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DISSERTATION

on

THE EXCRETION OF WATER AND SALT.

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Introduction:

It is disquieting to one who contemplates research into any aspect of renal function, to read, in Cushny's preface to his monograph on the Secretion of Urine (20), that no other organ of the body has suffered so much from poor work as the kidney. In 1917 Cushny was complaining of the enormous number of papers, then devoted chiefly to theories of renal secretion, in which the depth bore no proportion to the length. Whether the defect has been remedied since then it is difficult for me to judge. The literature has grown no less unwieldy. As our insight into the working of the kidney has deepened, so have the problems connected with it multiplied. The field of investigation has widened, and the number of workers in it continues to increase. With every year the co-ordination of their results becomes more and more difficult. We look for the day in which increasing knowledge will begin to simplify, instead of adding to, the riddles yet unsolved. But that day has still to dawn.

My experiments began on similar lines to those of Haldane, Davies and Peskett (21) who had studied the question of the "maximum" concentration obtainable by the kidney, and the effect of one electrolyte upon another in the process of excretion. Confirmation of their work seemed desirable as it was freely quoted, and Samson Wright had stated (6) that this subject required further elucidation. The research proved fascinating, and led on to the consideration of all that happened when large quantities of salt were eaten, and to the consideration of what caused the kidney to respond.

The thesis has been arranged in three parts. The first deals with the elimination of water, and the second, in rather more detail, with some aspects of the elimination of salt. The section on Thirst has been introduced to include some observations which are, to the best of my knowledge, original. For the sake of brevity I have been restricted to pure physiology. The direct application of our knowledge of salt and water metabolism to clinical problems, especially those concerned with diabetes insipidus and with nephritic oedema, offers a vast and interesting field for experimental investigation. But the discussion of these questions has been omitted, for it would fill a book many times this size.

None the less, I have undertaken the work with this secondary object in view, that the knowledge so gained may be applied to the problems of clinical medicine. For it is my hope that there may be found herein some new particles of information, some fresh interpretation, or some workable hypothesis, that may increase our understanding, and aid ultimately the conquest of disease.

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Historical:

Comfortable though it is to regard all theories of renal secretion which appeared prior to Cushny's monograph as obsolete, and to feel that one need no longer be drawn into the disputes that occupied the physiologists of the two opposing schools, no work on kidney function would be complete without some mention of the early history of the subject.

It is ninety-two years since the microscopic study of the kidney led Bowman to appreciate the relation of the Malpighian body to the renal tubules. The structure of the glomerulus caused him to believe that this was the point at which water was secreted to serve mainly as a means of flushing out the tubules, in which urea and other substances were excreted in solid form. In his original article (13) he wrote:- "It would be difficult to conceive a disposition of parts more calculated to favour the escape of water from the blood than that of the Malpighian body. Why is so wonderful an apparatus placed at the end of each uriniferous tube if not to furnish water, to aid in the separation and solution of the urinous products from the epithelium of the tube"?

The experimental work of Heidenhain in 1874, lent support to the theory and led to the coupling of his name with Bowman's. It was supposed, briefly, that the constituents of the urine were secreted by the vital activity of the epithelium of the capsule and of the tubules. The glomerular capsule secreted water and those salts which accompanied water everywhere in the organism, such as sodium chloride; but the tubules eliminated most of the solids and a considerable proportion of the salts, accompanied by a minimal amount of water. This sufficed for ordinary conditions. During diuresis the additional water came from the tubular epithelium and not from the glomerulus.

The capsule and tubules thus differed from one another only in degree of permeability, the tubule cells being normally more permeable to the solids of the plasma than to the water. During diuresis this difference disappeared, water coming from the tubules in larger quantity than from the capsule. Thus, in its simplest form, the conception of "vital secretion" regarded the kidney as producing urine in the same way as the submaxillary gland secreted saliva. It gave no satisfactory account of diuresis, postulating a variable site for the secretion of water, and under these conditions ascribed similarity in function to structures as different as the glomerulus and tubules.

The opposing view - which may be called the Mechanical Theory of renal secretion - was published byLudwig in 1844, two years after Bowman. The capsule was regarded by Ludwig as a simple filter which allowed all the constituents of the plasma to pass through it, except the proteins. In the tubules the filtrate was elaborated into the urine by the return of much of the water into the blood by a process of diffusion. The change in the ratio of urea and chloride to one another in the blood and in the urine was explained by supposing that chloride permeated the epithelium of the tubules more readily than urea. The important point was that filtration and reabsorption were considered to be simple physical processes.

Although this theory is now discarded (for urine of a higher osmotic pressure than the plasma could not be prepared in such a way), we are for ever indebted to Ludwig for his two fundamental ideas.

In Cushny's words: "The Modern View, in its gradual development, has accepted the general scheme of filtration and re-absorptior

Ludwig, but, appreciating the inadequacy of the known physical forces, has supplemented them as far as is necessary by the vital activity postulated by Heidenhain.

"The blood pressure in the glomerular capillaries suffices for filtration, and the capsule filters off the colloidal substances of the blood plasma by which it is impermeable, while allowing the rest of the constituents to pass through without alteration in their relative concentrations; the glomerular filtrate is thus practically deproteinized plasma. In its passage through the tubules this fluid is altered by the absorption of certain of its constituents by the epithelium. The passage of the absorbed water and solids of the glomerular filtrate through the epithelial layer entails the expenditure of energy by the cells; it is an active absorption, not the passive diffusion which was believed by Ludwig to be sufficient.

"The Modern View thus ascribes the function of the kidney to known factors except the reabsorption in the tubules, and that is reduced to the simple and unvarying propulsion of a definite solution through the epithelium towards the blood. It is thus a negation of vital secretion in the capsule and of discriminating activity in the tubules, and like all negations, cannot be proved directly".

It is unnecessary to relate in detail all the work that has been done by its supporters to substantiate vital secretion, or the criticisms that have been levelled at the "modern theory" and the way in which they have been answered. This is excellently set forth by Cushny in the monograph mentioned above.

For the purposes of my work the "modern theory" has been accepted, and, with some modifications to be mentioned shortly, has been used as a basis for my observations.

Influence of Diffusibility on Concentration Ratios.

When the degrees of concentration undergone by the several constituents of the urine are compared with one another, i.e. when their levels in the urine are divided by those in the plasma, it is found that under ordinary circumstances the sodium, chloride, and bicarbonate ions are least concentrated; potassium, urea and urate rather more so; phosphate still more; and sulphate and the creatinine bodies most of all. Of this Cushny was aware, but gave no explanation except on a basis of varying "thresholds" which caused him to state that even for sulphate there may be a very low threshold, just sufficient to differentiate it from the creatinine group of bodies. And, on this assumption, creatinine becomes the only "no-threshold" substance normally present in the urine.

The first to put forward another explanation was Mayrs (46) in 1922, who found that after the simultaneous injection of sodium sulphate and urea he could obtain a greater concentration ratio for the former substance. In addition, partial obstruction of the ureters caused a greater fall in urea concentration than in the sulphate. He considered them both to be "no-threshold substances" and regarded the differences in their concentration ratios as being due to diffusion from the lumen into the cells of the tubules. After additional experiments of the same nature he concluded: "The greater the diffusibility of any of the substances examined the lower appeared to be its concentration ratio".

This new conception did not receive the recognition it deserved, and it remained for Rehberg, working along similar lines four years later, to reach the same conclusion, and to publish his "modification" of Cushny's theory (57).

Rehberg studied the excretion of creatinine in the human subject making serial estimations of blood and urinary creatinine. On the assumption that all the filtered creatinine appeared in the urine he co calculate its degree of concentration, and from this the quantity of the glomerular filtrate and of the fluid reabsorbed in the tubules. In the same way it was possible to estimate the total amount of any other substance in the glomerular filtrate and the degree of reabsorption it had undergone.

After the ingestion of large amounts of creatinine the concentration ratio (urine/plasma) for this substance exceeded 200, this meaning that for every 10 c.c. of urine passed there had been over 2 litres of glomerular filtrate, 99.5% of which was reabsorbed. This is, however, not impossible. Rehberg calculated the total filtration surface of all the glomeruli as 0.9 square metres, and the surface available for reabsorption in the provisional convoluted tubules alone as 1.76 square metres. This "is so large that, provided it only shows the same power of reabsorption as the cloaca of a bird, it could reabsorb the whole quantity of fluid required in the concentration process in the tubules". The necessity for the formation of such a large quantity of glomerular filtrate was one of the points in the filtration-reabsorption theory most strongly attacked by the followers of Heidenhain. It is interesting to see that such a conception is not impracticable.

Working on the filtration-reabsorption hypothesis and using the creatinine concentration ratio as a measure of that of the urine as a whole, Rehberg found that in urines of high concentration the amount of urea excreted was only about half that present in the glomerular filtrate. Although the urea level rose as the urine became more concentrated the ratio of urinary urea :: blood urea did not increase as rapidly as that for creatinine. This proved clearly that the more the kidney attempted to concentrate the urine by the reabsorption of water, the greater was the strength of urea in the reabsorbed f

Rehberg put forward the following theory: "Large volumes of filtrate are formed in Bowman's capsules. This filtrate contains in solution all diffusible substances from the plasma............The percentage and amounts in which the no-threshold substances are excreted are determined by the amount of filtrate, the concentration index of the urine, and the ease of back-diffusion. As the concentration-index rises the concentration ratios of the different substances rise too, but at different rates. The group of no-threshold substances thus includes those which may be concentrated to very different extents, from alcohol, which is not concentrated at all, to creatinine, which may be concentrated several hundred times".

Cushny did not expect the Modern Theory "to attain finality in regard to the secretion of urine, but to serve as an advanced post from which others may issue against the remaining ramparts of vitalism". What has happened in the intervening years? The views of Bowman and Heidenhain have been superseded, and in this direction the vitalists can no longer raise their heads. But fresh problems have arisen. We can no longer believe with Cushny that the fluid reabsorbed in the tubules is of unvarying composition; there is some doubt about the existence of fixed thresholds; the conception of back-diffusion has altered our ideas of the concentrating mechanism; But most important of all, we are being forced to the realization of a controlling power behind the kidney, that can alter its ability to secrete and to concentrate urine. There is evident correlation between the kidney and the nervous system; and the composition of the tissue fluids is as important as the composition of the blood.

This new controlling factor we cannot yet explain in terms of physics and chemistry. Perhaps "vitalism" is not yet entirely quelled.
