disbanded, and all those residents who were not ill were sent home. Close contact was kept with them, and in no case did they or any of their home contacts develop illness. The ward in which Case 8 was working before contracting encephalomyelitis was closed from June 8 to 18 for the admission of all except urgent cases.

There was no spread to patients, although the probationers in training were visiting various hospitals in the group.

All the patients admitted to the sick bay of the Royal Free Hospital, Gray's Inn Road, were transferred to the infectious disease hospital of the group at Lawn Road as soon as the outbreak was diagnosed as acute infective encephalomyelitis, and succeeding cases were admitted directly to Lawn Road.

Every attempt was made to correlate this epidemic with the previous outbreaks in the various hospitals of the group, but no success was achieved. Such pathological examinations as were carried out showed the same negative results as in previous epidemics.

Some idea of the difficulties which arise during an outbreak of this description are typified by the fact that at the time of this small epidemic eight people working in or associated with the Royal Free Hospital were admitted or transferred to Lawn Road as suspected cases of acute infective encephalomyelitis which were not confirmed as such, the final diagnoses being as shown in the accompanying Table.

Patient	Final Diagnosis
A nurse from Royal Free Hospital	Headaches
A radiographer from Royal Free Hospital	Intercostal myalgia
A student radiographer from Royal Free Hospital	Acute exudative herpetic tonsillitis
A casualty receptionist from Royal Free Hospital	Stress syndrome
A patient in Royal Free Hospital with haemorrhage due to duodenal ulcer, and who developed ophthalmoplegia	Acute respiratory catarrh
A cardiological technician at Lawn Road Hospital	Small cerebral thrombus
A clerk at the Royal Free Hospital	Infectious mononucleosis
	Renal colic and congenital malformation of kidneys

Twelve other individuals associated with the Royal Free Hospital or seen in the out-patient department were sent home as suspected mild cases of acute infective encephalomyelitis. They were followed up. They did not develop typical symptoms of this condition nor did they convey infection to other persons.

During the course of the epidemic a patient from a suburb 10 miles north-west of London presented herself at the out-patient department of the Royal Free Hospital. She was admitted to the Fever Hospital as a typical case of acute infective encephalomyelitis with stiff neck, temperature, and paresis of the muscles of the left shoulder, without loss of reflexes or muscle wasting.

The occurrence of sporadic cases unassociated with the bulk of cases in the limited sphere of the hospital epidemic was a feature of the outbreak in the previous year and, in fact, of outbreaks described in other countries.

Summary

A small outbreak of acute infective encephalomyelitis is described in a residential training school for nurses.

Of 38 individuals resident and at risk 7 developed the disease.

In 6 cases the symptoms were mild—5 recovering within five weeks and 1 within two months.

One case was complicated by serious neurological manifestations, and recovery was delayed for three and a half months.

One nurse from the hospital group concerned was in contact with this more serious case for half an hour and

developed the disease. She showed marked neurological manifestations and was off duty for five months.

Two doctors contracted the disease. In one case the diagnosis was doubtful.

Eight cases of illness in contacts are described in which the diagnosis of acute infective encephalomyelitis was not confirmed.

There were no deaths.

It is possible that prompt administrative action localized and controlled the epidemic.

We would like to pay tribute to the physicians of the Royal Free Hospital Group, who have supplied us with most of the clinical information on which this report is based, and in particular to Dr. Ramsay, physician at Lawn Road Hospital. With his permission we saw all the cases ourselves repeatedly, and it was his kindness in helping us with the clinical details and progress of the patients that enabled us to make this report. We would also express our indebtedness to Sir Daniel Davies, senior physician of the Royal Free Hospital, for his ready help and advice. We would also like to thank Dr. Doreen Nutbourne, who was R.M.O. of the Royal Free Hospital at the time of the outbreak, for her daily co-operation.

UREA, THE FORGOTTEN DIURETIC

BY

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The introduction of mercurial diuretics marked an outstanding advance in the treatment of chronic congestive heart failure. This therapy can generally be relied upon to ease the distress of oedema and other accumulations of fluid. It is nevertheless sometimes found that after a while the diuretic effect wanes, and this development marks a critical stage in treatment. Increasing the dosage of digitalis does not then improve the urinary output; while the patient, who may have been taking the drug for years, has frequently become so sensitive to it that even small amounts cause bradycardia and coupling. Other standard methods of averting fluid accumulation may fail at the same time; thus rigid sodium restriction may worsen the general condition through electrolytic imbalance and the blood urea may steadily rise. Aspiration and acupuncture may bring temporary relief but do not arrest the downhill course. Nor do the newer diuretics solve the problem, since their efficacy is generally inferior to that of mercurial diuretics. These considerations prompted us to reassess, in a systematic trial, the value of urea, the only effective diuretic of the pre-mercurial days, now fallen into disuse.

Friedrich (1892) was the first to use urea for oedema due to various causes; with doses of 3–14 g. he reported favourable results. These were confirmed by Strauss (1896, 1921), and Feilchenfeld (1919). Volhard (1918) used even larger doses (40–60 g. a day) with good success in nephrotic oedema. Crawford and McIntosh (1925) gave the first detailed account of its use in eight cases of congestive heart failure. They were able to double the urinary output with a daily dose of 45 g. Prolonged administration gave rise to anorexia, vomiting,

and lassitude; after stopping the drug for a few days it could be resumed in small doses. They found an increase of urea excretion proportionate to the administered dose, and some increase of chloride excretion. The blood urea rose initially to 60–90 mg. per 100 ml. within a few days; then it remained at this level during the period of administration and fell quickly to normal when urea was discontinued.

Miller and Feldman (1932) reported five patients with cardiac dropsy who were treated with urea intermittently for 1½–3 years and in whom water retention could be prevented by combining this treatment with mersalyl. No signs of renal damage were seen on post-mortem examination. Marvin (1940) believed that the unpleasant taste was practically the only disadvantage of urea. He found it extremely valuable as a diuretic, emphasized its constant effect, and thought it deserved a more important place in therapy. Winternitz (1940) was able to reduce the frequency of mercurial injections or omit these in three cases of congestive heart failure, giving urea at the same time. He preferred one daily dose of 20–40 g. to more frequent smaller amounts. White (1951) thought that urea was worthy of trial when mercurial therapy was found inadequate. Friedberg (1956) and Gross and Jezer (1956) held similar opinions. Current editions of standard British textbooks either make little reference to the use of urea as a diuretic (Dunlop, Davidson, and McNee, 1953), or do not mention it at all (Wood, 1956; Davidson, 1956; Garland and Phillips, 1953), or regard it as not indicated in congestive heart failure (*Price's Textbook*, 1956).

The main objections to the use of urea have been that it is unpalatable and that it may cause vomiting and gastro-intestinal irritation. Fishberg (1940) believed the congested gastric mucosa to be particularly sensitive to the irritant action of urea, and fluid restriction was difficult to enforce since urea increased thirst. It was said that sooner or later all patients became intolerant to it (Goldring, 1929). Further criticism concerned the diuresis produced by urea. Keith and Whelan (1926) maintained that urea leaves sodium chloride in the tissues, removing only water, and is therefore a poor substitute for mercurial diuretics, which remove both water and sodium. Crozier and Mayrs (1940) thought that owing to its high diffusibility the concentration of urea in oedema fluid soon attained the concentration in the blood, and its diuretic power, based on osmosis, thus became exhausted. Vogl (1953) admitted success in some cases, but felt that the treatment was not dependable on account of the high incidence of nausea and vomiting.

The purpose of our investigation was to find out whether a positive water balance could be restored with urea alone; whether combined treatment with mercurial diuretics enhanced the effect of the latter by increasing urinary output on the day of injection by diminishing the "rebound" the day following injection; whether the diuresis produced by urea is different from that produced by mercurial diuretics; and, finally, if life can be prolonged and made more comfortable for these gravely ill patients.

Material and Method

Our series comprised 17 patients with obstinate and prolonged right ventricular failure in whom anasarca and ascites were the main features and in whom mercurial diuretics had become ineffective in clearing oedema and effusions. Fourteen patients had valvular heart disease, and these had been

in chronic congestive heart failure with auricular fibrillation for years. Ascites often persisted after the oedema cleared; this and the hard and enlarged liver suggested cardiac hepatic cirrhosis. Six of them underwent mitral valvotomy. The operation, which was done as a last resort, was ultimately unsuccessful in all; a second valvotomy in one, however, has produced a good immediate result. In the remaining eight the preponderant lesion was mitral or aortic incompetence, which precluded operation. All had functional tricuspid incompetence. Detailed in-patient data were available in 11 out of these 14; the remaining 3 were treated as out-patients. Two patients had coronary heart disease and developed congestive heart failure immediately after cardiac infarction. Failure persisted for three and six months respectively before the beginning of urea treatment. Hospital admission was possible in one only. One patient had hypertensive heart failure and bronchial carcinoma.

After admission the patients were kept for 10 to 14 days on the usual treatment, consisting of digitalis, mercurial diuretics preceded by ammonium chloride, and sodium restricted regime with fluid intake limited to 30–40 oz. (850–1,130 ml.). Blood electrolytes, blood urea, and urinary chlorides were estimated and effusions aspirated when necessary. The fluid intake and output were charted and the average fluid balance was calculated from a total of at least seven days without and separately from a total of 4 days with mercurial injections—mersalyl, "unephral" ("neptal"), or mercaptomerin ("thiomerin"). If the blood urea was normal 15 g. of urea was then given three times a day after meals, dissolved in 2 oz. (57 ml.) of water (25% solution) or grapefruit juice. This dose had to be reduced occasionally, but with one exception no patient received less than 30 g. a day. The laboratory tests were repeated during treatment, while the basic regime was continued. The same calculation of the average fluid balance was then repeated and compared with the one before urea was started.

We were surprised to find how easily most of our patients took urea. Those who objected to its taste in watery solution were able to take it in grapefruit juice. Anorexia and vomiting occurred in some, mostly when the patient deteriorated; it necessitated withdrawal of the treatment for a few days, and if a second attempt with a smaller dose was unsuccessful treatment was abandoned. There was thus no difficulty in carrying on with the treatment in most of our cases.

Except for two patients, treatment was maintained over periods ranging from 2½ weeks to 7 years (Tables I and II). Cases 6, 7, 10, 11, 12, and 13 were treated from 2½ to 4 weeks; Cases 3, 8, and 16 from 3 to 5 months; Cases 1, 4, 9, and 14 from 6 to 9 months; Case 17 for 1½ years; and Case 2 for 7 years.

Results

Treatment was regarded as successful when a patient who was a bedridden cardiac invalid before urea treatment was able to return to a sedentary occupation or to light housework and could be kept reasonably free of oedema and effusions on treatment by urea coupled with mercurial diuretics. These criteria were fulfilled in three instances: Case 2, who had congestive heart failure following bacterial endocarditis and who has been taking urea for seven years intermittently; Case 17, with congestive heart failure after extensive cardiac infarctions, who took urea for one and a half years and who died suddenly six years later of a further cardiac infarction; Case 14, with trivalvular heart disease, who has been taking urea now for six months.

Temporary improvement was achieved in 11 cases; this consisted in increased diuresis and clearance of oedema and effusions while under hospital treatment. But these patients, when seen subsequently as out-patients, continued to retain fluid. When readmitted and kept under strict control their diuresis improved; but as time went on urea became ineffective, and in the end had to be abandoned on account of nausea and vomiting. Ten of these had valvular heart disease, six of them dying within weeks or months after urea

became ineffective. The only patient who improved was No. 8, who underwent a second valvotomy. The last patient in this group (Case 13) had congestive heart failure following two cardiac infarctions; urea established a positive water balance when mersalyl failed. Treatment was stopped on account of high blood urea. This patient died two and a half weeks later.

Treatment failed in three. One of these (Case 12) had hypertensive failure; the second (Case 15), with valvular

heart disease, refused to take urea after one week; the third (Case 5), also with valvular heart disease, improved during six days of treatment in hospital, but died at home of pulmonary oedema before she could be reassessed.

The detailed results are summarized in Table I. Except for Case 11, all were in negative fluid balance before treatment by urea, the average daily fluid retention varying from 60 to 720 ml. In eight the fluid balance became positive on urea alone (Figs. 2, 3, and 4). In the cases in which it

TABLE I.—Urea Treatment of 13 In-patients in Obsolete Heart Failure

Case No.	Diagnosis	Age and Sex	Duration of C.H.F. Before Urea (Months)	Av. Fluid Balance Before Urea (ml.)	Av. Fluid Balance with Urea (ml.)	Av. Fluid Balance Hg Diur. Before Urea (ml.)	Av. Fluid Balance Hg Diur. with Urea (ml.)	Rebound After Hg Diur. (Before Urea)	Rebound After Hg Diur. (With Urea)	Daily Dose of Urea (g.)	Duration of Treatment	Comment	Result
1	M.I.-M.S.-T.I.-A.F.; C.H.C.	45 F	14	-280	-120 (15 g.) +190 (30 g.)	+450	+540 (15 g.) +1,290 (30 g.)	++	+	15-30	6/12 intermittently	Effect wore off during successive admissions. Treatment stopped on account of vomiting. Died 6/12 later	Temporary improvement
2 (Fig. 1)	M.I.-M.S.-T.I.-A.F.; C.H.F. (after S.B.E.). Gross ascites	50 M	14	-540	-15	+260	+2,800 (intra-perit.)	+++	None	30	7½ years intermit.	Gross ascites and anasarca on admission. Astonishing recovery in 3 weeks. Still active sedentary life. No further paracentesis required	Success
3	M.S.-M.I. (post-op.) A.F. T.I. Unsuccessful valvotomy	48 M	18	-60	-30	+168	+2,000	++	..	45	3 mths	In gross failure 2/12 after stopped urea. Further treatment ineffective. Probably dead	Temporary improvement
4 (Fig. 2)	M.S.-M.I.-A.S. (sl.). A.F. Unsuccessful valv.; C.H.F. 8 T.I. 3/12 later. C.H.C.	37 F	12 bef. op. 3 after op.	-390	+880 (45 g.) +110 (30 g.)	+250	+1,190	+++	..	45-30	9 ..	Restored to light housework. No fluid retention with urea and twice-weekly inj. Relapse after 9 months' treatment	..
5	A.S.-A.I.-M.S.-A.F. C.H.F. during preg. and following delivery	23 F	9	-615	-285	No effect	-	+++	-	45	6 days	Continued treatment at home; died 3 weeks later in pulmonary oedema	Failure
6	M.S.-M.I.-T.I.-A.F. Unsuccessful valvotomy. C.H.C.	22 F	30	-720	-510	+990	+1,230	++	+	20	20 ..	Renal involvement; reduced dosage. Died 4 weeks later	Temporary improvement
7 (Fig. 3)	M.S.-M.I.-T.I.-A.F. Unsuccessful valvotomy	42 F	32	-285	+360	+1,110	+1,050	+++	None	45	30 ..	Well at end of urea treatment. Relapse 2 months later. Urea stopped on account of vomiting	..
8	M.S.-M.I.-A.I. (sl.). T.I.-C.H.F.; after valvotomy C.H.C.	40 F	12	-510	+45	No effect	No immediate effect	+++	Good output for 3 days after inj.	30-45	4½ mths (1/12 intermission)	Result waning during successive admissions. 2nd valvotomy Sept., 1956, & good immediate result	..
9	M.S.-M.I.-A.I. C.H.C.	42 F	14	-240	+50 (1st adm.) +195 (2nd adm.)	+1,200	+1,680 (1st adm.) +1,460 (2nd adm.)	++	None	30-45	6 mths	Good result for 4/12. Effect waning during successive admissions. Died 1 year later	..
10	M.I.-M.S.-T.I.-A.F.-C.H.C. Unsuccessful valvotomy 4 years ago	36 F	5 yrs.	-660	+175	+360	+930	+++	No	45	3 weeks	Excellent result as I.P.; under obs. continues treatment as O.P.	..
11	A.I. Bronchial Ca. C.H.F.	60 M	6	+70	+135	One inj. +2,100 2 inj. no effect	No inj. needed	++	No inj.	45	14 days	Effect of Hg diuretic unpredictable. Even diuresis with urea; no inj. needed. On pos. balance before urea. No follow-up	..
12	H.H.D. C.H.F. C.H.C.	60 M	Year	-225	-210	+1,050	+660	++	++	45	3 weeks	Urea ineffective. Died 1½ years later	Failure
13 (Fig. 4)	C.H.F. after cardiac infarct	50 M	3 mths	-165	+360	+120	+570	++	No	45	2½ ..	Excellent result in critically ill patient. Urea stopped on account of B.U. 128 mg./100 ml. Died 2 weeks later	Temporary improvement

A.F.=auricular fibrillation. A.I.=aortic incompetence. M.I.=mitral incompetence. T.I.=tricuspid incompetence. H.H.D.=hypertensive heart disease. M.S.=mitral stenosis. C.H.F.=congestive heart failure. C.H.C.=cardiac-hepatic cirrhosis. A.S.=aortic stenosis. S.B.E.=subacute bacterial endocarditis.

TABLE II.—Urea Treatment in Four Out-patients in Obstinate Heart Failure

Case No.	Diagnosis	Age and Sex	Duration of Failure	Short History	Daily Dose (g.)	Duration of Treatment	Comment	Result
14	M.S.—A.I. A.S.—T.I. and T.S. A.F. C.H.C.	42 F	7 years on and off	Frequent previous admissions for C.H.F. and gross ascites. Urea started March, 1956. Within 3 weeks lost 6 lb. (2.7 kg.) in wt. and 2 in. (5 cm.) in abd. girth. Approx. daily output doubled—mercaptomerin inj. reduced from two to one a week	45	8 months	Well. Doing light housework. Under observation	Success
15	M.S. and A.I. —T.I.	48 F	1 year	Severe congestive heart failure. Greatly disabled	45	1 week	Urea made her thirsty; became worse—stopped treatment	Failure
16	M.I. and T.I.	51 F	1½ years on and off	Not severely disabled. Needs Hg inj. twice weekly; attempts to omit these failed previously	45	3 months	Much improved; no Hg inj. required since on urea. Under observation	Temporary improvement
17	C.H.F. after cardiac inf. C.H.F. C.H.C.	42 M	3 months	Extensive ant. infarct April, 1947, followed by extensive post. inf. Feb., 1948. 4 months later severe C.H.F.; gross fluid retention in spite of Hg inj. 3 a week. Urea started June, 1948; positive fluid balance restored. Left for abroad, July, 1948. Subtotal thyroidectomy, Nov., 1948. Feb., 1949, T.I., ascites, large liver. Urea resumed. Ascites and oedema disappeared within 1½ months. Urea stopped. Ascites again in May, 1949. From May to Nov., 1949, urea intermittently. From then onwards sl. C.H.F. successfully treated with digitalis and occasional Hg inj.	20-40	1½ yrs.	Sodium restriction could never be enforced. In spite of this, dehydration with urea successful. From 1950-5 fully active in sedentary occupation. From 1952 onwards no Hg inj. needed. Well compensated on digitalis and thyroid. Sudden death May, 1955, of further cardiac infarct	Success

remained negative, retention became less, and, while the output after mercurial injections rose considerably during urea administrations (Fig. 1), mercurials were largely ineffective before treatment with urea (Cases 2, 4, 5, 8, and 10). In Case 4 mercurial injections were not required because of the spectacular output on urea alone (Fig. 2). In Case 8 a greater output was obtained for three successive days after

such injection while the patient was taking urea, without the usual great diuresis on the day of injection. In Case 11, the only patient with positive water balance before urea, the average excess output during urea increased from 70 to 135 ml., and he did not need further mercurial injections, which had previously been uncertain in effect. The result obtained with urea was proportionate to the dose: in Case 6, with renal involvement, only one-third of the usual dose was given; she retained less, but still remained in negative balance. Case 1, unable to take the full dose, retained fluid when on 15 g. a day; raising the dose to 25 g. a day produced an excess average daily output of 195 ml. with a correspondingly greater output on injection days. When urea was stopped water retention immediately recurred (Fig. 2). Resumption of urea in smaller amounts resulted in a smaller

FIG. 1.—Case 2 (Table I). Urea in reduced dosage greatly enhances effect of mercurial diuretic, abolishes rebound after injection, but does not suppress entirely the negative fluid balance. N=neptal, 2 ml.; i.p.=intraperitoneally; P=paracentesis, 5 l. litres.

FIG. 2.—Case 4 (Table I). Urea in average doses suppresses fluid retention; no mercurial injections required. Stoppage of treatment results in fluid retention. Resumption of urea with smaller doses restores positive fluid balance, enhances effect of mercurial injections, and suppresses gross rebound present before treatment with urea. T=thiomerin, 2 ml. i.m.

output, though it still potentiated the effect of mercurial diuretics. As fluid retention became less, the effect of mercurial diuretics also diminished (Fig. 3). Rebound after mercurial injections was abolished in six patients (see Figs. 1, 2, and 3).

FIG. 3.—Case 7 (Table I). Urea in average doses restores positive fluid balance; only one further mercurial injection required. M = mersalyl, 2 ml. i.m.

Laboratory Data

Diuresis with urea is due to a rise in blood urea after its ingestion. The excess of urea circulating in the blood leads to the filtration of larger amounts of urea from the glomeruli. The rising concentration of urea increases the osmotic pressure in the renal tubules, hindering reabsorption of water. "Urea thus retains water in the tubules for its own elimination" (Wright, 1952). Patients on urea all have a raised blood urea, and the level depends on the amount ingested. In Case 9 the blood urea rose from 26 mg. per 100 ml. to 86 mg. during the administration of 45 g. of urea; Case 1 had a blood urea of 58–67 per 100 ml. while on 30 g., of 42 mg. while on 20 g., and of 26 mg. when on 15 g. a day. In Cases 4 and 14 the blood urea estimated three hours

after the first daily dose was 49 and 42 mg. per 100 ml. respectively. The rise of blood urea purposefully produced has a significance different from that caused by chronic renal disease, in which it is a sign of the inability of the kidneys to eliminate toxic waste products. The urea retention was well tolerated by our patients; vomiting was looked upon as a sign of intolerance of the congested gastric mucosa to absorb urea, and in these cases the blood urea was normal. In chronic renal disease, however, vomiting is a sign of toxæmia, and the blood urea is high.

The diuresis with urea has been thought to be less valuable than that produced by mercurial diuretics, on the ground that only water is eliminated, sodium being left in the body. The daily urinary chloride estimation in Case 7, with a normal blood chemistry, refuted this (Table III). The

FIG. 4.—Case 13 (Table I). Spectacular diuresis on urea alone after mercurial injections became ineffective. M = mersalyl, 2 ml. i.m.

TABLE III.—Chloride Excretion on Urea Alone and After Mersalyl in Case 7

Date	Urinary Chlorides (mEq/l.)	Urinary Output (ml.)	Daily Urinary Chlorides (g.)
26/7/56	51.7	1,200	3.6
27/7/56	34.5	960	1.9
28/7/56	34.5	2,700	5.4 (M)*
29/7/56	69.0	1,140	4.5
30/7/56	51.7	1,740	5.2
2/8/56	77.6	1,200	5.4
3/8/56	17.0	1,680	1.7

*(M) = 2 ml. of mersalyl injection.

chloride output in this patient was low because she was, as all our patients were, on a sodium-restricted regime. The relative chloride content in the urine after mersalyl was only one-half or less (34.5 mEq/l.) of that she had on some days while on urea alone (77.6 mEq/l.). Owing to the greater urinary output, however, the absolute amount of chloride excreted on the mersalyl day was equal to that excreted on urea days, when output was smaller.

Discussion

Our series was highly selective in that it comprised only patients with a consistently bad prognosis. To see bed-ridden patients with advanced heart failure and anasarca following bacterial endocarditis, extensive cardiac infarction, or trivalvular heart disease restored to gainful occupation, or to light housework in the cases of women, was remarkable or at least unexpected. Clearly, it was not urea alone which was responsible for this success: digitalis, mercurial diuretics, and sodium restriction all played their part. However, these measures were unsuccessful by themselves; the diuresis produced by urea, the potentiation of the effect of mercurial diuretics, and the abolition of rebound after mercurial injections were the decisive factors which produced the improvement. In Case 17, suffering from heart failure after cardiac infarction, subtotal thyroidectomy was performed, but this would not have been possible except for the diuresis produced by urea at a decisive moment when the patient was waterlogged and when mercurial diuretics had become ineffective. When oedema and ascites reappeared after operation, urea again restored the normal water balance. In Case 2 intraperitoneal unephral injections, during the administration of urea, produced an exceptional diuresis. The same combined treatment was effective in Case 9, but in her the intraperitoneal mercurial was ineffective without the aid of urea administration.

After these striking results it was disappointing to find patients failing to respond to a second or third course of urea. Failure to produce diuresis by urea coincided with a rapid downhill course, and, with two exceptions, all these patients died within one year, many within weeks. If cardiac strength wanes osmotic diuresis is bound to fail, since glomerular filtration becomes deficient. When this stage will be reached cannot be foretold; our findings show that even in the apparently hopeless case a good diuretic response may disclose unexpected cardiac reserves. Whether or not it prolongs life may be questionable, but the clearance of oedema certainly makes life more bearable.

Treatment with urea is far from being pleasant. This substance is unpalatable, but that drawback may be overcome by various devices. Grapefruit juice seems to be the best means of masking the unpleasant taste, though we have not tried giving it in beer or in raw tomato juice as advised by Miller and Feldman. Tolerance remains individual: many of our patients who were able to take urea for months and years did not object to the taste; others refused a second course on account of its unpalatability. Real intolerance was seen in the severely ill who vomited the mixture they had been able to tolerate earlier for weeks and months. While taking urea most patients complained of increased thirst, and on the average they drank about 300 ml. more daily, but only one stopped treatment on account of this. Urea has a sedative action and may produce tiredness; but this was

not a prominent complaint in our series, nor was diarrhoea. The dose may have to be adjusted to the need of the patient; the average dose was 45 g. daily. Less than 30 g. may not by itself be enough to increase diuresis, but it may be enough to potentiate the effect of mercurial diuretics and to abolish water retention the day after injection.

Summary

A new assessment of the diuretic properties of urea has been made. When integrated in action with mercurial diuretics urea has a special place in the therapeutics of chronic heart failure with oedema.

A group of 17 patients, all suffering from obstinate and prolonged right ventricular failure, has been studied. Fourteen had chronic rheumatic valvular heart disease, and some of these had developed cardiac hepatic cirrhosis with ascites; six underwent mitral valvotomy. Of the remaining three patients, heart disease in two was of coronary origin, and in the remaining one hypertensive.

Urea was administered in doses of 15 g. dissolved in 2 oz. (57 ml.) of water or grapefruit juice thrice daily. Treatment was maintained over periods ranging from two and a half weeks to seven years.

This treatment was found to be advantageous. In about half the patients a negative fluid balance was changed to positive on urea alone. In cases in which it remained negative, fluid retention became less. Urea was found to produce such effects even after mercurial diuretics had become useless. In several patients mercurial diuretics were greatly augmented in their effect when urea was given concurrently.

At worst, urea administration is never harmful, but it may have to be discontinued on account of distaste on the part of the patient or because of nausea and vomiting. At best it may be the means of maintaining in a quiet occupation for several years a patient with grave valvular heart disease in whom this result is unattainable by any other medicaments singly or in combination. Between these extremes are the patients in chronic congestive failure who may receive many months of benefit, at first by prolongation of quiet activity free from oedema, and latterly by mitigation or abolition of distressing oedema and effusions until the last days of the illness.

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ESSENTIAL HYPERLIPAEMIA AND IDIOPATHIC HYPERCHOLESTEROLAEMIC XANTHOMATOSIS

BY

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The purpose of this article is twofold. First, to examine the difference between essential hyperlipaemia and idiopathic hypercholesterolaemic xanthomatosis. Hitherto these conditions have been differentiated solely by the presence or absence of an increase in plasma neutral fat (hyperlipaemia) (Lever *et al.*, 1954; Malmros *et al.*, 1954). Secondly, to examine the significance of the hyperlipaemia when it does occur.

Essential Hyperlipaemia

Essential hyperlipaemia has been defined as a condition in which a primary increase in plasma neutral fat, sufficient to cause turbidity, occurs, usually associated with an increase in the blood cholesterol. It is familial in about a sixth of the cases—hepatosplenomegaly, recurrent upper abdominal pain, and skin lesions occurring, though not necessarily together, in about one-half. The upper abdominal pain is thought to be due to pancreatitis resulting from the hyperlipaemia (Klatskin and Gordon, 1952). Hyperglycaemia, which can be controlled by a low-fat diet, has also been described (Thannhauser, 1950). Approximately a third of the cases occur in children under the age of 10. None of the symptoms or signs depend on any particular critical level of plasma lipids.

Of the 41 cases reported prior to 1954, 19 had cutaneous lesions (11 adults and 8 children). In adults the lesions are remarkably constant in their morphology and are known as eruptive xanthomata (Wijnhausen, 1921; Marcus, 1937; Bloomfield and Shenson, 1947; Thannhauser, 1950; Frank and Levitt, 1951; Hand, 1951; Fulton, 1952; Gadrat *et al.*, 1952; Klatskin and Gordon, 1952). They occur suddenly, in crops, and vary in intensity, sometimes even clearing completely for short periods. The individual lesion is a yellow dome-shaped papule, 1 to 5 mm. in diameter, frequently surrounded by a bright-red halo. Itching may occur when the lesions are erupting and occasionally they are acutely tender. They vary in number from a dozen to thousands and may be grouped or scattered. The commonest sites are the knees, elbows, thighs, and buttocks, but any area of the skin may be affected. They disappear when the patient is placed on a low-fat diet, but recur when the diet is discontinued.

In children the cutaneous lesions may be the same as in adults (Burger and Grutz, 1932; Abegg, 1937; Bernstein *et al.*, 1939; Goodman *et al.*, 1940), but pin-head vesicles, from which a milky fluid can be expressed, have also been described (Holt *et al.*, 1939; Bruton and Kanter, 1951). In one infant aged 17 months transitory orange papules appeared (Crocker, 1951). The lesions were not described in Collett and Kennedy's (1948) case.

The following two cases are typical examples of the condition in adults.

Case 1

A man now aged 46 noticed in 1950 an extremely tender eruption on his elbows, trunk, and feet. He had no other