

THE USE OF UREA AS A DIURETIC IN ADVANCED HEART FAILURE *

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It has been known for a long time that the administration of urea in large doses produces a considerable increase in the volume of urine. Urea was, however, until comparatively recently little utilized for its diuretic properties. This was doubtless due to the prevailing idea that urea retention was the causative factor in uremia. Urea was considered a harmful substance and any measures undertaken to raise its concentration in the body were regarded with disfavor. With the advance of clinical chemistry it soon came to be recognized that although the urea in the blood is raised in uremia it is not the cause of the condition. It became established that if the function of the kidney is good urea can be given to patients for prolonged periods of time with impunity. Even in cases in which kidney disease was known to be present, large doses of urea have been given in order to estimate the functional capacity of the kidney and no untoward results have been observed. Recently, urea has been administered over prolonged periods of time in the treatment of certain cases of nephritic edema in which the blood urea was not raised and very favorable results have been reported.

Urea was first used as a diuretic by Friedrich ¹ in 1892. In this investigation he administered urea in edema due to various causes; the series included a few cases of cardiac edema. He gave from 2 to 14 gm. a day and reported very favorable results. Feilchenfeld ² conducted a similar study with similar results. He stated that the increase in urine volume was proportional to the dose. Strauss ³ gave urea in doses up to 100 gm. a day to twelve patients with cardiac edema following heart disease or arteriosclerosis, with very beneficial results. He commenced with doses of 40 gm. a day and gradually increased it as necessity demanded. In spite of the favorable results reported by the foregoing observers, urea has not come into common use as a diuretic in cardiac edema for reasons we have not been able to ascertain.

* From the Hospital of the Rockefeller Institute for Medical Research.

1. Friedrich, W.: (Ueber die harntreibende Eigenschaft des Uream) as ureum hugyhajto tulajdonsargarol. Kozlemeny u budapeste Magy. kir tud Egyetem gyogyozertani intezelebol, Magy. orv. Arch. **1**:400-415, 1892.

2. Feilchenfeld, J.: Ueber Harnstoff als Diureticum, Therap. d. Gegenw. **59**: 273, 1918.

3. Strauss, H.: Ueber Harnstoff als Diuretikum, **58**:375, 1921.

For our investigation we have selected cases of advanced cardiac decompensation which have responded only partially or not at all to the methods usually employed in the treatment of cardiac edema. The series included four cases of mitral stenosis with auricular fibrillation, two cases of mitral stenosis, one case of aortic disease with auricular fibrillation, and one case of exophthalmic goiter with auricular fibrillation.

The routine treatment of all patients included rest in bed, a salt free diet, thorough digitalization, and restriction of the fluid intake to 1,200 c.c. a day. Four of the patients had also received novasurol, and had been rendered edema free, but after the injections of this drug had been discontinued, the urine volume was subnormal and edema had gradually reappeared. Urea was given with a view to reestablishing a normal water balance by maintaining an adequate urine output, and also, when slight edema had collected, to bring about its removal. The other four patients of our series all exhibited marked edema when urea medication was instituted. These patients had not received a course of novasurol. One case of mitral stenosis with regular rhythm (Case 6) did not receive digitalis as we decided to study the effect of urea without previous digitalization.

In all cases twelve hour specimens of urine were collected, and in these, the volume, the specific gravity and the chlorid excretion were determined. Urea administration was not commenced until the urine volume and chlorid excretion had reached a constant level. In order to study in detail the changes that took place in the urine volume, urea excretion and blood urea, and their time relations, we collected a specimen of urine over a period of seventy-two minutes at frequent intervals and obtained a specimen of blood in the middle of this period. The time of making these tests was varied with relation to the administration of urea in order that its effect might be followed more closely. During these periods no food or fluid was given. The urea in the blood and urine was estimated by the method of Van Slyke and Cullen,⁴ the chlorid in the urine by a Volhard titration, and the chlorid in the plasma by the method of Van Slyke.⁵

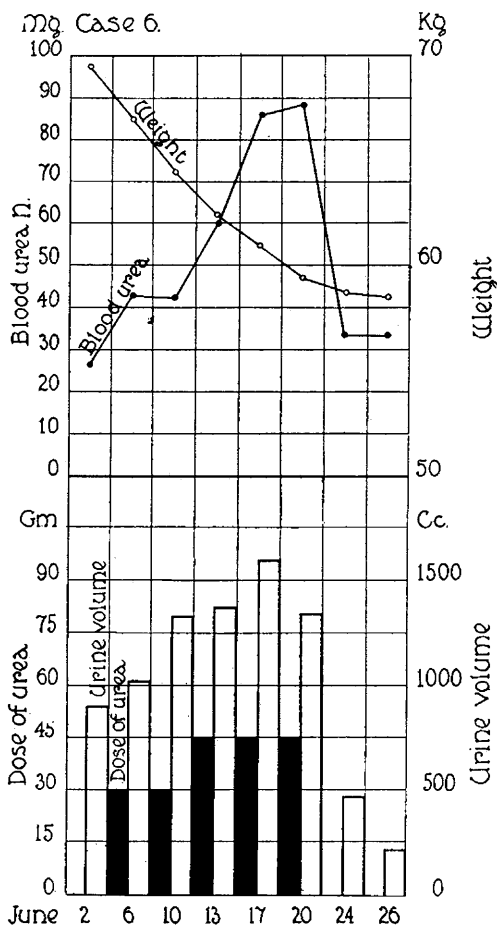
METHOD OF ADMINISTRATION

Urea was given in a small quantity of water a short time after a meal as it had been previously found that gastric disturbance was less likely to take place if it were given at this time. Urea has a peculiar metallic

4. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in the Determination of Urea, *J. Biol. Chem.* **19**:211, 1914.

5. Van Slyke, D. D.: The Determination of Chlorids in Blood and Tissues, *J. Biol. Chem.* **58**:523 (Dec.) 1923.

taste and is not pleasant to take. The patients soon become accustomed to it, however. In four of our cases we administered 30 gm. a day in divided doses of 15 gm. One dose was given at 8:30 a. m. and the other at 4 p. m. In the other four cases, we studied the effect of increasing the quantity of urea. At first 30 gm. a day was given. This



Effect of urea administration on urine volume, weight and blood urea. The patient had received one-third the daily dose of urea at 8:30 and 12:30; specimens of blood were obtained at 2 p. m.

was then increased to 45 gm. a day, and in two cases it was further increased to 60 gm. a day. In three of the cases these increases took place at weekly intervals. The urea was given in three equal doses at 8:30 a. m., 12:30 and 6 p. m.

OBSERVATIONS

Urine Volume.—The response of the cases with edema to urea feeding was prompt and, as a rule, very efficient (accompanying chart). In seven cases of the series, oliguria was present before treatment was instituted. Their average daily output during the control period varied from 340 to 776 c.c. After 30 gm. of urea a day, the average daily urine volume for each case varied, as a rule, between 900 and 1,300 c.c. When the amount was increased to 45 gm. a day, the average daily output increased to 1,400 and 1,500 c.c. A dose of 60 gm. daily was followed by a further slight increase (Tables 1, 2 and 3). The maximum response to a particular dose did not occur until the second or even the third day that the urea was given. The daily output then remained at this level as long as this particular dosage was continued. After urea administration was discontinued, a diuretic action was still distinguishable during the first twenty-four hour period thereafter.

The time relations between the dosage and the diuretic response can be still further analyzed by studying the rate of excretion during the seventy-two minute periods. From these data it may be seen (Table 2) that an increased urine volume was already established within three hours after the first dose was given. After the urea feeding had been discontinued, the duration of its diuretic action depended to some extent on the dosage. When 30 gm. a day was given, its effect had practically passed off within fifteen to seventeen hours. But with larger doses, its influence was still apparent at this time (Table 1).

Weight of Patient.—Patients with edema lost weight corresponding to the diuresis that took place. This loss of weight was gradual and continuous (chart). Patient 7, who did not have oliguria during the control period, is particularly noteworthy. In this case the diuresis was much greater than in any of the others and the weight loss much more rapid, amounting to 8 kg. in the first five days; this is to be contrasted with a loss of 1.6 kg. in the preceding control period of five days. In some cases continuance of urea feeding was necessary to prevent accumulation of edema, for when it was stopped the patient's weight tended to increase, until visible edema reappeared (Tables 1, 2 and 3).

Clinical Condition.—Corresponding to the weight loss, one noted a disappearance of edema, and of transudates from the body cavities. It was possible to clear all the patients of excess fluid in this way, with the exception of Patient 8. At the same time definite subjective improvement occurred. The most striking clinical improvement occurred in Case 7, in which rapid subjective improvement occurred simultaneously with the loss of edema. Patients 4, 5 and 6 also experienced very definite symptomatic relief which other measures had failed to give.

This relief was associated with a decrease in weight. Cases 1 and 2 were free from edema at the beginning of treatment, and there was no definite symptomatic improvement due to urea. Case 3 improved subjectively when urea medication was commenced, although edema was absent and weight loss did not occur. The value of urea in the last three cases was in maintaining a normal water balance. When the urine volume diminished consequent on the withdrawal of urea, edema tended to recur, with its concomitant symptoms. When the administration of urea was resumed, symptoms and edema were again controlled.

In Case 8, urea administration did not result in clinical improvement. This was a case of mitral stenosis with normal rhythm in which there was considerable ascites, and slight edema of the legs. The patient reacted to a slight extent to digitalis, but this effect was transitory. The dose of urea was gradually increased up to 60 gm. a day, each increase causing a definite rise in urine volume. Nevertheless, the clinical condition did not improve. After nineteen days of treatment the patient had lost 4.5 kg. in weight. The patient began to complain of nausea and on the last day of the course vomiting occurred. The blood urea nitrogen was high after the midday dose, 74.9 mg. per hundred cubic centimeters. Accordingly, urea was discontinued. The urine volume immediately fell and the general state of the patient became worse. It then became apparent that urea had been beneficial to the extent of postponing the unfavorable clinical course that subsequently developed.

Evidence of Intolerance.—When the dose was taken on an empty stomach, vomiting occasionally occurred immediately after, but this symptom gave little trouble when the urea was given after meals. In three of the cases (Cases 5, 7 and 8) the prolonged administration of urea in large doses gave rise to untoward symptoms. These manifestations consisted in loss of appetite, nausea and sometimes vomiting, and in one instance, a feeling of weakness and lassitude. In Cases 7 and 8 they were sufficiently urgent to call for the discontinuance of urea administration. In these cases the blood urea nitrogen, estimated in the afternoon after the second daily dose, was 89.0 mg. and 74.9 mg. per hundred cubic centimeters, respectively. These figures are practically identical with those found by Hewlett, Gilbert and Wickett⁶ in experiments designed to investigate the toxicity of urea. In normal subjects they found that similar symptoms occurred when the blood urea reached values above 150 mg. per hundred cubic centimeters (equivalent to 70 mg. of urea nitrogen per hundred cubic centimeters). In our cases the symptoms disappeared, as a rule, within twenty-four hours after urea

6. Hewlett, A. W.; Gilbert, Q. O., and Wickett, A. D.: The Toxic Effects of Urea on Normal Individuals, *Arch. Int. Med.* **18**:636 (Nov.) 1916.

TABLE 1.—Effect of Urea on Urine Volume and Body Weight; the Blood Urea Nitrogen from Fifteen to Seventeen Hours After Urea Was Given, with the Rate of Urea and Urine Excretion at This Time

Case	Disease	Age	Dose of Urea, Gm.	Number of Days on Which Urea Was Given	Weight at End of Period, Kg.	Average Daily Urine Volume, C.c.	Chlorid Excretion in 24 Hours as Sodium Chlorid, Gm.	Blood Urea Nitrogen per 100 C.c.	Rate of Urine Excretion per 24 Hours Calculated from 72 Minute Period, C.c.	Urea Nitrogen Rate per 24 Hours Calculated from 72 Minute Period, Gm.	Urea Excretion Index, 10 D.	Remarks
1	Aortic disease (syphilitic); auricular fibrillation	47	30	7	90.6	518	1.63	13.1	500	4.64	54.2	Before urea
			30	8	86.4	1,069	2.47
			30	8	84.3	848	1.06	14.7	560	5.70	56.0	Novasurol, 1 c.c. on second day*
			45	5	86.0	1,280	1.39
			45	10	85.2	1,544	0.77	25.8	1,460	18.90	63.2	...
			60	14	85.5	1,370	0.86	35.8	1,680	24.32	56.7	...
2	Mitral stenosis; auricular fibrillation	31	30	...	85.5	875	1.65
			30	...	85.5	1,558	0.62	37.6	1,520	23.70	55.3	...
			30	6	53.4	585	2.70	10.5	840	1.64	36.6	Before urea
3	Mitral stenosis; auricular fibrillation	37	30	4	53.8	980	3.09	15.8	720	9.34	95.2	...
			30	11	54.0	931	2.15
			30	...	54.4	743	3.96	10.6	888	5.62	76.9	...
4	Mitral stenosis; auricular fibrillation	20	30	...	53.9	965	3.15	18.8	666	9.68	84.3	...
			30	27	50.8	385	0.08	11.4	656	1.97	29.9	Before urea
			30	4	51.4	1,012	0.27	22.7	648	11.10	85.1	...
5	Exophthalmic goiter; auricular fibrillation; ascites; slight edema of the legs	46	30	6	41.1	447	1.70	14.3	400	4.10	69.2	Before urea
			30	12	38.2	863	2.37	24.7	780	4.64	34.8	Novasurol, 2 c.c. on fifth day*
			30	...	38.3	831	2.52	28.1	544	9.05	71.5	...
			30	...	38.0	573	0.90	18.6	780	9.64	84.0	...
			30	11	38.3	508	2.24	8.2	700	4.57	109.1	...
			30	...	37.2	845	2.48	Novasurol, 2 c.c. on fourth day*
			30	...	44.9	688	2.86	15.5	1,000	4.72	47.0	Before urea
			30	4	44.0	1,423	3.65	19.4	900	8.44	70.9	...
			30	9	41.8	1,199	2.69
			30	...	43.8	640	1.28
6	Exophthalmic goiter; auricular fibrillation; ascites; slight edema of the legs	46	30	5	43.1	1,413	3.42	24.3	890	5.19	35.6	...
			30	...	42.5	1,298	3.17
			30	...	42.4	964	2.12	6.6	560	2.31	31.5	...
			30	5	42.1	940	1.81
			30	22	42.7	1,339	3.89
			45	15	42.2	1,556	1.70	36.6	560	6.62	37.3	...
			42.0	1,125	0.51

* Days on which novasurol was effective are not included.

was discontinued. In Case 6, however, they persisted to a lessened extent for four days thereafter. This case had a coexistent nephritis. After urea had been discontinued on account of symptoms of intolerance, it was always possible after a short interval to resume treatment, with a smaller dose, without the production of untoward symptoms.

Most of the patients, although not all, complained of thirst while under urea medication; however, this was never severe enough to interfere with the continuation of treatment. Headache was an occasional but never a severe cause of complaint. It is not certain that any of these symptoms were entirely due to urea administration; the benefits derived from the urea were marked and in our judgment far outweighed the discomfort entailed.

CHANGES IN URINARY CONSTITUENTS

Urea.—A study of the rate of urea excretion shows that this ran parallel with the water excretion. The amount gradually increased for two or three days after treatment was begun and thereafter remained practically constant as long as the dosage remained constant, irrespective of the time it was continued. With larger doses the amount of urea excreted was increased. Cessation of treatment rapidly reduced the output of urea to its previous level. The increased excretion of urea began within from one and one-half to three hours after its administration (Table 2). Later in the day, after a second dose of urea had been given, the amount excreted was still greater (Table 3). On the following morning much less urea was excreted, the amount depending largely on the dosage. With the smaller doses, the quantity of urea in the urine seventeen hours after the last dose was only raised to a slight extent over the amount excreted before urea was given. With the larger doses, however, an increased output was still maintained at this time (Table 1).

Chlorid.—As a rule more chlorid is excreted during urea administration than during the control period. The changes in amount are slight, however, and show very little regularity.

Abnormal Urinary Changes.—We have seen no evidence of kidney irritation as shown by the presence of albumin, red blood cells or casts. When these were present before treatment was begun they became progressively reduced in amount and in almost every case disappeared.

CHANGES IN THE BLOOD

Urea.—The blood urea nitrogen was increased by taking urea. The extent of the increase varied with the dose (chart). When a certain amount of urea was given on succeeding days in divided doses, the hours of administration being the same on these days, the concentration

TABLE 2.—Effect of Urea on Urine Volume and Body Weight; the Blood Urea Nitrogen Shortly After the Morning Dose (One and a Half to Three Hours) During Time Urea Was Given Twice Daily, with the Rate of Urea and Urine Excretion at This Time

Case	Disease	Age	Dose of Urea, Gm.	Number of Days on Which Urea Was Given	Number of Days Without Urea	Weight at End of Period, Kg.	Average Daily Urine Volume, C.c.	Chlorid Excretion in 24 Hours as Sodium Chlorid, Gm.	Blood Urea Nitrogen per 100 C.c., Mg.	Rate of Urine Excretion per 24 Hours Calculated from 72 Minute Period, C.c.	Urea Nitrogen Excretion Rate per 24 Hours Calculated from 72 Minute Period, Gm.	Urea Index, 10 D	B/VW	Remarks
2	Mitral stenosis; auricular fibrillation	31	30	32	..	53.4	535	2.70	10.5	840	1.64	36.6		Before urea
			30	54.9	537	2.73	24.4	1,336	23.50	114.0		Received 15 gm. of urea 1½ hours before bleeding
			30	10	..	55.4	1,017	1.15	10.4	576	5.24	90.8		
3	Mitral stenosis; auricular fibrillation	37	30	50.8	335	2.21	25.5	1,392	23.45	106.6		
			30	2	..	51.0	940	0.08	11.4	656	1.97	29.9		Before urea
			30	23	..	52.3	1,043	0.50	25.1	1,066	16.47	89.5		Received 15 gm. of urea 3 hours before bleeding
								0.17	36.8	884	16.94	69.4		

of urea in the blood at a given time rose for a few days, until a certain height was reached. It continued at about this level however long this dosage was continued. As soon as the administration of urea was discontinued, the amount of urea nitrogen in the blood rapidly fell to its previous level. The volume of urine and urea excretion reflected the concentration of the urea in the blood. Seventeen hours after the last dose the urea in the blood was still raised—the height varying with the amount administered—but the increase was not great (Table 1). The urea given must have been rapidly absorbed for the amount of urea nitrogen in the blood increased within three hours (Table 2).

Plasma Chlorid.—The chlorid in the plasma remained practically unaltered.

INDEX OF UREA EXCRETION

A study of kidney function by the urea excretion index of Austin, Stillman and Van Slyke⁷ is of considerable interest. These authors have made a study of the changes in the rate of urea excretion with varying concentrations of urea in the blood and with varying urine volumes. They have expressed the relationships between these factors in the following equation: $K = \frac{10 D}{B \sqrt{VW}}$, in which D represents urea output (as grams per twenty-four hours), B the blood urea (as grams per liter), V the volume output (as liters per twenty-four hours), W the body weight (as kilograms), and K the excretory constant. For the normal subject K varies between 45 and 105. In kidney disease, values varying between 3 and the normal values have been observed.

With the exception of Case 1, all cases in the series fell below the minimum normal value of 45 on some occasion. In Case 6, this subnormal value was chiefly due to a chronic nephritis. In Cases 2, 3, and 6 there was a marked tendency of the index to rise as treatment was continued. This rise was coincident with a marked improvement in the clinical condition. Two cases in the series (Cases 7 and 8) showed low indexes during treatment. Case 8 showed a primary rise of the index with a subsequent fall to a still lower level. It will be recalled that this case did not improve with treatment. Case 7, however, showed a marked improvement, and finally the patient went home with compensation reestablished. The two markedly subnormal indexes found in his case are unexplained. There was no evidence of nephritis.

The general tendency of the index to rise during urea feeding does not occur in normal subjects.⁷ It would seem to reflect a general improvement in the clinical condition of the cases under urea treatment. It gives further evidence against the possibility of kidney damage due to urea.

7. Austin, J. H.; Stillman, E., and Van Slyke, D. D.: Factors Governing the Excretion Rate of Urea, *J. Biol. Chem.* **46**:607 (March) 1921.

TABLE 3.—Effect of Urea on Urine Volume and Body Weight; the Blood Urea Nitrogen One and a Half Hours After the Second Dose During Time Urea Was Being Given Thrice Daily, with the Rate of Urea and Urine Excretion at This Time

Case	Disease	Age	Dose of Urea, Gm.	Number of Days on Which Urea Was Given	Number of Days Without Urea	Weight at End of Period, Kg.	Average Daily Urine Volume, C.c.	Chlorid Excretion in 24 Hours as Sodium Chlorid, Gm.	Blood Urea Nitrogen per 100 C.c. Mg.	Rate of Urine Excretion per 24 Hours from 72 Minute Period, C.c.	Urea Excretion Rate per 24 Hours from 72 Minute Period, Gm.	Urea Excretion Index, 10 D.	B/VW	Remarks
6	Mitral stenosis; aortic disease (rheumatic); chronic nephritis; ascites; edema of the legs	47	30	69.9	776	2.30	24.1	1,080	8.14	16.4	16.4	Blood pressure 180 systolic, 90 diastolic
			30	4	..	67.1	1,129	2.30	43.2	1,700	10.57	24.7	24.7	
			30	4	..	64.7	1,042	2.39	43.2	1,480	
			45	3	..	62.4	1,453	2.47	60.9	1,900	10.30	16.0	16.0	
			45	4	..	61.0	1,416	1.77	86.6	1,720	9.16	13.0	13.0	
7	Chronic myocarditis; auricular fibrillation; edema of the legs	60	45	3	..	59.7	1,269	89.0	1,720	14.15	15.8	15.8	
			4	58.9	555	84.3	700	6.09	27.7	27.7	
			2	58.6	236	34.9	560	8.89	44.4	44.4	
			30	57.6	1,490	12.84	16.6	840	6.37	62.8	62.8	
			45	5	..	48.6	2,338	9.80	39.8	2,500	
8	Mitral stenosis; ascites; edema of the legs	47	45	3	..	48.1	1,569	3.50	53.5	2,100	14.68	37.0	37.0	
			45	4	..	47.2	1,285	1.00	60.0	1,900	10.05	17.7	17.7	
			2	47.5	796	13.5	990	6.25	58.7	58.7	
			5	48.7	980	1.06	21.0	1,500	3.82	21.6	21.6	
			55.6	844	0.71	21.4	680	6.14	48.6	48.6	Nine days after previous determination
			30	53.6	615	1.00	16.9	400	6.69	87.4	87.4	
			30	2	..	53.5	575	0.33	54.0	880	
			30	3	..	53.4	692	0.46	41.1	1,060	17.99	59.4	59.4	
			45	4	..	53.1	900	0.52	56.9	1,000	14.41	28.6	28.6	
			45	3	..	52.9	861	0.89	57.4	3,160	18.90	25.9	25.9	
			60	4	..	51.9	1,040	78.2	2,500	19.99	22.6	22.6	
			60	3	..	51.1	1,115	74.9	2,520	19.94	23.4	23.4	

COMMENT

Many of the most troublesome symptoms of cardiac decompensation are due to the accumulation of fluid in the tissues, in body cavities and in parenchymatous organs. The most important causal factor is certainly the failure of the efficiency of the myocardium, and it is to the amelioration of this that our first efforts must be directed. But frequently in the more advanced cases of heart disease, the maximum efficiency that can be obtained by treatment of the heart per se does not suffice to remove edema nor to maintain the patient free from symptoms. In the cases treated with urea a marked improvement in the clinical condition of the patient took place which could be assigned to the action of urea. The treatment succeeded in maintaining an adequate urine output and also in removing edema. As soon as the administration of urea was stopped, the urinary output immediately fell and the clinical condition became worse. When treatment was resumed an improvement again took place. We have studied some of our cases for months and have found that a particular dose will give the same daily urinary output with only slight variations throughout the period investigated. In these cases it has seemed that the maintenance of an adequate water excretion has been instrumental not only in preventing symptoms but also in avoiding a relapse. We have also prescribed its use at home by patients who have been discharged from the hospital after treatment for decompensation. Here again careful treatment of the cardiac condition is of prime importance, but it seems that urea has been of great assistance in keeping these patients comfortable through the maintenance of a normal water balance.

Urea is rapidly absorbed and an increase immediately occurs in the height of the urea in the blood. The mean level of the urea in the blood is dependent on the dosage, and the relationship between them is fairly constant in any particular case. The amount of urea excreted depends on the blood urea, so that with constant urea administration a state of equilibrium is reached between the intake and the output. During urea diuresis the excretion of water runs more or less parallel with that of urea, so that urine volume reflects the concentration of urea in the blood. Undoubtedly the explanation of the diuresis is that the excess of urea circulating in the blood is excreted by the kidney, and during the process carries with it a considerable amount of water.

CONCLUSIONS

1. Urea was given in doses of from 30 to 60 gm. a day to eight patients with advanced heart failure and was followed by a marked increase in urine volume. The drug was particularly useful in cases in which an adequate water excretion was not maintained after the

edema fluid had been removed by other measures. In some cases it relieved the edema when other remedies had failed.

2. The increase in urine output varied with the dose and followed closely the curve of urea excretion. With continuous administration the daily urine volume was maintained at an almost constant level. The response after administration was rapid, but the effect passed off in a short time unless the dose was repeated.

3. The changes in urine volume and in urea excretion were dependent on the concentration of the urea in the blood.

4. In several of the cases there was a subnormal index of urea excretion which seemed ascribable to advanced heart failure. The index tended to improve with urea administration, along with a general improvement in the clinical condition.

5. Toxic symptoms of any significance did not take place.

6. From these observations we would suggest that urea is a useful diuretic in cases of heart failure with edema in which treatment of the cardiac condition has failed to remove the edema or maintain an adequate water excretion.