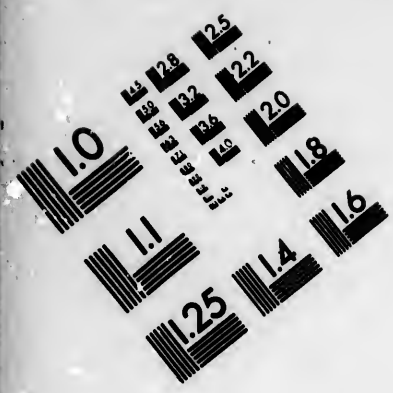

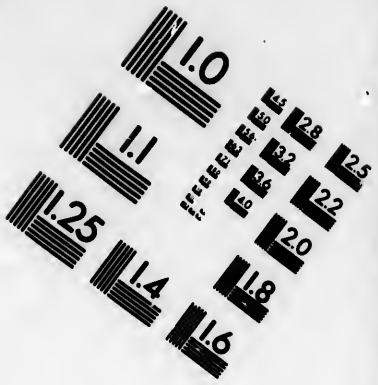

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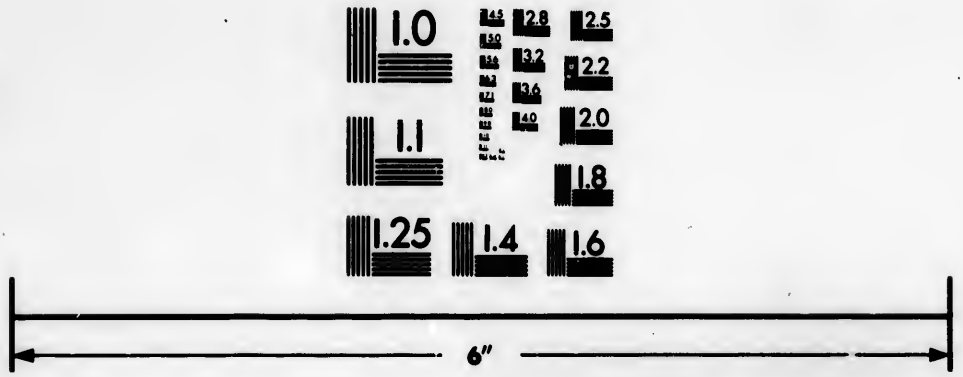

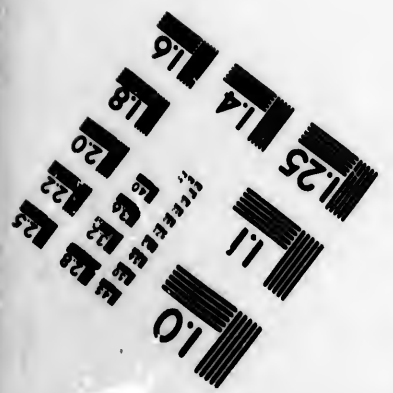

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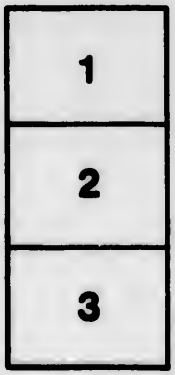

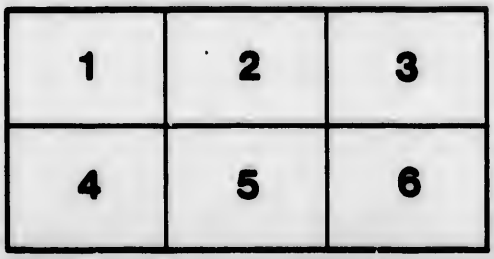

THE PRACTITIONER.

APRIL, 1889.

Original Communications.

ON THE FUNCTIONS OF THE GLOMERULI OF THE KIDNEY: A CONTRIBUTION TO THE STUDY OF ALBUMINURIA.[1]

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THE recent publication of a volume upon albuminuria by so eminent a clinician as Professor Grainger Stewart,[2] in which the glomeruli of the kidney are considered as mere filters, and the possibility that their epithelium may be of a secretory nature is ignored, renders this a not inopportune occasion to discuss the various theories of renal activity, especially with reference to the part played by the glomeruli. I am the more ready to accept this opportunity inasmuch as the works of the two great authorities upon the glomerular functions—namely those of Heidenhain[3] and of Cohnheim[4]—have not as yet received an English translation, nor do I know of any extended

[1] A thesis for the degree of M.B. Cantab.

[2] Grainger Stewart, *Lectures on Important Symptoms* (II. Albuminuria). Edinburgh, 1888.

[3] Heidenhain, *Hermann's Handbuch*, vol. v., Leipzig, 1880.

[4] Cohnheim, *Allgemeine Pathologie*, vol. ii. Second edition. Berlin, 1882.

account in our language of their views upon the subject, or rather of the arguments upon which those views are based.

The "mechanical" theory, based upon the excellent series of researches of Ludwig and his school—Hermann, Goll, Overbeck, and Ustimowitsch—has until recently influenced more than any other the opinions of those who have worked upon the kidney. The conception that the elimination of the urine depends upon a single great factor, the blood-pressure, that the whole of the urine is filtered through the glomeruli, and concentrated by diffusion through the cells lining the *tubuli uriniferi*, is one that can easily be grasped; and for many years this theory ruled alone, and was almost universally accepted. Heidenhain,[1] however, in 1874, reasoning by analogy, and observing that in its general nature the epithelium of the tubules corresponds to that of the definitely glandular organs which he had previously been studying, brought once more into the foreground the older theory of Sir William (then Mr.) Bowman, the theory that the watery elements of the urine are eliminated by the glomeruli, the characteristic solids by the tubules. And when, by injection of sodium sulphindigotate, he was able to demonstrate the passage of substances through the cells of the *tubuli contorti*, and to show that these cells, instead of absorbing, excreted into the lumen of the tubules, the mechanical theory broke down.[2] But to the present day there are still many who, like Grainger Stewart, consider the general blood-pressure as the determining factor in the production of the fluid part of the urine.

That blood-pressure plays a secondary *rôle* is however evident, when the cases are studied in which, the general arterial pressure remaining constant, there is an obstruction to the

[1] Heidenhain, *Arch. f. microscop. Anat.* vol. x. p. 30 (1874); *Arch. f. d. ges. Physiol.* vol. ix. p. 1 (1875).

[2] During the last few years Ribbert has revived the theory that the excess of urinary fluid is re-absorbed by the tubules. On extirpating the medullary substance of the rabbit's kidney he found that a more watery and profuse fluid passed away from the remaining functional cortex. These results cannot however be held to have any value, for, as has been pointed out, the kidney has a rich lymphatic supply, and the fluid passing from the maimed organ must contain a proportion of lymph probably very considerable, but not admitting of estimation. The presence of this lymph invalidates any such conclusions as those that Ribbert has sought to draw.

outflow through the renal veins. Ludwig himself[1] appears to have been the first to record the fact, since noted by numerous observers, that narrowing or temporary complete closure of the renal veins is accompanied by a rapid slowing or stoppage of the urinary flow—by a diminution in the urinary excretion—in spite of the undiminished general arterial pressure, accompanied as it is by an increased pressure in the glomerular loops. This, Ludwig held, was explicable on the assumption that the dilated capillaries so pressed upon the tubules as to constrict them, close their lumen, and prevent any passage of fluid through them. Heidenhain[2] has however combated this view, pointing out that the alteration in the excretion of urine is too immediate to be accounted for by such considerations, and he has propounded the theory that it is the *rate of flow* through the glomeruli, rather than the blood-pressure, that governs the passage of water from the kidney.

This theory, that the rate of flow controls the excretion of urine, does not in any way imply that the blood-pressure is not a factor in the process. Indeed, the rate of flow is itself determined by the blood-pressure, being the resultant of two opposing forces: (1) the general blood-pressure, and (2) the resistance against which the blood is forced through the kidney. The resistance remaining the same, increased blood-pressure causes increased rate of flow, and in such cases there is an increased formation of urine. But if the resistance be increased and the blood-pressure remain unaltered, or be not increased proportionately, the rate of flow is diminished. These conditions are met with in obstruction to the outflow from the kidney. The stoppage of the urinary excretion cannot be due to diminished arterial pressure in the renal capillaries, but may be explained by the diminished velocity of the blood-current.

The more recent work of Paneth[3] has wholly confirmed and established Heidenhain's contention. Paneth, placing round the upper abdominal, or thoracic, inferior vena cava a fine thread capable of being easily controlled, found that in every

[1] Ludwig, *Wiener Sitzungsber.* vol. xlviii. p. 275 (1863).

[2] Heidenhain, *Hermann's Handb. der Physiologie*, vol. v. p. 324. Leipzig, 1880.

[3] Paneth, *Ueber den Einfluss venoser Stauung auf die Menge des Harns, Arch. f. d. ges. Physiol.* vol. xxxix. p. 515 (1886).

case in which the constriction was sufficient to produce any obstructive effect (with a weight, for instance, of 35 grammes or under 1 ounce attached to the thread), the urinary excretion became less, and this often where there was a simultaneous increase in the aortic pressure. That the diminution was not due to compression of the tubules he proved by injecting a diuretic, sodium nitrate, along with chloral. When the flow from the ureter had almost come to a standstill in consequence of the continued constriction and obstruction of the inferior vena cava, and of the partial venous stasis in the kidney, the diuretic caused an immediate and copious excretion of urine, although the effect of the chloral had been very markedly to lessen the general arterial pressure, and although, as shown by Roy's oncometric observations,[1] the tendency of the sodium nitrate would be to cause a further expansion of the renal vessels.

Immanuel Munk, in his paper upon the extirpated kidney to which I shall refer later, cites experiments to prove the same law, namely that the rate of blood-flow and not simply the blood-pressure determines the glomerular excretion. With a constant pressure in the renal artery, he passed through the organ, first simple defibrinised blood, and then the same containing a diuretic (*e.g.* urea). And he found that under the influence of the latter there was a more rapid flow of blood from the renal vein and of fluid from the ureter. But, as Professor Heidenhain has pointed out to me, although the pressure in the renal artery is unaltered, it by no means follows that the blood-pressure in the glomeruli has not undergone an increase. Dilatation of the renal arteries and of the *vasa afferentia*, by reducing friction in these vessels, will cause the blood to enter the glomeruli under higher pressure than previously. Munk, therefore, has not with certainty eliminated the factor of pressure. It would be interesting to see what results ensued from this method if, instead of keeping the pressure in the renal artery constant, it were lowered upon injection of the diuretic.

Admitting, then, what is now very generally accepted by physiologists, that it is the velocity of the flow through the glomeruli, and not solely the blood-pressure in them, that

[1] Roy, *Proceedings of the Cambridge Philosoph. Soc.* May 23, 1881.

governs the excretion of the fluid of the urine, there remains the question as to the nature of this excretion; is it simply a process of filtration, or is it more nearly allied to a process of secretion?[1]

This problem of the nature of the glomerular activity is of special importance from a clinical stand-point, inasmuch as upon its solution depends the interpretation of that most grave symptom, albuminuria. Heidenhain,[2] in his classical work upon the *Physiology of the Processes of Secretion*, insisted on the secretionary view, and Cohnheim[3] was of almost the same opinion. But more recently Senator[4] has revived the theory that the glomeruli act simply by transudation, Runeberg holds consistently to the same view, and Grainger Stewart accepts Senator's conclusions.

Senator's theory is briefly—that the fluid portion of the urine is derived in part from the glomeruli by transudation, in part from the epithelium of the tubules. He considers that just as other glands in secreting any substance always excrete with this a certain amount of watery fluid, so in the cells of the tubules the like process occurs. And Grainger Stewart states[5] "at all events we may hold with certainty that the water is mainly eliminated by filtration through these structures (the Malpighian bodies). But the urea and other urinary solids are not discharged by a

[1] Let me premise that by a *filtrate* is understood the fluid which passes through the larger meshes of a membrane under the influence of pressure; such a fluid contains proportions of all the soluble substances present in the mother-fluid. A *transudation*, according to the general employment of the term, is a filtrate from the blood, and so should contain the salts and albumens of blood-serum, the amount of fluid transuding being directly dependent upon the blood-pressure; while the composition of a *secretion* is such that it cannot be explained by the laws of filtration, its quality being determined by the specific characteristics of the gland-cells. These cells in the simplest cases have only a selective power, extracting certain substances from the blood and excreting them. Where more highly differentiated, they have in addition definite synthetic or metabolic powers. A membrane, which while the blood-pressure remains constant at one time permits and at another prevents the passage of fluid from the blood, cannot be looked upon as wholly dependent upon the laws of filtration; such a membrane evidently possesses specific properties, properties of too complex a nature to be accounted for by the laws that govern a single and comparatively simple form of physical action.

[2] Heidenhain, *Hermann's Handbuch*, vol. v. p. 335 (1880), and also *Breslauer ärtzl. Zeitschr.* No. 22, 1879.

[3] Cohnheim, *Allgemeine Pathologie*, vol. ii. p. 319 (1882).

[4] Senator, *Die Albuminurie*. Berlin, 1882.

[5] Grainger Stewart, *loc. cit.* p. 50.

filtration, but by a secretive process performed by the cells of the tubules. Along with this secretion, as in the case of other glands, a certain amount of watery fluid passes."

The supporters of the filtration theory have however to explain how it is that a filtrate from the albumen-containing blood-serum is normally quite free from albumen, or if not quite free contains it in infinitesimal quantity. According to them the capillary loops of the glomeruli, with their covering of epithelium, form but a passive filtering membrane. The loops must consequently obey the same laws as, and in their action generally must correspond to, other simple animal membranes. Now all other "transudations" contain albumen; fresh animal membranes, also, when employed as filters permit the transudation of albuminous substances, and this not in small quantities but in large. Thus Runeberg,[1] filtering through a sheep's intestine blood-serum (from a horse) containing 8·4 per cent. of albumen, found that at a pressure of 100 ccm. of water, or about 75 mm. of mercury, the filtrate might contain as much as 8·0 per cent. of albumen; at a pressure of 10 mm. of mercury from 6·54 to 7·8 per cent. And if the thickness of the membrane be a factor of any importance, the filtration of albumen through the delicate glomerular wall ought surely to be still more complete.

Yet, as Grainger Stewart has shown that, even with the most delicate test, namely picric acid—a test that indicates the presence of albumen in the proportion of 0·00015 in the 100 parts[2]— when he examined the urine of 505 presumably healthy individuals he could detect albumen in little over 32·8 per cent. of the cases. And here the urines tested were forenoon or noon specimens; they were passed at the period when physiological albuminuria is most prone to become apparent. And of the 32·8 per cent., in 17·8, or more than one-half, albumen could not be discovered by the addition of cold nitric acid; in other words, the amount of albumen present did not exceed 0·003 per cent. Similarly among 525 patients taken at random[3] only

[1] Runeberg, *Arch. d. Heilkunde*, vol. xviii. (1877.)

[2] Grainger Stewart, *loc. cit.* p. 10.

[3] Private, indoor and outdoor hospital, children's hospital, fever, and maternity patients; the fever specimens to the number of fifty were tested upon the day on which it seemed most likely that albumen would be found in each variety of zymotic disease.

187 (or 35·6 per cent.) of the urines showed the presence of albumen, and in fifty-seven of these (or 10·8 per cent.) the presence was only discernible by adding picric acid. Further, Grainger Stewart found that even after considerable concentration albumen is not to be discovered in what he (as I think rightly) terms normal urine.[1] I cite these figures of Grainger Stewart, instead of those of numerous other observers, in the first place because his series embraces the largest number of observations, and in the second because the percentage of cases in which he discovered the presence of albuminuria was not lower but higher than in almost all the previous series.

This difference between the action of membranes outside the body, and the result of glomerular activity within it, of necessity demands explanation. If the glomeruli act by transudation or filtration, the absence of easily recognisable quantities of albumen in the urine must be accounted for.

By a modification of the "mechanical" theory[2] the absence of albumen in the normal urine is explicable on the supposition that the albumen transuded through the glomeruli is actively re-absorbed by the cells of the tubules; but, apart from the fact that the main principles of Ludwig's theory have, one after the other, been proved insufficient to elucidate the various phenomena of renal excretion, there is the evidence of Senator[3] that the cells of the tubuli, instead of absorbing albumen, are capable under certain conditions of excreting this substance; though, as Senator holds that this excretion is more of the nature of an exudation, I am not desirous of laying too much weight upon this point. Nor does the theory of albuminuria offered by Grainger Stewart appear more satisfactory. He inclines to the opinion that "the blood-pressure in the capillary loops, and the walls of these vessels with their epithelial covering, are so balanced as to permit of the transudation of fluid, and yet completely to prevent the passage of albumen"; and he immediately adds, "at all events we may hold with certainty

[1] Grainger Stewart, *loc. cit.* p. 19.

[2] Ludwig's original theory did not take into account the phenomena of albuminuria.

[3] Senator, *loc. cit.* p. 57.

that water is mainly eliminated by filtration through these structures." Apart from the slight ambiguity in the first of the

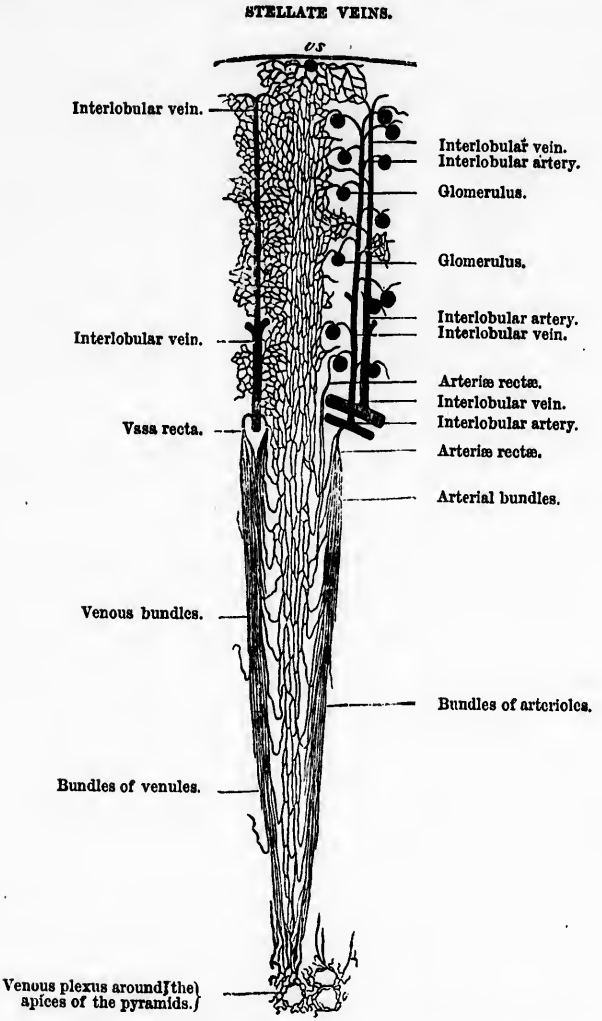

FIG. 1.—Diagram of the blood-vessels in the kidney (after Ludwig).

above sentences, this opinion can scarcely gain acceptance. There is little doubt that normally a very definite blood-pressure

exists in the glomerular loops; the greater part of the arterial supply of the kidney passes into the interlobular arteries, and so by the *vasa afferentia* direct to the glomeruli. A high pressure does not prevent the passage of albumen through simple animal membranes; and, on the other hand, with a pressure of 7·5 mm. of mercury, a pressure far below that which in the dog, and most probably in man, is accompanied by a total cessation of urinary excretion, the observations of Runeberg show that albumen continues to transude in large quantities through membranes outside the body. At what point then must the "balance" be supposed to occur?

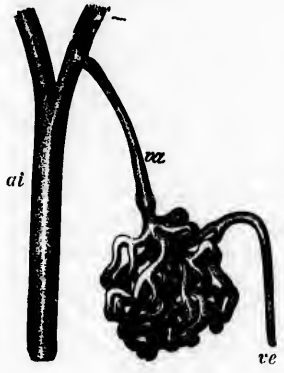

FIG. 2.—Malpighian glomerulus. *va* is the afferent vessel which springs from the interlobular artery *ai*, and breaks up to form the glomerulus; *ve* is the efferent vessel which conveys the blood from the glomerulus.

To declare that a comparison such as this, between dead membranes and those within the living body, is not just, is to acknowledge that in the living membrane some other factor comes into play, that the glomerular walls possess specific properties, and that the laws of filtration and transudation alone are insufficient to account for their normal action. This, it seems to me, is but one step from declaring that the glomerular epithelium is capable of exercising a selective function. Grainger Stewart, in acknowledging (p. 58) that altered conditions of the filtering apparatus may sometimes determine albuminuria, and that it is conceivable that transudation of albumen might result from changes either in the vessel-walls or in the epithelium of

the Malpighian tufts, or both, would appear very nearly to admit this; for in so doing he presupposes a filtering apparatus at one time preventing, at another admitting, the passage of albumen.

Senator[1] holds that the fluid passing from the vessels of the glomeruli must certainly (*ohne jedes Bedenken*) be considered a transudation and not a grandular secretion, that these vessels transude only one portion, but that indeed the greater portion, of the water of the urine, and that they are exceptional in that the lateral pressure is in them greater than in any other capillary system in the whole body. This last fact, he claims, is capable of explaining their action with regard to albumen: the greater the filtration pressure the greater is in general the amount of the filtrate and the less the percentage of albumen contained, although the total amount of filtered albumen is, in equal periods of time, greater with higher pressure than with lower. Thus, according to Senator, to the great lateral pressure that exists in the glomerular capillaries is due the copious filtrate through these organs, and this filtrate contains normally a comparatively small amount of albumen, although the total amount of albumen is larger than would be the case were the pressure less.

I have already referred to Runeberg's observations. From these it is deducible that through an animal membrane, at the medium pressure of 73 mm. of mercury, as much as 95 per cent. of the albumen in solution may pass (the mother-fluid containing 8·4 per cent., the filtrate 8·0 per cent. of albumen). At but a tenth of this pressure the percentage still remains very high. It is unlikely that at the ordinary blood-pressure of 120–150 mm. of mercury there would be any great diminution in the amount of albumen filtered. But what proportion of albumen do we find in the urine?

It is well ascertained that, in the majority of cases, a test (picric acid) capable of indicating the presence of 0·00015 per cent. of albumen in the urine is absolutely without effect. Or, in other words, 0·00015 per cent. corresponding to 0·000655 grains in the ounce of urine, and the amount of urine passed during the twenty-four hours being roughly 50 ounces, the amount of

[1] Senator, *loc. cit.* p. 57.

albumen secreted during the day, in health, must be below 0·0327 grains. Or, allowing that Grainger Stewart has estimated the delicacy of the picric acid test as thirty times higher than it really is, even then the amount of albumen excreted during the day must be less than 1 grain. The normal blood-serum, according to Hammarsten, contains 4·516 parts of serum-albumen. The presence, therefore, of even as much as a grain of albumen to the ounce of urine, of 0·2 instead of less than 0·0015 per cent., would, I infer, be still insufficient to harmonise with any theory of urinary filtration; and that even if, instead of declaring with Senator that the greater portion of the urinary fluid passes through the glomeruli, we admit that the greater portion is excreted through the tubules.

The filtration hypothesis presents us with another very grave difficulty. The blood-serum contains large amounts of two proteids: an albumen, serum-albumen, and a globulin, serum-globulin, or para-globulin, in the proportion roughly of three parts of albumen to two of globulin. In six separate observations upon human blood-serum, Hammarsten found that the percentage of the total albumen present varied from 7·1 to 8·1. And Salvioli[1] found relatively little change in the proportions of albumen and globulin when he compared different dogs in various conditions of hunger, and still less when the blood of one animal was taken at different periods. No one, in fact, has as yet come across mammalian blood-serum in which only one of the two proteids has been present. Both of these transude through fresh animal membranes, and inasmuch as globulin is the more diffusible of the two, it would not be unreasonable to suppose that in cases of albuminuria it should the more readily appear in the urine. We should at least expect the two proteids always to be present together, and that in what within moderate limits ought to be a fairly constant proportion. But this is singularly at variance with what really happens. Although in two cases Estelle[2] states that he found the relation between the two proteids in the urine almost exactly corresponding to the relation in the blood—a statement doubted by Maguire,[3] on the

[1] Salvioli, *Arch. f. Anat. u. Physiol.* (Physiological Section), 1881, p. 269.
[2] Estelle, *Revue mensuelle des Sciences Méd.* No. 9, 1880.
[3] Maguire, *Lancet*, vol. i. 1886, pp. 1062 and 1100.

ground that Estelle did not neutralise the urine before adding magnesium sulphate—in other cases the same observer found the albuminous urine to contain albumen only, the globulin being wholly absent.[1] Moreover Maguire[2] has shown that the proportions vary within enormous limits,[3] and in four cases, three of the nature of "cyclic" albuminuria and the fourth puerperal, he discovered globulin alone to be present, with at most only the faintest possible trace of serum-albumen, which it was impossible to estimate. Variations so wide as these can only be accommodated to a theory of glomerular filtration on the supposition that the relative amounts of the proteids in blood-serum undergo enormous alterations, that sometimes serum-albumen is absent, or almost absent, and sometimes globulin, a supposition which again, I think, no one will be prepared to admit. A more satisfactory conclusion is that the amount, and the relative proportions, of the proteids in the urine are only to a certain extent dependent upon the composition of the blood-serum; and that one of the functions of the healthy glomeruli is to prevent the removal of albumen and globulin from the blood when these are

[1] Estelle's statement with regard to the urine of one patient (*loc. cit.* p. 711), "*Ce n'est toujours que de la matière A*" (serum-albumen), is evidently from the context a misprint, B (globulin) alone being present. But by injecting a solution of serum-albumen into the jugular vein of a guinea-pig, Estelle obtained urine giving the reaction of albumen alone. And in the case of a young dog, to which amylic alcohol had been given, he obtained the following results (globulin being determined by the addition of magnesium sulphate):—Blood-serum: albumen 5·2 per cent., globulin 6·4 per cent.; Urine: albumen 0·34 per cent., globulin 0·8 per cent. The percentages of proteids in the blood-serum here given are much larger than those determined by Salvioli (*loc. cit.*), and the proportion of globulin present is placed at a figure much above the normal. It is doubtful whether even 0·08 per cent. of globulin was present in the urine, for, as Ott (*Zur quantit. Bestim. d. Eiweisskörp. im Harn, Prager med. Wochenschr.* 1884) has pointed out, magnesium sulphate brings down a portion of the serum-albumen as well, provided that 0·5 per cent. of acid phosphates be present in the solution. Nevertheless the above figures, even allowing a large margin for errors of experiment, show that there is no immediate relation between the proportions of the proteids in the blood-serum and urine respectively.

[2] *Loc. cit.*

[3] The results may be put roughly thus:—

I. Case of granular kidney—albumen : globulin : : 2·5 : 1.

II. Case of granular kidney and mitral stenosis—albumen : globulin : : 4 : 1.

III. Cases of anæmia and albuminuria with probable fatty degeneration of kidney. Albuminuria, absent at first with rest, came on upon getting up, and bore distinct relation to the amount of exercise taken—albumen : globulin : : 1 : 2·5.

present in normal quantities, but to excrete either or both of these, if present in definite excess.

If then we are compelled to abandon the theory that glomerular activity is of the nature of simple filtration or transudation, what are the facts and observations in favour of considering that the glomeruli possess functions of a selective or secretory nature, permitting certain substances to pass through their walls and preventing others?

In the first place the glomeruli are not solely blood-capillaries. Each capillary loop is covered by a fine membrane, by a single layer of epithelium composed of cells which, having large easily-staining nuclei, must be looked upon as having actively vital properties. And one vital property, that of contractility, they have been demonstrated by Hedinger[1] to possess. This epithelium is a visceral extension of that lining Bowman's capsule, and so is a continuation of the definitely glandular lining of the renal tubules. In the developmental stage the glomerular epithelium appears as a layer of cubical units, of a type much more in accordance with the usually accepted idea of the characteristic gland cell than in the adult stage, where the cells are so closely united that it is only with the greatest skill that any divisions are to be recognised, so much so that many deny that there is any clear cell-boundary at all. The passage of fluid between the cells would therefore appear to be guarded against; and that this epithelial layer can act as a barrier is demonstrated by the fact that in argyria, as Riemer[2] has shown, the glomeruli are found darkly-stained by minute granules of precipitated silver. These granules lie outside the capillary loops, but between them and their enclosing epithelial membrane. They must therefore have been carried with the stream of water through the capillary walls, and have been stopped in their course by the epithelium. The specific power of the simplest sheet of epithelium to resist the passage not only of solids but of fluid is well exemplified by an experiment of Leber[3] upon the cornea. He found that the delicate layer of cells forming Descemet's membrane is the sole agency whereby the cornea is able to resist a pressure so high as

[1] Hedinger, *Dissertation*, quoted to me by Professor Heidenhain.
[2] Riemer, *Arch. d. Heilkunde* vol. xvii. p. 344 (1876).
[3] Leber, *Arch. f. Ophthalmol.* vol. xix. No. 2, p. 125.

that of 200 mm. of mercury. Remove this membrane by pencilling, and the fluid easily invades and swells up the cornea. It is this membrane alone that in the living eye prevents the imbibition of the aqueous humour, and the production of a swollen œdematous condition of the cornea.

Apart however from these general considerations, there are certain observations which go very far to prove the secretory functions of the glomeruli. After ligaturing the renal arteries in the frog, or after cutting off the arterial circulation still more surely by cauterising and so dividing the (three to five) renal arteries, the blood-supply of the kidney is of a venous nature, and is confined to that reaching it from the lower limbs and coming through the renal portal vein. And although M. Nussbaum[1] has pointed out that there is a possible collateral arterial circulation, it is difficult to see how this can supply more than the glomeruli of the lower extremity of the organ. Nothwithstanding this, by injecting "laky blood" (or defibrinised blood containing hæmoglobin in solution), I found it possible to obtain evidence of the passage of hæmoglobin through the walls of the glomeruli of the kidneys generally within four hours after the injection, and this in cases where there had been no demonstrable excretion of urine.[2] On killing the animal and placing the kidneys momentarily in boiling water, the hæmoglobin was coagulated, and could be seen as a brownish, granular, but otherwise homogeneous crescent, in the "capsule chamber" of many of the Malpighian bodies. In other words, although the blood-pressure had been very greatly reduced, and the direct arterial supply to the glomeruli cut off, the glomerular epithelium allowed the passage of hæmoglobin even when apparently there was no excretion of water beyond the minimum amount necessary to keep the hæmoglobin in solution.

Here then it would seem evident that the glomeruli had excreted hæmoglobin under greatly lowered pressure, and without any corresponding watery excretion—a condition only explicable on the assumption that the glomerular epithelium possesses a definite selective secretory activity, as Heidenhain

[1] M. Nussbaum, *Pflüger's Archiv* vol. xli. (1887).
[2] Adami, *Journ. of Physiol.* vol. vi. p. 382 (1886).

had suggested. These observations were confirmed by experiments upon the dog. The experiments are to be found fully described in my paper above referred to (p. 398). Suffice it to say that the passage through the glomeruli of hæmoglobin (together, probably, with some albumen) could with certainty be demonstrated in animals, in which by lowering the blood-pressure below 40 mm. of mercury complete anuria had been induced, the cessation of the urinary flow being determined not by the empty state of the bladder, but by means of fine catheters placed in the ureters and connected with graduated glass tubes. Here again the appearance of concentrated hæmoglobin outside the glomeruli can only be explained by the hypothesis that the glomerular walls possess selective functions.

But further, the same series of experiments showed in another way that an amount of hæmoglobin could be present in the urine far beyond that explicable by a theory of filtration. In opposition to the view first propounded by Ponfick,[1] Afanassiew,[2] as the result of an elaborate investigation, has shown that not only a part, but all of the hæmoglobin in hæmoglobinuria passes through the glomeruli, and that the brown granular appearance of the cells of the *tubuli contorti* is due to the presence, not of hæmoglobin, but of the products of degeneration and destruction of the red corpuscles; and that when pyrogallic acid, for example, is injected in quantities not sufficient to produce hæmoglobinuria, while it causes a definite destruction of the corpuscles, the brown granules are to be observed in the cells of the tubules and again in the sediment of the urine. Nevertheless microchemical observation failed to detect hæmoglobin in this sediment. These statements of Afanassiew, so far as they refer to the passage of unaltered hæmoglobin out of the kidney, have recently been confirmed by Hunter.[3]

On examining and comparing the amount of hæmoglobin in equal quantities of the urine and of blood-serum from dogs in which hæmoglobinuria had been induced, I found that there could be a very great variation in the relative amount contained,

[1] Ponfick, quoted by Heidenhain, *loc. cit.* p. 351.
[2] Afanassiew, *Virchow's Arch.* vol. xcviii. (1884).
[3] Hunter, *Lancet*, October 6, 1888.

a variation dependent in part upon the degree of hæmoglobinuria, but mainly due to the state of renal activity. Thus diuretics, such as sodium nitrate, caused a dilution of the hæmoglobin-containing urine, although in a given time the total amount of hæmoglobin excreted was markedly increased.[1] This pointed to augmented activity of the glomeruli under the influence of the diuretic. The relation of the hæmoglobin in the "laky" blood-serum to that in the urine I found to vary from 1·0 : 0·22 [2] to 1·0 : 3·45 [3]; or in other words the urine contained in the one instance only about one-fifth of the hæmoglobin in the serum, in the other it held over three times as much. Variations so great as this, and the possible presence of so much more hæmoglobin in the urine than in an equal volume of blood-serum, can be accounted for by none of the theories of filtration at present put before us.

I am aware that Senator [4] has pointed out what is perhaps an error in my previous paper. It was there stated that if an excretion contained more of a given substance per unit-volume than did the original fluid, then some other laws beyond those of filtration must necessarily be at work. Now W. Schmidt [5] has found that in the filtration of solutions of gum and salt, and gum and urea, the filtrate may be richer in sodium chloride to the extent of from 0·02 to 0·07 per cent. and in urea from 0·006 to 0·08 per cent. And Runeberg [6] and Loewy, [7] in a series of observations upon albumen solutions containing salt, found that the salt in the filtrate might be one-tenth (Runeberg), and one-half (Loewy), more per unit-volume than in the original fluid. To all these observations objections may be brought. The separate results of each of the three appear to vary without adequate cause. Thus both Runeberg and Loewy found now more, now less, salt in the filtrate than in the mother-fluid. Nor again is there any consonance between the amount of excess found possible by each observer. But even granting that a filtrate may contain, as these observers contend, some increase in the relative amount of any one or more constitutents over

[1] *Loc. cit.* p. 415. [2] *Ibid.* p. 417. [3] *Ibid.* p. 407.
[4] Senator, *Virchow's Archiv* vol. cxi. p. 228 (1888).
[5] W. Schmidt, *Annal. d. Physik* vol. cxiv. pp. 364-389 (1861).
[6] Runeberg, *loc. cit.* p. 55.
[7] Ad. Loewy, *Zeitschr. f. physiol. Chemie* vol. ix. p. 537 (1885).

the amount present in the original solution, it is clear that not even the most favourable of their results can explain the great increase I have found in the proportion of hæmoglobin in the urine over that in the blood-serum, an increase of nearly 250 per cent. and one most striking to the naked eye.

In his experiments upon the *überlebende* kidney—that is to say, on the kidney after extirpation—Immanuel Munk [1] arrived at similar results with regard to other substances which are generally considered to be excreted through the glomeruli, using easily-diffusible salts such as the chloride, phosphate, and sulphate of sodium, and also sugar. Thus he determined that the secretion was without exception richer in chloride of sodium than the blood-serum passed through the kidney, to the extent of from 20 to 67 per cent.; in the case of sulphate of sodium 45 to 74 per cent., and in the case of sugar 60 to nearly 90 per cent. The method employed cannot however be considered wholly satisfactory. An organ removed from the body may in the absence of central nervous influence be more easily experimented upon; but no external warmth, and no artificial circulation commenced a quarter of an hour or more after removal of the organ from the abdomen, can ever replace exactly, or even nearly, the bodily conditions. Nevertheless positive results such as these (coupled with the fact that Munk was able to obtain under these conditions the synthesis of hippuric acid) cannot be explained away; rather it is to be considered that had the organ been in the body the results would have been still more marked. When, however, Munk declares that he cannot reconcile his hæmoglobinuria observations with mine, then I submit the implied criticism is invalid. Because in his extirpated kidney, with its greatly-diminished vitality, he could produce no increase in the percentage of hæmoglobin in what he himself terms the 'artificial' urine over that in the bloood-serum, he is still far from proving that under more normal conditions the increase does not obtain.

There is, then, direct and indirect evidence of the secretory activity of the glomeruli, evidence which would seem clearly to indicate that the passage of fluid through these bodies is not a mere transudation. It will be evident from what has preceded

[1] Immanuel Munk, *Virchow's Archiv* vol. cvii. p. 307 (1887).

that I do not claim for the glomerular epithelium any synthetic power: I do not say that the cells have the power of forming from the substances brought to them by the blood any new substance. All that I argue is that they have a selective power, and to this extent must be looked upon as active and not passive, as producing a secretion and not a transudation. From many considerations I am led to the opinion that there are two forms of secretory cells in the organism—the simple or *selective* secretory cells (in this category are to be included the glomerular walls, and most probably the epithelium lining the whole vascular tract), and the more complex *synthetic* or *metabolic* secretory cells, having still more extensive powers, of which the usually accepted glandular cells, such as those of the liver and of the *tubuli contorti*, are good examples.

Finally, assuming what I have shown to be most probable, first, that the secretion of urine depends not so much upon the blood-pressure as upon the rate of flow of the blood through the kidney; and, in the second place, that the glomerular epithelium has selective secretory powers, let me rapidly indicate the factors which go to determine the appearance of albuminuria.

That albumen, when it appears in the urine, passes through the glomeruli, has been demonstrated by so many observers that there is no need here to state the methods by which this statement can be verified. That some of the albumen may have its origin from the cells of the *tubuli uriniferi*, Senator's experiments would seem to prove, and it is not improbable that in parenchymatous nephritis and in venous engorgement of the kidney a certain, and it may be a large, portion of the albumen originates from the affected cells of the *tubuli*.

That normally albumen is present in the urine in infinitesimal quantities, if indeed it be not wholly absent, can scarce admit of denial. This absence is to be considered as due to the healthy state of the cells of the uriniferous tubules, and more especially to the normal functional activity of the glomerular epithelium. This epithelium possesses the power of preventing the passage of albumen and globulin out of the blood-serum in ordinary conditions of the body, provided these are not present in excess; and the amount of albumen allowed to pass by the glomerular epithelium, while in certain cases dependent upon the presence

of increased quantity, or altered quality, of the albumen in the blood, is in the main determined by the state of the glomerular epithelium. This when in a state of lowered vitality permits the egress of a fluid more of the nature of a transudation: the less the vitality of the epitheilum the more nearly does the fluid resemble a filtration in its constitution, and as a result of this loss of selective and controlling power the proteids of the blood-serum may sink to a percentage much below the normal.

These considerations, while applying to the graver forms of Bright's disease, are capable of explaining also many cases of transient albuminuria. Temporary determination of blood to the abdominal organs, with slight engorgement and slowed venous outflow; pressure upon the kidneys, or obstruction to the renal vessels; increased viscosity of the blood and diminished rate of flow; imperfect respiration, incomplete oxygenation of the blood, and the presence of excess of carbonic acid; imperfect metabolism of food-stuffs; direct irritation by some specific substance—these, singly or in combination, by temporarily lessening the rate of flow through the glomeruli and thus producing imperfect nutrition of their delicately sensitive walls, or by directly leading to such imperfect nutrition and lowered vitality, will I think be found sufficient to explain most if not all the cases of transient albuminuria, febrile, toxic, puerperal, and functional.