circumstances—in particular an intelligent patient and a very alert practitioner—led to reference of the case at a much earlier stage in the development of the disease than is usual. Although clinical deterioration until treatment was instituted was rapidly progressive, it is clearly impossible to claim with any certainty that the apparent response was more than coincidental. Nevertheless the relapse associated with objective evidence of physiologically inadequate dosage, and the resumption of improvement when dosage was increased, as well as the remarkably complete recovery which was evident within a matter of days, render coincidence a not entirely satisfying explanation: that resolution of the condition was related to the administration of A.C.T.H. would appear to be a distinct possibility.

Acute disseminated encephalomyelitis is a rare disease, and, although it is fully appreciated that no firm conclusions can be drawn from the present small series of treated cases, they are reported in the belief that the results are suggestive enough to merit similar trial on a larger scale. In the absence of any other effective or rational therapy such a trial would appear justifiable, though a word of caution is advisable. Diagnosis of acute encephalomyelitis following exanthemata is usually simple, but the "spontaneous" examples, and those following non-specific infections, may present difficult diagnostic problems. Administration of A.C.T.H. to cases of virus disease such as poliomyelitis is at best useless, and recent evidence suggests that it may be actively harmful. In bacterial infections such as cerebral abscess or tuberculous meningitis its use might well be disastrous. For these reasons, and also in order not to confuse assessment of the value of the drug in the disease under consideration, the employment of this experimental therapy should be limited to cases of acute neurological illness in which an unequivocal diagnosis of encephalomyelitis can be competently sustained. The present paper shows that in such cases the drug is harmless if nothing more.

Summary

Seven cases clinically diagnosed as acute disseminated encephalomyelitis have been treated with A.C.T.H. They comprise two cases of encephalomyelitis following varicella, two cases of transverse and one case of subacute ascending myelitis, and two (familial) cases of encephalitic illness following non-specific infection, in one of which there have been recurrent encephalitic illnesses. Acute disseminated encephalomyelitis has a pronounced tendency to rapid, spontaneous, and often complete recovery, and no final conclusions regarding the efficacy or otherwise of A.C.T.H. can be reached without extended observations on a scale which would permit of statistical evaluation. It is believed that the results reported here are suggestive enough to justify further trial.

I wish to thank practitioners and consultants in Region No. 1 who have been kind enough to refer cases for treatment, Dr. G. A. Smart for help and advice on technical aspects of the use of A.C.T.H., and Dr. M. J. Evans for his clinical assistance.

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ANURIA TREATED BY CORTISONE*

BY

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The present trend in the treatment of anuria is in favour of a conservative policy using a balanced fluid and electrolyte intake with a low-protein diet in the hope of a spontaneous remission (Bull *et al.*, 1949). In cases in which gross oedema or some electrolyte imbalance has already occurred active measures to substitute for the kidney must be used.

Methods of treatment based on the primary aetiology, such as decortication, nerve block (surgical or pharmacological), alkalization of the urine, etc., are not often successful. This relative failure may be due to the presence of other unsuspected aetiological mechanisms. The possibility that an acute allergic reaction in the kidneys is a causal factor in some cases is considered in this communication. To test this hypothesis we have tried the effect of cortisone in a miscellaneous group of four cases of anuria. The cortisone used was cortisone acetate ("cortone"), and was given by intramuscular injection, except where oral administration was specified.

Case 1

A man aged 33 was admitted to the Mater Misericordiae Hospital on October 27, 1950, suffering from rheumatoid arthritis, grade II, of ten years' standing. The previous history was irrelevant. There were four areas of alopecia areata on the scalp. His general physical examination was otherwise normal, but the urine contained a very faint trace of albumin, a few squamous cells, and a very rare leucocyte. The electrocardiogram was normal; the blood pressure was 140/80; and the E.S.R. 45 mm. (1 hour). Seven days after admission he was started on cortisone treatment. By November 30 the arthritis had improved by 80%, and cortisone was discontinued on November 26.

By December 1 a relapse of the arthritis was evident and cortisone treatment was resumed: 100 mg. a day orally, in three doses, was given, and because of a favourable response it was reduced to 50 mg. on December 5. As, however, a considerable amount of fluid had developed in the left knee, the dose was increased to 100 mg. a day by mouth on December 13. On December 15 the patient returned home on this dosage, and on the 24th he developed acute pharyngitis with pyrexia of 101° F. (38.3° C.), and was treated with penicillin. Some hours later there was a transient erythematous rash on the trunk. On December 25, contrary to instructions, he ceased taking cortisone; next

*Fourth report of the Cortisone Clinical Subcommittee (Professor Henry Moore, Professor W. J. E. Jessop, and Professor D. K. O'Donovan) to the Medical Research Council of Ireland. The material embodied in this report was part of a series of lectures delivered by one of us (H.M.) at the Mayo Clinic, the University of Minnesota, and the University of Chicago (June, 1952).

day he had almost complete anuria, passing only about 1 oz. (28 ml.) of urine during 24 hours. He was readmitted to hospital on December 26 by Dr. Jacob Robinson.

From time of readmission to December 27 inclusive he passed no urine, his temperature was about normal, but his pulse rate varied from about 100 to 120 a minute, and the respiratory rate from 38 to 50; he had a moderate amount of general oedema, which increased daily. On December 28, 15 ml. of urine was obtained by catheter; it was acid in reaction, contained +1 albumin, a few epithelial cells, a rare leucocyte, and a very rare erythrocyte, but no casts or bacteria. On the same day his blood urea was 210 mg. per 100 ml. Some fine crepitations were heard over both pulmonary bases, and an x-ray film of the lungs (portable apparatus) seemed to show a small area of consolidation at the base of the right lung, with a small pleural effusion at the left costophrenic angle. His blood pressure was 142/90 and varied little from this figure throughout the whole period of observation. Because of nausea he took nothing by mouth except a little fluid.

As the patient was seriously ill, in addition to the usual therapeutic measures peritoneal lavage by drip with alternating normal saline, Hartmann's solution, and glucose-saline

On January 4 the urea clearance figure was 45. On January 8 the urine showed only a trace of albumin, a few squamous cells, a very rare leucocyte, but no erythrocytes, and no casts.

The patient was discharged from hospital on January 18 apparently perfectly well so far as the kidneys were concerned, with no albumin, casts, or erythrocytes in the urine, no oedema, and still retaining the 80% improvement in his rheumatoid arthritis. During his second stay in hospital it was noticed that an abundance of long silvery hairs had grown on the former areas of alopecia (the normal hair was black). By June the silvery hair had returned to normal colour.

Case 2

This patient, a married woman aged 36, was studied in co-operation with Dr. Arthur Barry and Dr. M. B. Quane. She was admitted to hospital on June 1, 1951, complaining of almost complete anuria during the previous two days, and severe diarrhoea with some vomiting for three days. There was nothing of importance in her history except the occurrence of sore throats about twice a year between the ages of 15 and 23 years, when they ceased following extrac-

TABLE I.—Case 1

Date 1950-1	Cortisone Dosage mg./24 Hours	Urine; ml./24 Hours	Fluid Intake; ml./24 Hours	Average Respiratory Rate per min.	Oedema	Blood Urea mg./100 ml.	E.S.R. mm.	Plasma CO ₂ -combining Power; Vol. %	Serum Sodium mg./100 ml.	Serum Potassium mg./100 ml.	Plasma Chlorides mg./100 ml.	Eosino-phil Count per c.mm.
26/12	—	0	?	38	Tr.							
27/12	—	0	?	40	1							
28/12	—	15 (c)	?	52	2	210	72	29.4			480	
29/12	—	210 (c)	210	50	3				296	23		
30/12	—	360 (c)	960	40	3	240		18.0				200
31/12	400	960.5* (c)	1,110.5	44	4							
1/1	400	2,259 (c)	1,560	38	4	180		38				50
2/1	300	3,150	2,040	36	4							
3/1	350	3,930	2,660	33	4	264		40	293	17.6		
4/1	300	5,070	2,340	29	4	207						
5/1	250	4,170	2,730	24	4							
6/1	200	4,640	2,400	24	3							
7/1	200	3,810	2,640	24	3							
8/1	150	4,050	2,110	22	2	63	25	40				425
9/1	150	3,360	2,560	21	2				304	13.3		
17/1	50	?	?	0	0	36						
18/1	25	1,500	2,580	18	0							

(c) By catheter. * After 400 mg. cortisone. Under the heading Oedema, Tr. means trace, 1 slight, 2 considerable, 3 marked, and 4 massive. Readmission, 26/12/50. Discharge, 18/1/51.

was given by Mr. J. F. O'Sullivan and Dr. M. I. Drury; after this procedure had gone on for some hours the lavage fluid showed 90 mg. of urea per 100 ml. Procaine was also tried by intravenous drip, and antazoline by mouth. Next day (December 29) the patient's condition was much worse, the general oedema had increased, he was semi-conscious, nausea was intense, and the respiratory rate averaged 50 a minute. The pupils were not contracted and retinoscopy revealed no abnormality; 210 ml. of urine was obtained by catheter and showed +1 albumin, numerous squamous cells and leucocytes, a moderate number of erythrocytes, and a few granular casts.

On December 30 his general condition was so bad that the outlook appeared hopeless. The general oedema had increased, the respiratory rate was 40 a minute, with air hunger, and the blood urea was 240 mg. per 100 ml. By catheter we obtained 360 ml. of urine, which showed +2 albumin with a moderate number of erythrocytes and an increase in the number of granular casts. The plasma CO₂-combining power was down to 18 vols.%. On December 31 the position was so grave that it was decided to discontinue all other treatment and to try cortisone acetate, of which he was given 200 mg. twice on that day. On that evening, some hours after the second dose of cortisone, there seemed to be an improvement in the patient's condition, and during that day 960.5 ml. of urine was obtained by catheter. The subsequent course can be seen in Table I.

On January 1, 1951, the urine showed only +1 albumin, no casts, and only a rare erythrocyte. From January 2 the clinical condition improved every day and catheterization was no longer necessary. From January 5 diuresis, accompanied by intense thirst, was for some days considerable.

tion of 20 teeth. She had a recent recurrence of sore throat, having had two attacks during the month prior to admission. She had had two full-time normal pregnancies preceded by two complete abortions, but with none of these was there a history of toxæmia or of vascular hypertension. Her last menstruation was in November, 1950.

On examination the patient was found to be 27 weeks pregnant. Her pulse rate was 90, respirations 22, axillary temperature 98° F. (36.7° C.), and blood pressure 140/76 mm. Hg. There was slight oedema with pitting on pressure in the lumbar region and in both legs, but no oedema of the eyelids. The tonsils were apparently normal. The pupils reacted to light, and retinoscopy revealed nothing abnormal. The heart was normal, and the baby was alive. She was fully conscious.

On June 2 she complained of headache and "spots" before her eyes. We obtained 199 ml. of urine (partly by catheter) which showed some albumin, a considerable number of leucocytes and erythrocytes, but no casts. Next day the headache continued and the oedema had increased. There was no vomiting or diarrhoea. Bull's diet was started. On June 4 her condition was unchanged, except that she vomited three times. The blood urea was 159 mg. per 100 ml. A throat swab yielded non-haemolytic streptococci. On June 6 the headache was severe, she vomited six times, complained of dimness of vision, and was rather drowsy; 57 ml. of urine was obtained by catheter, and it contained albumin (+4), numerous erythrocytes, some epithelial cells, but no casts or bacteria.

On June 7, as the vomiting was severe, Bull's diet was replaced by 10% glucose drip intravenously (1 litre per 24 hours). The blood urea was 216 mg. per 100 ml. Next

day the vomiting was less, but she was very drowsy. Mr. Duff (urologist) examined her and did not advise surgical treatment. On June 9 she complained of marked dimness of vision and severe headache, and she was semicomatose; she went into premature labour, which resulted in delivery of a living infant weighing 2 lb. 12 oz. (1.25 kg.), at 9.35 p.m. The infant died ten and a half hours later from prematurity; a post-mortem examination was not permitted. On June 9 14 ml. of urine was obtained by catheter. On the same day treatment with cortisone was started (see Table II for details).

On June 10 her condition was unchanged, and, because she was vomiting less, Bull's diet was started again; Hb was 65%. On June 13 her condition was still unchanged. Because of moderate vomiting Bull's diet was discontinued,

On November 29, 1951, he complained of symptoms of pyrexia. Next day his temperature was 99.5° F. (37.5° C.), his pulse rate regular 80, and there were a few scattered rhonchi at the base of the left lung. At that time there were no urinary symptoms. A dessertspoon of "cremomerazine" was prescribed every four hours with rest in bed and abundant fluids. On December 3 his temperature was normal, but it was discovered that he had taken 4 oz. (114 ml.) of cremomerazine—that is, 16 g. of sulphamerazine—within 48 hours. This drug was then stopped and glucose and an alkaline mixture were prescribed, as on that day he complained of abdominal pain and vomited several times. He was admitted to hospital that afternoon. He passed no urine from admission to hospital on December 3 (except about 30 ml. on December 5) until January 7,

TABLE II.—Case 2

Date 1951	Cortisone Dosage mg./24 Hours	Urine; ml./24 Hours	Fluid Intake ml./24 Hours	Average Respiratory Rate per min.	Oedema	Blood Urea mg./100 ml.	Plasma CO ₂ -combining power; vol. %	Serum Sodium mg./100 ml.	Serum Potassium mg./100 ml.	Plasma Chlorides mg./100 ml.	Eosino-phil Count per c.mm.
1/6	0	57	568	22	1						
2/6	0	199	1,136	32	1						
3/6	0	71	1,136	26	2						
4/6	0	28	1,136	36	2	159					
5/6	0	43	1,136	26	2						
6/6	0	57	1,136	26	2						
7/6	0	71	1,136	22	2	216					
8/6	0	57	1,136	22	2						
9/6	200	14	1,136	26	2		30			658	32
10/6	200	114	1,136	24	2	318					
11/6	300	185	1,136	20	2	288					272
12/6	350	213	1,136	28	2	294		309	21		270
13/6	400	327	1,136	22	2	300					123
14/6	400	345	1,136	20	2	320	33			597	73
15/6	400	373	1,278	28	2	300	35			620	
16/6	400	681	1,846	26	2						
17/6	400	1,292	1,420	22	2	380	41				43
18/6	400	1,452	1,420	20	2	396				693	
19/6	400	1,481	1,420	22	2						
20/6	350	2,130	1,648	20	2		38				25
21/6	350	2,112	1,477	20	2						
22/6	300	2,556	1,420	26	2						
23/6	300	2,215	1,448	22	2						
24/6	250	2,187	1,534	18	2						
25/6	250	2,130	1,477	26	2	270					30
26/6	200	2,414	1,562	20	2		57				
27/6	175	2,063	1,477	20	2	186					45
28/6	150	2,613	1,704	24	2						
29/6	100	2,215	1,704	20	2	140					
30/6	75	2,187	1,846	18	2						
1/7	50	2,584	1,420	22	2						
2/7	25	2,783	1,562	24	2	87					120
3/7	25	1,817	1,562	22	2						
4/7	25	2,035	1,704	18	2						
5/7	0	2,035	1,704	20	1						
6/7	0	1,249	1,448	24	1						
7/7	0	1,903	1,364	18	1	72					
12/7	0	1,221	1,221	20	0						
19/7	0	1,876	1,335	22	0						
8/10	0	1,650	2,100		0	30					

Under the heading Oedema, 1 means slight and 2 means moderate.

and an intravenous glucose drip given (1 litre per 24 hours). On June 14 she did not vomit, and there was a slight improvement in her general condition. Some diarrhoea appeared; urine (catheter) contained +2 albumin, numerous erythrocytes, and some granular casts. On June 17 the improvement was continued. There was no vomiting or diarrhoea, and she was able to take fluids orally. Urine contained +1 albumin, fairly numerous erythrocytes, but no casts. On June 18 her general condition was much improved but headaches and dimness of vision were still present; Hb was 44%, and erythrocytes 2,300,000 per c.mm.; oral iron therapy was started. During her stay in hospital her blood pressure varied from 140/110 to 96/56. She was discharged on July 20 apparently quite well.

When seen in October, 1951, she felt and appeared perfectly healthy, and her general physical examination as well as blood pressure, blood count, urine analysis, intravenous pyelogram, and blood urea were normal.

Case 3

A man aged 45 was referred by Dr. A. F. Falvey to Mr. H. L. Barniville and Mr. J. Corcoran, who after some days of observation and treatment in the Mater Misericordiae Hospital, Dublin, referred him to one of us.

when he passed about 18 ml. He was treated by intravenous saline, as frequent vomiting during this period permitted nothing to be retained by mouth.

On December 5 the few millilitres of urine obtained by catheter contained a trace of albumin, a few squamous cells, numerous erythrocytes, but no bacteria, casts, or crystals. Next day a plain x-ray film of the abdomen showed no radio-opaque calculi. On December 6 epidural block was performed between L 1 and L 2 with 25 ml. of 1% lignocaine hydrochloride, but no improvement ensued. On the same day a catheter was passed into the left ureter, but a catheter could be passed only for about $\frac{1}{2}$ in. (1.3 cm.) into the right ureter, apparently owing to blockage; about 18 ml. of urine was collected next day, and the catheter was removed on December 9. On December 7 he vomited frequently. There was a slight mitral systolic murmur; the electrocardiogram showed left axis deviation with a high positive T wave in Lead 4 F. The blood pressure was 174/110 mm. Hg, the pulse rate 80, respiratory rate 28, and the oral temperature 98.4° F. (36.9° C.). He was somewhat drowsy and both eyes had considerable subconjunctival haemorrhages, but the pupils were not contracted. Retinoscopy (by Dr. D. O'Donoghoe) showed nothing abnormal. There was considerable gaseous distension of the abdomen and moderate

oedema of the lumbar region and legs. Some rhonchi were heard at the bases of both lungs.

Treatment with cortisone was started on December 7, and on that day he was given 500 mg. in two doses (see Table III). Next day he was given 400 mg. of cortisone in two doses, and on the same day (29½ hours after the first dose of cortisone) he passed 240 ml. of urine containing +2 albumin, no sugar, no crystals, an occasional leucocyte, and very numerous erythrocytes, but no casts; the nausea had improved so that he was able to drink a moderate amount of fluid. On December 9 he was given 400 mg.

rhage had by then practically disappeared. He returned to hospital on January 28 and a detailed investigation of kidney function revealed no abnormality.

Case 4

A man aged 64 was studied in co-operation with Dr. B. Mayne in the Meath Hospital, Dublin. He was suffering from symptoms of prostatic enlargement for about one year previous to admission. Prostatectomy was recommended by Mr. Lane, and was carried out by the retropubic method on January 29, 1952.

TABLE III.—Case 3

Date 1951-2	Cortisone Dosage mg./24 Hours	Urine; ml./24 Hours	Fluid Intake; ml./24 Hours	Average Respiratory Rate per Min.	Blood Urea mg./100 ml.	E.S.R. mm.	Plasma CO ₂ -combining Power; Vol. %	Serum Sodium mg./100 ml.	Serum Potassium mg./100 ml.	Plasma Chlorides mg./100 ml.	Plasma Inorganic Phosphorus mg./100 ml.	Eosino-phil Count c.mm.
3/12	—	0	?									
4/12	—	0	?									
5/12	—	30±	?		120							
6/12	—	0	?									
7/12	500	18±	?	28	217	46	34.2			442	8.7	25
8/12	400	240	?	24								
9/12	400	4,680	3,000	24								
10/12	200	5,700	3,031	16	246		49.7			494	10.8	50
11/12	400	390*	2,010	16			49.7	296	30			
12/12	400	4,080	2,280	18	318						10	
13/12	400	6,180	4,980	17	184					576	6.8	25
14/12	400	5,880	4,500	18								
15/12	400	4,200	4,020	16				310				
16/12	375	3,330	3,090	16								
17/12	350	3,360	3,990	18	56							
18/12	273	3,450	3,720	17	27							
19/12	250	3,180	2,850	18	21							
24/12	50	1,350	1,350	22								
31/12	0	1,290	1,560	20								
28/1					22	3						25

* No urine passed from 9 p.m., December 10 to 5.30 p.m., December 11 (20½ hours). Patient was given 325 mg. cortisone at 5.30 p.m., December 11, and passed 390 ml. urine two hours afterwards (see text).

TABLE IV.—Case 4

Date 1952	Corti- sone mg.	Fluid Vol. (oz.) through Catheter	Oral Fluid Intake oz.	I.V. Fluid Intake oz.	Blood Urea mg./100 ml.	Urea, mg./100 ml. in Fluid from Catheter	Plasma-CO ₂ combining Power; Vol. %	Serum Sodium mg./100 ml.	Serum Potassium mg./100 ml.	Plasma Chlorides mg./100 ml.	R.b.c. (millions)	Chloride in Gastric Juice
30/1		26	66	40								
31/1		10	110		148							
1/2		5	32		250		45			517		
2/2		1½	40		267		50			529		
3/2		2	32									
4/2		1½	40		365		38			520		
5/2		3	40		435		51	279	22.7	494	2.6	
6/2	400	3½	42		445		51			541		
7/2	500	2½	43		475		62			495	3.2	
8/2	500	2½	38	60	465	455	45			517		
9/2	500	3	28	55	515	545	50	296	24.2	447	3.1	
10/2	500	3½	39									
11/2	500	3½	42		515	502	51	279	28.8	447		
12/2	500	5½	43		635	1,050*	54			446	3.0	329
13/2	500	5	48		690	870	58	298	31.5	423		
14/2	500	5½	50		725	740	62			435		
15/2	500	15	48	20		890						482
16/2	500	19		103	665	910	59	288	30	400	2.6	635
17/2	500	28		99								795
18/2	250	40½		120	650		61	293	31.2	388		846

* Assuming the ammonia present was derived from urea.

of cortisone in two doses, and he passed 4,680 ml. of urine and drank 3,000 ml. of fluid; he had no nausea, vomiting, or oedema, and drowsiness had disappeared. His general condition was improved.

It was decided to reduce drastically the dose of cortisone to see if the diuresis of the previous day was a coincidental phenomenon. On December 10 100 mg. was given twice daily, and on the morning of the 11th 75 mg. No urine was passed from 9 p.m. on December 10 (the day the cortisone dosage was halved) up to 5.30 p.m. on the 11th; 325 mg. of cortisone was therefore given at 5.55 p.m. on December 11 and he passed 390 ml. of urine two hours after this dose (see Table III for details).

On December 19 the urine showed only the faintest trace of albumin and no erythrocytes. The latter never re-appeared again up to discharge. On December 24 the urea-clearance figure was 158.

He was discharged from hospital on January 4, 1952, apparently fully recovered. The subconjunctival haemor-

Pre-operative examination had not revealed any other abnormality in the urinary system. The blood urea was 37 mg. per 100 ml. The urine was clear and contained no albumin, cells, or casts. An intravenous pyelogram showed normal outline and concentration in both kidneys. Clinical examination revealed a few scattered rhonchi in the lungs and bilateral inguinal herniae. The heart and blood pressure were considered normal. Blood count, chest x-ray film, and glucose tolerance were also normal.

Some hours after operation his blood pressure was low, and he was given a transfusion of 2 pints (1,140 ml.) of blood, and 40 oz. (1,140 ml.) of normal glucose intravenously. On the following day he seemed well, but his urinary output was only 26 oz. (738 ml.), and his fluid intake (oral and intravenous) was put up to 106 oz. (3,010 ml.). During the next two days his urinary output continued to decrease (see Table IV). On February 1 an exploratory operation was done on the right kidney and ureter. Oedema of the perirenal tissue was noted, and the capsule over the

lower pole was incised. On February 4 his general condition was good and his mind was clear. Except for sighing respiration there was no other clinical sign to indicate the degree to which uraemia had developed. His blood pressure was 160/75 mm. Hg, and there was no oedema. On that date he was put on a high glucose intake (300 g. daily). Treatment with cortisone was started on February 6. This decision was made reluctantly, as there was no clue to the aetiology of the renal failure. He was given 400 mg., which was increased to 500 mg. the next day.

On February 5 his clinical condition was still good, and his electrocardiogram was normal. At that time his serum potassium was 22.7 mg. per 100 ml. The serum potassium subsequently increased further, and on February 17 the electrocardiogram showed the effect on his myocardium of this rise.

His general condition remained very good until February 15, when it became necessary to aspirate his stomach contents because of vomiting; much bile-stained fluid was withdrawn. At this time fluid was given intravenously and he began to excrete an appreciable quantity of urine again; during the next three days this increased gradually, and for the first time the blood urea ceased to rise; indeed, the blood urea began to decrease, having reached its peak of 725 mg. on February 14. Meanwhile, however, his general condition deteriorated, and he died on February 18 after a short convulsion.

The post-mortem examination report by Professor R. A. Q. O'Meara on the kidneys, suprarenals, heart, and liver, was as follows:

Macroscopically the liver was enlarged, but no gross lesion was seen in it or in the spleen. The kidneys were swollen and pale, and contained a fair number of cortical cysts about $\frac{1}{4}$ in. (0.6 cm.) in diameter; the pelvis appeared normal. Heart: some hypertrophy of the left ventricle and atheroma of the ascending aorta. Suprarenals much autolysed. Microscopically, the liver showed passive congestion. The kidneys showed: (1) old lesions of chronic glomerulonephritis with hyalinization of glomeruli; (2) recent focal glomerulonephritis; (3) much interstitial oedema; (4) marked congestion of the vasa recta; and (5) some tubules contained pus, others contained blood or altered blood.

Discussion

The onset of anuria in Case 1 appeared to be due to the sudden withdrawal of cortisone, which may have exaggerated an allergic type of reaction in the kidneys following on the throat infection and rash. It was this hypothesis which led us to try the effect of cortisone. The striking improvement in the patient's condition which followed was in agreement with this interpretation. It is debatable whether this patient had an atypical form of acute nephritis, and therefore the possibility that cortisone may be of value in such cases should be considered.

The anuria in Case 2 is difficult to explain and was probably due to mild acute nephritis complicated by pregnancy. Dr. Arthur Barry held the view that it was not entirely a symptom of pregnancy toxæmia for a variety of reasons, including the absence of toxæmia in previous pregnancies and the history of recent sore throats. The response to cortisone was not entirely satisfactory, and it would perhaps be more reasonable to explain, at least partly, the late onset of diuresis by the termination of pregnancy and by the spontaneous recovery which is likely to occur in such cases.

In Case 3 the anuria was interpreted as the result of an acute allergic reaction to sulphamerazine in the kidneys, as there were no sulphonamide crystals in the urine. The diuresis which followed cortisone administration seemed to be attributable to the hormone. This view was substantiated by the recurrence of anuria when the dose of cortisone was suddenly reduced and by the prompt reappearance of diuresis when the dose was increased.

In Case 4 the anuria followed prostatectomy and a moderate degree of glomerulonephritis was found at

necropsy. One apparently contributory cause of death was the high blood potassium.

There are theoretical reasons for caution in using cortisone in cases of acute anuria. One may ignore the well-established fact that cortisone acts in animals as an electrolyte-controlling corticoid causing water and salt retention. In humans this effect is less consistent and even contradictory, depending on the condition of the patient. Thus it has an antidiuretic effect in most normal people if the salt intake is above a certain level; it has a diuretic effect in some cases of nephrosis; whilst in toxæmia of pregnancy it may produce internal fluid transfer, causing ascites with diminution of subcutaneous oedema (Moore *et al.*, 1951).

A more serious objection is that cortisone promotes increased tissue catabolism and is therefore apt to increase the concentration of toxic metabolites in the blood. It is thus possible that some of the increase in blood urea noted in the above cases after cortisone administration could be attributed to this effect. A similar explanation may partially account for the increase in serum potassium noted in Case 4.

Another theoretical objection to using cortisone is suggested by its effect on rats' kidneys, resulting in marked hyperaemia of the glomerular capillaries and a shunting of blood towards the medulla, which becomes greatly congested. This may eventually lead to hypertension and nephrosclerosis. Cortisone is also described as aggravating the renal damage caused by mineral-controlling corticoids. Furthermore, cortisone has not a renotropic effect on the kidney which is characteristic of the anabolic steroids such as testosterone; indeed, it is only the steroids possessing this characteristic which have a protective effect on the kidneys of animals exposed to a wide variety of noxious drugs or violent physical treatment (Selye, 1951). Thomas and Good (1951) reported that cortisone-treated rabbits developed cortical necrosis after intravenous injection of bacterial toxin. Such adverse observations should not be considered decisive for clinical problems, since the reaction of different species is not constant and the doses used are not strictly comparable.

The possibility that an acute allergic reaction in the kidneys to a drug such as the "sulpha" compounds may be controlled by cortisone is of particular interest, as such reactions have often been reported in the literature, especially with sulphathiazole.

Five separate pathological manifestations in the kidney have been attributed to sulphonamide derivatives, and each has been associated with anuria. The best known is mechanical blockage due to crystalluria. The second, that of perifocal tubular nephritis, was recorded by Bergstrand (1946), who also emphasized that the renal findings were essentially the same as those found in the crush syndrome. An acute nephritis resembling the "mercury kidney," with parenchymatous degeneration of the convoluted tubules without inflammatory cell infiltration (More *et al.*, 1946), and a glomerulitis have also been described. Finally, a type mainly distinguished by arterial changes and cellular exudate suggestive of an anaphylactic reaction has been defined by Black-Shaffer (1945). That such reactions may arise after even a small dose of a sulphonamide is exemplified by the case of Bakken (1947).

It is evident from the pathological findings in cases of anuria due to sulphonamides that, while the allergic factor may be inhibited by cortisone, the hope of recovery will depend on whether treatment is given before irreversible changes have occurred in the kidneys. Since the type of allergic reaction is variable it remains to be seen if cortisone will be successful in only a limited number of such cases.

According to our limited experience in the treatment of acute rheumatic fever we believe it is probable that cortisone can not only prevent rheumatic carditis but perhaps even abolish it if given in proper dosage and before irreversible cardiac changes have occurred. If also it be true that cortisone is useful in acute diffuse glomerulonephritis due to allergy, one condition for success would seem to obtain in both these conditions: administration should begin early

in the attack and before organic damage is done to the heart or kidneys. This view was expressed over two years ago by one of us (H. M.) as regards the heart when introducing Professor Philip S. Hench for the Honorary Degree conferred on him by the National University of Ireland.

Summary

Four cases of acute anuria treated with cortisone are reported. In two patients an allergic reaction in the kidneys was suspected, and both responded satisfactorily, making a rapid and complete recovery; in one the allergy was attributed to an overdose of sulphamerazine; in the other it was attributed to the sudden cessation of cortisone, which was being taken (100 mg. daily) for rheumatoid arthritis, and to the development of a sore throat, pyrexia, and rash; both factors preceded the anuria.

No definite conclusions can be drawn from the three apparently successful cases, as acute anuria is prone to develop a spontaneous remission.

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N,N'-DIBENZYLETHYLENEDIAMINE PENICILLIN: A NEW REPOSITORY FORM OF PENICILLIN

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Szabo, Edwards, and Bruce (1951), during a study of the properties of certain penicillin salts, discovered that the coupling of N,N'-dibenzylethylenediamine with penicillin resulted in the formation of a complex only very sparingly soluble in water. These authors described the properties of this complex, its preparation, and the fact that one molecule of base was coupled to two molecules of penicillin. A shortened name for this complex—benzethacil—will be used in this communication. Seifter *et al.* (1951), reporting on the toxicity of benzethacil to animals, found that this compound was approximately 25% more toxic than procaine penicillin to mice by intra-abdominal injection, but was not more toxic when given by intragastric drip, whilst its local analgesic action compared favourably with that of procaine hydro-

chloride. Elias, Price, and Merrion (1951) followed serum penicillin levels in man after the intramuscular injection of this compound, and concluded that it showed no significant toxicity and gave serum penicillin levels of greater duration than any reported with other forms of repository penicillin.

Benzethacil can be administered orally, and shows therapeutic activity by this route (Lepper *et al.*, 1952), but the present communication deals solely with the serum penicillin levels obtained after intramuscular injection.

Materials and Methods

Penicillin assay was performed by the *Sarcina lutea* plate technique (Food and Drugs Administration, Washington), using *Sarcina lutea* C.P.I.-1001. This technique, which uses penicillin dilutions made up in serum, allows adjustment for the influence of protein-bound penicillin, and is thus of considerable assistance in evaluating the significance of low penicillin levels.

With this technique reproducible zones of inhibition were obtained throughout the period of the experiment, as shown by the figures given in Table I. In practice a complete set

TABLE I.—*Diameters of Inhibitory Zones of Sarcina Plates*

Standard Penicillin in Serum (units/ml.)	Mean Diameter of Zone of Inhibition in mm.	Standard Deviation
0.10	23.9	± 1.2
0.075	20.0	± 0.96
0.05	18.8	± 1.25
0.03	12.8	± 1.45
0.02	9.1	± 1.1

of control plates was run with each set of serum assays. Serum penicillin levels were estimated from a line calculated from the individual control plates (see Ungar, 1951).

Benzethacil was supplied as an aqueous suspension in "tubex" ampoules containing 1 ml. (1 ml. contained 600,000 units of penicillin). The needle provided with the tubex syringe had a diameter of approximately 19 s.w.g.; the suspension could be injected without undue difficulty through this needle.

Nineteen volunteer male subjects took part in this investigation; their ages ranged from 19 to 33 years, and their weights from 10 to 15 st. (63.5 to 95.3 kg.). A single injection of 600,000 units of penicillin contained in one tubex ampoule was given into the gluteal muscles. Blood was withdrawn by venepuncture, and the serum, after being separated by centrifugation, was stored in stoppered bottles over solid CO₂ until used for assay.

Toxicity

Most of the subjects complained of aching at the site of injection for 24 to 48 hours. In no case was this severe. One subject developed a "serum sickness" reaction ten days after the injection. This reaction could not be positively attributed to the benzethacil since another possible antigen had been given shortly before. Despite the lack of positive evidence as to causation, this case is recorded, since benzethacil is excreted extremely slowly, and may give rise to unusual types of sensitivity response.

Results

The serum levels recorded are presented in Table II. It is seen that benzethacil administered by intramuscular injection gives sustained levels of serum penicillin considerably superior to any repository penicillin preparation yet developed. The findings in Table II support the view that even if benzethacil injections were spaced as far apart as 14 days a summation of dose effect might occur.