"History of the Development of our Knowledge regarding Scurvy"
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1. Ancient Medicine

Physiology was one of the weak points of ancient medicine. It could hardly be otherwise. Dealing as it does with the processes of the living organism, and depending even more than the other branches of medicine on advance in physical and chemical science, physiology could not but be late in the world's history in securing a firm foundation for itself. And what is true of physiology in general, holds good with even greater truth of the knowledge of secretion. The fact that there are certain juices in the body, the product of certain organs, was of course recognized in the ancient world. But the true nature of these products, the method of their production, the functions which they played in the human economy were almost totally misunderstood by the ancients. Of speculation and theory regarding these secretions there was abundance; but of patient observation of their true nature or action there was very little. We can in fact hardly say that the foundations of our knowledge regarding secretions were laid until comparatively modern times, and the doctrines which until that time held sway, acted far more as deterrents from the truth than as helps toward it. When we compare the attainments made by the ancient world in surgery, or clinical medicine,
or materia medica, with the poor results reached in Physiology, we cannot but be struck by the contrast.

And yet the history of Physiology in the ancient world is full of interest. Men could not help speculating about the processes they saw going on in the human body. The various fluids which they saw circulating through the body, or exuding from its pores, or expelled from its interior, must, they knew, have an important part in carrying on the functions of life. What they were, where they acted, was very difficult to explain. But it seems probable that on these depended in great part the health and efficiency of the human body, perhaps even more the dispositions, tendencies of the human soul. Hence, however little these ancient speculations may have done for science, their influence on human language, thought, metaphor has been immense. They fixed attention else on the fluid secretions of the body as being more important, more directly concerned with the mystery of life, than the solid parts. After death, the solid parts of the body were little changed at first. The fluid parts, on the other hand, underwent an immediate transformation. This it seemed as if life, with the qualities of life, were linked on to the fluids of the body. This is an aspect in which the ancient theories of secretion may be said to have found their counterpart in the most recent views regarding secretion. We now know that the number of secretions in the body is far greater than used to be thought; they
are far more intimately concerned with the varied metabolism
of the body than is even yet fully understood. In a true
manner the ancient theories were a forerunner of this.
Without having any scientific foundation, they yet laid
emphasis upon the prime importance of secretions for the
organism. By so doing they become of great interest to us.

If we now turn to the records of
ancient thought which have come down to us, we find
the earliest beginnings of physiological speculation among
the Babylonians & the Egyptians. Among both these peoples
we find the beginnings of theories which later appear
fully developed as the "humoral" theories of Greek Medicine.
Thus among the Babylonian Physicians, phlegm, bile, and
wind were considered the causes of colic & other abdominal
affections. They seem to have held the view that the body
presents, particularly the blood, constituted the foundation of
life; and it is probable that a connection with this view
is to be traced in the Babylonian myth of the creation, where
one of the gods is decapitated, this blood mixed with the
earth to make it fruitful.

Babylonian

Sciences.

Egypt.

The physiological speculations of the Egyptians took a
somewhat similar direction, influenced however, to some
extent by the natural phenomena of the Nile-land in which
they dwelt. They compared the human body to the land made
fruitful by the rising waters under the influence of the solar
warmth. The heart & the stomach were supposed to constitute
a double system in which the blood was prepared from the ingested food. Disease was due to an excess of fluids; thus, for example, hypersecretion, as in the case of long-continued discharge from inflamed eyes, was described by the Egyptians as a "rising of water to the eyes" from the heart.

Ancient Indian theories regarding the body secretion took a fairly definite formal shape. According to them, three elements permeate the body - air, phlegm, bile, and to these some of their writers add a fourth - the blood. "The air serves the purpose of movement, and is located principally below the neck. The warmest-distributing bile has its place between the neck and the heart. The phlegm, which actuates the organs, is located above the heart." Their theories were largely guided by symbolical numbers. Thus the above three elements produce the seven primary constituents - chyle, blood, flesh, fat, bone, marrow, semen. There are also seven impurities corresponding to these seven primary constituents. They taught that the chyle originates from the products of digestion, which takes place by internal fires through a sort of cooking process. It then flows by twenty-four channels from the heart through the whole body, and changes every five days into the other six constituents in succession.

Ancient Chinese medicine, like the Indian was largely formal in nature, dependent upon symbolical numbers. Their physicians taught that there were five chief organs in the body, corresponding to the five elements of the
Each organ has an assistant, they both discharge a special function. Thus the liver, which corresponds with the element wood, has as its assistant the gall bladder, both serve to filter the juices of the body. The heart, which corresponds with the element fire, has as its assistant the small intestine, both turn the food first into chyle and then into blood. Similarly it follows with its assistant the stomach: the lungs with their assistant the large intestine; the kidneys with their assistant the ureters, have each a special function to discharge. The Chinese also had the curious and interesting idea, that each of the above five organs, in addition to its main functions, also exercised an influence upon a distant part of the body—e.g. a particular part of the face, or a special tissue, through which its influence might be detected.

It is of interest to note also that the Chinese in their therapeutics made extensive use of substances of animal origin—e.g. preparations of liver, lungs, kidneys, &c., of different animals were prescribed for liver, lung, kidney diseases respectively. The semen of young men, & nerve tissues of animals were given for conditions of weakness; their gizzards for diseases of the stomach; animal testicles for impotence. The Chinese also practised moxibustion & acupuncture, with the idea of so making a passage for the stagnant pathological material which had become localized in any particular part of the body.

Only when we come to Greek medicine, do we approach what must be regarded as the main stream. In this, as in most other departments of human thought, doubtless...
Greek medicine had its springs farther back in Babylonian and Egyptian science. But it was Greek thought and speculation and research that for long dominated the thought of the world, and eventually to its own overthrow, the building up of the far greater structure of modern science.

In the time before Hippocrates we find that even then the humoral theory, in one form or other, had the foremost place in men's thoughts about physiology and pathology. Thus Chilodes, one of Pythagoras' disciples, taught that the causes of disease are misplaced bile, blood, phlegm. Inflammation arises from accumulation of phlegm. Health depends upon the maintenance of equilibrium between different qualities.

The same idea is found again in Hippocrates, who thought that the human body, in common with all bodies in nature, consisted of the four primitive substances: Earth, air, fire, water, or modifications of these; health is conditional upon their equilibrium; disease arises from their disproportion.

In Anaxagoras we find the beginnings of a theory that recurs constantly throughout later medical speculation, viz. that most acute affections are caused by bile — of which he distinguished two varieties, black and yellow — which permeate the blood and the organs.

After Hippocrates, largely as a result of his teaching, the humoral pathology took a more definite form. The number of pathological humors recognized was limited to four — viz., blood, phlegm, yellow bile, black bile — which correspond respectively to the four elements: fire, air, water, earth. To each humor...
a definite quality was supposed to be attached—viz. warm, cold, moist, dry—corresponding to the humors in the above order. This was the theory which in various forms held sway right down to modern times. It had its foundation in some degree in clinical observation. Observation showed that improvement began, fever & pain ceased on the expulsion of mucus or pus, on emetation, or diarrhoea, or on the vomiting of bitter sour fluid. Therefore they inferred that all disease was caused by altered, excess or abnormally situated humors or secretions. Secretions were to the ancient world not so much the funtitturaries of the living organism as the seat or expression of life itself & the indicators above all of a healthy or a diseased condition.

Hippocrates is in many respects worthy of his name as the father of medicine. But his reputation does not rest upon either his anatomical or his physiological attainments. He added little to our physiological knowledge. He was above all a clinician. He emphasized the necessity of studying every case individually, from a great many points of view. The age, the temperament, the facial expression, the voice, the attitude, the power of movement & sensibility to pain were all to be noted; & Hippocrates made many acute observations as to the value of such symptoms.

In his Physiology Hippocrates adopted the humoral theory. The humors, quasi secretions we must regard them, were four in number, according to the four elements; i.e. life & health were intimately bound up with them. Each humor had
a corresponding quality. The blood, originating in the heart, repre-
-sents the warm, moist quality. Gall, bile, secreted by the liver,
-represents the warm dry; black bile coming from the spleen - the
cold dry; and phlegm, formed in the brain, the cold moist. By
means of food a constant supply of material is kept up
which renewa the Cardinal fluids. Health depends upon a
normal blending of these body juices; disease is produced by
this faulty admixture, or abnormal accumulation at one or
other situation. Nature may be seen in many diseases, e.g. Pneumonia, Dysentery &c. by trying to get rid of some
"materia praecons" in the form of expectoration, vomit, black bile,
chlearose &c. Hippocrates saw three stages in this endeavours
of nature to get rid of these precon humors. There was 1st
the stage of παρεξια - the uncorked state, before the discharge began.
Then the stage of πέτρια - coagulation, while the discharge was flowing.
And finally έπαλα - solution, as seen in the gradual thinning
of the secretions in coughs. Drug treatment in aid of this
discharge was to be carried on only in the stage of πέτρια.

For Hippocrates, therefore, there were four main fluids in
the body, each one with a corresponding secretion, & each also
with a power of attracting to itself & controlling the movement
of that secretion. The heart had the warm blood; the liver
had the warm (dry) bile; the spleen had the cold (dry) black bile;
the brain had the cold moist phlegm. The cause of disease,
Hippocrates most frequently found, was excess of phlegm coming
from the brain, leading to different diseases according to the place
where it accumulated; e.g. coming to the lungs, it caused inflammation and pleurisy; if blocking the blood vessels, it caused apoplexy or convulsions; &c. &c. That was exactly Hippocrates' view of digestion; it is not easy today. But if we may judge from that expressed by Diocles, one of his school, he thought of digestion as a sort of post-aerificative process, which was promoted by the inherent warmth of the body. The waste products of the food after digestion reached the intestines & the bladder; but they were in addition supposed to be got rid of, in part, by the sweat & the exhalations from the skin.

The Alexandria School is represented by Herophilus and Erasistratus. This famous school of medicine was the first home of anatomical research. The Egyptian custom of embalming the dead provided the opportunity for anatomical study of the human body, unhindered by the odium attaching elsewhere to dissection of the human frame. New anatomical knowledge did give an impulse to physiological inquiry - as it always has done in the history of medicine. But unfortunately the advances made were only slight; & physiology as well as pathology remained a free field for speculation.

Hersophilus. Hersophilus (about 300 B.C.) remembered in the term 'mural of Hersophilus' describes the liver, bile-duct, the salivary glands, the pancreas, & the genital tracts of both sexes. According to him there were four forces governing the operations of the body - those of nourishing, warming, perceiving, & thinking - with respective seats in the liver, heart, nerves, & brain. The humoral
theory was accepted by him as the basis of his physiology, but only because nothing better was yet known.

Erasistratus (born 330 B.C.) too held a modified humoral theory. Blood is derived from food, it comes into existence in the liver. Bile is separated from the blood in the liver, thus by means of the narrow human of the bile-duets, which allowed only the thin bile to pass, but not the viscous blood. Digestion he thought of as a mechanical triturating of food through the changing pressure of the walls of the stomach. A new advance was made by Erasistratus in his effort to give a mechanical explanation of the relationship between the various glands and their humors or secretions. He rejected the idea of a specific power or attraction exerted by the various organs. He put forward instead the doctrine of the “horror vacui,” in which nourishment and growth and secretions are all brought about. Erasistratus also made a new departure by his explanation of disease as being most frequently due to plethora — the overfilling of the vessels with alimentary matter, which distorted first the veins, then "by way of the synanastomoses" the arteries, impeding the action of the pneuma in them, causing inflammation.

Asclepiades (born 124 B.C.) who practiced in Rome, proposed a new and interesting theory of digestion. He held that food-stuffs were merely subdivided in the stomach and intestines into their ultimate particles, these were absorbed into the body unaltered, as they were taken in, and distributed through the narrower of the canals (πόροι). It is probable that Celsus, who was a
friend of Asclepiades, merely reflected the views of the latter in the luminous account he gives of gastric digestion (De Nat. Rerum II. 54) "in albo multa sunt mirabilia effusa: ... est antea multiplex et totus a, arcetque et continuo sine illud aurum, ut sine huminem, quod recipit, et in manu et concaeque posuit; ea tunc astringitum, tum relaxatione, atque omnis quod accipit, cogit et compunctus atfacie et calore, quare multum habeb, et tenuis ideo, it praeclara spiritus omnis evoca atque confusa in relicium corpus dividantur."

Health, according to Asclepiades, depended on a proper proportion of the atoms in the four elements. He thus sought to explain metabolism on purely mechanical lines, by his doctrine of the absorption of the finest food particles through invisible canals; and excretion as carried on in the same manner. As other medical writers of importance appeared until we come to Galen.

In Galen (130-201 A.D.) we see the greatest figure of antiquity as far as medical science is concerned. His influence on subsequent generations was immense. For centuries his views were accepted as the indubitable truth; and as far as physiology was concerned, no advance was made on his views until the time of the Renaissance.

In Galen's physiology the four elements—fire, water, earth, and air; the four corresponding primary qualities—warm, cold, moist, and dry; and the four corresponding cardinal fluids—blood, phlegm, bile, and black bile, are all accepted from preceding philosophy. But Galen built up on this foundation a system of his own. The main spring of life is the pνευμα (spirits) which manifests itself
in the body in three forms - the πνεύμα γράσσον (spir. naturally) which has its seat in the liver & veins; the πν. γρατίκον (spir. vitalis) which resides in the left heart & arteries; and the πν. ψυχικόν (spir. animalis) which has its seat in the brain & is distributed by the nerves. Galen postulates in addition that each organ in the body has its own peculiar force, by which it attracts, fixes, transforms, or expels the various substances with which it is brought into relationship. The food, then, is received into the stomach, & there & in the intestines it receives its first digestion (chyle) assisted by warmth set from the liver. Chyle is conveyed from the small intestines to the liver, where the πν. γρατίκον performs a second digestion (haemolysis), converting it into blood. The spleen, however, presides to this exercise its activity as a purifying organ. It extracts from the nutritient the thick Earthy portions which go to form black bile - which passes by a duct from the stomach, thence into the intestines, & is evacuated with the faeces. This action of the spleen is one phase of a third digestion (haemolysis) which goes on in all the organs, by which waste material is in various ways separated & excreted from the body. The blood then goes to the right heart where it undergoes a further purification by means of the inherent warmth - the residuum escaping as smoke during expiration. It then passes by invisible pores into the left ventricle where it is perfused by admixture with the πν. γρατίκον. This arterial blood then reaches the brain by the arteries, & these generate the πν. ψυχικόν - the animal spirits - which is carried along
he nerves, & brings about the movements of the body. In this highly speculative way Galen explained the process of digestion, the two other humors (besides blood & black bile) — yellow bile & phlegm, excreted by the liver & the brain respectively, helped to account for the diseases of the body. Chronic diseases Galen thought arose from disorders of phlegm & black bile; acute diseases arose from anomalies of blood & yellow bile. Inflammation & fever he explained as arising from a flux of the four humors, and by their stagnation the four cardinal symptoms — tumor, rubor, calor, vultus — are caused.

Regarding urinary drainage Galen held that it was produced in some way by the kidneys, that deficiency of it was due to obstruction in the urinary passages by over-thick urine, cataracts. As to the mammary secretion Galen considered it was the result of pressure by the enlarged uterine upon the abdominal vessels which are in communication with the vessels of the breast.

Oribasius (632 A.D.) made diligent compilation of the best Greek authors, especially Galen. He demonstrates how great were the attainments already made by medical science in anatomy, therapeutics & surgery; but in physiology he shows how little progress had been made.

Caelius Aurelianus, in the 5th century, in his work "De morbis acutis et chronicis", again shows how wide a knowledge had been acquired of the clinical symptoms of disease, of the best methods of treatment; but on how slender a basis of physiology at all was built.

After this writer there comes a period of well-nigh a
thousand years in which slight if any advance was made in medical science. The seat of medical knowledge was transferred from Rome to Byzantium, whence sprang the medical science of the Arabs. In Byzantine medical literature the attainments of the past were at least preserved, though nothing was added to them. Retaining Alexander of Tralles, Paulus of Aegina at least kept alive respect and admiration for Hippocrates and Galen, for the work they had done.

All the most important Greek medical authors were translated into Arabic — Hippocrates, Galen, Celsus, Alexander of Tralles etc. Often only by these translations are many Greek works preserved. This work was done first at Baghdad—especially under Khaulif Al-Mamum (813–33); and it was carried on later in Spain after its conquest by the Arabs in 711. Cordova became the Baghdad of the West. From the 9th to the 13th century its medical school was at the height of its reputation. But the great names of Arabic medicine — Rhazes (+923), Avicenna (+1038), Avicenna (+1167) Averroes (+1200) are remembered chiefly as those of men who preserved the best of what they had received, who excelled as clinicians in spite of the drawbacks under which they expressed their art.
II. Beginnings of Modern Physiology 1543-1824.

The Renaissance is usually taken as having begun at an earlier period than the one I have indicated. Any date must be more or less arbitrary; but it is convenient, following Sir W. Fothergill in his 'Lectures on Physiology,' to take the date 1543—the year of the publication of Vesalius' book "Fabrica humani corporis," as marking the transition point from ancient to modern medicine. It would carry us too far to consider the many causes which went to bring about the Renaissance. What concerns us is the fact that a new spirit was abroad in the world—a spirit of research and inquiry which was soon to cover every branch of human knowledge. In one aspect it was a spirit of revolt against authority—the authority of antiquity and tradition which had so long enchain'd human minds. In another aspect it was a spirit of humility. The dominance of faith was to be acknowledged. "Man, the servant and interpreter of nature"—was to be the motto henceforth. Theory and speculation were to be entirely subordinated to simple observation.

The first branch of medical science that came under the new spirit of research was Anatomy. This was natural, for Anatomy is observation pure and simple. But a new Anatomy has always meant a new Physiology. Therefore, although Vesalius' book is almost entirely taken up with a new description of the parts of the human body, it paved the way for a new inquiry into the functions of these parts; and thus the new methods of studying Anatomy led necessarily to a new Physiology also.
But other forces were also at work in the same direction. The new
sciences of Physics & Chemistry were also making progress. Through
their fresh light was soon to be shed on physiological problems. The
microscope also had come to the help of the anatomist - not merely
the simple lens which had long been known, but also the compound
microscope. Such men as van Helmont, Bonelli, Malpighi, Sylvius,
represent the influence in varying degree of these new sciences on
physiology. In the first instance, as we might expect, men were
too inclined to approach physiology from the side of that science in
which they were particularly interested. Thus throughont the early part
of the 17th century we find very varied views expressed as to digestion,
secretion &c., according as their authors their authors were most
interested in anatomy, or physiology, or chemistry. I shall try there-
fore to represent the progress in physiology from the stand-point of
these sciences which added most to its development.

I. Anatomy. In 1627, Aselli of Cremona discovered the
lacrimal, described them as filled with a milky fluid or glye; but
he thought they conveyed it to the liver.

In 1628 Harvey published his great discovery of the circulation of
the blood - a discovery which opened the way for a new inquiry into
the physiology of secretion. Friesenp in 1642 described the duct
of the pancreas known by his name - although Stephano, his pupil,
claimed to have made the discovery a year before his master; but
the evidence therefore is questionable. In 1657 Jean Régisnet, a
physician of Dijon, & later of Paris, published his description of the
receptaculum chyli, & thoracic duct; he showed how the lacrimal fluid
their contents into the thoracic duct, and the thoracic duct empties itself into the left subclavian vein, just where it joins the internal jugular. In 1653 Rudbeck of Upsala published his description of the lymphatics. Lepiscus in 1654 published his work on the liver, describing accurately its structure, and especially the sheath known by his name. He compared the liver to its secretion of bile to a filter (colostrum), but it is evident he does not mean by this to imply a mere mechanical filtration as being the function of the liver, for he says further that the secretion of bile is due to the affinity of certain particles of the parenchyma of the liver for bile, whereas the particles of the liver whose fibres lies with the pure blood attract this to themselves, and then give it up to the venous system. Wharton in 1656 published his "Anatomia," an account of all the organs he regarded as glands—excluding the brain and the tongue. He described the submaxillary duct—known by his name—and he described salivary as being a fluid distinct from phlegm and mucus—though he asserted no importance in it in digestion beyond that of a fluid aiding digestion and solution. He thought the nerves, which he found supplied in great abundance to all the glands, either gave rise to some part of their juices (successors nerves) or a sort of secretion through the glands, the success being by this means purified; or else the nerves take up something from the glands, by which they fortify the succesor nerves. Steensen in 1661 discovered the duct of the parotid gland—known by his name. He had learnt from his master Sylvius of the distinction to be made between coneomate glands such as the salivary glands, the pancreas, and compound glands like the lymphatic glands; and he laid emphasis upon the fact that the
formes were in the proper sense secreting glands, & therefore had ducts; whereas the latter had not. He pointed out that in the conglomorate (ductless) glands, the lymph flows to & through them; whereas in the conglomurate (secreting) glands it only flows from the glands in the form of secretion. Sclater also discovered the duct of the sublingual gland, those of the small breast gland, & the lachrymal gland; and he seems to have formed some idea of the nature of the process of secretion. viz. that the material for it was brought to the gland by the arterial blood, it was drawn up in the gland, to be conveyed away by the duct. He made a distinct advance on Wharton's view by regarding the nerves as only present strictly for the purposes of movement or of sensation, & he conjectured that they may by constructing the veins throw more material into the beginnings of the duct.

Bellini

Bellini in 1602 published a little treatise 'De Structura rennis', in which he described the straight tubules opening into the pelvis of the kidney. He professed, moreover, a physical theory of the secretion of urine. In the fashion of Borelli, he thought the particles of the blood must be of a different size & shape from those of the urine; so that when the minute arteries of the kidney had discharged their blood into the spaces of the kidney, out of these spaces the particles of urine passed into the tubules, while the particles of blood, owing to their size & shape could only pass on into the venules.

Malfigghi

Malfigghi (1628-94) is specially noteworthy because of his description of the liver & kidney & their secretions. He showed that the liver was made up of lobules (acini) similar to the acini of the salivary
glands, hence that it secreted bile after the same fashion as those glands did saliva, or as the pancreas, sweat glands, & lacrimal glands did their secretions. He proved that the bile was secreted in the liver, first in the gall-bladder, as many supposed, by tying the common bile duct close to the duodenum, & emptying the gall-bladder; then he found that the common bile duct soon filled with bile; from ligaturing the neck of the gall-bladder he found the common bile duct still full of bile.

Regarding the mechanism of secretion he says it can only be a matter of hypothesis, since the structure of the acini is so minute. As to the functions of the bile, he compares its mixture with the food (along with pancreatic secretion) to the mixing of sweet, sour, salt things in the preparation & cooking of food – the ingredients all in some way aiding in the process.

In the kidney, Haufler, described the papillae & their propulsors, also the convoluted tubules beginning in the capsules surrounding a knot of blood-vessels; but he did not make any fresh contribution as to the nature of the secretion of urine.

Peyer.

Jean Conrad Peyer (1653-1712) of Schaffhausen described in 1677 the intestinal glands called after him. He thought each gland opened by a minute duct into the interior of the intestine, & judged that this secretion must be of importance for digestion – explaining their increased number in the album by the supposition that as the pancreatic juice got gradually reduced, their secretion replaced it.

v. Brunner.

J. Conrad v. Brunner (1653-1737) – Professor at Heidelberg, in 1687 described the duodenal glands named after him, calling them a secondary pancreas, as he found they yielded a fluid like
pancreatic juice, which he thought was the really active agent in intestinal digestion. From experiments he performed—removing nearly the whole of the pancreas from dogs, & finding they yet were well nourished, he thought the pancreatic juice was not so important as Sylvius & de Graaf thought.

These discoveries in anatomy, it is evident, furnished the basis for a much more complete knowledge of the secretions of the alimentary tract than had been possible hitherto. In due place & importance that were to be assigned to each secretion, were still vaguely known, & were to remain so for many two hundred years.

II. Alchemy. The earliest investigations of chemistry—Valentinus (+ c. 1500) & Paracelsus (1490-1541) had hardly advanced beyond the stage of the alchemist. They were in the habit of casting a veil of mystery around their teachings, and largely because of the vaguely understood nature of chemical forces, they saw in them the effects of spiritual & mundane powers. Under the name of Acharaen they spoke of a spiritual force which governed all physiological & chemical changes—including those which go on in the human body.

J. B. van Helmont (1577-1644)—bornシーズ at Vilvorde near Brussels, was the first who exerted much influence on physiology from the chemical standpoint. He was a follower of Paracelsus in often calling in the aid of spiritual agencies to explain natural phenomena; but on the other hand he also endeavoured to carry out his exact chemical methods in dealing with physiological problems. He made frequent use of the idea of a ferment, by which he meant
Something used as an instrument by the Archaeans to produce certain changes, & which set free gas by its action as seen in the making of wine, or bread. He makes this idea of fermentation the basis of his physiology. It was an old idea that the digestion of food is similar to the fermentation of wine. But v. Helmont regarded all the changes in the body, including nutrition, configuration & movement, as well as digestion, as due to the action of ferments. Digestion in the stomach, he said, was due to the action of an acid ferment. He showed how insufficient was the idea that digestion was brought about merely by the heat of the stomach. He recognized, further, that mere acidity was not sufficient to explain the digestion of the constituents of the food. There lay a specific power in the acid ferment of bringing about digestion. “Fermentum ergo digestivum est proprietas essentialis consisting in vitali quaedam aciditatis et transmutationis potius, ideoque et specificae proprietatis.” (Otis, medic. 9, 28) The acid chyle he taught on passing into the duodenum is changed from an acid into a salt, & there the action of the acid ferment ceases, & the food undergoes a second digestion by means of the ferment furnished by the bile. He recognized another ferment also which was secreted by the liver and descended into the mesenteric veins, there to perform a third digestion or sanguification of the chyle. After these changes in the heart this sanguified chyle undergoes a final digestion in each part of the body where “a spiritus or ferment animates in each place, cooks its food for itself.”

Sylvius. François de la Boe (Sylvius) 1614-1672, born at Namur, Professor at Leyden, was in many respects a man of wide outlook.
Regnus de Graaf (1641-1673) studied at Leyden, and practised at Delft. He succeeded in 1664 in making, for the first time, a pancreatic fistula in a dog, by means of a delicate small needle inserted into the duct, and he thus drew off various amounts of pancreatic juice. Similarly, also he collected partially saliva and bile. He seems to have examined the pancreatic juice chiefly by tasting. He found it was sometimes insipid, sometimes acid, often salt, but most frequently acid-salt. He once examined the pancreatic juice of a sailor who had died suddenly, and found it similar to that of the dog. He discusses the use of pancreatic juice in his "Disputatio medicinae de natura et usu suis pancreaticis" in which we may probably find also Sylvius' teaching. He attached much importance to saliva in digestion — looking on it as a type of fermentative juices was the first agent in the chylification of food. The second stage was from the interaction of bile and pancreatic juices; the latter being insipid, the former being acid; so that its function was to ferment (or effervesce) with the bile, aided by the natural heat of the body. This effervescence was supposed to dissolve the viscid mucus lining the intestines, to favour the absorption of the chyle. — But how, was not explained.
These three men, therefore, may be held to have given chemical process especially fermentation, a new unimportant place in physiology. But the nature & functions of the secretions which they investigated were only vaguely known.

III. Physics. Since the days of Galileo the study of Physics had been pursued with much eagerness. The influence thus exercised on physiology was a very important one, as the habits of exact weighing & measuring which were so fruitful in physics, were now to be applied to the solution of physiological problems also.

Redi. Redi of Florence (1626-1697) was one of the representatives of this school; but the chief representative of the mathematical school, as it has been called, was Borelli.

Borelli. Borelli (1608-1679) - Professor at Pisa, laid stress on the mechanical view of digestion: the grinding force exerted by the stomach walls. He introduced & a turkey's stomach glass globules, 9 leaden cubes hollowed out, & next day he "found the leaden masses crushed & eroded, the glass pulverized." The force exerted, he reckoned, was equal to a weight of 1850 lbs. But he admits that in animals with a membranous stomach another process is superadded to that of triturating: "Numerosum fermenta quoque viribus validissimis carnis et cosa consumunt, et eae semper suavus corrosione metalla corrodebat at dieruentur. Tali ferro succin corrosione instillatur a glandulis corrosiis, quibus membrano ventriculi substantia infecta sit, ut eundem coram observi in ventriculis Delphini, cupis glandulace admodum etroscam et prominenter sunt" (Op. II. 189). It is noteworthy how Borelli here recognizes 1) the glandular nature of the lining membrane of the stomach, &
fact which came to be generally recognized after him, and of the action of the gastric juice by means of its ferment in dissolving and changing the food—much in the same way as corrosive liquids dissolve metals. The fact that Sylvius Vettius, who wrote after Bonelli, did not attach the same importance as he did to the gastric secretion, is probably to be explained from the idea held by those that glands with conspicuous ducts, like the salivary glands, the pancreas, &c., liver, were more likely to be the seat of an important secretion than a mere membranous surface like the stomach wall. Bonelli's view, however, was not forgotten. It is true that some of his followers, in their zeal, went further than Bonelli, and denied chemical action altogether as a part of gastric digestion, regarding such digestion as merely mastication. But such was not Bonelli's teaching; to him is due the credit of having made the first clear reference to the gastric glands & their acid secretion.

From these two stand-points, therefore, Anatomy, Chemistry, Physics, were the problems of Physiology being attacked. As yet the results gained were only fragmentary. But so far as they went, they were true. They were gained for the most part as the result of patient experiment & observation. The stimulus afforded by the anatomical discoveries was of particular importance in forcing physiologists to revise their teaching regarding the functions of the alimentary tract & the part played by them in digestion. It is true that chemistry was yet in too elementary a stage to enable them to take full advantage of the discoveries made in anatomy; but the observations made, if conflicting, sometimes even fallacious, were
on the right lines, achieved by what methods success might ultimately be attained. When towards the end of the 18th century chemistry began to make great strides onwards, as evidenced for example by the discovery of the four gases, Carbon Dioxide, Nitrogen, Oxygen, & Hydrogen—thereafter it became much easier for physiologists to discover what were the changes undergone by food in digestion, & what was the action of the secreted juices upon it. Meanwhile two men stood out above the first half of the 18th century as having done good service in gathering together the results already attained from experiment & observation so as giving an reasoned opinion regarding them. These were Boerhaave & v. Haller.

Boerhaave

Hermann Boerhaave (1668-1738) born near Leyden, Professor in Leyden from 1701 on, had a wide knowledge of the science of his time, & exercised a deep influence by his teaching upon the succeeding generation— one of whom was v. Haller. He spoke of six secretions as taking part in the digestion of food; these were saliva, a juice secreted in the oesophagus, the gastric juice, bile, pancreatic juice, & the intestinal juice. These all help in dissolving the food, but he denied any fermentative action in them. He denies also the acidity of the gastric juice, & also— as against Sydenham— that of the pancreatic juice. He thought also that a nervous fluid must have some share in digestion in the stomach, seeing that the supply of nerves to that organ is in excess of what is required for the purpose of sensation or movement. He gave full weight also to the view of the mechanical school, that distension played a great part in gastric digestion, chiefly, he thought, in expressing the dissolved constituents from the more solid framework of the food,
Another element in his teaching was the somewhat reactionary one that the air which was present in the stomach along with the heat of the body did cause a sort of fermentation, as he says "an incipient fermentation by means of which the chyle is impressed with the primary principle of vitality."

These, then, may probably be taken as the views which were most dominant in the early 18th century. Nehemiah Grew (1628-1712) an English writer in his work on Digestion - published in 1681 - writes: "By the joint assistance of the glandulars & the nervous membranes the business of chylification seems to be performed - the mucous excrement of the blood supplied by the former as an animal corrosive preparing, & the excrement of the nerves by the latter as an animal ferment, perfecting the work."

These somewhat vague views, however, were soon modified, chiefly through the teaching of v. Halle. Albrecht v. Halle. This man (1708-1772), a pupil of Leeuwenhoek, Swiss by birth, was Professor at Göttingen. His teaching regarding secretion was as follows. Saliva, he found, was neither acid nor alkaline. As against Sylvius he did not ascribe to it great virtues in digestion; it merely softened the food, he thought, 2 helped digestion. He regarded the gastric juice as consisting of a mucous part secreted by the gastric glands, & a liquid part secreted from the arteries of the stomach. He found it neither acid nor alkaline though he says, it often appears acid as many things do after the onset of putrefaction. He rejected therefore Boerlli's description of it as a corrosive liquid - for its frequent acidity was due to the degeneration or putrefaction of the digested food. Its main function
was that of softening and dissolving, for like saliva, it had no fermentative action. He regarded trituration as an aid to digestion in the stomach, as he rejected the idea of a nervous fluid.

Bile, he said, was not a mere excrescence. It is secreted in the substance of the liver, not in the gall-bladder, as many thought; and it is neither acid nor alkaline. It has the power of dissolving fats, forming an emulsion of them—an observation which had been made before, but was now for the first time given its due place as a factor in digestion. Haller surmised also that bile must have some other function besides this one, for he found that death soon followed in animals on removal of the gall-bladder.

Pancreatic juice. v. Haller thought the pancreatic juice had chiefly the duty of softening and diluting the somewhat viscous bile, as shown by the fact that both ducts opened together into the duodenum. But he added, there may be other functions of the pancreatic juice which are not yet known to us. To the intestinal juice he attached no importance, the chief asset in the intestines being the absorption of the chyle.

Réaumur. A contemporary of v. Haller's was Antoine-Francois de Réaumur (1683-1757), born at Rochelle, lived at Paris. His work is of epoch-making importance. v. Haller refers to his results, but does not seem to have realized the importance either of them, or of the methods by which they were attained. Steven of Edinburgh, and Spallanzani followed on the same lines as Réaumur, repeating and extending the same experiments, and to these three investigators must be assigned the credit of placing upon an unassailable foundation
the chief parts of digestion. Réaumur's work "Sur la digestion des viscères," appeared in 1752. The question he had to solve was, did gastric digestion a process of tincturation, or of solution, or of fermentation, or a sort of putrefaction, or how far does it consist in each or all of these? He experimented upon a tame lizard, which, like many birds of prey, regurgitates the indigestible portions of its food. He administered to it small metal tubes containing various kinds of food; the tubes were closed at one end, covered by muslin at the other, so as to preclude the possibility of mechanical tincturation, yet permit the gastric juice to exert its action. If meat was enclosed in the tube, he found it was digested after some hours. If meat was retained long enough, the surface was found softened, but the interior remained intact. Even bone was found softened and dissolved, if administered a second and third time. He found that vegetable grains, flour, on the other hand, were but little altered. It was noteworthy also that no odour, or other sign of putrefaction was attached to the food when regurgitated.

Réaumur next put pieces of sponge in the tubes, when they were rejected he was able to obtain some specimens of the gastric fluids, which he found to be a fluid of acid reaction, with a somewhat salt taste, of opalescent appearance. He next attempted artificial digestion with it, exposing meat to its action at 32°F for 24 hours, using similar pieces of meat in water as a control. He found that whereas the control putrefied, the meat in the gastric juice was little putrefied, but neither was it very much dissolved. On the death of his lizard he used a dog, giving it bones, some tubes, and killing it after 24 hours.
He found the bones not crushed, but partly dissolved, & much altered in appearance. The meat in the tubes was partly dissolved, & the tubes were not distorted. Reaumur also experimented similarly on sheep, giving them hay & green food; but the results gained from them were doubtful, the contents of the tubes being not greatly altered.

Dr. Stevens of Edinburgh carried these investigations one stage further than Reaumur, as recorded in his Inaugural Thesis 'De alimentorum condotione' (1777). He made use of a Hungarian juggler, who was in the habit of swallowing stones & other things, & regurgitating them at public exhibitions in Edinburgh. Stevens gave him little silver spheres to swallow, perforated all round, & made of two halves screwed together so that food could be placed inside. He used both raw & cooked meat, cake & also vegetables. He found that the contained meat was dissolved, & sometimes completely disappeared, but whole grains of wheat, peas, were little changed. Further, Stevens obtained the gastric juice from the stomach of a newly-killed dog, which had fasted for sixteen hours, & he found that a piece of meat was digested by the juice outside of the stomach in eight hours, provided it was placed in a vessel exposed to warmth; & there was moreover, no putrefaction nor production of gas bubbles. He concluded therefore that digestion is "not the effect of heat, fermentation, putrefaction, or fermentation alone, but of a powerful solvent secreted by the coats of the stomach, which converts the aliment into a fluid resembling the blood."

Giacomo Spallanzani. Lagus Spallanzani born near Reggio in 1729, Professor at Pavia, published in 1777 his 'Saggio di Fisica animale e vegetabile'. He also like Stevens used
Réaumur's methods, but experimented on a much wider range of animals, such as fishes, frogs, birds, horses, cats, dogs &c. on himself also. He used metal tubes like Réaumur, hollow spheres like Stevens, filling them with meat, bread, bone. He recovered them by rejection in birds of prey, or by opening the animals, or by attaching threads or wires to the package. He also got specimens of gastric juice from fasting animals by means of sponges, by making himself vomit before breakfast, and with the aid of heat he performed artificial digestion. By these means he found that in all animals food is in the living stomach "dissolved into the fruitaceous mass called the chyme" by means of the gastric juice. That this juice specially acts on divided or coarsely parts of animal or vegetable food - more quickly in some animals than in others. So he concluded that medication like trituration was a preparation for the action of the gastric juice. He found also that food being acted on by gastric juice did not putrefy, while that in a control of water did. Thence he inferred that digestion was different from putrefaction. He observed also that he could greatly hasten artificial digestion by letting gastric juice fall on the food drop by drop & then run away. From this he concluded that the ferment action must be something different from the fermentation he knew. He knew of vinous, acetic, but not fermentation. Digestion, he thought, was different from any of these, but more he could not say.

As to the acidity of the gastric juice, Spallanzani agreed with the majority of his contemporaries in denying it. The only evidence of acidity he could get in the stomach was when the food turned sour. This he thought an abnormal & unhealthy state. He could get no effervescence by dropping gastric juice on an
alkaline salt, not into an acid; so he concluded it was neutral. Yet on finding that it curdled milk he thought it contained an acid in a latent form.

After Spallanzani only two writers claim notice until we come to what may strictly be termed the modern period. One of these was the famous John Hunter, who in 1772 published in the 'Philosophical Transactions' a paper on the digestion of the stomach after death, and in 1786 his 'Observations on certain parts of the Animal Economy.' In these writings he criticizes Besler and Spallanzani — he himself being a supporter of the idea of a vital principle being the agent in digestion. Digestion, he thought, was neither a mechanical nor a chemical process, but depended on "something secreted in the coats of the stomach, petharam down into its cavity, which there animalizes the food, or assimilates it to the nature of blood." But Hunter found as a result of experiments in 1772 that there was an acid, though not a strong one, in the gastric juice contained in the stomach in a natural state.

The other writer was Carminati who in 1785 gave what seems to have been independent confirmation of Hunter's statement. He found that at least in Carminata the gastric juice, while neutral when the animal is fasting, is strongly acid after the animal has taken food.

After these writers there comes a pause in the progress of knowledge. No important discovery in this branch of physiology was made until well into the next century. The condition of Europe at the time was unfavourable to scientific investigation. It was the time of the French Revolution, following upon that the Napoleonic wars. The nations which had contributed most to the
progress of science - France, Britain, Germany, Italy - were all engaged in internecine warfare. Not till some years after the peace of Europe was assured in 1815 do we find science again taking a stride forward. From a date which we may conveniently take as 1824 - the year in which Priest discovered that the acid of the gastric juice was hydrochloric acid, the period of Modern Physiology may strictly be said to begin. From that date until the present day, there has been no break in the advance of Physiology. Year by year the bounds of knowledge have been extended, and the knowledge attained has constantly served as a sure basis for a further advance.

III. Modern Physiology 1824 - present day.

In this period the advance in all branches of physiology has been very great, including that with which we are specially concerned. The number of investigators also has been equally great. From many sides the problems of physiology have been attacked; the assistance of many cognate sciences has been called in. It would be impossible to refer to anything like the full number of even important names engaged in investigating the physiology of secretion. The plan I shall pursue is to take each secretion by itself, showing the important stages by which the present state of knowledge has been attained with regard to it. First will naturally come the digestive secretions, then the secretions concerned with excretions; finally, internal secretions.
A. Secretions concerned with Digestion.

1. Nature of the Secretion. Saliva has long been held to be chiefly a softening and moistening action on the food in preparation for the further action of the stomach juice.

In 1831, Lench (Kirstin's Archiv 1831) discovered that when saliva is mixed with starch, it gradually dissolves it with the formation of a body which possesses the reactions of grape sugar. Lench does not seem to have investigated further to what this action was due.

But about this time there began to be made a series of investigations which were to throw light on this problem, viz. inquiries into the nature of actions of ferments. Kirchhoff had discovered (1814) that germinating barley grains contained something which can be extracted by water, which can convert starch into sugar. Later, in 1833, this substance was separated by precipitation with alcohol, and it was given the name of 'diastase' by Payen & Perség (Mém. sur la Diastase 1833). A similar method was later adopted by Mialhe, for the separation of the ferment of saliva. He in 1845 (C. R. Acad. p. 5, XX. 1845) discovered that when human saliva is mixed with five or six times its weight of absolute alcohol, a small quantity of a flocculent body is deposited, which he collected and dried at the temperature of the air. He found that this precipitate had the property of converting solid starch into sugar, and from its apparent identity with the amylolytic ferment which Payen & Perség had lately separated from germinating barley, he applied to it the name of 'animal or salivary diastase.'

Bergelin. Bergelin (Traité de Chimie 1839) first applied the name 'salivolin'
to the organic matter of saliva generally - obtained by a method by which the ferment was destroyed. But soon the name came to be applied as a convenient term to the ferment itself.

Ludwig

2. Mechanism of Secretion, & nervous control.

The existence of secretory nerves to the salivary glands was discovered by Ludwig in 1851 (Zeitschr. f. Kat. med. 1851), and this discovery is of importance as marking the beginning of our knowledge regarding this function of nerve fibres. He found by experiment on the sub-maxillary gland of a dog that stimulation of the lingual nerve caused a flow of saliva.

Another important discovery made by Ludwig (1857) was that the secretory pressure in the sub-maxillary gland may considerably surpass the blood pressure - e.g., in the carotid. Thus, by stimulating the lingual nerve the jet in one case 190 mm. of mercury pressure in the salivary flow, compared with 112 mm. pressure in the carotid artery. It followed from this that the secretion of saliva was a true glandular secretion, and not a mere exudation through the gland.

Ludwig also discovered (1856) that the sympathetic fibres to the sub-maxillary gland also have an influence upon the secretion of saliva. He obtained a secretion by stimulating both the cervical sympathetic ganglia, & the nerve-filaments (sympathetic) on the artery to the gland.

Lozemark (Sitjynph. d. K. Akad. 1857) then pointed out that stimulation of the sympathetic fibres along with the cranial ones retards secretion. He thought this due to inhibitory fibres in the...
Sympathetic - a vein which was discovered by Huxley at a later date (Jour. of Physiol. 1878) when he showed that with minimal currents of not too long duration simultaneous stimulation of the chorda tympani & sympathetic nerves produced an amount of saliva greater than that produced by stimulation of either nerve alone; but on increasing the stimulus the amount fell off - probably from diminished blood supply owing to stimulation of the sympathetic fibres.

Then Claude Bernard (1856) amplified the first part of Ludwig's discovery by showing that the serous films of the sub-maxillary gland come from the chorda tympani, & so from the facial nerve; - though it should be remarked that the connexion between a flow of saliva & stimulation of the chorda tympani nerve had been stated by Schild in 1851. Bernard also discovered (1855) that all the salivary glands flush from increased blood supply on stimulation of the cranial nerve - roots, whereas on stimulation of the sympathetic nerves they become pale from diminished blood supply. He worked out the nervous effects on blood supply chiefly on the sub-maxillary gland of the dog.

Eckhard Further, Eckhard in 1860 amplified the second part of Ludwig's discovery by showing that the saliva secreted by the sub-maxillary gland on stimulation of the sympathetic was more viscid, and contained a much higher percentage of solids than that obtained by stimulating the chorda tympani; - the chorda tympani saliva being much more watery & abundant. Again, Kessler in 1862 showed that there are probably two distinct sets of fibres in the cranial nerves, - the one set causing an increased secretion, the
other causing dilatation of the vessels. He showed this by injecting atropine, under the influence of which stimulation of the chorda tympani still caused dilatation of blood vessels, but no secretion.

Then Bernard investigated the course of the nerve fibres to the parotid gland. He obtained secretion in a dog by stimulating the auriculo-temporal branch of the 5th nerve, & a cessation of reflex secretion by section of the otic ganglion. He considered that the secretory fibres came from the superficial petrosal nerve, that the superficial petrosals (as well as the chorda tympani) came from the nerves intermedius of Wrisberg.

Another discovery of Bernard's was made in 1864 (Jour. de l'Anat. et Physiol.) He found that section of the chorda tympani in dogs caused the sub-maxillary gland in two to three days to enter into a state of slow continuous secretion which continued for five to six weeks, then stopped, during this time the gland gradually diminished in size. He attributed this so-called 'paralytic secretion' to the complete removal of nervous impulses. Regarding this, Heidenhain later showed (Arch. Physiol. Inst. ji. Brasilie 1868) that in the dog section of the chorda tympani on one side causes a slight continuous secretion from the sub-maxillary gland of the other side - so-called 'antilisky secretion'. Further, Langley (Jour. of Physiol. 1875) showed that stimulation of the cut strands of the cut chorda tympani near the gland will still cause secretion thirteen years up to forty-two days after section. He concluded that the peripheral nerve cells when stimulated may cause gland activity long after section of the central nerve-fibres, and therefore the paralytic secretion was probably due to nerves
Stimuli of the local nerve mechanism.

We have already mentioned the name of Heidenhain in connection with discoveries regarding the nervous control of the salivary secretion. Of even greater importance was his discovery of the histological changes that occur in the salivary glands during secretion. He showed how in the salivary glands (as in the pancreas) there were structural and microscopic changes standing in close relation to their functional activity. During the resting stage the glands were large, but had comparatively little protoplasm; they contained instead a store of materials which had been elaborated in, probably at the expense of the protoplasm, and was stored up in the cells, for the most part in the form of granules. During activity the stored up material was converted into soluble constituents of the secretion, and at the same time there was a taking up of fixed material by the cells, which occurred more or less exclusively in the outer part of the cells, and was the chief cause of the formation of an outer non-granular zone (Pflüger's Archiv 1878 and Hermann's Handbuch 1883). These changes have since been confirmed and more fully described by Uchtein and Grützner, and most of all by Langley (Trans. of Physiol. 1878-9).

Normal Stimulation of Salivary Secretion.

Colin & Prompt observed (1874) that solid substances taken into the mouth cause more or less secretion from all the salivary glands. In the case of a girl with a parotid fistula they observed that chewing a piece of ribbon caused a secretion of only one drop of saliva in two minutes; whereas the sight, taste, smell of food
particularly of an agreeable kind caused an abundant flow. Mastication also considerably increased the flow of saliva. Many other observations have been made in this direction - with varying results. Pavlov (Work of the Digestive Glands 1902) has found that the three large salivary glands respond differently to different stimuli. Thus in the dog, the sub-maxillary gland responded readily to a large number of stimuli - such as the sight of food, chewing of meat, acids etc. The parotid gland, on the other hand, seemed to react only when dry food - dry powdered meat or bread etc. - was placed in the mouth.

3. Function of Saliva.

Kühne

Kühne (Verhandl. d. m. Ver. fur Hefl. 1876) showed that the digestive action of the enzymes (including that of saliva) is not stopped by disintegants such as Thymol, Chloroform etc., in a quantity sufficient to stop the action of organic ferment - particularly those of the putrefactive bacteria.

Kopfer, Seyler

Kopfer, Seyler showed (Archiv f. d. ges. Physiol. 1876) that ferment action is in all cases accompanied by hydrolysis.

v. Mering

v. Mering & Brunsveld (Archiv f. Physiol. Chemie 1878) showed that the action of diastase (Fermentation) on starch is to split it up to dextrose + a sugar (afterwards found to be maltose), that later the dextrose is further split up to a less complex dextrose liquid.

Many observations have since been made as to the conditions of the activity of this enzyme. Like other digestive ferment...
it has been found to have a particular temperature at which its maximum power is much obtained from those the enzyme is destroyed. Thus Kjeldahl found that the optimum temperature of ptyalin is 46°C., and it is destroyed at 68-70°C.; whereas the ferment dextrinase has its optimum temperature 59-60°C., and is destroyed at a slightly higher temperature than that.

Hammarsten 1877 found that the diastatic action of saliva ceased in the stomach when the quantity of HCl amounts to from .06 - .25 per cent.

Langley (Journ. of Physiol. 1883) observed that when saliva is digested with HCl of strength from .04 - .2 per cent. for times varying from 7 to 24 hours, the ferment was destroyed.

Chittenden (Physiol. 1884) confirmed this, but found that a smaller quantity of acid increases the diastatic activity; and Langley later discovered that neutralized saliva converts starch into sugar more actively than unneutralized saliva, and that the diastatic activity of ptyalin attains its maximum when the reaction of the fluid containing it is neutral or even faintly acid, provided the acidity is due to acid combined with ptyalin.

Many attempts have been made to separate ptyalin in pure form, and to discover its composition, the nature of its action, but success in these respects has not yet been attained.
II. Gastric Secretion.

1. Nature of the Secretion. Prout, as we have already observed, first showed (Phil. Trans. R. Soc. 1824) that the gastric juice contains hydrochloric acid. He distilled gastric contents, part with KOH added, part without, and calculated the difference in the chlorides as HCl which had evaporated. (It was later found that all the HCl is not so evaporated, especially if dextrose or dextrin is present.) The residue was dried and incinerated, and was shown to possess a considerable quantity of chlorides - greater when KOH was added. Prout's results were severely criticized, and not accepted for many years by most physiologists. They were confirmed, however, by W.R. Beaumont (1824), Friedemann & Gerlin (1826), and later, as we shall see, Bidder & Schmidt (1853).

Then came the classical observations (1825-33) made by Beaumont. Beaumont of the U.S. Army, in the case of Alexis St. Martin, a French Canadian, who as the result of a gun-shot wound had a gastric fistula established, which allowed both of the collection of gastric juice, and of the observation of the processes which go on within the stomach. Beaumont found (Physiology of Digestion 1833) that there is no accumulation of gastric juice in the fasting stomach; in other words, the secretion of gastric juice is not a continuous one, but, except in small degree, is only in response to a stimulus such as that given when food is taken. Beaumont observed further that whenever a foreign body such as a quill or a thermometer is brought in contact with the interior of the stomach, the mucous membrane very soon becomes turgid, and appears as if caused by
"innumerable lucid specks", which seem to burst, and "discharge a limpid thin fluid over the whole gastric surface." This flow of gastric juice, however, Beaumont observed to be largely a local one, limited to the area stimulated. But when solid food entered the stomach, there was a general turgidity of the vessels all over the lining membrane, and the flow of gastric juice was general and continuous.

Beaumont's observations also showed that while the gastric mucous membrane may have a neutral or alkaline reaction during activity, the gastric juice has invariably an acid taste and reaction.

The next advance was in the direction of obtaining a supply of gastric juice by artificial means. Tiedemann & Grublin obtained small quantities of gastric juice (1826) by causing fasting animals to swallow insoluble bodies such as pebbles, and killing the animal shortly afterward.

Uhrle in 1834 prepared an artificial gastric juice by acting upon the mucous membrane of the stomach with dilute HCL, and he showed that by means of it food could be digested just as by the natural gastric juice.

Basson (1842) & Bloudlot (1843) established the first artificial fistula in animals, and their method of preparation has since been frequently repeated and perfected (especially by using cathartic preparations) by such observers as Bastide, Bider & Schmidt, Bernard, Heidenhain and others. The matter still in dispute was to what the acidity of the gastric juice was due. Lehmann in 1847 found lactic acid in the gastric juice, and thought that the HCL present was really produced by its action on chlorides. It subsequently
modified this view, holding that both for lactic acid and HCl are originally present — an opinion which was shared by C. Bernard, Pelouze, O. Thomson, & others. At length, however, in 1852, Rieder and Schmidt proved in their classical work "Die Verdammungssäfte" that the gastric juice of animals which have previously fasted for a period of eighteen to twenty hours contains only free HCl and no trace of lactic acid, or any other organic acid.

Pepsin, Schwalbe, who in 1834 prepared an artificial gastric juice by acting upon a stomach mucous membrane with HCl, thought it was the mucous of the mucous membrane that preserved the proteolytic powers observed, and he thought that e.g. nasal mucous would do the same.

Schwann. Schwann (Über das Vorkommen der Verdammungssäfte 1836) showed the error in Schwalbe's view, & came to the conclusion that the gastric juice and its peculiar activity to a principle which he denominated "pepsin". He precipitated the extract of gastric mucous membrane with ammonium chloride, & thus succeeded in separating the pepsin, but still mixed with proteins. Briëcke (1863) used Phosphoric acid & then Calcium Hydroxide, & so got a precipitate of Calcium Phosphate + pepsin.

v. Withich. v. Withich (1869) prepared a solution of pepsin in glycerine — then precipitated this with absolute alcohol, & so approximated to a pure preparation of pepsin. But it is doubtful whether pepsin, or any of the other enzymes, has yet been got in a pure condition, & we are ignorant of their true composition and mode of action.

Renmin. It had long been known that the mucous membrane
Neisler of the early stomach has the property of curdling milk. Heaney first
saw the mammalian pancreas gland to form curds from milk. The pancreas
then exerts a solubilizing action on the fat, producing curds. Under
neural influence, the pancreas is stimulated to secrete digestive enzyme,
which breaks down the casein into polypeptide fragments. The fragments
then combine with the milk fat and curdle the milk. The curd is then
squeezed out, and the milk is separated from the curd. The milk is then
cooled to (alkaline) milk, a characteristic of neutral milk. The
preparation of curd milk when the rennet is neutral, results in a
coagulation occurring at 40-60°C. Complete curd formation occurs in the
early stomach (1872) that the rennet enzymes of the stomach has
been influenced by the condition of the milk.
pepsin is a product of the pyloric glands as well as of the cardiac ones. Further, Kleimansiegwig (1875) by making a pyloric fistula in dogs proved that the pyloric tube which he had established secreted an alkaline viscous liquid (serous pyloricus) which by itself did not digest proteins, but which did so after acidulation with HCL.

Kleimansiegwig, however, from not using antiseptic precautions got his secretion mixed up with pus. Heidenhain (1878) repeated Kleimansiegwig's procedure, using antiseptic precautions. He showed that food on entering the stomach slowly sets up a secretion of pyloric juice, which always has an alkaline reaction, is viscid, and is rich in peptic and in rennin, which acidulated with HCL digested protein abundantly. Heidenhain further proceeded to make a tubular fistula from the cardiac end of the stomach to the body wall. In such a preparation he found that a few minutes after the introduction of food into the stomach, secretion commenced in the toe, and continued throughout the whole period of digestion. This fluid secreted at the fundus he found was watery, of acid reaction, and contained pepsin and rennin. As a consequence of this and other observations he put forward the view that the central (chief) cells were connected with the formation of pepsin and rennin, and the border cells with the formation of the acid of the gastric juice.

Schröm showed (Arch. f. d. Physiol. 1878) that there is a close parallelism between the amount of rennin and pepsin produced in
the stomach, both increasing and diminishing together. It has therefore been concluded that the granules of the chief cells contain together the pepsinogen, both of rennin and pepsin.

Edkins and Starling have shown cause for believing that the pyloric glands form a substance which bears the power of acting as a hormone, or chemical excitant to the glands secreting the gastric juice; this hormone they have termed 'gastriole secretin.'

2) Form of the secretion. Sobrani and Gützgen have concluded from the difference in digestive power of a 1 N Cl extract compared with a glycerine extract of the gastric mucous membrane that there was a 'pepsino-crement' substance in the gastric mucous membrane which under the influence of HCl gives rise to pepsin. Langley was the first (1882) to bring forward conclusive proof of the existence of pepsin in the gastric glands in a zymogenic or pepsinogen form (Jour. of Physiol. III. 253 p.). He arrived at this conclusion from the different behaviour of pepsin and pepsinogen when digested at 40°C. with a solution (1/2-1%) of sodic carbonate, the pepsin being very rapidly destroyed thereby, the pepsinogen only comparatively slowly. Langley showed that the gastric glands contain no ferment during life, but much zymogen or substance capable of giving rise to ferment; and that by far the greater part of the zymogen can be seen in the chief cells in the form of granules. 'During digestion these granules are used up in such a manner as to give rise to an outer non-granular, and an inner granular zone in the chief cells.' Working further along
with, Eschin. Langley has determined (Jour. of Physiol. 1886) that pepsinogen is very rapidly converted into pepsin by dilute mineral acids. In neutral and alkaline solution its conversion is slow; and in a pepsin extract it may remain unchanged for years. Both pepsinogen and pepsin are rapidly destroyed when heated to 55-57° C.

3) Acidity of the gastric juice. Cl. Bernard (Regensr. 1859) by injecting a solution of ferrie carbonate + potassium ferrocyanide into the blood - from which a blue colour is formed only where free acid is present, - tried to find where the acid in the stomach was produced. He found that while the surface of the stomach was stained a Prussian blue colour, the deeper portions of the mucous membrane were unstained. This, however, might be explained from the larger supply of alkaline lymph in the deeper parts.

It was pointed out by Heidenhain & others that the border (organic) cells are most abundant in the mid region of the stomach, & that in that region the secretion is most distinctly acid; whereas in other parts the secretion is less acid or alkaline. Hence it seems probable that the border cells are the agents by which the HCl is secreted.

Maly first showed (1874) that by the action between di-sodium phosphate & the Carboxy acid of the blood mono-sodium phosphate is formed; and from mono-sodium phosphate & soda or chloride, HCl may be produced; and from its high diffusive power he thought that HCl might thus be set free in the favourable apparatus of the gastric glands.

Rafle & Brücke (1875) thought the process of separation of the HCl was an electrolytic one; but beyond the fact that the chlorides
are the most likely source of the acid (as shown by Hertiguer, 1875, &
other), our knowledge does not extend.

Richter

Richter (1878) has concluded that the cholionic-containing acid of the
gastric juice is not free HCl, but an acid combined with lecithin;
this chiefly from the amount of acid which is adsorbed from a solution
by ether ("coefficient of distribution"). But this view has not been
generally accepted. Richter also found that the acidity of the
gastric juice in the human stomach gradually increases during digestion;

Chieschi

and Chieschi (I. c., p. 142) 1894, first gave precise details on this
matter, and also as to the varying digestive powers of the gastric juice

Kihigine

on feeding with different kinds of food. Kihigine showed
further (Arch. d. sc. biol. 1895) that the amount of juice secreted is not
necessarily proportional to its acidity, or its digestive power, nor these
two latter to each other.

Beaumont

14) Nervous Control. Beaumont had observed (1833)
that mere mechanical irritation of the stomach, as by pebbles placed in
it, produces very slight and local secretion; whereas solid food produces
a general and continuous flow.

Bieder +

Schmidt

and that in dogs with gastric fistulae, which had been starved, the
sight of food caused an abnormal flow of gastric juice.

Richter

Similarly, Richter observed (1878) that in cases of obstrual stenosis,
if the patient chews savoury articles of food, there was along with
increased saliva secretion, a copious flow of gastric juice.

Heidenhain

Heidenhain (1878) confirmed these observations, and showed that
when solid food was swallowed, the flow of gastric juice followed
after a latent period of about fifteen minutes. Indigestible substan-
produced only a partial secretion. This only on drinking; from which he concluded that the products of digestion in the stomach act as the essential stimuli to the secreting glands of the stomach.

So much for the indirect nervous control. As to the direct nervous control - Rutherford (Trans. Roy. Soc. Edin. 1870) cut the vagi during digestion and found that the mucous membrane became paler. No effect resulted on stimulating the peripheral end; but on stimulating the central end the mucous membrane became redder; and normal gastric juice was still secreted after cutting both the vagi and the pharyngeal nerves.

Goltz Similarly Goltz (1872) and others showed that section of the vagi arrested the movements of the stomach, and for a time also the secretion of the gastric juice, but not permanently. Section of the sympathetic nerves also was found not to stop the secretion.

Pavlov Pavlov, along with Schramm and Simonowitsch, however, has greatly extended our knowledge of the nervous control of the gastric secretion ("Die Innervation der Magen wand" 1872). He showed that there is a distinct nervous influence acting upon the secreting epithelium of the stomach. His experiments were made on dogs which had a portion of the stomach isolated, but with the nervous connections intact. The esophagus was separated from the stomach. The cut ends of both esophagus and stomach were brought out at the neck. Food could thus be swallowed without entering the stomach (pseudo-eating); or could be introduced directly to the stomach. It was found that when the animal ate food without it entering the stomach, an abundant secretion of gastric juice followed. Evidently from the sensations developed during mastication
and swallowing, provided the vagi were intact. This method Pavlov has denominated 'psychical secretion.' By cutting both vagi, he found that the reflex secretion of gastric juice, normally produced by the sight or taste of food, was absent. By stimulating the peripheral end of the cut vagi, there resulted a flow of gastric juice varying according to the nature of the food taken, and after a certain latent period.

Lchischini (Jiang’s Dietet 1874) one of Pavlov’s followers, found that peptone when placed in the dog’s stomach (as in Pavlov’s experiment) was able to produce an abundant and sustained flow of gastric juice, much greater than that excited by water, egg-albumen, sugar or starch solution. He concluded that this first flow of gastric juice is determined by the reflex influences involved in taking food. The degested proteins are able later to evoke a secretion when the psychical influence begins to wane.

Pavlov and his school have thus shown:

1. That the secretion of gastric juice is normally dependent on afferent stimuli conveyed from the mouth, nostrils, throat, produced by the taste, smell, or of food; these stimuli are in turn conveyed by afferent fibres to the gastric glands.

2. Foods when taken into the stomach are able to cause an additional and continued secretion of gastric juice, this in very varying degree.

3. The products of digestion in the stomach are able to produce a further and continued flow of gastric juice.

Edkins has lately shown (Journ. of Physiol. 1906) that decomposing of the pyloric mucous membrane when injected into the blood cause a marked secretion of gastric juice. He has concluded therefore that the pyloric glands produce a substance of the nature of a hormone, which he
has designated 'gastric secretion'—which is able after absorption into the blood to stimulate the gastric glands to secretion. There would therefore appear to be this chemical means, in addition to the nervous one, by which the flow of gastric juice is controlled.

3. Function of the Gastric Juice.

Mesener first systematically investigated the products of gastric digestion (1857-62). When the products of digestion of a protein by gastric juice are almost neutralised, there is deposited a white, flocculent precipitate to which Mesener gave the name 'parapeptone.' It is insoluble in water, and is not acted upon by pepsin or an acid. He also described other peptones (now known as albumoses), as being formed in the filtrate from the above.

Kühne (1863) next studied the decomposition which proteins undergo when acted upon by pepsin and an acid, as compared with the decomposition effected by trypsin (as he termed the proteolytic enzyme of the pancreas) in alkaline solution. He found that while pepsin in acid solution is able to convert a protein into peptones, no further decomposition of these takes place, however prolonged the action of the gastric juice, or however abundant the pepsin at work. As intermediate bodies between the protein and the peptone stage he found a group of bodies which he divided into primary and secondary albumoses—the latter being more soluble than the former. The peptones he described as bodies which gave the litreat reaction, but which are not coagulated by heat, nor precipitated on passage saturation with ammonium sulphate.

Hofmeister. More recently Hofmeister has concluded (Ergel. d. Physiol. 1902) that the breaking up of the protein molecule by pepsin may be more complete than Kühne thought, if time enough is given for it to act. He believes
that along with the peptones are found bodies which no longer give the
biret reaction, but precipitable by phosphostaphylic acid, to which he gives
the name of peptoids. In addition he has found after pancreatic digestion
many of the amino-acids & nitrogenous bases which constitute the final
end-products of the breaking up of the protein molecule.

III. Pancreatic Secretion.

Tiedemann & Gmelin first definitely
established in 1826 that the pancreatic secretion obtained through a pan-
creatic fistula was alkaline in its reaction; and in 1831 they described
the rose-red colour which the pancreatic juice (of the dog) assumes when mixed
with chlorine water: (Due to Trypsinone, one of the products of trypsin digestion)

Wohle

Roselle announced in 1834 that a watery infusion of pancreas when
shaken with oil converted it into a creamy emulsion, and he
surmised that in this way the absorption of fat by the lacunae is
furthered.

Purkinje & Pappenheim discovered in 1836
(according to a statement made by Corvisart) that extracts of the pancreas
have the power of dissolving proteids. This discovery, however, seems to
have attracted almost no attention.

Bouchardat

Bouchardat & Sandras (C. R. de l'Acad. 1845) first discovered and
established by accurate observations on the pancreatic juice of rats and
guinea, that this secretion has powerful deastringic properties, starch
being rapidly converted into dextrine.

Ch. Bernard

It was, however, Claude Bernard who first (1846), by means of careful
experiments on dogs in which pancreatic fistulae had been established,
gave anything like a complete account of the nature of the pancreatic
secretion. He also discovered its fat-splitting ferments.

1) Diastatic Ferment. Bouchardat & Sandronc discovered the
diastatic action of pancreatic juice made watery extracts of pancreas,
and precipitated the solution with alcohol. The precipitate, soluble
in water, they called ‘panecratin’. It had a diastatic action, but had
of course, other ferment actions as well, which they did not describe.

Danielowski

Danielowski (1861) got this ferment in approximately pure form by
precipitating an aqueous infusion of the pancreas with colloidion, which carried
down the proteins & trypsin in gelatinsous form; then he concentrated the
precipitate & precipitated amylase with alcohol (Vierchow Archiv 25, 279)
Other methods have been similarly employed by Cohenheim (1863),
v. Wintic (1869), Robert, and others.

v. Mering

v. Mering & Musculus found (1876-9) that the action of amylase was
similar to that of ptyalin. They found that in both cases alpha-1,4-glucosidase,
maltase, & a little glucose sugar were formed from starch.

E. Bernard

2) Fat-splitting ferment - Steapsin. In 1846 E. Bernard while
making a comparative study of digestion in Carnivora & herbivora, found
that when dogs are fed on fat, the fatty matter appeared to undergo a
modification almost as soon as it entered the small intestine; whereas
in rabbits, similarly fed the change occurred farther from the pylorus.
Similarly the lachets of the dog from the pylorus down were found filled with
a white, opalescent chyle after a fatty meal; whereas in the rabbit the lachets
near the pylorus did not contain white chyle, while those lower down did.
He then found that this difference coincided with the different situations in the
dog & rabbit respectively, where the pancreatic duct joined the small intestine
- that in the rabbit being considerably lower down than in the dog. He therefore
was led to inquire whether pancreatic juice was not the active agent in the digestion of fat, and he discovered that the pancreatic juice had the property of 1) emulsifying fats, fluid at the body temperature; 2) decomposing such fats with the formation of fatty acids. The fact that there was a formation of an emulsion of fat in the intestines had been previously stated by Charle (1824). But Cl. Bernard first in his classical researches brought this fact into prominence. He thought that the formation of an emulsion in the intestines was due to a special ferment action on the part of the pancreatic juice. He spoke of an "emulsifying ferment" as being present (C.R. Acad. 2, Sc. 1844).

Brücke later showed (1870) that if an oil or fat is shaken with a weak solution of sodium carbonate, an emulsion is readily got; but not if the oil is perfectly neutral. The fat-splitting property which Bernard discovered was shown by him to belong also to the pancreatic tissue itself, but this only when it was fresh; for when it was kept, it became acid, its fat-splitting property became permanently lost.

Gürtner has found that the richness of the pancreas in the fat ferment varies in the same manner as its richness in diastatic and proteolytic ferments—being greatest about six hours after a meal (Dog), and least in the fasting animal.

Kastle and Hoemenhout (Annee. Journ. of Physiol. 1902) claim to have established that steapain (lipase) may exert in the case of a simple ester analogous to the fats—ethyl linoleate—not only a fat-splitting action, but also the reverse synthetic action of fat formation from butyric acid and ethyl alcohol. It is believed by them that steapain may exert a similar power in the case of the fats in
the body. If so, it is possible to explain by the action of such an enzyme both the formation of the absorption of fat in the tissues of the body.

3) **Trypsin.** — tenon Bernard stated that the pancreatic juice by itself had no action upon proteins; but he found that it is able to dissolve them if it was first mixed with bile. He does not seem, however, to have attached much importance to this function of the pancreatic juice. It was Corvisart (1857-8) who first showed that the pancreatic juice has in a high degree the power of digesting proteins at the body temperature, this in neutral, alkaline, or even slightly acid fluids. He showed that pancreatic juice extracts of the pancreas have the power not only of dissolving proteins, but also of converting them into peptones. Some observers, however, denied the results of Corvisart. 

**Fricke** (1859) corroborated Corvisart's statements; but he believed that a slightly acid reaction was absolutely necessary for pancreatic as for gastric proteolysis.

**Daniele-Foix** (1862) again confirmed Corvisart's statements, devised a method (as we have seen) of approximately separating the trypsin from amylopasta, and then he found that the former was only capable of digesting proteins in neutral or fully alkaline solutions — digestion being inhibited by the presence of free alkali or of free acid.

**Kühne** (1867) found that pancreatic juice has a far greater proteolytic activity, weight for weight, than gastric juice. He made the interesting discovery that when blood fibrin is subjected to pancreatic digestion, it yields not merely peptones similar to those resulting from peptic digestion, but also amino-acids, such as leucin, tyrosin, etc.
Heidenhain

Heidenhain (Pflügers Archiv X, 557 ff.) in 1875 published his remarkable paper on the changes in the cells of the pancreas during digestion; the further announced that the fresh pancreas contains the trypsin only in zymogen form which under suitable treatment yields the proteolytic ferment.

A good deal of the early dulicity as to the proteolytic function of the pancreatic juice may be explained by the discovery made by Chepomalnikows in Pavlov's laboratory (Thesis St. Petersburg 1899) that the pancreatic juice obtained from a fistula may have little or no digestive action on proteins, but if brought into contact with the duodenal membrane, or an extract of this membrane, it shows at once powerful proteolytic properties. Pavlov believed that there is an enzyme produced in the duodenum which activates the trypsin of the pancreatic juice, which he designated it enterokinase since it acts as a ferment of ferment.

2. Method of secretion

1) Mechanism. We have already referred to the epoch making paper of Heidenhain in 1875 (Pflügers Archiv X, 557 ff.) in which he investigated the method of formation of pancreatic secretion. He found that in animals which had fasted for 30 hours, there were two zones observable in the secreting cells: an inner one next to the lumen which was studded with fine granules; and a smaller outer zone which was homogeneous or marked with delicate strie. Then the pancreas of an animal during full digestion — some six hours after food was examined, the entire homogeneous zone was found to be much wider than before; the granular inner zone being corres...
pendingly narrower, and in some cases having actually disappeared. At the end of digestion the outer zone was again found to be narrower, the granular inner zone being full. The conclusion that the granular inner zone contained the materials for the secretion, that it, the outer zone furnished these materials out of its protoplasm at the expense of the blood supply. Köhne & Lea (1877 & 1882) corroborated the observations of Heidenhain, & described more fully the different appearances in the cells + alveoli. Heidenhain (1875) also investigated the normal flow of pancreatic juice. He found that immediately after food has been taken, secretion of pancreatic juice commences, the rate of secretion increases rapidly, reaching a maximum within three hours; it then diminishes till about the 6th hour; then rises again till about the 10th hour; then sinks, & absolutely ceases at about 24 hours. The early secretion is very viscous, and highly coagulable, & it gradually becomes less viscous & coagulable.

Much light was later thrown upon the normal mechanism of pancreatic secretion by the discovery made by Dolinszki (1895) that acids brought into contact with the mucous membrane of the duodenum set up a secretion of pancreatic juice. He concluded that as soon as any of the acid contents of the stomach pass into the duodenum this action begins. He believed (as also Poulton) that the action of the acid was upon the sensory endings of the nerve fibres in the duodenum, this stimulus being reflected to the pancreas by its secretory fibres. More recently, however, it has been shown by Baylis & Starling (Journ. of Physiol. 1905) that if the mucous membrane of the duodenum or jejunum is scraped off, & treated with acid (4% HCl), the
extract thus made when injected into the blood sets up an active secretion of pancreatic juice. They have concluded that this effect is due to a special substance, 'secretin', of the nature of a hormone, which is formed by the action of the acid upon a substance—pro-secretin', which is present in the cell contents of the mucous membrane.

2) Form of the secretion. Liversidge was the first (1873) to find indications of zymogenic form in which at least one of the pancreatic enzymes exists in its cells. He showed (Journ. of Anat. & Physiol. 8:28) how a minced pancreas after being presumably exhausted of its diastatic ferment by long continued washing in water, if transferred to a filter, & allowed to remain exposed to the air for a few hours, then again treated with a small amount of distilled water, would again give out a very active diastatic ferment; and many months were, he found, necessary under the action of glycerine to completely exhaust the minced pancreas of its diastatic ferment.

Heidenhain, however, first brought forward proof of the existence of such a zymogen in the case of trypsin. He found that the zymogen of trypsin was soluble in glycerine, & remained undecomposed in neutral glycerine solution; but that the zymogen splits up with the formation of free trypsin, a) in watery solution—with a rapidity increasing (to a certain point) with the temperature; b) in acid watery solutions more rapidly than in neutral; c) in solutions of neutral & of alkaline salts. It has been doubted whether there is a precursor (similar to trypsinogen) of either amylase or trypsin in the cells of the pancreas (c. Edkins, Schaffer's Physiology p.553). But some evidence has been brought forward recently by Dixon & Hamill (Journ. of Physiol. 1909) that there are three zymogens produced by the pancreatic cells—pro-trypsinogen.
proamylipase, and that the secretion produced in the duodenum acts on them all, liberating trypsinogen, amylipase, lipase.

3) Nervous control. Heidenhain found (1875) that (1) when all the nerves going to the pancreas were divided, secretion of a thin, watery juice was got; (2) paralytic salivation; (3) Electric stimulation of the medulla oblongata starts the secretion, or increases it, if already going on; (4) Secretion is arrested by stimulation of the central end of the divided vagus, or of sensory nerves generally, and this arrest lasts for some time after the stimulation has ceased.

Other observers, however, after Heidenhain got no constant secretion after stimulation of either the splanchnic nerve or the vagi.

Pavlov. Pavlov and his co-workers have more recently thrown much fresh light on the matter. Pavlov found (Arch. f. Physiol. 1893) that by stimulating the peripheral end of the cut vagus some 5 days after cutting it, i.e. after the vaso-constrictor fibres had degenerated, a marked secretion of pancreatic juice could be obtained. Also he found that stimulation of the other (intact) vagus produced the same result. It was found, however, that such nerve stimulation only produced a secretion after a long latent period of some minutes, a fact which was explained by the assumption that the nerve trunks contain both secretory and inhibitory fibres - the latter delaying the influence of the former.

Pupielski. Pupielski found (Centralbl. f. Physiol. 1896) that a flow of pancreatic juice excited by the introduction of acetic to the duodenum was inhibited by stimulation of the vagus trunk. So also was a flow excited by pilocarpine. He found further that if the stimulus be applied to the main mass of nerves passing from the coeliac plexus to the pancreas, a secretion of pancreatic juice is got without marked latent period, and uniform in character. He concluded therefore, that there are both secretory and inhibitory fibres running in the vagi.
to the pancreas; from the differences in latent period manifest on stimulation in different regions, he thinks it likely that the inhibitory impulses passing along the vagus do not react directly on the cells of the gland, but on some secondary centre which controls the secretion, & which he thinks is situated in the walls of the pylorus.

More recently still it has been found by Sawitsch (Centralbl. f. d. ges. Physiol. 1909) that the secretion of pancreatic juice induced by stimulating the vagus & splanchnicus (nervous secretion), differs in character from that induced by the action of secerhin (chemical secretion). The former is thick, opalescent, rich in ferments & proteins, but poor in alkalis. The trypsin contained in it may be secreted in active form, & it may be excited by pilocarpine, or suspended by atropine. The chemical secretion, on the contrary, is thin & watery, has relatively little ferment or protein, & is rich in alkalis. The trypsin in it is secreted in inactive form, & the secretion is not affected by the administration of pilocarpine or atropine.

3. Functions of Pancreatic Secretion. We have already alluded to the action of amylase & trypsin in digestion. As to tryptic digestion, Kühne (1883-9) was the first to make thorough investigations as in the case of ptycric digestion. He found that trypsin in alkaline solution was able to decompose proteins in such a manner that this resulted as final products a quantity of peptones (antialbumins) which roughly amounted to half the weight of the protein acted upon, together with a mixture of much less complex bodies, of which the chief were certain amino-acids, particularly leucine & tyrosine. He found also that the action of trypsin is greatest in solutions containing about 1% sodium carbonate, & it was injuriously affected by the presence of HCl, if in greater strength than .05%.
a result which has been confirmed by Langley (Jour. Physiol. 1851) and others.

Weinland and others that after prolonged pancreatic digestion, no peptone or peptone-like body can be found, in fact as substance which gives a brown reaction.

Vernon has tried to show (Jour. of Physiol. 1905) that the pancreatic secretion contains two proteolytic enzymes - trypsin proper, which converts proteins to peptones, and another - "pancreatic resin", which breaks up the peptones to amines - bodies. A. Abderhalden again (Zeitschr. f. physiol. Chemie 1905) has shown some reason for believing that a certain amount of a substance (polypeptide) intermediate in composition between the peptones and the simpler end-products, is left behind after tryptic digestion; and it, he thinks, may serve as a starting point for a synthesis of proteins in the human body. (Note: the secretion produced by the cells of the exocrine glands will be referred to under Internal Secretions).

IV. Liver Secretion. A. Bile.

1. Nature of the Secretion. We have already seen how the early physiologists attached great importance to bile as an agent in the general economy. The general trend of modern research has been to show that bile is, in great part, only a by-product of the liver cells, that the main function of the liver is to be found in other directions.

Jenemann. Composition of Bile. In 1826 Jenemann & Jacobin (Kdamerung, J. Berach.) discovered the bile pigments, and cholesterol, and they first described the play of the colouring matter in treating bile with nitric acid.

Demaray. (1838) pointed out the combination of cholic (or taurine cholic) acid with sodium, and he determined the empirical formula of
A. Streeker, choleic acid. 

Gundelach, by his mastery researches along with Gundelach at length isolated both of the bile acids (glycocholic and taurocholic), determined their formulas, and the manner in which they may be split up into a non-nitrogenous acid and amido-components.

Bergelius first attempted the separation of the colouring matters of bile — which he named cholepyrrohine (= biliurin), biliurin, which latter he thought was identical with the chlorophyll of plants (Berührung 1840). Heintz investigated (1851) the colouring matter of gall-stones; and Stöckel (1864, Über die Farbstoffe der Galle) gave the first full account of the bile colouring matters.

2. Method of Secretion. The means of securing bile artificially was first shown by Schwann (1844) who first established a biliary fistula in the dog. Schiff in 1870 first established an amphibolic fistula — without occlusion of the common bile duct; thus this way secured samples of bile under something like normal conditions.

a. Flow of Bile. Biber-Schmidt (1852) and later Kohne (1873) others noticed that the introduction of water into the stomach and intestines of dogs with biliary fistulae increased the flow of bile. Kohne found (1858) that the flow was somewhat influenced by the character of the diet, being most abundant if meat mixed with fat was given, but much less if the amount of fat was excessive.

Hoppé-Seyler found (Physiol. Chemie 1878) that the secretion of bile increases immediately after a meal; the increase being maintained for about an hour; then there is a certain diminution in the rate, followed by an increase again between the 3rd and 5th hours of digestion.

Rosenburg, 1890 (Arch. f. d. Physiol.) + Barbara (1894) found in dogs with a permanent fistula an increase in the
secretion of bile and the bile solids, after protein food, and also that the administration of fats markedly increased the bile flow.

Bruns has more recently found (Arch. der Sc. biol. 1894) that no bile appears in the duodenum as long as the stomach is empty; but when a meal is taken, the ejection of chyme into the duodenum excites, probably by reflex action, a contraction of the gall-bladder, and an inhibition of the sphincters closing the opening of the common bile duct into the duodenum; and he found that this reflex action was produced by proteins and fats, or some of the products of their digestion, but not by acids, alkalies, or starch.

Schiff. Many investigations have been made into the alleged cholepaque function of various tinctures, but results have not been constant. Schiff (1868) pointed out that the quantity of bile secreted by dogs with lithaury fistulae diminished when the bile was withdrawn altogether from the alimentary canal, but that it increased again within 12-15 minutes when bile flowed again into the intestines (v. Pflüger and K.)

Heidenhain (1875) found that the introduction of a solution of bile salts into the intestines by a duodenal fistula caused an increase both in the total quantity of bile, and in the bile solids secreted. He concluded that some of the bile absorbed from the intestines was returned to the liver by the portal blood, or (if the portal vein was tied) by the general blood of the body, and furnished it with a part of the material for the secretion of new bile. Schiff's observations were confirmed by Rutherford and Vignal (Journ. of Physiol. 1876) and others.

Socoloff (Pflüger Archiv 1875) provided evidence that the substances conveyed by the blood might not actually pass into the new secretion, but might merely act by exciting the secreting elements of the gland to increased activity.
Heidenhain's view by showing that if sodium glycocholate (which is not found in the bile of a dog) be injected into the stomach or the blood of a dog, it is found that no glycocholic acid is secreted in the dog's bile thereafter, but the bile acids normal to that animal. Wertheimer (1889-92 Arch. de Physiol.) following the method of Baldis (1883) injected the bile of a sheep containing cholehaematin into a dog (which has other pigments), he found that the bile excreted by the dog showed the absorption bands of cholehaematin, and along with this, there was an increased flow of bile. It would seem, therefore, that there may be some measure of "circulation of the bile," and in any case it is proven that bile itself has a strong chologogue value.


e. Function of hepatic cells. Friedländer & Barisch 1882.

Heidenhain showed that the secretion of bile takes place under a low pressure, compared with the salivary secretion. But Heidenhain (see Hermann, N.B. 1883) found that the pressure of bile secretion was considerably higher than the blood pressure in the superior mesenteric vein, being as 2:45:1. Therefore, he showed, the elimination of the content of bile must be by a process of secretion not of transudation.

Glimsen: Bile-pigments. Glimsen, and most of the older observers have thought of the liver as a sort of filter for the bile, or the bile constituents, which were performed in the blood. Stern (1885) showed that one tying all the blood vessels going to the liver, values the bile ducts, no bile colouring matter accumulates in the blood or in the tissues; he concluded therefore that the bile pigments were not performed in the blood.
Minkowski + Klemmer demonstrated (Arch. f. exp. Path. u. Pharm. 1886) that the bile acids are formed by the liver cells, not merely absorbed from the blood. They found on ligaturing the bile duct that bile salts appear in the blood, but on excluding the liver from the circulation, these salts again disappear from the circulation.

Cholesterin. Jankowski (1896) showed that cholesterin is found somewhere within the liver, and not merely excreted by it from the blood. He injected cholesterin into dogs, and gave it in their food; he found it was absorbed as food, but it did not cause any increase of cholesterin in the liver tissue or in the bile. Thomas, however, (1896) found that there is no constant relationship between the amount of cholesterin excreted, and the kind of food taken. It has been supposed that probably cholesterin is a product of the disintegration of the cells of the liver passages.

Water in Bile. Birch & Strong (J. Physiol. 1896) and Mayo & Robinson (Proc. Roy. Soc. 1890) showed that the water in bile is probably in part secreted from the walls of the bile passages, since when the cystic duct is occluded, the fundus of the gall-bladder is opened, a small amount of fluid is secreted (about 70 c.c. per day) from the walls of the gall-bladder, perhaps in part pathological.

L. H. Ebershain found (1867) that section of the cervical cord causes a fall in the amount of bile secretion, possibly due to a lowering of the general blood-pressure. He also found that stimulation of the cord, or of the sensory nerves in general, causes a diminished flow of bile from contraction produced in the vessels of the splanchic area.

Heidenhain found (Guttermann's H. B. 1883) that section of the splanchic nerves causes dilatation of the splanchic arteries, i.e., an increase in the
flow of bile. Stimulation of the splanchnic nerves causes constriction of the arteries, and a fall of bile secretion (Kunkel, Pflüger's Arch. 1874). There is no evidence therefore of direct nervous control over the secretion of bile.

Bainbridge + Dale (1874) found that the gall-bladder receives both motor & inhibitory fibers by way of the splanchnic nerves. Motor fibers were also found in the vagi. Stimulation of the central end of the cut splanchnic caused a dilatation of the bladder, while stimulation of the central end of the cut vagus caused a contraction of the gall-bladder, & a dilatation of the sphincter at the opening of the common bile-duct to the duodenum. These movements seemed to occur reflexly during the process of digestion.

3. Function of Bile. 1) Action on Starch. Bidder + Schmidt (1857) found that bile, if digested with starch solution for many hours, is able to convert traces of starch into sugar. It would seem therefore to have a very slight action on starch digestion.

2) Proteids. Bidder + Schmidt found that if bile is added to the acid products of gastric digestion, a precipitate is produced, composed of a mixture of proteins & bile acids, which carries pepsin down with it. (Bidder, Phys. Exp. 1857)

Bürcke found that though the quantity of bile may be insufficient to neutralise the acidity of the chyme, yet the proteolytic activity of the pepsin is at once arrested. Kühne, Hammarsten, & H. Kahle + Emich (1883) have found that bile does not precipitate albumen or pepsin, but only native albumen; this may favour the action of the panaclacini juice upon the latter.

Bürcke + Schmidt (1857) first ascertained with precision that when bile is cut off, the feces contain a large quantity of fat; and they conclude
that by removing bile the absorption of fat is in some way interfered with.

Bile has long been known to remove grease stains, from its power of dissolving small quantities of neutral fat. The formation of an emulsion of fat in the intestine was referred to by Eberle (Physiol. J. Verhandl. 1875).

But attention was first called to the action of alkaline salts of bile in promoting an emulsion of fats by Marcey (C.R. Soc. Fr. 1857). He found that bile when mixed with fatty acids can form a perfect emulsion of neutral fats at the body temperature.

Brücke (B. G. J. Akad. d. Wiss. 1870) found likewise that the presence of a certain amount of free fatty acid, such as is produced by the action of the pancreatic juice on fats, is sufficient to emulsify the remaining neutral fat. More recent observations have confirmed these results, and have shown that the bile salts aid in the absorption of the split fats by dissolving the fatty acids readily, thus bringing them into contact with soluble forms, with the epithelial cells (Moore & Rockwood--Jour. of Physiol. 1897; & Moore & Parker--Proc. Roy. Soc. 1901)

4) Antiseptic action of bile. Marcey & Enich showed (1883) that free bile acids--especially taurocholic acid--have a powerful antiseptic action.

But it has never been shown that these acids exist free in the intestines, although it is believed they may be developed from the action on bile salts of strong organic acids (e.g., lactic) produced by bacterial action on carbohydrates.

Capman & Winston, on the other hand, found (Jour. of Physiol. 1889) that microorganisms of many kinds develop well in bile media (bile-salts).

B. Urea-formation in the liver.

v. Schröder (Arch. f. exp. Path. u. Pharm. 1882 & 1883) first obtained evidence of the formation of urea in the liver, as against its formation in the kidney, as was previously believed. He found on extracting the kidneys of a dog...
that the amount of urea in the blood was increased four-fold. Also in blood containing Ammonium Carbonate which had passed through the kidney there was no increase of urea; whereas similar blood passed several times through the liver contained two to three times as much urea as it had before. Salomon (Virchow's Arch. 1854) repeated these experiments in sheep and dogs, and corroborated the results.

Richter further, Richter (C.R. Soc. de Biol. 1846) has shown that a urea-forming ferment can be precipitated by alcohol from aqueous extracts of the liver.

C. Glycogen-formation in the liver.

C. Bernard. 1. Formation of Glycogen. C. Bernard discovered in 1845 (C.R. Acad. 1845) that sugar is formed in the liver; but not till 1857 did he succeed in isolating the substance, glycogen, from which it is produced.

Henon Henon (Virchow's Archiv 1857) also independently discovered glycogen. Bernard found that during absorption of a meal containing carbohydrates the blood of the portal vein contained an excess of sugar. He concluded that the sugar was arrested in the liver. He also found that there was an accumulation of glycogen in the liver after absorption of such a meal; and also after the slow injection of a solution of dextrose into one of the mesenteric veins of a fasting dog. Bernard concluded also from his experiments that glycogen might be formed from proteins as well as from carbohydrates. This result has been confirmed by Ranney (Arch. f. exp. Path. u. Pharm. 1875) who fed porks for several weeks exclusively on muscle (stems) squeezed out, and found large quantities of glycogen in the liver.

V. Mering V. Mering also (Pflüger's Archiv 1877) fed a dog previously starved for 21 days, for 4 days exclusively on washed bull's blood, the
found, on killing it, that the liver contained 3-4% of glycogen.

2. Transformation of Glycogen. Bernard discovered that the transformation of glycogen to sugar occurs very rapidly after death if the liver is kept at the body temperature. He believed the transformation was due to an amylolytic ferment contained in the liver (lesions sur
le diabète 1877). He found, further, that except during the absorption of food the blood of the hepatic vein constantly contains more sugar than the blood of the portal vein. He concluded that the glycogen of the liver gives off carbohydrate material into the blood in the form of glucose. He found also that sugar is being continually passed from the liver into the tail vein hepatic blood - even during starvation (in the dog).

Bernard's observations were supported by Seegen (Die Zuckerbildung im Theikörper 1890) and others, but it has been shown by J. Munk, Tann and others that an excess of sugar in the hepatic blood occurs on any operation without anaesthesia (as Bernard's and Seegen's were) from transformation of glycogen to sugar in the liver.

Parry (Physiol. of the Carbohydrates, 1894) has found, in opposition to Bernard's theory, that blood taken from the inferior vena cava of an animal immediately after a sudden death shows no appreciable excess of sugar.

Support, however, is given to Bernard's theory by the fact that a ferment converting glycogen to glucose has been obtained from the liver by Arthur and Hühner (Arch. de physiol. norm. et path. 1892), and also by Bial (Arch. f. d. ges Physiol. 1893) who states that it is identical with a probably derived from the digestive ferment of the blood lymph.
Intestinal Secretion. Success Intestines.

1. Method of obtaining. Telemann & Kymelini (1826) & Latini Buscher & Schmidt (1852) isolated loops of intestines by ligatures, replaced them in the abdomen, & then examined the fluid which accumulated in 4-6 hours. Thiry (Sitzungsb. d. Wiener Akad. 1864) first isolated a portion of the small intestine, established a fistulose aperture between it & the abdominal wall. He divided 4-6 inches of small intestine at each end, then sutured the upper cut end to the lower, thus restoring the continuity of the gut. The resected part was sutured at one end; the other end was stitched to an opening in the abdominal wall. Vella (Medizin, Ueber, 1867) used antiseptic precautions & improved Thiry's operation by suturing both ends of the resected part to the opening in the abdominal wall.

2. Secretion of Success Intestines. a) Natural flow. Its secretion, or a very small amount was found by the above methods to be forced out, if no mechanical, chemical, or electrical stimuli were used. This was observed by Buscher (1852). Thiry, Vella & others. Then Thiry found that electric stimuli induced a powerful secretion. Vella got the same result by injections of pilocarpine. Rohmann (1887) found that solutions of starch, sugar, & pufiones provide a secretion of success intestines. But Gamgee (1893 Physiol. Chemistry) found that it was possible to produce considerable increase of other secretions by the administration of pilocarpine without affecting the flow of success intestines to any extent. Pregl (Arch. f. ges. Physiol. 1896) from a fistula in a lamb found that the secretion of success intestines was continuous; but it increased the first hour after food, & this went on to about the third hour, then diminished to the fifth hour — from which on it remained steady.
by Nervous Control. They found that stimulation of the vagi had no influence upon secretion of succus entericus. Bridge (1860) found there was an increase of secretion on excitation of the coeliac & mesenteric plexuses, and this was confirmed by L. Brunton & Pye-Smith (Jour. Physiol. 1874-6) when all nervous control between the intestines & the higher nerve centres had been cut off, and also when only the ganglia of the solar plexus, and the superior mesenteric plexus had been destroyed.

Paneth's finding (Arch. f. mikros. Anat. 1888) that the cells at the base of the crypts of Lieberkühn frequently contain definite granules, Hardy & Westbrook (Jour. of Physiol. 1895) found that in fasting animals these granules were large & numerous; in well-fed animals they were comparatively few & smaller than in the fasting state. But it has not been established that these granules are the source of a definite secretion.

3. Function of Succus Entericus. a). They believed that this secretion had a proteolytic function. Schiff (1867) ascribed that all proteids were converted into peptones by it; so also Henle (1868) and Masloff. But Masloff (Klin. Wochenschr. 1882) found that succus entericus has no action on proteids provided the action of proteolytic organisms is prevented by the addition of thymol. If acidified, he found it exerted a slight solvent action on fibrin. Due to this thought, to the presence of a trace of protamin.

Wenz (Festschr. f. Med. 1886) further found that albumins are not converted into peptones by the succus entericus.

Cohnheim—later, however, it has been discovered by Cohnheim (Festschr. f. physiol. Chemie 1901) that there is a proteolytic enzyme, erepsin, in succus entericus, which acts especially upon denatured albumins, peptones, & polypeptides.
Kutscher & Heller man

Converting them into amino acids & ammounia compounds. It has no action upon natural albumins; but Kutscher & Heller man (Koch's Jen. Physiol. Chemie 1907) found that the casein of milk is split by it into simpler compounds.

Bider & Schenót

b) Diastatic. Bider & Schenót (1857) attributed a diastatic action to the sucus entericus. But this was denied by Thiry, Schott, Keube, et al.

Paschertin

In 1871 Paschertin (Arch. f. Anatom. Physiol. 1871) found that the intestinal mucous membrane in its whole extent contains a ferment which converts (inverts) cane sugar to dextrose + lactulose. This was confirmed by Brown & Theron, Rohmann, et al. who all agreed that extracts of the intestinal mucous membrane have much more marked invertin action than the sucus entericus itself. Brown & Theron showed that the invertin action comes to an end as soon as about 25 per cent. of cane sugar was inverted; also that the invertin power of the mucous membrane of the duodenum was much further than that of the jejunum & ileum - which had a strong action especially in the situation of the Peyruss patches.

Brown & Theron (Annalen d. Chemie u. Pharm. 1856) also discovered that the sucus entericus had the power of converting starch into maltose; and this was confirmed by Gumilewski (Pflüger's Archiv 1856) & F. Rohmann (Pflüger's Archiv 1857) 

Maltase. Brown & Theron also discovered that another enzyme was present in the sucus entericus which quickly converts maltose to dextrose; they found that the activity of the sucus entericus in this respect is much greater as we approach the lower end of the small intestine.

A third invertin enzyme, lactase too, which converts milk sugar to glucose + galactose has also been discovered.
A fat-splitting ferment was discovered to exist in the succus entericus by Boldireff (Centr. f. Physiol. 1905).

Entero-kinase. We have already referred (p. 82) to the discovery of entero-kinase and secretin in the small intestine. Bayliss and Starling (J. of Physiol. 1903) have tried to prove that entero-kinase is a product of secretion only of the small intestine, mainly of its upper end, and that it is perfectly specific in its distribution and its action. Its sole action, they believe, is the transformation of trypsinogen into trypsin; and the smallest trace of it will, if sufficient time is given, convert a large quantity of trypsinogen to trypsin.

B. Other External Secretions

I. Secretion of Urine

1. Site of the secretion. The fact that the secretion of urine was in some way performed by the kidneys was known in very ancient times. Thus Aristotle states that the urine is derived from the blood passing through the kidneys, and it then flows through the ureters into the bladder. He also pointed out the relatively large size of the human bladder.

Soon after the Renaissance observations began to be made on the method of urinary secretion. Thus Bouganç (1521) observed on injecting water into the renal vessels that fluid escaped from the papillæ. Roussel (1581) pointed out the muscular nature of the walls of the bladder. He has already referred to the work of Bellini and Malfait on the kidneys.
Urine. v. Helmont in 1644 made the first important chemical investigations of the urine. He demonstrated sodium chloride as one of the solid constituents of the urine, Y explained the development of urinary calculi as being from these solid constituents.

Scheele in 1776 first separated uric acid from human urine. Ronselle in 1773 discovered urea, which was so named by Fourcroy & Vauquelin in 1799; and in 1828 it was obtained artificially by Wöhler by heating ammonium cyanate.

Jr. Liebig in 1853 discovered hippuric acid. Nencki & Pfitzner in 1857 discovered creatin & creatinin. Ramdohr was discovered by Garat in 1819 as a constituent of a urinary calculus, and its presence in urine was first demonstrated by Streeker in 1857. Bützke was the first (1858) to state that sugar is normally present in human urine, and this was again maintained by Parry (1878), but since then it has been generally denied. Bodecker in 1859 first described the urine of alkaptornia—describing its cause to an hypothetical substance called alkaptone.

2. Secretion of Urine. The modern investigations into the method of urinary secretion may be said to begin with Bowman. His theory was first forward in 1842 in the Phil. Trans. London. He founded his views upon the anatomical structure of the kidney in various animals. His view was that the Malpighian bodies separate the watery portion of the urine from the blood. He judged this because of the character of the glomerular epithelium, or because of the tuft-like arrangement of the blood vessels on the free surface of the glomeruli.
the specific constituents of the urine; this, because of their comparatively large extent of surface, their columnar epithelial cells, & the arrangement of the blood vessels.

Ludwig in 1844 first proposed his mechanical theory of urinary secretion in opposition to Bouman's. He believed that a fluid is filtered through the capillaries of the glomeruli containing all the constituents of the urine in dilute solution, so that it becomes gradually more concentrated from absorption of water as it passes along the tubules. The main points in support of this theory were: 1) that increase of pressure in the arterial system causes increased flow of urine; 2) The action of diuretics, which (crystalline) is easily explained on this theory because they cause the osmotic pressure of the urine to approximate that of the blood plasma.

Succeeding investigators have in general supported one or other of these theories. Hoeppe-Seyler (Viehmann Arch. 1859) showed that if urine were separated by an animal membrane from blood serum of the same animal, there was a flow of water from serum to urine - within the opposite direction.

Heidenhain supported & developed Bouman's theory (Viehmann Arch. 1861) He found: 1) that increased capillary pressure produced by ligature of the renal vein does not produce increased formation of urine, but abolishes the urinary flow. 2) the osmotic pressure of the urine in the tubules is generally higher than that of the lymph or blood plasma, therefore concentration (mechanical) of the urine there is impossible. 3) On injecting indigo-carmine into the blood of a rabbit he found the urine became deep blue within a few minutes; and, on dividing the spinal cord in the neck to check the flow of urine, the pigment appeared in the kidneys & in the epithelial cells of the convoluted tubules & the ascending limbs of Henle's loop; the capsule of the collecting tubules & the descending limb being quite free.
Heidenhain concluded from such experiments that the epithelial cells covering the glomeruli have the power of secreting the water and the general salts of the urine; but the tubular epithelial cells secrete the specific constituents of the urine.

Nussbaurn (Arch. f. d. ges. Physiol. 1878) made use of the fact that in amphibians the efferent vessels to the glomeruli are derived from the renal artery, whereas the capillaries round the tubes are derived from the renal portal vein and the efferent glomerular vessels. He therefore ligatured the renal artery (in frogs), and found that the urinary flow was abolished. On injecting urea to the blood it was found to be excreted not by the glomeruli but by the tubes, showing that under strong diuresis the latter could secrete the water of the urine. He found also that peptones, egg-albumin, sugar and carmine, when injected to the blood, were excreted in the urine of a normal frog, but not if the renal artery were previously tied. He concluded that the glomeruli secrete water and salts, and also peptones, sugar &c.; whereas the tubes secrete urea & perhaps urine acid, along with some water.

Adami (Jour. of Physiol. 1885) showed that ligature of the renal arteries in the frog may not cut off the blood from the glomeruli coming to the numerous anastomoses; & he thus diminished the value of Nussbaurn's experiment.

But more recently Bainbridge & Bedward (Jour. of Physiol. 1906) have confirmed & extended the results gained by Nussbaurn.

Ribbert (Virchow's Arch. 1883) found on excising the medulla of one kidney (in the rabbit) & removing the other, that the urine so jet was larger in amount & lighter in colour than normal. He believed this was confirmatory of Ludwig's theory - though it is not necessarily so.

Dresser (Ed. f. Biol. 1885) found on injecting acid phalbin (as an indicator) into the lymphatic sac of a frog that the part of the kidney in which the glomeruli
are situated) was colourless (= alkaline), but the tubules were filled with red secretion (= acid). He concluded that the glomerular transudate is alkaline, and the acid reaction of normal urine is due to the secretory activity of the cells of the convoluted tubules.

Munk & Senator (Virch. Arch. 1883) have found that in the secretion of urine there is a co-operation of physical & physiological factors: water & part of the urinary salts (e.g. NaCl) being transudated through the glomeruli; the specific urinary constituents, water, being secreted by the tubular cells.

Recent work has gone to support this view; e.g. Brodie & Cullen (Jour. of Physiol. 1902) found that a certain moderate resistance to the urinary flow in the ureters caused an increase instead of a falling off in the flow of urine.

Bernard: 3. Nervous Control. In 1885 A. Bernard showed that sometimes passage of the medulla oblongata (made to produce diabetes) caused increased flow of urine, but without sugar.

Eckhard (1869) showed that the same effect might be produced by mechanical or chemical stimulation of the neighboring portion of the cerebellum. He regarded this as due to possibly a stimulation of secretory-motor nerves to the kidney cells.

Gold (1861, May 1862) found that stimulation of the vagi in the neck sufficient to cause slowing of the heart & a fall of blood-pressure, caused shrinking of the kidneys & diminution of the urinary flow. But Eckhard (Berl. J. of Med. 1869) showed that such stimulation below the diaphragm has no effect on the urine, and therefore the result was due to change in blood pressure. Similarly Eckhard showed that if the cord is divided, & the peripheral end stimulated, universal constriction of blood vessels (including the renal vessels) ensues, & the urinary flow is abolished; and further that division of the renal nerves on one side causes vaso-motor paralysis in that kidney - with the result that the
Kidney swells, & the urinary flow is increased; whereas stimulation of the renal nerves causes constriction of the vessels, & diminished flow of urine.

Berkeley found (Ann. of Phys. Oct. 1873) that fine nerve filaments are distributed from the vascular plexuses of the kidney to the convoluted tubules and the glomeruli; & these have suggested the possibility of direct nervous control of the urinary secretion. But most purely physiological investigations have been adverse to the theory of secretory fibres, and in favour of an indirect nervous control through changes produced in the blood-flow.

II. Secretion of Milk.

1. Nervous Control. The earlier workers investigated the nervous control over this secretion. No marked or constant effects were found by Eckhard (1855) & others on section of the nerves passing to the mammary gland. Röhrig (Virchow's Archiv. path. Anat. 1876) found that some of the branches of the external spermatic supply vasomotor fibres to the gland, & so influence the secretion of milk by controlling the blood flow in the gland. Section of the inferior branch gave increased secretion, while stimulation caused diminished secretion. These results have however been denied by others. Minnow (Arch. f. s. hist. d. S. Gitterk. 1874) found that after complete separation of the gland from all its nerves (in animals), the secretion continued as before section, although less in quantity, and during pregnancy the gland increased in size, & became functional after the act of parturition. Goltz & Tasch (Blau's Archiv 1876) & others found that section of all the nerves going to the uterine does not prevent the normal effect on lactation after delivery.

Ribbert (Archiv. Phys. vuch. 1878) transplanted a mammary gland
a junction from its normal site to the region of the ear, he found that the gland enlarged during pregnancy and normal lactation followed deliveries. Basch (Ergeb. Physiol. 1903) found that interruption of the semilunar ganglion, or section of the splanchnic nerve does not prevent the secretion, but causes the appearance of colostrum corporelles.

2. Stimulants to the flow of milk.

While nervous impulses, as has been found above, are not important factors in milk secretion, it has been found that other factors of a chemical kind are of importance. Bachaerten (C.R. Soc. de Biol. 1902) found that by feeding women on sheep’s placenta, an increased secretion of milk was set up. Basch (Monats. f. Kinderheilk. 1909) got a similar result by injecting subcutaneously placental and placental extracts. Otte of Philadelphia in 1910 made the statement that “infundibulum is a galactagogue,” he along with Scott by experiment on goats in the same year found that the active principle of the posterior lobe of the pituitary body is a very rapid and powerful galactagogue. They also stated that extracts of the thyroids gland, the pituitary gland, corpus luteum are galactagogues, but to a less degree.

Mackenzie These results were confirmed and extended by H. Mackenzie, working along with Prof. Schäfer (Z. Imm. f. Exp. Physiol. 1911) who found that a galactagogue action was possessed by extracts of the posterior lobe of the pituitary body, the corpus luteum, the seminal gland, the mammary gland itself, the involuting uterus. He made the interesting discovery that the galactagogue substance is present in the pituitary body, not only of lactating females, but also of non-lactating females or males; also in the pituitary body of birds. And he discovered also that hormones inhibitory of mammary secretion are
produced by the foetus & placenta, but that drugs such as pilocarpine & atropine are without effect upon the mammary secretion.


Starling & Starling & Mies Lane-Claypon (Lancet 1905 & Proc. Roy. Soc. 1906) found that extracts made from the body of the foetus, or rather from the bodies of many foetuses, when injected repeatedly into a virgin rabbit, caused a genuine development of the mammary gland, closely simulating the growth that occurs normally during pregnancy. This was confirmed by Font (Arch. de Physiol. 1908) who found that the foetal hormone is not specific for any one species of animal.

In support of this theory that the onset of lactation is produced by the removal from the blood of the foetal hormone which causes growth of the mammary gland, Erries (La Pediatra 1910) found that on injecting into lactating hares the defibrinated blood of pregnant hares, the secretion of milk was thereby much diminished. A further discovery was made by Anpel & Brenin (Jour. de Physiol. 1911) that destruction of all the corpora lutea in the pregnant rabbit arrests the development of the mammary gland.


Rambau This has not been fully investigated. Rambau (Ws. J. Urspr. 1879) supposed that the organic materials of milk are derived from leukocytes which have migrated into & broken down in the mammary alveoli.

Heidenhain Heidenhain (Herrman's Hist. 1882) believed on histological grounds that the secretion products which are formed in the mammary alveoli become gradually accumulated within the free end of the cells, which projects into the lumen of the alveoli; and this free end thus bursts,
or becomes detached, setting free its contents.

III. Secreton of Sweat.

1. Nervous Control. The chief object of modern investigation regarding sweat secretion has been the question of its nervous control. Goltz (Arch. f. d. ges. Physiol. 1875) discovered that excitation of the peripheral end of the divided sciatic nerve caused the appearance of beads of sweat on the pads of the hind foot of the cat.

Ouchterlony (Schr. üb. d. Forstbuch. J. Physiol. 1877) showed that excitation of the abdominal sympathetic cord produced the same effect, this soon after ligature of the aorta. He also demonstrated the existence of sweat fibres for the lower limit in the abdominal sympathetic cord.

These observations have been confirmed and extended by Kendall, Luchsinger, and others, who have demonstrated the existence of sympathetic sweat fibres for the arms, the face, etc. They have shown that the production of sweat is an act of true secretion, regulated by the sympathetic nerves.

Luchsinger (Arch. f. d. ges. Physiol. 1877) showed that stimulation of the regions of the spinal cord from which the sweat fibres originate leads to an outflowing of sweat from the related part; and this was later confirmed by Kawrocki (Centralbl. f. d. med. Wiss. 1878). These two observers also showed that pilocarpine excites secretion of sweat after complete division of the nerves, that localized secretion might be produced by introducing it beneath the skin; but it was generally non-effective unless sufficient time was allowed to let the cut nerves degenerate. They concluded its action was upon the terminations of the nerves in the glands. This, however, has been partly contradicted by later observers.
Lucasheimer (1878) proved that both excessive cold & excessive heat retard the action of the sweat glands, showed that this may be a source of fatality in observations & of danger in actual life.

Langley (Jour. of Physiol. 1891 & 1893) has more recently studied the origin & distribution of the sympathetic sweat fibres in both the fore & the hind limbs of the cat.


Fauve

Fauve (C.R. Acad. Sc. 1853) found that normally sweat is acid in reaction, but in profuse sweating the acidity may give way to Ruutility followed later by alkalinity. Fauve also found (as have since) that urea is present in human sweat.

Fyreson

Fyreson found (Thiers & Lyons 1879) that while sweat is normally acid in reaction, the acidity is due to volatile fatty acids, which may be driven off, leaving an alkaline reaction at the surface of the skin.

Schinerbeck

Amount of Sweat. Schinerbeck (Arch. f. Physiol. 1873) calculated the amount of sweat given off by using a chamber from which the breath was conducted to the exterior by tubes. The amount of water given off by the skin was calculated from the readings of hygrometers in the outgoing & incoming currents of air. He found that under normal conditions the skin gives off two to three litres of sweat in 24 hours.
C. The Internal Secretions.

Only within comparatively recent years has it been known that certain glands of the body produce an internal secretion, which is conveyed into the blood or the lymphatic stream directly. By which the general metabolisms of the body as the functions of other organs are powerfully affected. The term 'internal secretion' seems to have originated with C. Bernard (F. de Phys. Expér. 1855) when he described the glycogenic function of the liver as the 'secrétion interne', while he referred to the preparation of the bile as the 'secrétion exténe'. Bernard also (1855) expressed the idea that every organ of the body by a process of internal secretion determines the composition of the blood, and thus affects to a greater or less extent the functions of all other organs of the body. But even before Bernard the idea of an influence exerted by certain organs through the blood stream has been found. Thus P. P. Berthold of Göttingen (according to Biedl - Path. Secrétions) in 1849 removed the testicle from a cock, and grafted it upon another part of the body; he found that they still retained their male characteristics. He concluded that these characteristics were produced by the influence exerted by the testicle on the body through the blood stream. In this way he may be said to have recognized the existence of an internal secretion.

The first clear conception, however, of the fact that the internal secretions play in the organism was expressed by Bérbier-Serre in an address to the Soc. de Biologie in Paris, when he recorded the effects of testicular extract upon himself - the production of invigoration and rejuvenescence - thus giving a therapeutic basis to the doctrine of internal secretions. He further amplified this idea by the assumption that all the tissues give off something which is characteristic, which is of importance for the general nutrition. These ideas have only in part been
provided experimentally to be true. But it has now been shown clearly that many of the ductless glands produce secretions of the very highest importance for the life of the organism. The glands which have been proved to be most important are: Thyroid + Parathyroid, Suprarenal, Pituitary, Pancreas, generative glands, Thymus, + Pudendal body.

I. Thyroid + Parathyroid Glands.

The older views of the function of the Thyroid were more or less speculative in nature. Thus J. Simon (Phil. Trans. 1844) believed that the Thyroid had a regulating function on the blood-supply to the brain—acting by means of its rich blood-supply as a short-circuit, which on dilatation or constriction diminishes or increases the blood supply of the brain. This idea has been supported in more recent times by Stahel (1887) and Waldeyer (1897) Egger (Ann. d. Physiol. 1897).

The history of the glandular function of the Thyroid may be said to begin with the observation of Schaff in 1856 (Untersuch. in die Thiercultur 1856) that extirpation of the Thyroid in dogs is always followed by death. This observation, however, was forgotten for the time. The disease of cretinism was the real cause of bringing the Thyroid into prominence. It had long been recognised, often with an accompanying goitre, as endemic in certain parts. In 1873 Sir Wm. Gull (trans. clin. soc. VII) described a series of symptoms similar to those met with in cretinism—(subsequently called 'myxoedema') • viz, apathy, low temperature, unsteady gait, diminution of cutaneous sensibility; with increase of contractile tissue.

Ord (med. clin. Trans. in 1875 first recognised the connection between myxoedema and affections of the Thyroid. Revedin (Rer. med. de la Suisse Rom.) in 1882 described the symptoms which followed on
Kocher (Arch. f. Klin. Chirurgie, 1883) described the symptoms similarly, viz., that they were most marked in the young, being less marked as age advances.

Schiff, 1884 (Riv. med. del. o. Suisse Rom.) again operated on dogs, and found in every case that thyroidectomy was fatal, death ensuing in 14 days or less, being attended by tremors, spasms, and convulsions — but without the symptoms of myxoedema. Horsley (Proc. R. Soc. 1884-6) then operated on monkeys, and found they survived thyroidectomy longer than dogs, and developed myxoedema as man does, along with the appearance of Gravesism.

Allara, 1885: And Ewald, 1890, found that no results followed thyroidectomy in birds; and other observers found the same in rodents and turtles.

Gley, generally: But Gley (C. R. Acad. 1891) found in the case of rabbits that if the accessory thyroids and parathyroids in these animals were removed, the animals died with the usual symptoms.

Vassali & Generali, 1896, Edmunds (Journ. Physiol. 1896), Gley (C. R. Acad. 1897) others that if all the parathyroids were removed, while the main body of the thyroid was left, the tetanic symptoms (tremors of described above followed, but the myxoedemiac symptoms did not.

1. Thyroid Secretion.

That the thyroid gland produces a secretion necessary for the health of the organism was proved by the above observations, and confirmed by the fact shown by Schiff and others that the results of thyroidectomy can be overcome by a graft of thyroid beneath the skin, or in the peritoneal cavity. Vassali & Generali, Gley, others showed that
similar results could be got by the administration of raw thyroid or thyroid extract. On the other hand, Horsley (Brit. med. jan. 1892) and Blumenreich & Jolly (1894) found that the urine of thyroidectomized animals was more toxic than normal, & their blood also became toxic for other animals, especially for those which had just been thyroidectomized. They believed therefore that the thyroid has the function of destroying certain toxic materials circulating in the blood.

Connection of the Thyroid with other organs.

Rogovitsch
Rogovitsch (Arch. de Physiol. 1888) found that extirpation of the thyroid in adult rabbits was followed by enlargement of the anterior part of the heart.

Olivier & Schäfer
Olivier & Schäfer (Jour. of Physiol. 1893) found that a secretion of the gland injected intravenously produces a marked fall of blood pressure without slowing the heart (- but see below)

Leichtentin &
Leichtenstein (1894), Donati (1896) found that thyroid extract causes increased metabolism in the body, with diuresis & diminution of fat.

Hofmeister
Hofmeister (Fortschr. der med. 1902) found that extirpation of the thyroid in young rabbits led to a retardation of the process of ossification, especially of the long bones, & of the vertebral columns, & so to an arrest of growth. He also found in such rabbits degenerative changes in the organs of generation - the ovaries showing premature maturation of many of the follicles. In male animals Jeandelzé (Jour. de la Physiol. 1902) found imperfect development of the testicles.

Falta & Rudinger
Falta & Rudinger (Arch. klin. Woch. 1908) found that removal of the thyroid (& hyperparathyroid) had a direct influence on the protein & carbohydrate metabolism; & they concluded...
that there is a balance maintained by the antagonistic activity of the thyroid and suprarenales (which favour metabolism), of the pancreas and parathyroids (which retard it).

v. Fürt & Schwarz (Phys.)

Arbeiten 1907 proved that the fall in blood pressure which followed the administration of thyroid extract is not specific, but is probably due to cholinergic substances which are also present in the suprarenales, heart, spleen, and other organs. They also found that the injection of iodothyrin into dogs or cats was not always followed by tachycardia, and believed that such tachycardia was due not to iodothyrin but to iodized albumin which the thyroid gland contains.

Bcinmann

Nature of Thyroid Secretion. Bcinmann (Klinik des Klin. der Chirurg. Chemie 1896) isolated iodothyrin as a brown amorphous substance, soluble in weak alkali, almost insoluble in water. He found it had 9.3% (of its dry weight) of Iodine, and showed in large measure the beneficial influence exerted by thyroid extracts.

2. Parathyroid Secretion.

The results of irritation of the parathyroids have been referred to above.

Lundborg

Lundborg (Dent. festschr. remennick. 1907) has shown some grounds for believing that myotonia congenita, myelitis, agitans, myoclonus are chronic progressive conditions due to lack of parathyroid secretion, whereas myotonia periodic and myasthenia gravis arise from an increased function of these glands.

Halstead

Koalstard (1909 Journ. of Orth. Med.) has described favourable results got in post-operative tetany by administration of parathyroid extract.

Macallum & Voellken (John Hopk. Hop. Bull. 1908) claim to have shown that injection of injection of Calc. salts removes completely the symptoms of tetany following on parathyroid removal.
Fromin

But this result has not been obtained by others. Fromin has found (C. R. Acad. 1908) that the urine of animals from which the thyroid and parathyroids have been removed, contains an excess of Ammonia & Carbonic acid, the regarded tyramine as the result of Carbonic acid poisoning, which when experimentally produced is relieved by administration of Calcium salts.

J. Ott (The Parasites. Handbuch 1909) observed that watery extracts of the parathyroids besides increasing intestinal peristalsis, & the uterine contractions, produced a marked diuresis, due to stimulation of the epithelial cells of the kidneys.

Kocher

Hyper trophy of the thyroid gland has been frequently found after removal of the parathyroids, & vice versa, by Edmunds, Wassalle & others, & hence it has been concluded that there is some inter-relationship between the thyroid & parathyroids. This is strengthened by the fact that thyroid administration is beneficial in treatment of tyramine following parathyroid removal (Kocher 1906).

II. The Suprarenal Glands.

Eustachi

1. The glands. Eustachi first described the suprarenals as separate organs in 1563. More minute descriptions of them were given by J. B. Winslow (1752), & by A. Seker (1846), & A. Kolliker (1854).

Addison

Addison first described in 1855, the extreme asthenia, anorexia, loss of muscular tone, & bronzed patches that accompany pathological alterations of the suprarenals. Brown-Sequard (C. R. Acad. 1856) tested this by removing the suprarenals from various animals, & found that death is usually followed - usually within twelve hours, with similar symptoms to the above, but more acutely, without the pyrexiation.

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Rothschild

Rothschild (Zeitschr. f. klin. Med. 1879) & others found that pyrogenic patches appeared if the suprarenals
were injured by crushing, or were gradually removed.

The results of treatment by suprarenal extract in Addison's disease, as well as in suprarenal insufficiency, are exceedingly diverse (v. Gilbert & Larrat, 1878). Transplantation of suprarenal tissue was attempted without success by Canalese (1887), Abéron & Langlois (1892), Bonnet (1896), & others; but it was success-
fully accomplished by v. Haberer & Stock, by implanting the suprarenal body in the kidney with its pedicle attached (Arch. f. klin. Chirurgie 1905). They found the functional results were very good.

Braun-Siemens had stated, as the result of his experiments, that the blood of animals dying in consequence of suprarenal removal is toxic to other animals which have been recently deprived of their suprarenals, but not to normal animals. This was confirmed by Abéron & Langlois (C. R. Soc. de Med. 1892) who found that the symptoms so produced were those of curare poisoning. They concluded that the similar symptoms produced by removal of these glands from animals were due to a toxic product of muscular metabolism which accumulates in the blood, which is normally removed or destroyed by the suprarenals.

But later, Moore & Purirow (Annals from Physiol. 1903) found that the toxic effects of blood taken from animals deprived of their suprarenals, was not due to anti-intoxication with the substances found in the normal gland; for the veins & tissues of such animals were found to be devoid of suprarenal active substance.

2. The Secretion of the Suprarenal glands.

Pellegrini & Foà (Arch. per la St. med. 1879-80) first investigated the effect of watery extract of suprarenal from normal animals. They found that dogs were killed by subcutaneous injection of self-suprarenal extract — as they thought — from paralysis of the respiratory Centre.
Olive + Schäfer (Jour. of Physiol., 1895) using watery + glycerine extracts, found that moderate doses given subcutaneously produced little effect; but large doses produced quickening & augmentation of the heart beat, shallow & fast respiration, fall of temperature, & frequently death. They further found that intravenous injection of suprarenal extract produced 1/ prolongation of the contraction of voluntary muscles; 2/ slowing or inhibition of auricular contraction - provided the vagi are intact; increased strength & frequency of auricular (and ventricular) contraction - provided the vagi are cut or paralysed; 3/ slight rise of arterial blood pressure (except if the vagi are cut) - as they believed from action on contraction of the muscular coat of the arterioles. This effect on the blood pressure they found passes off in the course of a few minutes - not from secretion of the suprarenal principle by the kidneys, suprarenals, or by oxidation, but probably by its being washed away in certain organs, especially the muscles.

They found also that the active material was yielded only by the medulla of the suprarenals, no appreciable amount being got from the cortex; that the dose necessary to produce the maximal effect was about 1/2 mgm. per kilogram of body weight. The active principle they found was not destroyed by boiling or by gastric digestion.

Takamine (Jour. of Physiol., 1897) first isolated the active principle of the gland, & called it adrenalin. He found it to be a white, crystalline, light body, with slightly bitter taste, sparingly soluble in water, & stable in dry form. He found it forms salts, & an aqueous solution of the chloride of 1:1000 will blanch the normal conjunctiva within a minute.

Velich (Wein. med. Blat. 1896) showed that suprarenal extract did not produce constriction of the blood vessels in the lungs. And Spina (Wien. Klinik, 1897) showed that intravenous injection of it produced a marked dilatation of the
Langley (J. Physiol. 1907) pointed out that adrenalin produces a contraction of the erector pili muscles in the cat; vasoconstriction of the pupils in horse, cow, which are both innervated from the sympathetic; also dilatation of the pupil and cataracts, as on stimulation of the sympathetic in the chick, this even more powerfully, an irritation of the superior cervical ganglia. Langley also found that moderately large doses of adrenalin produce profuse secretion on the part of all the salivary glands, mucous glands of the mouth, the lacrimal gland, while secretion; this continues on section of the superior cervical ganglia and the chorda tympani. He concluded the effect was due to peripheral stimulation, as it was not inhibited by acetylcholine, but was inhibited by large doses of atropine; he believed that superior cervical extract stimulates the same elements—nerve terminals on glandular cells, as are inhibited by the action of atropine.

Dreger showed (Ann. Journ. Physiol. 1898) that the amount of adrenalin in the suprarenal blood is increased by stimulation of the splanchic nerves.

Elliott (Journ. Physiol. 1917) has found that the secretion of adrenalin is controlled by the splanchic sympathetic nerves. Section of these nerves presents exhaustion of the glands of adrenalin; paralysis of these nerves discharges adrenalin into the blood, causing a rise of blood pressure (after a characteristic drop in the rising curve). Such phenomena as paradoxic painful dilatation. He also found that all ordinary conditions of anaesthesia (ether, chloroform &c.) are attended by exhaustion of adrenalin; that fright artificially produced, excitation of allantome nerves produces the same result, but that in all cases this effect is not directly, but reflexly through the splanchic nerves.

Blum Effects of adrenalin on metabolism. In 1901 Blum (Deutsche
Archie (Klin. Med.) discovered that suprarenal extract given subcutaneously produces glycosuria, but not so given by mouth. Hirtz & Walther (Arch. 1907) believed this was due to interference by adrenalin with the internal secretion of the pancreas. Berry & Mallinckrodt (C.R. Soc. Lond., 1908) found that after injection of the suprarenals, the sugar content of the blood in dogs was subnormal. So also were observed by Berry & Mallinckrodt (Berl. klin. Woch. 1908) followed that chloridrin produced only slight glycosuria in dogs from which the suprarenals had been extirpated; that in cases of Addison's disease, the tolerance of sugar is remarkably high. O. Schwarz (Berl. klin. Woch. 1909) found that rats deprived of both suprarenals showed a marked reduction in the amount of glycogen, and an increased consumption of proteins, yet in spite of this an increase of weight.

III. The Pituitary Gland.

The ancient writers from Galen to Vesalius believed that the phlegm secreted in the brain was ejected by the pituitary body. Later authors, Willis, Sylvius, Bœcheramus, thought the cerebro-spinal fluid was secreted by it. Rathke (Schiller's archiv., 1838) discovered the double origin of the pituitary, from developmental grounds he classified it among glands. Virchow (Untersuchungen, 1857) compared the anterior lobe to the thyroid gland, described its vesicles containing colloid material, which showed a great resemblance to the follicles of the thyroid.

Recent investigation into the functions of the pituitary dates from the description by Marie (Rev. de Méd. 1886) of the disease of acromegaly, which appears therein to be connected with an enlargement and degeneration of the
Mariesco

...pituitary body. He found that disease specially characterized by involvement of the bones—especially of the skull bones, the phalanges, and frequently degeneration of the sexual glands. Along with Mariesco (Arch.ry. med. 1899) Mariesco showed that changes in the pituitary body—especially tumors—were invariably found in acromegaly. Removal of the gland was most accomplished by Mariesco (C.R. med. 1892) in cats, by Vassalle & Sacchi (Arch. It. med. 1893) in dogs. They found that removal of complete, caused death within 14 days; the symptoms shown being fall of temperature, anemia, muscular twitchings and tremors, dyspnea. Pituitary extract brought some relief of symptoms. Vassalle & Sacchi therefore concluded that the pituitary produced an internal secretion which maintained the nutrition of the nervous and muscular systems.

Olivier & Schäfer

The next advance in our knowledge of the pituitary was made by Olivier & Schäfer. They found (Jour. of Physiol. 1875) that pituitary extract when injected intravenously caused great augmentation in the force of the heart's beat—without accompanying acceleration, rise of arterial blood pressure from contraction of the arteries by direct action.

Howell

Howell then discovered (Am. Jour. of Physiol. 1895) that this blood-pressure-raising substance is only present in the posterior lobe; and he also found that a second injection from 1/2 hour after the first has practically no effect upon the circulation. Schäfer & Vincent (Jour. of Physiol. 1879) further found that such a second injection is followed by a fall of blood pressure, which they attributed to a second substance with depressant properties present in the extract.

It thus became clear that different functions were exercised by the anterior and posterior lobe. The same fact became evident from further study of acromegaly. Benda (Arch. f. Anat. u. Physiol. 1879) found that the changes in the pituitary body in acromegaly consist in an increase of the glandular epithelium of the anterior lobe,
especially of the chromophile + eosinophile cells. Further, the condition of
gigantism came to be associated with the pituitary body. Lannoo has discussed
this condition with its abnormal elongation of the growing bones, but he did not regard
it as a pathological condition. But Bresaud & Neige (1883) main-
tained that gigantism is simply a growth in the period of growth, and is due
to the same cause, viz. pathological changes in the pituitary body. Lannoo
& Roy (1883) showed that gigantism is uniformly associated
with hypertrophy of the pituitary body. They also showed that reduction of
sexual activity with atrophy of the sexual glands was one of the clinical symp-
toms of gigantism.

The Anterior Lobe. It thus became clear that the pituitary body, prob-
ably the anterior lobe, had some connection with the growth of the skeleton.
That it also had a connection with the sexual organs had been already
pointed out (before this) by Comte (These de Lansanne 1898) who found that
the pituitary body regularly enlarges during pregnancy, that during lactation
it returns to normal. Fichera (1903) showed
that the changes in the pituitary body during pregnancy are accompanied by
a reduction in the length of the ovary. After castration of male & female ani-
imals he found hypertrophy and hyperplasia of the pituitary body, which
exactly resembled the hypertrophy of pregnancy.

Another pathological condition associated with changes in the pituitary
body was first described by Fröhlich (Münch. klin. Wschr. 1901) viz. a rapid increase
in adiposity, with infantile character of the sexual glands. Many other observers
have confirmed this; from the supposition that this condition was due to lack of
pituitary secretion, pituitary extract has been administered by Roy & Rothschild (1907)
& others, but the results have not been uniformly beneficial.
Bushing found (J. Am. Med. Assn. 1909) that after extirpation of the posterior lobe, animals usually survive, whereas no pathological signs are noted. Partial extirpation of the anterior lobe is consistent with the continuance of life. In some cases, however, such partial extirpation led to certain remarkable symptoms, such as increased defecation of fat, polyuria, glycosuria, pallor of the skin, hypertrophy of the thyroid, & a reduction in sexual activity, as shown by atrophy of the testicles & ovaries.

Falk & Jevons (B. Klin. Woch. 1909) found that an injection of an extract obtained from the anterior lobe into dogs & rabbits, they produced a profound fall in blood pressure -- in two instances to zero, which was relieved by adrenalin or extract of the posterior lobe.

Falk & Jevons (Proc. Physiol. Soc. 1901) discovered in 1901 that intravenous injection of saline extract of the posterior lobe is followed by a marked increase in the flow of urine.

Magnus & Schäfer (Proc. Physiol. Soc. 1901) subsequently confirmed this & showed the resemblance between the supranormal capsules & the posterior in development, structure, & function.

They found that extracts from the posterior lobe when injected into the blood cause a dilatation of the renal vessels, & an increased secretion of urine; but that these effects are independent of each other, & probably due to different substances. They also proved that the substance which produces diuresis is dialysable, is insoluble in ether & alcohol, & is not destroyed by boiling. The extract of the anterior lobe they found to be non-diuretic.

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Herring (J. Phys. 1908) made it probable that this internal secretion is furnished by the epithelial cells of the pars intermedia.

V. Fränkel, H. Huchens & F. Hochwalt (Wein. med. Woch. 1909) & B. B. Bell (New York Med. Jour. 1909) have described the effect of stimulation upon the muscles of the urinary bladder, intestine, & rectum. They found that the muscles of these organs are
stimulated, and also that the sensibility of the motor nerves governing them is considerably increased. Cushing & Gobeka (Am. Jour. of Physiol. 1910) have proved the presence of pituitrin in the cerebro spinal fluid.

IV. PANCREAS - INTERNAL SECRETION.

Mering, Mering & Minkowski in 1889 (v. Arch. f. Exp. Path. u. Pharm. 1893) and Minkowski, discovered that extirpation of the pancreas was constantly followed by the appearance of sugar in the urine. This Minkowski found to be so, even if there were no carbohydrates in the diet. There was also polyuria, increase of urine, thirst, with emaciation & death in 3-4 weeks. If only 1/5-1/4 of the gland, these effects did not follow; nor did they if part of the pancreas was grafted elsewhere in the body. They concluded that the pancreas supplies an internal secretion which aids in the decomposition of sugar in the body.

Minkowski also showed that on extirpation of the pancreas there is rapid reduction in the glycogen contents of the liver.

SEAT OF THE SECRETION.

Langerhans (1869) Disserat.: Berlin] first described the cell-groups which are named after him. Langerhans (Sur la fonction de l'ile V. 1873) first put forward the view that the internal secretion of the pancreas is elaborated by the cells of the islets of Langerhans. He also inferred from the presence of transition- forms of cells that there is a continuous transformation of acini into islands & vice versa - a view which has been supported by Frankowski, Daly, Vincent & Thompson, and others.
The findings in cases of clinical diabetes have been regarded by some as supporting the view that the islets are the seat of formation of the internal secretion; others have ascribed it on these grounds to the acini; and others to both. Schultze (Arch. f. mikros. Anat. 1905) observed that after ligation of the excretory ducts of the pancreas (of guinea-pigs) the acini atrophied and disappeared; but the islets also diminished, and there was absence of glycogen. Similar results were got by Soobolev in rabbit, frog, cat, and by Legueu in rabbits; but these results have not been uniformly got by others.

Conveyance of the Secretion

Biedl (Centr. f. Physiol. 1898) discovered that there is a substance contained in the chyle of the thoracic duct which influences the metabolism of sugar in the organism. He also, along with Offen (Wiener Klin. Wochenschr. 1907) found that the chyle in the thoracic duct possesses an inhibitory influence in regard to adrenalin, and that adrenalin glycerin may be reduced or abolished by injections of chyle. He concluded that this substance in the chyle was the pancreatic hormone, so that it reached the circulation by way of the lymphatics.

Action of the Secretion

Lepine (C.R. de l'Acad. 1879) first proved the theory that a glycolytic ferment is produced in the pancreas, and pancreatic diabetes is owing to its absence. He found that watery pancreatic extract has a glycolytic action, which was intensified by the addition of acids. He concluded that a ferment was present in the pancreas, which was converted by acids to a glycolytic ferment. But others (Jacoby, Sieder &c) have shown that glycolysis is carried out by ferment which are
Cohnheim (Kts. f. physiol. Chemie 1903) found from experiment that a complete destruction of glycogen is effected only by a combination of the expressed juice of the muscles and the pancreas, not by that of either separately. He believed that the glycolytic ferment in the muscles was activated by an agent present in the pancreas.

Rebel Weisch (Beitr. z. chem. Phys. u. Path. 1903) found that the glycolytic action of pounded liver is considerably strengthened by the action of pancreas extract. He assumed this was due to a pre-ferment or enzyme in the pancreas.

De Dominicis (Acc. Med. Ch., 1898 & 1903) whose discovery of glycosuria on pancreatectomy was almost simultaneous with though independent of that of Marx & Arndtowski - has found that the intestinal (duodenal) extract of dogs without pancreas produces severe glycosuria when injected into normal dogs. He concluded that the glycosuria was due to toxic formation & absorption following upon the absence of the pancreatic juice.

Forschbach (Drit. med. Woch., 1903) has proved by parasitic experiments with dogs, that if one of the dogs had its pancreas extirpated, this was followed only by very slight diabetes; whereas after separation from its fellow the dog robbed of its pancreas developed severe diabetes.

Eppinger, Falta, & Rudiger showed (Kts. f. Klin. Med. 1908) that preserving or simultaneouss extirpation of the thyroid in dogs increases the glycosuria considerably.

The administration of fresh or dried pancreas has been tried by various observers in pancreatic diabetes, but the results have been
very contradictory. On the whole it must be confessed that it is yet uncertain in what way the pancreatic secretion is related to the sugar contents of the blood—whether these contents are regulated directly by nervous centres, as is believed by some, or whether they are controlled by antagonistic hormones produced in the liver, the pancreas, or the suprarenals.

V. Thymus Secretion.

Friedeben. Friedeben (1858, Physiol. of the Thymus Gland) found that extirpation of this gland did not affect the life of animals, but that it caused changes in the bones of growing animals—viz., retarded growth, and a tendency to bend, and also certain metabolic changes.

Calgolani. Calgolani (1898 Arch. Ital. de Biol.) discovered that the removal of the sexual glands of rabbits was followed by hypertrophy of the thymus gland. Calgolani (La Pediatrista 1903) described the changes in young rabbits from which he had removed the thymus, these being arrest of growth, crookedness of legs, progressive cachexia.

Hindson. J. Hindson (Jour. of Physiol. 1903) showed that early castration of cattle is attended with a stimulation of the process of growth, and later a retarded atrophy of the thymus.

H. Paton. N. Paton (Jour. of Physiol. 1903) discovered that if the thymus is removed from guinea-pigs before they reach the age of puberty, the operation is followed by a rapid development of the testicles.

Basch. K. Basch (Jahrb. f. Kinderheilk. 1906) found that thymectomy was followed in various animals by retardation in growth & fragility.
of the bones - especially the long bones; also by an increase of calcium excretion, & a hypersensibility of the nerves to electric stimuli.

It has been made probable that there is an internal secretion of the thymus gland, & that it has some connection with the growth of the Skeleton, & with the genital glands.

II. Pineal Gland.
That the pineal body is an internal-secretory organ is supported by the observations made in a series of cases of tumours affecting that gland. Thus Gutzzeit (Dissertation 1876) Ogle, Osterhée & Ogle (Trans. Path. Soc. London 1879), Oestreich & Slavny (Arch. Med. 1879) & later by Frankel-Hochwart (Ber. dtsch. Ges. Neuro-physiol. (1909) found that in such cases of tumours affecting children under seven, along with a diminution of pineal tissue, there was abnormal growth in height, abnormal growth of hair, premature development of the genital organs, of sexual instinct, & mental peculiarity.
Dixon + Halliburton (Q. Journ. of Exp. Physiol. 1909) on the other hand, found that intravenous injection of pineal extract is without definite effect upon the blood pressure, or the cardiac action, & that it has no effect upon the respiration, the intestines, or the urinary secretion.
III. Generative Glands.

It has long been surmised that there is some connection between the generative glands, and those bodily and mental characteristics which distinguish the two sexes. These characteristics become more marked both in the male and the female at puberty, when the sexual apparatus is approaching maturity. The effects, moreover, which follow upon cessation of sexual life - e.g., at the menopause, or on castration, have been taken to indicate in some way an interconnection between the sexual glands, and the condition of the body as a whole.

When Brown-Séquard in 1849 in his address to the Soc. de Biologie in Paris recounted the experiments which he had carried out on his own person, describing the rejuvenation or rejuvenescence effected by the administration of testicular extract, he laid the foundation of the modern doctrine of internal secretions in general, and in particular of the part played by the generative glands in promoting the health of the organism. It was known as the result of experiments with animals (e.g., by Hegar 1878, Kehr 1884) that if the ovaries were removed from immature females, the development of the entire genital apparatus (uterus & Fallopian tubes) was retarded.

Knaus (Centralbl. f. Geb. 1876) showed that if the ovaries are removed from their place, and transplanted to another part of the body, atrophy of the uterus, which is the normal result of their removal, will not take place. Haller (Monats. f. Geb. u. Gynäk. 1901) transplanted the extirpated ovaries (in miniature females) under the skin, finding that perfect sexual development was yet accomplished. Thus showing that the influence of the ovaries is not a nervous one, but is effected by
the agency of an internal secretion. He also (Sitgunp. J. Kim, Akad. 1901) found in female baboons that when the ovaries were transplantated under the skin, menstruation occurred as normally; but it ceased as soon as they were removed. Marshall & Jolly (J. Anat. 1905) have shown that the presence of even a small portion of one ovary in any part of the body is sufficient to preserve the complete anatomical integrity & functional activity of the genital organs. The transplantation of ovaries from animals of another species has also been successfully performed by Bruce, 1907, Carmichael & Marshall, 1907, and others; and these also prevented atrophy of the uterus from taking place. But the subcutaneous injection of ovarian extract had not this effect. (Kendig & Kohnke, Th. d. Geburt. u. Gyn. 1900).

Effect of the secretion on other organs.

The positive influence of testicular extract upon muscular fibre has been proved by Roth & Pregl (J. Phys. 1899); they found that when combined with muscular exercises its administration produced an increase of 50 per cent. in muscular performance; but without such exercises there was no increase. Selheim (Beitr. 3. J. u. Gyn. 1898-9) found that castration of cocks, dogs, horses, sheep, etc., had the effect of causing increased longitudinal growth in the bones, with retarded ossification of the epiphyses. This has been confirmed by Brain, 1901, Harrisons & Ray, 1903 and many others. Lowry (Ergeb. d. Physiol. 1903) showed that the changes described by Selheim can be got rid of by the administration of testicular extract (in caps.) that a premature arrest of skeletal growth can be got in young horses by feeding them with ovarian extract.
Loewy & Richter (Centrall. f. Physiol. 1902) found that after castration there was a fall in the total non-proteinous metabolism of 14-20% in proportion to the body weight, and that this depression could be largely restored by administration of ovarian or testicular extract.

It has also been shown that castration is followed by changes in the thyroid gland - e.g. persistent growth, as described by Henderson (Journ. of Physiol. 1907), Noel Paton (Journ. of Physiol. 1907), and others. Increase in size of this pituitary body was shown to result in the case of animals by Ficher (J. Physiol. 1908); and diminution in the size of the thyroid gland in a mammoth was recorded by Jander (Arch. f. Entwicklungsmech. 1909).

Serradelli & Pares (C.R. Soc. de Biol. 1907) made the interesting discovery that intravenous injection of a glycerine emulsion of testicular substance produces reflex closing of the neck of the bladder, relaxation of the bladder walls, and on the ejaculation of semen.

**Seat of the Secretion.** As regards the seat of the internal secretion of the testicles and ovaries, it had been suggested by Reinke (Arch. f. mikr. Anat. 1896) that the interstitial cells of Leydig in the testicle might provide an internal secretion. But the proof of this was first brought forward by Ancel & Bronin (C.R. Soc. de Biol. 1903-4). They based this view upon the observation that in cases of double eunuchoid testis (cryptorchidism) in man & animals, there is usually absence of spermatogenesis, but at the same time the sexual instincts & the male sex characteristics are present; and in explanation of this they found that the cells of Leydig (as well as the cells of Sertoli) show a normal development in these animals, presumably from their internal secretion into the blood. Similarly they found that on ligating the vasa deferentia,
spermatogenesis ceases, the spermatagonia degenerate, but the cells of Leydig, the cells of Sertoli remain active, the sexual characteristics are preserved. Further, in performing unilateral castration in these animals, obliterating the vas deferens of the other side, they found that while the seminiferous tubules, ultimately also the cells of Sertoli degenerated, the cells of Leydig showed a great amount of hypertrophy; and hence, they concluded that this hypertrophy of growth was a compensatory one, indicating that these cells of Leydig were the source of the internal secretion. These results have been largely confirmed by Vincent, Copeman, Tandler, Sperm, and others.

Lémoin

As regards the ovary, Lémoin (Arch. d'Anat. micro. 1902) has suggested that the epithelial cells in the interstitial tissue are the source of the internal secretion; but the results of investigation here are largely contradictory.

Prinont

Prinont (Rev. gén. de Sénie 1898) on morphological grounds regarded the corpus luteum as the source of an internal secretion which prevents ovulation during pregnancy.

Frankel

Frankel (Arch. du Gyn. 1902-9) experimenting on rabbits found that destruction of the corpora lutea by the galvanic current prevented the occurrence of pregnancy, or caused involution of the already embedded ova if pregnancy had occurred; while current of the other parts of the ovary had no influence upon pregnancy. But his results as to this, was to the function of the corpus luteum of menstruation in preparing the uterine mucosa for the reception of the ovum, have been contradicted by others; and the questions involved are still matter of dispute.
VIII. Internal Secretion of the Kidneys.

Brown-Séquard suggested in 1869, and along with d'Arsonval (1893) Arch. de Physiol.) tried to show that anaemia was due to the suppression of an internal secretion of the kidney. They found that animals died much more rapidly after removal of both kidneys than after ligation of both ureters. Also that renal extract (from guinea-pigs or rabbits) injected into nephrectomized animals lessens the symptoms of anaemia.

Lépine (Sém. médicale 1873) found that working extract of kidney injected into the blood produces a rise of temperature and dyspnoea. Olivier-Schäfer (Jurm. Physiol. 1875) showed that renal extract was like the extract of many other organs in producing a rise of arterial tension on injection to the blood; and therefore no specific internal secretion of the kidney is required for this.

Bradford (Jurm. Physiol. 1877) found that striking metabolic changes—viz. rapid decomposition of the tissues, particularly of the muscle; followed a reduction of the renal parenchyma; and Biel (Internat. Journ. 1849) has observed polyuria on excision of about a quarter of the renal parenchyma.

Tunifarn (Arch. f. exp. Phys. 1884) showed that the working extract of healthy kidneys injected into the kidneys has a marked lymphagogue action.

There has, however, been no proof of any specific internal secretion of the Kidneys.
Books Consulted.

Neuburg — History of Medicine Vol I. (Trans.)
Withington — Medical History
Foster — Lectures on Physiology
Schröer — Text-Book of Physiology (2 vol.)
Ganea — Physiological Chemistry (2 vol.)
Landis — Text-Book of Physiology
Howell
Lyle
Halliburton
Hill (ed.) — Recent Advances in Physiology
Hammarsten — Physiological Chemistry
Biedl — Internal Secretions (Eng. Trans.)
Journal of Physiology (trans.)
Quart. Jour. of Exp. Physiology
Brit. Med. Journal
Lancet