or at present hardly beyond the speculative stage. Professor Turkguy is of opinion however that "there is every reason to believe that the action"
is in the general tissues and not in any special organs, that the normal pancreatic secretor is carried into the blood, and that its presence in the muscles and other organs enables them to utilize glucose. (Cushny: Pharmacology 8th Ed., 1924.)
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 now classed among internally secreting glands (Schöpf), but the development of our knowledge with regard to its endocrinological relation 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 melancholy, and Aristoteles and later Galen taught that it was the seat of the "melancholic humor." These sages were aware that it was quite inessential to life, and splenectomy was frequently practiced by them without serious results; in the belief that such a procedure improved the "wind" of humors (Oliver). No other record of the conception of its physiology appears to have been made till after the middle of the 19th century, when Priessnitz (1866), H. C. Wood (1871), and Berti (1882) attributed certain forms of anemia to an enlargement of the spleen ("splenomegaly"), but no evidence was ever adduced of the relation of an internal splenic autodidact.
Modern theories regarding its supposed internal secretion.

The spleen has of late years (chiefly 1917) been described as furnishing an internal secretion which activates the proteolytic ferment, i.e. trypsin, of the pancreatic juice. Also, Vinicer and Obren (1903), J. B. and E. H. Miller (1911), Stern and Kothlieh (1919) from spleen and some other authorities have obtained parietal effects indicating that these either cause contraction or produce relaxation of contracted, or the plain muscles of the blood vessels, intestine, uterus, etc. and this has been ascribed by them to the presence of an intrasplenic autacoid. These effects, however, resemble those of certain bodies such as histamine and adrenalin, which have been found in many tissues and organs, and their presence, Sie, Shapley, Schäfer points out, cannot be regarded as sufficient reason for assigning to the organ which yields them an intrasplenic secreting function. Moreover, as stated above, it has been known for some time in membro 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 intrasplenic secreting function is erroneous with the spleen is no superior to that which we have passed regarding for instance, the thyroid, pancreas or seminal vesicles. This is an

hy pothecary — for it cannot even be raised to the dignity of
4. INTERNAL SECRETION OF THE TISSUES.

HISTORICAL SURVEY

The amplification by Bernard in 1889 of the idea of an internal secretion to include the secretion of all the tissues of the body has already been referred to (p. 28). Pasteur and Rosenthiel shortly after Bernard showed that carbon dioxide, a product of metabolism in all tissues, stimulates the respiratory center if it was produced in excess in the blood. The hypothetical ferment "thermobin" was shown first by Schmidt (1893), then by Morawitz (1903) to be present in the tissues, leukocytes and platelets, and it was demonstrated that its liberation from these structures intensified the phenomenon of blood coagulation. Hypoglycine, arginine, and similar internal agents which regulate carbohydrate and protein metabolism were also shown to be present in the tissues, especially muscle and embryonic tissue.

Conclusion.

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

* 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 endocrine logical nature. However, Poppielaski and Banek in 1909 (Arch f. d. ges. Physiol., 128, 1909) and more recently T. J. Abel, Kubota, and D. J. March in 1919 (J. Pharm. and Exp. Theraps., 15, 14, 1919) have shown that such lowering of blood pressure was due to substances which are quite common to all animal tissues, viz.: vasodilators, histamine, and, in a few cases, choline. The blood pressure finding is not therefore a proof of true endocrine function.

(Schafers)

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* F. Q. 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, School of 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, 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.

These glands were first recognized by Bartholomeus Cystachius Sancto-severinatus in 1563. Wirsung, in 1756, fully described them, and later Heubel (1806), Eber (1846), Leydig (1857), and Kölbe (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 body".

The History of systematic Clinical Studies of the function of the Gland: Bright, Addison, etc.

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, Torosy, 1856) appears in Lobstein's treatise: "De nervi sympathici
humani fabricae et morbis”, Paris, 1823, from which is the following (translated) extract (Pancoast’s):

"...... I have myself observed the nerves forming the suprarenal glands much thicker in disease where the capillaries resemble, 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 spasm analogous to the epileptic" and at the autopsy, "nothing unusual was discovered in the body of the woman, but the aforesaid change in the suprarenal, and the enlargement of the nerves." Notwithstanding the fact that there is no record of any thickening in the complication, this account by Lobstein was undoubtedly a typical case what would now be called "Adrenal 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. Schottle in October 1823, and was published in vol. vii of the Deutsche Archiv f. Klein, Med. by Riesel in the course of his article: "Zur Pathologie des Morbus Addisonii". The third case came under the observation of Dr. Richard Bright of Guy’s Hospital, London, in July 1824. This case is contained in:

* from Bock: "Handbook of the Biological Sciences"
Bright's classical "Reports of Medical Cases," and also figures in Case v. in Addison's original memoir. The lesions of the glands were characteristic; there was an oedema affecting many cases, reported by Lobstein 6 years before, and for the first time in the history of this disease, Bright recorded that "the symptoms were very dark". A few other cases were reported by Aran and others in 1842; but it was reserved for the majority 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 suprarenal glands and the brain of the well-marked constitutional symptoms of the affection, which now bears his name. (Brownsea, 1856).

The attention of the clinicians and physiologists was not drawn to the disease until 1853 (some authorities give the date as 1852), 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, deafness, general languor or debility, tremors, convulsions, apathy, ....... fulness of the chest, 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 preface to his memoirs appended to the reprint of that monograph in Addison's collected writings published by the New Sydenham Society in 1868 — i.e., eight....
years after Addison's death — we read that "even it (i.e., Addison's disease) does not find a place in the nomenclature of some writers". In fact, although Greenhow, in his London 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 of the disease, besides the fact that the anaemia, a symptom regarded as pathognomonic by Addison, is by no means common.

Addison's account of this disease led Brown-Séquard 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-Séquard's results were confirmed by Notthoffel (1879), Stilling (1888), Tizzoni (1889), and others. Stilling in 1888, and later Horley, established the additional facts —

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

(ii) That some of Brown-Séquard's findings of 1857 were in no considerable measure the consequence of surgical shock and especially sepsis;

and (3) That animals (e.g. rabbits) which possess
necessary suprarenals ("chromophils bodies") did not die after removal of the capsule.

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

We may now have that feeding of extract of suprarenal gland to suprarenalecetomised animals or to humans in Addison's disease have led to abortive results. Indeed, at present condition in the therapeutic regarding the suprarenals is in the exact opposite of our knowledge of thyroid replacement therapy.

Sir William Osler (in his First Books on Medicine, 1901) stated that in the large series of Addison's disease treated with various suprarenal preparations, only 3 showed marked improvement. It was early shown that the tuberculous nature of the lesion (P. Lobstein's account, p. 68) in most cases of the disease and the attendant widespread involvement of the sympathetic system was a formidable obstacle to treatment. Some cases, however, have markedly benefited by administration of suprarenal extract per os or hypodermically. O. Sivinbaum (Journ. Physiol., 24, 1899) obtained a rise of blood pressure on internal 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, or 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.I., Feb 18, 1926) 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-Séquard and others attracted much attention at the time they were performed (1857), but they were almost forgotten for many years. Whilst Brown-Séquard's experiments clearly proved that the suprarenal furnished an antecedent which was absolutely essential to the life of the organism, and whilst, in fact, Vulpian had a year before Bernard's experiment isolated from these glands a substance which he found showed remarkable action reacting with various chemical reagents (C.R. Acad. Sci., 43, 1856), yet the precise nature of this active internal principle of the glands remained unrevealed until the time of Sharpey-Schafer and Oliver (1895). These two investigations
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 vasocostriction of the blood vessels through stimulation of the sympathetic endings (mono-neural junction) occurred. This effect, they found, was not produced by cortical extracts. Nothing definite could be learned regarding the effects of the extract, although it was found that its loss resulted in marked asthenia, coma, inanition, and rapid death.

Further Physiological Researches: 1897 et seq.

The experiments that followed, those of Albrecht and Sharpie-Schaper, brilliant results were chiefly concerned with investigating the nervous mechanism of the secretion of the suprarenals. Biedl in 1897, and Dreger two years after (1899), showed that stimulation of the splanchnic nerves produced a rise in blood pressure, the first owing to direct effect of the stimulation and the second, to a discharge of the suprarenal autacoid, presumably derived from the medulla. Trend and Marchand, more years later produced hyperglycemia by injection or by stimulation of the splanchnic after suprarenalectomy, proving other structures, i.e., the chromaphil bodies, could produce the minimal secretion of the suprarenals. Langer also showed that emotions, like anger and fright, caused a reflex discharge of the autacoid which he found was responsible for the peculiar vascular and sensations usually experienced during these
conditions, and for a rapid dephosphorylation of glycogen resulting in the so-called emotional glycemia or hypoglycemia

Biochemical Researches: 1898-1901:

Adrenalin.

The production of the Schaffer-Ohlson suprarenal extract of 1898 immediately led to a reprinted investigation of the biochemistry of this substance, and to Abderhalden the credit of being the first to isolate from this medullary extract in 1898 (now authenticated: the date is 1897) a somewhat impure chemical substance which he found was an epinephrin hydrate of the formula \( C_{10}H_{13}NO_3 \cdot \frac{1}{2}H_2O \). The substance was also demonstrated to be present in the external urethral glands of a tropical toad. Abels' epinephrin was later proved to be but a benzophenol compound of the pure extract. Later, Alrich and Takeda isolated its free base (laboratory), adrenalin, to which biochemists have given the formula \( C_{10}H_{19}NO_3 \cdot OH \), or, structurally -

\[
\text{OH} \quad \text{CH(OH)}_{2} \quad \text{CH}_{2} \quad \text{NH} \quad \text{CH}_{3}
\]

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

Recent....

* The chemical active principle has been claimed to have been obtained by S.'Frenkel in 1896 (Die Ann., med Bl., 19, 1896) and by v. Forthi (who gave 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 adrenaline,

[the laboratory variety of which Professor Aston (Journ. Phys. 37, 138; 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

that its action was a very general one involving

the activation of the structures innervated by these autonomic sympathetic

nerves.

and it was found that the function of these structures could be

augmented or inhibited according to the structural features of the

effective element so affected—a reaction which was found to be

stimulation of the identical nerve that induced by sympathetic nerve fibres themselves.

Thus it was found that, whilst adrenalin produced an abrupt

rise in blood pressure by direct action in the cardiac innervation

and on the "sympathetic junction" (Langley) of the sympathetic

nerve endings in the arteries (and dismayed such exquisitely

minute quantities as the 1/400 of a milligram per kilo body weight

(Dutton & Fitl)), it became the cardiac frequency through

vagal inhibition (if the vagus is intact), or, characteristically,

accelerated the heart (if the vagus is cut). On the contrary,

old proved that small quantities could produce a vaso-
dilator effect (capillary) and a consequent fall in blood pressure.
Blum, in 1901, showed that its intravenous injection was invariably followed by hyperglycemia and glycosuria. Mettler, in 1902, showed that intravenous injections shrunk the pupil (especially if the sympathetic ganglia were removed), arrested peristalsis, caused a loss of tone of the walls of the stomach, intestines, gall bladder, urinary bladder, the bronchi, and the non-pregnant uterus, while its gravid uterus, the pylorus, ileo-colic, and internal anal sphincter, the muscularis mucosae of the intestines, the bile duct, vas deferens, seminal vesicles, the salivary and lacrimal glands, and kidneys were stimulated to further activity. Hence, it was further demonstrated that the action of adrenaline consists in a stimulation of the sympathetic autonomie fibres—this effect on the tissues varying according as their sympathetic supply is either excitatory or inhibitory. In 1906, Underhill and Claman showed that it stimulated hepatic cells through activating the sympathetic fibres regulating the formation of glycogen from glycogen (thus producing "adrenalin glycosuria") and that, in addition to these effects on the neuromuscular and neurosecretory reflexes, it also influenced the metabolism of the different food stuffs, especially the carbohydrates. Cannon, Altschul, and Gropper in 1913 demonstrated that intravenous injection of adrenaline was followed by a temporary improvement in the contracting power of fatigued muscles, especially in cases of Addison's disease. Cannon in 1914 showed that the intravenous injection of this agent in amounts of 0.001 mg. per kilo. of body weight shortened the circulation time of the
blood. Gunn (1913), and later Hogbin, Gunning, and Berry (1916) found that the blood vessels of the heart and of skeletal muscle were dilated by doses of adrenaline which would cause constriction in the arteries of the skin or intestine. Stewart and Rogoff showed recently (1916):

1. That the amount of adrenaline "spontaneously" liberated in the body is at a definite rate of about 0.001 G. per min.

2. That, normally, in the body, adrenaline aids in keeping the vascular system in a state of tension, and that it is only in consequence of definite stimuli, for instance, during strong emotion, 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 relationship between the internal secretion of the suprarenal gland 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 adrenal secretion was increased by continuous feeding of animals with thyroid substance. Further, adrenaline glycouria has been shown to be less easy to produce in the absence of thyroid, although paracrinectomy still produces it. Again, it was found that glycouria was often associated with Graves' disease. This it would appear that
these two organs, suprarenals, and thyroid, are much closely related, the correlation was effected possibly through the autonomic system (Cour). Reference has been made above to Cannon's observation on emotional hyperglycaemia. This was known to represent a phenomenon of protective mechanism on the part of nature, whereby the animal could use its muscles actually without fatigue (owing to their being abundantly supplied with oxygen under less central conditions), and could thus fight for its existence or run for its life to the best advantage (Bainbridge & Menzies).

In 1917, Stewart and Rogoff observed, in a careful experimental study, that, by sectioning one suprarenal and cutting the suture to the other, the liberation of adrenaline into the blood was stopped. This, they found, did not have any effect on 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 adrenaline output under these conditions.

It is of some interest to note here into that Sir Sharpey-Schafer and D. R. S. Lewis in 1919 (Quart. J. Exp. Phys., 12, 1919) definitely proved that the pulmonary vessels are constricted by adrenaline, 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 adrenaline 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 Borger have described certain principles which they called "sympathetic" amines, which occur in infusions of spiced meat and are biochemically related to adrenaline. An examination of the structural formulae of these amines will reveal their close relationship to adrenaline.

\[
\text{Boa amplamine.} \\
\text{p.-hydroxyphenethylamine (ot. tyramine).} \\
\text{Phenylethylamine.} \\
\text{Ephrine (an artificial amine (Caudron)).} \\
\text{ADRENALIN.} \\
\text{Also, in 1917, Hartmann and Fromm found that, although adrenaline could be successfully administered in cases of congestive or bleeding like post-partum haemorrhage, yet fairly safe doses could produce vomiting, intestinal haemorrhage, oedema of blood vessels, and paralyses of the respiratory center through rupture of blood vessels. These investigators also clinically confirmed Dale's finding that minute quantities of adrenaline not infrequently produce vasodilatation and a fall of blood pressure.}
\]
Sergent has also shown that favourable results were obtained on administration of suprarenal extract in cases of ordinary adrenalin insufficiency (hypoadrenalinism). 

The Internal Secretion of the Cortex.

Modern Findings up to 1922.

Whilst the embryonic development of the medulla from neuroblasts is enough by itself to suggest its internal secretion may have some influence over the nervous system, the mesodermal development of the cortex gives no clue whatever as to its precise principle. The endocrinologists tell us comparatively little about it. Acland, Soule, and Youjan in 1904 (C. r. soc. Biol., 57, 1905) claimed to have obtained from it what they found your adrenalin reaction better after incubation for 24 hours and regarded it as a precursor of adrenalin. This has been denied by several authorities like Voegtl and Mack. The Italian worker Antonio in 1911 (Arch. int. de biol., 50, 1911) obtained effects from the extract of the cortex antagonistic to those yielded by extracts of the medulla, whilst Voegtl and Mack in 1913 (Zwe. chem. Rev. Med., 60, 1913) claimed to have isolated a vasoconstrictor principle from ethereal extracts of the desiccated cortex. Further, Cannon and Weichert in 1914, and Swale Vincent in 1917, observed that there is little doubt that the rapidly fatal effects of interruption of both suprarenals is to be ascribed rather to the removal of the cortex than of the medulla.

And this, it would appear
that the cortex is the more vitally important of the two!

Clinical evidence has of late years been accumulating of the cortex to show that the internal principle influences the secondary sexual character, which undergoes remarkable changes in tumour and other lesions associated with the cortex - the so-called "supra-renal genital syndrome" (Osler). Pseudohermaphroditism has been observed in hypofunction of this part of the gland. Thus, Tuffer recently described a case in which an old lady who developed a supra-renal cortical tumour after the menopause and assumed male characters - heavy beard, lactation, ability to perform heavy labour without fatigue, etc. ("virilism" or "hermaphroditism") - this was followed in later years by emaciation, pigmentation, and mental deficiency. Again, such tumours have also been shown to lead to very precocious sexual development in children (Bullock and Sequiera), and this affords the ground for the suggestion that has since been persistently made that the adrenal cortex furnishes an auteroid which influences sexual development. Dr. Robert Hutchison has also described a remarkable syndrome in children, of adrenal tumours associated with exophthalmus and cranial tumours, and Dr. Pepin (1923) has described a form characterized by rapid growth in conjunction with diffuse involvement of the liver unaccompanied by any signs of 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 (Verdaggi). 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 (Tourn. Obstet. and Gynecol., 1921) 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 beta-blocked rats with suprarenal cortex grew more rapidly than controls, thus suggesting that the internal secretion of this portion greatly influences the metabolic processes.

Recently, several authorities like Elliott, Tucker, Leignel-Levastine, Rosenheim, Joffe 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" (Parkes). 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 followed invariably by degenerative changes in the medulla.
sheets of nerves, and have therefore concluded that the cortex provides an apparatus which is especially concerned with the formation and development of the myelin (lipoid) of nerve fibres and of the central nervous system. (Schröffer; Erde, Org. 1914).

**General Conclusion.**

We see, then, that quite successful results have attended experimental work on the superficial glands, but it still remains to explain why the by-passing that 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 slow and universally destructive process of the disease. At present, however, it is but poorly a process of exclusion that we may guess at an etiological relationship between the destruction of the cortex as Starling has pointed out, and the Addisonian bronzing. No doubt 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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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 inter-ventricular 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 by a cleft: the posterior lobe consisting of a pars intermedia and a pars nervosa. A pars tuberalis 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. Paulersco, and later Hornby in 1886, showed that the total removal of the pituitary body was accompanied by symptoms not unlike cachexia thyreo-dermatitis, 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 this 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 the
"acromegaly" and "gigantism", his description of the malady applied
expressing its most prominent sign, viz. "hypertrophie singulière
non-congéritale des extrémités supérieures, inférieures et
congénitale"—i.e., a marked non-congenital enlargement of the
dimensions and head. Shortly after Marie's discovery, Kayowitz
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.

Poulot's and Howley's 1885 observations on the
removal of the pituitary were confirmed by Baston in 1887,
by Clay in 1891, by Casselli in 1900, by Seghis in 1902, by
Fischer in 1905, by Archers in 1912, by Lushin in 1912, by
Biedl in 1913, and by Howley in 1913 (Burton-Offit). 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 Autocoid:

1895 — 1923
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 Harris’ discovery of 1886.

(a) 1895 - 1899. In 1895, Oliver and Schäfer 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 extract
of the posterior lobe only (especially the zona intermedia) was
responsible for this action. In 1899, Vincent and Schäfer found
that the successive injections of the extract caused increasingly
large rises in the blood pressure.

(b) 1901 - 1909. In 1901, Förlich demonstrated the re-
lationship between hypopituitarism and what Barbauld afterwards
called “dystrophia adiposogenitalis” (“Förlich’s disease”).
Benda, in 1904, showed that hypoplasia of the glandular element
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, Schäfer and Hornig showed that the
extract augmented the flow of urine. Cramer in 1908 demonstrated
that the action of the pituitary extract was different from that
of adrenaline in that it (i.e., the former) acted directly on the
muscular elements, and not upon the nervous terminals like
adrenaline. In 1909, Frankl-Hochwald and Förlich found
that the first injection of an extract of pituitary also 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 showed a large number of clinical conditions which he grouped together under the term "dyspituitarism," the causative part which the pituitary plays in these conditions being brought well to the fore. (Cushing: "The Pituitary Body and its Disorders," C. B. Liiphencott Co., 1912.) Oliver and Mackenzie, and Ott and Scott, in 1911 demonstrated the galactopoietic effect of the pituitary extract on pregnant or parturient animals. This same year also marked the brilliant researches of Engel and Lebsche, who isolated "pituitrin" or "hypophysin" as they termed it - from the posterior lob. Sharp and Shawyer in 1912 obtained favourable results on growth by feeding preparations of the anterior lobe to young rats. In 1915, Simpson and Hill found that pituitrin had the same galactopoietic effect that has been so satisfactorily demonstrated for pituitary extract by Oliver, Mackenzie, and others four years previously (1911), and proved that it also induces a copious flow of the cerebrospinal fluid and urine, and its glyconia-producer-producing faculty was also demonstrated by Sir Byron Bramwell (Bramwell: "Intercranial Tumours," 1915). Robertson in 1916 succeeded in isolating
from the anterior lobe a substance which he called "tethelin," containing nitrogen and phosphorus and stimulating the growth of
young mice. Magnus, Levy, and Taddei also reported that the
administration of these extracts increased protein metabolism;
and, in this connexion, we may note the admirable experimental
work done by W. H. Dott and reported in the Arch. Jowm. Exp.
Phyjiol. 0p. Nov. 1923, P. 141. This investigator found

(1) that the secretion of the anterior lobe has a marked
influence on cell activity, especially in embryonic tissues like
epiphysis etc. ;

(2) that the pars nervosa had no effect on metabolism;
(3) that hypophyseal polyuria was due to increased secretion
of the pars intermedia; and
(4) that the pituitary and thymus in conjunction has
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 a blood pressure, and influences the metabolism
of the carbohydrates, proteins, and perhaps, fear (Burston, Chishol).

**Recent work by J. Cana and G. Rosanu (La Pruss. Med., 1924, p. 377-378), and by P. Bailey and F. Brauer, (Endocr. 1923, s. 761; also Bailey, Eng. 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 sub-hypothalamic region. This finding is perhaps logically, as yet unconfirmed.**
SECTION X.

THE INTERNAL SECRETION OF THE PINEAL GLAND.

THE CAROTID & COCCYGEAL GLANDS.

L: THE PINEAL AUTACOID.

The pineal gland is a small structure that lies in the posterior aspect of the brain between the anterior and posterior commissures. 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 an ancient, Descartes (1596 - 1650 AD); and for more than 3/2 centuries, this was the type of men known of the function of the gland (Order). It was in fact for very long regarded as representing but a vestigial remnant of the eye of an extinct amphibian vertebrate ancestor of mankind (Bied). What we now know regarding this gland is derived chiefly from clinical cases. Thus, Virchow in 1909 called attention to the fact that cystic growths and tumours of the gland presented a clinical picture not dissimilar to those of diseases of the pituitary body, except that sexual infantilism was absent. He also showed their lesions...
Recent papers on the function of the internal secretion of the gland increasingly show that the gland plays a no mean role in the process of growth, but whereas particular phases of this role occupy the endocrinologists are by no means agreed, and their findings have been, moreover, very contradictory.

Thus, in 1914, showed that feeding of penial to young guinea pigs hastened their sexual maturity and growth, whilst, on the contrary, Horrobin in his paper 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 females (Budden-Otto): it would thus appear that hypophysectomy and hyper-phenolism produce identical results! Further, too, showed that removal of the penial gland also produced, in cockerels, not only a more rapid growth of the body but also an earlier development of the testicles and to secondary sexual characteristics: these findings have been confirmed by Szent-Györgyi. Intravenous injection of an alcoholic extract of the gland has been shown also to produce a marked but temporary fall in blood pressure; and plethysmographic observations have further demonstrated a diminution in kidney function (Dr. Sharpay-Schaper, Endocr. Org., 1930). A galactoencephalographic effect has also been recorded (? Starling).
In the state of our present knowledge, then, we may conclude that the active principle of the pancreas contains a cholesterol as well as a hormone which undoubtedly acts on growth. Our notions of the function of the gland as hormones and excretory bodies, and their uselessness in nutrition, require further clarification by the endocrinologists.

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Mi. The Carotid and Coccygeal Glands.

These are minute ductless glands lying respectively at 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 chromaphile nature. (*Schröer's Essentials of Endocrinology, 11th ed., p. 254*)

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

*George Dock, M.D., in Osler's System of Medicine, Vol. VI, Part II, page 358 states that Biedl, Wisenel, & Müller have succeeded in producing an adrenaline-like glycocyria 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 genital organs in young animals usually prevented the development of the accessory genital organs and of the features which characterize the male sex generally. There are numerous references in ancient Eastern literature to the effects of castration in the bunches of royal harem. 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, particularly adipose, which softens their contours and gives them a feminine appearance . . . . . The testes, too, were quite known in ancient times to influence growth and to control the development of sexual characteristics. However, the precise mechanism of the nature of this influence was an unresolved question.

Early Developments to 1849.

According to Berman, 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 Cordon in the 18th Century. In fact, John Hunter (according to Professor H. N. Walker in his Hunterian Lecture on "Testicular Grafts" delivered before the Roy. Coll. of Surgeons of England on Feb 1st 1924 — reported in Lancet of 16th Feb 1924) as long ago as 1750 succeeded in transplanting the testicle of a dog. The full import of this experiment was, however, unappreciated till Berthold in 1849 definitely affirmed the existence of a testicular autoid (and incidentally founded endocrinology as an organized and coherent science). Berthold based his belief in the results of testicular transplantation in foals 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.

Even so, anticipating Claude Bernard (1855), and the eminent French endocrinologists who succeeded him:

**Later Developments: 1850-1896.**

Although Leydig a year after Berthold's experiments described the interstitial cells of the testis (1850), and 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 Hancar de la Cour (Albrecht and Rolleston), yet, it was not till some 40 years after that renewed
interest was taken in the subject. Brown-Squard in 1899
(1) found that subcutaneous or intramuscular injections of testicular extracts produced eugorulating qualities
which manifested themselves in improvement of mental and
physical vigor, not only in cases of general depressions, neurasthenia, deficiency of normal testicular functional activity, but also
in old age (Brown-Squard was 72 years old at this time).
Later work has, however, not corroborated Brown-Squard's findings,
which were the result of perfunctory enthusiasm and auto-
suggestion rather than of accurate, scientific observation. Two
years after Brown-Squard's observations, Poehl (189) claimed
he had extracted a substance which he believed to be the
active principle of the testicular extract. This substance
he gave the name "Sperrmone", with the formula C5 H4 N2,
which he found three years later (1894) acted as a
"physiological catalyzer" which increased the action of the heart
and of the digestive organs. In 1896, Lotte and Frégel 
"ergonomically" recorded that testicular extract augmented the
muscular power by as much as 50%, and diminished muscular
fatigue.

20th Century Findings: 1900 - 1924.

In experiments that have been performed in this
subject since 1900 to the present day are so numerous,
and their literature is so extensive, that justice could
hardly be done to them by quoting them all here.
Only very brief reference may be made to the work of many investigators whose work has advanced our knowledge of the testicular hormone. A very few of them are:

Dixey and G. Walker (1900); Arndt and Bonnin (1903); Ball, Forem and Schlegmann (1904); Gowers (1905); Marshall (1910); Steinach ("Pituitary Gland", 1912); Holzinger (1912); Biering; Karl (1917); Rasmussen and Lipschitz (1919); Thyng, Isbin, Fiedje, and Sand (1921); Prof. H. Morgan (1922); Otten, Wagner, and Bormann (1924) — to mention but a very few.

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

1. that the sex character is 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 is trophic rather than secretory).

* Some authorities state that this had already been noticed by Tandler in 1904 and again in 1910 (Bostert-Ofelt).

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 intestinal cells of Leydig, having a considerable influence on growth and on the development of sexual characters, and especially sexual desire (Steinach).

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**O: THE OVARIAN AUTACOID.**

The function of the ovary was described by von Graaf (1641–1673) who discovered and described 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 secretory factor of this phenomenon. Subsequent clinical observations have shown that adult women in whom the ovaries had been removed for the cure of diseases or cystic tumors showed retrogressions changes in their genitalia, such as atrophy of the uterus and vagina, and peculiar vasomotor and psychoneurotic conditions, led attention to the endocrinological function of the organ. Subsequent to this, the successful results of the administration of ovarian extracts in cases

*Eminently successful results have been obtained from grafts of monkey testis to human beings.*

by Dr. Voronoff — British Medical Journal, March 22, 1924.
confirmed the theory that it may furnish 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. 1901).

Modern Experiments: 1887–1915

Lowry and Ritchie[2] in 1887 showed that the internal secretion of the ovaries exerted a remarkable effect on general nutrition; and they demonstrated that removal of the ovaries did not exert a favourable influence upon the course of the disease "osteomalacia". Green in 1899 and Halban and Morris in 1904 found that the cessation of normal fluid 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 sterility ("heat") could be induced 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 1907, Bonin[3] found that extracts of the entire ovary were more beneficial than those of the corpus luteum in granuloma uterinum pelvicum alone. He therefore referred the ovarian function to the peculiar stroma cells, which he designated as the

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* 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 1899, when a woman aged 33 died at the Southern Brit. Med. Journ. Mar 22/1924, page 513.
"grande interstitielle l'ovaire" (interstitial cells of the ovary).

Casmich and Tilly, and Marshall and Tilly, during this year, found also that removal of the ovaries in young girls prevented the normal development of the uterus, which, removed in adults, caused a degeneration of this organ — which could be avoided by a successful transplantation of ovarian tissue.

Vagin action was already existing at this time (1907) for the phenomenon of menstruation, was dependent upon a periodically discharged substance furnished by the ovaries. Friedeke was the first to confirm this view 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 crude extracts of the ovum'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 the organs. Thus, in 1915, Sir Byron Bramwell reported a case of acromegaly and gigantism in whom castration had been carried out before puberty (Byron Bramwell: "Clinical Studies," Edin. Med. Journ., June 1915). Further, castration has been proved to be associated with increase in weight of the hypophysis, thyroïdes, and suprarenal glands (Burton Opitz), and to intensify the symptoms of hyperthyroïdism. Recent investigation,
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 prominent male germinative organs and female secondary characteristics.

Dr. M. Itohaki of Kyushu University, working recently in Prof. Dr. Schäfer's laboratory in Tübingen, found that the extracts of the interstitial cells invariably inhibited, while those of the Graafian follicles or corpus luteum increased, uterine contraction. It would thus appear that the ovarian operation is a typical endocrino which comprises a hormone as well as a (V. Schäfer's Ztschr. 1916, p 141).}
SECTION XII.

THE INTERNAL SECRETION OF THE SEX ORGANS (CONT'D):

THE UTERUS, MAMMARY GLAND, &C.

P: THE INTERNAL SECRETION OF THE UTERUS.

Despite the fact that the uterine functions fall into abeyance after complete amenorrhea, yet some eminent surgeons and gynecologists have adopted the view that the uterus possesses an internal secretion in which the functional activity of the ovary depends. Moreover, that was the first who in 1884 (Arch. f. ges. Physiol., vol. 44, 1884) suggested the theory that the uterus has a distinct endocrine function.

Experimental & Clinical Observations etc. 1898-1917.

Bowd in 1898 reported an experiment upon a rabbit in which the ovaries, after transplantation in an abnormal position, were found to retain somewhat aberrant "corpus luteum of pregnancy" in association with a gravid uterus. He interpreted these observations as supplying evidence of uterine uterine secretion acting on the ovaries and so causing a growth of normal tissue and he further supposed that this secretion was quite different from the saline extract elaborated from the aneurysm uterine.

Accordingly Zweifel and Abel during the next year (1899) demonstrated that atrophy of the ovaries with menopausal symptoms followed complete hysterectomy, the symptoms being obviated if a portion of the uterine mucosa was left. Mundy and Burger, in their monograph of 1905, expressed the belief that the ovaries,
after complete hysterectomy, showed a gradual cessation of functioning, which Dorré, on his careful clinical observation on subtotal hysterectomy in the November of that year, confirmed Zweifel and Abell's findings of 1899 (vi last page). In 1906, Holzbach on the contrary, stated that the ovaries did not usually atrophy after hysterectomy and that if their condition did occur, it was due to interference with nervous connections consequent upon its operation rather than with the endocrine function, if any, of the uterus. During the same year, Band 124 put forward the view that the ovarian secretion is influenced by a poetic secretion from the ancestrum uterinum;

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

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

In 1907, Boston (London: Jan 1907) recorded 34 cases of women in whom the uterus was congenitally absent, the development of the breasts and other changes relating to puberty (excluding menstruation), were present. Blair Bell in 1916, made the suggestion that ovulation and menstruation were produced by a uterinum不尽然 secretion which he termed "uterine".

(Blair Bell: "The Sex Complex" London, 1916) and has since been proved to comprise a galacto-phylogenetic hormone. In 1917, Gravis showed that emotional disturbances after
by stratification occurred with approximately equal frequency, while the ovaries be retained in situ, totally obliterated, or transplanted. (Harrington)

Recent Scientific Researches: 1918–1922.

Of modern research, that of Marshall and Carmichael on the most important in that they mark an epoch in the history of the systematic investigation of the nature of the uterii and their influences. The experiments of these observers show that the clinical evidence regarding the endocrinological function of the uterii, as now means agreed with careful scientific investigation; and that its growth and development of the corpus were in no way dependent on the presence of the uterii, as has been previously supposed by Zweifel, Abel, Doran, and others (pages 111 or 113 of Holzbecher's treatise on the endocrine diseases).

Conclusion.

We see then, that our knowledge of the internal secretion of the uterii is by no means clear; the question has been, and will perhaps for some time be, a matter for ipolemious debate. The clinical evidence for the endocrinological function of the uterii, especially the corpus (cf. Zweifel and Abel, p. 110), acting on the characteristics and the various phenomena attending thereof, is by no means convincing; how much careful experimental work remains to be done, before the problem could be regarded as being uncontroversiably settled.

THE HAMMARY

P.T.O.
Q. The Mammary Gland: Its Internal Secretion

& The Influence of Other Internal Secretions on Its

(Galactagogue) Activity.

Its Internal Secretion

The state of our knowledge of the internal secretion of this gland is rather poor. The only reference is that which one finds in the literature on the observations of Steely and Kastle in 1912 (Bulletin 160, Ky. Agric. Exp. Sta., 1912). These investigators stated 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 (Galactagogue) 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 Foltz and Towle, who, in 1896, found that if a bitch in whom the ovaries had been completely excised became pregnant and lactated, within two years later (1898) confirmed these experiments, and further demonstrated that mammary tissue transplanted to the neighborhood of the ears and covered from all its nervous connection enlarged and secreted milk during a subsequent pregnancy—thus showing that a purely chemical process was involved in lactation.
These findings were subsequently confirmed by many other observers, especially Halban who, in 1905, expressed the opinion that the specific internal (hormone) stimuluses arose mainly in the chorionic villi and placenta.

(8) 1906 - 1909: The "Foetal Hormone" Theory. The specific nature of this hormone was not conclusively demonstrated until the time of Miss Tom - Claydon and Prof. E.H. Starling. 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; similar extracts from the ovaries, placenta, or uterus had no such effect. 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 100°C. (Henderson's Phys. of Reprod. 2nd Ed., p. 612.)

(8) 1910 - 1922: This period was devoted chiefly to further observations on the influence of ovarian, placental and other autocrine or mammary secretion. Pasteur in 1910 described the case of the hydropoxytuses - the Blaschke sisters - in whom pregnancy and parturition in one was followed by lactation in both. This observation, with the fact that existence of secretion of milk-like secretion in virgin animals, led to a very acrimonious controversy regarding the Lan Claydon - Starling "foetal hormone theory". It must in justice be remarked, however, that it was not of any
Time centered by Thai Kin Cogan in drips, by Professor Swiss that the
foetuses were the sole source of the stimulus for mammary development;
indeed, these observers especially demonstrated that the mammary growth
that occurred at puberty, for instance, could only be attributed
to ovarian influence, since the growth did not take place if the
ovary had been removed before puberty. However, since that time,
it has been definitely experimentally proved by Cott and Scott (1910),
Schaper and Backenstos (1911), Russell and Bouin and Schill (1912),
Tzanckel and Sieme (1913), Savini (1913), Hill and O'Donoghue (1913),
Hammond and Marshall (1915), Simpson and Hill (1916), Atlee (1916),
Holman Flavette (1917), Hesselberg (1917), Loeb and Kunitz (1919),
Woodman (1922) and various other investigators, that extracts
of the ovary (Corpus luteum), the posterior lobe of pituitary,
placenta, involuting uterus, the so-called "myometrial gland" of the uterus (Russell and Bouin), lactating mammary gland
itself, and of the parietal gland as well as tissue of footed
beasts, have a marked galactogetic 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 6, Part 3, art. 3.

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 its many difficulties, how it has encountered its manifold activities, to comprehend the universe, to discover the truth, to conquer disease, and to erect from nature her jealously guarded secrets. We have observed the vicissitudes of its fortune and its ultimate success that have attended the slow but sure steps by which Man passed from an age of fanciful, theoreticalism 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, 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 discoveries are no less so than others.
men. — And so we have been weightily impressed with regard to the history of the development of our knowledge of the internal secretion. We have seen from our study of the many researchers on this great subject that, in scientific research, there exists quite as many methods as there are endocrinologists, though, doubtless, many of these methods claim a common source of inspiration. We have observed that the lack of these physiological investigators is "to correct old creeds" (Emerson), to discern 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 disentangle the facts of nature are not of much consequence, so long as these methods are sufficiently scientific; nor need they, as mighty men of science, pre-occupy themselves over much with the "ultimates" of Nature. But the points that vitally affect the career 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 far-reaching 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 “subtileties and more fanciful conjectures” based on totally unscientific methods, a Bernard or a Banting or a Sharpey-Schafer passed cautiously from observation to inference, from inference to verification, and from verification to application, in an orderly and statable sequence.

The organ of internal secretion represents but an infinitesimal portion 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 stored away in a man’s next pocket; and yet, it is on this very organ that most, if not all, of the vital processes of life depend. Endocrinology offers indeed a most fascinating field for speculation and theorisation! Psychologists have already described in it a solution of some of their most acute problems! (Cf. H. Crockett Miller in his paper on the influence of the thyroid glands, and suprarenal on emotions, read before the Section of Psychiatry of the Royal Med. Soc. on Feb 12/1921 and reprinted in Lancet 23 Feb/1921). Eminent anthropologists have even begun to
assume as 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 Associa-
tion 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 delination
of the Caucasian face, the tendency to strong eyebrow
ridges ... the bulk and height of stature ... or 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 ... genetic,
anthropological, phylogenetical, 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 therapeutics which are sometimes more profitable to the
manfacturing chemist than to the patient! Further,
the theories on which such are evolved "shew", as one eminent authority (Lushky) 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 commercialized use of these plasma extracts are usually of an equally primitive order. Indeed, no more fruitful source of quackery, 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 (vi: General Introd.: p. 7), by Brown-Séquard in 1889, or which are in use at present, and can lead to any progress in the field, can be more successfully in the future!

However, there can be no question that, of the numerous vaunted tissue extracts, four, namely: ton 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. Finally, the fourth and latest arrival in organo-therapy, viz., ad as has been noted...
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 justified will be a matter of a few more years of careful observation.

Despite our many advances, further research remains to be done to add to the symposium of our knowledge of the endocrinological internal secretions. The function of the carotid and coeliac bodies and of the thyroid gland and adrenals 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 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 to be found to prevent its alleged deterioration in tropical countries. We may confidently hope, however, that, with time, these problems will be elucidated.

THE END.
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. Celsus described diabetes.

150. Aretaeus of Cappadocia first used the word "diabetes" (from the Greek diabetes - a disease).

1563. Hydropsalpinx first recognized by Eustachius Santorio Santorius.

1644-74. Sylvius differentiated between true secreting glands and ductless glands.

1642-73. Vieussens discovered the pancreatic and other ducts, and described certain ductless glands.

1643-73. De Graaf described the ovarian (Gr着眼卵的) follicles.

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

1660. Vieussens gave the first complete account of the thyroids.

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

1679. William differentiated between saccharin and non-saccharin forms of diabetes. (mellitus and incipitida)

1775. Phosphopluoridum demonstrated certain views which have been suggested, to indicate a clear conception of internal secretion. (This has been denied by some authorities).

1776. Dobson first chemically demonstrated sugar in diabetic urine.

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

1788. Courbet 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 of Pulitation of the Heart."
1835.  Graves described the disease (exophthalmic goitre) more fully.
Klinge first demonstrated the connective tissue of the thyroid vessels.

1839  THE FIRST IDEA OF INTERNAL SECRETIONS WAS FIRST DEFINITELY ADVANCED BY BERTHOLD.

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

1850  Leopold described interstitial cells of testicle.

Lehm in Switzerland, 1850, first observed that thyroid was absent in certain cases.

1856  Schiff first studied the fatal effects of thyroidectomy.
Nelphman obtained certain suprarenal extracts giving marked colour reactions with chemical reagents.

1857  Brown-Séquard first investigated effect of removal of suprarenals.

The name "internal secretion" first employed by Claude Bernard in 1854, who discovered the glycogenic function of liver.

1864  Langerhans described the islet cells of the pancreas.

1873  Sir Wm. Gull described myxedema adultorum; and
Horley and Semon showed that it, and cirrhosis, and post-puerperal myxedema were related to hypothyroidism.

1860  Sandebronn discovered the parathyroids.

1882  Kocher first employed the term cachexia strumiprae for the effects of thyroidectomy.

1884  Lenhart first suggested that the adrenal furnished an internal secretion.

1885  Paratono and Horlsey first studied the effect of removal of pituitary.

1886  Marie described acromegaly and gigantism, showing their relation to hyperpituitrinism.

1889  The effects of testicular extracts were studied by
Brown-Sequard.

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

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

They differentiated between cachexia strumiporosa and osteitis paratyphica.

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

1895. Schafer and Obier 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 proved endocrinological function of the adrenal.

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

1901. Schulze and Ophé first found that the islets of Langheran showed atrophy and hyaline degeneration in diabetes.

Adrenalin was first isolated by Addison and Takamine from suprarenal extract.

Halban first studied the amenorrhoeal effects of ovariotomy.

The removal of hypophysis with adipsogenitalis was demonstrated by Fröhlich.
1902 Szekeres demonstrated that ablation of pancreas parathyroid only by ligation of the blood vessels of the islets followed a pancreatic duct.

Bayliss and Starling discovered secretion of gastric juice.

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

1905 Goodall and Lathor studied the effects of thyrectomy.

1906 Edkins discovered "gastrin".

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

Lowe, Clifton and Starling promulgated their "football hormone" theory.

1908 Macallum and Vorburger found that parathyroid extract and especially calcium salts abolished the effect of tetania parathyropeptica and that the parathyroid glands 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 pelvic enlargement.

1911 Kutscher isolated pituitrin from pituitary extract.

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

The influence of thyroid on growth was demonstrated by Enders and Kehl.
1914. McLeod first demonstrated the effect of thyroid on growth.

1916. Robertson isolated "tachelin" from the anterior pituitary lobes, 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 gluconeic.

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 Riche found that the thyroxin 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.
REFERENCES

1. Aristotle: "Book of Problems Concerning the State of Man's Body."

Vassalle: Neurol. Zentralblatt, 1891.


...: Studies on Thyroid, Bull. U.S. Lab., Washington, 1909, no. 47.


Bing: Zeitschr. f. d. Physiol. u. Pathol. u. Stoffwechsel, 1908, ser. 1, 1, 2; also Biedi: loc. cit., "Tetania Parathyrospinia."


45 Goodall: J. Physiol. 32, 1905; also, Pappenheim: Jour.

46 Paton: Jbid., 32, 1905, 28; also, 42, 1911, 267.


54 Hpic: Jour. Exp. Med., 5, 1901, 897.


56 Szabolcs: Virchows Archiv., 158, 1902.

57 Albutt and Rolleston: Medecine.


65 Kleiner: Jbid., 1914, 40, 153.


67 Bensley: Harvey Lecturer, New York, 1915.


Bonting and Bent: Jour. Lab. and Clin. Med., 92.1, 2.51

Brown-Sequard: Compt. rend., 1887. The amputations do not appear to be agreed as to the exact date, some given as in 1886, others as 1887, and some others as 1858.


Stilling: Rev. med., 1888.

Fitzg.: Zeiger's Beiträge, 1889.

Biedl: Pfleger's Arch. 67, 1897.


Vulpian: Compt. rend., 43, 1856.

Oliver and Schapcr: J. of Phys., 18, 250, 1895.

Biedl: Pfleger's Arch. 67, 443, 1897.


Takamine: Jour. Pharmaceut., 73, 523, 1901.


Meltzer: Amer. J. Physiol., 9, 252, 1903.


Cannon and Nice: Ibid. 32, 44, 1913; Gruber: Ibid. 23, 335, 1914; and Endocrinology 3, 45, 1914.


94. Hartmann and Fransen: Endocrinology 3, 1909, 45.
95. Oliver and Schaffer: Journ. Physiol. 18, 23, 1898.