

## Papers and Originals

### Nitrogen Balance in Patients with Chronic Renal Failure on Diets Containing Varying Quantities of Protein

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**S**ummary: Twenty-four nitrogen balances have been performed in 16 patients with chronic renal failure, with a protein intake of 0.23 to 1.0 g./kg./day. The results show that most patients with chronic renal failure require about 0.5 g./kg./day (35 g. for a 70-kg. man) to remain in nitrogen balance. The proportion of high-quality protein in the diets varied from 40 to 98% and the calorie intake from 23.6 to 59.0 calories/kg./day (1,330 to 3,310 calories/day). Within these ranges the proportion of high-quality protein and the calorie content did not have a detectable effect on the nitrogen balance.

It is concluded that when other forms of treatment for renal failure are available, reduced protein diets should be used for only short periods, and that the protein intake should be 0.5 g./kg./day to maintain the patient in nitrogen balance.

#### Introduction

The treatment of advanced renal failure with a very low protein diet is now well established (Giordano, 1963, 1964; Giovannetti and Maggiore, 1964; Giordano *et al.*, 1967). Some of the original low-protein diets which were evolved for Italian consumption contained large quantities of pasta and also a relatively large proportion of high-quality as opposed to low-quality proteins (Giovannetti and Maggiore, 1964; Giordano *et al.*, 1967). Shaw *et al.* (1965) modified the diet to be more in line with British tastes. Nitrogen balances have been performed in some patients on the Italian type diet, whereas very few have been performed on patients on the British modification of the diet. This paper describes the effect of diets containing varying quantities of protein on the nitrogen balance of patients suffering from advanced renal failure.

#### Methods

The investigation was carried out in a metabolic ward according to the principles of Reifstein *et al.* (1945). Sixteen patients were studied on 24 separate occasions. Before balances were begun the patients had been on controlled protein intake for periods varying from 5 to 415 days (average 96 days). The controlled protein diet was started either when in hospital or as an outpatient. During the initial three to seven days in hospital changes were made in the constituents of the diet to

establish a diet suitable both for the individual's tastes and for balance purposes. The patients were encouraged to be up and about for most of the day. Balances were performed for 6 to 55 days; on 19 occasions the balance continued for 15 days or more. Faecal collections were made over balance periods of four to six days. Chromium sesquioxide was used as a continuous faecal marker. Capsules containing 0.5 g. of acid-washed chromium sesquioxide were given three times a day with meals (Whitby and Lang, 1960). Carmine markers were used at the beginning of the balance to delineate the equilibration period. Urine was collected in 24-hour periods and kept at 4° C.

Faeces, diet, urine, and plasma were analysed for nitrogen by a micro-Kjeldahl method (Clarkson *et al.*, 1966). Chromium was estimated by the method of Clarkson *et al.* (1965, 1966). Urea, creatinine, sodium, and potassium were measured with an autoanalyser; bicarbonate was measured in a Van Slyke constant volume apparatus. Urinary and serum proteins were estimated by a biuret method (Weichselbaum, 1946). Blood was taken between 9 a.m. and 12 noon, without the use of a sphygmomanometer, one sample being placed into a heparinized tube and another into a plain tube for estimation of serum proteins.

The nitrogen balance results have been corrected for changes in plasma urea that occurred during the balance periods. Urea was assumed to be distributed equally throughout the total body water at the same concentration as in the plasma. Total body water was taken to be 65% of the average body weight during a balance period, and the changes in plasma urea between the beginning and end of such a period were converted to changes in total body water nitrogen (g./day). The balance was then adjusted so that nitrogen retention due to a rise in plasma urea was subtracted from the daily balance, while the nitrogen loss due to a fall in plasma urea was added to the daily balance. For the calculation of nitrogen balance the estimated urinary loss of protein during each balance period was subtracted from the estimated dietary intake of protein.

#### Diet

Diet histories were taken from each patient to ascertain the diet taken before the balance was started. In order to gain the co-operation of the patients the aims of the balance study were carefully explained. The principles of the diet and the types of food allowed were described to the patients who had not previously been on a controlled protein intake. After a discussion on suitability and availability of foods for the balance, a menu to cover two days was drawn up according to the patient's tastes. The quantity of each item was then determined.

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Periodically the nitrogen content of portions of chicken, lamb, wheat-starch bread, and potatoes (high-quality proteins) were estimated.

**High-quality Protein.**—In the first two balance studies the main source of high-quality protein in the diet was egg white. Subsequently two patients were studied with meat and egg white separately as the chief sources of high-quality protein while the rest of the diet was unchanged. As this change made no difference to the nitrogen balance meat was used instead of egg white as the main source of protein. Lean roast lamb and steamed chicken were chosen. These two meats were found to produce consistent nitrogen figures on repeated laboratory analyses. Some patients chose to have lamb and chicken on alternate days, others preferred one meat throughout. The total nitrogen intake was adjusted in each balance by controlling the proportion of meat in the diet. The meat intake varied from 0.18 to 0.51 g. of protein/kg./day. Also included under foods of high-quality protein were potatoes and low-protein wheat-starch bread, the quantities of which were determined according to the patients' tastes. The wheat-starch bread was included because of the high proportion of yeast in the recipe and also because several patients consumed almost a whole loaf a day (2.9 g. of protein/loaf). One patient (Case 8) had 340 g. of ordinary white bread and 24 g. of homogenized milk a day; another (Case 16) had 240 g. of ordinary milk, 80 g. of beefsteak, and 90 g. of ordinary white bread per day in addition to the foods mentioned above. In the earlier studies the low-protein bread was supplied from Welfare Foods Ltd., Stockport, Cheshire. Later the bread was made in the kitchen of the metabolic ward from Energen Wheat Starch. The essential amino-acid content of each diet was calculated only on the high-quality protein content of the diet.

**Low-quality Protein and Other Foods.**—Part of the diet consisted of foods which contributed little to the essential amino-acid content of the diet. It contributed 0.6–14.4 g. of protein/day. Foods included under this heading were: unsalted butter, vegetable oils, jam, honey, marmalade, sugar, glucose, boiled sweets, green and root vegetables, salads, fruit, Aprotin pasta (Carlo Erba U.K. Ltd.), and double cream. Two portions of vegetable or salad and three portions of fruit were served daily. Cream (60–100 g./day) was served with fruit and in tea and coffee. At the beginning of each balance the nitrogen content of an aliquot of part of the diet was estimated.

**Calories.**—Each patient was encouraged to eat 3,000 calories/day, but not all patients were able to do this; the calorie intake therefore varied from 1,330 to 3,310 calories/day (23.6 to 59.0 calories/kg./day). Hycal provided a palatable source of calories for nearly all patients (400 to 1,000 calories/day).

**Sodium, Potassium, and Vitamins.**—The diet contained 8–21 mEq of sodium/day. All food was prepared without the addition of salt, except the low-protein bread, to which 1 g. of sodium chloride per loaf was added. Additional sodium was given according to the patients' clinical requirements in the form of capsules (0.5 g. NaCl) to sprinkle over food, or as Slow-Na tablets. The potassium contents of the diets ranged from 45 to 60 mEq potassium/day. Each patient was given one tablet of Orovite a day, containing aneurine hydrochloride 50 mg., riboflavine 5 mg., pyridoxine hydrochloride 5 mg., nicotinamide 200 mg., ascorbic acid 100 mg., and pantothenic acid 5 mg./tablet.

## Results

Tables I and II summarize the relevant clinical and balance data on the 16 patients studied.

### Clinical Data

The main clinical problems in our patients were gastrointestinal symptoms, hypertension which was difficult to treat, malaise, and tiredness. Two patients (Cases 3 and 12) were without symptoms before they began the controlled protein diet. In three (Cases 2, 6, and 14) satisfactory control of symptoms was not obtained. The 11 remaining became relatively free of symptoms for one month to two and a half years; in five of these (Cases 5, 7, 8, 10, and 11) this period exceeded 15 months.

Of the 16 patients studied, seven have since died (Cases 2, 8, 10, 12, 13, 14, and 15), six are being treated with maintenance haemodialysis (Cases 1, 3, 4, 6, 9, and 11), and three remain on controlled protein diets and are well (Cases 5, 7, and 16); two of these three have been on reduced protein intake (about 0.4 g./kg./day) for about 18 months (Cases 5 and 7).

Of the seven patients who died, two died suddenly—one from gastrointestinal haemorrhage (Case 10) and one from papillary necrosis and anuria (Case 13)—at a time when their symptoms had been controlled. Two patients deteriorated gradually, one dying after transplantation (Case 15), the other from gross pyelonephritis, pyonephrosis, and nephrolithiasis (Case 8). One of the two patients who had never had any symptoms despite a very low glomerular filtration rate died after renal transplantation (Case 12). Another patient did not respond to the diet. She remained depressed and tired, and died at home from an unknown cause (Case 14). The patient who was on a reduced protein diet for the longest period (415 days) died from liver failure a few weeks after starting treatment with maintenance

TABLE I.—Age, Weight, and Certain Biochemical Data Related to Renal Function and Protein Metabolism in the 16 Patients Studied. The Letters a, b, and c Refer to Separate Nitrogen Balances on the Same Patient.

Case No.	Age in Years	Weight (kg.)	Creatinine Clearance (ml./min.)	Plasma Creatinine (mg./100 ml.)	Plasma Urea (mg./100 ml.)	Plasma Total Bicarbonate (mEq/l.)	Serum Protein (g./100 ml.)		Urinary Protein Loss (g./day)
							Total	Albumin	
1	32	66.0	10.0–7.0	10.0–12.0	110–75	24.0	6.0–5.4	2.8–3.8	2.0
2	46	66.3	5.0	5.0	134–58	13.5	6.8–5.6	3.8–3.5	0.4
3	46	65.0	8.0	12.0	137–67	23.5	7.0	4.9	1.1
4	32	77.9	12.0	10.0	115–66	23.0	5.6	3.2	3.9
5 { (a)	25	43.0	12.0	6.0	74–35	17.5	7.0–6.0	3.7–3.2	1.7
(b)		44.5	8.0	7.3	44–43	20.0	6.0	3.8	0.9
(c)		44.5	7.2–5.2	9.0	75–59	19.0	6.4	4.0	2.0
6	35	68.5	5.2–3.6	16.0–20.0	142–165	27.0	6.6	4.7	1.6
7 { (a)	50	57.0	14.0	4.5	45–35	20.0–24.0	6.3	3.5	2.0
(b)		61.0	7.0–9.0	7.2–6.2	84–72	27.0–30.0	6.2	3.7	2.6
8	48	48.0	2.5	15.0	290–172	20.5	5.4–6.0	3.8–2.8	3.3
9 { (a)	44	67.0	6.0–9.0	9.0	106–90	20.0	6.2	4.5	1.0
(b)		65.8	6.4–4.1	12.0–15.6	140–110	23.0	5.2	3.3	3.0
10	58	60.0	2.5–2.0	18.0	300–210	16.5	6.0–6.5	3.3–3.1	2.4
11 { (a)	31	57.5	12.0	7.0	94–57	21.0–25.0	5.6	3.9	1.0
(b)		60.0	10.5	7.0	77–55	21.0–25.0	6.6–6.0	3.9–3.6	0.6
12 { (a)	22	48.0	3.5	16.0	170–82	24.0–19.0	6.4	4.1	1.6
(b)		48.0	3.0	16.0	85–82	19.0–25.0	6.8–5.3	4.2–3.2	1.6
13	63	52.3	6.3–4.3	10.5	155–130	13.5	6.4	3.7	0.3
14 { (a)	52	59.0	3.5	13.0	180–165	16.5	6.4	3.9	1.1
(b)		59.0	3.5	13.0	175–210	17.0	6.3–5.9	3.7–3.4	1.1
15 { (a)	17	59.0	6.0	13.5	155–130	15.5–26.5	6.0	3.3	3.3
(b)		59.0	6.0–4.0	14.0	130–120	25.0	6.0–6.4	4.0–3.7	3.3
16	42	51.0	7.0–9.0	5.8	180–96	22.5	8.6–7.8	4.5–3.9	1.1

TABLE II.—Balance Data. The Letters a, b, and c Refer to Separate Nitrogen Balances on the Same Patient

Case No.	Date of First Day of Balance	Duration of Balance Study (Days)	Main Source of High-quality Protein	High-quality Protein Intake		Net High-quality Protein Intake (High-quality Protein Intake Less Urinary Protein Loss)		Low-quality Protein Intake		Ratio High-quality to Low-quality Protein Intake (%)	Total Protein Intake		Effective Total Protein Intake (Total Protein Intake Less Urinary Protein Loss)		Calories Intake		Duration of Controlled Protein Intake Before Start of Balance (Days)	Nitrogen balance (g./day)	
				g./kg./day	g./day	g./kg./day	g./day	g./kg./day	g./day		g./kg./day	g./day	g./kg./day	g./day	cal./kg./day	cal./day		At End of First Balance Period	At End of Last Balance Period
1	4/8/66	20	Meat	0.11	7.2	0.08	5.2	0.12	7.8	40	0.23	15.0	0.20	13.0	36.2	2,385	5	-2.10	-2.48
2	23/10/67	25	Meat	0.17	11.6	0.16	11.2	0.09	5.7	66	0.26	17.3	0.25	16.9	39.2	2,600	415	-1.29	-1.65
3	29/10/66	20	Meat	0.17	11.2	0.16	10.1	0.11	7.4	58	0.28	18.6	0.27	17.5	34.7	2,185	12	-2.09	-1.86
4	11/9/67	33	Meat	0.27	21.4	0.22	17.5	0.10	7.6	70	0.37	29.0	0.32	25.1	39.5	3,145	5	-2.36	-0.06
5	(a) 3/12/66	20	Meat	0.26	11.3	0.22	9.6	0.19	8.0	55	0.45	19.3	0.41	17.6	30.9	1,330	5	-1.26	-0.15
	(b) 15/3/67	11	Meat	0.21	9.3	0.19	8.4	0.22	10.0	46	0.43	19.3	0.41	18.4	45.0	2,000	107	-0.75	-0.50
	(c) 11/7/67	10	Meat	0.21	9.3	0.16	7.3	0.16	7.3	50	0.37	16.6	0.33	14.6	45.0	2,000	225	-2.06	-0.76
6	3/5/67	8	Meat	0.27	18.6	0.25	17.0	0.12	8.1	68	0.39	26.7	0.37	25.1	29.8	2,040	44	-0.73	-0.72
7	(a) 9/1/67	20	Meat	0.26	14.6	0.22	12.6	0.15	8.6	59	0.41	23.2	0.37	21.2	41.4	2,360	7	-0.74	-0.31
	(b) 9/7/67	15	Meat	0.30	18.4	0.25	15.8	0.12	7.0	69	0.42	25.4	0.37	22.8	45.6	2,790	188	-0.46	+0.02
8	12/4/67	15	Meat	0.41	19.8	0.34	16.5	0.07	3.2	86	0.48	23.0	0.41	19.7	33.3	1,600	5	-1.09	+0.33
9	(a) 5/5/67	35	Meat	0.31	20.9	0.30	19.9	0.12	8.5	70	0.43	29.4	0.42	28.4	49.3	3,310	31	-1.30	-0.67
	(b) 9/7/67	20	Meat	0.32	20.9	0.27	17.9	0.14	8.0	67	0.46	28.9	0.41	25.9	50.2	3,300	96	-0.71	+0.53
10	22/10/63	55	Egg	0.35	20.8	0.31	18.4	0.10	6.3	74	0.45	27.1	0.41	24.7	41.6	2,500	339	+0.66	+0.77
11	(a) 21/11/66	30	Meat	0.25	14.5	0.23	13.5	0.19	11.2	55	0.44	25.7	0.42	24.7	45.0	2,590	11	-1.02	-0.33
	(b) 1/3/67	11	Meat	0.24	14.5	0.23	13.9	0.19	11.2	55	0.43	25.7	0.42	25.1	43.2	2,590	110	+0.34	+0.40
12	(a) 3/5/66	20	Meat	0.30	14.6	0.27	13.0	0.16	7.4	66	0.46	22.0	0.43	20.4	44.0	2,110	33	-0.43	+0.21
	(b) 1/6/66	15	Egg	0.30	14.6	0.27	13.0	0.16	7.4	66	0.46	22.0	0.43	20.4	44.0	2,110	62	+0.53	+0.73
13	(a) 12/7/67	15	Egg	0.30	15.7	0.29	15.4	0.18	9.4	62	0.48	25.1	0.47	24.8	59.0	3,080	29	-1.38	-1.22
	(b) 16/5/64	15	Egg	0.34	20.0	0.32	18.9	0.18	10.7	64	0.52	30.7	0.50	29.6	42.3	2,500	8	+0.20	-0.30
14	(a) 7/7/64	32	Egg	0.47	27.9	0.45	26.8	0.20	11.5	70	0.67	39.4	0.65	38.3	23.6	1,390	29	-0.15	+1.25
	(b) 13/6/65	6	Egg	0.57	33.4	0.51	30.1	0.24	14.4	68	0.81	47.8	0.75	44.5	42.5	2,500	15	+1.60	+1.62
15	(a) 23/6/65	20	Meat	0.57	33.4	0.51	30.1	0.24	14.4	68	0.81	47.8	0.75	44.5	42.5	2,500	25	+1.43	+2.40
	(b) 13/6/65	20	Meat	0.57	33.4	0.51	30.1	0.24	14.4	68	0.81	47.8	0.75	44.5	42.5	2,500	25	+1.43	+2.40
16	10/3/68	28	Meat	0.99	50.8	0.98	49.7	0.01	0.6	98	1.00	51.4	0.99	50.3	30.4	1,545	10	+0.80	+1.07

haemodialysis (Case 2). Dialysis was begun when her uraemic symptoms returned and when vitamin-D-induced hypercalcaemia had caused a further reduction in glomerular filtration rate.

Of the six patients now on maintenance haemodialysis, one was asymptomatic from the outset, but after receiving tetracycline from his general practitioner there was a profound fall in glomerular filtration rate and his symptoms became uncontrollable (Case 3). Four patients deteriorated suddenly, three with uncontrollable hypertension (Cases 1, 4, and 6) and the other with pericarditis (Case 9). One patient deteriorated very gradually, with recurrent urinary infections and hypertension (Case 11).

The plasma creatinine throughout the balances varied from 4.5 to 20 mg./100 ml. (mean 10.9 mg./100 ml.). Creatinine clearance varied from 2 to 14 ml./min. (mean 7.1 ml./min.). The blood urea level ranged from 44–300 mg./100 ml. before to 35–210 mg./100 ml. after the balances; there was a mean fall of 37 mg./100 ml. per patient, and the blood urea fell during 22 of the 24 balances.

Serum albumin levels were measured at the beginning and end of each balance. There was no change in serum albumin in 14 balances, a fall in six (average -0.48 g./100 ml.), and a rise in four (average +0.65 g./100 ml.). The mean change in serum albumin was -0.02 g./100 ml. These changes were not related to the quantity of high-quality protein intake.

None of the patients were subjected to peritoneal dialysis before or during the study.

**Protein Intake and Nitrogen Balance**

Fig. 1 shows the relationship between nitrogen balance in g./day and the effective total protein intake in g./kg./day in 24 balance studies performed on 16 patients over 6 to 55 days. The effective amount of protein ingested varied from 0.23 to 1.0 g./kg./day; it was calculated as the total protein intake less the urinary protein loss. There was a positive relationship between the effective quantity of protein ingested and the nitrogen balance. During 21 of the 24 studies the nitrogen balance became either less negative or more positive. In five of the 21 studies the nitrogen balance started negative and became positive; in six the nitrogen balance started positive and became more positive; and in the remaining 10 studies there was a progressive diminution in the extent of the initial

negative nitrogen balance but the nitrogen balance did not become positive.

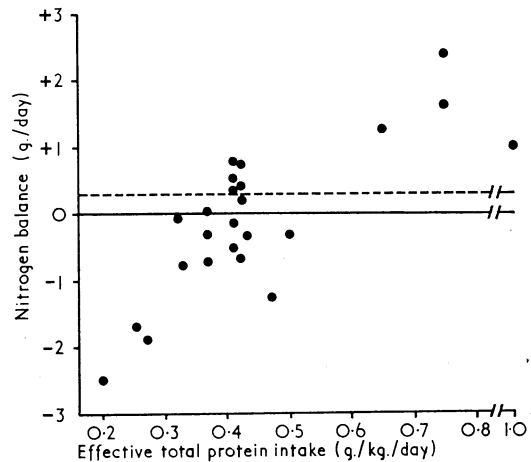


FIG. 1.—Nitrogen balance at the end of each study plotted against effective total protein intake. The interrupted horizontal line denotes average nitrogen loss per day in sweat in a moderate climate (Wolthuis, 1961).

During 3 of the 24 studies the nitrogen balance became less positive or more negative. Two of these patients (Cases 1 and 2) received the smallest amounts of protein (0.23 and 0.26 g./kg./day). The third (Case 14) failed to retain nitrogen when given 0.52 g./kg./day but when the protein intake was increased to 0.67 g./kg./day the nitrogen balance became positive.

Four patients (Cases 5, 7, 9, and 11) were admitted for a second balance study 107, 188, 96, and 110 days respectively after they had been on a controlled intake of protein of about 0.4 g./kg./day (Table II). The nitrogen balance of all four patients had been negative throughout the first study. In the initial period of the second study one patient was in positive nitrogen balance but the other three were still in negative nitrogen balance; in two of these three, however, the balance became positive during the second balance, while only one remained in negative nitrogen balance.

One of these patients (Case 5) was admitted for a third balance 225 days after the start of a reduced protein diet. At the beginning of the third balance she was in severe negative



Hocken (1968) and Shaw *et al.* (1965), however, claimed that with a diet of 0.26 g. of protein/kg./day "not more than 10 out of 82 patients were in negative nitrogen balance" and that "62 were in positive balance."

Giordano (1963, 1964), Giovannetti and Maggiore (1964), and Giordano *et al.* (1967) used low-protein diets in which all the protein was supplied as pure essential amino-acids and egg whites. These diets were not particularly palatable and Giordano even found it necessary to tempt his patients with rum and anise. In the present study reduced protein diets have been devised to suit the British palate for periods as long as two and a half years. One of the main improvements was to use meat as opposed to egg white as the main source of high-quality protein. The variability in the patients' eating habits, pattern of meals at home, and personal fads and tastes were all taken into consideration when arranging each diet. This accounts for the variation in total calories and the different proportions of high-quality to low-quality protein in each diet.

The results show that in patients with chronic renal failure a total protein intake of less than 0.4 g./kg./day is associated with an initial negative nitrogen balance which remains negative for many months thereafter.

Within the range studied the ratio of high-quality to low-quality protein and the protein-sparing effect of the carbohydrate intake had no apparent effect on nitrogen balance. The total protein intake was the most important factor affecting the nitrogen balance. This is in keeping with the conclusions of Snyderman *et al.* (1965). The type of high-quality protein did not appear to be important. Fig. 3 illustrates in two patients (Cases 12 and 15) that an improvement in nitrogen balance was obtained when either egg white or meat was used as the main source of the high-quality protein. Reversal of the main source of high-quality protein did not affect the nitrogen balance, which in both cases became more positive.

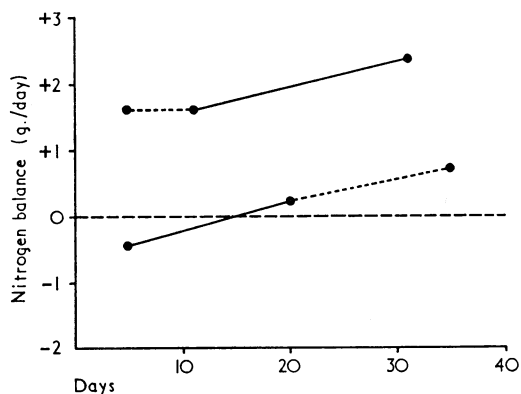


FIG. 3.—Nitrogen balance in two patients (Cases 12 and 15) during 26–35 days. ---- Main source of high-quality protein was egg white. — Main source of high-quality protein was meat.

In our patients the nitrogen balance was negative at the beginning of 17 of the 24 balances, but in 15 of these 17 balances it became positive or less negative subsequently. The change in nitrogen balance from negative to positive or less negative may have been due to the patients having been on a higher protein intake outside hospital and that they were therefore coming into equilibrium. In some patients who were studied on a second occasion there was again an initial negative nitrogen balance (which subsequently improved) despite the fact that in the interval between the two balances they were supposed to be on the same diet that they had ingested during the first balance. This suggests that the patients' protein intake outside hospital was higher than that prescribed; and this suggestion is supported by the fact that in such patients there was a small fall in blood urea during the second balance study. The improvement in nitrogen balance seen during 21

balances could therefore be partly due to an adaptation to the reduced protein intake.

For more than a century it has been known that when protein intake is suddenly reduced there is a net protein loss (negative nitrogen balance) which after a short period is counteracted and equilibrium restored. Similarly on returning to a higher protein intake protein is laid down in body tissues (positive nitrogen balance) until equilibrium is again reached (Voit, 1867). Nitrogen balance therefore exists at varying levels of total body protein. The readily mobilized protein used for equilibration has been called "labile" body protein and constitutes up to 5% of total body protein (*Lancet*, 1963).

Patients with chronic renal failure have additional mechanisms to adapt to a reduced protein intake. Giordano (1964) showed that, provided adequate amounts of the essential amino-acids are supplied, uraemic patients are able to manufacture non-essential amino-acids from their own nitrogenous waste products. Richards *et al.* (1967) showed that the incorporation of  $^{15}\text{N}$  ammonia in patients with chronic renal failure is greater the lower the protein intake and the longer it has been administered, the ammonia being derived by bacterial breakdown of urea in the intestine. Giordano (1963, 1964) also found that positive nitrogen balance could not be obtained on a low-protein diet unless the diet had been preceded by a period when the only source of protein was essential amino-acids. Giovannetti and Maggiore (1964) found it necessary to precede essential amino-acid diet with a period of protein-deficient diet (1 to 1.5 g. of nitrogen). Allison (1951, 1957) had found that dietary protein requirement was reduced by feeding a protein-deficient diet, and Forsyth *et al.* (1955) showed that protein depletion was a strong stimulus to the synthesis of body proteins. It is therefore possible that the continued improvement in nitrogen balance which developed over several weeks in some of our patients was due to a slow adaptation to new metabolic pathways as a response to reduced protein intake. The work of Allison (1951), Giordano (1963, 1964), Giovannetti and Maggiore (1964), and Richards *et al.* (1967) suggests that this adaptation might have been quicker had the reduced protein diet been preceded by a period of complete protein depletion.

The three patients whose protein intake was 0.28 g./kg./day or under did not show any evidence of adaptation, and in two of them the nitrogen balance became increasingly negative. This increasing negative nitrogen balance was probably due to the fact that, at these low nitrogen intakes, the essential amino-acid content of the diet was insufficient even when the high-quality to low-quality protein ratio was as high as 70% (Table II). These findings are in keeping with those of Giordano *et al.* (1967), who found that patients kept on a diet containing 0.3 g. of protein/kg./day, of which 60% was high quality, developed plasma aminogram problems characteristic of kwashiorkor, with reduced quantities of several essential amino-acids and some non-essential amino-acids.

Our results agree with those of Herndon *et al.*, (1958), Giordano *et al.* (1967), Kerr *et al.* (1967), and Kopple *et al.* (1968) that in patients with chronic renal failure the protein intake should be nearer 0.5 g./kg./day than the 0.26 g./kg./day which has been advocated by Berlyne and Hocken (1968) and by Shaw *et al.* (1965). It is difficult to explain the results of these latter workers, who found that with intakes of 0.26 g. of protein/kg./day 75% of patients with chronic renal failure were in positive nitrogen balance. It is possible that the balance techniques they used were not suitable. They state that they did not measure faecal nitrogen, and it appears from the results that the dietary nitrogen was not measured individually.

It must be kept in mind that though reduced protein diets may prolong the patient's life they allow time for the insidious development of many complications. We have noticed that when patients are placed on maintenance haemodialysis they recover their health more quickly if they have not been on a reduced protein diet for very long before dialysis is begun, whereas those patients who have been on a low-protein diet

for some time before they start treatment with maintenance haemodialysis are more liable to have renal osteodystrophy and peripheral neuropathy. After dialysis is begun their anaemia remains more severe, they gain weight more slowly, and wound healing is often markedly impaired. In some of these patients full recovery may take up to one year.

It appears reasonable therefore to increase protein intake to a level where nitrogen balance is achieved. An increase in protein intake from around 0.3 to 0.5 g./kg./day is usually associated with only a small rise in blood urea. It would seem that when other forms of treatment for terminal renal failure are available reduced protein diets should be used only for short periods, and that the intake of protein should be 0.5 g./kg./day (35 g. for a 70-kg. man) to keep the patient in nitrogen balance.

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## Broken Heart: A Statistical Study of Increased Mortality among Widowers

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**S**ummary: A total of 4,486 widowers of 55 years of age and older have been followed up for nine years since the death of their wives in 1957. Of these 213 died during the first six months of bereavement, 40% above the expected rate for married men of the same age. Thereafter the mortality rate fell gradually to that of married men and remained at about the same level.

The greatest increase in mortality during the first six months was found in the widowers dying from coronary thrombosis and other arteriosclerotic and degenerative heart disease. There was also evidence of a true increase in mortality from other diseases, though the numbers in individual categories were too small for statistical analysis.

In the first six months 22.5% of the deaths were from the same diagnostic group as the wife's death. Some evidence suggests that this may be a larger proportion than would be expected by chance association, but there is no evidence suggesting that the proportion is any different among widows and widowers who have been bereaved for more than six months.

### Introduction

To most of us death from a "broken heart" is a figure of speech, yet the term reflects a bygone belief that grief could kill, and kill through the heart.

In 1963 a report was published of a follow-up of a cohort of all men of 55 years and older who were widowed in England and Wales during January and July of 1957 (Young, Benjamin, and Wallis, 1963). This showed that during the first six months of bereavement the mortality rate was 40% greater than the mortality rate for married men of the same age, and that this increase gradually fell thereafter to the level of the rate for married men.

More recently Rees and Lutkins (1967) reported the results of a survey of the death rate among 903 relatives of patients dying in a semirural area of Wales. They found that 4.8% of bereaved close relatives died within a year of bereavement compared with 0.68% of a non-bereaved control group. The greatest increase was found among widows and widowers, their mortality rate being ten times greater than that of the matched controls. After the first year of bereavement mortality rates fell off sharply and were not significantly higher than in the control group.

The study by Cox and Ford (1964) of mortality rates among widows shows a rise during the second but not the first six months of bereavement. This study relies on the widow having

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