periods of time without the risk of serious toxicity. The drug therefore is useful where a patient is infected by a penicillin-resistant staphylococcus and cannot be given one of the new penicillins because of drug-sensitization, or where resistance to one or other of the new penicillins has been demonstrated. Because there is now in certain hospital areas an additional risk of infection with erythromycin-resistant staphylococci the drug should also be considered in these circumstances. It may be that there is a theoretical risk of the ultimate emergence of cross-resistance between the macrolides and lincomycin as suggested by Barber and Waterworth (1964). At present, however, this does not appear to have clinical significance, and since lincomycin is not related chemically to the macrolides the possible danger may be minimal. From a clinical point of view the drug appears to be particularly valuable in the treatment of staphylococcal osteomyelitis and there is some theoretical and clinical evidence to support this (Holloway *et al.*, 1963 ; McDougall *et al.*, 1964). Further studies are at present being initiated to assess the value of lincomycin in experimental osteomyelitis in animals.

Summary

Twenty-four patients with various infections caused by Gram-positive organisms were treated with a new antibiotic, lincomycin hydrochloride. Treatment succeeded in 19 patients and there were no untoward side-effects or toxicity in the series.

We wish to thank Dr. R. G. Jacomb, of Upjohn Limited, England, for generous supplies of lincomycin hydrochloride. We also thank Miss Edith Wallace for technical assistance, and Dr. J. C. Gould, of the Western General Hospital, Edinburgh, for the *in vitro* studies of staphylococci in his laboratory.

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Haemodialysis Disequilibrium

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Brit. med. J., 1964, **2**, 672–675

Several observers have noted a deterioration in the clinical condition of some patients during haemodialysis at a time when there is improvement in the blood biochemistry (Merrill, 1961 ; Kennedy, Linton, and Eaton, 1962 ; Sitprija and Holmes, 1962). The first evidence of this deterioration is increasing lassitude, headache, drowsiness, and confusion. In more severe cases there is an increase in blood-pressure, pulse rate, and respiratory rate. Fatalities may occur after cardiac arrest or pulmonary oedema. The syndrome is more severe when the plasma urea is very high before dialysis, and may last for 24 hours after the termination of dialysis.

Kennedy *et al.* (1962) noted that urea is removed more slowly from lumbar cerebrospinal fluid (C.S.F.) than from blood and suggested that the abnormal urea gradient thus established between C.S.F. and blood is responsible for this deterioration.

Investigations have therefore been performed to determine the relation between the concentration of plasma urea before dialysis and the size of the abnormal urea gradient established during dialysis, the duration of this abnormal urea gradient, and whether a similar phenomenon occurred with uric acid, creatinine, inorganic phosphorus, and bicarbonate. Observations were also made to correlate these changes in biochemical equilibrium with changes in the C.S.F.–plasma osmolality gradient.

Methods

Ten patients with acute renal failure were dialysed for periods of four to eight hours on a twin-coil kidney at blood-flow rates of approximately 200 ml./min. The rinsing fluid contained a concentration of 2% dextrose and 30 mEq/l. of bicarbonate ion. Simultaneous samples of lumbar C.S.F. and arterial blood were obtained anaerobically immediately before dialysis, immediately after dialysis, and 16 and 24 hours after dialysis. Analysis of lumbar C.S.F. and plasma was performed for concentration of urea by the urease method with nesslerization (Varley, 1962), uric acid (Henry, Sobel, and Kim, 1957), creatinine (Owen, Iggo, Scandrett, and Stewart, 1954), and inorganic phosphorus (Fiske and Subbarow, 1925). Osmolality of C.S.F. and plasma was determined from the depression of freezing-point, using the Fiske osmometer. *p*H and P_{CO_2} were estimated in blood and C.S.F. by means of the micro Astrup apparatus, and the concentration of bicarbonate ion was calculated using the equation $HCO_3 = \text{antilog}\ (pH - pK^1)\ (P_{CO_2} \times S)$. A value for S of 0.0304 was taken for plasma (Severinghaus, Stupfel, and Bradley, 1956) and a value of 0.0320 for spinal fluid (Shohl and Karelitz, 1926). pK^1 was calculated from the equations pK^1 plasma $= -0.062\ pH$ plasma $+ 6.56$ and $pK^1 = -0.143\ pH$ C.S.F. $+ 7.15$ (Cowie, Lambie, and Robson, 1962).

One sample of arterial blood and lumbar C.S.F. was also obtained anaerobically from fasting control subjects without renal dysfunction, and analysed by the above techniques.

Results

The relation of the urea gradient (C.S.F. minus plasma) to the concentration of plasma urea before dialysis is shown in

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Fig. 1. The plasma urea concentration at the beginning of dialysis ranged from 210 to 460 mg./100 ml. In all 10 cases the urea gradient before dialysis was negative, with values of between −10 and −30 mg./100 ml., the urea concentration in lumbar C.S.F. being lower than that in plasma. Immediately after dialysis the urea gradient became positive in all cases, ranging from +30 to +160 mg./100 ml. Moreover, the higher the plasma urea concentration the greater the urea gradient between C.S.F. and plasma at the termination of dialysis, even though no allowance has been made for variations in total urea pools between the different patients and differences in efficiency of dialysis.

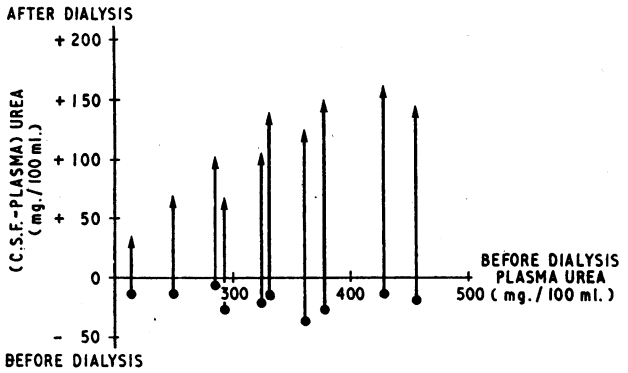

FIG. 1.—Relation of plasma urea before dialysis to urea gradient between C.S.F. and plasma before and after dialysis.

Serial observations on urea concentration in C.S.F. and plasma in one of these patients is shown in Fig. 2. At the start of dialysis the plasma urea concentration exceeds the C.S.F. by 16 mg./100 ml. At the end of a six-hour dialysis there is a reversal of the gradient, the C.S.F. concentration exceeding that of the plasma by 150 mg./100 ml. After the termination of dialysis the C.S.F. urea concentration continues to fall, but the plasma urea rises slowly, so that at 16 hours the gradient has diminished to +50 mg./100 ml. and at 24 hours has returned to its value before dialysis. Some patients who had a more rapid increase in blood urea after termination of dialysis re-equilibrated before 24 hours, and others who had a less rapid increase in blood urea took longer than 24 hours to re-equilibrate.

Fig. 3 shows the mean of the ratios

$$\frac{\text{urea concentration in C.S.F.}}{\text{urea concentration in plasma}}$$

in nine control subjects and the 10 patients who were dialysed. The mean of the ratios before dialysis was 0.91 (with a standard deviation of 0.08), and was not significantly different from that in the control series. Immediately after dialysis the ratio had increased to 1.99, and 24 hours after the termination of dialysis it had returned to the value before dialysis.

The mean of the uric acid ratios also increased during dialysis. However, 24 hours after the termination of dialysis the ratio had not returned to the level before dialysis (Fig. 4), showing that uric acid re-equilibrates more slowly than urea.

In the case of creatinine the mean of the ratios was 0.48 immediately before dialysis. This was significantly lower than that in the control series (Fig. 5). Immediately after dialysis the ratio increased to 0.89 and returned to 0.51 24 hours after the end of dialysis.

Haemodialysis causes a similar pattern of alteration to the ratio of inorganic phosphorus. The degree of alteration, however, is much less (Fig. 6). This was due to the fact that dialysis decreases the concentration of plasma inorganic phosphorus to a less extent than urea, uric acid, and creatinine.

The acid-base changes which occurred during haemodialysis are shown in Table I. The mean blood bicarbonate-ion concentration increased from 20.6 to 25 mEq/l., but the C.S.F. bicarbonate remained constant at 21.9 mEq/l. Twenty-four hours after dialysis the C.S.F. bicarbonate-ion concentration has increased to 24 mEq/l. although there has not been significant alteration in the blood bicarbonate. Thus there was a delay in the transfer of bicarbonate from blood to C.S.F.

The mean of the osmolality gradients between C.S.F. and plasma in a control series of nine is shown in Table II and can be compared with a series of patients with acute renal failure who underwent dialysis. The mean gradient (C.S.F. minus blood) before dialysis was −3 mOsm/kg., but immediately after dialysis had increased to +4.6 mOsm/kg. Twenty-four hours

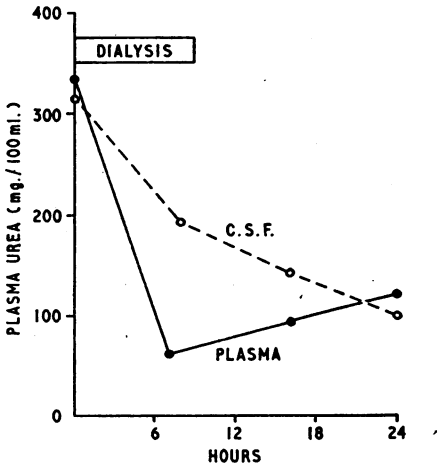

FIG. 2.—Serial observations on urea concentration in samples of C.S.F. and plasma obtained simultaneously from a woman aged 48 with acute renal failure, before, immediately after, and 16 and 24 hours after dialysis.

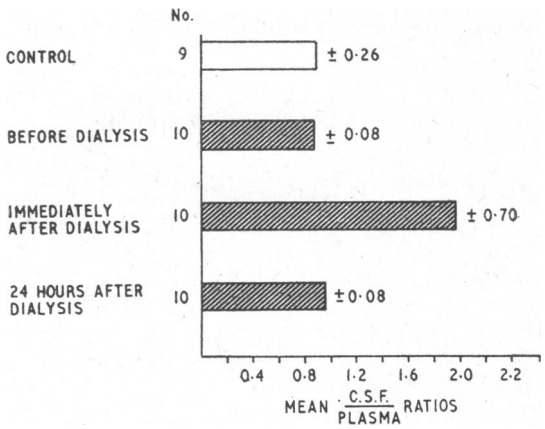

FIG. 3.—Mean of ratios of $\frac{\text{urea concn. in C.S.F.}}{\text{urea concn. in plasma}}$ in nine control subjects and 10 patients with acute renal failure before and after haemodialysis.

TABLE I.—*C.S.F./blood-acid-base Relationships*

Group	No. of Patients	HCO_3 (mEq/l.)		*p*H		P_{CO_2} (mm. Hg)	
		Blood	C.S.F.	Blood	C.S.F.	Blood	C.S.F.
Control	8	26·7	24·4	7·44	7·34	39	45
Before dialysis ..	10	20·6	21·9	7·41	7·25	33	40
Immediately after dialysis	10	25·0	21·9	7·50	7·24	31	38
24 hours after dialysis	10	25·1	24·0	7·49	7·37	33	40

TABLE II.—*C.S.F./blood Osmolality Gradient*

Group	No. of Patients	C.S.F.-blood (mOsm/kg.)
Control	9	− 0·4
Before dialysis	6	− 3·0
Immediately after dialysis	6	+ 4·6
24 hours after dialysis ..	6	− 2·6

after the termination of dialysis the gradient was −2.6 mOsm/kg. Thus dialysis had caused a net alteration of +7.6 mOsm/kg.

Discussion

Our results confirm that there is a delay in removal of urea from lumbar C.S.F. during haemodialysis with the creation of an abnormal urea gradient between C.S.F. and plasma. The size of this abnormal gradient in our series was proportional to the concentration of plasma urea at the start of dialysis. The precise duration of this abnormal gradient after the termination of dialysis varied on each occasion, but averaged 24 hours. Two factors are responsible for the speed of re-establishment of the normal urea gradient between C.S.F. and plasma. Firstly, the rate of rise of plasma urea, and, secondly, the rate of transfer of urea between C.S.F. and plasma. We tried to assess the latter factor by making serial and simultaneous observations on urea concentration in lumbar C.S.F. and plasma in patients who required prolonged haemodialysis for a period of 60 hours because of a very high catabolic rate. The results of these observations in one of these patients is shown in Fig. 7. During the first 36 hours of dialysis there was a persistent decrease in plasma urea concentration from 340 to 69 mg./100 ml. and the C.S.F. urea concentration decreased from 295 to 105 mg./100 ml. During the last 24 hours of dialysis the plasma urea concentration remained virtually constant, but sufficient urea did not pass from C.S.F. to plasma for re-establishment of the normal urea gradient. These results indicate that the rate of transfer of urea from lumbar C.S.F. to plasma is usually slower than the rate of rise of plasma urea in acute renal failure.

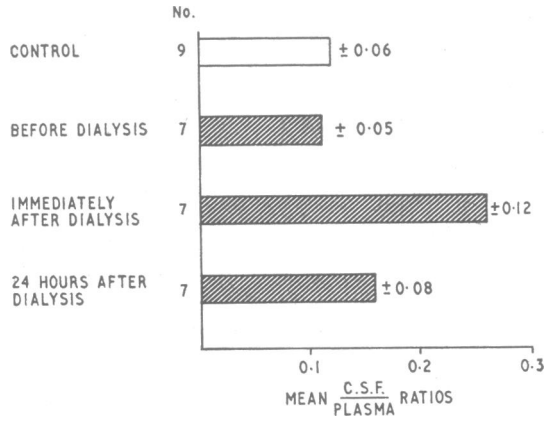

FIG. 4.—Mean of ratios of $\frac{\text{uric acid concn. in C.S.F.}}{\text{uric acid concn. in plasma}}$ in nine control subjects and seven patients with acute renal failure before and after haemodialysis.

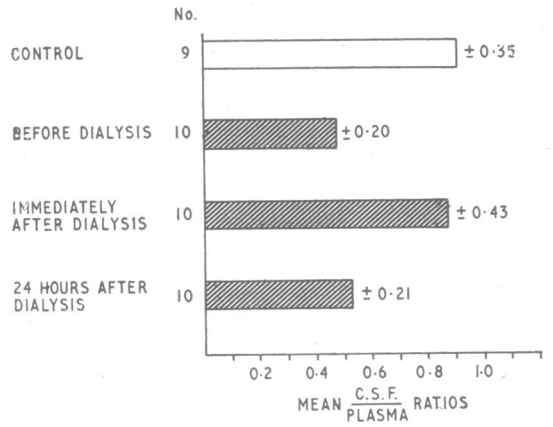

FIG. 5.—Mean of ratios of $\frac{\text{creatinine concn. in C.S.F.}}{\text{creatinine concn. in plasma}}$ in nine control subjects and 10 patients with acute renal failure before and after haemodialysis.

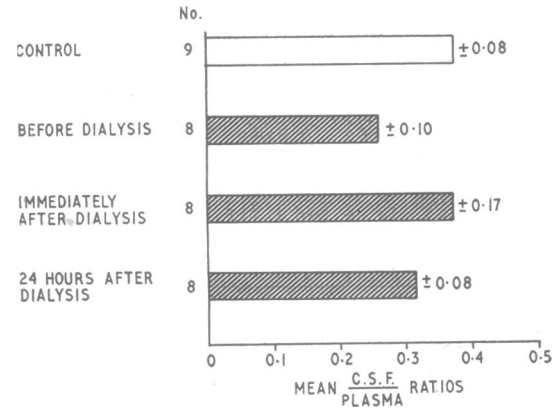

FIG. 6.—Mean of ratios of $\frac{\text{inorganic phosphorus concn. in C.S.F.}}{\text{inorganic phosphorus concn. in plasma}}$ in nine control subjects and eight patients with acute renal failure before and after haemodialysis.

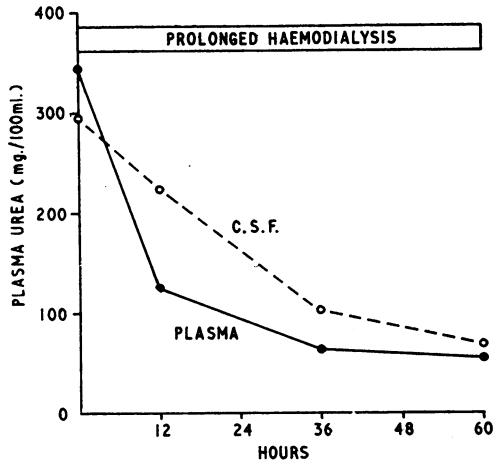

FIG. 7.—Serial observations on urea concentrations in samples of C.S.F. and plasma obtained simultaneously in a man aged 60 with acute renal failure who was dialysed continuously for 60 hours.

The mean alteration in osmotic gradient (C.S.F. minus plasma) caused by haemodialysis was 7.6 mOsm/kg. This is equivalent to a net alteration in transfer pressure of 100 mm. Hg. This would result in the transfer of water from plasma into C.S.F. with a subsequent rise in intracranial pressure and consequent symptoms.

Urea was the main substance responsible for the change in osmotic gradient, because the alteration in concentration of other substances was relatively small.

We did not measure C.S.F. pressures in our series, because the patients were often restless and conditions for measurement could not be standardized. However, Sitprija and Holmes (1962) have shown that there is a rise in the intracranial pressure of uraemic dogs after haemodialysis against a rinsing fluid free from urea. This rise in pressure did not occur if the rinsing fluid contained a concentration of urea equivalent to the plasma urea.

Prevention of symptoms due to biochemical disequilibrium may therefore be expected if biochemical gradients between C.S.F. and plasma are limited by dialysing for short periods of time and at frequent intervals. This can be effected economically by the use of indwelling catheters and storage of the dialysis circuit (Shaldon, Silva, and Rosen, 1964).

Summary

The size of the abnormal urea gradient between C.S.F. and plasma produced by haemodialysis is proportional to the concentration of plasma urea at the beginning of dialysis, and this abnormal gradient persists for approximately 24 hours after the termination of dialysis.

The delay in removal of urea from C.S.F. is associated with a change in the osmolality gradient between C.S.F. and plasma. This results in the passage of water into C.S.F., with consequent symptoms due to an increase in intracranial pressure.

It has also been demonstrated that haemodialysis creates a disturbance in equilibration of uric acid, creatinine, inorganic phosphorus, and bicarbonate between C.S.F. and blood.

It is therefore suggested that haemodialysis be performed at low levels of biochemical disturbance, for short periods of time, and at frequent intervals so that minimal biochemical disturbances be opened up between C.S.F. and blood and the dialysis disequilibrium syndrome be prevented.

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Medical Memoranda

Renal Vein Thrombosis in Acute Hyperparathyroidism

Brit. med. J., 1964, **2**, 675–676

The diagnosis of primary hyperparathyroidism is usually suggested by the presence of renal stones or bone disease (Dent, 1962). Two cases are recorded here in which the presenting features were mental abnormalities associated with hypercalcaemia and rapidly progressive uraemia. In neither patient was there radiological evidence of bone disease or renal stones, and, though parathyroidectomy was undertaken as an emergency, both patients died and were found at necropsy to have renal-vein thrombosis. The absence of radiological bone or renal disease is uncommon in primary hyperparathyroidism, being found in 3% to 6% of cases (Keating, 1961 ; Hodgkinson, 1963).

Case Reports

Case 1

A 38-year-old miner was admitted four times to hospital between April 1960 and June 1962 with vomiting and epigastric pain, and on each occasion the results of a barium meal were normal. He had nocturia, but his urine was protein free in 1961 and the blood urea was normal between bouts of vomiting. In June 1962 he became confused and was admitted for a short period to a mental hospital. In September 1962 vomiting recurred and the serum calcium was found to be 20 mg./100 ml. and the blood urea 192 mg./100 ml. Despite a maintained output of urine his blood urea rose and he was transferred to Hammersmith Hospital on 29 September 1962.

He was a well-built, febrile, stuporose man without corneal or tympanic membrane calcification or a palpable tumour in the neck. Clinically he appeared dehydrated: the blood-pressure was 100/70 mm. Hg. He had moist sounds at both lung bases. On admission the blood urea was 385 mg./100 ml., serum sodium 144 mEq/l. ; potassium 3.6 mEq/l. ; bicarbonate 28 mEq/l. ; calcium 19.2 mg./100 ml. ; inorganic phosphate 2.1 mEq/l. ; alkaline phosphatase 9 King-Armstrong units ; haemoglobin 13.0 g./100 ml. Radiology of the hands showed no evidence of hyperparathyroidism and there was no renal calcification or stone on the abdominal film, but the radiograph of the chest did reveal bilateral bronchopneumonic changes. The electrocardiogram showed deep S-T depression in all the chest leads.

Haemodialysis was performed on admission before surgical exploration of the neck. The blood urea fell to 175 mg./100 ml. but there was no significant change in the serum calcium. On 30 September 1962 a parathyroid adenoma measuring $1.5 \times 1.5 \times 0.5$ cm. was excised by Mr. Selwyn Taylor from behind the left costochondral junction. By 2 October 1962 the serum calcium had fallen to 13 mg./100 ml. and the blood urea had risen to 475 mg./100 ml. when the patient suddenly died and could not be revived. His pneumonia had worsened but his daily output of urine had remained about 1 l.

The tumour consisted mainly of chief cells and areas of transitional clear cells. At necropsy both lungs showed bronchopneumonic changes. The right kidney weighed 230 g. and the left 192 g. In both kidneys the interlobar and arcuate veins were distended with recent dark thrombi and both main renal veins were occluded to just short of the inferior vena cava. Calcification was present in the renal tubules and also in small arteries in other organs. A few minute foci of osteitis fibrosa were seen in the sternum and spine.

Case 2

A 62-year-old clergyman had had impairment of memory and lack of concentration for one year. For one month before admission he had become more drowsy and confused, and he had developed dyspeptic symptoms and nocturia. On 10 August 1963 when he was admitted to hospital he was stuporose, dehydrated, and becoming progressively more uraemic, despite a daily output of urine of over 1 l. He was transferred to Hammersmith Hospital on 14 August.

He was a well-built man, with mild icterus and corneal calcification. His pulse rate was 110/minute and the blood-pressure was 100/70 mm. Hg. He had abdominal distension with scanty bowel sounds and tenderness in the right hypochondrium. He had no localizing neurological signs. Twelve hours after admission he developed thrombosis of the left femoral and external iliac veins. The blood urea was 275 mg./100 ml. ; serum sodium 137 mEq/l. ; potassium 3.0 mEq/l. ; bicarbonate 33 mEq/l. ; calcium 19.0 mg./100 ml. ; inorganic phosphate 2.9 mg./100 ml. ; alkaline phosphatase 13 King-Armstrong units ; serum bilirubin 2.8 mg./100 ml. ; amylase 375 Somogyi units ; haemoglobin 12.4 g./100 ml. A radiograph of the chest was normal, but abdominal films showed gaseous distension and fluid levels in the large and small bowel. There was no radiological evidence of hyperparathyroidism in the hands and no renal calcification or stones. The electrocardiogram showed S-T depression in all chest leads. The urine contained a trace of protein.

Emergency exploration of the neck was performed by Mr. Selwyn Taylor on 16 August and a tumour $2.8 \times 2.8 \times 1.5$ cm. was excised