H. Sect.

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

Wellcome Medal in the History of medicine.

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Synopsis

The Humoral Theory in Early Medicine - Hippocrates, Galen. The Schools - humours and the "elements" - Burton's Anatomie of Melancholy.

The Renaissance in Science - anatomy, physiology. Secretion - Malpighii, Müller; - Ductless glands and their secretion, Carpenter; Old idea of internal secretion and the "Consensus Partium" - Borden Legallois - Berthold, first experimental proof.

Modern History - Claude Bernard - Brown-Séquard - theory of internal secretion - Starling. New experimental methods and clinical observations

Methods used in determining function of ductless glands.

Methods of proving internal secretion.

History of Individual Ductless glands:- Thyroid, Parathyroid a Adrenal bodies, Carotid body (coccygeal body), Pituitary body, Thymus, Pineal Body, Islets of Pancreas, Liver, Secretin of duodenum, Generative Glands - testis, ovary, corpus luteum - uterus and mammary gland, foetus and placenta

Interrelation of Internal Secretions - Coordination - Starling; Noel Paton - effect of reproductive organs - carbohydrate metabolism - pigmentation - racial characters - colloid - lipoid - growth - body temperature - relation to infections - new growths - psychology. Possibilities of future research.

History of Nomenclature

History of Organo therapy - opotherapy

Conclusion

He knew the cause of everich maladye,
Were it of hoot or cold, or moiste, or drye,
And where engendred, and of what humours,
He was a verray parfit practisour.

Chaucer Prologue

HUMORAL THEORY

From the very earliest times the dominating theory of medicine seems to have been the humoral theory - that there were in the body certain liquids or fluids, which by their varying relative proportions, their mixture and their distribution affected the state of health or disease of the whole body, and which caused the varying symptoms of disease by their secondary concoctions and by their expulsion by the natural passages.

It is interesting to trace this theory through the whole of the early history of medicine, and the various criticisms of it and theories which arose in opposition in the "Solidist" or "Pneumatic" schools, and the additions to it at various times of metaphysical and superstitious conceptions - the vital "spiritus" of the Romans - the astrology of the middle ages. Since the philosopher of old took all knowledge as his study he must make some attempt to correlate the different branches, and so the connection between mathematics, medicine and metaphysics was demonstrated, and, when all treatment was empirical, a learned doctor must rationalise and explain his cures by including the whole universe in his argument.

The theory of humours was well established by the Greek philosophers - Pythagoras spoke of the surplus of humours in disease, Anaxagoras taught that the chief acute diseases

were due to the deposit of bile.

In Hippocrates treatise "On Ancient Medicine", the theory of humours is fully expounded, and although there is some doubt as to whether this treatise is as old as Hippocrates himself, certainly the theory is one of the Hippocratic doctrines. He recognised four "crude" humours, blood, phlegm, yellow bile and black bile and he held the belief that in the natural process of recovery from disease the humours went through a stage of "coction" or digestion and finally were "resolved" by "crisis", and expelled by one or other of the natural passages. Belief in the healing power of nature was at the basis of the thought of his school and for this reason prognosis or foretelling the day and hour when "crisis" would occur in disease became of great importance and was worked out very exactly by mathematical methods - using the numbers of Pythagoras.

Galen expanded and explained the theory in his system and also correlated it with another doctrine of the followers of Hippocrates - the Doctrine of the Pneuma or spirit of life - a fine substance which is present in the atmosphere and is inhaled into the lungs and through the blood reaches all parts of the body where it helps to produce the vital phenomena.

The Alexandrian and Arabian schools adopted the humoral theory with the doctrines of Hippocrates and Galen; and although to it were opposed the "atomic" theory of Asclepiades, as upheld by Lucretius in "De Rerum Natura", the pneumatic and eclectic schools, and later the theory of the microcosm and macrocosm of Paracelsus - who publicly burnt the books of Hippocrates and Galen and claimed that he could explain man's body and the whole universe - yet the old theory never completely lost its hold, perhaps because it did

so satisfactorily explain many facts.

The early philosophers ideas about the composition of the universe became quite compatible with the humoral theory in medicine. The four properties hot, cold, wet and dry were recognised at the beginnings of chemistry and physics - Milton in Paradise Lost Bk ii 898 sees them at "endless wars" in chaos.

"For hot, cold, moist and dry, four champions fierce,
Strive here for mastery, and to battle bring
Their embryon atoms"

Thales believed that water was the primary element and source of all things, Aristotle developed the idea suggested by Empedocles of binary elements - such as hot and dry etc. So that now they had four "elements" fire, hot and dry; water, cold and wet; air, hot and wet; earth, cold and dry. The elementary properties were soon divided up in a similar manner among the humours of the body - blood was hot and moist, phlegm or pituita cold and moist, choler (bile) hot and dry and melancholy (black bile) cold and dry

The terminology of the humours passed into common language [Dr Johnson has no less than nine definitions for the word humour in his Dictionary]., they were universally believed in and studied as the cause of everything abnormal in body or mind - the cause of dreams as Dame Pertelote told Chanticleer, and of the temper of mind or character as well as of bodily diseases. "An exact balance of the four primary humours makes the justly constituted man", and allows for the undisturbed production of the concoctions or process of digestion and assimilation and of "those excrementitious humours of the 3rd concoction sweat and tears". a good summary of the properties and origin of the humours is to be found

in Burton's "Anatomie of Melancholy" [1577 - 1640]

When we observe how the theory persisted with very little change in its essentials right up to the 16th century and the scientific renaissance and formed the basis of all physiology, pathology and therapeutics, it is scarcely to be wondered at that at the present day its revival in the scientific form of endocrinology should meet with such ready belief, and hormones taking the place of the old humours should be credited with such far-reaching and almost miraculous effects not only on the body but on the intellect, character even the soul of man.

RENAISSANCE IN SCIENCE

The theory of humours, overgrown with superstition and mixed with astrology and magic in the darkness of the Middle Ages was gradually lost sight of in the interest aroused by the rediscovery of the facts of anatomy and the gradual development of the scientific method which was applied to physiology by Harvey and others.

Descartes' philosophy returned to the mechanical conception of living bodies, and the natural explanation of vital phenomena, and confined the soul of man to the brain suggesting the pineal gland as the possible site of the soul. About this time also anatomists were setting more in order their ideas about secretion; previously any roundish solid pink or white organ was called a "gland" but Malpighii in 1665 described the minute elementary parts of glands - the acini, he had not yet seen with his microscope that these acini were composed of cells.

Ruysch in 1696 injected the blood vessels of glands and Heller following him also believed that all glands were simply masses of blood vessels of which the smallest poured a secretion directly into the ducts of the gland

It remained for Johannes Müller to prove that the secreting

canals in all glands form an independent system of tubes with capillary blood vessels in their walls.

Later the changes in the histological appearance of the secreting cells during secretion were described by Heidenhain.

Certain organs were described by the anatomists as having all the structural appearances of glands except that no excretory ducts were demonstrated so that the idea of their pouring their secretion into the blood stream directly was postulated.

W. B. Carpenter in 1852 writes

"--- We refer to that elaborating agency, which is now generally believed to be exerted upon certain materials of the blood by the spleen, thymus and thyreoid glands and suprarenal capsules (which are sometimes collectively termed vascular glands) ... "The vascular glands" exactly correspond with ordinary glands in all that part of their structure by which they withdraw or eliminate certain matters from the blood; and they differ only in being unprovided with excretory ducts for the discharge of the products of their operation. These products instead of being carried out of the body, are destined to be restored to the circulating current apparently in a state of more complete adaptiveness to the wants of the nutritive function."

The idea of internal secretions is probably older than these observations. A probably incorrect quotation (Vincent) attributes to Caspar Friedrich Wolff (1733-94) the statement that "each single part of the body, in respect of its nutrition, stands to the whole body in the relation of an excreting organ" (Stewart). Théophile de Bordeu in "Analyse médicinale du sang 1775 looks upon each organ as the source of a "humeur particulière" which exerts its influence on the body generally. Hemberger and Biedl maintain that Bordeu's views indicated an even clearer conception of internal

secretion. However that may be Borden's view was not that generally held about the year 1832. Cuvier stated that the correlation of different organs and tissues of the body - the "consensus partium" of older writers - depended on the nervous system.

Legallois in 1801 wrote on the relationship of the secretion of all glands to the nervous blood - not only those which are ductless. Müller in 1838 thought that the glands without ducts consisted almost wholly of vessels - the "vascular glands" and that they exerted some plastic influence on the blood circulating through them.

Berthold in 1849 transplanted the testes of young cockerels to the surface of the intestine and found that instead of showing the ordinary symptoms of castration they developed into normal cocks. Berthold concluded from this that the testes affect the whole organism through the blood, he believed however that the nervous system also has a part in the "consensus partium." Berthold's work was however overlooked till Bieds brought it to light in his Innere Sekretion 1913.

MODERN HISTORY

The modern history of the study of internal secretion dates from the work of Claude Bernard on the glycogen function of the liver in 1855. It was he who first used the term "secretion interne" for the passage of glycogen from the liver cells into the blood as opposed to the "secretion externe" of bile from those cells into the bile ducts. Bernard stated clearly that certain glands - the spleen and lymphatic glands, the thyreoid and suprarenals produce an internal secretion. Lécons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organism 1859

Brown-Séquard with his more spectacular but less scientific demonstrations of the action of testicular extracts

aroused a great interest and much speculation in many quarters which has never since died down. He was of the opinion that every organ and tissue in the body furnished an internal secretion which affected the body as a whole through the consensus partium which he believed to be humoral and not nervous.

Carpenter also had believed that even adipose tissue contributed an internal secretion.

The actual theory of internal secretion has not been changed much in the last seventy years - since Carpenter's statement in 1852 but most people have agreed to restrict the name and the idea of internal secretion to the definite chemical products produced by certain glandular structures - the ductless glands, and not to include as Starling does "every substance taken by the blood from the cells of one part of the body and carried to distant parts which it affects for the good of the organism as a whole." This definition would include as well as adrenalin and secretin such products as carbon dioxide urea, glucose, water and inorganic salts. Every year, however, new facts are discovered and further experiments performed so that a mass of knowledge of detail is now at our disposal and awaits further efforts at correlation, classification and nomenclature.

In the development of knowledge of the internal secretions as in other branches of physiology great importance has always been attached to the discovery of new methods of experiment as well as to the aid given by clinical observations and pathological findings.

Of clinical observations which have been of great importance the discovery of the analogy between thyroidectomy, myxoedema and cretinism and their cure by grafting injecting or feeding thyroid; the connection

of diabetes with the pancreas and of acromegaly with the pituitary may be mentioned here.

Of experimental methods the most important innovation was the intravenous injection of gland extracts begun by Oliver and Schäfer in 1894 which led immediately to the discovering of the active substances in the medulla of the suprarenal and the pituitary body

METHODS OF DETERMINING FUNCTION

The chief methods which have been used in determining the function of the ductless glands may be mentioned here before each body is taken up separately with regard to the history of the discovery of its function up to the present day.

These methods are :-

1. Removal (a) experimental - by surgical operation on animals. (b) accidental - by disease or by operation on man (as in the case of removal of the parathyroids along with the goitrous thyroid by old Swiss surgeons.

2. Administration of the gland or its extracts

(a) Enteral by mouth or rectum - "feeding" the gland is used in "Organotherapy" but the active substance of all these organs are probably destroyed by the process of digestion except the thyroid and probably never get into the blood. Experiments on feeding thyroid, thymus etc to tadpoles were done by Gudernatch in 1912.

(b) Parenteral - hypodermic and intramuscular injection was the method used by Brown Séquard in 1889 and since by Helges and others for suprarenal and pituitary extracts. Intravenous administration has been used, inhalation by the lungs, and also isolated organs have been perfused with or immersed in the extracts

(c) Intravenous injection was first used by Oliver and Schäfer in 1894

3. Study of the effects of outpouring of the secretion of the gland in the body, by stimulation of its nerves etc implantation (grafting method used by Halsted 1909), the results of overgrowth and overfunctioning as hypertrophy of anterior lobe of pituitary, hyperthyreoidism etc.

PROOF OF INTERNAL SECRETION

In order that any tissue may be definitely proved to produce an internal secretion, firstly :- there must be histological evidence that the cells are secreting cells secondly :- some special chemical substance must be found in the lymph or venous blood coming from the tissue thirdly :- the effect of injection etc. of this substance must be different from that of tissue in general - ["vaso dilation" - perhaps histamine or choline, is present in many organs and tissues and causes a fall of blood pressure when injected]

It is not always possible to prove that a substance fulfills all three principles. If removal of the tissue shall cause definite symptoms while if some of the tissue be replaced in any part of the body or extracts of it administered these symptoms disappear, this is considered a sufficient proof that the tissue produces an internal secretion - Berthold in 1849 proved the internal secretion of the testis by this method, and this condition is fulfilled by the thyreoid and parathyreoid but the second condition above has not been satisfied as yet, whereas the medulla of the suprarenal satisfies all three postulates but an animal appears to be able to live without the passage of this secretion into the blood.

HISTORY OF INDIVIDUAL GLANDS:- THYREOID

Galen and the other early writers supposed that the <u>thyreoid body</u> protected the delicate vocal cord region by acting as a soft elastic spongework full of blood, and that the amount of secretion in it was regulated by the pressure of the muscles in front of the gland.

The thyreoid body is present in all vertibrates and it appears early in the development of the embryo and is connected by a duct with the pharynx – in amphioxus and Ammocoetes this open connection of the gland with the pharynx persists. Probably this early connection with the alimentary canal accounts for the good results of enteral administration of this gland or its extracts, whereas most of the other ductless glands have no effect when taken by the mouth.

In 1856 Schiff showed that complete thyreoidectomy in dogs was usually fatal after 1-4 weeks – the symptoms being muscular tremors and convulsions, cachexia and a condition of apathy. Surgeons [Reverdin and Kocher 1882 ✱] noticed that thyreoidectomy performed for goitre in some cases was followed by convulsive attacks in others by chronic malnutrition. About the same time ✱

✱ Gull described five cases of "cretinoid state in the adult" in 1874. Ord in 1877 called this condition myxoedema and found changes in the thyreoid. Curling and Fagge found the thyreoid atrophied in cretins, Charcot, Savill and Hadden associated myxoedema with atrophy of the thyreoid.

of animals after thyreoidectomy and noticed that the symptoms disappeared. This result suggested the use of thyreoid for cretins and myxoedema in man and immediate success followed its administration.

Later extracts were injected and at length it was found that feeding the dried gland of sheep removed the symptoms and if continued at intervals in small doses prevented recurrence.

In 1896 Baumann isolated from the gland a substance rich in iodine, 9·3% of dry weight. It is in combination with protein and can be separated by digestion with gastric juice or boiling with acids. This substance was found to produce the same effects on metabolism as extracted or dried gland

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– it was evidently the active principle of the thyroid. It is undetermined whether the iodine is an essential constituent of the physiologically active substance, or an injurious substance bound and made innocuous by thyroid cells – Howell. In 1919 Kendall isolated a crystalline compound of iodine which he called thyroxin – a derivative of tryptophane.

Cameron observes that thyroxin has, for its iodine content, appreciably less effect than dried thyroid quantitatively, only a quarter of the effect [Reid Hunt] Here must therefore be some other active principle.

Thyroid secretion has not been found in the blood and injected extracts cause not much effect on circulation, respiration secretion etc. Prolonged administration of thyroid extracts produces marked effects on metabolism, increasing it to the extent of causing symptoms like those of exophthalmic goitre or other diseases due to hyperthyroidism. Tadpoles fed on thyroid stop growing and metamorphosis takes place – dwarf frogs being the result Gudernatch 1912. There is some evidence to show that secretion may be poured out on stimulation of the sympathetic nerve supply.

The histology and microchemistry of the thyroid has been extensively studied with the result that the normal variations in the appearance of the gland at different times are found to be considerable.

Langendorff and also Bensley have described two types of epithelial cells, if these are present and are both secretory, there is a possibility that two secretions may be formed in the gland.

The secreting cells have been examined by Goetsch who believes that the mitochondria of the cell increase in number as it increases in activity; by Bowdry who finds that the golgi apparatus moves from one pole of the cell to

the other during secretory activity; by Bensley who believes that the polarity of these cells is reversed so that they pour their secretion into the blood capillaries instead of into the vesicles; and recently Williamson and Pearce have described a network of tubules stretched beneath the free surface of the epithelium and these workers have some new views on the general structure, lymph supply etc of the gland.

THYREOID It was early found that discrepancies occurred in the results of extirpation of the thyreoid - sometimes the animal died quickly with convulsions - tetany at other times slowly of inanition; and it was found that complete thyreoidectomy in certain animals - rats and rabbits was not fatal, fully one half of such herbivorous animals surviving with no effects except a diminished resistance to infection. It was found that in the rapidly fatal cases with tetany the <u>parathyreoids</u> had been removed along with all the thyreoid, and Gley and others proved that if the parathyreoids were removed also in herbivora they also die with symptoms like the carnivora.

Moussu, Gley, Vassale and Generale performed experiments which showed a marked difference in the results of thyreoidectomy - cachexia thyreopriva and parathyreoidectomy - tetania parathyreopriva. Vincent and Jolly believe the parathyreoids may be completely removed in some cases with impunity.

Some still maintain that the parathyreoids are merely underdeveloped thyreoid tissue because after thyreoidectomy colloid-containing vesicles have been found in the parathyreoids, and probably the functions of the two organs are correlated in some way, as may be also the anterior and posterior lobes of the pituitary, the cortex and medulla of the suprarenal - it seems unlikely that such close and constant anatomical

relationship should have no relation to function.

Further experiments on the parathyroids suggest that the function of the parathyroids is to neutralise certain toxic substances in the blood, products of metabolism.

Paton says:- "the parathyroids control the metabolism of guanidin in the body by preventing its development in undue amounts." Macallum showed there was a definite toxic substance in the blood in cases of tetany, because by bleeding and infusion of normal salt solution he so diluted the toxin as to cause the tetany to disappear. Injection of parathyroid causes the tetany to disappear but does not prevent death. Macallum and Voegtlin find in both animals and human beings that the ingestion or injection of calcium salts restores the normal condition, the toxins formed therefore seem to be related to insufficiency of calcium in the blood. Ethel M. Luce finds that deficiency of calcium in the diet give rise to hyperplasia of the parathyroids.

ADRENAL BODY

Brown Séquard in 1856 showed that removal of the <u>adrenal bodies</u> is followed by death either in a few hours or after 2-3 days with great prostration, muscular weakness and marked diminution of vascular tone. These symptoms are present in the condition known as Addison's disease in man which is often found to be associated with pathological changes - tuberculous foci in the suprarenals.

In the exceptional case where death does not follow extirpation of the adrenals it has been found that accessory cortical bodies were present sufficient to maintain life. Addison had published his results in 1855.

In the elasmobranch group of fishes the cortex and medullary tissues of the adrenal are separate anatomically - the cortical tissue - three layers of cells as arranged in higher vertebrates and most distinct in man - is represented by the single

intermal body or cortical gland, which lies on the vertibral column between the kidneys and between the chains of sympathetic ganglia. Accessory cortical bodies may be present in all even the higher vertibrates. The medullary tissue - the so-called chromaphil or chromaffin tissue because all these cells show a yellow or brown colour after treatment with potassic bichromate is represented in these fishes by paired bodies lying on each side of the vertibral column associated with the sympathetic ganglia. In mammals groups of chromaphil cells are found in the abdomen, in some, for instance the dog, a long abdominal chromaphil body lies along the aorta (Vincent), and these cells are also found inside the sympathetic ganglia - the paraganglion cells of Elliott. It has been thought that there was no physiological connection between the cortex and medulla, and that their coming together gradually anatomically in the course of phylogeny was not associated with any function. Braner, however, in 1919 in some interesting experiments on the effect of exposure to cold in mice has shown by the old osmic vapour method, which he uses, that the cortex does take some part in the functional activity of the medulla - the zona reticularis is seen swollen and its cells contain black droplets [not yet proved to be adrenalin but which are not fat or lipoid] Braner believes that in mammals the two portions of the suprarenal in conjunction with the thyroid have something to do with regulation of body temperature and this function would be acquired by the higher warm-blooded animals, while absent in fishes etc.

In 1896 Oliver and Schäfer injected extract of the medulla of the suprarenal intravenously in animals and noticed the very marked change which occurred - great rise of blood pressure associated with slowing of the heart

beat done to action on the cardio-inhibitory centre as this effect was eliminated by cutting both vagi.

The active substance was given the name of adrenalin or epinephrine.

Langley showed that adrenalin acted on plain muscle supplied by the sympathetic part of the autonomic system of nerves, and that it produced exactly the same effect on muscles glands etc. as electrical stimulation of the sympathetic nerve. Elliott showed that the drug acted at the myoneural junction. The initial work on the isolation of adrenalin was done by Abel and it was finally isolated in a pure state by Takamine and Aldrich independently. Aldrich got the formula $C_9 H_{13} NO_3$ and later Stolz and Dakin demonstrated the chemical structure to be dioxyphenyl-ethylol-methylamine $C_6 H_3 (OH)_2 CHOH - CH_2 NH CH_3$.

The oxyphenyl group suggests that it is probably derived from tyrosin. It is a crystalline substance with definite colour reaction, basic, easily oxidised in alkaline solution to a substance which has lost its characteristic physiological effect. It has been prepared synthetically.

Dreyer in 1899 proved that the production of adrenalin was increased by stimulation of the splanchnic nerve, probably the gland is regulated by definite secretory fibres. There is little doubt that sensory stimuli of various kinds, pain, strong emotional excitement in anger or fear and asphyxia cause reflex stimulation of the gland so that it is supposed by many that the reflex vaso-constriction in such conditions is secondary to outpouring of adrenaline into the blood. At any rate it has been shown that the cells of the medulla are exhausted of secretion after asphyxia, anesthesia etc., in the "hungry" dogs of Stilling, after ether and after Bernard's piqûre of the medulla oblongata. Braun affirms that depletion of adrenal medulla occurs in

acidosis, after haemorrhage and anesthesia as well as after bacterial infections.

Cannon tested the venous blood from the adrenals in animals after great excitement and found that it stopped contraction of a piece of isolated intestine, and when exposed to oxygen lost this power (as adrenaline does) whereas in the resting state this blood had no such effect, and there was no effect after excitement if the adrenals had first been removed. This calling forth of adrenalin in response to excitement - the "emergency theory" - is widely believed in, but Stewart and others still oppose it, as after extirpation or denervation of all medullary substance the life and health of the animal does not seem to affected.

The proofs for an internally secreting function for the medulla of the suprarenal are complete. Braun especially has given histological evidence of secretion in the cells. Carlier saw deeply staining granules in the cells of the medulla and similar granules in the venous sinuses either singly or in clumps, masses described known masses in the blood vessels of the suprarenal and small highly refractive colourless granules in the adrenal vein of a dog. Hultgren and Andersson believe they can observe the passage of characteristic granules through the endothelium of the blood vessels. Some writers claim to recognise these granules as adrenalin by their micro-chemical properties. Félicine and Biaccio found them in intercellular canals.

That the venous blood from the adrenals contains adrenaline is proved physiologically by its action on the blood pressure when injected intravenously, by dilatation of the pupil of the excised eye of a frog - Meltzer; by contraction of the ring of arteries, Meyer; and by relaxation of strips of intestine, Cannon - Boskin. It is difficult to prove that

adrenaline is present in the general circulation as probably its amount is so minute and excess above the normal is probably quickly destroyed perhaps by oxidation - [Biedl Innere Sekretion 1913]

It is as yet impossible to prove an internal secreting function for the cortex. Histologically there are seen doubly refractive lipoid granules in the cells which may or may not be the true forerunner of the secretion or they may merely be deposited there, as in the "glandless adipose tissue" the "lipoid gland" which in many animals surrounds the adrenal body (Cramer). The injection of extracts of the cortex is without definite effect.

Biedl removed the cortical body in lower fishes and found it followed by progressive muscular weakness and death. Crowe and Wislocki 1914 believe the cortex not the medulla to be the part essential to life.

There is some association between the cortex and sexual glands. It is hypertrophied during pregnancy and shrinks noticed increase in its weight in the male during breeding season. Feeding the cortex to young animals affects the growth of the testis. Histological changes have been noticed by various people in the adrenals at the different phases of sexual life or following castration.

In young people growths which affect the cortex only and apparently diminish its function are followed by precocious development of the sex organs while later in life of females similar growths cause loss of female sexual characters.

There seems to be some relation between the suprarenal bodies in disease and the thymus because in several cases of Addison's disease, thymus enlargement was found and other evidences of the "status lymphaticus"

CAROTID BODY

Haubauer described the carotid body in 1786, it had been observed long before by different writers. Andersch first called it "ganglioium intercaroticum" Mayer rediscovered it in the 19th century. Luschka called it the "glandula carotica" as he found it was not similar to the sympathetic ganglia as had been thought. Stilling discovered that some of its cells stain brown with potassium bichromate; this was confirmed by Kohn who called it the paraganglion intercaroticum. It is agreed now that this little body belongs to the chromaphil tissues.

The coccygeal body discovered by Luschka in 1860, described as "glomus coccygeum" by Schumacher is probably a kind of safety valve in the peripheral circulation, producing no internal secretion.

PITUITARY BODY

Pituita, or the secretions of the mucous membrane of the nose was one of the four primary humours and Galen, Vesalius etc supposed it to be derived from the pituitary gland.

Viessens and Sylvius believed that it was concerned in the formation of the cerebro-spinal fluid.

In 1672 Lower disproved the old theory of Galen and showed that the secretion of the pituitary "distils not upon the palate but is poured again into the blood and mixed with it."

Magendie believed it was a species of lymph gland which collected the cerebral lymph and poured it into the circulation.

For many years it was believed to be a vestigial organ, until attention was drawn to its physiology by the discoveries of Marie 1888-89. on acromegaly and pituitary tumours - here again as in the case of the adrenals and Addison's disease clinical observations were the starting point of the study of the physiology of a ductless gland.

In the development of the pituitary body or hypophysis a pouch of buccal ectoderm - Rathke's pouch - becomes from the posterior wall of the pharynx becomes associated with a downgrowth from the floor of the 3rd ventricle of the brain. From the buccal ectoderm the epithelium of the anterior lobe is formed and also the epithelium which invests the posterior lobe and is called pars intermedia. The posterior or nervous lobe retains its association with the floor of the third ventricle.

The activity of extracts of the posterior lobe of the pituitary was discovered by G. Oliver and Schäfer by intravenous injection. As with adrenalin the heart rate is slowed and the blood pressure raised but the effect is not so great and is more prolonged than that of adrenalin [Howell 1898, Schäfer and Vincent 1899.] A depressor substance which is also present causes some discrepancy in the results at times. The extracts have a stimulating effect on involuntary muscle causing contraction and increase of tone specially on the muscle of the uterus, and also on certain glands, stomach glands, kidney causing diuresis, and on the mammary gland producing an increased flow of milk - probably this is only an apparent increase of secretion & is due to contraction of the involuntary muscle fibres in the gland squeezing out the milk, for pituitary does not cause an increase in the amount of milk in twenty-four hours. There is acceleration of rate of flow of cerebro-spinal fluid, and of metabolism generally specially of carbohydrates, glycosuria being caused by acceleration of glycogenolysis in the liver. A similar result follows injection of adrenalin [Cash and Scott 1910-11 and Weed and Cushing 1915]

In 1908 Herring stated his belief that the colloid material seen in the posterior lobe is formed by the epithelium of the pars intermedia, the cells of the latter

migrating into the pars nervosa and there becoming degenerated and hyaline and being discharged into the cerebro-spinal fluid in the third ventricle.

Dixon 1923 has found the cerebro-spinal fluid of normal animals to act upon the uterus etc. like extracts of posterior lobe of pituitary and this action to be increased after administration to the animal of ovarian extracts - he therefore believes that the pituitary pours its internal secretion into the cerebro-spinal fluid - it must be remembered however that experiments on isolated involuntary muscle are always liable to error.

Evans and Rooney on the action of extracts of pituitary remark:- "It is true that these extracts produce a contraction of the uterus. Seeing, however, that the effect is procurable by extracts obtained from bulls and steers, to deduce from the action of the extract the part played by the normal gland in the living bull or steer, is a somewhat embarrassing problem." No decisive results follow injection of the anterior lobe of the pituitary.

With regard to removal of the pituitary, it has been agreed since Paulesco's work that complete hypophysectomy is a fatal operation, the animal dying in several days after showing fall of temperature, unsteady gait, rapid emaciation and diarrhoea. Removal of anterior lobe alone is fatal, whereas removal of the posterior lobe is followed by polyuria and disturbance of carbohydrate metabolism, tardy formation of sexual organs or eunuchism and increase of fat formation - these effects are probably due to loss of the pars intermedia as it is difficult to remove the pars nervosa alone.

In the clinical observations it is difficult to separate the effects due to the different lobes but it is agreed that pressure on the hypophysis by a tumour etc., and therefore probably gradual diminution of the function of the organ causes obesity

sexual infantilism and increased tolerance to carbohydrate - all effects of the hysterior lobe. Deficiency of the anterior lobe gives rise to disturbances of growth and metabolism in young animals. Hypertrophy of the anterior lobe, which is presumably in a state of hyperactivity is found in cases of acromegaly - a curious disease characterised by overgrowth of the skeleton especially the bones of the face, hands and feet in adults, while in young people gigantism results from the overgrowth of all the long bones as well [Cushing 1912 and Goetsch 1916.

Cannon and Rowson 1914 and Bailey and Brewer 1921 believe that many of the effects which were supposed to follow damage to the pituitary, are really due to lesions in the base of the brain - the opto-hedunicular region and the tuber cinereum, where they believe regulation of water retention and of carbohydrate metabolism to be situated. Even the "adiposo-genital syndrome" they transfer from the pituitary to some point in the base of the brain. If these experiments are repeated with the same results, our ideas of the function of the pituitary will be revised, so that the hysterior lobe extracts only retain their potency on blood pressure, uterine muscle etc.

Pituitary extract given by the mouth to normal people is said to retain its diuretic action but has no other effect. Some helpful action is claimed for it in cases of hypo pituitarism.

THYMUS

There is doubt as to whether the thymus produces an internal secretion or not. Schäfer looks upon it merely as a lymphoid structure concerned in the production (or destruction) of morphological constituents of the blood like the lymph glands and spleen.

Injection of extracts of the thymus causes a fall of blood pressure Svehla, which however is not a specific action.

There is probably some connection between this organ and the thyroid, as it is enlarged and presumably over-active in many cases of exophthalmic goitre.

Basch found that removal of the thymus in young dogs caused a mal-development of the bones resembling rickets and increased excitability of peripheral nerves to galvanic stimulation.

It was found that thymectomy on dogs under ten days old caused increased fat formation at first and later atrophy and underdevelopment of bone, asthenia and mental deterioration.

It is agreed now that the thymus does not atrophy as was supposed after the second year of life in the human being but persists into the prepubertal period and gradually atrophies after puberty.

Henderson found that castration caused persistent growth and retarded atrophy of the thymus. Paton believed that removal of the thymus hastened the development of the testes, and in association with this it is interesting to note that Gudernatch found that tadpoles fed with thymus showed excessive growth and delayed metamorphosis - giant tadpoles being formed (c.f. thyroid produces dwarf frogs)

It must be stated however that Park and McClure got negative results from thymectomy after careful experiments.

Klose and Vogt believe the thymus is concerned in the processes of synthesis of nucleic acid.

PINEAL BODY

The <u>pineal body or epiphysis</u> has a glandular structure which reaches its greatest degree of development about the seventh year and the nuclei especially after puberty to fibrous tissue and calcareous concretions - "brain sand" appear in it in some cases even in early life. About the stage of amphibia, the pineal body reached the surface of the head and certainly functioned as a third eye.

Early work on the pineal body was done by Howell, 1898. Intravenous injection of extracts shows the body to contain a depressor substance.

Ott and Scott found a galactogogue action similar to but not so great as that of pituitary but their results were not confirmed by Schäfer and Mac Kenzie.

Sarbeschi in 1910 destroyed the gland by the cautery with negative result. It has been observed that invasion of the pineal body by growths in children causes accelerated development of the reproductive organs mental precocity and increased growth of the skeleton. Pellizzi "macrogenito-somia-praecox" therefore some infer that it produces a secretion which inhibits growth and retards development of the reproductive glands. This is not supported by experimental evidence total extirpation of the epiphysis in animals gave no decisive results (Dandy)

Feeding experiments were first tried by Kidd in 1913. Dana and Berkeley got some increase in weight in some animals but not in children.

The pathology has been studied by Marburg cysts and teratomata occur and Hempel describes carcinoma.

ISLETS OF LANGERHANS

In 1889-90 Langerhans described the "islets" of a different tissue which occurs in the pancreas. They are originally developed from and may retain their connection with the secretory ducts of the gland but their cells have developed a specific property and possess a separate blood and nerve supply.

Von Mering and Minkowski in 1889 showed that complete extirpation of the pancreas in animals is followed by all the signs and symptoms of diabetes mellitus in man - sugar in the urine even when carbo-hydrate is omitted from the diet, polyuria with increased excretion of urea, thirst and hunger, acetone in urine, emaciation, muscular weakness and death in 2-4 weeks.

They also showed that if a small fraction - less than one fifth of the pancreas be left behind though it have no connection with the duodenum, or if a portion of pancreas is grafted under the skin or in the peritoneum of a depancreatised animal, or if the pancreatic ducts are ligatured or blocked with paraffin, these signs and symptoms of diabetes do not appear and the animal survives.

Schäfer suggested that the internal secretion of the pancreas was produced in the "islets" of Langerhans and it was he, in 1916, who gave the name of "insulin" to the as yet not isolated substance secreted by the islets.

Sobolew in 1902 and Homans in 1914 showed that the islets do not atrophy as does the rest of the pancreas after ligature of the ducts and insulin has been extracted from such a pancreas after atrophy of the tubules, and also from the islet tissue of certain fishes in which this tissue is separate anatomically-

from the pancreas.

In the pathology of diabetes mellitus in man Opie, Sobolew and Herzog and others have found signs of disease in the islets of Langerhans, hyalin degeneration or atrophy or complete absence in severe cases. Pratt, however, in 1910 found the islets unaffected in diabetes.

Some believed that the islets are really a stage in the development of the secreting alveoli, Dale 1906 Vincent and Thompson 1906, Bensley 1912

Lagnesse and Vincent and others have seen increase in the islets as the result of inanition but Bensley does not agree with this.

Allen observed granules in the resting cells of the islets which disappeared on feeding with carbo-hydrate by the histology of the secretion is as yet indefinite.

Banting and Macleod found that "insulin" had the power of reducing the blood sugar when injected beneath the skin in animals and this result is now used in the treatment of diabetes by insulin. Insulin is prepared by fractional alcoholic extraction of the pancreas - it has not yet been obtained in a state of purity, it is dialysable and is probably formed from amino-acids. Injected in the proper dosage and with adjustment of diet, rest etc, both hyperglycaemia, glycosuria and ketonuria are prevented.

It was suggested that insulin is a kind of enzyme necessary for the hydrolysis or oxidation of sugar in the body, but this is denied by Macleod and Pearce 1913 and Verzar 1914 who show by experiments that the tissues of a depancreatised dog are still able to take up sugar

from the blood circulating through them -- whether it is further metabolised in the tissues is another question.

Others say that the hyperglycaemia is produced by the loss of the regulating power of insulin on the glycogenolysis of the liver.

Zuelzer assumes that adrenalin and insulin between them regulate this function, so that if insulin is absent adrenalin causes increased glycogenolysis. It is said that hyperglycaemia does not occur in a depancreatised dog if the adrenal veins are ligatured. Probably, however, the connection of the internal secretions with the carbohydrate metabolism is not so simple as this - thyroid and pituitary extracts also cause hyperglycaemia. Rojima working on the histology of the islet finds changes in the staining reactions of their cells in rats on feeding with posterior lobe of pituitary.

Cramer and Krause 1913 found that thyroid feeding inhibits the formation of glycogen in the liver, and thyroidectomy is said to produce an increase in the ~~anterior~~ amount of islet tissue in the pancreas.

LIVER

Claude Bernard in 1855 was the first to describe and name the glycogenic function of the liver as an internal secretion - it is generally agreed nowadays not to regard this function as a secretion but rather as a special arrangement for storing carbohydrate and releasing it again into the blood but the function is intimately related to the internal secretions of the pancreas and the adrenal medulla and other ductless glands.

SECRETIN

Experimentors on the gastric secretions noticed that the

rush of acid gastric contents into the duodenum, or painting the mucosa of the first part of the duodenum with dilute acid caused a flow of pancreatic juice, but this was supposed to be due to a reflex nervous mechanism.

Bayliss and Starling in 1902 extracted the epithelium of the duodenum by boiling with dilute hydrochloric acid, and, after neutralisation, injected it into the blood stream of an animal, when a rapid flow of pancreatic juice was observed.

Therefore an internal secretion must be formed by the action of acid on the mucosa of the duodenum which is absorbed into the blood and conveyed to the pancreas which it activates.

Bayliss and Starling called this substance "secretin", and its forerunner which is produced in the cells of the mucosa - pro-secretin so that pro-secretin + acid = secretin. They believe that pro-secretin is produced by the ordinary cells of the mucous membrane not by any specialised cells.

REPRODUCTIVE ORGANS :- TESTIS

It has been known from time immemorial that the generative glands had to do with the development of sexual characteristics. Castration of animals and of men in oriental lands has always been practised and it was of course noticed that removal of the testicle prevented the development of the accessory male generative organs such as the prostate, that the infantile condition of the hair and voice was retained, while the growth of the skeleton might be increased producing gigantism.

Berthold in 1849 gave the first experimental proof of the internal secretion of the testis when he transplanted it into the intestine after castration and showed that the animal developed normally. His results were lost however till Bidel brought them forward again in 1913.

Steinach (1912) performed the same experiment transplanting the testis to other parts of the body in young animals and found full sexual development occurred as in normal animals, and in the grafts he found that although the germ cells or spermatogonia had disappeared there were little groups of cells - called the interstitial cells of the testis, described by Leydig - surviving and these cells he called collectively the "puberty gland".

It was found that if the vas deferens was ligated the germ cells died but these interstitial cells remained and even increased in number.

It has been pointed out that these cells are grouped about the blood vessels suggesting a process of internal secretion. They develop very early in embryonic life before the differentiation of the germ cells also from the epithelium of the germinal ridge. Throughout life they are liable to form tumours.

Rasmussen states that in some animals these cells show cyclical changes, being reduced in number

during liberation. Their secretion appears to be of a lipoid nature.

Recently K. M. Walker asserts that the interstitial cells of Leydig are trophic rather than secretory and that the internal secretion of the testis is produced in certain cells (of Sertoli) in the tubules.

The action of extracts of the testis was investigated by Brown Séquard in 1889-92. He found that hypodermic injections caused a stimulation of the nervous system, increased activity of the spinal centres improved mental and physical vigour especially in cases of prostration, neurasthenia and in old age.

Poehl even isolated a substance which he called "Spermin" and to which he gave the formula $C_5H_{14}N_2$ which was supposed to be a powerful physiological tonic.

Zoth (1896) and Pregel gave proofs of the stimulating action of testicular extracts on the neuro-muscular apparatus in man by the ergograph, the lessening of subjective fatigue being a noticeable feature, and suggesting the interference in all such results on man of the psychological element of suggestion.

OVARY

When the ovaries are removed before puberty the female characters do not develope and complete ovariotomy in women causes symptoms exactly comparable to those of the menopause, complete stoppage of menstruation, atrophy of the uterus and vagina and external genitals, and the various nervous and mental changes of the climacteric are often more marked in these cases as the change is so sudden.

Halban 1901 transplanted the ovary in rats and found the menses returned. This was performed in the human female by Morris and Glass 1899 and 1901.

Marshall and Jolly (1905) found that grafting a piece of ovary from another animal anywhere in the body restored the cyclical condition of "heat"

Steinach grafted ovary into castrated males and found that both ova and interstitial cells survived and the animal was evidently completely feminised.

Marshall and Jolly found that extracts of the ovaries of an animal in or just before "heat" (proestrum or oestrum period) injected into an animal during the anoestrum bring on a transient condition of "heat"

Schäfer believes that the internal secretion of the ovary has an inhibitory function - it prevents the development of male characters, because as Knox has shown in birds when the ovary is removed the hen becomes in outward appearance and apparently in mental characteristics a cock - flaps her wings, crows and behaves like a cock to other hens. If a part of the ovary is now transplanted the restraining influences are restored and the male characters disappear.

The effect of the removal of the ovary on metabolism has been in many cases a laying on of fat and increase in weight of the body.

Loewy and Richter experimenting on dogs in 1899 found that removal of the ovary was followed after several weeks by diminution in the consumption of oxygen. On giving ovarian tablets (ovarian extract) the amount of oxygen taken in increased to above normal, and these extracts had a similar result on castrated males so they believe the ovary contains a specific substance capable of increasing the oxidations of the body.

CORPUS LUTEUM

It is now agreed that the <u>corpus luteum of the ovary</u> supplies an internal secretion which regulates the fixation

of the ovum in the uterine mucosa, and perhaps prepares the decidua to receive it or makes it more sensitive to the mechanical stimulation of the ovum. In the early months of pregnancy removal of the corpus luteum causes abortion after the formation of the placenta, its removal has no effect.

Fraenkel's hypothesis (1903) is that if pregnancy does not occur after an ovulation the decidua formation caused by the internal secretion of the corpus luteum is abortive and menstruation occurs - this is a scientific explanation of the old theory that "women menstruate because they do not conceive". Marshall and Runciman 1914 do not agree with this as they find that ovulation (and the commencement of growth of the corpus luteum does not occur till after "heat" has begun.

Utt and Scott (1911 & 1912) suppose the corpus luteum to have some effect on the growth of the mammary gland during pregnancy.

There is a debate as to whether the luteal cells are developed from the tunica interna of the Graafian follicle (von Baer) or from the membrana granulosa (Bischoff & Sobotta) If the former be correct they are of connective tissue origin from the mesoblastic layer of the embryo which is not usually associated with secretion.

But miss Lane-Claypon believes that the tunica interna itself is formed from the germinal epithelium and not the connective tissue of the ovary.

TERUS

Goltz and Rein cut all nerves going to the uterus in dogs and found they could become pregnant and give birth to young; similarly later (in 1894) Mirowa showed that the mammary gland became functional in the ordinary way after delivery even when completely cut off from its nervous supply

MMARY

LAND

Basch in 1910 observed that when one of the Blazek sisters, who were twins with a common circulation and separate nervous systems, became pregnant the mammary glands of both functioned.

Basch in 1903 found the secretory nerves of the mammary glands, and it is well known that the secretion of milk may be altered by emotional shock, epileptic attacks etc. acting through the nervous system.

Starling and Jane-Clayton (1906) extracted the bodies of foetal rabbits and injected the extract into a virgin rabbit and found it caused gradual development of the mammary glands as in pregnancy while extracts of ovary and uterus had no effect.

They believe that there is a hormone in the foetus itself which causes the glands to grow and when it is withdrawn by the birth of the young a catabolic process is induced which leads to the formation of milk, and the milk flow is stopped if a new pregnancy begins.

Utt and Scott (1911-12) found extracts of post-pituitary and of corpus luteum also have a stimulating effect on the mammary gland.

The onset of labour is probably also due to internal secretions probably from the foetus or the placenta - the increasing metabolism of the foetus producing a substance which stimulates the uterus and yet there must be a connection with ovarian hormones too, because the tenth menstrual period after conception is the commonest time for delivery to take place and when abortions occur, they are found to be most frequent at the times of the missed menstrual periods.

Healy and Kastle (1912) suggest that a hormone from the mammary gland initiates labour.

INTERRELATION OF INTERNAL SECRETIONS

The idea of the interrelation of the internal secretions is of course an old one – as old as the humoral theory and the "consensus partium". Starling suggests that this means – the chemical – of coordinating the activities of the various parts of a complex organism may be regarded as the most primitive, while the better known coordination through the medium of a nervous system is of later development. Certainly in the one cell stage of life coordination must have been a chemical process but it is not far up the tree of animal life – Ciliata – the highest Protozoa before the first attempts at nerve fibres appear in the body – it may quite well be, however, that these fibres are merely hollow tubes for conveying an active chemical substance.

Noel Paton (1913) is very sure of the interdependency of the internal secretions. He says:– "A certain minimum amount of each seems to be essential, and some proportion between the amounts of each must be maintained if the metabolism is to continue in its normal course ... Such a conception is more in accordance with the facts which we possess than that of a series of hormones or excitors calling forth the activity of the various tissues."

The internal secretions have been compared to a Cabinet of ministers, each with his own particular duty in the government – Finance, Defence, Foreign affairs etc and presided over by a Premier – the Organ of Reproduction probably in the case of the body. There may even conceivably be Ministers without portfolio.

EFFECT OF REPRODUCTIVE ORGANS

Blair Bell says that gonad fatigue is made up for by overactivity of the thyroid and pituitary and certainly the thyroid is often visibly

enlarged in pregnancy, and at the menstrual periods especially just after puberty when the menstrual flow is not quite established. At the menopause there are signs of decreased thyroid activity.

In pregnancy the "chief" cells of the anterior lobe of the pituitary increase in size and number and never again return to the virgin state thereafter.

The cortex of the suprarenal is also hypertrophied during pregnancy.

The effects of castration on many of the ductless glands is noteworthy.

CARBOHYDRATE METABOLISM

Another function of the interrelated endocrine organs is in carbohydrate metabolism - the thyroid suprarenal medulla and post-pituitary seem to be ranged against the islets of the pancreas and the glycogen function of the liver itself was looked upon by Claude Bernard who discovered it and by others as an example of internal secretion.

PIGMENTATION

The pigmentation of the body is another interesting study in relation to internal secretions.

It is stated that the pigment in addisons disease is melanin formed because tyrosin cannot be converted into adrenaline owing to the insufficiency of chromaffin tissue.

The pigmentation of the breasts etc., in pregnancy may have some connection with the general upheaval of endocrine metabolism which occurs then.

RACIAL CHARACTERS

Keith in the "Lancet ii 1919" suggested that racial characters may depend on the relative development of these organs.

COLLOID

An interesting point in the biochemistry of the endocrines is the frequency with which we find colloid in these glands, thyroid, parathyroid, pars intermedia and pars nervosa of pituitary (Vincent)

IPOID

The metabolism of fats and lipoids in the body seems to be affected by several ductless glands and many have cells showing appearances which suggest that their secretion is lipoidal:- adrenal cortex, parathyroid, interstitial cells of testis and ovary and corpus luteum.

ROWTH

Growth seems to be affected by thyroid thymus anterior-pituitary as well as by the sex glands.

ODY
EMPERATURE

The regulation of body temperature - a very difficult subject and one with an important bearing probably on the resistance of the body to disease, the formation of antitoxins etc has been shown by Brown to have some relation to the adrenals and thyroid.

NFECTIONS

The relation of the ductless glands to various infections has been pointed out, for instance except the testis (and suprarenals) it is very rare for these organs to be attacked by the tubercle bacillus [Mills]

EOPLASMS

They are being taken into account by the Cancer Research Committee, however, and result as yet- many of these organs are subject to new growths like other tissues - thyroid adenoma, suprarenal (one form of hypernephroma is still believed to be from cortical "rests") and pituitary.

YCHOLOGY

Psychologists claim the endocrines to account for many of the mental diseases or symptoms, which is not strange when we observe the great mental changes which accompany pathological conditions of these bodys. Graham-Brown describes the typical appearance of Grave's disease of the thyroid as "crystallised fright"

Hypersecretion of the adrenals would prepare an animal either for flight or for fight - Langdon Brown - the muscles get a good supply of blood, the processes of digestion and movements of the stomach and intestine ceasing, and the

blood pressure rises, and of sugar to be used in violent exertion.

If it be true as some psychologists have believed that the physical signs of anger etc must precede the mental feeling - that is we feel angry or afraid <u>because</u> our gorge rises or our knees tremble, - then indeed Endocrinology is at the basis of psychology as well as of physiology.

SSIBILITIES FUTURE

Much research has yet to be done on the relation of the endocrines to the phases of sexual life. especially puberty, the monthly cycle in women, and the menopause, probably a better knowledge of how the internal secretions normally interact would enable us to prevent many abnormalities and to cure many cases of "functional nervous disorder", visceral neuroses and the like. Many of the disorders of pregnancy also will be curable when its physiology is better understood - already we know that removal of the ovaries cures osteomalacea and that foetal and placental extracts affect the mammary gland through the blood.

It may be observed that the lower animals in eating up the placenta and membranes after parturition may be instinctively dosing themselves with some hormone which is intended to be helpful in the puerperium.

NOMENCLATURE

The history of the nomenclature of this subject requires a paragraph to itself as a good deal of time has been spent by the investigators in disagreeing about it, which is scarcely wonderful when their fundamental ideas of the meaning of internal secretion are so different.

The term "internal secretion" was introduced by Claude Bernard about 1855 but the idea was familiar to physiologists before that time. Brown Séquard extended the meaning of the name because he believed that all organs and tissues give off something to the blood which is of importance in general nutrition.

In 1905 Starling introduced the term hormone (to stir up or excite) for the actual substance secreted in the process of internal secretion and this word is most generally used. Bayliss would have preferred a word implying "chemical messenger" and Schäfer suggests this would have been better expressed by hormone (Mercury-the messenger)

Gley in 1911 proposed the name of harmozones (to govern or regulate) for these substances which regulate the chemical process of the body. He further divided them into three groups:- 1, those helping in nutritive exchanges, 2. those serving to maintain the composition of the blood and lymph 3, those having a morphogenetic function and he wished to restrict Starlings word-hormone for definite functional excitants such as adrenaline, while he suggested par-harmone as a suitable term for CO_2 and other waste products of metabolism whose excitory function is secondary.

Starling himself used the word hormone in its

widest sense. In 1914 he says:- "By the term hormone I understand any substance normally produced in the cells of some part of the body and carried by the blood stream to distant parts, which it affects for the good of the organism as a whole."

Schäfer in 1915 tried to confine the use of the word hormone to substances with a definitely excitatory function, and he suggested the word "chalone" (to relax or make slack) for those internal secretions which inhibit the chemical processes etc in the organs on which they act, and to include both hormones and chalones he introduced the term antacoid substances (from "self" & "a medicinal agent or remedy") pointing out as did Starling the close similarity between many of these substances and the organic alkaloid drugs, their comparatively simple chemical structure (unlike enzymes) that they produce no antibodies in the body and some definitely stimulate cells e.g. secretin on the cells of the pancreas, while others depress or inhibit - e.g. extract of placenta inhibits the secretion of milk.

His definition is as follows:- "An antacoid is a specific organic substance formed by the cells of an organ and passed from them into the circulating fluid to produce effects upon other organs similar to those produced by drugs as excitation by excitory antacoids or hormones and inhibition by inhibitory or restraining antacoids or chalones." Unfortunately for the subdivision antacoids, like drugs, sometimes excite one tissue and depress another, therefore adrenaline for instance is both a hormone and a chalone and its action in some tissues depends on the dose (in the lungs Hoskins 1922)

"Endocrine" (within, to separate) is a term much used at the present day. "Incretion" is the opposite of excretion not of "secretion" and therefore is not very suitable

Matthews uses a non-committal term "cryptorrhetic"

(hidden, to flow) which expresses very well the exact state of our knowledge of the processes in question at the present time.

GANOTHERAPY With regard to the history of Organotherapy or the therapeutics of the endocrine glands it really began when Hippocrates, Celsus and Dioscorides each in his time advised the use of the various organs taken from animals the to supply the deficiency of these organs in disease :- the wolf's liver for hepatic disease, the brain of the hare for tremors and so on (Vincent quotes Batty Shaw) and in modern times some of the attempts made in opotherapy have had quite as little experimental justification, such as giving extracts of heart muscle hypodermically for heart disease.

A. E. Gow [Feb 25th 1924] states the present position of organotherapy :- "Glandular extracts which have a definite action when given by the appropriate route are thyreoid, parathyreoid, pituitary, pancreas and adrenal; extracts of intestinal glands given by the mouth in cases of atonic constipation may be helpful. But of these, thyreoid and pancreatic alone afford true substitution therapy. There is no evidence that any extract other than thyreoid and parathyreoid is absorbed as such from the alimentary tract; adrenaline, for example is only employed by the mouth as an astringent or to inhibit peristalsis in the stomach in cases of haematemesis and vomiting, but no "substitution effect" in Addison's disease is obtainable by feeding with or injection of the gland."

NCLUSION In conclusion we may quote the words of Harvey Cushing in 1921 :- "We find ourselves embarked on the fog-bound and poorly charted sea of endocrinology. It is easy to lose our bearing, for we have, most of us,

little knowledge of sea-faring and only a vague idea of our destination. Our motives are varied; some unquestionably follow the lure of discovery; some are earnest colonizers; some have the spirit of missionaries and would spread the gospel; some are attracted merely by the prospect of gain and are running full sail before the trade winds."