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ORIGINAL ARTICLES.

THE FUNCTION OF THE KIDNEYS.

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Origin of Urea and Uric Acid.—Some of the recent editorials on this subject would lead us to infer that the function of the kidneys is not well understood, or that there is a wide difference of opinion regarding it.

Merck's *Bulletin*, Dec. 18, 1892, says editorially: "Through the agency of the epithelial cells lining the uriniferous tubules the urea, uric acid and creatine are normally formed and discharged," etc. Again: "The function of the glomeruli is comparatively simple, being entirely under the control of the vasomotor system."

Indeed, such statements as the foregoing are comparatively common, but ought not to go unchallenged. A knowledge of physiology should precede and serve as a basis for rational therapeutics, and the more thorough and more nearly correct the former, the more scientific and satisfactory will be the latter.

Instead of calling the kidneys secreting organs and the urine an excretion, it seems more rational to say that we know that an average constant composition of the blood as regards normal constituents, such as sugar, etc., and of waste products such as urea, must be maintained, in order to preserve health and life.

To the kidneys is assigned the duty of maintaining this invariable composition; of eliminating from the blood all those substances which do not belong to it normally, whether it be an abnormal constituent, or a normal one that has increased beyond the normal amount.

The parts concerned are the glomeruli with Bowman's capsule, and the epithelium of the convoluted tubules.

There are two principal theories in regard to the secretion and excretion of urine.

Ludwig's mechanical theory, promulgated in 1844, that the urine is simply filtered in a dilute form by the glomeruli; further additions are made by osmosis and diffusion through the tubular epithelium.

In favor of this theory we find such physical conditions existing as would make such a theory tenable; we find the conditions favorable for osmosis, etc., and we may explain the failure of the proteids to pass, by saying that they do not filter readily through animal membranes. Against such a theory is the evidence, first, of analogical reasoning from what we know of other glands; second, the positive evidence. The urine is unlike the blood in composition and reaction; after destruction of the tubular epithelium, the urea is not eliminated but accumulates in the blood. If benzoic acid be given it is

converted in the kidneys into hippuric acid, being formed synthetically in the kidney;—besides other evidence to be introduced.

The other theory, known as Bowman's vital theory, was introduced in 1842 and is as follows: filtration in the glomeruli; excretion of the specific constituents by the cells; the tubules; reabsorption of some water. But even this does not explain all the facts as shown by the following evidence:

First, then, as regards the filtration in the glomeruli and the statement in the paper referred to in which it is stated that it is a "comparatively simple process." In transudations elsewhere we find that they contain serum albumen. But serum albumen although a normal constituent of the blood, is not a normal constituent of the urine and is not allowed to filter through the capsule of Bowman under normal conditions. Egg albumen is allowed to pass, however. How does the capsule discriminate if it is only a filter?

Again, we find that sugar is a normal constituent of the blood, but not of the urine, although readily soluble in water. When, however, the percentage of sugar rises above the normal it is immediately allowed to pass, justifying the definition of the function of the kidney: "To maintain the average, normal, constant composition of the blood stream."

Furthermore, we find that in disease of the capsule, both sugar and serum albumen are allowed to pass freely. Blood pressure higher than the normal allows the albumen to appear in the urine. There is a limit therefore, to the extent to which the capsule can prevent the transudation of the normal constituents of the blood.

In the amphibian kidney, we find a double blood supply and we can introduce sugar and egg albumen into the circulation and they are at once eliminated.

If we cut off the blood supply to the glomeruli we find no sugar or peptones in the urine, although the blood supply to the tubular epithelium remains normal. We must, therefore, conclude that if they are not eliminated by the tubular epithelium they must be by the glomeruli.

In regard to high pressure in the glomeruli, we find that if the renal veins be tied, thus giving us a maximum pressure, there is no secretion. Therefore the conditions favoring glomerular filtration are, *a*, high blood pressure in the glomeruli; *b*, velocity of flow. The blood pressure is controlled and varied by the vasomotor nervous system.

And, lastly, urea and sugar are both soluble in the blood. The urea is eliminated because it is a waste product and no longer useful. The sugar is retained because it is of value in the production and maintenance of those chemical processes, the sum of which constitutes life itself. We recognize the purpose of the Divine plan without being able to explain the reason.

It seems too evident that the glomerular secretion instead of being a "comparatively simple" affair, is a complicated complex process, and that anything like a mechanical explanation is narrow, faulty, inadequate. Filtration and diffusion play their part but they are not masters of the situation.

Let us now consider the function of the tubular epithelium. In favor of the so-called vital theory we have the following evidence:

1. Indigo and bile pigment are eliminated by the cells of the convoluted tubes and Henle's loop.¹

2. Uric acid is eliminated by the tubular epithelium in birds. The purpose is manifest. If it were eliminated by the malpighian bodies concretions might form, but while eliminated by the tubular epithelium it is constantly washed down by the urine.

3. If, in the amphibian kidney, we shut off the circulation from the glomeruli and then inject urea, it leads to an increased excretion of urea plus some water.

4. Sulphindigotate of soda is also eliminated by the tubular epithelium.

"If the blood becomes too alkaline, as it may by the conversion of vegetable salts of alkalies into alkaline carbonates, the renal cells separate the excess of these carbonates from the blood.

"If the alkalescence of the blood be diminished, perhaps by the liberation of sulphuric acid and phosphoric acid, caused by the decomposition of the proteids, of nucleins and lecithins, the renal cells take up the neutral salts of the blood, separate them into acid and alkaline, convey the acid salts into the urine and the alkaline back into the blood until the normal alkalescence is restored."²

Therefore, we can say that the tubular epithelium excretes urea and some water and has other functions in maintaining the normal condition of the blood. But the how, is not known to us. We are here confronted with the problem, the life of the cell, a term of whose meaning no one has any conception. But we do know that it possesses those incomprehensible qualities which bring about synthesis in the organism.

THEORY OF THE SECRETION OF THE URINE.

1. The secretion and excretion is partly mechanical and partly a vital process.

2. The water and most substances soluble in it, are eliminated by the glomeruli chiefly by filtration, the amount depending upon blood pressure in the glomeruli, provided, at the same time we have *a*, velocity of flow; *b*, normal condition of the blood; *c*, intact condition of kidney structures; *d*, average amount of urea, salts, etc., (including those which act as diuretics) present in the blood.

3. That this blood pressure is under the control of the vasomotor system.

The function of the glomeruli is not mechanical alone, but also vital, as it will allow egg albumen, an excess of sugar, etc., to pass through but will not allow any serum albumen to pass under normal conditions, and no sugar unless it be in excess.

4. Urea, uric acid, etc., are eliminated by the tubular epithelium, the *concentration* of the urine therefore depending upon: *a*, the amount of salts in the blood; *b*, intact condition of the tubular epi-

thelium. Some water is also eliminated by the tubular epithelium.

5. A hearty meal increases the quantity of urine by *a*, increasing the fluids taken; *b*, by increasing the proteids which increase the urea, it in turn stimulating the tubular epithelium.

Thus we see that the work done by the kidneys depends on the condition of the blood, this furnishing the normal stimulus and thus explaining why secretory nerves are not found, simply because they would be superfluous. The greater the percentage of abnormal constituents, or the excess of normal ones, the more active the kidneys.

6. There is a compensatory relation existing between the skin and the kidneys and cold applied to the skin increases the quantity of urine by diminishing the amount of sweat, and also by increasing blood pressure it increases renal pressure and thus the amount of urine.

7. In fever the renal artery is less full and therefore there is less urine.

8. In case of weak heart, dropsy is caused by *a*, increased venous pressure brought about by diminished arterial pressure; *b*, slowing of the current of blood and thus increased venous pressure in the kidneys, thus diminishing elimination of water.

9. Diuretics act in one of the following ways: *a*, by increasing pressure and velocity in the glomeruli; *b*, by acting locally on the tubular epithelium.

10. In hysteria, etc., where there is polyuria it is possible that there may be dilatation of the vessels entering the glomeruli, but this is pure speculation.

11. Certain substances as hippuric acid, are formed synthetically in the kidneys.³

From the foregoing it must be evident that the composition of the urine must vary within rather wide limits even in health. There are in the urine:

1. Certain normal constituents in considerable amounts, whose origin, place of formation as well as composition, etc., are well known.

2. Others which appear only in small amounts.

3. Those which are found only under abnormal or pathological conditions.

4. Those which have been accidentally introduced as foods or medicine and are eliminated with the urine.

ORIGIN OF SOME OF THE URINARY CONSTITUENTS.

The proteids are, by the action of the digestive ferments, converted into peptones; the peptones further converted by having a part of the nitrogen split off in the form of amido caproic acid, or leucin, an aromatic amido acid, tyrosin, amido succinic acid, or aspartic acid, and also glycocoll. These are probably the precursors of urea as shown by the experiments of Schulzen and Necki, Salkowski and Emeriem.⁴ Hoppe Seyler and Salkowski regard cyanic acid as the immediate precursor of urea.⁵ Dreschel considers that urea arises from the carbamate of ammonia. Carbamate of ammonia stands midway between carbonate of ammonia and urea.

But the question of interest and importance, (aside from the precursors) is, *where is urea formed?* The most complete and reliable researches as to where urea is generated have been made by W. von

³ Bunge, p. 317. Foster, vol. v, p. 136.

⁴ Bunge, "Physiological and Pathological Chemistry," p. 319.

⁵ Op. cit.

⁶ W. von Schroeder, "Archiv. of Exper. Path. in Pharm.," vol. xv., p. 364, 1882, and vol. xix., p. 373, 1875. Bunge, p. 364.

¹ Bunge, "Physiological Chemistry," p. 351.

² Bunge, "Physiological Chemistry," p. 351.

Schroeder.⁶ He shows conclusively that urea is *not* formed in the kidneys, but merely excreted by them.

Although we would naturally turn to the muscles as the next most likely place of generation, he also shows that it is not formed here nor in the nervous system, and if it is present in the blood, the blood probably obtains it from the liver. The evidence in favor of its formation in the liver is both clinical and experimental and is abundant and conclusive. Experimental:⁷

1. The synthesis of carbonate of ammonia into urea occurs in the liver.

2. In disease of the liver as interstitial hepatitis, the elimination of urea is interfered with and the amount of ammonia rises from one-half gram (normal) to two and one-fifth grams in twenty-four hours in cirrhosis of liver.

3. The creatin formed in the muscle is also converted into urea in the liver.

4. The blood contains 1 part in 3,000 to 5,000 parts and the renal artery contains more than the renal vein.

5. In the case of leucin, there is distinct evidence that the conversion into urea is effected by the liver.⁸

6. The amount of urea is increased principally by proteid food.

The amount of urea is augmented in congestion of the liver or markedly diminished by such diseases of the liver as yellow atrophy, diabetes and hepatic cirrhosis.

8. In those diseases of the liver which interfere with urea formation, the immediate precursors of urea such as leucin, tyrosin, ammonia, cyanic acid, etc., are eliminated with and are found in the urine. It is evident therefore, that urea is formed in the liver from various substances brought to it by the blood stream, that the original source is the proteid foods, and that it does not all represent tissue metabolism; the amount of urea depending upon or being influenced by foods, breaking up of body proteids, diminution of or loss of blood, plenty of water and drugs—as morphin, the salicylates, mercury euonymin, arsenic, etc.

URIC ACID.

This is one of the unilluminated pages in physiology. But in the following brief note I give the more recent views concerning this important, though much disputed question and I venture to quote rather fully and to give many references because the observers are not by any means a unit in regard to theories. The views of Sir Wm. Roberts seem to me to be particularly well sustained by evidence.

Uric acid is the nitrogenous end product which, next to urea, carries off most of the nitrogen from the body. The amount varies from 8 grains (average) to 35 grains on a flesh diet. Proportion to urea 1 to 45 (Landois), 1 to 32, (Haig, "Uric Acid," p. 10.)

OCCURRENCE.

1. *Free Uric Acid.*—Not known physiologically, neither in the body nor in the urine. Known clinically and pathologically as the crystalline sediment in the urine, and as gravel and calculus in the urinary passages.

2. *Neutral Urates.*—Not known physiologically nor pathologically, only known as laboratory products.

3. *Bi-Urates.*—Known pathologically as compo-

nents of gouty concretions in the tissues. Known in the urine only after the secretion has undergone (ammoniacal) fermentation. It is doubtful if they ever exist physiologically in the blood or the tissues.

4. *Quadri-Urates.*—These are specifically the physiological salts of uric acid. They exist normally in the urine and probably in the blood. They constitute the entirety of the urinary excretions of birds and serpents. All the morbid phenomena due to uric acid arise from secondary changes in the quadri-urates. (Sir Wm. Roberts, "Uric Acid, Croonian Lectures" 1892, p. 31.) He also says (p. 38): It would appear that whenever uric acid exists in the healthy body, it exists exclusively as quadri-urate. The quadri-urates may, therefore, be regarded as being in a special sense the physiological salts of uric acid, and as constituting the only form in which uric acid subsists in the living body in the normal state. It may, moreover, be inferred further that when uric acid gives trouble and originates morbid phenomena the mischief arises proximately from the uric acid department, in one direction or another, from this normal state of combination.

Viewed in this light, pathological gravel may be regarded as due to an exaggeration of the conditions which prevail in a less pronounced degree in the normal state; and an elucidation of these conditions may be reasonably expected to throw light on the etiology of gravel and calculus, and perhaps furnish hints which may be turned to therapeutical uses. The conditions of the urine which tend to accelerate the precipitation of uric acid are:

1, high acidity; 2, poverty in salines; 3, low pigmentation; 4, high percentage of uric acid.

The conditions which tend to postpone precipitation are:

1, lessened acidity; 2, richness in salines; 3, richness in pigments; 4, low percentage of uric acid.⁹

The foregoing conclusions furnish a key to the rational therapeutics of uric acid gravel, which resolves itself largely into preventive measures. Roberts also says that he found that lithium carbonate was a better solvent of uric acid than is any of the other three carbonates, and this well known fact has led to the universal employment of that remedy in this condition, and more especially to the indiscriminate employment of the various "lithia waters."

In the employment of these waters, the benefit derived is from the water and not from the lithia, as shown so well by Bunge (p. 357). Because the combination of uric acid with lithia is more soluble than with soda or potash it is thought best to treat these cases with the so-called lithia water, which simply implies an ignorance of Berthollet's law:

"We know that in solutions of bases and acids, every acid is distributed to all the bases in proportion to their quantity. It follows that only the very smallest portion of uric acid will combine with the lithia, the largest proportion combining with the preponderating quantity of soda which we introduce as chloride of sodium. The largest proportion of lithia will reappear in the urine united with the chlorine, with sulphuric and phosphoric acids. There will be no increase in the solubility of the uric acid."

Cheese is said by Bunge (p. 356) to be especially apt to cause the precipitation of uric acid in the urinary tract. It is much better to keep the urine

⁷ Bunge, p. 334.

⁸ Foster, vol. v, p. 163.

⁹ Roberts, p. 54.

alkaline by a diet of fruits containing the vegetable organic acids. After combustion of the acids the potash appears in the urine as a carbonate. Potatoes cause a strongly alkaline urine because they contain little albumen and therefore little sulphuric acid, and much malate of potash which is converted into a carbonate. Citrate of potash is probably the best drug to employ. Dose, 40 to 60 grains at night.

ORIGIN OF URIC ACID.

The locality of the formation of uric acid in animals has not been experimentally investigated, although this seems important from physiological as well as from a pathological point of view. The most complete investigations upon the subject of recent times have been made by von Schroeder and Minkowski. (Bunge, p. 342.) Minkowski shows that in birds, ammonia is a normal antecedent of urea, and that the uric acid is formed synthetically in the liver by the union of ammonia and a non-nitrogenous substance and imagines this latter to be lactic acid, having a common source in proteids; that it is increased by proteid foods and is independent of carbohydrates. This form of lactic acid is saccolactic acid and not the lactic acid produced by the fermentation of the carbohydrates.

In cirrhosis of the liver and in cases of phosphorus poisoning large quantities of lactic acid have been observed in the urine.¹⁰ The liver is therefore probably one of the places of uric acid formation. In leukemia the amount of uric acid is double that in health on the same diet. It is not an antecedent of urea.¹¹ It is not a product of sub-oxidation.¹²

REMARKS ON THE TREATMENT OF DIABETES.

Read before the Section of Practice of Medicine, at the Forty-fourth Annual Meeting of the American Medical Association.

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It will be my aim in presenting the subject of the treatment of diabetes, to call attention to some facts which my own experience has impressed upon me and to one or two of the most recent suggestions that have been made in regard to it.

I believe that patients are often placed too quickly on a rigorous diabetic diet. A sudden, very great change in one's régime will invariably disturb the appetite and if only one or two articles of food are constantly eaten a disgust for these will be produced. Very considerable depression is frequently noticed after such changes. In two cases that came under my observation, though in the practice of others, the sudden restriction of them to a diet that was ungenial produced a disinclination for food, and growing out of this a diminished secretion of urine and apparently great mental depression and physical malaise which soon culminated in fatal diabetic coma. There may have been no causative relation between the restriction of the diet and the fatal result of the disease but as I watched the progress of the cases it seemed as though a degree of mental and physical depression was produced that intensified the disturbed nutritive changes which the disease

caused. Often patients to whom a diabetic diet is distasteful can be educated to take it and even enjoy it. To accomplish this it is best to first ascertain what the individual's habitual regimen is. It can be modified day by day by diminishing first the amount of the articles that must finally be dropped and later omitting them altogether. In a majority of cases this is not a long process. By the end of the first week patients can usually be gotten onto a sufficiently restricted diet.

Moreover, it is frequently not necessary for patients to limit themselves to a strictly diabetic diet. How much of farinaceous food can be safely permitted to any one individual can only be learned by experiment. If the taking of a potato each day for dinner does not increase or its omission diminish the amount of sugar excreted daily by the kidneys it can, I think, be taken with safety. The diet which I prescribe is similar to that usually recommended. I generally permit the use of a little bread except in the severest cases and I prefer that patients should use ordinary wheat bread rather than gluten bread, for a feeling of false safety is usually engendered by its use and it is eaten too freely. I am inclined to believe the statement made by many good chemists that all the gluten flours on the market are very impure and contain a large percentage of starch. In a half dozen samples of such flour that I have tested starch was present in large amounts. Macaroni is forbidden in some diet lists and permitted in others. Practically, I find it can be taken without detriment by most diabetics.

Of drugs that have been recommended and somewhat widely used the last two or three years antipyrin has been in my hands the least useful. Germain See claimed for it a strong controlling influence over the production and excretion of sugar. In his hands it seemed to be of marked benefit. He recommended it especially when patients were weary of their diet, as by its use it was possible to return for a short time with safety to a mixed diet. I have had an opportunity repeatedly to try it in cases of moderate severity, cases that are amenable to treatment but relapse often. In these cases I have observed no uniformly good results from the employment of the drug. In most instances the glycosuria did not seem to be modified at all by it. In a few cases it seemed decidedly beneficial. Whenever I attempted to rely upon the administration of antipyrin and to discontinue the regulation of diet an increase of sugar in the urine took place. I was greatly disappointed in these results for I rely upon no one's therapeutic judgment more than upon Germain See's.

No drug has seemed to me so uniformly to give good results as Clemen's solution of arsenic and bromin. In 1885 I published a series of cases that were treated with this drug with good results. I might now extend this list very much for I have tested it thoroughly in nearly two hundred cases. In the brief time allotted to the discussion of subjects it will, however, be better to state conclusions and the basis for them rather than to enumerate cases. I have had under observation four diabetics who would not adhere to even a tolerably restricted diet. The administration of Clemen's solution was uniformly followed by good results. In other cases, and they have been more numerous, a strict régime reduced the excretion of sugar to a certain point, but further improvement could not be obtained even by

¹⁰ Bunge, p. 345.

¹¹ Bunge, p. 359.

¹² Bunge, p. 339.