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

Welcome Medal in the History of Medicine.

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Synopsis

The Humoral Theory in Early Medicine - Hippocrates, Galen.
The Schools - humours and the "element" - Ruther.
Anatomic of melancholy.

The Renaissance in Science - anatomy, physiology.
Secretion - Malpighii, Miller; - Ductless glands and their secretion, Carpenter; Old ideas of internal secretion and the "Consensus Pantheum" - Border.
Lagalle - Berthold, first experimental proof.

Modern History - Claude Bernard - Brown-Squard.
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, Pancreas.
Adrenal bodies, hormone body (cerebral body), Pituitary body, Hypothym, Pituic Body, Islets of pancreas.

Interrelation of Internal Secretions - coordination - Starling.


History of human relative

History of Organotherapy - opotherapy.

Conclusion.
He knew the cause of every ill malady,
were it of heat or cold, or moisture, or drugs,
and where engendered, and of what humours
He was a veriey perfect practiser.

Chancer 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 concomitants and by their expulsion by the natural passage.

It is interesting to trace this theory through the whole of the early history of medicine, and the various criteria of it and the theories which arose in opposition in the "solivisit" or "Pneumatic" schools, and the additions to it at various times, of metaphysical and supernatural conceptions—the vital "spirits" of the Romans—the astrology of the Middle Ages. Since the philosopher of old both all knowledge as his study he must make some attempts 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 rationalize and explain his cures by including the vital mixture 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 deposits of bile.

In Hippocrates treatise "The Ancient Medicine", the theory of humors is fully elaborated, 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 doctines. He recognized four "emote" humors, blood, phlegm, yellow bile and black bile and he held the belief that in the natural process of recovery from disease the humors 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 force 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 prenasce or shield 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 Asklepiadean and Aetnian schools adopted the humoral theory with the doctrines of Hippocrates and Galen, and although it was opposed the "atomist" theory of Anaxagoras, as upheld by Lucretius in "The Rheaume Natura", the pneumatic and celestial schools, and later the theory of the microcosm and macrocosm of Plato, 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 constitution of the universe became quite compatible with the humoral theory in medicine. The four properties hot, cold, wet and dry were recognized at the beginnings of chemistry and physics - Milton in Paradise Lost 13 ii 898 sees them as 'endless was in Chaos'.

"for heat; cold, moist and dry; four characters fierce, Strive here for mastery, and to battle bring Their empyrean atoms."

Philosophers 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 now divided up in a similar manner among the humors of the body - blood was hot and moist, phlegm or phlegma cold and moist, choler ( bile) hot and dry and melancholy (black bile) cold and dry.

The terminology of the humors passed into common language [Dr Johnson has no less than nine definitions for the word humors 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 Some people told them to sleep, and of the nerves, of mind or character as well as of bodily diseases.

"An exact balance of the four primary humors makes the justly constituted man", and allows for the undisturbed production of the concordia or process of digestion and assimilation and of those excreenturition humors of the 3rd concordia sweat and tears. A good summary of the properties and origin of the humors is the four
in Burton's "Anatomy 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 therapeutic, it is scarcely to be wondered at, that at the present day its revival in the scientific form of endocrinology shared much with such ready belief, and honours taking the place of the old humors 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 humors, overcrowned 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 pituitary gland as the possible site of the soul. About this time also anatomists were setting out in order their ideas about secretion, previously any connexion solid body of white organs was called "gland." But Malpighi in 1665 observed the minute elementary parts of glands - the acini, he had not yet seen with his microscope that these acini were composed of cells.

Rumphius in 1696 injected the blood vessels of glands and Keller following him also believed that all glands were simply tubes of blood vessels of which the smallest lanced a secretion directly into the ducts of the gland.

It remained for Johannes Muller to prove that the secreting...
cases in all glands from 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 secretory 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 exercised upon certain materials by the blood by the spleen, thymus, and thyroid glands and represented capsules (which are sometimes collectively termed vascular glands) --- "the vascular glands" exactly correspond with ordinary glands in all but part of their structure by which they withdraw or eliminate certain matters from the blood; and they differ only in being supplied with secretory ducts for the discharge of the product 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 adhesion to the parts of the nutritive function."

The idea of internal secretion is probably older than these observations. A probably incorrect quotation (Vieuss) attributes it 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" (Stewarv). Théophile de Boveri in "Analyse médicale du sang" 1775 looks upon each organ as the source of a "chimäre particulière" which exerts its influence on the body generally. Heberer and Biedell maintain that Boveri's view indicated a new clearer conception of internal..."
secretion. However, that may be Morley's view was not generally held until the year 1832. Burzynski stated that the correlation of different organs and tissues of the body — the "consensus partium" of older writers — depended on the nervous system.

Legallais in 1801 wrote on the relationship of the secretion of all glands to the venous 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.

Bertillon 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 cockerels. Bertillon concluded from this that the testes affect the whole organism through the blood, as he believed. Moreover, he the nervous system also has a part in the "consensus partium." Bertillon’s work was largely overlooked till Biedl brought it to light in his "Nature Selénica" 1911.

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 intérieure" for the passage of glycogen from the liver cells into the blood, as opposed to the "secretion extérieure" of bile from those cells into the bile duct. Bernard stated clearly that certain glands, like the spleen and lymphatic glands, the thyroid and suprarenals produce an internal secretion. Léonard de la Grange, physiologist, and the alterations pathologiques des liquides de l'organisme 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 nerves, ruining the body because the nervous system, which is believed to be the nervous and not sensory.

Bartet 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 Bartet's statement in 1852 but more 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 Steinberg 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 salt. 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 generalization.

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 experimentation 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, myxoeft and cretinism, and their cure by grafting, injecting or feeding thyroid; the connection
Methods of Determining Function

The chief methods which have been used in determining the function of the endocrine 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 excision on animals.  
   (b) accidental — by disease or by operation on man (as in the case of removal of the parathyroid along with the thymus by Del. and Swiss surgeons).

2. Administration of the gland or its extracts
   (a) external 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 even get into the blood.  
   (b) intravenous — normal and intermittent injection was the method used by Brown-Séquard in 1889 and since by Budge and others for submaxillary and pituitary extracts.  
   Intravenous administration has been used, injections by the lungs, and also isolated organs have been infused with or mixed in the extracts.
   (c) Intravenous injection was first used by Wohlfahrt and Schäfer in 1894.
3. Study of the effects of autotransplantation of the section of the gland in the body, by stimulation of its new site implantation (grafting method used by Haber in 1909), the result being overgrowth and hyperplasia, a hypersecretion of the anterior lobe of the pituitary, hyperthyroidism etc.

PROOF OF INTERNAL SECRETION

In order that any tissue may be definitely proved to produce an internal secretion, firstly, these must be histological evidence that the cells are secreting cells; secondly, some special chemical substance must be found in the lymphatic 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 - [e.g., if adrenaline, adrenalin, histamine or choline, is present in many organs and tissues and causes a fall of blood pressure when injected.]

It is not always practicable to prove that a substance fulfils all these principles. If removal of the tissue shall cause definite symptoms, while if one 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. Bell found in 1849 proved the internal secretion of the testis by this method, and this condition is fulfilled by the thyroid and parathryoid, but the second condition above has not been satisfied as yet, whereas the radicles of the suprarenal satisfy all these postulates, but an animal appears to be able to live without the presence of this secretion in the blood.

HISTORY OF

Galen and the other early writers supposed that the thyroid body protected the delicate cerebral cord region by acting as a sort of elastic framework, 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 thyroid body is present in all vertebrates, and it appears early in the development of the embryo and is connected by a duct with the pharynx. In amphibians and amniotes, this duct usually persists. Probably this early connection with the alimentary canal accounts for the good results of internal 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 thyroideectomy in dogs was usually fatal after 1 to 4 weeks, the symptoms being muscular tremors and convulsions, cachexia, and a condition described as absolute atrophy. Surgeons noticed that thyroideectomy performed for goitre in some cases was followed by convulsive attacks in others by chronic subsitution. About the same time, Cullen described five cases of "cachexia state in the adult." In 1874 Bodin in 1877 called this condition myxoedema and found changes in the thyroid surrounding tissue found the thyroid atrophy in cachexia, blepharochalasis, and myxoedema associated with atrophy of the thyroid.

Graaff, after thyroideectomy and noticed that the symptoms disappeared. This result suggested the use of thyroid for cachexia and myxoedema in man and immediate success followed its administration.

Later studies were made 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 Baermann isolated from the gland a substance rich in iodine, 9.3% of dry weight. It is in combination with proteins and can be extracted by digestion with gastric juice or boiling with acids. This substance was found to produce the same effects on starvation as extracted or dried gland
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In 1856 Schiff showed that complete thyroidectomy in dogs was usually fatal after 1-6 weeks, the symptoms being muscular tremors and convulsive contractions of the muscles of respiration. Surgeons noticed that thyroidectomy performed for goitre in some cases was followed by convulsive attacks in others by chronic malnutrition. About the same time.*

The two conditions of cretinism in children and myxedema in adults began to be associated with atrophy or underdevelopment of the thyroid. In young animals when the thyroid was removed a condition of underdevelopment resembling cretinism occurred while in grown animals thickening and dryness of the skin developed but not true myxedema as in man.

Schiff and others grafted pieces of thyroid into the backs of animals after thyroidectomy and noticed that the symptoms disappeared. This resulted suggested the use of thyroid for cretinism and myxedema in man and immediate success followed its administration.

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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 substances, or an inorganic
substance bound and made innocuous by thyroid cells.

In 1919 Kendall isolated a crystalline compound of iodine which he called thyroxine—
a derivative of tryptophane.

Cameron observes that thyroxine has, for its wide action,
appearently less effect than dried thyroid quantitatively, only
a quarter of the effect [Reid, 1913]. There must then be
some other active principle.

Thyroid secretion has not been found in the blood
and injected extracts cause no marked effect on circulation,
perfusion secretion; etc. Prolonged administration of
thyroid extracts produces marked effects on metabolism,
causing it to the extent of causing symptoms like those
of neurotrophic goitre or other thyroid diseases due to hyperthyroid
ism. Tumours fed on thyroid stop growing and
metabolism takes place—dwarf frogs being the result.

Andersdorn 1913. 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.

Jangendorff 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 Brownsey who finds that
the Golgi apparatus moves from one pole of the cell to
the other during secretion activity, by Bensly who believes that the activity of these cells is reversed so that they pass their secretion into the blood capillaries instead into the vessels, and recently Ullmanson and Pearce have described a network of tubes 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.

Thyroid

It was early found that discrepancies occurred in the results of extirpation of the thyroid, sometimes the animal died quickly with convulsions—lactation at other times slowly or inaniation, and it was found that complete thyroidectomy in certain animals—roosters 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 lactation the parathyroids had been removed along with all the thyroid, and Gley and others found that if the parathyroids were removed also in herbivora they also die with symptoms like the carnivora.

Mowson, Gley, Vassal, and general perfused spleen, which showed a marked difference in the results of thyroidectomy—cachexia thyreopriva and parathyreoidectomy—lactasia parathyreopriva. Vincent and Goley believe the parathyroids may be completely removed in some cases with impunity.

Some still maintain that the parathyroids are merely underdeveloped thyroid tissue because after thyroidectomy colloid containing vesicles have been found in the parathyroids, 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 supraren—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 parathyroid is to neutralize certain
basic substances in the blood, products of metabolism.

Rats show: “The parathyroid controls the metabolism
of glycogen in the body by preventing its development
in undue amounts.” Macallem showed there was a
definite toxic substance in the blood in cases of tetany,
because by bleeding and injection of normal salt
solution he so diluted the toxic as to cause the tetany
to disappear. Injection of parathyroid causes the tetany
to disappear but does not prevent death. Macallem and
Vegelin find in both animals and human beings that the
injection or injection of calcium salt restores the normal
condition; the toxic formed therefore seems to be related to
insufficiency of calcium in the blood. It is in these facts
that deficiency of calcium in the diet give rise to
hypophosmia of the parathyroids.

Brown Seaward in 1856 showed that removal of
the adrenal bodies is followed by death, either in a few hours
or after 2-3 days will 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 in the nervous and
In the exceptional case where death does not follow
ablation 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 elementary group of glands the cortex and
medullary tissue of the adrenal are separate autonomically
the cortical tissue—three layers of cells as arranged in higher
vertebrates and more distinctly in man—is represented by the single
interrenal body or cortical gland, which lies on the vertebrae column between the kidney and between the chains of sympathetic ganglia. Accessory cortical bodies may be present in all even the lower vertebrates. The medullary birtie - the so-called chromophil or chromaffin tissue because all the cells show a yellow or brown color after treatment with potassium bichromate is represented in those fish by paired bodies lying on each side of the vertebral column associated with the sympathetic ganglia.

In mammals groups of chromophil cells are found in the abdomen in the more anterior the dog, along anterior of the adrenal body lie 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. However, in 1919 in some interesting experiments on the effect of adrenalin on urine he showed by the red-onyx vapor method, which he used, that the cortex does take some part in the functional activity of the medulla - the zona reticularis is seen smaller and its cells are rich in droplets [not yet proved the adrenalin but which is not fat or lipoid] Graves believes that in mammals, the two portions of the suprarenal in conjunction with the thyroid had something to do with regulation of body temperature and this function would be acquired by the higher warm-blooded animals, while absent in fish etc.

In 1896 Oliver and Schaffer injected extract of the medulla of the suprarenal into animals and noticed the very marked change which occurred - great rise of blood pressure associated with slowing of the heart.
been close to action in the cardio-inhibitory centre as this effect was eliminated by cutting both vagi. The active substance was given the name of adrenaline or ephedrine.

Langley showed that adrenaline acted on brain nerves supplied by the sympathetic part of the autonomic system of nerves and that it produced exactly the same effect as reserpin, ergotoxin etc, as electrical stimulation of the sympathetic nerve. Elliott showed that the drug acted on the myoneural junction. The initial work on the isolation of adrenaline was done by Abel and it was finally isolated in a pure state by Takeda and Abderhalden independently. Abel fixed the formula C_{9}H_{13}NO_{3} and later Stöber and Fabre demonstrated the chemical structure to be dimethylamylmethylaniline C_{6}H_{3}(OH)_{2}CHOH - CH_{2}NHCH_{3}.

The dimethyl group suggests that it is probably derived from tyramine. It is a crystalline substance with definite color reaction, basic, easily oxidized in alkaline solution to a substance which has lost its characteristic physiological effect. It has been prepared synthetically.GGLEn in 1899 proved that the production of adrenaline is increased by stimulation of the hypophysis, probably the gland is regulated by definite secretory fibers. There is little doubt that arousing stimuli of various kinds - pain, strong emotional excitement in anger or fear and sympathic nerve reflex stimulation of the gland so that it is increased by many that the reflex ves- constriction in such conditions is secondary to bringing of adrenaline into the blood. At any rate it has been shown that the cells of the radicle are adventitiously secretory after ethyl alcohol, chloroform etc, in the 'hungry period of Stillig, after ether and after Bernard's pithing of the radicle oblongata brama appears that deflection of cranial radicles occurs in.
andoxin, after lavandenate and amethan as well as after local anaesthetics.

Cannon tested the venous blood from the adrenals in
animals after great excitaments and found that it stiffened
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 real
effect, and there was no effect after excitement of the
adrenals had just been removed. This calling
forth of adrenaline in response to excitation—the
"emergency theory"—is widely believed in, but interest
and others still oppose it, as after stimulation or
denervation of all mediatory substance the life and
health of the animal does not seem to affect.

The proof for an internally secretory
function for the "nudules of the suprarenal adrenals"

Cannon especially has given histological evidence
of secretion in the cells. Barlow saw deeply staining
granules in the cells of the "nudules" and similar granules
in the venous sinus, either singly or in clumps, these
seem to be brown masses in the blood vessels of the suprarenal
and more highly refractive colorless granules in the adrenals
vesicle of a dog. Hultgren and Anderson believe they can
observe the passage of characteristic granules through the
endothelium of the blood vessels. Some writers claim to
recognize these granules as adrenaline by their micro-
chemical properties. Félixco and Bisceco found them
in intercellular canals.

Yet the venous blood from the adrenals contains
adrenaline is proved histologically by its action on the
blood pressure when injected intravenously, by dilatation of
the pupils of the rectal eye of a frog—Hultgren, by contraction
of the wing & arteries, Hegyi, and by relaxation of strips of
intestinal, cannon & roeckin. It is difficult to prove that
adrenaline is involved in the general circulation as probably its amount is 20 minute and mere above the normal is probably quickly destroyed. However, by oxidation [Biede, Hone Schretter 1913]

It is as yet impossible to prove an internal secretory function for the cortex. Histologically there are near doubly adrenergic lified organs in the cells which may or may not be the true presursors of the reaction or they may merely be depots. They are in the glands, adrenocortical tissue, the "hyper gland" which in many animals surrounds the adrenal body (Brone). The injection of starch of the cortex is without definite effect.

Biede removed the cortical body in lower pigs and found it was followed by progressive nervousness and death. Brone and Vigeschi 1914 believe the cortex was the weakness that the part essential to life.

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

In young male growth which affects the cortex, as and apparently diminishes its function are followed by precocious development of the sex organs, while late in life of females minor growth cause loss of female sexual elements.

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 evidence of the 'status lymphaticus'.
Humbert described the carotid body in 1786. It had been observed long before by different writers. Andersen first called it "ganglion caroticum" Mayer rediscovered it in the 19th century. Luschka called it the "ganglia caroticum." As he found it was not similar to the sympathetic ganglia as had been thought. Stillmagn discovered that some of its cells stain brown with potassium dichromate; this was confirmed by Köhn who called it the paraganglionic intercarnicin. It is agreed now that this little body belongs to the chromaffine tissues.

The carotid body discovered by Luschka in 1860, described as "agens congezans," by Schumacher is probably a kind of safety valve in the peripheral circulation, producing an intense sensation.

Pituita, or the secretion of the nervous adrenaline of the nose was one of the four principal humours and Galen, Vesalius etc supposed it to be derived from the pituitary gland. Virensus and Sylvius believed that it was concerned in the formation of the cerebro spinal fluid.

In 1642, Zöllner disproved the old theory of Galen and showed that the secretion of the pituitary "diffils not upon the palate but is forced again into the blood and mixed with it."

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

For many years it was believed to be a vestigial organ, until attention was drawn to it physiology by the discovery of Marie 1888-89. In amenorrhea and pituitary tumours, there again as in the case of the adrener 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 portion of neural ectoderm — Rathke's pouch — becomes from the posterior wall of the pharynx. Becomes associated with a derangement from the flow of the 3rd ventricle of
the brain from the neural ectoderm. The epithelium of
the anterior lobe is formed and also the epithelium which
lines the posterior lobe and is called pars intermedia.

The posterior or median lobe retains its association with
the flow of the third ventricle.

The activity of anterior and posterior lobe of
the pituitary can be divided by ultras and solutes by
intensive injection, as with adrenalin the least rate is
plotted out and the blood pressure raised but the effect is not
so great and is not prolonged then that of adrenalin
[Howell 1898, Schiefl and Vincent 1897]. A depressor
influence which is also present causes some disinterest
in the variety of tests. The actions have a stimulating
effect on involuntary muscle causing contraction and
increase of tone especially on the muscle of the uterus,
and also on certain glands, stomach glands, kidney causing
diuresis, and on the hormones gland producing a normal
flow of milk. Probably this is only an apparent increase
of reaction, it is due to contraction of the involuntary muscle
plus in the gland squeezing out the milk. For pituitary
does not cause an increase in the amount of milk in
nearly four hours. Yore is acceleration of rate of flow
of cerebro-spinal fluid and metabolism generally,
especially of carbohydrates, glycogen being caused
by acceleration of glycogenolysis in liver. A similar
result follows injection of adrenalin [Ditt and Scott 1910-11
and Weed and Brodie 1915].

In 1905, Henning 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 par nervous and there becoming degenerated and liquefied and being discharged into the cerebral-spinal fluid in the third ventricle.

Since 1923 has found the cerebral-spinal fluid of normal animals to act upon the urine, etc. like extracts of posterior lobe of pituitary and this action to be increased after administration to the urine of ovarian extracts - he therefore believes that the pituitary from its nature secretes into the cerebral-spinal fluid - it must be regarded however that ovarian and pituitary conditions are always likely to occur.

Barnes and Krogsby on the action of extracts of pituitary remark - "It is true that these extracts produce a contraction of the uteri. 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 lives of bulls or steers is a somewhat unsatisfactory 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 Ponsford's work that complete hypophysectomy is a fatal operation, the animal dying in several days after showing high fever, extreme thirst, retching, diarrhea, and death. Removal of anterior lobe alone is fatal, whereas removal of the posterior lobe is followed by languor and disturbance of carbohydrate metabolism, tend to function of sexual organs or locomotion, and masses of fat formation. These effects are probably due to loss of the pars intermedia so it is difficult to remove the pars intermedia alone.

In the clinical observations it is difficult to separate the effects due to the different lobes but it is agreed that presence of the hypophysis by a tumor etc., and therefore probably gradual diminution of the function of the organ cause obesity.
sexual interlude and increased tolerance to carbohydrate meals effects of the posterior lobe. Dependence of the anterior lobe gives rise to disturbances of growth and metabolism in young animals. Hypoactivity of the anterior lobe, which is presumably in a state of hypometabolism, is found in cases of acromegaly, a curious disease characterized by overgrowth of the skeleton especially the bones of the face, hands, and feet in adults, while in young lizards gigantism results from the overgrowth of all the long bones as well. [Bushby 1912 and Gestel 1916.]

Garens and Roussey 1914 and Bailey and Brain 1921 believe that many of these effects which are supposed to follow damage to the pituitary, are really due to lesions in the base of the brain— the optic—peduncular region and the tuber cinereum, where they believe regulation of motor secretion and of carbohydrates metabolism take place. Even the "adipose—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, one idea of the function of the pituitary will be revised, so that the posterior lobe extinct only retain their rooting as blood former, and—

Pituitary extract given by the mouth to normal lizards is said to retain its diuretic action but has no other effect. Some helpful action is claimed for it in cases of hyperpituitarism.
There is doubt as to whether the thymus produces an
internal secretion or not. Schiøtz looks upon it merely as a
lymphoid structure concerned in the production (or destruction)
of morphological constituents of the blood like the lymph gland
and spleen.

Injection of extracts of the thymus causes a pile of
blood plasma to swell, which however is not a specific action.

There is definitely some connection between this organ
and the thyroid, as it is removed and permanently resected in many cases of goiter and cretinism.

Bass found that removal of the thymus in young
dogs caused a rapid development of the bones resembling
vicious and increased susceptibility of peripheral nerves to
galvanic stimulation.

It was found that thymectomy in dogs made 10 days old
causd increased fat formation at first and later atrophy
and underdevelopment of bone, anemia 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
atrophy after puberty.

Henderson found that cortisone 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 Gershon found that tadpoles fed with thymus
did not develop eviscerate growth, and delayed metamorphosis—tadpoles being formed (cf. thyroid produces dwarf frogs).

It must be stated however, that Vanne and Bachelier
get negative results from thymectomy after careful
experiments.

Kline and Vogt believe the thymus is concerned in
the processes of synthesis of nucleic acid.
The priapal body in Chilomyctes has a glandular structure which needs it greater degree of development about the seventh year and the urochilus especially after puberty. Fibrous tissue and calcification connate the "nem rod" appears in it in some cases, but in early life. About the stage of Amphibiæ, the priapal body reached the surface of the head and certainly functioned as a third eye.

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

Witt and Scott found a galactozogogue action similar to but not as great as that of pituitary but their results were not confirmed by Sheil e and Mac Kenzie.

Sarvesshi in 1910 destroyed the gland by the cautery with negative result. It has been observed that invasion of the priapal body by growths in children caused accelerated development of the reproductive organs, mental precocity, and increased growth of the skeleton. Pellizzi, "macrogênito comum," 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 ablation of the chilomyctes in animals gave no definite results (Dandy).

Yeasting's experiment was 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 Harding cysts and teratoma occur and Heindel describes carcinoma.
In 1889-90, Langhans 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 form a separate blood and nerve supply.

von Mering and Minkowski in 1889 showed that complete section of the pancreas in animals is followed by all the signs and symptoms of diabetes mellitus in man—sugar in the urine and blood, etc. Glucose is omitted from the diet, polyuria with increased excretion of urine, thirst, and hunger, acetone in urine, emaciation, muscular weakness, and death in 2-4 weeks.

They also showed that if a small portion—less than one fifth of the pancreas—is left behind though it has no connection with the duodenum, or if a portion of pancreas is grafted under the skin or in the peritoneum of a depancreatized 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.

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

Skolew in 1902 and Moomans 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 islets transplanted to certain sites in which this tissue is separate from others.
from the pancreas.

In the pathology of diabetes mellitus in man Upisie, Soboless and Kerszeg and others have found signs of disease in the islets of Langerhans. Lysideic degeneration or atrophy or complete absence in severe cases. Pratt, however, in 1910 found the islets unaltered in diabetes.

Some believed that the islet as really a stage in the development of the secreting alveoli. Late 1906, Vintine and Thompson 1906, Bensley 1912.

Laquesse and Vintine and others have seen increase in the islets as the result of inflammation. But Bensley does not agree with this.

Allen observed granules in the resting cells of the islet which disappeared on feeding with cori-o-glucides by the histology of the secretion is as yet indefinite.

Banting and Macleod found that 'insulin' had the power of lowering 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 dialyzable and is probably formed from amino-acids. Injected in the proper dosage and with adjustment of diet, rest, etc., both hyperglycemia, glycosuria and ketonuria are prevented.

It was suggested that insulin is a kind of enzyme necessary for the hydrolysis or oxidation of sugars in the body, but this is denied by Macleod and Pearce 1913 and Verzar 1914, who show by experiments that the toxicity of a dipharm-creatid that is still able to take up sugars
from the blood circulating through them... whether it is further metabolized in the tissue is another question.

Others say that the hyperglycaemia is produced by the loss of the regulating hormone insulin in the glycogenolysis of the liver.

Zondek assumes that adrenaline and insulin rather than regulate this function so that if insulin is absent adrenaline causes increased glycogenolysis. It is said that hyperglycaemia does not occur in a fasting state or if the adrenal vein is ligatured. Probably, however, the connection of the internal secretion with the carbohydrate metabolism is not so rigid as this. Thyroid and pituitary extracts also cause hyperglycaemia. Kojima working on the histology of the islet finds changes in the staining reactions of their cells in rats on feeding with protamine; also of pituitary.

Bravo and Krauss 1913 found that the thyroid feeding inhibits the function of glycogen in the liver, and thyroideectomy is said to produce an increase in the anterior annex of islet tissue in the pancreas.

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 secretion of the pancreas and the adrenal medulla and other ductless glands.
most of the 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.

Bayles and Stanford in 1902 extracted the
epithelium of the duodenum by boiling with dilute
hydrochloric acid, and, after neutralization, injected
it into the blood stream of an animal, when a
reflux 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 secretes it.

Bayles and Stanford called this substance
"secretin," and its foreunner 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 specialized cells.
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 practiced and it was of course noticed that removal of the testes prevented the development of the secondary male generative organs such as the prostate, the seminal vesicles, the hair and voice were 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 testes when he transplanted it into the intestine after castration and showed that the animal developed normally. His results were lost however the Brandt brought them forward again in 1913.

Stetmarck (1912) performed the same experiment transplanting the testis to other parts of the body in young animals and found that 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 Zondek—surviving and these cells he called collectively the "maturity gland."

It was found that if the testis of a woman was ligated the germ cells died but the 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 foetal life before the differentiation of the germ cells also from the epitheliun of the gemmial 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 stimulation. Their secretion abounds the of a
a fluid nature.

Recently K. H. Walther asserts that the identically
cells of Leydig are epithelioid rather than secretory and
that the internal secretion of the testis is produced
in certain cells (Sertoli) in the tubule.

The action of extracts of the testis was investig-
ated by Brown-Séquard in 1889-92. He found that
hydrostatic injections caused a stimulation of the
nerve system increased activity of the spinal center
improved mental and physical vigor especially in
cases of impotence, senility, and in old age.

Pohl later isolated a substance which he called
"Phermin" and to which he gave the formula C_{11}H_{10}N_{2}
which was supposed to be a powerful physiological
tonic.

Zöll (1896) and Pregel gave proofs of the
stimulating action of testicular extracts on the nerve-
nerve reflex arcs in man by the ergographic, the
examination of subjective pains being a noticeable feature
and suggesting the interference in all such results
on man of the psychosomatic element of perception.

When the ovaries are removed before puberty
the female characteristics do not develop and complete
atavism in women causes symptoms exactly comparable
to those of the menopause, complete atrophy of
reproduction, atrophy of the uterus and vagina and
external genitals, and the various nervous and mental
changes of the climacteric are the more marked in
these cases as the change is no sudden.

Hallam in 1901 transplanted the ovary in dogs and
found the ovaries returned. This was performed in the
human female by Lemb's 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".

Sterilized grafted ovary into castrated male and found that both somatic and interstitial cells survived and the animal was evidently completely feminized.

Marshall and Jolly found that extracts of the ovary of an animal in or just before "heat" (proportion or action period) injected into a animal during the andromyrmic stage in a transient condition of "heat".

Schiffer believes that the internal secretion of the ovary has an inhibitory function—its prevents the development of male characters, because as has been done in birds when the ovary is removed the hen becomes in outward appearance and affectively in mental characteristics a cock—flaps her wings, crowing and behaves like a cock to other hens. If a part of the ovary is now transplanted the remaining influences are restored and the male character dissolves.

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

Loewy and Hilger experimenting on hares in 1889 found that removal of the ovary was followed after several weeks by diminution in the consumption of oxygen. By giving oophoron 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 oxidation of the body.

It is now agreed that the corpus lutenum of the ovary supplies an internal secretion which regulates the function
of the ovum in the uterine mucosa, and perhaps prevents the decidua to receive it or makes it more resistant to the mechanical stimulation of the ovum. In the early weeks of pregnancy removal of the corpus luteum causes abortion after the formation of the placenta. It remove does no effect.

Fraenkel's hypothesis (1903) is that if pregnancy does not occur after ovulation, the decidua formation caused by the uterine secretion of the corpus luteum is abortive and reabsorbed or occurs. This is a scientific explanation of the old theory that "women menstruate because they do not conceive." Marshall and Runzheimer (1914) do not agree with this as they find that abortion and the conversion of growth of the corpus luteum does not occur the after "luteolysis 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 lutein cells are derived from the tumenic internal of the Graafian follicle (von Baer) or from the neurematic grandula (Bischoff & Soelotte). If the former be correct they are of connective tissue origin from the neurematic layer of the embryo, which is not usually associated with secretion.

But Miss Lane-Clayson believes that the tumenic intestine itself is formed from the germinal epithelium and not the connective tissue of the ovary.

Goltz and Reim cut all nerves going to the uterus in dogs and found they could become pregnant and give birth to young; similarly later (in 1894) Minow showed that the mammary gland became functional in the uterine way after dehiscence even when completely cut off from its nervous supply.
Bosch in 1910 observed that one of the Blaschke sisters, who were twins with a common cervix and separate nervous systems, became pregnant but the mammary glands of both functioned.

Bosch 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.

Stapley and Lane-Clayson (1906) injected the bodies of foetal rabbits and injected the testicle into a virgin rabbit and found it caused gradual development of the mammary glands in pregnancy while injection of ovary and uterus had no effect.

They believe that there is a hormone in the foetal body 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.

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

The onset of labour is probably also due to internal secretion, probably from the placenta or the decidual - the menstrual metobolism of the foetus produces a substance which stimulates the uterus and yet there must be a connection with ovine hormones too, because the tenth menstrual period after conception is the common time for delivery to take place and when abortion occurs they are found to be most frequent at this time of the missed menstrual periods.

Healy and Kaster (1912) suggest that a hormone from the mammary gland initiates labour.
The idea of the interrelation of the internal secretions is of course an old one - as old as the binomial theory and the "consensus partition." 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 so-called stage of life coordination must have been a chemical process but it is not far up the tree of animal life - Bacteria - the highest Protococc 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 interdependence 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 relationship is to continue in its normal course... such a conception is more in accordance with the fact which we possess than that of a series of hormones or secretions called 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. These may even conceivably be ministers without portfolio.

Blair Bell says that general fatigue is made up for by over-activity of the thyroid and pituitary, and certainly the thyroid is often visibly
enlarged in pregnancy, and at the menopause 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 hyperplastic during pregnancy.

The effect of contraction on many of the ductless glands is noteworthy.

Another function of the interrelated endocrine organs is in carbohydrate metabolism. The thyroid gland, parathyroid gland, and pituitary seem to be antagonistic to the insulin of the pancreas and the glucagon function of the liver. It is itself a hormone upon which Claude Bernard was founded on by others in an example of internal secretion.

The pigmentation of the body is another interesting study in relation to internal secretion. It is stated that the pigment in Addison's disease is melanin formed because tyrosine cannot be converted into adrenaline owing to the inapparent change of chromatin tissue.

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

Keith in "Journ. 1917" suggested that racial character may depend on the relative development of these organs.

An interesting point is 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 (Virchow).
The secretion of fats and lipids in the body seems to be affected by several different glands and many lining cells showing appearance which suggest that their secretion is lipoidal—adrenal cortex, parathyroid, intestine's cells of tissus and many and corpus lutenum.

Growth seems to be affected by thyroidal thyrops anterior—pituitary as well as by the sex glands.

The regulation of body temperature—a very difficult subject and one with an important bearing possibly on the resistance of the body to diseases, the pituitary's antitoxic activity has been shown to have some relation to the adrenal and thyroid.

The relation of the ductless glands to various infections has been pointed out. For instance, muscletissue, skin, and other organs are subject to new growths like other tissues—thyroid, adrenals, submaxillary (as from Pancreas), etc., is still believed to the present contains "rare" and pituitary.

Psychologists claim the endocrines to account for many of the mental disease or symptoms, which is not strange when we observe the great mental changes which accompany pathological conditions of the body. Adrenals—true adrenal, described the thyroids and thymus—true complexness of the adrenals would prepare our mind for flight or for fight. Lemoine Brown the muscles get a good supply of blood, the processes of digestion, and saturation of the stomach and intestine casing, and the
blood pressure rises, and if anger take place in return reaction.

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 because our gorge rises or our knees tremble - then indeed endocrinology is at the basis of psychology as well as of physiology.

Much research has yet to be done on the possibilities of the endocrine 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 disorders" sexual cancer, and the like. Many of the disorders of pregnancy also will be curable when the physiology is better understood - already we know that removal of the ovaries, even after maladies and that placenta and placental extract affects the mammaries gland through the blood.

It may be observed that the lower animals in eating up the placenta and membranes after parturition may be instinctively doing themselves with some hormones which is indicated the helpful in the menstruation.
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. Bunsen thought 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 now generally used. Bayliss would have preferred a word implying "chemical messenger" and Schüller suggests this would have been better expressed by hemoone (mercury-the messenger).

Glyy in 1911 proposed the name of hormonones (to govern or regulate) for these substances which regulate the chemical processes 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 role in genetic function, and he wished to restrict Starling's word hormone for definite functional excitants such as adrenalin while he suggested para-hormone as a suitable term for CO₂ and other waste products of metabolism whose sanitary function is secondary.

Starling himself used the word hormone in its
widest sense 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."

Schulze in 1915 tried to confuse the use of the word hormone to substances with a definitely secretory function, and he suggested the word "chalone" (to release 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 antecedent substance (from itself as "an antecedent agent or reagent") pointing out to this similarity between many of these substances and the organic alkaloid drugs, their constructively similar chemical structure (while engaged that they produce no antibodies in the body and are definitely stimulants e.g., secretions in the cells of the pancreas, while other depress or inhibit e.g. extract of placenta inhibiting the reaction of blood.

His definition is as follows: "An antecedent is a specific organic substance found by all the cells of an organ and passed from them to the circulating fluid to produce effects on other organs similar to those produced by drugs as stimulation by stimulating antecedents or homines and inhibition by inhibiting or restricting antecedents or chalones.

Unfortunately for the subdivision of antecedents, like drugs, sometimes excite or tissue and depress another, therefore adrenalin for instance is both a hormone and a chalone and its action in some cases depends on the dose (in the lungs)," (Hartings 1922)

"Endocrine" (within to separate) is a term much used as the present day. "Incretion" is the opposite of secretion, and "secretion" and therefore is not very suitable. Matthews use a non-commital term "cryptosthetics."
(hidden to flow) which expresses very well the exact state of our knowledge of the processes in question at the present time.

SANDOTHERAPY

With regard to the history of organotherapy or the therapeutics of the endocrine glands, it really began with Hippocrates, who, and his successors, each in his time advised the use of the various organs taken from animals, due to supply the deficiency of these organs in disease: the wolf's liver for hepatic disease, the brain of the horse for tremors, and so on. (Veinage, quoted Batho Shaw) and in modern times some of the attempts made in organotherapy have had quite as little experimental justification, such as giving extracts of beard roots phytochemically for heart disease.

A. F. Gow [Feb 25th, 1924] states the present position of organotherapy: “Glandular extracts which have a definite action when given by the appropriate route are thyroïd, parathyroïd, pituitary, pancreas and adrenal; extracts of intestinal glands give by the mouth in cases of atomic constipation may be helpful. But if these, thyroïd and pancreas, alone upset the substitution therapy. There is no evidence that any extract other than thyroïd and parathyroïd is absorbed as such from the alimentary tract: adrenaline, for example is only employed by the mouth as an antithyroid or to inhibit peristalsis in the stomach in case of hemorrhage and vomiting, but no "substitution effect " in Addison’s disease is obtained by feeding with an injection of the gland.”

CONCLUSION

In conclusion we may quote the words of Harvey cushing in 1921: “We find ourselves embarked on the fog-bound and hoary 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 line 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."