clude the possibility of a direct effect of metoclopramide and propantheline on absorption across the intestinal mucosa.

We have tested the effects of these compounds and of phenobarbitone on D-xylose absorption from rat small intestine in vitro. Everted sacs were used with Krebs phosphate buffer containing calcium and glucose.¹ Transport of 50 mM xylose was measured with a concentration gradient—that is, with buffer only and no xylose initially within the sac. The drugs were added to the mucosal and serosal solutions of alternative sacs at a concentration of 1 mmol/l. Phenobarbitone and metoclopramide significantly reduced xylose transport but propantheline had no such effect.

Our finding of inhibition by metoclopramide agrees with the clinical findings of Kendall¹ in individuals with normal gastrointestinal function. He also showed that propantheline increased urinary excretion, and presumably intestinal absorption, of xylose in one case of carcinoid syndrome. No such effect of propantheline was observed in our investigation in vitro.

The in-situ intestinal loop preparation with anaesthetized rats has been used to study antibiotic absorption. This showed good correlation when predicting antibiotic absorption in man. By contrast, results with the everted sac as a model for gastrointestinal absorption had to be interpreted with extreme caution.⁵ Our results agree with this latter view. Thus phenobarbitone⁶ and metoclopramide show similar effects on xylose absorption both in vivo and in vitro but there is no such correlation with propantheline.—We are, etc.,

D. F. EVERED

JACQUELINE M. MCMULLEN

Department of Biochemistry,
Chelsea College (University of London),
London S.W.3

¹ Kendall, M. J., *British Medical Journal*, 1973, **2**, 179.

² Nimmo, J., et al., *British Medical Journal*, 1973, **1**, 587.

³ Manninen, V., et al., *Lancet*, 1973, **1**, 398.

⁴ Wass, M., and Evered, D. F., *Biochemical Pharmacology*, 1970, **19**, 1287.

⁵ Perrier, D., and Gibaldi, M., *Journal of Pharmaceutical Sciences*, 1973, **62**, 1486.

⁶ Matthews, D. M., *Journal of Physiology*, 1966, **182**, 468.

Metoclopramide and Prolactin

SIR,—Dr. M. Shakkai and others (18 May, p. 385), reporting the occurrence of cardiac arrhythmia during the administration of metoclopramide, make reference to the fact that this drug is considered to be free of side effects in adults. In recent studies we have discovered that metoclopramide is a potent stimulator of prolactin release in both men and women when given intramuscularly, intravenously, or orally in a dose of 10 mg. Levels increased from 3- to 8-fold within five minutes of either an intramuscular or intravenous injection and within 60 minutes after oral administration; these levels remained elevated for at least eight hours. Long-term administration of metoclopramide has occasionally been associated with galactorrhoea.

Metoclopramide is a derivative of procainamide and we have previously reported¹ that a related compound, sulphuride, is also a very potent releaser of prolactin in man. In view of a recent report on the effects of prolactin on the rat heart in vitro, causing

changes in both heart rate and amplitude of contraction and inducing dysrhythmia,² it would seem possible that the effects observed by Dr. Shakkai and his colleagues in their patient may be related to the elevation in the circulating prolactin. We are at present investigating the site of action of metoclopramide and the effects of other procainamide derivatives on prolactin secretion in man.—We are, etc.,

A. S. MCNEILLY

M. O. THORNER

G. VOLANS

G. M. BESSER

Medical Professorial Unit,
Departments of Chemical Pathology and
Clinical Pharmacology,
St. Bartholomew's Hospital,
London E.C.1

¹ Thorner, M. O., et al., *Journal of Endocrinology*, 1974, **61**, 132.

² Nassar, B. A., et al., *British Medical Journal*, 1974, **2**, 27.

Isolation System for General Hospitals

SIR,—Professor N. R. Grist (8 June, p. 555) has overlooked the evidence¹ that spread of infection in infectious hepatitis derives from anicteric and preicteric cases. I suggest that it validates the statement in my letter (11 May, p. 331) and also that the modern attitude to the icteric form of infectious hepatitis is as misguided as was that of our ancestors to leprosy. But unlike us they had the excuse of not knowing that those whom they banished from their midst were the least infectious patients, if they were infectious at all.²—I am, etc.,

H. G. EASTON

Clinical Department of Infectious Diseases,
Ruchill Hospital,
Glasgow

¹ Gowen, G. H., *Lancet*, 1964, **2**, 478.

² Easton, H. G., *World Medicine*. In press.

Transplacental Passage of Chlordiazepoxide

SIR,—Benzodiazepines are widely used in the management of eclampsia and fulminating pre-eclampsia. We were therefore interested to read the article by Dr. Jean E. Cree and her colleagues (3 November, p. 251) and the letter of Dr. J. Kanto and others (30 March, p. 641) on the use of diazepam in labour.

Over the past 18 months a regimen of chlordiazepoxide, hydrallazine, and frusemide has been used in St. Mary's Hospital to control severe pre-eclampsia and eclampsia. Chlordiazepoxide was chosen following the results reported by Lean and others.¹ One patient was given chlordiazepoxide 500 mg intravenously over a period of four hours before caesarean section. The baby had Apgar scores of 8 at 1 minute and 10 at 5 minutes but was unresponsive, hypotonic,

hypothermic, and reluctant to feed for 48 hours. The atonicity persisted for a week but ultimately the baby did well. A full range of tests was normal but it was not possible to measure drug levels in mother or baby.

The similarity between this syndrome and that described by Dr. Cree and her colleague led us to do a pilot study of chlordiazepoxide levels in maternal and mixed cord blood at delivery in three patients with severe pre-eclampsia and in one with eclampsia who had been treated with the drug. The results (see table) showed that chlordiazepoxide crosses the placenta and may affect the neonate. None of the effects persisted but long-term minor sequelae cannot yet be ruled out. Bearing in mind the value of the drug in the treatment of a potentially dangerous condition, however, the therapeutic balance must be in favour of its judicious use. A fuller study is in progress.—We are, etc.,

G. M. STIRRAT

PAUL T. EDINGTON

DAVID J. BERRY

St. Mary's Hospital,
London W.2

Poisons Unit,
New Cross Hospital,
London S.E.14

¹ Lean, T. H., Ratnam, S. S., and Sivasamboo, R., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1968, **75**, 856.

Adjustment of Plasma Calcium Measurements

SIR,—We cannot agree with the statement of Dr. R. B. Payne and his colleagues (1 June, p. 504) that the clinical usefulness of their adjustment is enhanced by the inbuilt errors.

With a low ionized calcium level the adjustment applied is larger than it should be, whereas with a raised calcium level it is smaller. Thus only in cases where the adjustment is subtracted from the measured total will one observe the enhancement claimed by them. This, of course, requires that the albumin level be higher than normal. Where the albumin level is lower than normal the adjustment must be added, thus giving an adjusted total higher than it should be with low ionized calcium, and lower than it should be with high ionized calcium. It is well known that abnormalities of plasma albumin are generally towards low rather than high concentrations. In such circumstances the inbuilt error of the Payne adjustment, far from enhancing the usefulness of the correction tends to negate it.

Apart from recommending direct measurement of plasma ionized calcium, we agree with Dr. A. M. Parfitt (16 March, p. 520) that the McLean-Hastings nomogram is still the most appropriate way of allowing for variations in plasma protein because it is

Case No.	Chlordiazepoxide Dosage before Delivery		Last Dose and Time (hr) before Delivery	Birth Weight and Fetal Condition	Serum Chlordiazepoxide Levels (µg/ml)	
	7 days	24 hr			Mother	Cord
1	1,900 mg	100 mg	100 mg I.M. 15 hr	1,802 g. Apgar 7/1, 9/5. Listless, hypotonic, reluctant to feed, hypothermia 3 days 900 g. No problems	5.0	5.3
2	450 mg	400 mg	100 mg I.M. 6½ hr		3.2	3.4
3	300 mg	110 mg	100 mg I.M. 5 hr	2,602 g. Apgar 9/1, 10/5. Hypotonic, reluctant to feed	1.3	0.5
4	100 mg I.V. over last 8 hr			3,240 g. Apgar 9/1, 10/5. No problems	1.4	1.6

based on a *proportionate* change in total calcium with protein rather than an *absolute* change. A slightly improved nomogram would be based on the plasma albumin rather than the total protein and would be derived from the known calcium-albumin association constant. Such a nomogram can be prepared by any physical chemist and will be included by us in a forthcoming publication.—We are, etc.,

R. W. MARSHALL
B. E. C. NORDIN

M.R.C. Mineral Metabolism Unit,
General Infirmary,
Leeds

Ketotic Hypoglycaemia

SIR,—Ketotic hypoglycaemia occurs in undergrown infants and children, many of whom were small at birth. The hypoglycaemia is intermittent, occurring after a short period of calorie deprivation. It is sometimes associated with periods of increased calorie requirements such as anorexia associated with a minor infection. The biochemical hallmarks are found only during the hypoglycaemia; they include ketonuria and the failure of intramuscular glucagon to increase the blood glucose, while hypoalaninaemia may also occur. The basic defect is not known, though an error of metabolism has been extensively sought. Hepatic gluconeogenesis from glycerol, fructose, and alanine is intact, ketone metabolism is normal, and hormone responses appear to be appropriate with the possible exception of reduced catecholamine excretion in some children. The hypoglycaemia gradually disappears during childhood and is successfully treated with corticosteroids. The unique identity of this disorder is questioned by some authors¹ since similar ketonuria and lowering of blood glucose are seen in normal children during a prolonged ketogenic diet or starvation.

Most of these children have a normal forehead size. Glucose requirements cerebral metabolism are therefore high relative to the small body size, either during normal feeding or during starvation. I have never seen this condition in a robust and well-nourished child and I am led to consider whether the problem is not purely one of nutrition rather than an inborn error of metabolism.

In a 2-year-old child weighing 12 kg the normal energy requirement would be around 50 kcal/hr. In the face of total glycogen depletion about 50% of this would come from alanine (5.7 g/hr) derived from pyruvate and amino-acids in the muscle. These patients are carbohydrate-depleted, as shown by the exhaustion of the hepatic glycogen reserves. In view of their small size and muscle mass it seems reasonable to postulate a deficiency in total available muscle amino-acids which could result in the hypoalaninaemia and consequently in hypoglycaemia.

Hypoglycaemia may occur in overt malnutrition and Schutt-Aine has reported it in maternally deprived children.² We have occasionally observed ketotic hypoglycaemia in neglected children. Sizonenko *et al.*³ have also shown that after a period of unrestricted feeding children with previous ketotic hypoglycaemia respond to fasting and glucagon administration in a normal fashion. These findings seem to indicate that ketotic hypoglycaemia is yet another facet of nutritional

deprivation rather than an inherent defect in glucose homeostasis.—I am, etc.,

NEIL R. M. BUIST

Department of Pediatrics,
University of Oregon Medical School,
Portland, Oregon

- Schutt-Aine, J. C., Drash, L., and Kenny, F. M., *Journal of Pediatrics*, 1973, **82**, 809.
- Pagliara, A. S., *et al.*, *Journal of Clinical Investigation*, 1972, **51**, 1440.
- Sizonenko, P. C., *et al.*, *Pediatric Research*, 1973, **7**, 983.

Deep Venous Thrombosis: a Hypothesis

SIR,—I wonder whether a case which happened some years ago in my own experience fits the hypothesis put forward by Mr. J. Charnley (1 June, p. 499).

A woman aged 58 had an emergency operation for a ruptured cystic ovarian granulosa cell tumour on 2 July 1963. She had a mild degree of rheumatoid arthritis and was taking phenylbutazone at the time of admission to hospital. Her recovery following the operation was quite uneventful and she was discharged from hospital on 16 July. On 17 August she was readmitted with severe pain in her chest, worse on deep breathing. We did not tumble to the diagnosis until five days later, when we discovered in the morning that she had a very swollen, painful, blue leg, undoubtedly due to a left iliac vein thrombosis. We immediately concluded that the preceding chest pain must have been due to an embolism. Treatment with anticoagulants caused all the symptoms and signs in the leg and the chest to disappear within four weeks.

The interesting point is the chronological sequence—the obvious embolism preceding the obvious thrombosis. What I thought was that she must have had a symptomless thrombosis in the deep veins of either the pelvis or the lower limb. I imagined a long, snake-like clot floating in the blood, part of it becoming detached or else growing long enough to reach the point where the vein joined one of the major veins of the lower limb. There perhaps it coiled up or flapped over the point of confluence with the larger vein suddenly blocking it.—I am, etc.,

BRUCE ETON

Buchanan Hospital,
St. Leonards-on-Sea,
Sussex

Hypoglycaemia Action of Onion on Rabbits

SIR,—We found¹ that onion and garlic juice fed to rabbits resulted in a better utilization of glucose. We report here the results of a further investigation to see what effects various extracts of onion had on blood glucose levels in rabbits with alloxan-induced diabetes.

Fresh onions were cut into pieces, dried for 24 hours in a hot-air oven at a temperature of 60–80°C, and then powdered. The powder was extracted in a Soxhlet apparatus successively with ethyl alcohol 95%, petroleum ether (B.P. 40–60°C), chloroform, and acetone, each extraction lasting for a period of 18 hours. The powder was dried in between each extraction. The extracts were concentrated under vacuum and the residue of each was tested for hypoglycaemic effect.

Test Substance	Mean Blood Glucose Levels (mg/100 ml) in 6 Rabbits					Maximum % Fall in Fasting Blood Glucose (± S.E.M.)
	Fasting	1 hr	2 hr	3 hr	4 hr	
Ethyl alcohol extract	210.5	204.5	170.8	182.4	190.5	18.57 ± 2.4
Petroleum ether extract	218.4	207.5	200.2	207.5	210.4	8.25 ± 1.1
Chloroform extract	200.0	196.0	205.2	200.5	194.4	3.00 ± 0.9
Acetone extract	196.0	190.4	184.5	180.0	192.7	3.20 ± 1.0
Distilled water (control)	205.0	207.0	203.0	200.6	208.6	2.30 ± 0.6

Diabetes was induced in 30 rabbits by the method of Duffy.² Alloxan monohydrate 150 mg/kg was infused as a 5% aqueous solution into the marginal vein of an ear. The rabbits developed diabetes in seven days. The 30 rabbits were then divided into five groups of six. After 18 hours' fasting each of four out of the five groups was given one of the test substances at a dose of 250 mg/kg. Distilled water was given to the fifth group as a control. Blood glucose concentrations were then measured at hourly intervals by the Folin-Wu method as described by King and Wootton.³ The results (see table) showed that all the onion extracts had antidiabetic-like activity. Their potency was expressed as maximum fall percentage on the blood glucose level.

It seems that the mode of action of onion extracts differs from that of tolbutamide. The principal action of tolbutamide is to stimulate release of insulin by the beta cells of the islets of Langerhans. Thus it is ineffective in alloxan-induced diabetes in rabbits. Onion extracts, however, have hypoglycaemic activity when insulin secretion by the pancreas is almost stopped. The hypoglycaemic action of onion may be to enable cells better to utilize glucose. The findings so far are encouraging and further work on the isolation and purification of the hypoglycaemic principles is warranted. We are grateful to B.D.H. Chemicals, London, for the supply of alloxan.—We are, etc.,

R. C. JAIN
C. R. VYAS

Department of Pathology and Biochemistry,
R.N.T. Medical College,
Udaipur (Rajasthan),
India

- Jain, R. C., and Vyas, C. R., *Lancet*, 1973, **2**, 1491.
- Duffy, E., *Journal of Pathology and Bacteriology*, 1945, **57**, 199.
- King, E. J., and Wootton, I. D. P., *Microanalysis in Medical Biochemistry*, p. 85. London, Churchill, 1957.

Encroachments on the Patient's Responsibility

SIR.—Writing about doctor/patient responsibilities, Mr. R. F. N. Duke (8 June, p. 557) paints his moral blacks too black and his whites too white. He ignores several lines of relevant argument.

Firstly, the legal position is not clear. If, after careful exposition of the risks by the doctor, the patient chooses to ignore the proffered advice, the surgeon agrees to carry out non-essential surgery nevertheless, and a greater or lesser tragedy results the surgeon's legal position may be in doubt and much more so in some other countries than in Britain. This is especially so in the case of the 10-day rule, where it might well be argued that the woman cannot waive her child's rights.

Secondly, the patient bears responsibility to the surgeon as well as the other way round. If a grossly obese patient fails even to attempt weight loss before undergoing planned major surgery it is at least arguable that the surgeon is within his rights and acting in everybody's best interests (including his own) in insisting on further delay