Thesis
by
William Shaw MB

October, 1881

Charleston
Source: Observations on the Secretion of Urea

Urea is the principal factor of the solid constituents of normal urine, existing in the large proportion of one part in two, and as such, on these grounds alone, is entitled to a large share of consideration both from the Physiologists and the Physicians.

By the former this substance has been subjected to numerous experimental investigations for the purpose of ascertaining as far as possible its source, use, and manner of elimination; from which undoubtedly very many valuable results have been directly or indirectly derived. Different observers have however varied somewhat in stating their results. The opinions expressed have been so diverse, so many discrepancies having made their appearance, that for some time it seemed as though conflicting theories were likely to prove permanently irreconcilable and all practical deductions rendered impossible.

The elaborate researches of Dr. Parkes, Payy, Sidney Ringer, in this Country, with those of Voit, Oppler, Salkenb, Bichoff, Hesse, and other Continental writers have however done much of late years towards the solution of this intricate problem, though there still remains abundant room for further investigation.

To the Physicians obviously the secretion of urea excites an all important one, an acquaintance with the Physiological conditions...
Cancer its variation, and still more the pathological departure from, in which its appearance may be looked for in some abnormal quantity, either very diminished or enormously increased, being of the greatest possible interest to the practitioner of medicine—

It will be the aim of this paper to make some attempt to further this object by giving:

(a) A short resume of our present knowledge of urea formation in the body.

(b) Sketching briefly its natural history in the body, and passing in review some of the more important investigations in regard thereto.

(c) Reference to some of the physiological and pathological conditions that modify its excretion and elimination; and lastly,

(d) To urge the more general application of the simple and satisfactory method now at our disposal for its quantitative analysis in urine.

Unfortunately, however, no means have been discovered whereby we can obtain any aid to diagnosis by making an examination of the urine for urea. We can deduce nothing of any practical value for this purpose from the fact that in a certain person there may be a press increase in its amount, although we may learn much with regard to the prognosis and treatment. It is therefore behoove the careful practitioner to make a thorough examination of the urine of any doubtful case, not confining himself with the ordinary loose and careless testing for albumen, or, if it is of high specific gravity, for sugar, but systematically and
a point of carefully estimating the quantity of the normal constituent, as influenced by certain abnormal states of the system, or by the influence of any particular drug.

In the first place then it must be understood that urea, in itself serves no purpose whatever of nutrition in the body. It is merely an excrementitious substance, being in fact a final product of oxidation and metamorphosis of tissues. That this is so is proved by the fact that if in consequence of any hindrance to its elimination it is retained in the system, it immediately acts as a violent poison producing the phenomena together known as "toxicemia," which too frequently body in the death of the patient. This results of the retention of urea is an not infrequent ending of some forms of kidney disease, these organs being especially concerned in its elimination from the body. More conclusive still is the fact that when animals are fed experimentally on urea, they speedily become feeble and emaciated, and die with all the common symptoms of infancy.

There are some diseases where there is an accumulation of urea in the body, and one of these is where the reverse condition obtains. That urea excretion instead of being diminished is enormously increased; to this class of cases belong especially feeble kind of which mention will be made more particular further on. Such then being the examples of interference in either direction with its excretion from the body, it is obvious that great interest attaches to the nature of this substance which is so
What then is Urea? Is this question must be given both a chemical and physiological answer.

1. Chemically, Urea is a bland crystalline substance possessing the properties of a solid base. Its best known combinations are the nitrate and acetate, both of which are much less soluble than urea itself. When artificially produced, it exists (in the pure state) in long silky acicular crystals. It is represented by the formula $\text{CO}_4\text{NH}_2\text{O}$ and may be prepared as follows:

"Mix together yellow prussiate of potash and manganese brucite, heat when heated form cyanate of potassium, dissolve in water mix with ammonium sulphate and evaporate to dryness. The urea thus extracted with alcohol." (Pozemic Chemistry, p. 380)

Another and simpler method is by direct transformation of ammonium carbonate, discovered by Holbe of Leipsic and described by him in 1868 (cited in Med. Times & Gazette Vol. 68. p. 417). It consists substantially, in heating any carbonate of ammonium in a closed tube to a temperature just short of that at which urea decomposes, as the point it loses its water and becomes converted into urea.

Urea is easily soluble in water and alcohol only very slightly in ether; it is decomposed by heat in the presence of water into carbonic acid and ammonium, and, by nitrous acids into carbonic acid, nitrogen, and water. It is never found alone as a urinary deposit.
Physiologically, urea is a product of metabolism of tissue and as such, constitutes one of the chief waste products of the body, being, for the most part, an ultimate result of the oxidation of the albumen of the food. The quantity of urea excreted is accepted as a very fair estimate of the changes going on in the system. That it is a waste product is shown by its absence from the tissues and except in very occasional instances, from the substance of glandular organs, although it is found constantly present in the blood, and has been detected in other fluids of the body, e.g., chyle, saliva, and serous fluids. (P. Foot). The question has arisen, whence does the blood derive its supply of urea? Looking to its chemical composition, there is no difficulty at all in accounting for the presence of its elements in the body, but how do they come to be combined in the proportions in which they are found to exist? Take for example, the muscles of a limb, the blood in which they are bathed or being subjected to examination affords abundant evidence of the presence of urea, but on examining the muscular substance itself, not a trace of urea is to be found. Clearly, then, some metabolic change must have taken place which accounts for this transformation, and this is undoubtedly the case, for on further investigation, we find that there are analogous bodies present in the muscle which do not occur in the blood. These compounds are modified albumens to which the
names of Creatin (C₄ H₉ N₃ O₂) and Creatinin (C₄ H₇ N₃ O) have been given. (Other than but these are the chief.) Liebig declared that it was impossible that these could have any other origin than the metamorphosis of the Nitrogenous tissues, and he further stated his opinion that the quantity of tissue metamorphosis in a given time is measurable by the amount of Nitrogen in the urine. (Cited in Brit. andForeign Med. Clin. Res. Vol. I. 154. p. 348.)

It will hardly be necessary to refer shortly to the manner of entrance of Nitrogen into the body and I cannot do better than quote from Parker's lectures in the Lancet, Vol. 1. 184. p. 399. Besides the all important action of the gas (Nitrogen) in diluting the oxygen of the atmosphere, thus rendering it fit for the purposes of animal respiration, it has another scarcely less essential part to perform in the maintenance of organic life, by entering into the composition of vegetable substance in the form of Ammonia, and thus to a large extent, though indirectly, supporting animal existence. Nitrogen also enters the body in some slight degree in its free state through the lungs, and also mechanically mixed up with food. From this we see that by far the greater part of the supply is derived from food. Of the various kinds of foods that supply us with Nitrogen, Animal food furnishes us with a large proportion in the shape of albumen on which we depend so largely for nutrition, and from which is derived the majority of those nitrogenous bodies existing so abundantly.
an analysis of the products of digestion. Practically, the introduction of the albumen of the food may be considered the essential origin of the Nitrogen in the body. The great function of albumen in the blood is to supply it with sustenance, it is however quite a passive agent, having no power of self-accumulation, being merely acted upon and transformed by the tissues. The serum may be looked upon as a reserve store of albumen. "Two processes of metamorphosis are continually taking place, progressive or formative, and retrograde or destructive, the former is the means whereby the several tissues are built up, the latter is characterized by the breaking up of the albumen into two sets of bodies, one with the Nitrogen, forming urea for excretion, the other, minus the Nitrogen, either forming fat and being stored up for future expenditure, or ultimately being resolved into carbonic acid and water." (Vide Laplace's Physiology, p144.)

The immediate origin of urea has been much disputed, and indeed is still somewhat shrouded in mystery. Amongst the more important of the numerous experiments that have been made on this subject are the following:

Oppler & Zalewsky (Virchow's Archiv. xxii. 260) found that when the renal arteries from an animal were ligatured or the kidneys removed there was an increase in the blood not of urea, but of creatine or creatinine thus tending to show that these latter substances...
are converted by the kidneys into urea. They suggested that this change was brought about by the action of the renal epithelium and they further found that if the ureters were ligatured and blood allowed free access to the kidneys, that there was an increase of urea and not of creatine and creatinin. That these substances do become converted by oxidation into urea is acknowledged, but the exact site of this change, as far as, asserted is much disputed... E.g. Frechet [Cib. med. liv. 1870 p. 249] stated with reference to the above experiments, that if the ureters be ligatured there is no perceptible difference from the ligature of the arteries, for the simple reason that in the former case the distension of the tubules soon under the epithelium incapable of performing its function, the experiments practical results in the same condition as the entire removal of the organs themselves.

Another possible source of urea is Lecine, a substance formed in considerable quantity as a result of pancreatic digestion, and which does not normally appear in the urine. If this substance be injected in any large quantity there is the same result as after the partaking of a highly nitrogenous meal, viz: a large increase in the amount of urea.

Do not all the nitrogenous tissues by their continuous disintegration assist in the production of urea, and as this increase in its excretion or after the ingestion of nitrogenous food is generally admitted, we may well
believe that the albuminoids (of which tissue and
fertilizers may be said to be the chief) are found
in muscle and gland tissue in cachetic, principle,
patient the main supply.
If nitrogenous food be withheld and a
non-protein diet substituted, e.g., if an
animal be first fed on gelatin and then on
sugar, the alteration will be readily noticed;
in the first case the urine will be eliminated
in considerable quantity and in the second, it
will be materially diminished.
Dr. Parke pointed out (vide Lancet Vol. 37, p. 448)
that the excretion of nitrogen from the body in
health is so nearly constant with the amount
taken in, that from the one we may very fairly
calculate the other, and this too, quite independently
of the mental or muscular exertion.

If a known amount of nitrogen be given to
an animal and an estimation made of the
quantity discharged, they will be found very
nearly to coincide; if now, after a few days
the supply be discontinued, the amount pares
off rapidly. Amines, and if the
deprivation be persistent, will continue to
diminish down to a certain point, beyond
which it does not pass, but remains until
the animal dies. O. Brödel (Vol. II,
J. Biol. IV. 77) supposing however the
supply to be resumed, after an interval of
three or four days in its original quantity,
a small amount of nitrogen, only is again
eliminated, gradually increasing until
the full amount is again arrived at, showing
that some is retained to supply the deficits.
in the urine. This goes far to disprove the old theory of "cupric consumption" advocated by Bödder-Schmidt by which they maintained that the increase in the amount of urea after meals was mainly owing to the excess of albumen in the ingested food, which, not being utilized by the tissues, was immediately reduced in the blood into urea and forthwith eliminated. This theory is ably refuted by Bischoff (Die Freilegung des Heilgesetzes 1860) who denies that there is any possibility proof of urea formation at the direct expense of the blood albumen, and even supposing the blood to contain sufficient oxygen to effect the transformation, its constant presence would prevent any persistence of albumen and so render nutrition impossible, and it would only be from excess in quantity that any would arrive oxidation. Further, it is objected to on the ground that no excretion during starvation must necessarily be the result of tissue metabolism. Also that urea being the ultimate result of oxidation, we should be able to bring about the same artificially if there were an intermediate stage, but this has not yet been done. Bischoff states his belief that "food is never directly digested into urea but the exception of gelatin, that is not a natural aliment.

Bödder-Schmidt also declared that creatin creatinin chic acid cannot be regarded as an intermediate step in the formation of urea, yet traverses the renal capillaries undecomposed.

Schott's however (Archiv f. Heilkunde Jahrgang 1880)
found that although creatin and creatinim do not appear in healthy urine, they were present in some cases of typhoid fever. These there was an increased taste of urea also heard and also an interference with their further transformation into urea. Be detected in different cases from 3 to 17 grains in the 24 hours, and in spite of careful examination, was never able to find any in normal urine, even on purely animal diet.

A further argument against the theory of Riddle Schmidt's maybe found in the common phenomena of increased excretion after what was or restricted diet, the amount is largely exaggerated.

It may therefore be safely asserted, to Dr. Parker (Lancet Vol. 1, p. 468) that "the conversion of albuminoids into urea is not a mere process of simple oxidation but is connected with vital actions going on in the body". When these "vital actions" are, harder to be determined!

The actual site of the production of urea is less more obscure. From the above noted experiments (Oppenfelder's) it would seem probable that some, at any rate, is secreted directly from the blood in the kidneys by the renal epithelium. Lyon stated that he was found in the liver; he passed a scheme of blood through the organ in a recently killed animal, and found a great increase of urea on its liver from the hepatic veins (C. Path. Med. Misc. 1870 p. 380). This however, did not prove anything, as the increase was probably due to the
area being simply washed out of its previous situation in the glands. A more striking argument in favour of this view is the fact that in some cases of acute yellow atrophy of the liver, the cells being more or less entirely destroyed, the area disappears almost entirely from the urine and is replaced by leucin & tyrosin. Thiereiner said that there was formed in the liver from the disintegration of red blood corpuscles into area, slycopen, and biliary colouring matter (cited in 'lances' vol. 11. p. 70). It has also been discovered in the plasma in some cases of leucocythemia.

The whole subject however is still upon very debatable grounds and we are scarcely justified in coming to any definite conclusion though it may be received by stating the probably that in part it is withdrawn from the blood by the kidneys, and that it antecedents in blood, liver, spleen or, are creatin, creatinine, lecin, tyrosin, and other similar substances; though is what way and where, they are actually converted is doubtful. Although by far the greater part of the Nitrogen entering the body leaves it again as urea, some yet remains to be accounted for. In an analysis of cases recorded by various observers, it is recorded that the mean average amount of urea in the urine of healthy adults males to be 572.14 grains per diem (24 hours) (or the urine pH 7.08). He estimated the quantity of Nitrogen leaving the kidneys as area, as about four fifths of the whole quantity entering the body, leaving
The remainder was accounted for in the urine and in the skin. Some observers attach more importance to these latter channels of elimination, as Fick declared that 10 grains were given off by the skin daily, whereas another found it perceptible in the breath as Ammonia.

Urea, since it is the urine in simple solution, not in any chemical combination, the average daily amount is, as we have seen, put down at about 5 to 6 grains, varying of course with the incidental occurrences of everyday life, and is therefore modified even in health; in disease this variation is still more marked.

The circumstances affecting excretion generally may be classified into Physical and Physiological:

1. The Physiological Relations of Urea.

These shall be little more than referred to as the elaborate investigations of Sarau in his work on the urine leave very little to be desired. With regard to sex and age it would appear that women excrete rather less than men, probably owing to their average lighter weight.

The amount of urea excreted throughout life seems to attains its maximum at an early age (3 to 10 years) at which time healthy children excrete almost double the amount (as compared with their weight) of adults. Gradually thereafter it becomes white after puberty (17 to 20 yrs.) when it reaches the adult average and again diminishes towards old age. The effects of food is very important, more so than any other circumstance; it acts in many ways, supplying...
Case 2. Exophthalmic Goitre.

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- **Disease of Knee Joint**
- **Temperature**:
  - 101°
  - 100°
  - 99°
  - 98°
  - 97°
**Case 5 - Phthisis Pulmonalis**

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Case 6: Morbus Colarins
**Case 7: Disease of the Brain**

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*Temperature (°F):*

- 101°
- 100°
- 99°
- 98°
- 97°

*White cells (per mm):*

- 275, 275, 275, 275, 275, 275, 275

*Erythrocytes (per mm):*

- 56, 40, 48, 38, 39, 570, 40

*Pulse:* 223, 194, 170.3, 170.3, 140, 297.6, 248
### Case 8: Disease of Knee joint

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### Temperature:

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- Feb 27: 98.7°F
- Feb 28: 99.9°F
- Mar 1: 98.3°F
- Mar 2: 99.9°F
- Mar 3: 98.3°F
- Mar 4: 99.9°F

### Pulses:

- Feb 26: 48
- Feb 27: 46
- Feb 28: 38
- Mar 1: 48
- Mar 2: 30
- Mar 3: 48
- Mar 4: 30

### Blood Pressure:

- Feb 26: 212/141
- Feb 27: 134/54
- Feb 28: 212/35
- Mar 1: 139/5
- Mar 2: 340/0
- Mar 3: 227/6

- Feb 26: 150
- Feb 27: 150
- Feb 28: 150
- Mar 1: 150
- Mar 2: 150
- Mar 3: 150
- Mar 4: 150
Case 9  Chronic Rheumatism

Date  Feb 27  28  Mar 1  2  3  4  5

Temperatures:
- 37.3
- 37.1
- 37.4
- 37.1
- 37.3
- 37.4
- 37.1
- 37.3
- 37.4
- 37.1

Fever:
- 103.0
- 102.4
- 103.0
- 103.0
- 101.0
- 101.0
- 100.0
- 99.0
- 98.0
- 97.0

35  60  40  56  50  65  40

418.5  265.67  370.5  583.2  365.67  403  288.27

367.44  367.44  367.44  367.44  367.44  367.44  367.44  367.44
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Case 11. Dyspepsia

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Inflammatory cells and necrosis of the alveoli.
Substances which are partly used for nutrition and partly rejected as useless, it may hasten or retard metamorphosis of tissue according to circumstances, or it may supply material for tissue formations of tissue. The effect of an ordinary meal on the urine is to increase its amount, more or less, according to the substances contained in it, on a high nitrogenous diet it may be doubled in an hour or two (Parke, p. 51) on a non-nitrogenous diet the amount is greatly lessened. Gelatine increases it, though this is probably owing to the direct oxidation of the substance in the tissues. This circumstance has given rise to long and still unsettled discussions as to the value of this substance as an albumin, it being obvious that if it be directly oxidised into urea it can be of very little use in feeding fever patients, although as it absorbs oxygen it must thereby undergo metamorphosis. The subject is at any rate an interesting one and worthy of full investigation.

Excess of water, mental and muscular activity, all increase the quantity of urea, whilst tea, coffee, alcohol, and were diminished it. It is also lessened by the addition of sugar in excess to ordinary food, by the exclusive use of

vegetable diet, and necessarily also by total abstinence from food. By drinking large quantities of water, Dr. Levin of Leeds pointed out the urine is increased by increasing the action of the urinary organs and helping to promote tissue change by carrying off effete material. Professor Naughton in numerous carefully conducted experiments, found that
new employed in manual and routine bodily
labour, on a vegetable diet discharge about 200
grains of urea per diem and that when the work
is mental instead of muscular and therefore
of a higher order, better food must be employed
in order to furnish an equivalent amount. [Dublin
]

Dr. Edward Smith in a series of experiments
found that the elimination of urea in health
is affected by the period of the day, season
of the year, food, and labour. He ascertained
the largest hourly excretion to occur about
midday and the lowest during the night.
The greater quantity was excreted on Sunday
with increased food and rest. The amount was also
greater in the weather, either or unusual
food caused an increase, provided the digestive
organ were in good order. Labour (on the
headwheel) also increased it considerably.

3. The Pathological relations of Urea
In acute febrile diseases the excretion of urea
is markedly increased as a rule, though it is
very doubtful whether this increase is due to
the high temperature, indeed some experiments
seem to point more to the contrary and assign
as a more probable cause some perversity
of the nervous system. It is certainly a
matter of great interest when we remember
that influence the secretions of the body,
generally are diminished, as evidenced by the
dryness of the mouth, the constipation, and
the hard, clayey, bulky stools. [Dr. Beccornor]
in his experiments on S. Martin observed through his gastric fistula, that when feverish, the secretion of gastric juice was lessened, the mucous membrane became dry. Notwithstanding, however, the absence of these fluids that normally aid excretion, we have, in fever, increased tissue changes. These cannot depend chiefly on increased temperature, for it has been often shown that the exacerbations of temperature, caused by any means, necessarily correspond in point of time to the periods of the greatest discharge of urea.

Sydney Meigs in some cases of Typhus fever observed that a larger excretion of urea began before the fever developed, and continued long after the crisis. Also in 18 cases recorded by Dr. Scamur (Braithwaite's Retrospect Vol. 1, p. 31) where the daily amount was measured, although the quantity of urea was increased during the first week when the temperature was highest, it did not attain its maximum until after the temperature had been falling for some days.

Dr. Parks suggested that the excessive thirst of fevers might be due to the osmotic action of some (ferrous) substance which has a powerful and attraction for water as sugar has in cases of Diabetes mellitus, e.g. supposing some sialinum compound formed in the transformation of albumen thus, in consequence of a physical law, the sialinum would at once take the water from the albuminous tissues, thus giving rise to great thirst.
Further these substances, unlike sugar, could not be discharged, but converted into urea and uric acid. In order, however, to prove this statement, it must first be proved, that the transformation of albumen does show at some stage of urea formation, and further that saline in itself could take so much water as to produce the intense thirst. It is in this connection that the "ferm theory" comes to the front claiming support. Take, for example, the probable course of events in an ordinary case of increased urea excretion in some specific fever as Typhus. The entrance here of the poison in the form of ferms brings about as a consequence their propagation and multiplication. This must be at the expense of matter of some kind, and as their composition is chiefly albuminoids, it follows that there is increased change in the albuminoid tissues. They also absorb water and nitrogen, hence the thirst and quickened circulation, and in their multiplication too, maybe found a reason for increase of temperature. Their increase would also lead to a loss of tissue in the body. Nichols supported this view when he asserted that "increase of waste of nitrogenous tissues is due to increased tissue changes.

In certain cases however, there is no increased urea excretion concurrently with increased temperature and acts as a very satisfactory reason for this has been given; it has been suggested that in these cases the transformation does not
extend to the formation of urea, or that although urea be formed it is not eliminated. This
however remains to be proved and at present the "germ theory" can only offer the most feasible
explanation of these phenomena, for in the anomalous case referred to we may it is better
to say the assumption of defective tissue change & this to such an extent that even when the germs
are most active, and do raise the temperature, they still are unable to raise the urea excretion
to the usually high standard, or even perhaps to increase it at all. In the fineness of
case, however, where the area is involved simultaneously
both with the temperature the explanation given above
is sufficiently feasible, provided there is a sufficient
amount of water to carry away the waste products.
Further as in nutrition there is constant focus
on both a formative and disintegrative process
the former in the one here chiefly affected, the
latter, not being attacked, continues as usual,
except where the supply of water is diminished
are to interfere with the solutions of waste products
and hinder their elimination.
In the relation really existing between the
secretion of urea and the temperature of the
body, but few observations of any importance
have been made. Dr. Parker refers the paragraph
to come by Kratzer (Ein Beitrag zur Urologie 1835, p. 18)
and Dr. Ringer has recorded very minute some
valuable observations on a case of acne in the
Med. Chirn. Transactions 1837 which points to the
existence of a well defined relationship. In
some cases of scarlet fever, however, the latter observed.
found no increase of urea although there was very high temperature ( lucr. T. & Gas. Vol. 7. p. 61. p. 66.)

A rather more definite statement may be made with regard to the excretion in non-febrile diseases, accompanied by more or less impairment of function of various organs, while we generally

find it either somewhat decreased or not materially affected, and I shall now, having

briefly sketched the natural history of urea in the body and referred to its increased elimination in febrile diseases proceed shortly to consider

the scarcely less important class of these non-febrile, and sub-acute or chronic conditions left by other more acute disorders.

Not much has been done hitherto in the investigation of the means of excretion in these cases, chiefly I suppose, because these being

mouse or particular phenomena to attract attention, their consideration has been deemed of little moment. The study of febrile conditions seems to have absorbed the minds of observers almost universally to the entire exclusion of the numerous varieties of the abnormalities which doubtless exist in more obscure and "less interesting" forms of the cases.

Surely this anomaly is to be regretted, for may we not justly assume that as these very diseases so persist in co-intractable, and unsatisfactory as regards the result of their treatment, are very much more numerous, and of more common occurrence, than those to which attention in this direction has been paid, so it behoves us henceforward every possible means at our command for the solution of the difficulties with which they are
surrounded? I take an example:

The treatment of Dyspepsia, with all its difficulties, is best and will more often be attended with success if we are constantly having to combat obstructive symptoms, and, roughly speaking, all our successes are resolved into two great classes of remedies respectively, acid and alkaline in character, with which we (frequently in vain) seek to neutralize, or at least modify, the existing condition of the gastric mucous membrane. Much information may be possibly be gathered from the examination of the urine for urea in such cases was very plainly shown in a paper read by Dr. Fuller before the Medical Society in Nov. 1837, in which he related that in certain cases of Dyspepsia accompanied by marked nervous and hypochondriacal symptoms, he had observed a great excess of urea, without the slightest elevation of temperature, and he maintained that this excess was "owing to defects in the primary processes of assimilation from perversion of the nervous system, and not from any destructive processes depending on wear and tear of tissue."

Other examples might easily be found, where a systematic practice of estimating urea might aid so materially in the treatment of disease, and considering the simple and easy methods now at our command, I would strongly urge the desirability of making such an estimation a matter of every-day routine.

Appendix are charts illustrative of
method I venture to suggest would be found very satisfactory and useful for the purpose.

Before giving any notes on explanation of the following cases I may say that they are merely intended to serve as examples of the method I would recommend and to indicate the direction in which investigation are desirable. Being taken from the ordinary class of cases met with in every day practice they do not present any features of extraordinary interest, though they will show clearly enough what seems to me the a good way of recording such observations. I will begin then by describing the mode of procedure:—

The patients, who were not in any way selected, but taken consecutively in their beds in a hospital, were kept as nearly as possible under the same conditions throughout the time of observation. They were kept in bed in wards of fairly meanable temperature and amnestic conditions as any rate reduced to a minimum. Their food was supplied regular in known quantities. The notes taken extended in all but two cases over a period of seven days during which time the temperature was taken at regular intervals during the day and night; the urine collected, measured, and examined every 24 hours. The Nitrogen of the food was estimated according to the table of the Royal used by Parry in his experiments on Weston (vide Cancer Vol 2, 46, p. 447).

The method of testing the urine was as follows:—

The reaction of pH: Digitally, first taken, it was tested in the usual way for albumen, which if present (in one case only) was separated by
filtrations. The area was estimated by means of the apparatus devised by Dr. Russell West and therefore checked by the volumetric process. The former is, however, by far the most convenient for general use and is, for all practical purposes, very reliable, and certain the method should recommend in preference many of its modifications that have since been introduced. Moreover, the advantages of being cheap and simple in construction. For the principle of which it is our embodiment, we are indebted to Davy, who discovered that the Hypochlorite had the power of decomposing Urea into Nitrogen and Carbonic acid gas. With this apparatus, Bromine is used, which, in the presence of a caustic alkali, effect the same purpose. A standard Hypobromite Solution is made by adding Bromine to a solution of Caustic Soda, which, on its addition to the urine in a certain definite proportion, causes the Decomposition of the Urea and the Evolution of Nitrogen, the Carbonic acid being absorbed by the Soda solution. The collecting tube is so graduated that the amount of Nitrogen obtained represents the percentage amount of Urea, from which an easy calculation gives the total amount excreted. (Full details of the apparatus together with the method of testing it will be found in the Journal of the Chemical Society Aug. 1874.) Several modifications of this are described and recommended, one by Sir Apsloe in the Chemical News Jan. 22, 1876, and the other by Mr. Blackley in the
Journal of the Chemical Society Nov. 1876. - Sir W. Roberts of Manchester speaks favourably of the former, but for myself, I must say that I have found the original more satisfactory to work with than either.

Case 1. E., a domestic servant aged 19, admitted to the Kensal Green Hospital Jan. 24, 1881. She complained of pains irregularly in menstruation with dyspeptic symptoms and three days before admission had noticed a "breathing" in her legs. No further history of importance; never had any venereal disease. Began to menstruate at 16 and was always regular until present attack. Is anaemic & pale, tongue sunken, bowels constipated. Both arms and legs covered with spots of erythema (not eczema) for this she was treated with treatate of potassium. After being under treatment for a fortnight, she was much better, the eruption had disappeared, and her appetite improved. On Jan. 25 there was a slight appearance of the catarrh, and at night she was seized with a sharp rigor, temperature rising from 99.7 to 101.4° F. At the same time she began to complain of one throat. On exam. the fauces and uvula seemed reddened and congested. Next morning the whole body was covered with a profuse rash, exactly like that of scarlatina, this, coupled with the bad throat suggested the propriety of isolation. The morning temperature being 104.6° F. commenced. The observations were on the chart at 4 p.m. Four hours later, the temperature had fallen 1.4 degrees and the rash began to fade; by four p.m. the following day (36 hours from its first appearance) it had entirely disappeared.
The menstrual flow was now abundant, though attended with much pain, and continued so for four days, during which time the throat remained acutely inflamed and for about a week afterwards was very painful. The urine was examined for uric acid on the first day of the attack, and was found to contain a very large quantity, but unfortunately the whole amount was not ascertained in the first 24 hours.

I have placed this case first and given it somewhat at length, not so much on account of its bearing on the subject of this paper, as from a desire to record it as being one of a series of similar ones that I have met with in Hospital practice. The interest attaching to it is, of course, the coincidence of the pain in the head with the menstrual flow, and also the occurrence of the rash. The only reference I have been able to find to such an occurrence is in Sondelich's "Medical Therapeutics," where at p. 102 in a footnote he refers to some cases in which he had observed exactly similar phenomena, but they were all in "young girls in their first menstruation." All my cases had previously menstruated, though not naturally, the flow being in some way or other abnormal, and not in the note of the other cases as the leading symptoms mentioned above were present in them all.

Case 2. C.Jt., a domestic servant. Admitted Dec. 1859. Complains of great throbbing in head, neck with swelling on the latter also. Persistent. First noticed the swelling in the neck about 6 weeks ago. Three
month since was perfectly well in every way. A review was then made of the case, and it was found he had well marked symptoms of a disease with some evidences of consumption. In addition to these complaints, he was noticed to be easy. After being treated with ergot, iron, iodide of potassium, and without any apparent benefit, all medicines were stopped and the patient was ordered complete rest in bed. During this time I took any notice of his case. It will be noticed that in spite of the increased circulation, the amount of urea was not materially increased.

Case 3. Mr. A, a farm labourer. On 21st April a year ago caught a severe cold, at his work, which brought on an attack of rheumatic fever. He was laid up for 2 months and on beginning work about again noticed a swelling and stiffness above left knee joint. He was advised to rest but it continued getting worse and some time later became flexed. On admission, joint was distended with fluid, very painful, leg flexed as an acute angle. He was placed on a McFurteen splint and gradually extended. Evaporating lotion was applied to the joint. The more acute symptoms were relieved in about a week, but the joint remained in almost the same condition for a long time, and at the time of my examining his urine he had been lying in bed with his leg in a splint for 3 months. He was somewhat feeble and emaciated. His appetite being however fairly good, and bowels regular. On the evening of the 7th day he had a fever, the temperature, however, accompanied by an
A slight intemperance had occurred, together on the 3rd day.

Case 4. J. D., a married woman, Avc 63. Admitted in Feb. 1887 with cardiac pains, slight fever, and troublesome cough. Had been ailing some time under chronic rheumatism for years. Her health was slight. During treatment she had a sharp attack of typhoid fever had been in hospital a month with very little improvement, to the general symptoms. Appetite had -

The urine was small in quantity, showing defective assimilation. The temperature was highest throughout in the early part of the afternoon.

Case 5. W. S., a carpenter, Avc 28. Admitted Feb. 1887. Had been ill about two years. On admission had all the ordinary symptoms of phthisis. On exam. canicula was diagnosed in both lungs. No family history of any importance. The chief feature in this case was the remarkable daily fluctuation of the temperature.

The largest amount of fever occurred will be seen to be on the 6th day, after, and not coincident with the highest temperature, which had occurred on the preceding day.

The average elevation does not exceed the normal. He had lost 30 lbs. in weight during the 8 months previous to admission.

for which he was fitted with Thomas's splint and sent home. He was brought again in January 81 with aggravated symptoms and on exam - distinct fluctuation was felt in the capsule of the joint. After waiting three weeks to try to improve his health, this was aspired, and it continued discharging thereafter, the boy rapidly becoming hectic and emaciated. At the latter end of March, excision was performed, but the shock of the operation proved too much for him and he died 36 hours afterwards. At the time of excision, the wound was lying unbed on a distant splint with a free discharge of thick curdy pus from the opening in the groin.

Case 7. (W. a married woman 51) admitted Dec 1880 with pain in knee, being especially tender at one spot on pressure. She was afraid of herself though there were suspicions of syphilitic joint asepsis. The knee was treated for several months by rest and repeated blistering. No good was done however and about the middle of February fluid was diagnosed on the inner side of the joint. This was let out under the spray, the patella found bare, on its inner edge. After waiting some weeks further the patella was excised, and the whole of its joint arthritic surface found. Cavities subsequently the wound became septic and empyemic sepsis. The joint rapidly became aseptic and amputation of the thigh had to be performed some weeks later.
say that the urine was examined before any operative measures had been adopted.

Case 8. Mr. A. a dressmaker. Age 34. Disease of knees (not very similar to the preceding but much less severe). No special features.

Case 9. R. F. Alabaster. Age 63 admitted Feb. 1881 to have a cataract removed from the right eye. The operation was not performed at once however on account of an attack of subacute rheumatism which came on shortly after his admission, eventually caused in latter portion and indefinitely. He came under my observation whilst under treatment for the rheumatism. The quantity of urine was slightly increased. There was a rise in temperature with rigors on the fourth day of the course and at the same time the area was marked increased. The daily amount of urine also will be seen to be larger than any of the other cases noted, though this of course is partly owing the greater quantity of urine passed.

Case 10. J. H., a boy. Age 12 admitted in Jan. 1881 with symptoms of his joint disease placed on a diet and slight, and an attempt made to avoid suppuration. Here again the relation between the temperature and area is indefinite, there being an increase in both on the first day, but on the 4th day when there was again a rise in the former the latter was not increased until the day following.

in Feb. 1887 complaining of indigestion, weakness, and constipation. Also dysmenorrhoea. Small mouth. Tongue flatly, indented at edges, but much fur. Area slightly abnormal. No abnormal physical characteristic of the wine.

Case 12. J. B. - a married woman. Admitted Feb. 1887 complaining of pain in cardiac region, with palpitation and dyspnoea. Has been suffering since an attack of rheumatic fever 24 months ago. Cannot undergo any exertion, as any extra effort brings on the difficulty of breathing. On exam. - A marked presystolic aperic murmur was heard, running up to first sound, which was followed by a blowing murmur. She had been treated for swellings with Digitalis, but before her visit was examined (it was left off during the week of trial). The quantity of urine was too small, and hence there was a small amount of urea.

I have given but a very superficial sketch of the main facts of these cases, my object being simply to render the chart intelligible. The following table presents all the facts at a glance, and need no explanation.

Twenty years ago Professor Haughton stated that the healthy standard of urine excretion was about 2 grains to the pound of the body weight. (J. Med. Sci. 1860.)

This is probably, however, rather under the average. For Robert, five 2½ grains at the

quantity per lb. (Urineal and Chemical Analysis, p. 105).
In the above cases therefore, if we accept the latter standard, the amount will be seen from the table to be under the averages, which is what we should expect under the circumstances.

<table>
<thead>
<tr>
<th>Sex</th>
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<th>Sex</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Eliminated Urea</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>F</td>
<td>128</td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>F</td>
<td>129</td>
<td></td>
<td>40.2</td>
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</tr>
<tr>
<td>4</td>
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<td>M</td>
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<td>F</td>
<td></td>
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<td>F</td>
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<td>41</td>
<td>F</td>
<td>135</td>
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<td>30.5</td>
</tr>
</tbody>
</table>

The weight omitted were not obtainable, owing to the patient being confined to bed, and in a fixed position on a splint—no medicines were given, so that the results might be as free as possible from external causes of variation. All the cases may I think be included under those classified by Parke as 'Chronic febrile diseases' where the vital powers are at a low ebb, and the exertion both mental and muscular at a minimum. On these grounds alone, we should theoretically expect a diminished elimination of urea, and practically we find the average amount to be decidedly below the normal. Of course in
estimating such results much will depend on
the digestive powers of the patient. If they are impaired.
this will undoubtedly be decreased. As pointed out by Fdchman (Pathology of the Kidney 1878).
In the foregoing case however, nutrition although
impaired was not markedly so, and hence the
lesserening was not great, as at all events not during
the time of the observations recorded.

With regard to case 6, and its unfortunate
termination, the idea suggests itself that more
terminating might have proved of some service
in helping to determine the propriety of surgical
interference. We are in the habit of deferring
operations in cases of albuminuria, but there
are many cases such as the one here referred
to, where although there be no albumen in the
urine and hence presumably healthy kidneys,
yet the vital powers are so affected by some
long continued strain upon them that they
collapse entirely under any additional strain.

Might we not then, by a careful and timely
measure of the tissues waste, obtain valuable
information as to the advisability of operating.
On the contrary, long before the dread sign of
kidney disease set in and render our case a
hopeless one, it is frequent a question whether
some surgical operation shall be performed.
On account of the presence of some existing
disease, day by day, the urine is tested for
albumen which, perhaps may not be present
at the operation takes place; before many
hours have elapsed the patient dies of shock,
and we are reluctantly compelled to admit
the failure of our expedients.
such cases the area was to be carefully estimated daily for a week or a fortnight previously, and the amount of tissue waste thus ascertained, our future procedure might often be advantageously modified by the results obtained, and we might think we could, reasonably hope to avert such a catastrophe as the one here recorded, by a more judicious selection of the time of operation, having our calculations on the conditions of the nitrogenous tissues. Having thus been shown that there may be laid down a fairly definite standard of urea elimination in health and that in certain diseases this may be departed from in either direction, is there anything we can do by means of medicinal treatment to affect the secretion so as to restore the normal standard?

Unfortunately here again owing to the lack of observation we are very much at fault. The increased metabolism of tissue in cases of febrile disease is not infrequently arrested by certain drugs which seem to act by lowering the temperature, though how far the reader is owing to the latter factor alone or to the action of the remedy need be open to question; for example the action of quinine in ague fever (see "Handbook of Therapeutics", p. 339) that although in large doses may check the symptoms, even including the periodical elevation of temperature, it does not always affect the increase of urea and urinary water which may occur as during a severe paroxysm. It is possible however, that quinine, being a powerful antiseptic agent, may act
as a germicide and to bring about a lowering of temperature by preventing the further propagation of bacteria. Bearing in mind its destructive action on the white corpuscles of the blood, this theory at any rate is a plausible one.

Other drugs as Aconite and Digitalis also have a wonderful power of reducing temperature, by acting on the circulation, though the latter must be given in large doses to effect this purpose. With the temperature, the area likewise falls though by no means constantly. Salicylic acid and its salts also are powerful agents in this direction. I have repeatedly been able to confirm the statements made by their advocates in the treatment of Rheumatic fever. During August last I have attended a case illustrating this where the effects of Salicylate of Soda was very marked:

<table>
<thead>
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* See next page.
This case was accompanied by serious heart lesion of old standing, and it was on account of the great irregularity and rapid action that I was induced to leave off the salicylate, in order to substitute the Digitalis and tone. This however was almost immediately followed by a marked exacerbation, causing me to resume the salicylate after an interval of four days. The area again fell with the temperature, though I am not quite certain that all the urine was saved, on the 17th and therefore the figures for that day are not to be relied on as giving the real amount. The temperature never rose above the normal limits afterwards, and the patient is now convalescent. I must also add that the drug most certainly relieved the articular pains, which were very severe, it also relieved severe pains in the cardiac regions from pericarditis which set in soon after the beginning of the treatment.

As this patient was treated at home and had no removal to cause any increase of pain or fever, the case is undoubtedly free from the fallacy complained of by Dr. Huger (1858) and I may add that I have also frequently remarked in cases that have been under treatment for some time, when an exacerbation has occurred, how marked the pain subsides as a rule after two or three full doses of salicylate of soda.

Cases of deficient elimination of urea present many varieties; there are those dependent on
nal-accumulation of food, or on weak and low state of the system generally, such as those recorded above. In these of course the indications for treatment are obvious, though the results are not always beneficial as the causes are, as often seen above. In cases of the nervous system and some due to the digestive organs by poisons and nutrition of food, are amongst the more likely plans of treatment that suggest themselves. Other cases there are, more complicated and difficult to combat, e.g. in some forms of Bright's Disease, where there is a more general decrease in the daily amount of urine, sometimes falling as low as 20-30 grains. This is easily accounted for by the interference with the function of the kidneys caused by the blocking of the tubule (in the acute form of the disease) with inflammatory products, and in the chronic form by the presence of adhesion fibrous tissue. Treatment in these cases, particularly the latter, is extremely unsatisfactory, for whilst the urine is voided in diminished quantity, its essential constituents accumulate in the blood, and if the poison be present, in the serous fluids likewise. This gave rise to the notion which was held, for some time, that it was the presence of these substances, urea, uric acid, etc., in the blood, that gave rise to the phenomenon termed "uremic". The symptoms of uremia however are not present by any means in all cases of Bright's Disease, nor indeed, always even in cases of complete suppression of urine. When they do occur, although of a varied character, they are evident in the outcome of a disturbance of the central nervous system, and often being much manifested by involuntary muscular
twitches, sometimes, however, taking the form of
convulsions, and even passing into fatal coma.
Several theories have at different times been
suggested, and abandoned, in the attempt to
explain these enigmatic phenomena. As yet
no pathological lesion has been found constant
present in cases examined "post mortem".
Nothing has ever been discovered in the brain,
although the predominant symptoms are
essentially cerebral. Hammond maintained
that the blood was poisoned by urine itself
being retained in it. (Amer. Jour. Med. Sci. 1861)
Freichs denied this, and asserted that the
cause was the decomposition of urine into
carbonate of ammonia. This again, has been
upset by the experiments of Oppel & Sahly.
referred to as by the latter point out that, as
it was, but its antecedents accumulate in the
blood to give rise to the condition. Even this
however does not explain those anomalous cases
of suppression of urine from obstruction. Here
in spite of the non-existent uraemic symptoms
are rarely, if ever, present until after the lapse of
couler days. 

Owen Reid (Nature & treatment
of diseases of the kidney, 1830) and Franca (Deutsche
Welt, 1839 pp) contended, that the phenomenon
was due to stagnation of the blood, causing
cerous hemorrhages through the cerebral
capillaries giving rise to edema of the brain
which in its turn by compressing the minute
bloodvessels, caused anaemia, and hence
the convulsions and coma.

None of these theories are however, alone
sufficiently conclusive, and all we can do...
At present it is to put them together and pursue our investigations further.

The treatment of these cases is practically attended with negative results, and this cannot surprise us when we consider the organic changes that are usually present in the kidneys, particularly in cases of anemia, where more or less of the substance of the organ has become converted into fibrous tissue. The more that can, as a rule, be done, is to try to prevent further extension of the mischief, to ward off the obvious symptoms, and to treat the various complications as they arise.

In conclusion, I would remark that the very superficial nature of this paper is in itself a strong argument in favour of the opinion I have ventured to express, with regard to the desirability of pushing forward investigations on this subject. The daily examination of urine for albumen involves very little time or trouble, scarcely more than that required for the determination of albumen, and if, in any one case, be systematically recorded, as a rule, for several days consecutively, there would very soon be collected a mass of information of no small clinical value.

William Shaw.