靜脈內營養者身體組成的研究

Body composition studies with intravenous nutrition

R.C. Smith

University Department of Surgery, Royal North Shore Hospital, St Leonards, NSW, Australia.

Intravenous nutrition is a complex nutritional support system which is used for patients who are unable to take food through the normal enteric route. The nutritional protocols are complex and the patients being studies have many complicating factors which make determination of outcome difficult to measure. Body composition measures have proven to be very accurate in determining appropriate protocols for patient care. Because most of the patients being studied have a short term nutritional problem, appropriate period of study was found to be two weeks. In this model we have been able to consistently measure small changes in groups of between 10–15 patients. A large change which may occur in a more severe case could be demonstrated in simple patients. This model has demonstrated that 0.3 g of nitrogen per kg per day and 40 kcal of energy are necessary to maintain body composition over a 14 day period. This nutritional input appeared to be similar whether the patient was in the post-operative non septic state or in the pre-operative depleted condition. Studies were undertaken to show that nutritional benefit of changing from all-glucose to a lipid containing solution did not affect the nutritional outcome of therapy. Thenutritional gains seen over the first 14 day period were sustained in a longer study of a small group of patients who were studied at two weekly intervals for 3 months.

Subsequent to these studies it has been considered important to determine whether peripheral intravenous nutrition would be as effective as central intravenous nutrition. By adjusting the nutritional protocol such that it fulfilled the rules obtained by central intravenous studies we have demonstrated that peripheral iv nutrition can maintain body composition but that the amount of glucose required for this to occur is at least 30% of non-protein calories.

Body composition measurements allow accurate long-term assessment of nutritional outcome in surgical patients requiring intravenous nutrition[1] in whom other measures may be inaccurate because their interpretation is complicated by sepsis and the response to surgery. Intravenous nutrition (IVN) is a form of artificial gut which is needed for treatment of patients who are unable to sustain themselves with oral or enteral food. Patients requiring IVN have severe gastrointestinal diseases, which frequently are temporary for relatively short periods of weeks to months, but occasionally are permanent. Because IVN is relatively expensive compared to oral and enteral nutrition, and because it is associated with complications of venous access and the metabolic consequences of continuous feeding, careful assessment of successful nutritional outcome is needed. Body composition studies are important for measurement of successful nutritional outcome because maintenance of normal body composition is in essence maintenance of the normal nutritional state.

Historically, IVN developed through two separate schools. The 'Swedish school' had developed protein hydrolyzate and intravenous lipid emulsions by the 1960s and devised a system which mimicked oral nutrition as closely as possible[2]. Using the recommended daily allowances for oral nutrition they were able to demonstrate satisfactory long-term outcome of patients treated with IVN delivered into peripheral veins. The 'American school' did not have lipid emulsions available to them because their early solutions, which were manufactured from cotton-seed oil, had side effects which led to their discontinued use. Professor Stanley Dudrick and co-workers devised a system that used concentrated glucose infusion as the non-protein energy source[3]. This solution was hypertonic and therefore needed to be given through a central line. But to prevent septic events the central line required a special protocol for the care of dedicated lines with emphasis on sterility by nursing and medical teams employed a manage intravenous nutrition. Dudrick's group called their nutrition hyperalimentation because they believed that a large amount of nutrition was necessary to establish nitrogen balance in sick patients who required such therapy. By the early 1970s the literature was confused regarding the amount of IVN that should be prescribed for ill surgical patients.

Numerous methods were devised to determine the energy and nitrogen requirements for IVN. Nitrogen balance and indirect calorimetry were the most popular methods used. Both of these methods require correction factors for unmeasured faecal nitrogen loss or activity, respectively, indicating a degree of inaccuracy. Francis Moore pointed out that if nitrogen balance were used continuously over a few years a human being would grow to the size of an elephant[4]. Nonetheless, these two techniques are reproducible and have been considered satisfactory for comparison of studies between groups. To get a more accurate determination of the long-term outcome of nutritional therapy, direct measures of body composition are needed.

The 'nutritional principle', from which inferences can be

Correspondence address: Assoc. Prof. Ross C. Smith, University Department of Surgery, Royal North Shore Hospital, St Leonards, NSW 2065, Australia.

drawn from measures of changes in body composition, is very simple. For body composition to remain constant there must be a balance between the energy provided and that released from the body. If energy were insufficient patient would lose tissue, mainly fat, and if it were excessive the patient would be expected to gain tissue, mainly fat. A similar balance may occur with nitrogen metabolism but here the changes are less certain and there must also be a balance of other elements. Rudman[5] demonstrated that by leaving one of the intracellular ions out of IVN there would be no accumulation of the remaining intracellular ions. The effect of exercise and stress on nitrogen metabolism may also interfere with the accumulation of nitrogen.

To demonstrate the difference between the methods of measuring nitrogen accumulation, we undertook a study to compare accumulated nitrogen balance with changes in body composition over a two-week period in patients undergoing IVN[6]. In Fig. 1, the accumulated nitrogen balance over 14 days was 64 ± 21 g nitrogen (P <0.001), which is clearly different from the changes in total body nitrogen (TBN) of –16 ± 110 g nitrogen which indicated no significant change. It is interesting to consider why these two results are different. Firstly, the variance of measurement of nitrogen balance is relatively smaller than that of TBN. However, there is a systematic error which is approximately 65 g of nitrogen over 14 days and is equivalent to 4.6 g of nitrogen per day.

When the data are presented in relationship to nitrogen intake the problem with these sets of data can be emphasized (Fig. 1). If the least square best fit regression lines are extrapolated to zero, assuming a linear relationship, nitrogen equilibrium, from the nitrogen balance would occur at 3.9 g nitrogen per day. Alternatively, if the point of maintenance of body composition were extrapolated from changes in TBN then balance would occur at a nutritional intake of 13.8 g nitrogen per day. Given that the patients being studied were in the stressed post-operative state, it is unlikely that 3.9 g nitrogen per day would be a satisfactory nitrogen intake being less than recommended daily oral intake of 9 g nitrogen per day. Alternatively, 13.8 g nitrogen per day from the TBN values is more likely to approximate nitrogen requirements in these patients although, because of the larger variance of the data, the exact point of equilibrium is not as precisely measured.

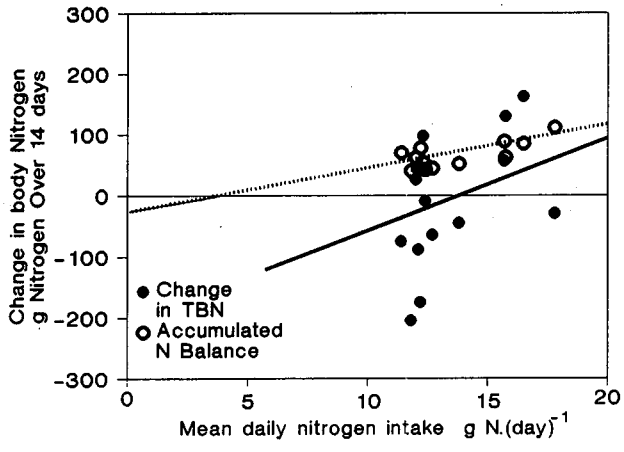

Figure 1. Relationship between nitrogen intake and change in nitrogen as measured by accumulated nitrogen balance results (open circles) or changes in TBN, TBN (closed circles). Dotted line is the line of best fit for nitrogen balance. The solid line is the line of best fit for changes in TBN.

The Leeds technique for body composition

The Leeds technique for body composition exposed a patient to eight 0.5 or 5 mSV of fast neutrons (14 MeV neutrons) and then transferred the patient to a shielded room to measure the resultant radiation spectrum. When 5 mSv was used, a multi-element analysis of the body was achieved giving results for nitrogen, phosphorous, chlorine, sodium, calcium, potassium and carbon. Multi-elemental[1] studies were undertaken in patients to determine changes in fluid compartments as well as TBN. The precision of the method is seen in Table 1.

Table 1. Reproducibility (CV%) results from Bush Phantom with high and low radiation exposures.

	0.50 mSv	5 mSv
Potassium	2	2
Nitrogen	2	1
Sodium	24	2
Chlorine	14	2
Phosphorous	16	3
Calcium	23	4

The Royal North Shore Hospital method

At Royal North Shore Hospital the technique adopted uses slow neutrons and prompt measurement using sodium iodide[7] and Bismuth-Germanate[8] detectors. The method allows the measurement of both nitrogen and chlorine with precision of 3 and 5%, respectively.

Results of Leeds studies

The value of a 14-day study period to determine nutritional outcomes using body composition has been examined. Repeat measures of TBN determined by in vivo neutron activation was shown to have a standard deviation of 54 g of nitrogen. With such an error, in one patient one would be able to show changes of greater than 110 g of nitrogen. This is a relatively large change representing between 5 and 10% of TBN. If small differences are to be measured groups of patients would need to be studied to determine mean changes. It can be shown, using the standard error rule, that 10–15 patients would be needed to show a difference of 34–38 g of nitrogen, over 14 days. Would this be a clinically important change? In the most severe catabolic state it is known that patients with septic burns lose about 30 g of nitrogen a day and in the most anabolic state that patients gain up to 14 g of nitrogen a day. With these changes, one would expect a range of differences over a 14-day period to be between a loss of 400 g and a gain of 200 g of nitrogen. A change of less than 0.5 kg of normal lean tissue can be measured. Therefore a weight loss of 10% ie generally between 5 and 7 kg, which is regarded as a significant change in nutritional state affecting patient outcome, can be easily measured using this methodology.

Applications of the Leeds model

I was fortunate to be able to apply the methodology developed by the Leeds tean of Hill et al.[1] to examine some important clinical questions comparing different protocols of IVN. The earlier studies of IVN demonstrate the fact that the majority of weight gain during IVN was water[9]. This finding was unexpected and therefore some very important questions needed to be addressed to gain a better understanding and these were done through studies using body composition as end points:

1 Does enteral nutrition cause the water accumulation in excess of that expected for changes in normal lean tissue observed during treatment with IVN?
2 Would giving greater amounts of dietary energy and nitrogen improve the quality of tissue gained in patients requiring IVN?
3 Does this phenomena of water retention continue in patients treated for prolonged courses of IVN?
4 Does exogenous insulin or the use of lipid as an energy source improve the quality of tissue gained?
5 Was it possible to localize the site of the water retention seen in these patients?

The first study was undertaken in patients who were not randomized but had undergone similar surgical procedures[10]. The group requiring in IVN was unable to take oral food because the surgical procedure interfered with oral intake. It may be that the patients receiving IVN in this study were slightly sicker than those receiving enteral nutrition but was not apparent by demographic and clinical observation. These patients were studied over 14 days. There were 16 in each of two groups which were well matched for age, sex, degree of weight loss, duration of nutrition and type of surgical procedure. There were differences between the groups in relationship to the total energy and nitrogen input. The enteral nutrition patients received 35.8 ± 9.9 kcal/kg/day compared to the intravenous nutrition group who received 42.4 ± 8.8 kcal/kg/day. The nitrogen intake was much less in the enteral nutrition patients who received 0.14 ± 0.04 g of nitrogen/kg/day compared to the IVN group which received 0.26 ± 0.05 g of nitrogen/kg/day.

It is interesting to observe the changes in body composition in these two groups. The enteral nutritions patients (Fig. 2) showed no change in weight and they preserved body fat, protein and water so that all compartments were preserved in this period of treatment. In comparison, the IVN patients gained a significant amount of weight, 2.2 kg, and this weight was mainly water and fat. These patients lost 0.5 kg protein during the study. Thus the gain in weight was due to a spurious gain in water and was seen despite the fact that these patients had been given nearly twice as much nitrogen as the enteral patients.

A subsequent examined the role of giving a larger amount

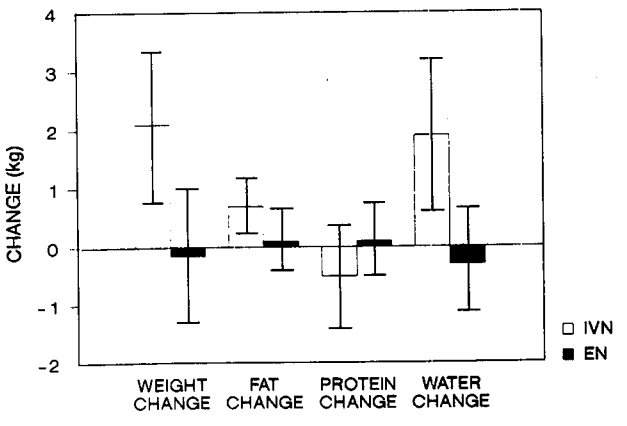

Figure 2. Mean and 95% confidence in interval of the mean changes in body composition in the two groups. EN maintained body composition but IVN resulted in significant gains of weight fat and water. The loss of protein did not reach significance in the IVN group.

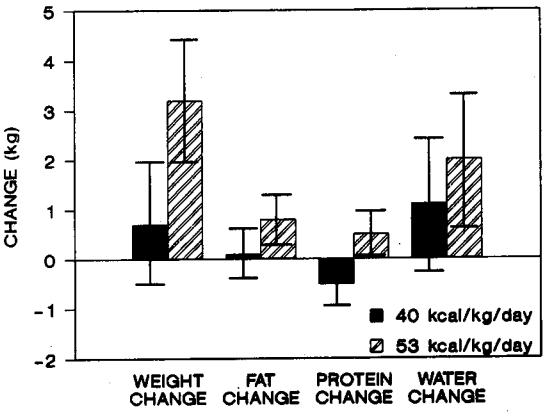

Figure 3. 95% mean and confidence intervals of changes in body composition after different nutritional protocols. Patients receiving 53 kcal/kg/day had gains of fat, protein and water and the water gain was that expected from the protein gain if normal lean tissue had formed. Patients receiving 40 kcal/kg/day lost body protein. Water tended to be gained above the expected loss associated with the protein loss.

of nutrition[11]. In this study 30 patients were randomized to receive either 40 kcal/kg/day or 53 kcal/kg/day. The patients were again surgical patients and were well matched for age and clinical and nutritional criteria. The nutritional solution provided 1 g of nitrogen for every 150 kcal of energy. The outcome of changes in body composition can be seen in Fig 3. The patients receiving the lesser amount of nutrition had a relatively excessive gain in water considering that the protein loss would be expected to be associated with a loss of water if part of normal lean tissue. In comparison, patients who received a greater amount of nutrition gained significant amounts of weight which was due to gains in fat, protein and water. The relationship between the gain in protein and the gain in water was appropriate for gains of normal lean tissue. Furthermore, in Fig. 4, when the total body electrolyte changes were examined, the group receiving the lesser amount of nutrition were seen to have gains in total body potassium in excess of that expected from changes in total body protein, but non-significant losses of total body sodium

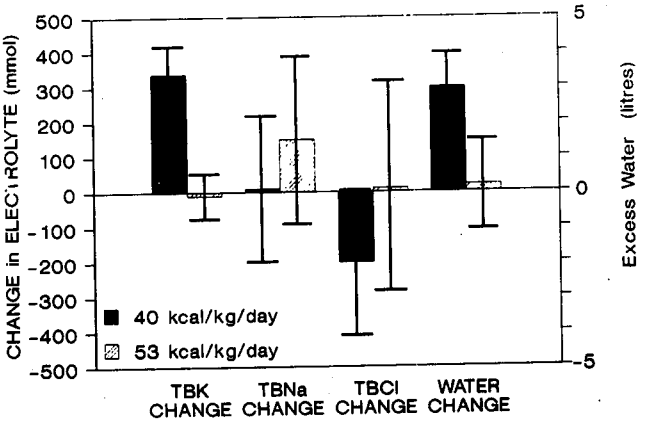

Figure 4. Mean 95% confidence intervals of changes in total body electrolytes and water above that expected if changes in protein were associated with normal lean tissue. Results are for IVN infusion over 14 days of either 40 kcal/kg/day or 53 kcal/kg/day. Changes of TBK and TBW are significant ($P<0.01$) in the 40 kcal/kg/day group but not in the 53 kcal/kg/day group.

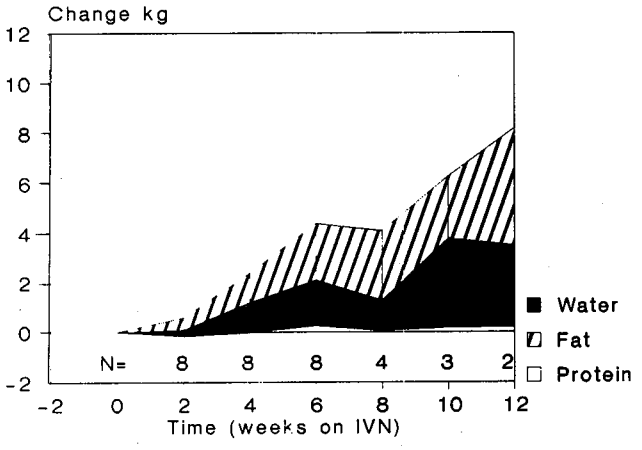

Figure 5. Accumulated mean changes in body composition over 12 weeks for eight septic patients entering the study.

and total body chlorine compared to expected changes if the nitrogen loss was due to a loss of normal lean tissue. This indicates that the water gained was in the intra-cellular compartment. In comparison, the patients receiving the greater amount of nutrition did not have changes in total body sodium, chlorine and potassium after subtraction of the electrolytes expected to accompany protein gains with normal lean tissue expansion. This supports the finding that the greater IVN infusion has resulted in growth of the lean body mass.

The long-term effect of IVN on body composition was examined in eight patients who required IVN for up to 12 weeks because of septic complications of surgery[12]. No septicemic episodes occurred after the onset of treatment. These patients had repeat measurements every two weeks. They lost nitrogen in the first two-week period but gained nitrogen over the subsequent two-week periods. Most of the weight gained was due to gains in fat and water and the gains in protein appear trivial (Fig. 5). Although there appears to be only a small gain in protein it is associated with approximately expected gains in water. Furthermore, from the shape of the curves it is interesting that the gain in potassium is what one would expect if normal lean tissue were gained in association with the gain in nitrogen (Fig. 6), ie 1 g nitrogen gained was associated with a 3 mmol gain in potassium.

Therefore, it was shown that IVN could cause gains in nor-

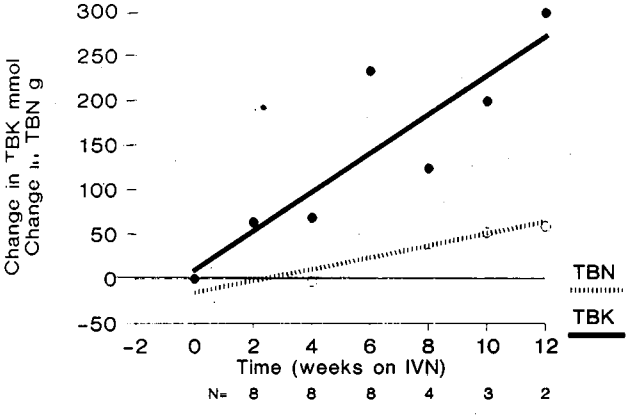

Figure 6. Mean accumulated change in total body nitrogen and total body potassium in eight patients requiring IVN for up to 12 weeks. The solid line is the best fit regression line for changes in TBK. $\delta TBK = 10 + 3.1$ (days treatment) r=0.88.
The dotted line is the best fit regression line for changes in TBN. $\delta TBN = -15 + 1.0$ (days treatment) r = 0.79.

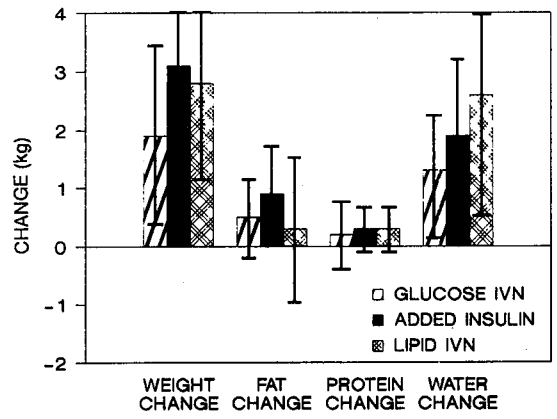

Figure 7. Mean and 95% confidence intervals of changes in body composition after different nutritional protocols. Patients receiving glucose IVN, glucose IVN with added insulin or IVN providing 50% pf enmergy as lipid. Energy input was 49 kcal/kg/day. There were no significant differences between the groups.

mal lean tissue and that the gains could continue for periods of up to 12 weeks, but for this to happen there needed to be a large infusion of IVN. The total dose of nitrogen given to these patients needed to be excess of twice that required for maintenance of body protein by enteral nutrition.

We went on to examine whether the source of non-protein energy was important in determining the outcome of IVN[12,13]. Thirty patients were randomized to : (a) glucose-based in IVN; (b) in IVN augmented with insulin at 30 units/litre of glucose TPN mix; or (c) intravenous lipid emulsion to provide 50% of the non-protein energy in the 'lipid' TPN solution. Details of the IVN protocol showed that each patient received 49 kcal/kg/day and 0.33 gN/kg/day. Differences in response to IVN solution were found in relationship to total body fat. Patients receiving extra insulin had greater gains in fat, whereas the patients receiving lipid had no change in their body fat. Body protein changes were similar in all protocols. There was an apparent gain in weight in these patients. From these studies we concluded that neither the energy source or exogenous insulin produce a greater gain of normal lean tissue in the post-operative period.

The differences in the change in total body electrolytes fol-

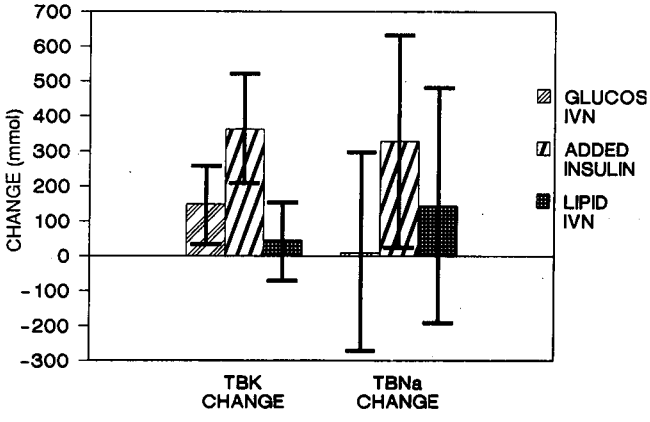

Figure 8. Mean and 95% confidence intervals of changes in total body electrolytes and water above that expected if changes in protein were associated with normal lean tissue. Patients receiving glucose IVN, glucose IVN with added insulin or IVN providing 50% of energy as lipid.

lowing the different non-protein energy protocols is interesting (Fig. 8). The greatest gain in TBW occurred in the insulin group and this was accompanied by gains in TBK and TBNa. The glucose only in IVN group, who had smaller but significant gains in water, had gains in TBK. The lipid IVN group had no significant gains in TBK or TBNa. These different fluid shifts would be directly related to the expected value of plasma insulin concentrations.

To examine the location of 'Excess water' it will be important to examine the changes of electrolytes in the patient having the more accurate measurement before and after IVN. Thirty patients underwent body composition measures using the higher dose of neutrons 5 mSv to examine the compartment that the water was accumulated in during IVN. The change in total body nitrogen was assumed to be protein part of normal lean tissue. The definition of excess water was:

$$\text{'Excess water'} = \delta\text{TBW} = \left[\frac{\delta\text{TBN} \times 6.25 \times 3.71}{1000}\right].$$

The 'Excess chloride space' was defined as:

$$\text{'Excess } Cl^- \text{ space'} = \left[\frac{\delta\text{TBC1} - \delta\{Cl^-\}p.TBCl_1 - (\delta\text{TBN} .0.72)}{[Cl^-]_{p1}}{100}\right]$$

The 'Excess potassium space' was defined as:

$$\text{'Excess } K^+ \text{ space'} = \frac{\delta\text{TBK} - (\delta\text{TBN} \times 3)}{150}$$

'Excess Water' = water in excess of that associated with gains of normal lean tissue (kg).

TBN = total body nitrogen (g).

'Excess Cl^- Space' = change in volume of extracellular water after subtracting that expected to follow TBN assuming changes in TBN follow changes in normal lean tissue and gains in total body chlorine are confined to the extracellular space (L).

TBCl = total body chlorine (mmol).

δTBCl = change in total body chlorine (mmol).

$\delta\{Cl^-\}_p$ = change in plasma chlorine concentration ($mmol \cdot L^{-1}$).

$TBCl_1$ = initial measure of TBC1 (mmol).

δTBN = change in TBN (g).

$[Cl^-]_{p1}$ = initial plasma concentration of chlorine ($mmol \cdot L^{-1}$).

TBK = total body potassium (mmol).

'Excess K^+ Space' = change in volume of intracellular water after subtracting that expected to follow TBN assuming changes in TBN follow changes in normal lean tissue and gains in TBK are confined to the intercellular space.

δTBK = change in total body potassium (mmol).

In these patients the 'Excess Water' was found to be related to both 'Excess Cl^- Space' and 'Excess K^+ Space' (Fig. 9). By multivariant analysis these effects are seen to be additive with relative coefficients of 0.51 and 0.53 and therefore having a similar influence on the 'excess water' measures. From

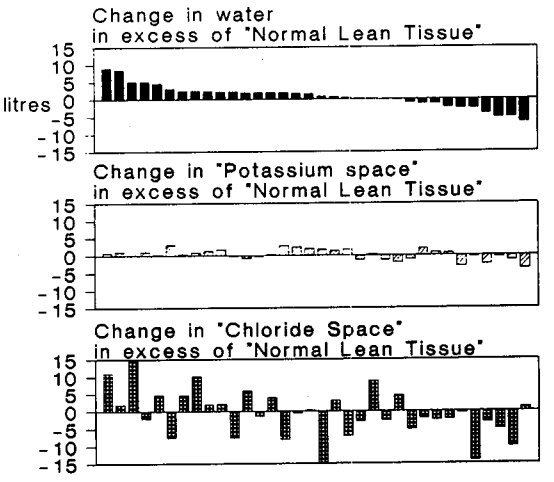

Figure 9. Changes in 'excess water' — change in TBW in excess of expected if changes in total body protein were due to changes in normal lean tissue for patients on IVN ranked along with the changes in 'excess potassium space' and 'excess chloride space' in excess of expected changes. An independent and additive relationship was seen for both indicating that this fluid was distributed in both the intracellular and extracellular spaces.

this figure the relative distribution from expansion of 'extracellular fluid' seems to be greater than the relative expansion of 'intracellular fluid' although statistically both compartments contribute equivalently to the 'Excess Fluid'. Intracellular fluid expansion in excess of protein may be associated with accumulation of glycogen in muscle and liver[14] or increasing potassium concentration within the cell.

After analysis and consideration of the data collected at Leeds, I thought that body composition studies had solved many of the important questions which had interested me about intravenous nutrition. I felt that it was clear that large amounts of nutrition were required. The much cheaper glucose solutions were preferred because of cost when compared to lipid-based in IVN solutions, but also because the use of central lines ensured full nutrition input. Furthermore, glucose-based intravenous nutrition could be safely given through central lines when appropriate sterile protocols were adhered to. Emphasis was placed on the importance of the guaranteed outcome which could be obtained by adhering to the guidelines outlined by Professor S. Dudrick 15 years earlier.

Confirmation of effectiveness of peripheral intravenous nutrition

Clinical experience over many years on many patients did not make the problems with maintaining sterile delivery any less risky. These patients continued to develop septicemic at a risk of about 3% or one in 33 patients treated. Such septicemia and other risks associated with the placement of central lines remain as major problems in the evolving role of IVN support.

We therefore set about trying to determine whether a new form of IVN through a peripheral vein (a 'hyperalimentation' form of Professor Arvid Wretlind's technique from the 1960s) would establish peripheral IVN as being equally potent to central IVN. We had already seen that the lipid-based solution giving 50% of energy as lipid was equally potent to glucose-based solutions in respect of changes in

TBN but to provide IVN peripherally and minimize the risk of thrombophlebitis, a greater proportion of the non-protein energy would need to be given as lipid. We commenced our studies using the maximum concentration of lipid recommended in the literature[15]. Our initial studies used 75% of non-protein energy as lipid and we were able to show that this could be delivered through a peripheral line[9,16]. The nutritional outcome after use of this solution was equivalent to that following glucose IVN for nitrogen balance, plasma proteins and total peripheral amino acid flux[17]. Interestingly, the peripheral flux of the amino acids associated with glucose production, alanine and glutamine, indicated the gluconeogenesis persisted with use of the 75% lipid-based TPN protocol. Because of this we have also studied a solution providing 66% of energy as lipid in an attempt to reduce the peripheral production of alanine.

Body composition measures have been undertaken in three groups of similar patients undergoing IVN in the post-operative period. These patients had similar age, weight and fat-free mass (FFM) measures. The nutritional input, Table 2, shows that the nitrogen and energy input in relation to weight was similar in each group and they had undergone similar operations. Table 3 shows, however, over the 14-day study period the change in body composition was different in the group receiving less glucose (Fig. 10). The patients who had 75% non-protein energy as lipid lost weight and protein in comparison to these receiving either glucose IVN or 66% of non-protein energy as lipid. As the solution with the higher glucose input 33% of non-protein energy is compatible with peripheral infusion, it is now considered the more ideal solution of peripheral IVN. Further studies are needed to prove this conclusively.

Table 2. Nutritional input with IVN regimens.

	GLUCOSE IVN	75% LIPID IVN	66% LIPID IVN
N input (gN/kg/d)	0.35	0.35	0.30
Lipid input (kcal/kg/d)	0	27	22
Glucose input (kcal/kg/d)	42	9	11
Total input (kcal/kg/d)	49	45	41

Table 3. Patients receiving IVN protocols.

IVN	Glucose IVN	75% Lipid IVN	66% Lipid
Number	11	11	13
Age (years)	54	58	64
Weight (kg)	62	65	72
Fat-free mass	51	47	47
Surgical procedures: Pancreatic	4	4	7
Gastric	6	6	3
Bowel	1	1	3

Conclusion

Body composition studies have demonstrated the reduced efficacy IVN in comparison to normal daily requirements and enteral nutrition. These studies have helped develop a suitable protocol for peripheral IVN and shown nutritional efficacy. There are numerous developments which are expected to improve the efficacy of IVN: the use of dipeptides, improved lipids, growth factors and others. Body composition studies will be important to demonstrate efficacy of such protocols given it is difficult to show differences with other measures. Much more work is required in the field of body composition analysis to determine the best nutritional protocol for different clinical situations.

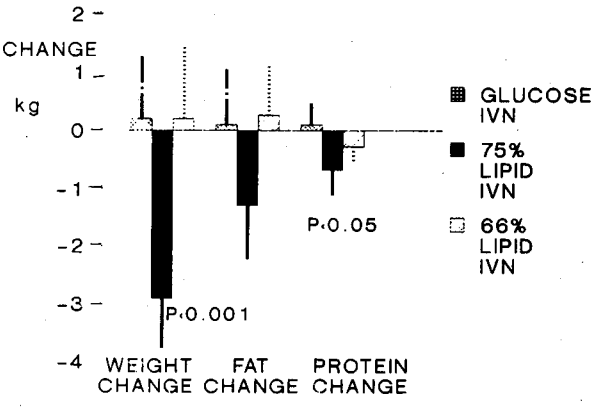

Figure 10. Mean and 95% confidence intervals for changes in weight, total body fat and total body protein in patients on different peripheral IVN protocols.

References

1 Hill GL, King RF, Smith RC, Smith AH, Oxby CB, Sharapi A, Burkinshaw L. Multi-element analysis of the living body by neutron activation analysis – application to critically ill patients receiving intravenous nutrition. Br J Surgery 1979; 66: 868–872.

2 Wretlind A. Complete intravenous nutrition. Theoretical and experimental background. Nutr Metab 1972; 14 (Suppl.) 1–57.

3 Dudrick SJ, Ruberg RL. Principles and practice of parenteral nutrition. Gastroenterology 1971; 61:901–910.

4 Moore FD. Energy and the maintenance of the body cell mass. JPEN 1980; 4:3:228–260.

5 Rudman D, Millibar WJ, Richardson TJ, Bixler TJ, Stackhouse WJ, McGarrity WC. Elemental balance during intravenous hyperalimentation of underweight adult subjects. J Clin Investigations 1975; 55:94–104.

6 King RFGJ, McMahon MJ, Burkinshaw L, Lauugland A, Almond AJ, Yeung CK, Smith RC. Comparison of changes in body nitrogen measured by in vivo neutron activation analysis and urinary nitrogen balance. Clin Nutr 1988; 7:231–236.

7 Allen BJ, Blagojevic N. In Vivo Body Composition Studies in Malnourished Patients, ANZ Nuc Med 1987; 7:21–23.

8 N. Blagojevic N, Allen BJ, Rose AR. Development of a total body chlorine analyser using a bismuth Germanate Detector System and a ^{252}(f neutron source. In: Yasamura S, Harrison JE, McNeill KG, et al., eds. In Vivo Composition Studies. New York: Basic Life Sciences Plenum Press, 1990.

9 Hill GL, Bradley JA, Smith RC, Smith AH, McCarthy ID, Oxby CB, Burkinshaw L, Morgan DB. Changes in body weight and body protein with intravenous nutrition. J Parenteral and Enteral Nutr 1979; 3, 4:215–218.

10 Yeung CK, Smith RC, Hill GL. Effects of an elemental diet on body composition, a comparison with intravenous nutrition. Gastroenterology 1979; 77:652–657.

11 Smith RC, Burkinshaw L, Hill GL. Optimal energy and nitrogen intake for gastroenterological patients requiring intravenous nutrition. Gastroenterology 1982; 82:425–452.

12 Smith RC. Effect of intravenous nutrition on body composition in seriously ill gastrointestinal patients. MD thesis, University NSW, 1982.

13 Macfie J, Smith RC, Hill GL. Glucose or fat as non-protein energy source? A controlled trial – gastroenterological patients requiring intravenous nutrition. Gastroenterology 1981; 80: 103–7.

14 King RFG, Macfie J, Hill GL, Smith RC. Effect of intravenous nutrition with Glucose as the only calorie source of muscle glycogen. J Parenteral and Enteral Nutr 1982; 5, 3:226–229.
15 Jeejeebhoy KN, Baker JP. Parenteral nutrition in harrisons principles of internal medicine 11th edn. In: Bramwald E, et al., eds. New York: McGraw Hill, 1987.
16 Kohlhardt SR, Smith RC, Wright CR, Sucic KA. Fine-bore peripheral catheters versus central venous catheters for delivery of intravenous nutrition. Nutrition 1992; 8:412–417.
17 Smith RC, Mackie W, et al. The effect on protein and amino acid metabolism of an intravenous nutrition regimen providing seventy percent of nonprotein calories as lipid. Surgery 1992; 111: 12–20.