OBSERVATIONS
UPON THE
ELIMINATION OF UREA IN CERTAIN
DISEASES.

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I HAVE the honour of submitting to the Society some observations which I have lately made upon the excretion of urea in certain diseases.

Before doing so I wish to take this opportunity at the outset of expressing my thanks to Dr. Andrew for the kindness with which he placed all the advantages of his ward in St. Bartholomew's Hospital at my disposal, and of acknowledging how much I owe to his encouragement and assistance during the preparation of this paper.

The experiments were made by a method and apparatus described in a paper read by Dr. Russell and myself at one of the meetings of the Chemical Society about three months since, and published in the August number of the Chemical

Society's 'Journal.' I may refer for a full description of the method and apparatus to that paper, and I will pass without further comment to the observations I have made.

The following are the cases in which I have examined the excretion of urea :—Two cases of Addison's disease; three cases of pneumonia; four cases of rheumatic fever; and one case of diabetes mellitus.

I propose in each of these cases to give first the results of the experiments, then to make a few remarks on each case, and to complete my paper by drawing a few general conclusions which a review of the cases on a whole seems to suggest.

Each case is prefaced by a table giving the observations made each day during the period the case was under notice.

I will commence with the cases of PNEUMONIA, and I propose to divide the results into two groups, as I have also done, where it was possible, in the cases which are to follow, the first group containing the results *during fever*, and the second those *during convalescence*.

CASE 1.—The first case of pneumonia is that of Ellen C— (see Table I), and the following observations were made during a relapse :

TABLE I.—Ellen C—. Mary Ward (26). Pneumonia (relapse.)

Date.	Total urine.	P. c. urea.	Total urea.	Tempe- rature.	Specific gravity.	Diet.
May 29th .	385 ...	3·4 ...	13·10 ...	— ...	— ...	May 26th.—D.L. ¹ Milk Oj. Eggs ij. Brandy ʒij. Beef-tea Oj. Essence ʒv. Wine ʒiv, in- stead of brandy.
„ 30th .	425 ...	3·5 ...	14·87 ...	104·2 ...	1030†	
June 1st .	510 ...	4·1† ...	20·91 ...	104·3 ...	1025.	
„ 2nd .	375 ...	3·7 ...	13·88 ...	103·8 ...	1020.	

¹ D. L. = Dieta lactis. D. D. = Dieta dimidia. D. C. = Dieta carnis, of the St. Barthol. Hosp. Pharmacopœia.

Date.	Total urine.	P. c. urea.	Total urea.	Tempe- rature.	Specific gravity.	Diet.
June 3rd.						
„ 4th .	350 ...	3·3 ...	11·55.			
„ 5th .	600 ...	3·2 ...	19·2 ...	102	1022.	
„ 6th .	500 ...	3·5 ...	17·5 ...	104	1025	
„ 8th .	350 ...	3·6 ...	12·6 ...	—	1026	{ D. D. Eggs ij. Brandy 3i ij. Ale Oss. Lemon j.
„ 9th .	350 ...	2·4 ...	8·4 ...	—	1018	
„ 11th .	390 ...	3·5 ...	13·65 ...	100	1026	
„ 12th .	500 ...	3·4 ...	17· ...	—	1022	
„ 13th .	275 ...	4·05† ...	11·14 ...	—	1032	
„ 15th .	250 ...	2·5 ...	6·25 ...	—	1022.	
„ 16th .	650 ...	2·2 ...	14·3 ...	—	1023.	
„ 17th .	675 ...	2·1 ...	14·18.			
„ 18th .	1150 ...	1·1 ...	12·65.			
„ 19th .	700 ...	2·1 ...	14·7.			
„ 20th .	300 ...	2·4 ...	7·2 ...	—	1026.	
„ 23rd .	— ...	— ...	— ...	99·3.		
„ 25th .	375 ...	2·65 ...	9·92.			

Smell very putrescent, with occasional traces of albumen, and a very deep colour with nitric acid.

During *the fever* (which lasted until the 15th June) we have these averages.

Total vol. of urine.	P. c. urea.	Total urea.
400 cc. ...	3·4 ...	13·85.

Each column in Table I being taken separately, it will be seen that the total quantity of urine is much reduced, and, though fluctuating round the mean of 400 cc., cannot be shown at present to depend upon any definite cause. This reduction occurs also in spite of the extreme thirst of the patient. The percentage of urea remains fairly constant, varying from 2·4 to 4·1 and giving the mean of 3·4, with which most of the experiments agree. The two highest percentages, and it must be noticed they depart in a most marked way from the average, follow upon the alterations of diet. Crosses stand against the altered diet and the percentage in which it caused alteration. It must be noticed that these changes in diet produced only a temporary rise in the percentage, which falls the next day to the average, or

slightly below it. It would appear as though the balance of nutrition was disturbed by such changes in diet, and that it required some hours to restore itself. I do not know that it is possible to point out any but a very general relation between the percentage of urea and the temperature. As long as the temperature remains above normal the percentage is high. As soon as the temperature falls the percentage is reduced, but at present it cannot be stated that a rise or fall in temperature is attended by a rise or fall in urea percentage, nor can we show any inverse proportion between the urea percentage and the volume of urine.

In this case it is to the total excretion of urea in the twenty-four hours that I would wish to draw special attention. The mean excretion during the fever was 13·85 grammes, and the reduction in amount is very marked, and this, too, when the patient was upon an extremely rich nitrogenous diet, one which, until it was changed on June 12th, contained an amount of nitrogen to which that excreted in the form of urea bears but a very small proportion. I propose to return to this strange fact after speaking of the other cases of pneumonia.

I have to show lastly, in this case, the entire independence of the total excretion of urea upon the temperature, as is seen in the following table :

Temperature	.	.	104·2	...	104·3	...	104·
Urea	.	.	14·87	...	20·91	...	17·5.

During *convalescence* (which commenced on the 15th June) we notice, looking at the figures in the respective columns after the 15th June, a remarkable diminution from the normal in the volume of urine and the total excretion of urea. In the urea percentage are to be observed curious oscillations, to which I shall draw attention again, later. In this case the oscillations take the form of a gradual decrease, and again of a gradual rise.

It remains for me to add, before passing to the other cases of pneumonia, that the urine in this case contained occasionally slight traces of albumen, had a most unpleasant

putrescent odour, and gave an extremely deep reddish-purple colour with nitric acid.

CASE 2.—The second case is that of Alfred E— (see Table II).

TABLE II.—Alfred E—, æt. 74. Mark Ward (20). Pneumonia (right side).

Date.	Total urine.	P. c. urea.	Total urea.	Temperature.	Specific gravity.	Diet.
June 16th	— ...	— ...	— ...	— ...	1020	
„ 17th	600 ...	3· ...	18· ...	102 ...	— ...	D. L.
„ 18th	600 ...	3·3 ...	19·8 ...	101·8.		Essence Oss.
„ 19th	700 ...	3·6 ...	25·2 ...	101·9 ...	1022	Arrowroot Oj.
„ 20th	925 ...	3·2 ...	29·6 ...	99·9 ...	1020	Egg j.
„ 21st	640 ...	3·3 ...	21·04 ...	98·3.		Brandy $\frac{3}{4}$.
„ 22nd	640 ...	3·3 ...	21·04 ...	101·7.		Beef-tea Oss.
„ 23rd	600 ...	2·7 ...	16·2 ...	98·4 ...	1020.	
„ 25th	900 ...	2· ...	18· ...	98·4 ...	1016.	
„ 26th	1200 ...	1·85 ...	22·2 ...	— ...	1018 ...	Chop.
„ 27th	1750 ...	1·2 ...	21·			
„ 28th	1250 ...	1·1 ...	13·75.			
„ 29th	1550 ...	1·05 ...	16·3 ...	98·2.		
„ 30th	1500 ...	1· ...	15·			
July 1st	1550 ...	1·3 ...	20·15.			
„ 2nd	1200 ...	1·55 ...	18·6.			
„ 3rd	1400? ...	1·65 ...	23·1.			
„ 4th	1650 ...	1·75 ...	28·87.			
„ 5th	1425 ...	1·75 ...	24·94.			
„ 6th	1100 ...	1·85 ...	20·35.			
„ 7th	950 ...	2·15 ...	20·4.			
„ 9th	1150 ...	2·3 ...	26·45.			
„ 10th	700 ...	2·2 ...	15·4.			
„ 11th	? ...	2·2 ...	?			

Went out of hospital well.

During *the fever* the mean results for the six days on which experiments were made are—

Total urine.	P. c. urea.	Total urea.
700 ...	3·28 ...	22·45.

The total volume is here considerably reduced, though not to the same extent as in the previous case. It is subject also to very considerable variations from day to day.

The percentage amount of urea is fairly constant, varying from 3·0 to 3·6, and giving as mean 3·28. Here again it is to be observed that the percentage does not vary inversely, or depend upon the volume in any way at present evident.

The total urea here again is certainly not above the normal, in spite of the increased temperature, though its reduction is not nearly so marked as in Ellen C—'s case. Variations from day to day are also to be observed which are independent of the urea percentage or of the temperature.

The total amount of urea is also considerably below what the quantity of nitrogen in the food would lead us to expect.

During *convalescence* the results show a gradual increase in the volume of the urine for the first few days, when it reaches its normal, though there are now, as during the fever, curious variations, for which we cannot account, in the total volume.

The percentage of urea which, during the fever, is nearly 3·3, falls gradually for the first seven days, until, on the seventh day, it is as low as 1·0, and it subsequently rises again slowly until it reaches a mean of about 2·2, at which it appears to become fairly constant.

A series of percentages such as these shows very clearly that there is at any rate no simple relation between the volume of the urine and the percentage amount of urea, to which fact, however, I shall have to refer again.

In the total amount of urea we notice, for the first week of convalescence, a considerable fall as compared with that excreted during the fever, so that the mean for the first seven days of convalescence is only 17·5 grammes. In the subsequent eight days a considerable rise occurs again, the mean being for these days twenty-three grammes, and in both these periods we have these curious variations from day to day.

CASE 3.—The last case of pneumonia of which I wish to speak is that of G— (see Table III), in which the result was death. In both of the other cases recovery took place.

The results in this case are complicated by the nervous symptoms of the patient. The man had been a hard drinker, and died ultimately rather from his nervous symptoms than his pneumonia.

The temperature was high throughout, and the patient was in an extremely excitable condition, with tolerably frequent attacks of delirium.

The total quantity of urine varies considerably, giving as the mean 835 cc., a quantity larger than is found in either of the other cases. The same irregular variations from day to day are to be observed.

The percentage of urea gives as the mean 2·5, which is much lower than in the other cases, while the total urea excreted is subject to very considerable oscillations; is below the average, the mean being twenty-one grammes; does not depend in any way upon the temperature; and is below the amount we should expect from the food.

TABLE III.—G—. Mark Ward (9). Pneumonia.

Date.	Total urine.	P. c. urea.	Total urea.	Temperature.	Diet.
June 26th .	700 ...	2·2 ...	15·4 ...	103° ...	D. L.
„ 27th .	950 ...	2° ...	19° ...	103·9.	Beef-tea Oj.
„ 29th .	Not saved ...	2·2 ...	— ...	102·4.	Eggs ij.
July 1st .	850 ...	2·55 ...	21·675 ...	103·2.	Essence ʒv.
„ 3rd .	1025 ...	3° ...	30·75 ...	101·1.	Brandy ʒvj.
„ 4th .	650 ...	2·8 ...	18·2 ...	102·2.	
„ 5th .	Passed in bed.				
„ 6th .	Ditto	2·8 ...	104·		

Edward P—. Mark Ward (20). Pneumonia.

June 13th .	1250 ...	2·15 ...	26·875 ...	— ...	Specific gravity 1015, acid with putrid smell.
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R—. Mark Ward (15). Pleuro-pneumonia.

July 13th .	600 ...	4·2 ...	25·2.	
„ 14th .	250 ...	2·85.		
	Whole not saved.			
„ 16th .	500 ...	2·225 ...	11·125.	

In another fatal case (Edw. P—, in the same table) extremely like that just mentioned, in which also the nervous symptoms preponderated, and in which there was also a history of intemperance, we got, on the only day on which examination of the urine was possible, strongly analogous results. The percentage urea is much the same, though the total volume of urine, and the total amount of urea, are on this particular day much larger than the mean in the previous case.

It is interesting to observe that, while it is stated to be a physiological fact that nervous excitement increases the excretion of urea, though the nervous symptoms were the most prominent features in both these cases, the total excretion of urea is certainly not proportionately increased.

What general conclusions can be drawn from comparison of the cases already brought forward? There is a considerable reduction in the total volume of the urine, which agrees with the general statements found in books (Niemeyer, 'Medicine,' vol. i, p. 171; Parkes 'On Urine,' p. 270), though in different cases we find great differences. In the three cases given the averages are as follows:

Ellen C—.		Alfred E—.		G—.
400 cc.	...	700 c.c.	...	840 cc.

I cannot discover any very close relation between the volume of the urine and the temperature of the patient. The cause of this reduction is in great measure no doubt the increased perspiration, but the lungs doubtless play an important part in the diminution of water, while a third cause may possibly be the altered nutrition of the kidney which the common presence of albumen in the urine of pneumonic patients proves to exist (Parkes, 'Urine,' p. 270).

During convalescence the quantity of urine returns to the normal, as Table II shows (Parkes, 'Urine,' p. 270). *The percentage of urea* is in all cases very high, even in those in which there is a reduction instead of an increase in the total amount of urea.

In these cases the percentage is 3·4, 3·28.

In Moos (Henle and Pfeuffer, 'Zeitschrift,' n.f., iv, 3), 4·27.

In Vogel (" " " "), 4·8.

In Unruh (Virchow, 'Arch.,' 1869, 48, S. 227), 4·8, 4·3, 3·33, 3·62, 3·13, 4·57, 4·43.

I should state that there are two cases quoted by Vogel (*ut supra*) which give a very low percentage—1·25 and 1·5, and that in these cases the quantity of urine passed was also very large. In the two other cases mentioned above, viz., those of G— and P—, there is also a reduction in the percentage, viz., 2·15 and 2·5; but here we have complications on the side of the nervous system, so that it is hardly right to argue from these instances.

Though, as I have stated in analysing Case 1, there is no relation between the temperature and the percentage of urea from day to day, yet a very marked relation exists between the fall of temperature at the termination of the fever and the percentage of urea. With the fall in temperature a fall in the percentage occurs, which may be clearly seen in both the cases in this paper, and may be noted in experiments on pneumonia made by other observers (Unruh, *ut supra*).

As regards the total amount of urea we find very contradictory statements in the books. In all the cases I have cited above the amount of urea is certainly not above the normal, but, on the contrary, reduced, the reduction in the first case quoted being very remarkable, and still more so when the amount of nitrogen which the food contained is taken into consideration. In the first two cases we have a quantity of food consumed which contains at a very low estimate 280 grains of nitrogen, which is equivalent to 600 grains of urea, or 40 grammes, while Ellen C— excreted in urea only an average of 14·1 grammes, and E— of 23·0 grammes. The question arises at once, what can have become of this nitrogen? There are several possible means by which it could have escaped estimation.

1st. It may have been *not digested*, and so have never entered the system at all; but against such an explanation

are the facts that the appetite was good and that there was no diarrhœa.

2nd. If digested, it may have been *excreted or stored up*. If excreted, either it left the body by the kidneys, in which case it must have been in some other form than urea (let us suppose leucin, or tyrosin), or it left the body by some other channel, viz., the lungs, the skin, or the intestines. If stored up, the question remains, in what form, and where?

I am afraid I cannot do more than balance the probabilities of these various means of elimination. Experiment alone can decide the question, and at present we have none to guide us. It is improbable that the escape of nitrogenous products by the lungs should be sufficient to account for so great a deficiency. The skin is a more probable channel, but even this we could only conceive to account for part of the deficiency, and on the side of the intestines we have no evidence of such loss.

We are thus reduced to the two last possible means of elimination, and first by the kidneys in some other form. This is very probable; pneumonia being an affection of the chief oxygen-introducing organ in the body, we might expect to get deficient oxidation, and hence to find in the urine such substances as leucin and tyrosin, the primary products of the decomposition of albumen, which, under ordinary circumstances, are oxidised to urea (Schultzen and Riess, *ut supra*); or we might get uric acid, but I know of no experiments bearing on this question.

Lastly, it may be stored up.

(a.) By *retention*, in which case we should expect a critical discharge after the pyrexia, such as Dr. Parkes states to occur in such cases (p. 278); but in the case he quotes it was uric acid, and not urea, and this would, to a certain extent, support the theory of the excretion of nitrogen by the kidney in some other form than urea. However, in my cases, as regards urea no increase in its quantity was observed after the pyrexia.

(b.) By *going to form tissue*, and we might thus connect the absorption of nitrogen by the body with the increased

production of cells in the lungs and the disappearance of the chlorides ; but it is unlikely that we should get such extensive carpentering without chips, and such great formation of new growth without proportionate waste, for in children, in whom cell-growth is very rapid, we have a proportionate increase in the production of urea. We should further expect that *resolution* would cause increase in the urea, and this we do not find. We have, moreover, direct statements to the contrary by Vogel and others, Moos, and Wachsmuth, who affirm that the excretion of urea is greater before than after resolution.

	Vol. of urine.		Urea.
On each of 3 days before resolution .	. 926 cc.	...	37·65
On each of 7 days during resolution	. 1073 cc.	...	21·16

If it be true that the absorption of nitrogen during the fever is due to cell-growth, the reason that such excess does not appear in the urine during convalescence may partly be that there is a subsequent reabsorption to reform the wasted tissues akin to that which occurs during violent exertion.

It seems, therefore, most probable that we have in pneumonia the elimination of nitrogen by the kidneys, but not in the form of urea. Whether this is so, and in what form it is excreted, remain for experiment to determine.

As regards the urea in convalescence from pneumonia, we notice, in both the cases quoted above, a diminution during the first period. In the latter stage it appears to be increased again and to reach about the normal amount.

	Ellen C—.		E—.
Convalescence, 1st period	. 12·16	...	17·0
During fever	. 14·1	...	23·0

From consideration of the cases of pneumonia in which analyses of the urea are given we are led to the conclusion that there must be two distinct classes of cases—1st, those in which the urea is increased, and 2nd, those in which it is diminished.

1. *Those in which it is increased.*

Dr. Parkes ('Urine,' p. 271) quotes a number of cases, reported by different observers, in which the urea ranged from 33·45 to 85·56 grammes, or from 516 to 1321 grains.

Vogel, Moos, and Wachsmuth, quoted in the same chapter by Dr. Parkes, state similar results.

Unruh (Virchow, 'Archiv,' 1867, 48, f. 227) gives a number of cases in which the average during the fever varied from 22·98 to 38·8 grammes.

Moos (Henle and Pfeuffer, 'Zeitschrift,' n. f. iv, 3),
and Vogel (" " "),
make similar statements.

2. *Those in which it is diminished,*

as in the cases here quoted; in certain cases mentioned by Dr. Parkes as extremely rare; and in a few cases quoted by Unruh (*ut supra*), and in two quoted by Vogel (*ut supra*).

Dr. Parkes states that a small excretion of urea affords a bad prognosis; yet in the two cases I have quoted, in which there was marked deficiency, recovery took place; but even these bear out, in a fair degree, Dr. Parkes's statements, for, though in both the urea was reduced, yet in Ellen C—'s case, in which the reduction was most marked, convalescence was most tedious, and it is probable that recovery was not quite complete when she left the hospital, for her temperature never returned to normal, though all signs of lung mischief had disappeared, and we should expect, *à priori*, such marked reduction to be a bad sign, for it must mean serious interference with the normal nutrition of the body, if those substances which should leave it oxidised as urea are not so oxidised, and the prognosis will be better or worse according as there is less or more interference with the normal processes, of which in this respect urea may be taken as an estimate.

It remains only for me to add that the excretion of urea appears to vary very considerably in the different chest diseases. In pleurisy Dr. Parkes (p. 280) says it is almost natural. In bronchitis it is certainly not increased in

Brattler's cases ('Ein Beitrag zu Urologie,' 1858, p. 42), while Moos ('Zeitschrift f. rat. Med.,' B. vii, 362) gives a case which passed only nine grammes during the fever, while during convalescence twenty-four grammes was passed. It may be that these differences are to be explained by the different degrees to which oxidation is interfered with in the different cases. Unfortunately, in nearly all these cases quoted no reference is made to the diet of the patients.

I pass now to the cases of RHEUMATIC FEVER, of which the first is that of Thomas C—, (see Table IV), and the results in this case I propose to divide as before.

CASE 1. TABLE IV.—James C—, æt. 13. Mark Ward.
Rheumatic fever.

Date.	Total urine.	P. c. urea.	Total urea.	Tempe- rature.	Specific gravity.	Diet.
May 30th .	860 ...	2·85 ...	24·51 ...	—	—	Arrowroot made
„ 31st .	1000 ...	1·85 ...	18·5 ...	101	1015	with water.
June 1st .	525 ...	2·7 ...	14·175 ...	101	1015	Arrowroot bis-
„ 2nd .	810 ...	1·6 ...	12·96 ...	100	1010	frothy cuits, do.
„ 3rd .	1000 ...	1·6 ...	16 ...	—	1013	Aquæ destil. 3j just acid ter die.
„ 4th .	850 ...	1·6 ...	13·6 ...	—	1012	Brandy 3ij.
„ 5th .	750 ...	1·2 ...	9 ...	100·3	1012	neutral.
„ 7th .	500 ...	3·26 ...	16·3 ...	100	1020	neutral June 6th.—Egg.
„ 8th .	500 ...	4·34 ...	21·7 ...	—	1025	„ 7th.—L.D.
„ 9th .	400 ...	3·8 ...	15·2 ...	99·6.		acid, deeper colour.
„ 10th .	880 ...	2·8 ...	23·24 ...			
„ 11th .	770 ...	3·2 ...	24·64 ...	—	1023	
„ 12th .	725 ...	3·05 ...	22·11 ...	—	—	D.D.
„ 14th .	950 ...	3 ...	28·5 ...	—	1023	Milk Oj.
„ 15th .	1325 ...	2·35 ...	31·14 ...	—	1025.	
„ 16th .	1075 ...	1·55 ...	16·7 ...			
„ 17th .	1050 ...	1·5 ...	15·75 ...			
„ 18th .	1050 ...	1·5 ...	15·75 ...			

Date.	Total urine.	P. c. urea.	Total urea.	Temperature.	Specific gravity.	Diet.
June 19th	. 1375 ...	1.75 ...	24.06 ...	—	... 1017.	
„ 20th	. 1150 ...	1.75 ...	15.52.			
„ 21st	. 925 ...	2.05 ...	18.96.			
„ 22nd	. 925 ...	2.05 ...	18.96.			
„ 25th	. 900 ...	1.95 ...	17.55.			

1st.—During *the fever* the averages are—

Total vol. of urine.	P. c. urea.	Total urea.
719 cc.	...	16.19.

The total volume of urea is much reduced, but shows very considerable variations, and it is to be observed that they are entirely independent of the temperature.

Temperature . . .	100	...	100.3	...	100°.
Total vol. . . .	810	...	750	...	500.

In discussing the results contained in the other two columns of the table it is impossible to separate the effects produced by the fever from those produced by the treatment. The treatment consisted in the absolute deprivation of nitrogenous food, so that the patient was placed upon a diet consisting of arrowroot made with water, arrowroot biscuits, and as medicine Aq. destil., 3j ter die. This treatment, first practised by Dr. Andrew at St. Bartholomew's Hospital, and suggested to him by certain statements in Dr. Parkes's lectures, has yielded, in those cases which would bear it, extremely good results. They are described and discussed in the 'St. Bartholomew's Hospital Reports' for 1874.

The temperature in this case was not very high on the first day on which it was taken, but the patient had already been ill some days, and had been placed on a low diet before this treatment was adopted.

The patient began with this diet on the 29th of May. On the 30th the urea percentage is 2.85, and from that day progressively falls, the gradual fall being interrupted on the third day of treatment by one of those oscillations to which reference has been previously made. The fall is

extremely rapid, and on the fifth day the urea percentage is 1·2 only. The specific gravity follows fairly closely the fall in the percentage, and with it certain changes in the general character of the urine occur. Being at first of high specific gravity (1025) and strongly acid, its specific gravity falls until on June 5th it is 1012, and the acidity is reduced more and more until on the 3rd, 4th, and 5th the reaction is neutral. With this change in the percentage a similar change is observed in the total amount of urea. At first 24·5 grammes, a fairly large amount, it falls with a single oscillation (which, by the way, does not coincide with that observed in the percentage), until it reaches nine grammes, and it is possible that we have at this time eliminated the complication of food, and that we may take the nine grammes as the measure of the tissue waste.

In the remaining three days of the fever I propose to consider the effect of the change of diet upon both the percentage and the total amount of urea together. An egg was eaten on the 6th, and on the 7th we have a sudden rise in the percentage to 3·26 and an increase in the total amount of urea of about 7 grammes. The egg could not have accounted for more than 1·5 grammes on the most liberal allowance, so that we have a rise and increase totally out of proportion to the food. With the rise, it should be observed, there was a slight return of pains, which, while the percentage was low, had almost entirely disappeared.

On the 7th the diet was again changed, and again we notice a marked rise in the percentage and in the total amount of urea. On the third day of treatment both the percentage and the total urea fell, so that here we notice again those oscillations produced by change of diet to which I have before referred.

2nd.—During *convalescence* the averages are—

Total vol. of urine.	P. c. urea.	Total urea.
1000 cc.	...	21·16.

And we notice that there is a gradual rise in the total amount of urine, but with fluctuations from day to day such as all the other cases show.

The changes in the percentage of urea admit of the division of convalescence into two periods. In the first there is a gradual but progressive diminution in the percentage, and the second is characterised by a gradual and progressive rise, until a mean of about 2·0 is established. In the first period the average of total urea excreted is much higher than in the second, but we have here again variations from day to day for which we cannot at present account.

It is to be observed that the specific gravity here follows fairly closely the variations in the percentage.

CASE 2. In the next case to which I now pass, that of William T— (see Table V), we have the fever at an earlier stage, and we notice here the small volume of the urine, the very high urea percentage (4·4 and 4·1) with at the same time a not excessive excretion of urea. As soon as the effect of the diet begins to make itself apparent we have a large increase in the total amount of the urine, a very considerable and sudden drop in the urea percentage, while, however, the total urea remains fairly constant, so that we do not get here, as in the last case, so marked an effect produced upon the total urea excreted. But this may be due to the fact that the patient was not kept so long upon a purely non-nitrogenous diet.

TABLE V.—William T—, æt. 16. Mark Ward (21). Rheumatic fever (pericarditis).

Date.	Total urine.	P. c. urea.	Total urea.	Tempe- rature.	Specific gravity.	Diet.
July 2nd .	500 ...	4·4 ...	22·	101 ...	1025	Neutral. Arrowroot biscuit, Arrowroot water, Aq. distil.
„ 3rd .	500 ...	4·1 ...	22·55 ...	99·3 ...	1025.	
„ 4th .	1100 ...	1·95 ...	21·45 ...	99·		
„ 5th .	1200 ...	1·95 ...	23·4.			
„ 6th .	1100 ...	1·6 ...	17·6 ...	100·3 ...	—	Neutral. Egg j. D. L.
„ 7th .	1150 ...	1·95 ...	22·4 ...	— ...	— ...	Fish.

Date.	Total urine.	P. c. urea.	Total urea.	Temperature.	Specific gravity.	P. c. urea in ur. sang.	Diet.
July 8th .	1150 ...	2· ...	23·				
„ 9th .	750 ...	3·25 ...	24·38.				
„ 10th .	450 ...	3·45 ...	15·5 ...	—	—	... 3·5.	
„ 11th .	750 (?)	2·85.					
„ 13th .	1000 ...	2· ...	20· ...	—	—	... 2·6.	
„ 14th .	750 ...	2·5 ...	18·75 ...	—	—	... 1·8	July 15.— D. L. Milk.
„ 16th .	1150 ...	1·3 ...	15·5 ...	—	—	... 1·175.	
„ 17th .	850 ...	1·4 ...	11·9 ...	—	—	... 1·.	
„ 20th .	— ...	— ...	— ...	—	—	... 0·9.	
„ 21st .	— ...	— ...	— ...	—	—	... 1·225.	
„ 24th .	1250 ...	0·83 ...	10·38 ...	—	—	... 0·93.	

The effect upon the urea percentage and the total urea of change in diet is the same as in the previous case, except that the rise takes place a day later. Again, we notice in this case, as in the last, a diminution of the volume accompanying the rise in the percentage, though no definite relation can be traced between them.

During convalescence there is the same gradual fall in the urea percentage, but there is no subsequent rise again, probably because the observations were not carried so far into convalescence as in the previous case.

The averages during convalescence are—

Total vol. of urine.	Urea p. c.	Total urea.
830 ...	* ...	17·7.

In the total amount of urea we observe here also a diminution in the amount excreted during the day.

CASE 3. In the next case, that of Arthur S— (see Table VI), we have a series of facts which are suggestive as to the cause of rheumatic fever. This man was sent into Mark Ward for threatened rheumatic fever, but on examination the chief pain, which was in the hip, was found referable to a sprain which he had got while riding, and he was removed to a surgical ward. Here he was kept for a week on full meat diet and a pint of porter. His bowels did not act during the whole of this time, and he was sent back to Mark Ward,

complaining of considerable pain in his joints, and with every sign of commencing rheumatic fever, so that we have here a disease very similar to rheumatic fever produced by simple digestive derangement, and by accumulation in the body of effete nitrogenous products, which were too abundant for the kidneys to remove sufficiently. As soon as the supply was stopped in the food the surplus was quickly worked off by the kidneys and health restored.

TABLE VI.—Arthur S.— Mark Ward. Rheumatism (?).

Date.	Total urine.	P. c. urea.	Total urea.	Tempe- rature.	Specific gravity.	Diet.
June 23rd .	—	... 4·1	...	—	...	Refused to take the food, and had none. Arrowroot water, arrowroot biscuits, Aq. distil.
„ 25th .	650	... 4·45	... 28·9	... 98·5	... 1032	June 24th.—D. L.
„ 26th .	1000	... 3·25	... 32·25	...	... 1025.	
„ 27th .	650	... 2·5	... 16·25.			
„ 28th .	1250	... 1·75	... 21·87.			

John E—, æt. 24. Radcliffe Ward. Rheumatic fever.

	P. c. urea in ur. sang.	Tempe- rature.	
June 11th .	— ... 3·5	...	103·2 ... — ... D. L.
			Milk Oj.
			Alk. Excess of Phosph.
„ 12th .	— ... 3·15	...	— ... 102·.
„ 13th .	350 cc. 3·75	...	— ... 101·8.
„ 16th .	— ... 2·65	...	— ... 100 ... — ... No pains.
„ 17th .	— ... 3·1	...	— ... 99·2.
„ 18th .	— ... 3·1.		
„ 19th .	— ... 1·65.		
„ 20th .	— ... 1·65	...	— ... 99·8 ... — ... Pudding.
„ 24th .	— ... 3·5	...	— ... — ... — ... Fish.
„ 26th .	— ... 1·9.		
July 8th .	— ... 1·45.		

The percentage of urea was very high (4·1). The patient was at once placed upon the arrowroot treatment, which he

refused, so that for one day he had no food at all. On the next day, the 24th June, he was placed upon milk diet.

The quantity of the urine oscillated considerably, but was never large. The urea percentage fell gradually day by day, and as it fell the patient got better, the pains left him, and at last when the percentage reached 1.75 he got well.

The total quantity of urea was large, but still not in excess, considering the full diet upon which he had been placed. With this change in his diet and his recovery the quantity fell.

This effect of change of diet upon the urea percentage was as strongly marked as in the other cases, a rise occurring from 4.1 to 4.45, followed by a fall.

Lastly, it is to be observed that the specific gravity varies more definitely with the percentage than with either the volume of urine or the total urea. This is what we should expect to occur.

CASE 4.—I have now to refer to the case of John E—(see same table), a fairly severe case of rheumatic fever treated by alkalies and placed upon a diet of milk. Here only the percentage of urea in the *urina sanguinis* was taken. I shall have to refer to this later. At present all I wish to do is to point out how closely the results obtained from this agree with those given by the percentage of the volume during the whole twenty-four hours.

We observe the height of the percentage during the height of the fever, its gradual fall during defervescence, convalescence commencing as soon as the percentage reaches about 1.5, the marked rise produced by the change of diet when fish was given, and the subsequent fall again. Lastly, I have to point out that on July 8th, when convalescence was almost complete—twelve days after the last percentage was taken—the percentage of the *urina sanguinis* was 1.45, which shows sufficiently clearly the relation the percentage bears to the condition of general health.

From a general review of these four cases I may state that in rheumatic fever, so far as I am able to judge, *the percentage* is very much increased, while I am inclined to

question whether there is any *such* great increase in the total excretion of urea as the books state to occur.

Dr. Parkes, in his work on 'The Urine,' quotes Vogel's observations, which give a mean excretion, in three cases of rheumatic fever in men, of 39 grammes, *i. e.* 600 grains, and Brattler's results, quoted also by Dr. Parkes, give an even larger amount, viz. 56·5 grammes, *i. e.* 870 grains, as a mean of four days. In this case the man in health passed 27·4 grammes, or about 450 grains.

I proceed now to the cases of ADDISON'S DISEASE.

CASE 1. A. B— (see Table VII) came into the hospital on July 12th. When admitted she was extremely weak and thin. Her weakness increased rapidly, and after about ten days she died. Her appetite, which had been long failing, was, on her admission, very bad, and for the last few days she was prevented by nausea and sickness from taking food at all.

TABLE VII.—A. B—. Addison's disease.

Date.	Total urine.	P. c. urea.	Total urea.	P. c. ur. sang.	Diet.	
July 12th .	700 ...	1·65 ...	11·55 ...	— ...	Appetite very bad.	N. 70
					Fish,	56
					Wine 3iv,	—
					Milk Oj.	126
						8½ grms.
„ 13th .	900 ...	1·65 ...	13·95.			
„ 14th .	700 ...	1·7 ...	11·9 ...	1·725.		
„ 15th .	450 ...	1·925 ...	8·66 ...	1·9.		
„ 16th .	470 ...	2· ...	9·4 ...	2·075.		
„ 17th .	500 ...	2·125 ...	10·6 ...	2·225 ...	Complete loss of appetite.	
20th .	470 ...	*1·775 ...	9·4 ...	2· ...	*From urine kept twenty- four hours longer than the urina sanguinis.	
Mean . . .	600 ...	1·83 ...	10·8.			

The mean excretion for the seven days on which observations were made were—

Total vol. of urine.		P. c. urea.		Total urea.
600	...	1·83	...	11·

The total volume is very much reduced, a reduction which was especially marked on the last four days of life.

The percentage, which on the average was about normal, rose towards the last, while the total excretion of urea was greatly diminished, the mean for the seven days being 10·8 grammes. There is to be noticed, with the rise in the percentage at last, a rise also in the total amount of urea, showing that tissue waste was more rapid just before death.

CASE 2. In the second case of Addison's disease, that of Emma T— (see Table VIII), we notice similar results.

TABLE VIII.—Emma T—. Mary Ward. Addison's disease.

Date.	Total urine.	P. c. urea.	Total urea.	Specific gravity.	Diet.	N.
May 20th .	650 ...	1·9 ...	12·35 ...	— ...	D. L.	
					Eggs ij,	150
					Chop,	20
					Brandy ʒiv.	70
						<u>240</u>
						Approx. 16 grms.
„ 26th .	850 ...	1·6 ...	13·6 ...	—		
„ 27th .	780 ...	1·6 ...	12·48.			
„ 29th .	1000 ...	1·65 ...	16·5.			
June 2nd .	600 ...	1·7 ...	10·2.			
„ 4th .	875 ...	1·15 ...	10·06.			
„ 5th .	620 ...	1·4 ...	8·68 ...	1012.		
„ 6th .	550 ...	1·85 ...	10·18.			
Mean . .	<u>740</u> ...	<u>1·6</u> ...	<u>12·</u>			
June 12th .	— ...	1·6	} Urina sanguinis.			
„ 13th .	— ...	1·7				

The averages are—

Total vol. of urine.		P. c. urea.		Total urea.
740	...	1·6	...	12·.

The volume of urine is much reduced. The urea percentage is fairly natural, and the total urea much reduced. But both the volume of the urine and the total urea are somewhat larger in this case than in the preceding one, due, doubtless, to its being hardly so late comparatively in the disease. The urine just before death was not examined. We have only two percentages taken later in life, on June 12th and 13th, and these agree fairly with those previously obtained.

In this case the slight increase in the total amount of urea is probably due to the food (for at this period of the disease there was still some appetite, though it was considerably impaired), especially since it is likely that here the tissue waste was less rapid, the illness in this case having been throughout of a less acute character than in the first case quoted and of longer duration.

The post-mortem examination in this case confirmed the diagnosis.

I have only to add that, in these, as in the other cases, the variations from day to day in the total volume of urine and in the total urea are equally evident, while the percentage remains throughout fairly constant.

The results obtained in these two cases bear out the statements in books, to the effect that the urea in Addison's disease is much diminished, but this diminution I should be inclined to refer almost entirely to the loss of appetite which is so characteristic of the disease. The rate of tissue change, so far as I am able to judge from these cases, and by comparison of these with other cases of partial abstinence from food, is not increased, but remains fully normal until the last, so that the emaciation and loss of strength would be due, not to increased tissue waste, but to diminished tissue repair.

The last case to which I wish to draw attention is one of DIABETES MELLITUS (see Table IX).

TABLE IX.—George F—, æt. 40. Mark Ward. Diabetes mellitus.

(Twelve months ago micturition frequent).

Date.	Total urine.	P. c. urea.	Total urea.	Specific gravity.	Diet.
June 26th .	2300 ...	1·475 ...	33·925 ...	1037 ...	Appetite } very bad } indeed. } Bran biscuits, Milk Oj, Greens.
	(not all)				
„ 27th .	2500 ...	1·5 ...	37·5 ...	1036.	
„ 29th .	2500 ...	1·475 ...	36·88 ...	— ...	Full diet.—
July 2nd .	3350 ...	1·35 ...	45·2.		Chop,
„ 3rd .	3350 ...	1·25 ...	41·88 ...	1032.	Bacon.
„ 4th .	3350 ...	1·4 ...	46·9.		
„ 5th .	3250 ...	1·6 ...	52·0 ...	— ...	June 30th.—Eggs iv, 24
„ 6th .	3100 ...	1·7 ...	52·7 ...	1032.	hours previously.
„ 7th .	3100 ...	1·45			
	(about)				
„ 9th .	2700 ...	1·65 ...	44·55.		
Mean .	2640 ...	1·485 ...	39·15.		

He was taken away by his friends in a dying state, and died the next day, July 11th.

The total volume of urine passed in the twenty-four hours is, we notice here, below the average for the disease. Dr. Roberts gives the total volume as varying from 8 to 15 pints (*i. e.* from 4500cc. to 8500cc.), so that here we have a very considerable reduction in the quantity of urine for the day. Variations in this total volume are to be observed similar to those noticed in the other cases.

The percentage of urea is not excessive, but gives an average such as is usual in healthy men upon a moderate diet. It is, moreover, fairly constant throughout, varying from 1·25 to 1·7, the mean being 1·485. I may state here again that the variations in the percentage do not depend upon variations in the total volume of the urine.

We come to that which is the most suggestive feature in this case, viz. the total daily excretion of urea. This is considerably above the average, varying from 33·925 to 52·7 grammes, and giving as the mean 39·15. Variations are to be observed here also in the total amounts from day to day. These variations are due to the compound variations in the percentage urea and the total volume of urine, and there-

fore depend, as do those in the total volume of urine, upon some cause which we do not at present comprehend. The broad fact, then, which we have to observe is the great increase in the total excretion of urea. To what is this increase due?

Urea, being one of the products of the decomposition of nitrogenous substances, has two sources of production—first, the peptones, or products of the digestion of albuminous food, *i. e. the circulating albumen*, and, secondly, the nitrogenous tissue, or what may be called the *fixed albumen*. The increase in the urea in diabetes, which has been a long-recognised fact, has generally been referred to the first of these sources, and connected with the ravenous appetite most diabetic patients have. But in this case it was not so. The diet upon which the patient was placed, as seen in the scale, was rich and highly nitrogenous, yet during the whole time he was under observation his appetite was very bad, and for the last few days of his life food produced so much nausea that he practically took none. We are obliged to abandon, then, this source of the excess of urea, and we are thrown at once upon the tissues as the only other possible source. That there is excessive waste of nitrogenous tissue in diabetes is shown by the extreme emaciation which takes place, and which is due to more than simple loss of fat or drainage of water from the system, by such experiments as these just quoted, and further by the researches of Liebermeister and Reich (quoted in Niemeyer, 'Med.,' vol. ii, p 775), who found that the production of urea in diabetes not only was greater than that of healthy persons moderately supplied with mixed food, but also exceeded that of a healthy man who ate as much food as this diabetic patient did. The amount of urea fluctuated in the patients from 32 to 59 grammes, and in a healthy subject from 29 to 32 grammes. The other explanations of the increased production of urea in this disease we cannot accept, viz.—1st, that it is due to increased metamorphosis of tissue, produced by transudation of water (Roberts on 'Urinary Diseases'), since no such increase is observed in polyuria, where the excretion of urea is, if any-

thing, below rather than above the normal; or 2nd, that it is due to diminished elimination by the skin, for though Liebermeister and Reich show that the proportion in diabetes may be reduced to one third its normal amount, yet, inasmuch as only one thirtieth part of the nitrogen excreted leaves the body by the skin, we have not here shown a sufficient cause to account for an increase which is at least half as much again as the normal. It is right to note, in passing, that this increase has not always been observed, for Dr. Prout ('Stomach and Renal Diseases,' ed. 5, p. 25) states that he met with certain cases in which there was a diminution instead of an increase in the amount of urea. Now, urea is not an absolute measure of the oxidation going on in the body (Voit and Bauer, 'Journ. of Chem. Soc.,' vol. xxiv, Abst.; Voit, 'N. Rep. Pharm.,' xx, 340, 349), for in certain cases of phosphorus poisoning the urea was found to be much increased, while at the same time the amount of carbonic acid evolved was 47 per cent., and that of oxygen absorbed 45 per cent., below the normal.

We may hence have increase of urea without increase of oxidation, which is consistent with other facts in diabetes which seem to point to want of oxidation as a notable feature in the disease, viz. the diminished combustion of the sugar, the commonly low temperature of the patients, and the loss of the power in diabetic patients which healthy men possess of absorbing more oxygen during the night than they need at the time, and of using it up during the day.

We are justified, then, in referring the increased production of urea in diabetes in great measure to decomposition of fixed albumen, of organised albuminous tissue. Can we refer the sugar to the same source?

We will take, to simplify matters, muscular tissue as the type of albuminous tissues. Muscles destroy sugar, as such, in the blood, convert it into glycogen (Bernard, 'Revue Scientifique,' 2me série, tome iv, p. 1022), store it up in themselves, and reconvert it as they require it into sugar. Lactic acid and glycerine are the products of decomposition of sugar (Bernard, *ut supra*, p. 1050), and to these forms

it must be reduced for combustion (Ludwig and Scène-remetjewski, Ludwig's 'Arbeiten,' 1868, p. 144). Lactic acid is a measure of sugar decomposition (Bernard, *ut supra*, 1150). Sarcolactic acid is formed by a muscle during contraction (Dubois Reymond, 'J. für Chemie,' 1859, vol. lxxvii, p. 233). Ranke ('Physiologie,' p. 628) has obtained sugar from muscle, after contraction in tetanus, both in the body and out of it.

All these experiments point to the glycogen in the muscle as the source of sugar, or of the acid it produces, so that here muscle is only an apparatus by which sugar is converted and reconverted to meet the demands of the organism.

The fact that glycogen remains in muscle, long after it has disappeared (as the result of starvation) in the liver, shows the extreme difficulty of obtaining proof of production of sugar in muscle independently of the glycogen it contains, and I have been unable to find any exact experiments of the kind to prove it. Yet there are certain experiments which render such a source of the sugar extremely probable.

1st. It is formed in diabetic patients on a pure albuminous diet, *i. e.* from peptones.

2nd. Schultzen and Riess's experiments on phosphorus poisoning lend strong confirmation (Schultzen and Riess, "Ueber Phosphorvergiftung," Separat-abdruck aus der 'Annalen der Charité,' Band x). The albuminous tissues (muscles) undergo extreme fatty degeneration. At the same time urea disappears from urine, but leucin and tyrosin take their place, and a kind of lactic acid (aldehyde of glycerine) appears in the urine (Schultzen, 'Berliner Klinische Wochenschrift,' 1872, No. 35, p. 417).

Here we have just the converse of what we want. In phosphorus poisoning albumen splits up into leucin, tyrosin, &c., and sugar, which is oxidised, and forms lactic acid.

In diabetes, albumen splits up into leucin and tyrosin, &c., which are oxidised to form urea and sugar. In one case the leucin and tyrosin, &c., are oxidised, and in the other the sugar.

This imperfect combustion in diabetes is attributed, not to want of oxygen, but to want of ferment which should prepare the sugar for oxidation.

3rd. Lastly, we have the experiments of Dr. Sydney Ringer ('Trans. Med.-Chir. Soc.,' 1860, p. 323), who found in starving animals a definite relation between the amount of urea and sugar, the proportion being 1 to 2.35, and that upon a purely flesh diet this proportion was maintained, showing that in both cases the albumen must have split up into urea on the one hand and sugar on the other.

It is not in all cases of diabetes that emaciation or loss of tissue is a marked feature. Are there any facts which suggest a possible cause for such rapid tissue waste, or hint at any possible way in which it could be produced?

i. Peptones, we know, give rise to sugar and urea (Dr. Sydney Ringer, *ut supra*).

ii. Hypertrophy of the pancreas is observed in certain cases of diabetes (Niemeyer, 'Med.,' *ut supra*).

iii. Pancreatin is an active ferment in the digestion of albumen (Hermann, 'Phys.,' p. 111).

iv. It is active (unlike pepsine) in an alkaline fluid (Hermann, 'Phys.,' p. 111).

v. Pancreatin has been found in every tissue in the body.

Hypertrophy or over-activity of the pancreas would cause increased production of pancreatin. This would be carried all over the body. Being in an alkaline fluid—the blood—it would be in a condition to act upon the albuminous tissues. These it would convert from the insoluble to the soluble form, producing peptones, which the diabetic diathesis, to whatever cause that may be due, would split up into urea and sugar. So that we might assert the emaciation and loss of tissue in diabetes to be due to a process of *self-digestion*, the products passing out of the body by the urine. This, of course, is pure hypothesis, and must be

¹ Hermann ('Physiol.,' p. 43) "Es ist der Zusammensetzung nach sehr leicht möglich dass Fette, Glycogen, Zuckerarten aus der Eiweisskörpern hervorgehen."

taken simply for what it is worth ; but it serves to bind together a certain number of facts hitherto independent in the pathology of diabetes.

Professor Haughton's authority (' Phenomena of Diabetes Mellitus,' Dublin, 1871) lends support to such a view of the splitting up of albumen.

Dr. Brunton, in his paper (' Brit. Med. Journal,' 1873 and 1874), tabulates the causes of diabetes in the following way :—Diabetes may arise, i. from increased formation, and ii. from diminished combustion of sugar. To take the last first—

From diminished combustion, due—

(a) To insufficiency of the ferment which should convert sugar into lactic acid and glycerin.

(b) To an altered quality of the sugar, which enables it to resist the action of the ferment.

(c) To diminished circulation through the muscle preventing the sugar from coming sufficiently into contact with the ferment.

From increased formation, due—

(a) To excessively rapid digestion of starch or sugar.

(b) To failure of glycogenetic function of the liver, and possibly of the muscles also.

(c) To increased transformation of glycogen into sugar, due (1) to accelerated circulation through the liver ; (2) to a larger proportion of ferment (a) in the organ, (b) in the blood.

To these I would beg permission to add a fourth—

(d) To the direct decomposition of albuminous tissue into urea on the one hand and sugar on the other.

I have now placed the Society in possession of all the cases I propose to bring before it this evening, and it remains only to consider what conclusions these cases suggest. I will first speak of the results in their general aspect, then in their relation to states of fever and convalescence, and lastly I will endeavour to indicate the direction in which the observations made seem to point.

And in the first place with reference to the relation of

the total volume of urine, the percentage of urea, and of the total urea to each other.

Water has four main channels provided for its elimination from the body—the kidneys, the skin, the lungs, and the intestines, and hence the total volume of urine will vary inversely with the compounded variations of the other three, and the activity of each and every one of these organs of elimination is subject to very considerable vicissitudes in dependence upon varying influences both internal and external. So that we should expect, *a priori*, very considerable variation to occur in the total volume of urine in different individuals, and in the same individual at different times, and this we find to be the case in the observations made, and, until we are able, which at present we are not, to define the exact part each of these organs takes in the excretion of water, we cannot fairly expect to derive any but the most general information of clinical value from consideration of the variations in the total volume of urine. (In Bright's disease, however, these variations assume a clinical importance which does not belong to them in other diseases.) To this conclusion I have drawn attention frequently in speaking of the separate cases, and I may refer for confirmation to a case of aneurism (see Table X), treated on Mr. Tufnell's plan, in which the diet was known and could be tolerably accurately estimated. This case I shall discuss in another place, and I do not propose to-night to do more than use it for reference, according as I find it convenient for illustration.

TABLE X.—Thomas S.—. Aneurism.

Date.					Total urine.
July	9th	.	.	.	450 ... ʒviij of liquid.
„	10th	.	.	.	450.
„	11th	.	.	.	475.
„	12th	.	.	.	350.
„	13th	.	.	.	600. 3x of liquid, varying from
„	14th	.	.	.	400 ... 520 cc. to 600 cc.
„	15th	.	.	.	250.
„	16th	.	.	.	550.

Date.	Total urine.
July 17th	525.
„ 20th	400.
„ 21st	500.
„ 22nd	450.
„ 23rd	475.
„ 24th	550.
„ 25th	500.
„ 26th	400.
„ 27th	300.
„ 28th	300.
„ 29th	425.
„ 30th	400 (?).
„ 31st	575.
Aug. 1st	475.
„ 4th	550.

The quantity of water ingested was constant, being eight ounces above the line and ten ounces below, and in spite of this the variations to which I have referred are very considerable. I may state in passing that these results may be accepted as trustworthy, for I took every pains to ascertain each day that the total quantity was passed.

The *total volume of urine* will, then, we are forced to conclude, give us very little information of value. From the *percentage of urea*, however, I think we can obtain more definite results. Given fairly constant conditions of disease or health, the percentage urea remains fairly constant. Any sudden alteration in these conditions causes alterations in the percentage.

In all the cases of fever I have quoted, during the fever the percentage remains high and constant. In Ellen C—'s (Table I) case the average is 3·5, with which, as I have stated, nearly all the experiments agree. So also in E—'s case (Table II), in John E—'s (Table VI), and in G—'s (Table III). With the termination of the pyrexia the percentage falls, but of this I shall speak more in detail when I reach the question of fever. Small variations of temperature, however, do not, in the cases I have quoted, seem to me to produce similar changes in the percentage. Nor does the percentage vary inversely with the volume of

urine, and this agrees with the result of physiological experiments which show that with increased volume of urine there is increased excretion of urea (Kaupp, 'Archiv. f. Phys. Heilkunde,' 1856). Nor, indeed, is the percentage dependent in any way upon the total amount of urea excreted, a conclusion which, indeed, follows from the statement above.

As instances of the effect produced upon the percentage by sudden alterations in the conditions of life, I may quote the sudden drop observed at the termination of pyrexia, and, again, the effect of alterations of diet, which produce at first a sudden rise followed immediately by one or two oscillations in the percentage, which then becomes again constant. See Ellen C—'s case on June 1st and on June 13th; James C—'s case on June 7th and June 8th; William T—'s on July 8th and 9th; John E—'s on June 24th; and Thomas S—'s case on July 9th.

Lastly, I may state that in health the percentage appears to vary fairly definitely with the specific gravity of the urine, a fact of some importance in pathological conditions to which I shall have again to refer.

I will defer what more I have to say as to the information to be derived from the consideration of the urea percentage until I discuss it in its relations to fever and convalescence.

There is one great practical difficulty which attends all quantitative examinations of the urine of the whole day, and this is its collection. It is necessary to depend so much upon the nurses and the patients that it is only in very carefully conducted observations, and at cost of considerable watchfulness on the part of the observer, that trustworthy and accurate results can be obtained. This objection applies no less to the percentage of the total urine than to the volume. If, then, it could be shown that whatever practical information can be derived from the percentage of the total urine can be equally well obtained from the percentage of a part of the urine, an immense difficulty would be overcome and future investigations much facilitated. The *urina sanguinis*, I hope to show, gives a percentage which bears so

close a relation to the percentage of the total urine of the day as to justify us in accepting this as a sufficient substitute for the latter.

In the second case of Addison's disease quoted the percentage of the total urine of eight days during the early part of the illness gave a mean of 1.6 grammes. On June 12th and 13th the percentage of the *urina sanguinis* was taken. This gave 1.6 and 1.7, the mean being 1.65, which agrees very closely with the average percentage of the previous experiments.

Again, in the first case of Addison's disease, we have these two series of percentages (see Table VII) :

		P. c. of total urine.	P. c. of <i>urina sanguinis</i> .
July 14th		1.7	... 1.725.
„ 15th		1.925	... 1.9.
„ 16th		2.	... 2.075.
„ 17th		2.125	... 2.225.
„ 18th		(?) 1.775	... 2.

Also in the cited aneurism case we have the following series of percentages (see Table XI) :

Date.	P. c. of total urine.	P. c. of <i>urina sanguinis</i> .
July 9th	. 4.7	... 4.7.
„ 10th	. 4.85	... 4.9.
„ 11th	. 4.95	... 5.1.
„ 12th	. 5.25	... 5.4.
„ 13th	. 5.	... 5.25.
„ 14th	. 5.2	... 5.18.
„ 15th	. 5.55	... 5.385.
„ 16th	. 5.25	... 5.25.
„ 17th	. 5.3	... 5.4.
„ 20th	. 5.025	... 5.1.
„ 21st	. 4.5	... 4.425.
„ 22nd	. 4.53	... 4.575.
„ 23rd	. 4.65	... 4.65.
„ 24th	. 4.35	... —
„ 25th	. 4.	... —
„ 26th	. 4.875	... 5.175.
„ 27th	. 4.4	... 4.6.
„ 28th	. 4.8	... 4.4.

Date.	P. c. of total urine.	P. c. of urina sanguinis.
July 29th	4·6	4·9.
„ 30th	4·56	—
„ 31st	4·1	4·425.
Aug. 4th	4·05	4·2.

In some instances in the last series of observations the figures in the two columns agree, while in none is this difference very marked, and throughout it is to be borne in mind that, from the extreme concentration of the urine, the height of the percentage, and the dilution required for the convenience of manipulation, the errors of experiments are here multiplied threefold. At any rate, a number of consecutive experiments which agree so closely as these do appear to prove conclusively the point upon which I am insisting. I would refer, lastly, to John E—'s case (Table VI), in which the percentages of urina sanguinis alone were taken. It will be observed, on comparing these with the percentages taken in the other cases of rheumatic fever, that we have here a similar series of percentages with similar variations produced by similar change in the condition or diet of the patient. We have the high percentage of fever, the sudden fall of convalescence, and the oscillation due to change of food.

I have some hesitation, however, at present, in stating that such a definite relation exists between the percentage of the urina sanguinis and of the total urine of the day in persons in robust health, and not just recovering from illness, for, though I think it extremely probable that even here a similar relation exists, I have not yet sufficient observations to decide the question.

The facts stated above justify the conclusion, I think, that whatever practical information can be derived from the percentage of the total urine of the twenty-four hours can equally well be derived from the percentage given by the urina sanguinis.

As regards *the total urea* excreted, if what I have said with reference to the constancy of the percentage and the indefinite variations in the total volume of urine be correct, it is evident that we cannot expect to derive very much

information from day to day from the total amount of urea, this being the product of two factors, one of which has been shown to vary indefinitely and according to no law which we are at present able to determine. As to the kind of information which we may hope to derive from the total amount of urea, I shall speak again later.

So far, then, it seems probable that it is to the percentage, and not either to the total volume of the urine or to the total excretion of urea, that we must look for the chief indications of clinical importance.

I wish now to draw attention to the results which these observations suggest as to the pathology of urea in the two conditions of fever and convalescence. I may merely state, in passing, with reference to the *total volume of the urine*, that, beyond the broad fact that in fever the volume is much reduced, and that it gradually rises to the normal as convalescence advances, we appear to be at present able to draw no other conclusion of clinical importance. The *percentage*, however, gives us a very interesting series of results, but, as I have referred to these in discussing the particular cases, I need only here briefly recapitulate what has been observed.

i. During fever the percentage is high and remains fairly constant as long as the fever lasts.

ii. During the fever it does not follow the slight variations of temperature.

iii. Nor does it depend on the volume of the urine.

iv. Changes in diet cause, during the fever, the same oscillations as they cause during convalescence.

v. With the termination of the fever the percentage falls.

vi. Convalescence may be divided into two periods.

vii. The first period is characterised by a gradual and progressive fall in the percentage, even until it is considerably below the normal.

viii. The second period is characterised by a gradual and progressive rise in the percentage, until at last a mean varying from about 1·5 to 2·0 is established, when it becomes constant.

ix. There is between this specific gravity and the percentage of urea during convalescence generally a fairly definite relation.

It remains now to consider what conclusions can be drawn from the *total amount of urea*, and as I have already dwelt upon them, I need here again only briefly sum them up.

During the fever—

i. The total amount is much reduced, and is not in large excess (as stated commonly in books).

ii. The total amount varies very considerably from day to day, independently of any law which we can determine at present.

iii. These variations are independent of the diet.

iv. And also of the temperature, hence the total urea is not a measure of fever.

v. The variations depend upon the total volume of the urine rather than upon the percentage urea.

vi. The variation was considerable in the different cases quoted.

During convalescence—

vii. The total amount is often extremely reduced.

viii. It gives an average which is different in the two periods of convalescence, but sometimes that of the first period is higher, and sometimes lower, than that of the second period. This may be accounted for, perhaps, by the different fevers from which convalescence is taking place.

	First period.	Second period.
— Pneumonia . . .	17.7	23.0.
— Rheumatism . . .	21.74	—

ix. The same variations, independent in great measure of the diet and of the percentage, and varying with the total volume of the urine, are to be noticed during convalescence or during fever.

It is commonly stated that urea is the measure of tissue change, and also that its excretion is governed by the same laws in health and in disease (Neubauer and Vogel, 'Analyse

des Harns,' p. 338). With these statements the results of the present observations seem hardly to agree, for it has been pointed out that the relation between the amount of nitrogen in the food and that estimated in the urine as urea is by no means so close as it is asserted to be in health. This conclusion is more definitely and clearly shown in the case of aneurism to which I referred before.

Again, as regards tissue change, which must necessarily be in health constant, if it be true that the excretion of urea varies directly with the amount of nitrogen in the food, it is not possible to trace here any proportion between the amount of urea excreted and the amount of tissue change which we know from other sources must be going on. But, apart from the tissue change which we know to be so much increased in fevers, we have not in these cases sufficient urea to account for the nitrogen of the food alone, a fact which of itself is sufficient to show how changed the relation of urea to its source, the tissues and the food, must be in disease. And I may refer, in confirmation, to the two cases quoted of fatal pneumonia, in which there is certainly no great excess, if any, in the amount of urea excreted, although we have in these two cases extreme nervous excitement and high fever, conditions each of which is said by itself to produce increased elimination of urea. Further, it is stated that, under similar conditions in the same person, the quantity of urine passed in the day remains fairly constant. This, again, the observations now made do not appear to support. In convalescence, however, the present results agree fairly with the statements made by Neubauer and Vogel ('Analyse des Harns,' p. 338).

In speaking of the cases of pneumonia I endeavoured to point out that the peculiar diminution in the amount of urea excreted was probably due to some interference with the process of oxidation, and I quoted Schultzen and Riess's experiments to show that albumen is normally split up into leucin and tyrosin, &c., and that these are subsequently oxidised to urea; but that, if the oxidation process was interfered with, urea disappeared from the urine, and leucin

and tyrosin, &c., took its place. The diminution of urea, therefore, from the normal amount excreted in health may perhaps give us a fair means of estimating the amount of interference which exists with the normal nutrition and oxidation of the tissues. The other explanation offered of the facts was that these products, instead of being excreted, were stored up, as such, in the body, and were subsequently, during convalescence, excreted. This explanation was supported by a case quoted by Dr. Parkes, in which he observed a critical discharge, during convalescence, of uric acid. We are justified, I think, in the absence of direct experiment, in assuming that it is by the urine that any excess of nitrogen during fever leaves the body, but that if so it must be in some other form than urea, probably leucin and tyrosin, as suggested above.

This conclusion, in the particular case of pneumonia quoted, is supported by the want of relation between the specific gravity of the urine and the amount of urea contained in it, a difference which suggests the presence of a large amount of solid apart from the urea, and which is applicable on the above assumption. The specific gravity is, of course, but the roughest guide. That which is really required is a comparison between the amount of urea and the total nitrogen of the same urine. At present we have, I believe, no definite experiments of this kind, and, important as the results obtained from the estimation of the amount of urea in urine are, yet far more accurate and important results would, I believe, be obtained from an investigation into the variations of the total nitrogen. Until we have such experiments, and are able to compare the total urea with the total nitrogen in any urine, all interpretations of the total urea excreted will, I think, be unsafe and unsatisfactory.