PROCEEDINGS OF THE NUTRITION SOCIETY

ABSTRACTS OF COMMUNICATIONS

The Four Hundred and Fifty-ninth Meeting of the Nutrition Society (First Meeting of the Clinical Metabolism and Nutritional Support Group) was held at the Medical School, Royal Hallamshire Hospital, Sheffield, on Friday and Saturday, 25/26 November 1988, when the following papers were read:

https://doi.org/10.1079/PNS19890043 Published online by Cambridge University Press

Lack of insulin stimulation of skeletal muscle protein synthesis in type I diabetic subjects during amino acid infusion. By W. M. BENNET[1,2], A. A. CONNACHER[2], K. SMITH[1], R. T. JUNG[2] and M. J. RENNIE[1], [1]*Department of Anatomy & Physiology, University of Dundee, Dundee DD1 4HN* and [2]*Department of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY*

Insulin infusion in healthy postabsorptive man with no provision of exogenous amino acids is reported to have no stimulatory effect on skeletal muscle protein synthesis (Gelfand & Barrett, 1987). This finding suggests the hypothesis that insulin may only stimulate protein synthesis when amino acid availability is increased. To test this hypothesis we studied eight type I diabetic subjects after overnight insulin withdrawal.

A primed continuous infusion of [1-^{13}C]leucine was established and an initial muscle biopsy (anterior tibialis) was taken 30 min later; a second biopsy was taken after 4 h of continued insulin withdrawal and a third after 4 h of insulin infusion (2·4 units/m^2 per h). Mixed amino acids (Synthamin 14, Travenol Laboratories Ltd) were infused continuously (42 and 167 mg amino acids/kg body-weight per h in the first and second phases respectively) to maintain elevated amino acid concentrations in both phases of study. Labelling with ^{13}C of plasma α-ketoisocaproate, and of leucine incorporated into muscle protein, was measured by mass-spectrometry after gas chromatographic separation. Anterior tibialis mixed protein synthetic rate was 0·068 (SD 0·020) %/h during insulin withdrawal and was not significantly different during insulin replacement (0·071, (SD 0·017) %/h).

The results of the present study suggest that insulin does not acutely stimulate skeletal muscle protein synthesis even when amino acid provision is maintained by amino acid infusion.

Gelfand, R. A. & Barrett, E. J. (1987). *Journal of Clinical Investigation* **80**, 1–6.

The determination of tumour protein synthesis rates in patients with colorectal carcinoma using the 'flooding dose' technique. By S. D. HEYS[1], R. A. KEENAN[2], J. WERNERMAN[3], M. A. MCNURLAN[1], E. MILNE[1], A. G. CALDER[1], V. BUCHAN[1], O. EREMIN[2] and P. J. GARLICK[1], [1]*Rowett Research Institute, Bucksburn, Aberdeen AB2 9SB,* [2]*Department of Surgery, University of Aberdeen, Foresterhill, Aberdeen AB9 2ZD* and [3]*Huddinge University Hospital, Karolinska Institute, Stockholm, Sweden*

Whole body protein kinetics have previously shown a varying response to cancer, with both increases and no change in protein synthesis being reported. These studies, however, simply reflect an average of rates in all tissues and give no information on the control of protein synthesis by nutrition or other factors in the tumour itself or individual host tissues. Few studies have investigated tissue protein synthesis in cancer but Mullen *et al.* (1980) measured colorectal tumour tissue protein synthesis with constant infusion of [^{16}N]glycine and obtained a value of 14·5%/d. However, with continuous infusion of tracer doses of labelled amino acids, particularly with rapidly turning over tissues, it is difficult to satisfy the essential criterion that the enrichment of the precursor pool of free amino acids must be known throughout the period of measurement. This problem has been overcome in small-animal studies by giving the labelled amino acid together with a large amount of unlabelled amino acid—the 'flooding dose' technique. This method has been used to measure human muscle protein synthesis (Garlick *et al.* 1988) and we have now applied it to the measurement of protein synthesis in tumours in man.

Patients with colorectal carcinoma undergoing abdominoperitoneal excision of the rectum or low anterior resection were studied and were fasted for 12 h before determination of protein synthesis by injection of 4 g L-[1-^{13}C]leucine (20 atoms % enrichment). Biopsies of the tumour were taken immediately after induction of anaesthesia either at 10 min after commencement of injection, for determination of free leucine enrichment, or at 45–90 min for measurement of free and protein-bound leucine enrichment by mass-spectrometry.

The free leucine enrichment in plasma fell linearly between 10 and 90 min after injection of amino acid. The free leucine enrichment in the tumour tissue 10 min after injection of label ranged from 93 to 99% (mean 96·3 (SD 2·6), *n* 4) of the plasma enrichment at the corresponding time whilst at 45 to 90 min after injection the tissue enrichment values ranged from 79 to 100% (mean 89·4 (SD 8·7), *n* 6), showing that 'flooding' of plasma and tissue free leucine pools to similar enrichments had indeed occurred.

The fractional rate of protein synthesis in colorectal tumour tissue was estimated from the increase in enrichment of protein-bound leucine and the average free leucine enrichment in plasma and was 22·5% (SD 6·3)% (*n* 6). This technique, therefore, enables a precise determination of protein synthesis in human tumour tissue in vivo to be made whilst overcoming some of the limitations of previously described methods.

Garlick, P. J., Wernerman, J., McNurlan, M. A., Lobley, G. E., Milne, E., Calder, A. G., Essen, P. & Vinnars, E. (1988). *Journal of Parenteral and Enteral Nutrition* (In the Press).

Mullen, J. L., Buzby, G. & Gertner, M. H. (1980). *Surgery* **87**, 331–338.

Increased protein turnover with normal energy metabolism in response to feeding in patients with lung cancer. By S. MELVILLE, *Department of Surgery, University Medical School, Aberdeen AB9 2ZD* and M. A. MCNURLAN and P. J. GARLICK, *Rowett Research Institute, Bucksburn, Aberdeen AB2 9SB*

The mechanism of weight loss in cancer has been investigated by assessing both protein and energy metabolism in subjects with carcinoma of the lung. Nine patients with newly diagnosed carcinoma of the lung confined to the chest were studied before treatment and compared with nine control subjects of similar age, weight, sex and smoking habits recruited from patients with peripheral vascular disease. The study included both the post-absorptive state, to assess underlying metabolic changes, and a period of eating to assess the impact of lung tumours on the normal response to food.

Protein synthesis and degradation, and fat, carbohydrate and protein utilization were measured simultaneously by continuous infusion of [1-^{14}C]leucine combined with respiratory gas analysis, with an 8 h protocol including 4 h of fasting and 4 h of giving small meals hourly (Garlick *et al.* 1987). Lean body mass (LBM) was assessed in all subjects by heavy-water dilution.

Energy metabolism was not altered by tumours of the lung. Energy expenditure (EE) in the post-absorptive state was (mean (SD)) 156 (14·6) kJ/kg LBM per d in the cancer group and 147 (15·9) in the control group with similar patterns of nutrient oxidation: cancer *v.* control, 61 (13) *v.* 65 (7) % of energy as fat, 26 (10) *v.* 21 (7) % as carbohydrate and 13 (2) *v.* 14 (2) % as protein. EE during feeding was 183 (21·3) and 181 (17·6) kJ/kg LBM per d in the cancer and control groups with contributions of 32 (11) *v.* 36 (7) % from fat, 52 (9) *v.* 48 (8) % from carbohydrate and 16 (5) *v.* 16 (4) % from protein.

Protein metabolism (μmol leucine/kg LBM per h) was altered in those subjects with carcinoma of the lung, with increased rates of synthesis and degradation ($0·05>P>0·01$) in both the fasted and fed states (see Table).

	Fasting				Feeding			
	Cancer		Control		Cancer		Control	
Protein	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Synthesis	101	7	86	3	106	7	89	2
Degradation	126	6	110	3	59	4	42	5

Although protein turnover was increased, net leucine balance remained the same in the two groups. Hence, abnormalities in protein and energy metabolism, including the responses to feeding, do not account for loss of weight in these lung cancer patients.

Garlick, P. J., McNurlan, M. A., McHardy, K. C., Calder, A. G., Milne, E., Fearns, L. M. & Broom, J. (1987). *Human Nutrition: Clinical Nutrition* **41C**, 177–191.

Starvation reduces the rate of oxidation but not the rate of storage of infused glucose. By P. I. MANSELL and I. A. MACDONALD, *Queens Medical Centre, Clifton Boulevard, Nottingham NG7 2UH*

Insulin resistance and associated glucose intolerance occur in starvation. The present study was designed to investigate the effect of starvation on the partitioning of glucose disposal between oxidation and storage and on the thermic effect of infused glucose.

Six healthy, young, non-diabetic men were starved for 48 h. They were studied both in the normally fed and starved states using a glucose clamp wherein blood glucose concentration was maintained at 3·5 mmol/l using a variable rate infusion of dextrose (200 g/l) in conjunction with a primed-continuous infusion of insulin (100 mU/min per m^2). Respiratory gas exchange measurements were used to determine the effects of starvation on the thermic effect of infused glucose and on the partitioning of the disposal of glucose between oxidation and storage. Forearm uptake of glucose was also calculated by measuring the arterio-venous difference in concentration and forearm blood flow.

With starvation, baseline blood glucose concentration fell from (mean (SEM)) 4·2 (0·04) to 3·1 (0·07) mmol/l ($P<0·001$). At steady-state during the infusion of glucose, total glucose disposal was reduced from 7·1 (0·81) to 4·3 (0·37) mg/kg per min in starvation ($P<0·01$) and glucose oxidation fell from 3·9 (0·24) to 1·4 (0·08) mg/kg per min ($P<0·001$). Glucose storage was estimated as 3·1 (0·70) and 2·9 (0·34) mg/kg per min in the fed and starved states respectively (not significant). With starvation, the increment in forearm muscle glucose uptake during the infusion of glucose was reduced from 8·6 (2·1) to 3·8 (1·2) mg/min per l forearm ($P<0·05$). There was a significant rise in metabolic rate due to glucose-induced thermogenesis in the normally fed state only, the changes from baseline being 0·27 (0·07) and 0·11 (0·09) kJ/min in the fed and starved states respectively ($P<0·05$).

The decrease in the rate of disposal of glucose following starvation due to a fall in glucose oxidation with no change in glucose storage. Starvation also led to a diminution in the thermic effect of glucose.

Water and ion redistribution in sepsis does not result in hyponatraemia. By R. J. HANNON, *Department of Surgery, Queen's University of Belfast, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ* and V. E. BOSTON, *Royal Belfast Hospital for Sick Children, Grosvenor Road, Belfast BT12*

Altered membrane function and migration of osmotically active ions from the intracellular space to the extracellular space (sick cell theory; Flear & Singh, 1973) has been proposed as a major cause of hyponatraemia in acute sepsis. Therapeutic intervention in acute sepsis makes it difficult to study the underlying pathophysiology in patients but several experimental shock studies have documented redistribution of water and electrolytes without the development of hyponatraemia. Whether electrolytes are redistributed in a similar fashion in animals suffering from hyperdynamic sepsis is unknown.

Using a technique based on measurement of membrane potential (MPD) and formulae derived from the Nernst equation (Gibson *et al.* 1977), we studied the redistribution of water and electrolytes in the skeletal muscle of Wistar rats at intervals following induction of hyperdynamic sepsis by caecal ligation and puncture (CLP). The method used gives water distribution values that are almost identical to other electrode techniques and shows close correlation with inulin space measurements (Hinke, 1977). Animals were given a small amount of normal saline (9 g sodium chloride/l; 30 ml/kg body-weight) at the start of the experiment only and this is therefore a dehydration model. Muscle biopsies were taken and dried and underwent fat extraction to determine water content in terms of fat-free dry weight (FFDW). The specimens then underwent acid digestion to determine the electrolyte content. Plasma urea and electrolytes, blood glucose, packed cell volume (PCV) and osmolar gap were measured. Osmolar gap equals measured osmolality (by freezing point depression) minus calculated osmolality (by estimating the osmolality from the 'routine' plasma electrolytes (Weisberg, 1975)).

		Sham animals				Sepsis animals		
Period after CLP (h) . . .		0	6	12	18	6	12	18
MPD (mV)	Mean	–90·8	–90·7	–89·2	–88·7	–89·1	–80·2**	–69·9***
	SE	6·3	4·7	3·6	3·5	4·5	8·8	9·9
Na(i) (mmol/l)	Mean	6·7	8·37	7·65	8·87	8·33	11·72*	15·48**
	SE	2·77	2·83	2·56	3·51	2·02	4·97	4·62
ICW	Mean	2·84	2·84	2·75	2·52	2·85	2·92	3·02***
(kg/kg FFDW)	SE	0·20	0·18	0·23	0·85	0·24	0·25	0·16
Na(p) (mmol/l)	Mean	141·4	142·8	142·4	142·2	141·3	140·8	141·6
	SE	1·58	2·23	2·5	2·1	1·7	2·58	3·14
Osmolar gap	Mean	–4·87	–4·54	–4·05	–3·69	–3·0	–1·78	–0·48*
(mosmol/kg)	SE	2·98	1·81	1·60	1·54	3·67	3·18	2·94

Na(i), intracellular sodium; ICW, intracellular water; Na(p), plasma sodium.
Mann Whitney U-test between equivalent groups: *P<0·05, **P<0·01, ***P<0·001.

To ensure that this 'microenvironment technique' reflects the trend in overall fluid compartment size, the PCV was correlated against the extracellular water content of muscle tissue. A highly significant negative correlation existed between the two (r –0·5514, P<0·001).

We conclude that (1) membrane malfunction as detected by an altered membrane potential is present early in the development of sepsis; (2) isomotic redistribution of electrolytes takes place early in the course of sepsis and is accompanied by intracellular swelling and extracellular shrinkage; (3) despite redistribution and the development of an osmolar gap, hyponatraemia was not observed.

We suggest that antidiuretic hormone production in acute sepsis, which would be stimulated by bacterial products and the decline in circulating fluid volume, is likely to lead to fluid retention of excess administered fluid with dilution, and that this is a likely mechanism for hyponatraemia in such circumstances.

Flear, C. T. G. & Singh, C. M. (1973). *British Journal of Anaesthesia* **45**, 976–994.
Gibson, W. H., Cook, J. J. & Gatipon, G. (1977). *Surgery* **81**, 571–577.
Hinke, J. A. M. (1977). In *Glass Microelectrodes*, pp. 349–375 [M. Lavalee, editor]. New York: John Wiley & Sons.
Weisburg, H. F. (1975). *Clinical Chemistry* **21**, 1182–1185.

Are ketone bodies an appetite suppressant? By A. J. RICH, PAULINE CHAMBERS and I. D. A. JOHNSTON, *Department of Surgery, New Medical School, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne NE2 4HH*

Most appetite suppressants act centrally and are not believed to have any effect on the composition of weight loss. Oral β-hydroxybutyrate (BHB) has been used during fasting in obese patients to preserve lean body mass (Pawan & Semple, 1981) and subjects reported an absence of hunger during its administration. However, this effect has not been tested experimentally.

Three groups of adult female rats (initial weight 230–250 g) were housed in metabolism cages and provided with standard rat chow which had been bulked with methyl cellulose so as to provide one-third of their normal daily nutrient requirements for 5 d. In addition, each animal was given daily 1 ml of normal saline (9 g sodium chloride/l) (controls) or normal saline containing 0·065 g of either a racemic mixture of the sodium salt of BHB, i.e. β-DL-hydroxybutyrate (group DL) or a similar quantity of the sodium salt of the metabolically active isomer, β-D-hydroxybutyrate (group D) by gavage. Each day the voluntary intake of chow was measured and the animals were weighed.

	Chow intake (g/d)							
Period of experiment (days) . . .	1		2		3		4	
Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Controls	23·4	1·2	22·7	2·2	23·1	1·7	22·2	0·9
DL	22·7	0·8	19·2*	3·1	11·6**	1·8	11·6**	1·8
D	22·5	1·8	18·5*	3·3	13·0**	3·2	12·0**	2·7

Significantly different from controls: *$P<0·05$, **$P<0·01$.

All groups lost weight, but otherwise showed no ill-effects. During the first 24 h period, chow intake did not differ between the groups (see Table). However, voluntary chow intake declined progressively in groups D and DL and on the second, third and fourth 24 h periods fell significantly below that of the controls. There was no difference in intakes between the groups receiving the DL-racemic mixture and the D-isomer.

These results suggest that in addition to the reported prevention of excessive nitrogen losses during therapeutic starvation, BHB has an authentic anorectic effect. Further studies are required to identify the nature and extent of this effect.

Pawan, G. S. & Semple, S. J. G. (1981). *Lancet* **i**, 15–17.

The effect of prefeeding lipid on energy intake from a meal. By C. P. SEPPLE and N. W. READ, *Sub-department of Human Gastrointestinal Physiology and Nutrition, University of Sheffield, Royal Hallamshire Hospital, Sheffield S10 2JF*

Evidence from work in both animal and human beings suggests that food intake can be terminated by the stimulation of nutrient receptors within the gut (Gibbs *et al.* 1981; Welch *et al.* 1985). Infusing lipid into the human small intestine reduces food intake and induces early satiety, and jejunal infusion of lipid suppresses fasting hunger levels (Welch *et al.* (1988). These infusions are also associated with a delay in gastric emptying and the reduction in food intake may be secondary to this effect. The aim of the present study was to look at the physiological relevance of these mechanisms under normal conditions.

Previous experiments have shown that a soup homogenized with 60 g fat can delay the emptying of a meal given 20 min later. We carried out experiments on six volunteers to investigate the effect of giving the high-fat soup on the intake of either a low-fat solid meal (22 g fat/kg) or an appetizing meal, which the volunteers had chosen. The meals were given 20 min after the soup. The time taken to complete the meal, the amount of food and drink consumed and the rate of eating were measured. Subjective sensations such as hunger and fullness were measured using visual analogue scales. Further experiments investigated the effect of giving a high-fat breakfast (65 g fat, 3880 kJ (927 kcal)) *v.* a low-fat breakfast (8·1 g fat, 1750 kJ (418 kcal)) on food intake of an appetizing chosen meal at lunchtime. The two breakfasts were similar in appearance and in protein and carbohydrate contents.

Giving the high-fat soup had no effect on the amount of the low-energy meal or the appetizing meal consumed and did not influence sensations of hunger and fullness.

The high-fat breakfast significantly reduced the amount of meal eaten at lunchtime ($P<0·02$), the total energy intake from this meal ($P<0·05$) and the rate of eating ($P<0·05$).

Lunch	Breakfast			
	High-fat		Low-fat	
	Mean	SE	Mean	SE
Amount eaten (g)	790	82	1047	94
Energy intake: (kJ)	3950	393	5372	473
(kcal)	944	94	1284	113
Rate of eating (g/min)	52	4	62	5

Subjects felt significantly less hungry at lunchtime after the high-fat breakfast than after the low-fat breakfast.

Thus, although prefeeding lipid as a soup did not appear to inhibit energy intake from a subsequent solid meal, eating a high-fat breakfast inhibited energy intake from an appetizing meal consumed at lunchtime. However, the energy intake from the two meals combined was not significantly different, indicating that the energy consumption at lunchtime compensated for the amount eaten at breakfast.

Gibbs, J., Maddison, S. & Rolls, E. (1981). *Journal of Comparative Physiology and Psychology* **95**, 1003–1015.

Welch, I., Saunders, K. & Read, N. W. (1985). *Gastroenterology* **89**, 1293–1297.

Welch, I., Sepple, C. P. & Read, N. W. (1988). *Gut* **29**, 306–311.

Comparison of electrical impedance and skinfold techniques to measure body fat. By CERI J. GREEN[1], P. HAMMOND[2] and I. T. CAMPBELL[1], [1]*University Department of Anaesthesia* and [2]*Institute of Bioengineering, Royal Liverpool Hospital, Liverpool L69 3BX*

Probably the commonest technique used to measure percentage body fat is skinfold thickness used in conjunction with the formulae of Durnin & Womersley (1974). Body composition can also be assessed using total body impedance (Lukaski *et al.* 1985). This entails measuring the electrical impedance between electrodes placed on the dorsum of the hands and feet and could be useful in performing serial assessments of body composition when skinfold measurements are impracticable, such as in hospital patients confined to bed. A study has been carried out to compare values for percentage body fat derived from skinfold thickness with three different estimates derived from electrical impedance measurements using equations relating impedance to body density and to body water (Pasco & Rutishauser, 1985; R.J.L. Systems, personal communication) and a third unpublished equation used in a commercially available 'Bioelectrical Impedance Analyser' (R.J.L. Systems, Model BIA–103B, Body Composition Analyser, R.J.L. Systems, Detroit, USA) which also utilizes abdominal girth. Total body fat was calculated from body density (Durnin & Womersley, 1974) and from total body water (TBW), assuming lean body mass to be 73·2% water.

One-hundred and sixty-eight volunteers (hospital staff and surgical patients free of systemic disease) were studied (116 female, 52 male, age range 15–85 years, median 40). Measurements of weight, height, abdominal circumference, and skinfold thickness at four sites (Durnin & Womersley, 1974) were made by one observer. Total body impedance measurements were made by a second observer within 24 h. Total body resistance and reactance were measured using standard electrocardiogram electrodes, two on the dorsum of the foot and two on the dorsum of the hand on the right side of the body, using a current of 800 μA at 50 kHz. Reproducibility of the impedance measurements as represented by the coefficient of variation of repeat measurements made over 7 min were 0·1–0·6 (median 0·3)%, with new electrodes over 10 min were 0·2–2·8 (median 1·0)%, measurements made three to five times on the same day 0·5–2·0 (median 1·3)% and over 5 d 1·3–5·0 (median 2·0)%.

Compared with the skinfold measurements the TBW and body density equations overestimated percentage body fat in women under 30 years by 4·9 and 4·5% respectively ($P<0·01$). The TBW equation overestimated by 1·7% in the 30–39 year old age group ($P<0·05$), the 'Impedance System' equation underestimated by 2·6% in the 40–49 year old age group and all three equations underestimated percentage body fat by between 3 and 7% in the 50 and 60 years plus age groups ($P<0·01$). When all age groups were considered the 'Impedance System' equation underestimated by (mean (SD)) 3 (6)% ($P<0·001$), and the TBW equation overestimated by 0·6 (5·3)% (not significant) and the body density one by 0·1 (5·9)% (not significant). In the males the body density equation overestimated by 2·8% ($P<0·05$) and the 'Impedance System' equation under-estimated by 3·4% ($P<0·01$) under the age of 30 years. The 'Impedance System' equation underestimated by 4·7% ($P<0·01$) in the 30–39 year old age range and the TBW equation by 4·2% in the 40–49 year old age range. When all age groups were considered, the TBW equation underestimated by 2·1 (6·3)% ($P<0·05$), the 'Impedance System' by 2·5 (6·0)% ($P<0·01$) and the body density equation overestimated by 0·2 (5·9)% (not significant). There were no other significant differences between the skinfold technique and any other equation.

In conclusion, measurement of percentage body fat by impedence measurements used in conjunction with the body density equation appears to give the best agreement with skinfold measurements for the population as a whole. This is perhaps because the equations relating skinfold to percentage fat were derived from measurements of body density. However, for individuals the discrepancy between the two can differ by up to 10–12% fat. There is no way of knowing which of the two measurements is the more accurate.

Durnin, J. V. G. A. & Womersley, J. (1974). *British Journal of Nutrition* **32**, 77–97.

Lukaski, H. C., Johnson, P. E., Bolonchuk, W. W. & Lykken, G. I. (1985). *American Journal of Clinical Nutrition* **41**, 810–817.

Pasco, J. A. & Rutishauser, I. H. H. (1985). *Human Nutrition: Clinical Nutrition* **39C**, 365–369.

The influence of epidural analgesia on post-operative fatigue. By M. R. ZEIDERMAN[1], E. WELCHEW[2] and R. G. CLARK[1], [1]*University Department of Surgery* and [2]*Department of Anaesthetics, Northern General Hospital, Sheffield*

Persistent fatigue after surgery is associated with an increased cardio-respiratory effort to perform simple tasks such as walking (Zeiderman & Clark, 1987) and is most common in patients with post-operative weight loss (Christensen & Kehlet, 1984). It has been suggested (Christensen & Kehlet, 1984) that therapeutic regimens to lessen fatigue should include measures to decrease the magnitude of post-operative weight loss. Epidural analgesia results in afferent neurogenic blockade, thereby reducing the metabolic response to surgery, and its use has been shown to improve post-operative nitrogen balance (Scott & Kehlet, 1988). The aim of the present study was to examine the influence of epidural analgesia on post-operative fatigue and cardio-respiratory function in patients admitted for abdominal surgery.

Twelve patients (six male, six female; age range 27–78 years), admitted for elective operation, were randomized to receive post-operative analgesia with intermittent intramuscular morphine or a continuous infusion of epidural fentanyl. Fatigue was assessed on an analogue scale from 1 (fit) to 10 (fatigued). Steady-state measurements of oxygen consumption (V_{O_2}), minute ventilation (V_E) and heart rate were made by ergospirometry at rest and while walking on a treadmill at a workload of 20 kpm/min. Measurements were made before surgery and on the third post-operative day. Results are expressed as the change (Δ) in measurements, i.e. those made while walking minus those made at rest.

		Fatigue (arbitrary units)		Δ Heart rate (beats/min)		Δ V_{O_2} (l/min)		Δ V_E (l/min)	
		Epidural	Non-epidural	Epidural	Non-epidural	Epidural	Non-epidural	Epidural	Non-epidural
Preoperation	Mean	2·8	2·7	8	21†	0·21	0·36†	4·5	0·5
	SE	0·4	0·5	2	6	0·04	0·02	1·3	0·6
Post-operation	Mean	8·6**	7·0**	14*	21	0·33*	0·38	7·2*	7·3
	SE	0·7	0·8	3	4	0·04	0·04	1·7	1·0

Comparisons of preoperation *v.* post-operation values were made by paired Wilcoxon test: *$P<0·05$, **$P<0·01$.

Comparison of epidural *v.* non-epidural values were made by the Mann-Whitney U test: †$P<0·05$.

The use of epidural anaesthesia was associated with an increased cardio-respiratory effort in the performance of ambulatory tests and a greater feeling of fatigue. Such changes may be important in limiting the mobility of post-operative patients.

Christensen, T. & Kehlet, H. (1984). *British Journal of Surgery* **71**, 474–476.
Scott, N. B. & Kehlet, H. (1988). *British Journal of Surgery* **75**, 299–304.
Zeiderman, M. R. & Clark, R. G. (1987). *British Journal of Surgery* **74**, 1161.

The effects of metabolic consequences of surgery on post-operative mobility. By S. E. STOCK[1], M. B. CLAGUE[2] and I. D. A. JOHNSTON[1], [1]*Department of Surgery, New Medical School, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne NE2 4HH* and [2]*Newcastle General Hospital, Newcastle upon Tyne NE4 6BE*

Post-operative fatigue is a well-recognized but poorly understood phenomenon, experienced during recovery from surgery, which may have socio-economic consequences for all concerned. Recent work, based on a subjective assessment of fatigue, implicated the loss of body nutritional stores as a factor in its aetiology (Christensen & Kehlet, 1984; Christensen *et al.* 1985).

Ambulatory monitoring of activity was undertaken in 106 patients before surgery, employing a lightweight cassette recorder and sensors to monitor posture and movement over a 24 h period in the patients' home environment. Anthropometric measurements of nutritional status were made and clinical details of patients and their surgery were recorded. The recordings and measurements were repeated 2, 4, 6 and 12 weeks after surgery. A single post-operative value for each activity (time spent lying down, sitting and standing, and number of steps walked) in each patient was derived using weighted means and the results assessed by computer using multiple regression analysis to identify variables influencing patient activity post-operatively.

Change in time standing (S, h) after surgery was related to both weight change (W, kg) at 2 weeks ($t = 3{\cdot}80$, $P<0{\cdot}005$) and duration of surgery (D, h; $t = -2{\cdot}32$, $P<0{\cdot}05$; $S = 8{\cdot}08 + 0{\cdot}40\ W - 0{\cdot}87\ D$). Increase in time spent lying down (L, h) was only related to muscle loss (M, cm) at 2 weeks ($t = 3{\cdot}63$, $P<0{\cdot}005$; $L = 15{\cdot}14 + 0{\cdot}91\ M$), change in fat stores just failing to reach significance ($P = 0{\cdot}066$). Number of steps (N) walked was only influenced by weight change at 2 weeks (W, kg; $t = 2{\cdot}35$, $P<0{\cdot}05$; $N = 15869 + 1391\ W$).

Reduction in post-operative mobility is related to the metabolic consequences of the surgery and its effects on depletion of nutritional stores. The technique described here might be of value in assessing the role of nutritional support in reducing post-operative fatigue.

This work was funded by an MRC project grant.

Christensen, T., Hougard, F. & Kehlet, H. (1985). *British Journal of Surgery* **72**, 63–65.
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Cytokine regulation of acute-phase protein synthesis by human hepatocytes. By Y. S. TAKTAK, D. THOMPSON, S. W. EVANS, A. M. GRANT and J. T. WHICHER, *Department of Chemical Pathology, Old Medical School, Leeds University, Leeds LS2 9JT*

Infection or inflammation results in the orderly activation and expression of a group of genes in the liver producing proteins known as acute phase proteins (APP). There is still controversy about which agents are responsible for regulation of this response. We have investigated the role of three cytokines (IL-2 1β, IL-6 and TNFα) and leucocyte-conditioned medium (LCM) on the regulation of APP synthesis by two human hepatocyte cell lines (Chang and HepG2).

Cells (4×10^5/ml) were cultured as sub-confluent monolayers in twenty-four well Falcon culture plates in Modified Eagles Medium (MEM). Different concentrations of cytokine or (LCM) were added to the cells for 40 h. The culture supernatant was then replaced with 36 Ci [^{35}S]methionine in MEM. After 3 h the supernatant fraction was collected and labelled proteins were analysed by sodium dodecyl sulphate–polyacrylamide gel electrophoresis and fluorography.

Action of cytokines and LCM on hepatocyte APP synthesis

		α1GP	α1aCT	α1aT	FN	CRP	SAA	Alb	pAlb	TF
Chang	LCM	+ + + +	ND	+ + + +	ND	+ + +	+ + +	– – –	– – –	– – –
	IL-1β	o	o	+ +	ND	o	o	– –	– –	– –
	TNFα	o	o	o	ND	o	o	o	o	o
	IL-6	o	o	o	ND	o	o	o	o	o
HepG2	LCM	+ + +	+ +	+ +	+ + +	ND	+ + +	ND	– –	ND
	IL-1β	+	o	o	+ + +	ND	+ + +	ND	– –	ND
	TNFα	– –	o	o	– –	ND	o	ND	– –	ND
	IL-6	+ +	+ + +	+ +	+ + +	ND	o	ND	o	ND

α1AG, α1-acid glycoprotein; α1aCT, α1-anti-chymotrypsin; α1aT, α1-anti-trysin; FN, fibrinogen; CRP, C reactive protein; SAA, serum αamyloid A; Alb, albumin; pAlb, pre-albumin; TF, transferrin.

Changes in levels of APP: +, increase; –, decrease; o, no change; ND, not determined.

*Increased over control but inverse dose response.

It is apparent that whilst the effect of LCM on both Chang and HepG2 was similar, the effect of individual cytokines was very different. In fact IL-6 had no effect on Chang but stimulated APP to a greater extent than LCM in HepG2. Initial investigations have revealed that a component of LCM responsible for regulation of positive APP synthesis by Chang cells is a low molecular weight, relatively heat-stable material. We also have evidence that Chang cells do not express the IL-6 receptor.

The evidence suggests that whilst IL-6 is a potent regulator of acute phase reactants in one cell line (HepG2), the inability of a second cell line (Chang) to respond to IL-6 does not prevent proper induction of APP synthesis by LCM. It is suggested that alternative low molecular weight mediators are synthesized by leucocytes and may play a role in the regulation of the acute phase response.

The plasma interleukin-6 (IL-6) interleukin-1 (IL-1) and tumour necrosis factor (TNF) response to elective surgery. By A SHENKIN[1], W. D. FRASER[1], J. J. SERIES[1], P. WINSTANLEY[1], C. MCCARTNEY[2] and H. J. G. BURNS[2], *Departments of* [1]*Biochemistry* and [2]*Surgery, Glasgow Royal Infirmary, Glasgow G4 0SF* and J. VAN DAMME, *Rega Institute, Leuven, Belgium*

IL-6 (B cell stimulating factor 2, interferon 2) is probably a key mediator of the acute phase protein response to trauma. The kinetics of IL-6 release post-trauma have not been established. We have investigated changes in serum IL-6 following cholecystectomy (six patients) and resection of colonic neoplasm (five patients). In addition, we have assayed for plasma IL-1 and TNF.

Multiple venous blood samples were taken before, during and after operation. Serum was analysed for IL-6 by hybridoma growth stimulation assay using mouse hybridoma 7TD1 and purified IL-6 as standard. 1 unit IL-6 produced half maximal stimulation and is approximately 1 pg. C-reactive protein (CRP) was measured by fluorescence polarization. Plasma was also analysed for IL-1 by a two cell bioassay (LBRM/HT2A) (Series *et al.* 1988) and for TNF by radioimmunoassay (Medgenix, Brussels).

Serum IL-6 increased in all patients within 1 h of incision, reaching a maximum between 2 and 4 h after incision for cholecystectomy (median 50 U/ml; range 22–79 U/ml) and between 4–8 h after incision for colorectal surgery (median 72 U/ml; range 32–354 U/ml) (not significant; Mann-Whitney test). The maximum IL-6 correlated with length of operation (cholecystectomy r 0·95; colonic resection r 0·89; overall r 0·71). Serum IL-6 returned to basal level by 48–96 h post-operation. There was no significant change in plasma endotoxin concentration in either group.

Serum CRP was detectable (>10 mg/l) by 8–12 h of incision, maximum concentrations being reached by 36–48 h in both groups. Maximum serum CRP did not correlate with maximum serum IL-6 concentration or length of operation. Although some pre- and post-operation samples had detectable IL-1 there was no consistent increase, and no patient developed detectable plasma TNF (assay sensitivity 100 pg/ml).

All of these patients made an uneventful recovery. One other patient who subsequently died developed septicaemia and respiratory failure post-colonic resection. He had extremely high serum IL-6 (4500 U/ml at 12 h post-incision) and also had the highest peak CRP (320 mg/l). This patient also had detectable plasma IL-1 at 12 h but TNF was not detected in any sample.

We conclude that serum IL-6 but not IL-1 or TNF increases rapidly following elective surgery, that this may be related to the magnitude of the surgery, and this precedes the rise in serum acute phase proteins. Measurement of IL-6 in serum may be an early guide to the extent of tissue damage and of prognostic value in development of post-operative complications.

We gratefully acknowledge support of the Scottish Hospitals Endowment Research Trust.

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Leukotrienes and prostaglandins may be involved in the hypothermic effects of recombinant TNFα in rats. By D. C. BIBBY and R. F. GRIMBLE, *Human Nutrition Department, Southampton University Medical School, Southampton SO9 3TU*

Fevers and chills are side effects which may limit the usefulness of recombinant tumour necrosis factor α (TNFα) as an antineoplastic agent. In rats both lethal (Kettlehut *et al.* 1987) and sublethal (Bibby & Grimble, 1989) doses of TNFα produce a rapid fall in temperature. Indomethacin has been shown to prevent both the fall in temperature and lethal effects of TNFα (Kettlehut *et al.* 1987). As endotoxin is a potent inducer of TNFα production and leukotrienes have been implicated in endotoxin-induced shock (Hagman *et al.* 1985), the role of leukotrienes and prostaglandins in TNFα-induced hypothermia was investigated using a lipoxygenase inhibitor (AA861) and a cyclooxygenase inhibitor (indomethacin) at two equimolar doses.

Male Wistar rats (161 ± 5 g), individually caged and kept at 25° were pretreated with an intraperitoneal injection of either sterile nonpyrogenic saline (9 g sodium chloride/l), or AA861 (0·75 and 7·5 mg/kg; Takeda Chemical Co., Osaka, Japan) or indomethacin (0·79 and 7·9 mg/kg), 2 h before an intravenous (i.v.) injection of either sterile nonpyrogenic saline or recombinant human TNFα (300 μg/kg; BASF Knoll AG, Ludwigshaven, FDR). Rectal temperatures were measured throughout the experimental period until 6 h after the i.v. injections.

A rapid fall of 1·4° occurred 1 h after injection of recombinant TNFα in animals with no drug pretreatment. However, pretreatment with both doses of AA861 and with the lower dose of indomethacin prevented this fall. The highest dose of indomethacin delayed the onset of the fall by 2 h and extended its duration. In all cases where the fall was prevented, a fever occurred 4 h after i.v. injection of TNFα. Peak values were 0·6° and 0·9° for the 0·75 and 7·5 mg/kg doses of AA861 and 1·1° for the 0·79 mg dose of indomethacin.

The results suggest that febrile effects of TNFα may become apparent if hypothermic effects are prevented and that while febrile effects of TNFα may involve prostaglandins, leukotrienes may play an important role in the hypothermic effects of TNFα. The exacerbating effect of high doses of indomethacin on hypothermia may be due to increased arachidonate substrate availability for leukotriene production following blockage of the cyclooxygenase pathway of arachidonate metabolism.

The authors thank BASF/Knoll AG for the gift of TNFα and the Takeda Chemical Company for the gift of AA861.

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Does subclinical vitamin deficiency predispose to infection? By N. D. PENN[2], L. PURKINS[1], J. KELLEHER[1], R. V. HEATLEY[1] and B. H. MAACIE-TAYLOR[2], *Departments of* [1]*Medicine* and [2]*Medicine of the Elderly, St James's University Hospital, Leeds LS9 7TF*

Nutritional deficiency has been stated to be the commonest cause of secondary immunodeficiency in man (Chandra *et al.* 1978). The role of the dietary anti-oxidants in immune function may be particularly important due to their protective role in preventing oxidative damage of cell membranes by free radicals.

The present study was in two parts. First, the dietary anti-oxidants vitamins A, C and E were assessed in three elderly populations; an elite community group (*n* 18, age range 71–86 years), a group of acutely ill patients admitted to hospital (*n* 46, age range 74–93 years) and a group of long-stay patients (*n* 19, age range 77–96 years). Second, the effect of supplementation for 28 d with vitamin C (100 mg), vitamin A (26 mg) and vitamin E (50 mg) on cell-mediated immune function was assessed in the long-stay group (*n* 19). Assessment of cell-mediated immune function included lymphocyte and T cell counts, T cell subsets (T4 and T8) and in vitro lymphocyte culture with phytohaemagglutinin (PHA).

Individuals with vitamin deficiency (vitamin C <15 μg/10^8 cells, vitamin A <300 μg/l, vitamin E <5·2 mg/l) were found in all three groups. Of the acute admissions, 69% had an abnormal vitamin profile compared with 53% of the long-stay patients and 22% of the elite. The lowest mean vitamin levels were found in the acutely ill group, with vitamins C and A being significantly lower ($P<0·01$) than in the elite. Vitamin C was found most frequently to be deficient followed by vitamin A. Supplementation for 28 d improved the vitamin status of the long-stay patients, with a significant increase in vitamin A (mean (SE)) from 521 (45·9) μg/l to 600 (52·3) μg/l ($P<0·05$). This was associated with an improvement in cell-mediated immunity.

	Before supplementation		After supplementation		
	Mean	SE	Mean	SE	*P* value
T cell no. (10^8 cells/l)	7·65	1·32	10·0	1·06	<0·05
T4 subset (10^8 cells/l)	5·45	1·01	7·72	1·03	<0·05
T4:T8 ratio	1·92	0·13	2·88	0·31	<0·01
PHA 1/200 (dpm)	9562	2632	15690	2656	<0·01
PHA 1/400 (dpm)	3355	840	12863	2724	<0·05

dpm, disintegrations/min

In conclusion the anti-oxidant status of elderly patients is often compromised. This most frequently occurs in long-stay and acutely ill patients. Anti-oxidant supplements improved cellular immunity in long-stay elderly patients. We suggest that in the acutely ill group either anti-oxidant requirements are increased or deficiency predisposes to illness and, in particular, infection.

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Copper balance in intravenously fed patients. By ANNE M. CRUICKSHANK, PAMELA RODGERS, PEGGY DUNBAR, GORDON S. FELL and ALAN SHENKIN, *Department of Biochemistry, Glasgow Royal Infirmary, Glasgow G4 0SF*

Based on recommendations for an oral diet, copper requirements during total parenteral nutrition (TPN) have been calculated at about 20 μmol/d (Shenkin & Wretlind, 1978). However, Shike *et al.* (1981) have suggested that Cu balance may be obtained with 6–10 μmol/d. Cu is largely secreted in bile and hence losses may be high in patients with biliary or intestinal fistulae.

The aim of the present study was to assay Cu losses in TPN patients with biliary/intestinal fistulae, ileostomies and drains *in situ* and hence assess the adequacy of Cu provision in intravenous nutrition.

Nine surgical patients (one female, eight males; mean age 56 (SD 1·5 years) who had received TPN for a minimum of 24 h and who had intestinal (*n* 7) or biliary (*n* 2) fluid losses were studied. Cu supplements (20 μmol Cu, Additrace®, Kabi Vitrum) were added or omitted for periods of at least three consecutive days in each patient in random order. All urine, fluid and faecal (if any) losses were collected daily and the Cu contents measured.

There was no significant difference (Wilcoxon test) between average daily Cu excretion during Cu supplementation (median 2·0, range 0·2–23·2 μmol/d) and that when supplementation was withheld (median 3·0, range 0·2–30·1 μmol/d). Cu content of fluid was dependent on the source: average content (μmol/l) in a pure biliary fistula being 36·1; in a mixed biliary/intestinal fistula 9·85; and in patients losing small-bowel fluid (median) 1·0, range 0·7–5·5.

Urinary Cu excretion (μmol/d) did not change significantly with Cu supplementation (with Cu, median 1·0, range 0·90–3·7; without Cu, median 1·0, range 0·4–8·3).

During the period of Cu supplementation, the patient with a pure biliary fistula had negative Cu balance (–8·6 μmol/d) whereas all patients losing small-intestinal fluid were in positive balance (+13·8 to +18·7 μmol/d). Serum Cu concentration did not change over the study period (pre-study mean 22·2 (SD 3·5); post-study 21·5 (SD 3·7) μmol/l).

Intestinal and biliary excretions of Cu were therefore independent of intravenous intake. Urinary excretion of Cu was relatively small. Patients losing significant volumes of bile may require supplements in excess of 20 μmol/d. Patients losing small-bowel fluid probably do not require as much Cu but requirements depend on the volume and type of intestinal fluid loss.

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The effects of fibre and phytate on zinc absorption in normal subjects. By R. I. RUSSELL, A. DUNCAN, R. R. MOSS, D. A. FARAH, and J. C. WYATT, *Gastroenterology Unit, Royal Infirmary, Glasgow G31 2ER*

We have previously demonstrated that small amounts of wheat bran can significantly impair zinc absorption in normal subjects (Farah *et al.* 1984). It is unclear, however, which of the principal components of wheat bran (phytate or fibre) is responsible. We have now studied the individual effects of fibre and phytate on the absorption of Zn in normal human volunteers. Subjects were randomized into one of four groups and given test meals with different amounts of fibre and phytate. Fibre content was determined by the method of Southgate (1969), modified by Englyst *et al.* (1982). Phytate was measured by the method of Holt (1955), modified by Davies & Reid (1979). Group A received 20 g Rice Krispies containing low fibre (0·33 g) and low phytate (0·08 g); group B 20 g Rice Krispies with added 0·36 g low-phytate fibre (0·33 g), high phytate (0·44 g); group C 20 g dephytinized bran containing high fibre (10·51 g) and low phytate (0·10 g); and group D whole bran containing high fibre (10·18 g) and high phytate (0·44 g).

Zn absorption was assessed by whole body monitoring after subjects were given 4·0 μCi ^{65}Zn in a 10 ml solution of Zn sulphate containing 15 mg elemental Zn. Zn content of the Rice Krispies and wheat bran preparation were measured by atomic absorption spectrophotometry and were approximately equivalent in all the preparations used. Group A (low fibre, low phytate) had a percentage Zn absorption of 15·65 (SD 5·5); group B (low fibre, high phytate) 3·4 (SD 1·43); group C (high fibre, low phytate) 7·0 (SD 4·08), and group D (high fibre, high phytate) 2·86 (SD 1·36). Group D showed a significant reduction in percentage Zn absorption compared with group A ($P<0·005$), and group B had lower Zn absorption than group A ($P<0·005$).

These results indicate that phytate is more important than fibre in reducing Zn absorption. This observation has important clinical implications with respect to the use of high-bran diets for lengthy periods, and raises the possibility of the future clinical use of diets containing dephytinized bran.

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Nutrition improved with intensive enteral feeding in children awaiting liver transplantation. By C. P. J. CHARLTON[1], E. BUCHANAN[1], C. HOLDEN[1], A. BAKER[1], I. W. BOOTH[2] and M. J. TARLOW[1], [1]*Liver Unit, Birmingham Children's Hospital Ladywood Middleway, Ladywood, Birmingham B16 8ET* and [2]*Institute of Child Health, University of Birmingham, Francis Road, Birmingham B16 8ET*

An initial study of twenty-four patients attending the liver clinic showed five wasted (weight for height <2 SD) and nine stunted (height <2 SD). Ten such children with cirrhosis (biliary atresia, six; other causes, four) with median age 9 months (range 4 months–8 years) who were being considered for liver transplantation were prospectively studied for 8 weeks intensive enteral feeding. Continuous nasogastric infusions were given using a formula incorporating whey protein enriched with branched-chain amino acids, (BCAA; as % of protein: whey protein 73%, added BCAA 27%, total BCAA 31% (supplied as Generaid, Scientific Hospital Supplies, Liverpool)), fat as 34% medium-chain and 66% long-chain triglycerides, and dextrose polymer (supplied as Duocal (Scientific Hospital Supplies), containing (g/kg) carbohydrate 727 and fat 223). Dietary assessments, biochemical indices and anthropometric measurements were calculated before and after intensive enteral feeding. The weight (Wt) and triceps skinfold thickness (TSF) were expressed as standard deviation (SD) scores, which are the observed measurement minus the median for the reference population divided by the reference population SD (reference values 0–1 years, Sann *et al.* 1988; 1–8 years, Tanner, 1973). The mid-upper arm circumference (MAC) and the arm muscle area (AMA) were expressed as percentages of the medians for the reference population (Frisancho, 1981).

		Wt SD score		TSF SD score		MAC % of median		AMA % of median	
Study	Energy intake (% requirements)*	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pre	129	−2·6	0·9	−3·0	1·7	76·9	7·0	67·2	12·5
During	168								
Post		−1·3	0·8	−0·7	1·1	95·1	4·7	90·2	12·2
P		<0·001		<0·001		<0·001		<0·001	

*Food and Agriculture Organization/World Health Organization/United Nations University (1985).

The dramatic improvement in nutritional status in all ten children was associated with parental reports of less crying and more playing. Such intervention should be started early to improve growth and well-being in children who are potential liver transplant candidates.

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Urea absorption by the functioning human colon. By B. J. MORAN[1], C. PERSAUD[2], A. A. JACKSON[2], *Departments of* [1]*Surgery* and [2]*Human Nutrition, University of Southampton Medical School, Southampton SO9 3TU*

It is becoming increasingly accepted that the colon, with its normal microflora, plays a significant part in human nutrition and metabolism. Its role has been largely neglected, partly due to the relative inaccessibility of the normal, functioning colon. The intestinal hydrolysis of urea occurs mainly in the colon and is known to be a function of the microflora. This function is thought to be of importance in hepatic and renal disease, may play a role in the genesis of colonic cancer, and is a potential source of nitrogen and amino acids in states of low-protein intake or increased demand for protein. Previous investigators have used perfusion techniques and the defunctioned colon as a model, and have concluded that the human colon is virtually impermeable to urea (Wolpert *et al.* 1971; Bown *et al.* 1975). However, a colon devoid of its normal contents is unlikely to be representative of normal physiological function.

The movement of urea and nitrogen through the bowel can be traced safely and non-invasively with the use of ^{15}N-labelled urea (Jackson *et al.* 1984). We studied twelve male patients, who were admitted for a colonoscopy and found to have a normal colon. After completion of colonoscopy a tracer dose of [$^{15}N^{15}N$]urea, 1·5 mg/kg, was introduced through the biopsy channel of the colonoscope and flushed with 10 ml normal saline (9 g sodium chloride/l). Six patients had urea placed in the caecum and six distal to the splenic flexure. All urine and stool passed in the next 72 h were collected and analysed for enrichment with stable isotope in urea and total N, by isotope ratio mass spectrometry.

	% excreted as [$^{15}N^{15}N$]urea		% excreted as [$^{15}N^{14}N$]urea	
	Median	Range	Median	Range
Right colon	6·4	2·0–9·4	18·3	5·2–29·4
Left colon	3·7	1·2–10·0	8·4	2·0–34·0

Less than 5% of the dose was recovered in the stool. Although a proportion of the dose was hydrolysed, reformed into urea and excreted as [$^{15}N^{14}N$]urea, the presence of [$^{15}N^{15}N$]urea in the urine implies that the functioning human colon is permeable to urea. The majority of the label, 74% from the right colon and 82% from the left colon, could not be recovered from urine and stool and is presumed to have been retained by the body. As ammonia in the portal tract is preferentially converted to urea, the implication is that the label had been actively incorporated into amino acids at the level of the large bowel.

These results suggest that the absorptive capability of the functioning human colon has been underestimated. The majority of research into human colonic function has entailed preliminary cleansing, followed by perfusion of the solution in question, with sampling of the effluent. The present study would suggest that much of the previous work on the cleansed colon might not represent colonic function and requires re-evaluation.

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The effect of amino acids on the stability of total parenteral nutrition mixtures. By G. HARDY, *Oxford Nutrition, PO Box 31, Oxford OX4 3UH*

Stable 'All-in-one' mixtures for total parenteral nutrition (TPN) can now be prepared in the hospital pharmacy providing that sufficient consideration is given to the various physico-chemical factors influencing stability. We have previously described the protective effect that amino acids and buffering agents bestow on lipid mixtures (Hardy *et al.* 1983), and the stability of various individual TPN mixtures has been subsequently reported (Jeppsson & Tengborn, 1987).

The aim of the present study was to compare the stability of isoenergetic (9200 kJ (2200 kcal)), isocationic (565 mmol/l) TPN regimens containing different concentrations of amino acids, 14 g nitrogen (LoN) or 28 g N (HiN) prepared from two different amino acid solutions: Vamin Glucose® (Kabi Vitrum, Sweden) and Eloamin® (Leopold & Co., Austria).

The mixtures were prepared in triplicate from 20% Intralipid® (Kabi Vitrum), glucose (300 g/l) and Eloamin or Vamin Glucose in 3 litre Mixieva® bags (Miramed, Italy). The total concentrations of sodium, potassium, calcium, magnesium and phosphorus were 237·5, 182·5, 17·5, 7·5, 37·5 mmol respectively. Bags were stored at 4° and sampled at 7 and 30 d to determine particle size distribution (percentage of particles <1 μm; PSD), pH and free fatty acids (FFA) by standard methods.

After storage for 7 d, PSD for all mixtures was relatively unchanged (95% <1 μm). FFA and pH also remained virtually constant. After 30 d both LoN mixtures and the Vamin Glucose HiN mixture had deteriorated, with PSD ranging from 61 to 65% <1 μm. pH had also changed in the HiN mixture (5·2 to 4·91) and FFA had increased (136 to 267 μmol/l). In contrast the Eloamin HiN mixture remained stable at 30 d (PSD 93% <1 μm, pH 6·14 and FFA 120 μmol/l).

In an extension of the study, HiN mixtures based on Vamin 18 (KabiVitrum), Aminoplex 24 (Geistlich, Chester) and Synthamin 14 (Baxter) all exhibited similar stability profiles to that of Eloamin after 30 d (PSD 90 to 95% <1μm, pH>6·0).

The principal difference in the various amino acid formulations is in the relative proportions of the basic amino acids (BAA) lysine, arginine and histidine, compared with the acidic amino acids (AAA) aspartic and glutamic acids. With the exception of Vamin Glucose, all products have an excess of BAA, with a ratio of BAA:AAA ranging from 2:1 to 6:1. Vamin Glucose on the other hand has a ratio of 2:3, i.e. an excess of AAA.

Increased quantities of BAA therefore appear necessary to offset the de-stabilizing effect of AAA and electrolytes. The ratio of BAA:AAA needs to be at least 1·5:1 and the initial pH>6 in order to maintain mixture stability during long-term storage. This requirement is satisfied by Eloamin, Aminoplex, Synthamin and Vamin 18, which have comparable stability after 30 d storage.

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When, why and which home parenteral nutrition patients die? By N. A. SCOTT, M. A. STOKES and M. H. IRVING, *Department of Surgery, Hope Hospital, Eccles Old Road, Salford M6 8HD*

A total of fifty patients (22%) of 228 recorded on the UK home parenteral nutrition (HPN) register, between 1977 and 1987, died while on HPN. This retrospective survey of the register was conducted to discover when those patients died, what the cause of death was and which patients died.

Exactly 50% of all HPN deaths (*n* 25) occurred within the first 6 months of HPN and the large majority (*n* 42, 84%) within 18 months of starting HPN. A greater proportion of those patients started on HPN in the period 1977–1981 died on HPN (10/29, 34%) than did so in the latter years surveyed (36/199, 18%).

Patients died because of complications of their HPN (*n* 14; 28%), progression or complications of their underlying disease (*n* 30; 60%), or, in six (12%) patients, because of other reasons (renal tubule acidosis, *n* 2; cardiac arrest, *n* 2; cerebral haemorrhage, *n* 1; bronchial carcinoma, *n* 1). Complications of the HPN that were associated with death included septicaemia (*n* 6), superior vena caval thrombosis (*n* 3), endocarditis (*n* 1), line reinsertion (*n* 1) and hepatic failure (*n* 3).

Death on HPN was associated with slightly older patients (median age HPN deaths 39 years *v.* 36 years for all HPN registered patients) and the male sex (HPN deaths, male sex 28/50 (56%); all HPN patients, male sex 91/237 (39%); $P<0{\cdot}05$). The mortality rate of patients on HPN varied considerably according to the underlying disease that led to HPN. Crohn's patients had the lowest mortality on HPN; patients with scleroderma or malignancy had a much higher mortality rate on HPN.

	Patient deaths	
Disease	No.	%
Crohn's disease	9/100	9
Mesenteric vascular occlusion	9/29	31
Malignancy	16/26	61
Scleroderma	4/6	67

The proportion of patients who were to die on HPN but managed to return to full-time or part-time work or housework (*n* 14; 28%) was much less than for all patients on the HPN register (*n* 159; 67%).

HPN should be used with caution in patients with malignant disease and scleroderma. Although only a minority of patients die due to a direct complication of their HPN, further study is required to eliminate these potentially preventable causes of death.

The value of home parenteral nutrition in Crohn's disease. By N. A. SCOTT, M. A. STOKES and M. H. IRVING, *Department of Surgery, Hope Hospital, Eccles Old Road, Salford M6 8HD*

Of 237 patients on the UK home parenteral nutrition (HPN) register, 100 (42%) were commenced on HPN for complications of Crohn's disease. The three principal indications for HPN in Crohn's disease were the short bowel syndrome (*n* 60), fistulating disease (*n* 29) and disease exacerbation (*n* 41). A total of thirty patients had two of these problems while on HPN.

Patients with Crohn's disease on HPN had a significantly better lifestyle than patients on HPN for other reasons:

	HPN Crohn's (*n* 100)		HPN Other (*n* 137)	
	No.	%	No.	%
Full-time work	58	58	46	34*
Part-time work	21	21	31	23
Cannot work	20	20	39	28
Housebound	1	1	21	15*

*$P<0{\cdot}05$.

No complications, requiring admission to hospital, were seen in fifty-two patients. In the remaining forty-eight Crohn's patients, the incidence of all complications (0·28/patient per year) and septic complications (0·13/patient per year) was significantly lower than for all patients on the HPN register (all complications 0·80/patient per year, $P<0{\cdot}001$; septic complications 0·35/patient per year, $P<0{\cdot}01$).

The duration of HPN was related to the original Crohn's complication. Patients with the short bowel syndrome required HPN for longer periods (median duration 18 months) than those with either fistulating disease (median duration 5 months) or an exacerbation of their Crohn's disease (median duration 5 months). A total of forty-one of the 100 Crohn's patients continue on HPN. Of the other fifty-nine, eighteen have stopped because of either HPN-related complications (*n* 8) or because they died while on HPN (*n* 9); four patients have ceased HPN for other reasons. Normal oral feeding has been re-established in thirty-eight patients (short-bowel syndrome, *n* 15; fistulating disease, *n* 9; exacerbation of Crohn's disease *n* 14).

Analysis of a subgroup of thirty-five Crohn's patients on HPN (short bowel, *n* 21; fistulae or disease exacerbation, *n* 14) was performed to delineate changes in weight, serum albumin and mid-arm muscle circumference (MAMC) while on HPN. In the twenty-one short-bowel patients the mean of all three nutritional indices increased (weight 51·2 → 56·1 kg; albumin 29·8 → 41·5 g/l; MAMC 201 → 217 mm) but this improvement was only significant for serum albumin ($P<0{\cdot}05$). Amongst the other fourteen Crohn's patients, with fistulation or an exacerbation of their disease, both the increase in weight and serum albumin was significant (weight 44·4 → 53·0 kg, $P<0{\cdot}05$; albumin 27·7 → 39·7 g/l, $P<0{\cdot}05$; MAMC 206 → 219 mm).

HPN is a safe and effective treatment for patients with intestinal failure due to complicated Crohn's disease.

Cardiac complications of total parenteral nutrition: the role of echocardiography. By T. O'Hanrahan, H. Chamsi-Pasha, M. Stokes and M. H. Irving, *Department of Surgery, Hope Hospital, Eccles Old Road, Salford M6 8HD*

The use of central venous catheters for total parenteral nutrition (TPN) has become commonplace in adults and children with serious illness and injury. Cardiac complications, which include bacterial endocarditis, right atrial thrombosis, and catheter tip thrombosis, have rarely been recorded.

Two-dimensional echocardiography (2-D echocardiography) has been shown to be useful in detecting intra-cardiac masses. We report four cases which demonstrate three cardiac complications secondary to TPN, where the diagnosis was made by echocardiography.

Case no.	1	2	3	4
Sex	Male	Male	Male	Female
Age	21	32	17	19
Diagnosis	Inflammatory bowel disease	Crohn's disease	Volvulus	Polyarteritis nodosa
Indication TPN	Bowel rest	Fistulae	Short bowel	Short bowel
Admission	Pneumonia	Fistulae	Pulmonary embolus	Septicaemia
Cardiac signs	None	Aortic incompetence	None	Tachycardia
2-D Echocardiography findings	Valvular vegetations	(a) Aortic incompetence (b) Right atrial thrombus	Right atrial thrombus	Catheter tip thrombus
Outcome	Surgery: valve replacement	Surgery: thrombectomy/ valve replacement	Surgery: thrombectomy	Dissolution therapy

Patients on HPN with suspected catheter sepsis or new cardiac symptoms should undergo 2-D echocardiography to exclude a cardiac lesion.

https://doi.org/10.1079/PNS19890043 Published online by Cambridge University Press

How can selenium deficiency be detected in patients on home parenteral nutrition? By J. L. SHAFFER[1], H. CHAMSI-PASHA[2], M. STOKES[2], A. SHENKIN[3], I. HOLBROOK[1], and M. H. IRVING[2], *Departments of* [1]*Medicine* and [2]*Surgery, Hope Hospital, Salford, Lancs M6 8HD* and [3]*Department of Biochemistry, Glasgow Royal Infirmary, Glasgow G4 0SF*

Patients on long-term parenteral nutrition are at risk from developing skeletal and cardiac myopathies. Selenium deficiency has been implicated. The currently accepted method for assessing Se status is the measurement of plasma levels of Se and the Se-dependent enzyme, erythrocyte glutathione peroxidase (*EC* 1.11.1.9; RCGP). An alternative approach is to monitor any potential effect of Se depletion on a physiological function. We have used M-mode echocardiography (Hewlett Packard) to assess cardiac muscle function.

In thirty-two patients (sixteen male, sixteen female, on home parenteral nutrition for 0·5–8 years) the mean Se was 0·69 μmol/l (95% confidence limits 0·6–0·78) and RCGP 11·4 U/g haemoglobin (range 10–12·8). Mean percentage fractional shortening was 32·6% (30·4–34·8), and ejection fraction was 60·5% (57·2–63·8). There was a significant correlation between Se and fractional shortening percentage (r 0·448, $P<0·005$, Spearman) and ejection fraction (r 0·448, $P<0·005$) but not erythrocyte glutathione with the two cardiac indices. Nineteen patients had a low ejection fraction (<64%); seventeen of these had a low Se (<0·8 μmol/l). None of the remaining thirteen had an abnormal ejection fraction or plasma Se (specificity 87%, sensitivity 100%).

Repeat sampling after 3–9 months and after variable Se supplementation in seventeen of these patients showed a rise in both Se to 0·8 μmol/l (0·69–0·93) and ejection fraction to 65% (60·5–69·5) (specificity 89%, sensitivity 80%). Vitamin E levels as assessed by total tocopheral remained within the reference range throughout the study.

Echocardiography is a widely available, non-invasive test that appears to predict the effects of Se status on cardiac muscle function. Many patients on home parenteral nutrition have a sub-normal cardiac performance.