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UREA IN HEALTH AND DISEASE*

BY

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In one of his alchemical writings, *The Economy of Minerals*, Paracelsus speaks of "the superfluous nutritional salt not yet digested by the animal decoction when it is driven off into the urine." Such a description might well apply to urea, the chief nitrogenous waste product of the higher animal, and one of the simplest and most widely distributed biological forms of organic nitrogen.

THE FUNCTIONS OF UREA

1. *An End-Product of Protein Metabolism.*—The most obvious use of urea is the provision of a neutral, inert, and very soluble form in which nitrogen can be eliminated from the animal body. Within the organism urea is stable and unlikely to undergo further change; outside the organism it is readily resolved into ammonia and carbon dioxide by the various ureases of the environment, and the nitrogen is able to enter into the life-cycle of the plant. Indeed, from the vegetable point of view the animal's chief end might be said to be the manufacture of urea.

2. *A Diuretic.*—Urea is easily excreted by the healthy kidney, and has been used therapeutically as a natural diuretic. Probably the effect is osmotic and due to the effort of the kidney to keep the urea concentration in the urine below 2 per cent., but there is some evidence that it has a specific action on the renal apparatus. After administration of 30 to 60 grams of urea the urinary volume has been more than doubled, and favourable results are reported in conditions of oedema of cardiac and nephritic origin.

3. *A Galactagogue.*—Addition of urea up to the effective maximum of 150 grams per diem to the diet of cows has raised the milk production over a period of 100 days, the

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increased yield in some animals being 6 to 8 per cent. Here again the action is osmotic and part of the general secretagogue effect of the easily eliminated solute.

4. *A Solvent.*—Urea has a solvent and peptizing action on proteins, and can bring about denaturation (Hopkins, 1930). While this effect must be almost negligible at the ordinary concentrations of urea found in health, it may become important in conditions of severe hyperuraemia.

5. *A Precursor of Urinary Ammonia.*—Ammonia formation by the kidney is an emergency factor in the regulation of the H-ion concentration of the blood, and it is suggested, on rather hesitating evidence, that this involves a decomposition of urea in the renal tissue.

Many other speculations have been made regarding possible functions of urea in metabolism, including its ability to replace, supplement, or spare protein in the dietary, but there is no direct evidence that this metabolic reversal can occur.

THE ORIGIN OF UREA

Urea is formed almost entirely by the hepatic deamination of surplus amino-acids. The location of this process has been accomplished experimentally by Bollman, Mann, and Magath (1924), who have been unable to detect any urea formation in dogs after complete removal of the liver.

That small quantities of urea may arise from other sources is shown by the work of Clark, Gaddie, and Stewart (1931) on the metabolism of the isolated frog heart, which oxidizes amino-acids and produces urea and ammonia in traces. Indeed, it seems reasonable to suppose that any tissue capable of metabolizing amino-nitrogen is also capable of degrading it into urea or some precursor of urea, but the general trend of recent work indicates either that this is not so, or that non-hepatic urea is relatively unimportant.

Ureagenesis is an effective and sustained physiological process, and is one of the last functions to fail in liver disease.

Its constancy is illustrated by the accompanying graph showing the half-hourly excretion of urea in the urine over a period of twenty-four hours. The experiment

is one of an unpublished series carried out by Professor J. W. Jessop of Dublin.

THE SIGNIFICANCE OF UREA

Urea is derived chiefly from the surplus amino-acids of the diet. The organism is only able to store these units by building them up into tissue proteins, and as this is restricted by the capacity of the tissues, the unwanted amino-acids circulate in the blood stream and are removed by the liver. The important practical question arises as to the necessity for these surplus units. The adult daily output of urea ranges from 25 to 30 grams, dependent on the consumption of 80 to 90 grams of food protein, which may cost anything from a shilling upwards.

The graph shows: (a) a slight fall in urea excretion immediately after food ingestion, and (b) a steady rise beginning within half an hour after food. Similar variations have been seen in the other graphs. The output rises throughout the day, and is at a higher level at the end of the experimental period. This probably is due to metabolic stimulation accompanying enforced wakefulness. The subject of the experiment was in a condition of equilibrium, and the observations were made while on the normal diet. The urea estimations were made in duplicate by the nitro-metric method of E. A. Werner.

That is to say, for each shilling's worth of organic nitrogen assimilated we get a return of about a penny-worth of urea—and even that is thrown away. From an economic standpoint, if for no other reason, the urea industry needs investigation. Our physiological extravagance appears to be due to the way in which natural proteins are constructed from a variety of essential and non-essential amino-acids. The protein molecule may be compared to a box of assorted biscuits. Each variety of biscuit represents a particular species of amino-acid; there are many duplicates, and the least attractive are the most abundant. Sampling is not allowed. To obtain the biscuit one wants it is necessary to buy the entire box. To get the rarer amino-acids it is necessary to digest an entire molecule of albumin. This is the first reason, I believe, why our protein requirements are set at the comparatively high level of about one gram per kilogram body weight. Speculation can provide other reasons. For example, it may be necessary to keep the amino-nitrogen in the blood above a certain critical value to restrain tissue autolysis, such as occurs in starvation. Again, the residues of the deaminated acids may have important and specific functions, although most of these residues can arise equally well from aliphatic acids or sugars. Lastly, deamination may be an essential aspect of general hepatic metabolism, a process necessary for life, and maintained by the combustion of amino-acids. Such problems form a small part of the heritage of the research worker of to-morrow.

THE DISTRIBUTION OF UREA

Urea is universally and fairly uniformly distributed throughout the animal, the concentrations being of the same order as those in the blood. Outstanding exceptions are adipose tissue, which has a low water content, and renal tissue, which contains urine. The urea values of the human tissues have not been exhaustively explored, but from analogy with those of other animals the normal range is between the limits of 15 to 45 mg. urea per 100 grams fresh material, corresponding to the average blood values of 18 to 38 mg. per 100 c.cm., the extremes for normal blood being 10 and 50 mg.

The uniformity of distribution is due to the unique diffusibility of urea. It can pass readily from corpuscle to plasma, and from plasma to tissue, or be excreted into the alimentary tract (Pendleton and West, 1932). Almost a non-electrolyte, it is not restricted at phase interface or cell membrane by the Donnan effect, and it is probably the only important solute equally distributed between the cellular and the liquid constituents of the organism. "Urea is one substance for which plasma and whole blood analyses have nearly the same significance" (Peters and van Slyke, 1931).

One result of this diffusibility is that urea retention in the organism cannot cause oedema such as occurs when partially or non-diffusible solutes like NaCl accumulate in the plasma and lymph and dehydrate the neighbouring tissues.

HYPERURAEamia

Owing to the incessant working of the deaminating mechanism, urea is always present in the blood; the level may be altered by many conditions, some of which are of great clinical and pathological significance.

Since the word "uraemia" has long been in popular misuse, I shall employ the term "hyperuraemia" to denote all conditions in which the blood urea is above its normal concentration value. Physiologically, two types of hyperuraemia may exist—one due to increased production and one due to decreased removal of urea. Both types are present in many clinical conditions and may be hard to distinguish.

A. Increased Production of Urea

1. *High Protein Consumption*.—This is typical of increased production hyperuraemia. In the normal subject the ratio $\frac{N}{U} = 1$, where N is the nitrogen metabolized per diem in grams and U is the blood urea value in mg. per 100 c.cm. With a protein consumption of 1.1 gram per kilo body weight per diem, the blood urea range is 20 to 35 mg. per 100 c.cm., corresponding to a urea nitrogen value of 9 to 17 mg. (MacKay and MacKay, 1927).

2. *Fever*.—Increase in blood urea has been observed in most if not all acute infective diseases, and is attributed to active destruction of tissue protein. The increase depends more on the intensity of the intoxication than on the degree of pyrexia, and probably is aided by renal disturbance.

3. *Thyroxine Administration*.—The increased metabolism following administration of the thyroid autacoid may raise the level of the blood urea. The effect is non-specific, and can be inhibited by protein-sparing food-stuffs such as glucose.

B. Decreased Excretion of Urea

Urea leaves the animal by the kidneys, the skin, and the intestine. Of these the first is by far the most important, but in conditions of renal inefficiency the cutaneous output of urea may rise greatly above its normal value of 70 to 90 mg. per diem. The intestinal elimination of urea in hyperuraemia awaits investigation.

4. *Acute Renal Incompetence*.—Exemplified in acute nephritis, in oliguria and anuria due to renal poisons, such as uranium, mercury, chromic acid, and, to a lesser extent, cantharidin and arsenic (MacNider, 1924); in bilateral obstructions; and in post-operative urinary suppression.

5. *Chronic Renal Inefficiency*.—Exemplified in the second and terminal stages of glomerulo-tubular nephritis.

6. *Toxaemias of Pregnancy*.—The tendency may be compensated by the hypo-uraemia common in normal pregnancy.

7. *Acute Intestinal Obstruction*.—Exemplified in high mechanical obstruction and in adynamic ileus due to peritonitis.

8. *Diabetes Mellitus*.—Although no simple relation has been found between the concentrations of sugar and urea in diabetes mellitus (Brunton, 1925), it is reported that 50 per cent. of cases of diabetic coma show hyperuraemia (Lyll and Anderson, 1932). This may be due to many factors, including disturbed protein metabolism, tissue autolysis, ureagenesis from non-protein sources such as glucose and ammonia, and, most probably, renal poisoning by ketones or other abnormal metabolites. The last factor is suggested by the observation that diabetic hyperuraemia may persist after the period of actual ketosis has passed.

9. *Destruction of Renal Tissue*.—Renal tuberculosis, congenital polycystic kidney, pyonephrosis, and hydro-nephrosis.

10. *Starvation*.—The first few days of complete starvation are marked by a rise in the blood urea level, which persists throughout the fast (Lennox, O'Connor, and Bellinger, 1926). This may be a metabolic response to the autogenous diet imposed on the organism, or, as Peters and van Slyke suggest, a retarded renal excretion of urea.

HYPO-URAEamia

Abnormally low values of blood urea have been observed in conditions due to decreased ureagenesis and increased excretion, the chief of which are:

1. *Acute Hepatic Inefficiency*.—Although the greater part of the liver may be removed or incapacitated without much change in the blood urea level, subnormal values of 5 to 10 mg. per 100 c.cm. have been recorded in severe and usually fatal conditions of acute yellow atrophy, acute necrosis due to arsenic, phosphorus, chloroform, and carbon tetrachloride, and in post-operative "hepatic shock." A corresponding rise in the amino-acid level of the blood usually accompanies this type of hypo-uraemia.

2. *Diuresis*.—Increase in the volume output of urine tends to lower the level of blood urea, and may explain the minimal values recorded in diabetes insipidus and other diabetic polyurias.

3. *Lipoid Nephrosis*.—This controversial condition has been associated with blood urea values of 7 to 12 mg. per 100 c.cm.

4. *Pregnancy*.—The hypo-uraemia of pregnancy is probably due to renal stimulation by the extra load imposed upon it.

UROTOXAEMIA

Pathologically, the chief interest of urea is in relation to the condition of "uraemia," the late manifestation of nephritis, and other forms of oliguria. It is difficult to isolate and identify the various signs and symptoms that have been included in the uraemic syndrome, but a distinction can be drawn between simple uraemia, or *urotoxaemia*, due entirely to retention of urinary waste products, and the uraemias complicated by extrarenal factors, notably: vascular hypertension, diffuse arteriolar and arterial disease, abnormal vasomotor sensitivity, and myocardial degeneration. The biochemical syndrome of a simple uraemia following total nephrectomy in man has recently been described by Thompson (1932). It was accompanied by the following changes in the blood during the last five days of life.

Composition of Blood in Simple Uraemia. Values in Milligrams per 100 c.cm.

	Average	Sixth Day	Eighth Day	Ninth Day	Tenth Day
Total non-protein N ...	20-40	215	218	210	268
Urea ...	20-40	250	240	224	272
Uric acid ...	2-3	—	11	12.8	13.3
Ammonia ...	0.1	—	—	—	130
Sodium chloride ...	450-500	412	379	363	361

The term "urotoxaemia" in many ways is preferable to "uraemia" and may be defined as the pathological condition due to retention of urinary solutes in the blood. The identification of these solutes is important and must precede any attempt at the rational treatment of the disease. Up to the present this identification has not been accomplished with any degree of certainty, but there is reason to suspect that urea is one, at least, of the active agents in urotoxaemia.

In the ordinary ways of life urea is non-poisonous. Doses up to 100 grams have been assimilated and excreted by healthy subjects, and smaller quantities are given repeatedly in the concentration test for renal function. But there is a profound difference between the effect of a transient acute hyperuraemia due to excessive ingestion and a sustained and increasing hyperuraemia due to abnormal retention. Hewlett, Gilbert, and Wickett (1926) have raised the blood urea level to as much as 245 mg. per 100 c.cm. in healthy subjects, and have reproduced many of the characteristic symptoms of urotoxaemia.

Although the analogy must not be pressed, the fact that all the dialkylbarbituric acid hypnotics are derived from urea suggests that the coma of urotoxaemia may be an autonarcosis following urea accumulation in the

central nervous system. The high diffusibility of urea makes such an accumulation probable, but whether the concentrations reached in severe hyperuraemia would be sufficient to affect the nervous system can only be decided by experiments similar to those conducted by Quastel (1932), who has shown that all narcotics have a specific inhibiting action on oxidations by the brain. A survey of the urea content of the nervous system after death from urotoxaemia should be of value. Unfortunately, even if urea were shown to be implicated in the development of the urotoxaemic syndrome there is no direct line of treatment available, since there is no means of inhibiting the ureagenetic activity of the organism and allowing the renal tissue time to recover. Perhaps future technicians may devise a method of aseptic vividiffusion, whereby the blood can be freed at intervals from diffusible waste products; perhaps when an adequate supply of amino-acids is at last available for research it may be possible to give the fasting subject the individual units he requires, and thus turn him from his fatal onslaught on the fabric of life.

THE TREATMENT OF GLAUCOMA*

BY

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Ever since the auditorium of medicine surrounded the Plane Tree at Cos the treatment of glaucoma has been that of dominant symptoms with scant regard to primary physiological disturbances. The pathological travesty of physiology has sufficed to illustrate gross structural defects of morbid anatomy, but the essential primary cause of physiological derangement has remained obscure, and while this obscurity persists the treatment of glaucoma must be empirical and can have no accurate scientific basis. It follows, then, that any study in disturbed intraocular pressure must include a consideration of the factors which control normal intraocular pressure.

CAUSES OF GLAUCOMA

The following classification of the various causes of glaucoma will indicate how varied may be the methods of treatment, for in many examples the treatment is obvious, in others it is unknown, and for the more important types it is disputed.

Congenital.—(1) Buphthalmos; (2) aniridia; (3) glaucoma of facial naevus.

Hereditary familial glaucoma.

Trauma.—(1) Hyphaemia; (2) cataract; (3) capsular; (4) dislocation; (5) post-operative.

Inflammation.—(1) Hypopion (acute or organized); (2) acute iritis; (3) anterior synechiae; (4) peripheral synechiae; (5) ectasia of the cornea; (6) closure of corneal fistula; (7) iris bombe.

Accidental mydriasis.—(1) Following drops; (2) following third nerve paralysis.

Neoplasm.—(1) Innocent and parasitic cysts; (2) sarcoma of the uveal tract: secondary carcinoma; (3) glioma of the retina.

Degenerations.—(1) Primary glaucoma, acute and chronic; (2) absolute glaucoma; (3) post-cataract: (i) intumescent, (ii) hypermature; (4) detachment of the retina; (5) vascular: (i) thrombosis of central vein, (ii) after Coats's disease, (iii) after severe retinal haemorrhage; (6) capsulo-cuticular glaucoma.

Many of these examples are rare and demand specific treatment, ranging from simple puncture to removal of the globe; for general purposes the common type of glaucoma simplex merits more detailed discussion.

* Abstract of essay awarded the Middlemore Prize of the British Medical Association, 1933.