

THE HISTORY OF OUR KNOWLEDGE REGARDING THE  
FUNCTIONS OF THE KIDNEYS.

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Up till the beginning of last century the curiosity of man as to the mode of action of the kidneys was scarcely roused beyond mere vague speculations, and even these were scanty. Their function was not a spectacular process like that of the heart and respiratory system over which there had been so much controversy, and man was content with the explanation that the kidneys filtered the urine from the blood - a statement which in its broadest sense still holds true to-day. Almost as far back as records are obtainable, this view exists, and seems to have persisted with little opposition for over three thousand years.

The "humoral" theory, which probably goes back long before Hippocrates, states the process of metabolism thus (21). The chyle from the intestine is carried by the portal vein to the liver which is the seat of the process of sanguinification. Here the four humors are formed. The crude blood, or cruor/

cruor, passes to the heart to be endowed with the vital spirits: the black bile to the spleen; the bile to the gall bladder; and the serous humor passes to the kidneys where it is excreted.

When analysed carefully this process bears a remarkable similarity to our conception of the process of urea formation, as we know it in the twentieth century; yet this theory of the ancients, based on their shrewd observations of the anatomical arrangement of the organs, has taken over two thousand years to prove.

Little information is to be gleaned from the Egyptians, who, though great physicians and surgeons, had little knowledge of anatomy and physiology. In the Ebers papyrus (9) the bulk of the document is occupied with fantastic prescriptions and therapeutic measures. Concerning the kidneys it states that there are two vessels to the kidneys, one to the one kidney, the other to the second kidney; and two vessels to the bladder which convey the urine.

In the Bible there are numerous references to the kidney, where it is prescribed as one of the organs to be sacrificed to Jehovah. "The two kidneys and the fat which is upon them, which is by the flanks/

flanks", together with certain other portions of the viscera were sacrificed, while the remainder of the carcass was consumed by the worshippers. The rationale of this was that these parts next to the blood were the seat of life, and, with the blood, were to be given back to the Author of Life. Later it came to be believed that these were the choicest parts of the animal, and we find such metaphors as "the kidney fat of wheat" meaning the best wheat. Further extension of the idea led to the belief that they were organs of feeling, impulse, affection, and moral sentiments; and we find the word "Reins" used synonymously with heart.

A later Jewish idea was that the one kidney prompted a man to do good, and the other bad.

These curious ideas persist in some primitive modern peoples, and when certain Australian natives kill an enemy in blood revenge, they always abstract the kidney fat.

Hippocrates did not contribute much towards our knowledge of the workings of the kidney. His works consist of a large mass of clinical data without much reference to either anatomy or physiology. His acute faculties for observation, however, led him to/

to draw attention to various urinary changes associated with kidney disease.

The first man to contribute much in the way of original biological investigations to our knowledge was Aristotle (25). He was a pupil of Plato, and the founder of the studies of Comparative Anatomy and Embryology. He examined a large number of animals, and many of his deductions are based on their comparison.

The bladder was, he believed, the seat of the formation of urine, and the kidneys existed "not of actual necessity, but as a matter of greater finish and perfection". Only animals with fleshy lungs containing blood, possessed bladders for they had a greater thirst. Thus in the birds and reptiles in which they were absent the excretion of waste products took place through the skin where the excreta were deposited as the exoskeleton, in the form of scales or feathers. There was only one exception to this rule, the tortoise, which possesses a small bladder, for the presence of which he accounts by the dense shell which would not allow of excretion.

To Aristotle the existence of kidneys without  
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a bladder was impossible. The function of the kidney was to excrete residual fluid and provide an outlet for excess of blood.

He recognised the pelvis of the kidney, and noted that the blood vessels end in the substance of the organ, and not in the cavity, so that blood is not found in the cavity even after death. The ureters, and renal arteries are described as stout ducts leading to the bladder, and aorta respectively.

The organs are arranged in this way to allow the superfluous fluid to pass from the blood vessels into the kidney, and the resulting renal excretion to collect by percolation of the fluid through the solid substance of the organ in the pelvis, whence it is conducted by the ureters to the bladder. The secretion of the kidneys was only subsidiary to the bladder, and the urine secreted by the kidneys was not exactly the same as the urine voided, but was perfected in the bladder.

The Peri-nephric fat seems also to have attracted the attention of Aristotle, and he gives a curious explanation of the way in which this large deposit of fat is laid down around the kidney.

After the residual matter percolates through the/

the kidney the blood left behind is pure and of easy concoction. The final result of thorough blood concoction is lard or suet. For, just as a certain amount of heat is left behind in the ashes of solid substances after combustion, so also a remnant of heat remains in fluids after concoction, and this is the reason why oily matter is light and floats on the surface of the fluid. The fat cannot be formed in the kidneys on account of their density but is deposited on their external surface as lard or suet depending on the fat of the animal". This fat was to protect and conserve the heat in the organs which were not encased like the thorax. The occurrence of air in this fat, he states, is the cause of rot in sheep.

Describing the human kidney, Aristotle states that it is lobulated. This probably is accounted for by the fact that he had never dissected a human body but only a foetus. Hence he says renal disease is serious in man for it not only affects one kidney but many.

This erroneous conception of the function of the bladder seems to have been corrected by the time of Galen (21), and he holds that the urine is secreted by the kidneys from the blood. Galen's anatomical/

anatomical knowledge was far ahead of that of the Greeks and he traced the ramifications of the renal artery on the pelvis of the kidney. The urine, however, he believed was secreted not from the arteries, but the veins. He was not certain as to how this separation took place, but greatly mocked at Erasistratus, of the Alexandrian school, who believed that the blood entered the upper part of the kidney, and its serum sank to the lower part of the organ whence it was led away as urine. Why did this subsidence not occur when the blood was in the vena cava was Galen's reply to this theory?

By a series of ingenious experiments, resembling those by which Harvey proved the circulation of the blood, he described the course of the urine through the urinary tract and called attention to the valve like action of the oblique insertion of the ureters into the bladder wall.

At this time the view was held that the urine was only the waste portion of that blood which nourished the kidney. With this statement Galen disagreed, and gives a very fine piece of physiological reasoning: "for from the very large size of the renal blood vessels, compared with the size of the kidneys/

kidneys themselves, he argues that the vessels were not intended solely for the nourishment of the kidneys, being capable of affording nourishment to organs of much larger size, and he therefore concludes, that from the blood contained in them, not only are the kidneys nourished, but the urine is also secreted".

With the fall of the Roman Empire all forms of learning decayed, and the Church became the sole patron of scholars. This remained the state of affairs for about twelve centuries and all scientific knowledge came to be so closely bound up with the doctrines of the Church, that the Church was afraid to allow original investigations lest the doctrines of the ancients be proved wrong, and the prestige of the Church be lost.

The Reformation had already undermined the Church from the spiritual aspect, when in 1543 Andreas Vesalius (32) gave us almost the first contribution to anatomy since Galen based on his own dissections and observations. Many of his statements contradicted those of Galen, and he met with considerable opposition from the Church. Vesalius was content, however, to correct the mistakes/

mistakes of anatomy which he could prove by his own dissections, but he did not enter into the realm of physiology, though many of his remarks throw doubts on the existent beliefs. It is curious how an anatomist, capable of such minute observations as the structure of the malleus and the incus, can describe the kidney as containing a large central cavity divided into two compartments by a sieve-like membrane on the one side of which opened the renal artery and vein, and from the other the ureter carried the urine to the bladder (19). This arrangement served as Vesalius says, to strain off some, but not all the serosity of the blood. In another part (16) he says that it was difficult to understand how the substance of the kidney, dense and firm, like the substance of the heart, could effect this straining, a doubt similar to that which he expressed on the passage of the blood through the pores in the intra-ventricular septum.

A century later the English anatomist, Highmore, (19, 20) gave us another fantastic description of the structure of the kidney, which he supposed to consist of an outer parenchymatous or liver-like portion, and an inner fibrous component. Within the latter/

latter he pictured an extensive net-like anastomosis of arteries and veins, the spaces thus formed communicating with the pelvis and constituting a system for the separation and excretion of the urine.

In 1662 Bellini (16, 19), a pupil of Borelli, discovered the straight tubules, and recognised that they were excretory channels of the urine. They had been seen by Eustacius, who misinterpreted their function and described them as "fuscous sulci". Bellini failed to recognise the convoluted tubules, and considered that the kidney consisted entirely of straight tubules extending from the papillae to the cortex. He propounded a theory on the mode of function of the kidney which was probably to a great extent influenced by his master.

The blood is poured out from the minute arteries into the parenchyma of the gland, whence the serous portion finds its way to the urinary canaliculi and the rest of the blood finds the way out by the veins. This separation, he says, depends on the size and configuration of the particles. Those of the aqueous serosity fit into the canaliculi, whereas those of the blood do not/

not.

The discovery of the microscope by Galileo was a great advance in the study of the structure of organs. One of the earliest, and also one of the greatest microscopists of all time was Marcello Malpighi, and in his book "De Viscerum Structura" published in 1669, (19, 23, 16) his descriptions of the various organs would do credit to modern histologists, especially considering the primitive instruments with which he had to work. Malpighi was a truly great man, with an aptitude for making original discoveries, the interpretation of the significance of which was based on the soundest of reasoning. He himself says in his writings that he has not read books but merely described what he has seen with his own eyes, and thence deduced his theories.

He describes the lobulations of the foetal kidney and their disappearance in adult life, and describes how by injection of the adult organ, the distribution of the arteries shows the true developmental structure of the kidney. Malpighi seems to have been a great exponent of the injection technique, and uses it to demonstrate many of the points in his work.

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The vascular architecture of the kidney is described with the skill and accuracy of any modern text book, and he calls attention to the "Glands" which we now call Malpighian corpuscles "attached like apples to the blood vessels, the latter swollen with the black liquid and stretched out in the form of a beautiful tree". These, which are almost innumerable, and situated in the outer part of the kidney, he considers play some special function in the excretion of the urine, and probably correspond in number to the urinary tubules. He recognises the convoluted tubules, lying just under the capsule, which he assumes to be continuous with the straight tubules which open on the papillae.

Malpighi had great difficulty in satisfying himself on the connection which he believed to exist between the "Glands" and the urinary tubules, but of which he could never obtain adequate proof, either by fluid injected by the arteries, or the ureters. More satisfactory evidence was obtained by experiments on a living animal. He ligated the renal vein and the ureter, so that when the kidney was examined after the animal had lived for some time, it distinctly showed branches of the urinary vessels/

vessels, together with the glands, between which, in some places, the cortex of the kidney was more distended by the intercepted blood. When the fasciculi of urinary vessels in turn were opened out, he seemed to see a certain connection and continuation, although not such as satisfied the senses in all particulars. Nevertheless, Malpighi firmly believed in the continuity between the glomerulus and the tubules, more perhaps by his own power of reasoning than by experimental evidence, for in his own words he states: "Reason, however, can bring assistance, for if in the liver, brain, and other glands, it is the inevitable rule that each single acinus or globule of the gland throws out its own excretory duct, besides the arteries and veins, the same will have to be said about glandular bodies of this sort". Doubtless, Malpighi was to some extent influenced by the prevalent views of the time, as it was an epoch noted for the discovery of glands and their ducts, Stenson, a short time previously, having discovered the parotid duct, and it is not to be wondered at that the brain was classified as a gland. All ages have had their fads, and doubtless even our own age may go down to posterity with the stigma of focal sepsis or some/

some other theory attached to it.

In his conceptions of the kidney, Malpighi was nearly two hundred years before his time, as it was not till 1842 that Bowman produced definite histological proof of its structure. Even Johannes Muller in his treatise on glands, published in 1830, staunchly denied the existence of any continuity between the glomeruli and tubules (29).

Malpighi also showed that the urine was poured out from the ducts opening on the apices of the papillae, and was not secreted through the pores of the pelvis.

The diversity of the constituents of the urine seems to have impressed Malpighi, for he says: "I marvel at this that so many different substances are separated through these glands by the process of nature, for water with salty, sulphurous, and similar particles go through, and in disease the remains of abscesses, and sometimes the defiled particles of the whole body are separated from the parts of the blood which are retained".

He accounts for this as follows:-

"I think that nature has made the structure of these glands very small and most simple, so that we cannot doubt that these things which are excreted through/

through the urinary vessels, go together into one mass, so that the particles of the salt and other substances entering in turn, form one great body of definite shape. And whatever is of larger size or of different shape does not enter the little pores, and small spaces of the excreting body, and is not excreted. From this it follows that there escapes through these urinary glands, what otherwise is useful to the animal economy. For particles similar to all these which are excreted remain in the arteries and veins for the use of the animal."

His conception of the mechanical process for separating the constituents of the urine doubtless arose from his friendship with Borelli, who was professor of physics and a colleague at Pisa.

The last two sentences quoted from Malpighi appear to me to be of exceptional interest, and I make no apology for including them, because in them I think I see the forerunner of the idea of excretion of substances up to a threshold level.

He also realises that there are waste products in the blood, which are acted on by ferments, and changed, so that they are totally excreted when they come to the kidney, and "thus advantage accrues to/  
to/

to the animal". Thus the composition and character of the urine depend on the process of fermentation going on in the body.

We see from the above that Malpighi had an excellent conception of the significance of kidney function; and in denying that spermatozoa were formed in the kidney, he remarks that since they are formed from the blood in the testis, disease of the kidney may cause sterility, since the waste products will accumulate in the blood and hinder the activity of the testis; surely an observation, which, if perhaps untrue, yet would do credit to any thoughtful clinician.

Borelli was a physicist and a pupil of Galileo. His association with Malpighi led him to take an interest in physiology, and he set his mind to a life work of applying mathematics to its study.

In his book "De Motu Animalium" (7, 16) published after his death in 1681, we find the actions of all the muscles worked out mathematically, a study which is finding great favour in Germany at the present day.

Borelli was truly a mechanist and an upholder of the "iatro-mathematical" school, and scorns the idea/

idea of the separation of the urine by a process of fermentation. "Who would imagine," he says, "that the particles of the urine could be separated by some magnetic virtue, or some ferment, acting like a servant possessing eyes?" We are bound to confess, unless we would appear mad, that there are two kinds of orifices, like two sieves, a venous one, which on account of its shape and size receives particles of blood only, and another which is constructed to receive the particles of the urine only. This theory is typical of all Borelli's work, and seems to have influenced many of his contemporaries. It is curious to observe the similarity which it bears to the loss of the smaller albumen molecules through the damaged capillary endothelium, and the retention of the larger globulin molecules, which we believe to occur in parenchymatous nephritis at the present day.

The sixteenth century saw the rise of chemistry (14) which was destined later to become one of the principal handmaids to physiology. Prior to this time, chemistry or rather alchemy, had been almost entirely in the hands of the monks whose main object was the discovery of the philosopher's/

conception was the forerunner of the modern view that the kidney only excreted urea which was brought to it, having been synthesised elsewhere, but I am inclined to think that it was only a garbled edition of the old humoral theory.

Malpighi's followers strayed far from the truth, which was not again revealed till the time of Bowman.

Frederick Ruysch (28) in Amsterdam made injection preparations of the kidney, and showed that the arteries were continuous with the tubules, giving grounds for the old view of exhalent arteries with open mouths opening directly into the ducts of secreting glands. This view survived almost till the time of Bowman, who pointed out that the error probably arose from mistaking the efferent artery, which is often fairly large, and takes a similar course, for the uriniferous tubule (29). Ruysch completely failed to recognise the continuity between the glomeruli and the tubules.

In 1749 Antoine Ferrin (16) of Montpellier described the rays of straight tubules shooting out into the cortex, which are now known by his name.

During the next half century chemistry made great/

great advances of a more substantial and practical nature than any which had been made up to that time (14).

In 1773 Rouelle isolated urea by extracting with hot alcohol the residue obtained by careful evaporation of the urine.

Twenty-five years later Fourcroy and Vaquelin obtained urea nitrate in a crystalline form by the addition of nitric acid to human urine, and the urine of animals. They showed that it gave rise to ammonium carbonate on decomposition, and was the chief nitrogenous constituent of the urine of higher animals.

Prevost and Dumas discovered urea in the blood in 1825.

The first accurate analysis of urea was made by Prout in 1824, and the chemical composition of natural urea was definitely established and recognised when Wohler of Gottingen in 1828 synthesised urea while attempting to prepare ammonium cyanate, and obtained a normal constituent of the urine, "without the aid of a kidney, an animal, a man, or a dog". It is interesting to note that shortly after making his discovery Wohler came over to Edinburgh, and in a paper delivered there, communicated/

communicated his findings to the Chemical Society(34).

Sir William Bowman, an ophthalmic surgeon, was the first since Malpighi, with the exception of Schumlansky (29), to recognise the continuity of the glomerulus, and the tubules. In the Philosophical Transactions of the Royal Society of London for 1842 he published his original treatise (29). Commenting on the failure of the earlier observers to see the continuity between the glomerulus and the tubules he states "that he was not astonished since, as the Malpighian bodies are placed in every possible direction, it often happens that a thin section parallel to the neck of the tube cannot at once be obtained, but with perseverance this may always be done". He describes the blood vessels with great accuracy and detail, but his account of the tubules is not so clear. The capsule now known by his name, but which was first pointed out by Muller, he erroneously maintains is formed by an extension of the basement membrane of the tubules, and is perforated by the vessels.

Bowman seems to have been particularly impressed by the arrangement of the blood vessels; namely the two sets of capillaries, one within the capsule/

capsule, and the other surrounding the tubule, and says: "To these distinct capillary systems, I am inclined to attribute distinct parts of the function of the organ".

He calls this curious arrangement "the portal system of the kidney", and suggests an analogy with the liver. In the Boa Constrictor, he points out, that the two sets of capillaries are actually fed from different vessels, those of the capsule being supplied by the renal artery, and those of the tubules by the renal portal vein. This arrangement also exists in the frog, and was first utilised by Nussbaum (12) and since has been used by many modern investigators in proving the function of the various parts of the nephron.

The glomerular tufts lay bare in the expanded ends of "the secreting tubules of the kidney, which like those of all other glands, are strictly speaking, an involution of the outer integument of the frame". Obviously he did not recognise the syncytium covering the tuft, or that the kidney was a coelomic organ. The first reference I find to the true structure of the capsule was that of Isaacs (1856) (5) in a paper read to the New York Academy of Medicine, who, quoting Bidder (1845), describes the/

the vascular tuft as "being similar to a head within a double night-cap". This unique arrangement of the blood vessels was, Bowman thought, ideally adapted for filtration.

The tubular epithelium suggested the function of secretion and Bowman had a curious belief that there existed an analogy between secretion and growth, both consisting firstly of assimilation, and secondly of rejection of effete products. He considered that the waste products in the blood were changed in the process of secretion by the cells of the tubules, and thus required to be dissolved by the glomerular filtrate, for if they were not changed they would still be in free solution, as in the blood, and would not require to be dissolved.

The ideas on secretion seem to have been somewhat vague, for he says that there are two processes, one in which the secretion products pass through the cell which is left unchanged and another in which they accumulate in the cell, which is then cast off.

Bowman seems to have recognised the function of the kidney in maintaining the water balance of the body, and the action of diuretics.

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In the same year as Bowman's paper appeared, John Goodsir (29) read a paper on kidneys before the Royal Society of Edinburgh, and conceived the remarkable idea that the capsule of the kidney was like Glisson's capsule on the liver, and that it penetrated into the organ surrounding the vessels after the same fashion.

About this time also Dumas and Cahours suggested that urea was an oxidation product of protein metabolism. Experiments were unsuccessfully carried out at first by Beauchamp and Fosse to oxidise natural proteins by potassium permanganate, but later Hofmeister succeeded in obtaining urea by oxidising amino acids. These experiments led on in time to liver perfusion by Ludwig and his pupils, who proved the power of that organ to synthesise urea from ammonia salts and amino acids. The invention of Ecks fistula further confirmed these findings (14). Thus the ancient process of "sanguinification" was at last elucidated.

The following year, in 1843, Ludwig (8, 22) sowed the seeds of the mechanical theory of the formation of urine, and thus started a controversy with the vitalist school of Bowman, which has not abated/

abated even to the present day. The multiplicity and ingenuity of the experiments, designed to score a triumph for one or other side, are masterpieces of modern physiology. An experiment will be used to uphold one theory and in a short time the identical experiment will prove the opposite.

Ludwig believed that a dilute urine was formed in the glomerulus, and that water was then reabsorbed by osmosis into the more concentrated lymph surrounding the tubules.

This was brought about by a purely physical process, the filtration through the glomerulus depending on the blood pressure in the capillaries, and the reabsorption by the tubules depending on the difference of osmotic tension between the dilute urine in the tubules, and the more concentrated lymph surrounding them. This view has required several modifications from its original form, as the proportions of the various constituents in the blood differs from that in the urine, and therefore it becomes necessary to consider the absorption from the tubules as a selective one, thus departing from the purely mechanical theory. Ustimovitch, a pupil of Ludwig, in 1870 showed that when the medulla/

medulla of a dog was divided there was a fall of blood pressure, and consequent stoppage of urinary secretion. When, however, urea was injected, the urinary flow returned, showing that the secretion was not entirely dependent on the blood pressure. This experiment opened up a large field of work on tubal diuresis, which was eventually solved by Bancroft's researches on the gaseous metabolism of the kidney. Our knowledge of the minute structure of the uriniferous tubules was further added to by Henle, a favourite pupil of Muller, who described the medullary loop tubule, now known by his name in his "Handbuch der Systematischen Anatomie" published in 1862. This opened up the way for Ribbert's experiment (1883), in which by gouging out the medulla he proved the absorption of water by the distal part of the tubule. The exact histological structure of the distal convolutions was shown by Schweigger-Seidel in 1865, and that of the proximal convolutions by Schachowa in 1876 thus completing our knowledge of the structure of the nephron.

In 1859 Claude Bernard (4) investigated the nervous control of the secretion of urine. Following section of the splanchnics in dogs and rabbits, he found/

found that the flow of urine was increased. Stimulation of the peripheral end then stopped secretion of the urine. Section and stimulation of the peripheral end of the vagus produced no change in the urinary outflow, but on stimulating the central end there was an increased flow. He also observed that section of the spinal cord stopped the secretion of urine, which could be re-established by artificial respiration. Similar results were found following the administration of curare.

Bernard considered that these effects were produced by the nerves acting on the capillaries, and it is interesting to note that he conceived the idea of functional intermittency which was later worked out by Krough.

Cohnheim and Roy introduced the oncometer, and showed that section of the splanchnics did not increase the kidney volume. Stimulation of the peripheral end, however, caused contraction and a rise of blood pressure. A similar contraction was observed on the stimulation of the cut central ends of the vagus and sciatic nerves. In the denervated kidney on the other hand, increase in volume was/

was accompanied by a rise in blood pressure and vice versa. Bradford located the nerves in the 10th to the 13th dorsal segments in dogs. He found that, depending on the kind of stimulus applied, either contraction or dilation of the kidneys could be obtained. Thus the existence of both vasoconstrictors and vasodilators was proved.

In 1866 Heidenhain set himself to produce definite experimental evidence to prove Bowman's theory, which had been based on purely histological grounds.

Supporting secretion by the tubules, he made his well known calculation, that, of the seventy litres filtered by the glomerulus in twenty-four hours, not less than sixty-eight must be re-absorbed in the tubules to form two litres of urine if there were no secretion by the tubules. This process he regarded as wasteful, and therefore not likely to occur in nature, but others have interpreted it as an adaptation from aquatic to land environment in the course of evolution.

He also performed a series of experiments, varying the blood supply to the kidney. By blocking the renal vein, he raised the capillary pressure/

pressure in the glomeruli, and found that the secretion of the urine stopped. This was supposed to prove that the process of secretion by the glomerular epithelium was a vital one, the stoppage of the secretion resulting from a local asphyxia. The mechanists, however, believed that this contrary result was due to pressure on the tubules by the engorged interlobular veins.

Clamping of the renal artery was likewise followed by stoppage of secretion, which recommenced on removing the clamp.

Heidenhain points out that, in these experiments, there is not only a change in capillary pressure, but also in rate of flow; mere rate of flow should not influence filtration, but would markedly affect secretion.

In 1876 he produced the famous dye experiments. His ingenuity led him to the idea of injecting dye into the circulation, so that when the animal was killed, and the kidneys examined, the path of excretion would be shown. Using indigo carmine, he found that the dye was deposited in the convoluted tubules, and the cells lining them, and in no case was there any glomerular staining. From this he deduced that the dye was secreted by the tubal epithelium/

epithelium.

Von Sobieranski (33), repeating the same experiments in 1895 was led to the conclusion that the dye was actually filtered through the glomerulus, but on account of its dilution did not produce staining. He proved this by restricting the animals on fluids, and purging with Glauber salts before carrying out the experiments, when the glomerular tuft was found to be stained. The presence of dye in the tubules, and their lining epithelium, was taken as evidence of reabsorption and concentration.

Caffeine is supposed to cause diuresis by stimulating the tubal epithelium, and thus it would be expected, that the cells of the tubules would be stained darker after its administration, but Von Sobieranski found that the reverse occurred. Whatever the interpretation of the results may be, the experiment is certainly a most ingenious one. The credit for introducing the dye technique apparently belongs to a rather less known American physiologist, Charles Edward Isaacs (5). He was a man of particular ingenuity, whose aim was always to correlate the scientific with the clinical aspect of medicine as is well instanced by one case in which he obtained/

obtained the kidneys from a patient who had died in deep jaundice, and, applying Petenkoffer's test, demonstrated bile pigment in the uriniferous tubules.

In 1908 George Schafer (31) made a very complete series of dye experiments. He performed Heidenhain's work again and confirmed it. He also made use of various leuco compounds, which were oxidised readily outside the body, and found them deposited in the tubules. Other dyes such as sodium carminate, were proved to be secreted by the capsule. From this series, which is one of the most satisfactory and complete, Schafer concluded that certain dyes were secreted from the tubules, while others were secreted by the glomerulus.

Bunge and Schmiedeberg (4) in 1876 discovered a function of the kidney hitherto quite unknown. They found that the kidney could bring about synthesis and detoxication, functions which were to lead to a wide and important field of discovery.

When a kidney was perfused with a solution containing benzoic acid and glycine, it was found that it had the power of combining the toxic benzoic acid with the glycine, and eliminating it as hippuric acid.

Continuing/

Continuing investigations into this function of the kidney Nash and Benedict (24), in 1921 found that the kidney had the power of converting urea into ammonia especially in conditions of acidosis, (thus serving to maintain the reaction of the blood) by combining with the acids brought from the tissues, linked with the free bases and proteins, and being excreted as ammonia salts in the urine.

Having determined an accurate technique for the estimation of ammonia in the blood, they applied it to phloridzinised dogs and animals following bilateral nephrectomy and ligation of the ureters. They failed to find any accumulation of ammonia in the blood despite a rise in its other constituents, and were led to believe that the kidney was the seat of its formation. It was further found that the concentration of ammonia in blood drawn from the renal vein was higher than in blood from the carotids.

The source from which the ammonia is formed is probably urea, as a rise in ammonia nitrogen in the urine is accompanied by a corresponding fall in the urea nitrogen.

Behre and Benedict (6) in the following year studied/

studied the methods of estimating creatinine in the blood, and found that the blood did not contain creatinine. The chromogenic substance, which we estimate clinically, is not creatinine, since it resists heating in an alkaline solution. Working on these lines they found that creatin produced by the breakdown of phosphagen or creatin-phosphoric acid in the muscles, is converted to creatinine in the course of excretion by the kidneys. The muscles seem to possess the property of taking up creatin from the circulation, as it disappears rapidly on injection, with no corresponding increase of creatinine in the urine.

Following up the work of Bunge and Schmiedeberg, in 1924 Snapper and Grunbaum (4) performed perfusion experiments on mammalian kidneys. Using the higher homologs of benzoic acid, they found hippuric and phenaceturic acid were formed, depending whether in the higher homologs there was an odd or an even number of carbon atoms in the chain. These results were similar to those obtained by Knoop while working on fat metabolism (1904-1908). From these experiments the workers considered that the kidneys might also possess the power of oxidising ketone bodies. Liver perfusion experiments had shown that the organ could/

could only oxidise fatty acids as far as ketone bodies.  $\beta$ -hydroxy butyric acid, and aceto-acetic acid were perfused through kidneys and found to disappear. They also showed that the muscles were capable of performing the same oxidation process. From the above findings we see that in diabetes, not only are keto acids excreted and ammonia formed, but also the ketone bodies are oxidised by the kidneys. Thus we see that the kidney plays a very important role in conditions of ketosis, and certain cases of diabetes which do not respond to insulin, may be associated with kidney damage.

At this point it might be well to consider the way in which the kidney reacts to the opposite though less common condition, i.e. an excess of base. In this case carbonic acid, which is readily available, and normally principally eliminated by the lungs, takes the place of ammonia, and combines with the free base to be excreted as bicarbonate in the urine. Unlike any of the other constituents of the urine the kidney does not concentrate carbonic acid which exists in the same proportions as in the/

the plasma.

The large volume of dilute urine passed by persons suffering from kidney damage, had been recognised by Bright in 1836, but it was not till 1897 that Koranyi (15) made the first quantitative estimation of the renal function. He found that when the kidney was severely damaged the freezing point of the urine was not as low as normal. By similar observations he also noted that, not only is the damaged kidney unable to produce concentrated urine, but also very dilute urine. In other words, "when renal function is severely damaged, the molecular concentration of the urine approaches that of the blood". Since that time innumerable tests have been devised to estimate the ability of the kidney to concentrate both normal and abnormal constituents of the urine. Among the better known are Volhard's specific gravity test, which is merely an extension of Koranyi's original idea; Maclean's urea concentration test, and Calvert's modification of it, which utilises the increased activity of the kidney during sleep. Various dye substances have also been used to test for renal function. Perhaps one/

one of the most reliable of these is Rowntree and Geraghty's phenol-sulphonephthalein test.

In studying renal excretion tests, it is found that substances which the kidney finds most difficult to concentrate are the first to be retained. This uric acid, which is only concentrated twenty times, will show signs of accumulation in the circulation long before urea which is concentrated sixty times.

Kingsbury and Swanston (4) hoped to find mild degrees of renal damage by estimating the synthetic power of the organ in forming hippuric acid, but the test has not met with general acceptance.

In 1906 Cushny, in whom we have special interest, as he later occupied the chair of Materia Medica in Edinburgh, brought forward a new theory, which has been enlarged on by many other workers, and is now known as the "Modern Theory".

He studied the effects of injecting equivalent amounts of sodium chloride and sodium sulphate together. A diuresis immediately followed the injection as the result of hydraemia, chloride and sulphate ions being excreted in equal proportions. As time went on, the number of chloride ions fell, but the sulphate ions persisted and prolonged the diuresis. The excretion of sulphates in preference to/  
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to chlorides was explained by a different threshold level for the two substances existing in the blood, both being reabsorbed by the tubules up to that level. He compared the kidney tubules to the bowel, and explained the prolonged diuresis following injection of sulphate by the osmotic tension which it exerted in the tubules, preventing reabsorption of water (11).

Bainbridge (3) in 1914 performed experiments to prove the reabsorption of chloride from the tubules. Utilising the dual blood supply to the nephron in the frog, it was found that the percentage of chloride in the perfusing fluid was greater than that in the fluid collected from the ureters. The difference was accounted for by reabsorption by the tubules, for when the tubules were poisoned with corrosive sublimate, the concentration was equal in both the perfusing fluid and the filtrate collected.

Starling (12) working on the mammalian kidney, showed with a kidney, heart, lung preparation, that when cyanide was added to the perfusing blood, the tubule cells were poisoned so that they could no longer perform any oxidative process, and the urine secreted was of the same composition as a colloid free/

free filtrate of the plasma.

Having perfected a technique for the estimation of minute quantities of glucose, Clarke (12) in 1922 proved that the reabsorption of glucose by the tubules of a frog's kidney depended on the concentration in the fluid perfusing the tubules, i.e. the fluid perfused by the renal portal vein.

From the above experiments the theory was propounded that the glomerulus filters all the non-colloid constituents of the plasma, which are reabsorbed by the tubules up to their threshold value in the blood.

Cushny (12), commenting on the school of thought that believed that only certain of the urinary constituents were filtered through the glomerulus, while others were secreted by the tubules, made the interesting statement that the osmotic tension necessary to retain in the circulation any one constituent, such as urea, would be so great as to prevent any filtration whatsoever occurring.

With the discovery of the hormones it was recognised that many organs were not only dependent on nerves for regulating their activity, but also on various chemical messengers borne by the blood. Thus  
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in 1908 Schafer (30) showed that extracts of the posterior lobe of the pituitary caused an increased secretion of urine. In diabetes insipidus the extract produced the reverse effect causing a diminution in the output of urine. Modern views would, however, lead us to believe that this water balance centre is actually situated in the hypothalamic region.

Little more confirmatory evidence in favour of any one particular theory was advanced till 1924, when Wearn and Richards introduced micro-technique in the study of renal secretion. Since then it has provided the solution to many problems, which could not be solved along other lines of investigation.

The first experiments utilising this technique were performed by Wearn and Richards (4, 33) in 1924, and consisted in collecting and analysing the glomerular filtrate obtained by a micro-pipette. The fluid collected was alkaline in reaction and contained urea, sugar, chloride, and also the dyes, indigo-carmin and phenol red, which were injected into the circulation during the experiment. Urine from the bladder was also collected but contained neither sugar nor chloride. These observations provided strong evidence/

evidence in favour of reabsorption from the tubules. The finding of indigo-carmin in the glomerular fluid confirmed the experiments of Von Sobieranski carried out thirty years before. This experiment was only conducted on a qualitative method, and gave no indication whether the glomerular fluid was produced by filtration or secretion.

The following year the same workers made quantitative estimations of chloride in plasma and glomerular fluid, and found the concentration to be equal in both, indicating that the process in the glomerulus was one of filtration.

In 1928 White made use of Barger's method for estimation of the molecular weight, and found that the molecular concentration of the filtrate was higher than that of the plasma; but on repeating the experiments, following a contrary result obtained by Walker, he found the molecular concentration in both fluids to be the same.

Leonard Bayliss conceived the idea that a cell might be constructed to measure the electric conductivity of very small quantities of fluid; and co-operating with Walker in 1930, found that the difference in electric conductivity between the glomerular/

glomerular fluid and the plasma was the same as between the plasma and an ultra filtrate from it. These findings agreed with the experiments on molecular concentration performed by White and Walker.

Elaborating the dye technique, Richards and Walker discovered that they could make very accurate quantitative estimations of phenol red, and, following injection of the dye, they compared the concentration in the plasma and the glomerular fluid, which they found to be equal.

Walker, in 1931, made quantitative estimations of urea. Since then it has been possible to estimate uric acid, glucose, inorganic phosphates, and creatinine with similar results. Thus it seems to be proved that the concentration of the constituents in the glomerular filtrate is the same as in the plasma and indicates that the glomerulus acts as a filter.

This work provides very conclusive proof of Starling's original "Cyanide Kidney" experiments.

In the long controversy as to whether filtration or secretion occurred in the glomerulus, Winifred Cullis showed in 1906 that the frog was able to form urine against a pressure higher than that at which filtration/

filtration was possible.

Hayman made direct observations of the intra-capsular pressure using a micro-pipette in 1927, and found that the capillary pressure in the glomerular tuft was adequate for filtration.

Hill and McQueen, using a different technique, considered that the capillary pressure was not sufficient to overcome the osmotic tension of the plasma, but their work is not considered accurate.

In 1929 White, using micro-methods, claimed to have observed secretion against a pressure higher than the capillary pressure in the tuft, but further experiments in 1932 proved this work to be wrong.

Richards' criticism of White's first experiment gives us a good idea of the difficulties and sources of error entering into this micro field of work. Firstly, would the adjustment necessary to estimate the glomerular capillary pressure not damage the tuft, and cause an expansion of the capsule which could only be recovered from after some time, as the experiment proceeded? Secondly, was the tonicity of the saline used to raise the inter-capsular pressure the same as the serum? Thirdly, was the capillary tube containing a bubble of air, used as an indicator, of uniform calibre and absolutely horizontal?

horizontal?

All this evidence goes to show that the glomerulus acts as a filter, allowing equal passage to all the non-colloid constituents of the plasma; and it is extremely improbable that the process involves any selectivity, or vital secretory activity.

Isaacs, in his early dye experiments (1857), had noted that some glomeruli were stained more than others, and Claude Bernard had foreseen the idea of functional intermittency, but it was not till 1922 that Richards (27), applying Krough's methods to the study of the kidney, actually observed the process with his eyes. He found that stimulation of the sympathetic, or the central end of a cut sensory nerve such as the sciatic, increased the intermittency of the glomerular flow. The intermittency of the glomerular flow persisted even after destruction of the brain and spinal cord. Since then other factors have been found which affected the flow.

In 1927 Andrews (2) showed that when oedema fluid was liberated into the circulation of a dog there was a reduction in the urinary output. Bieter (4) applied the same principle to frogs, and showed a reduction in the number of functioning glomeruli. This/

This did not occur in the denervated kidney.

This curious and interesting experiment may, I think, eventually throw some light on the etiology of the nephrotic syndrome, and may enable us to attack the disease from a different and more successful standpoint.

Similar results were obtained by Bieter (1930) following the application of a clamp to the ureters; but if a local anaesthetic were applied to the ureter before carrying out the experiment, there was no reduction in the number of functioning glomeruli, even when the splanchnics were intact.

This series of experiments is very interesting, as it serves to explain the reflex anuria following certain surgical proceedings on the urinary tract, such as the catheterisation of the ureters etc.

Micro-methods have also been of service in solving the functions of the tubules. In 1924 Bieter and Hirschfelder proved the absorption of water from the tubules by watching the concentration of phenol red. Two years later White produced a most ingenious experiment to demonstrate the absorption of chloride from the first convoluted tubule. He injected red blood cells into the intracapsular space, and found that they became invisible in/  
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in passing through the first convoluted tubule. This he attributed to reabsorption of the chlorides to such an extent as to cause haemolysis. Fluid has now been collected from different levels in the tubules, and it has been shown that glucose is absorbed from the proximal convoluted tubule, while chlorides are absorbed from the distal, and water is absorbed from both, but more from the proximal. If the change in reaction as the fluid passes down the tubules, can be taken as evidence of absorption of hydroxyl ions, then this occurs in the distal convoluted tubule.

Experimental pathology has also yielded some interesting facts as to the functions of the tubules. Shaw Dunn (13) produced uraemic conditions in animals by oxybate poisoning which damaged the proximal convolutions. This was brought about by the damaged epithelium allowing a heterogeneous diffusion back into the blood stream of all the constituents of the glomerular filtrate.

In concluding the section devoted to the modern work on kidney, I would apologise for the numerous omissions which its enormous bulk has necessitated. I hope that my selection has not been/

been too much influenced by my own interests, and in choosing the matter, I have tried to emphasise those points which I consider to be milestones of genuine advance along the highway of kidney research.

Our knowledge of the functions of the kidneys has thus developed parallel with the rise and growth of other branches of science and of the human mind. It has developed from the mystical folk-lore such as we have seen in the Bible to a complicated mass of knowledge based on innumerable investigations, which have drawn from every field of science and utilised every natural force to solve the problem of the nature and functions of the kidney. In our present state of knowledge, despite the factor of various controversies, we feel that we must be very near the truth; yet perhaps even the Greeks in their day possessed the same feeling of satisfaction, unaware, and never even thinking of the development of modern lines of investigation. Perhaps the future may open up avenues of approach which we too have not even dreamt of, which may shatter or substantiate our knowledge.

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