

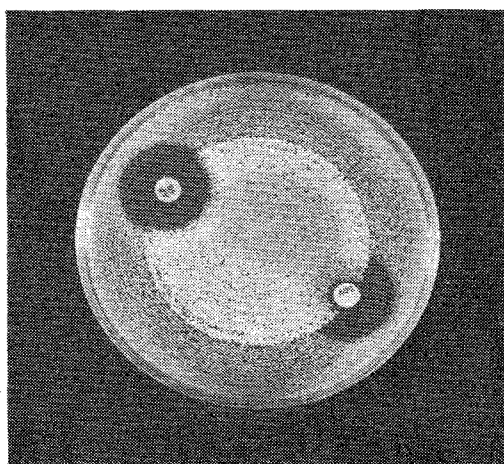
thioridazine, our evidence suggests that it is incorrect to invoke a "site specific" action for this drug on dopamine receptors in mesolimbic areas of human brain. Its anticholinergic properties probably represent an adequate explanation for the rarity of drug-induced parkinsonism associated with thioridazine treatment.

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### ENTEROBACTER RESISTANT TO AMOXYCILLIN/ CLAVULANATE

SIR,—We wish to report the isolation of a strain of *Enterobacter cloacae* which is sensitive in vitro to ampicillin but resistant to amoxycillin/clavulanate ('Augmentin'). The organism was isolated from a wound swab taken from an infected leg ulcer of a woman aged 70. Disc testing on 'Isosensitest' agar by a modification of Stokes' method<sup>1</sup> revealed a measurable zone of inhibition by a 10 µg ampicillin disc but negligible inhibition by a 30 µg augmentin disc (figure). The results were similar on subculture. When a



Disc sensitivity testing of *Enterobacter cloacae*.

Control *Escherichia coli* NCTC 10418 on outer part of plate. Augmentin disc (AUG) contains 20 µg amoxycillin, 10 µg clavulanic acid.

chromogenic cephalosporin<sup>2</sup> (nitrocefim) was used to test for β-lactamase production, the colonies in the immediate presence of the augmentin disc showed strong activity, in contrast to weak activity elsewhere in the culture. Further work is in progress to seek an explanation for this effect. Clavulanic acid can induce β-lactamase activity in *Enterobacter* spp.<sup>3</sup>

The patient was treated with oxytetracycline and metronidazole (there was no history of recent use of either ampicillin or augmentin). The infected ulcer improved and six days later the *Enterobacter cloacae* could no longer be isolated. The strain was sensitive in vitro to tetracycline. This case shows that an augmentin-resistant organism can be sensitive to ampicillin. Isolates should therefore be tested against both antibacterial agents.

We believe this to be the first reported isolation of an ampicillin-sensitive, augmentin-resistant organism. *Enterobacter cloacae*, however, is not a common pathogen and this is likely to be a rare phenomenon.

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### HYPOCARNITINAEMIA IN DISORDERS OF ORGANIC ACID METABOLISM

SIR,—The report by Dr Roe and Dr Bohan of a response to L-carnitine in a child with propionyl CoA carboxylase (PCC) deficiency (June 19, p. 1411) is an important observation in the management of this serious disorder. We have observed a dramatic clinical response to carnitine in an infant with a severe encephalomyopathy due to homocystinuria (5,10-methylenetetrahydrofolate reductase deficiency).<sup>1</sup> This enzymatic defect causes a secondary form of systemic carnitine deficiency, presumably because of defective methylation of lysine. The infant was hypomethioninaemic, with reduced muscle and plasma carnitine levels (table, patient 1).

We have since measured plasma free-carnitine<sup>2</sup> in several infants and children with various metabolic diseases, and some examples are given in the table.

PLASMA FREE-CARNITINE IN VARIOUS METABOLIC DISORDERS

Patient	Age	Plasma free-carnitine*
1. Homocystinuria (5,10-methylenetetrahydrofolate reductase)	3 mo	26.0
2. Propionic acidaemia (propionyl CoA carboxylase)	19 yr	20.8
3. Branched-chain ketoaciduria (maple syrup urine disease)	10 yr	43.6
4. Homocystinuria (cystathionine synthase)	13 yr	31.5
5. Biotin-responsive multiple carboxylase deficiency		
6. (i) Sibling A: periodic acidosis	4 yr	28.3
7. (ii) Sibling B: alopecia	3 yr	42.0
8. Leigh's disease	18 mo	21.8
9. Phenylketonuria (classical)	15 yr	47.8

\*Normal plasma free-carnitine 54.3 nmol/ml (range 31.1-81.6)<sup>3</sup>

It is of interest that the plasma carnitine was low in the first patient identified with PCC deficiency in whom the enzyme defect was established in 1969.<sup>4</sup> This young adult is in excellent health despite reduced plasma carnitine. The addition of biotin to her low-protein regimen seemed to improve her wellbeing even further. Plasma carnitine was especially low during an acute illness with metabolic acidosis treated by dialysis (a procedure associated with reduced plasma carnitine<sup>5</sup>). We found an infant with Leigh's disease whose affected (pathologically confirmed) sibling died with low plasma carnitine; and also one of two children with multiple carboxylase deficiency (the one with bouts of acute metabolic acidosis).

Roe and Bohan report a reduced urinary carnitine but does this reflect the plasma level? It is important to establish this relationship since urinary levels in infants are lower than those in older children and adults.<sup>6</sup> A reduced protein intake does not seem to reduce plasma carnitine in patients (maple syrup urine disease, classical homocystinuria, or phenylketonuria) who have been on altered aminoacid diets or reduced protein intake.

Nonetheless the observation by Rose and Bohan is important. The effectiveness of treatment in some metabolic diseases is presently limited even with a maximum vitamin-coenzyme response or dietary aminoacid/protein restriction. The response to biotin, for example, may be very slight in PCC deficiency, especially during acute episodes of metabolic acidosis.<sup>7</sup> In the long-term care of

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patients with organic acidaemias, it would be important to establish whether the continuous use of carnitine improves protein tolerance, which would also make life more tolerable. Roe and Bohan suggest that their baby with PCC deficiency tolerated greater amounts of protein while taking carnitine.

Carnitine supplementation may be a new approach to the treatment of several diseases causing reduced muscle tone, hyperammonaemia, reduced protein tolerance, and lactic acidosis. Carnitine is known to reverse the defect in mitochondrial  $\beta$ -oxidation and oxidative phosphorylation accompanying a number of organic acidaemias.<sup>8</sup> Fortunately, oral carnitine seems to be safe and nontoxic.

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### RANDOMISED TRIAL OF FETAL MOVEMENT COUNTING

SIR,—Scientific evaluation of the various tests of fetal wellbeing is easier when the test in question aims to identify a baby with a relatively unambiguous abnormality (for example, a neural tube malformation), than when its purpose is the identification of conditions which prompt non-specific “diagnoses” such as fetal compromise, placental insufficiency, and chronic fetal asphyxia.

In these latter circumstances, the assessment is more difficult not only because a firm diagnosis is frequently elusive after as well as before delivery, but also because treatment which aims to improve the outcome is often interposed between the results of the test and the outcomes against which the test results are being compared. In these circumstances, a poor correlation between test results and outcome may indeed be the consequence of a poorly predictive test, but it may also be the result of successful treatment. These considerations, which we have discussed in more detail elsewhere,<sup>1</sup> are relevant in assessing your suggestion (Aug. 7, p. 309) that formalised fetal movement counting may lead to a false-positive (“alarm”) rate as high as 50%—that is, that half of those cases in which delivery was prompted by test results have normal Apgar scores.

In evaluating formalised fetal movement counting, and indeed any other tests of fetal “wellbeing”, there is often no alternative to conducting a randomised trial in which the test in question, together with the treatment prompted by the test results, is compared with an alternative test and resultant treatment.<sup>2</sup> So far, only a handful of such studies have been reported,<sup>3-7</sup> among them the trial of formalised fetal movement counting conducted by Neldam.

We agree with you that it is important to replicate Neldam's evaluation and we have designed a trial with this objective. The success of the trial we envisage would depend on the support of consultant obstetricians. We have so far received an encouraging response to an informal approach to all obstetricians in one health

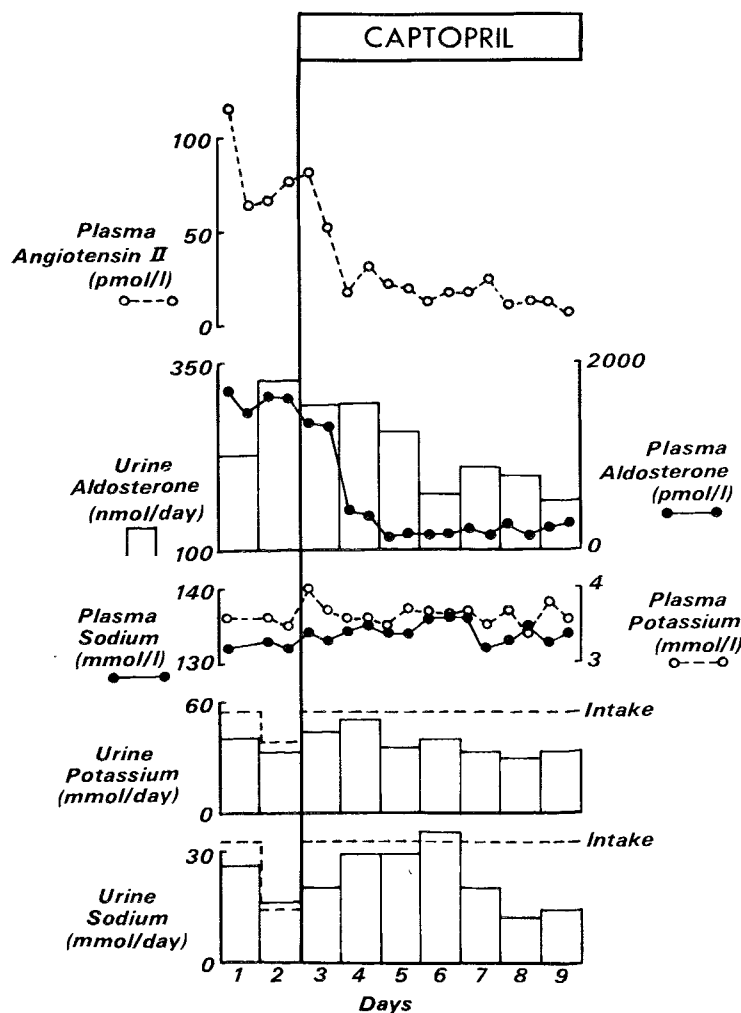
region, and we would be pleased to hear from anyone else who would be interested in participating.

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### HORMONES AND FLUID RETENTION IN CIRRHOSIS

SIR,—In your editorial (June 12, p. 1341) you discuss the role of aldosterone in sodium retention and the possibility that “aldosterone receptors are hypersensitive in cirrhotic patients”. If this is true, an abrupt reduction in plasma aldosterone should initiate natriuresis. We have used the angiotensin I converting enzyme inhibitor, captopril, in a patient with profound oedema and ascites due to alcoholic cirrhosis. The accompanying figure shows hormone and electrolyte data before and during captopril treatment



Change in plasma angiotensin, aldosterone, and electrolytes during captopril treatment in a patient with cirrhotic oedema.

Captopril dose was 30 mg on day 3, 125 mg on day 4, 400 mg on day 5, and 450 mg daily thereafter.

while the patient was studied on a fixed sodium intake (32 mmol/day) during conditions of controlled posture and metabolic balance. Before captopril, plasma and urine aldosterone were high and supine plasma angiotensin II was also raised. After starting captopril, both plasma angiotensin II and plasma aldosterone fell dramatically and low levels of both hormones were observed for at least the following six days of study. Despite this fall, body weight did not change and no increase in sodium excretion ensued. Supine systolic blood pressure fell from 110 to 85 mm Hg (lowest level 75 mm Hg) but plasma urea (5.5 mmol/l) and creatinine (0.12 mmol/l) did not change from pretreatment values.

The failure to achieve a natriuresis in the face of such reductions

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