ALBUMIN METABOLISM IN CHRONIC RENAL FAILURE

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(Received 8 December 1969)

SUMMARY

1. Plasma albumin concentration was measured in fifty-eight patients with chronic renal failure. The mean value was 3.27 g/100 ml (SD 0.44 g/100 ml; range 2.4-4.3 g/100 ml) which is significantly lower ($P < 0.001$) than normal (mean 3.94 g/100 ml; SD 0.23 g/100 ml; range 3.5-4.4 g/100 ml). In thirty-eight of the fifty-eight patients (65%), plasma albumin concentration was below the normal range. Treatment by maintenance haemodialysis or renal transplantation usually corrected the hypoalbuminaemia.

2. Radioactive iodine-labelled albumin turnover was investigated in twelve patients. Although plasma albumin concentration was reduced in eight of the twelve patients, the plasma half-life ($T_1/2$) of the labelled albumin was normal or increased in all but one of these patients. Fractional and absolute albumin degradation rates (which include urinary albumin loss) were reduced in six of the twelve patients. In two of the four patients with normal plasma albumin concentrations the fractional albumin degradation rate was reduced.

3. Albumin synthesis was estimated by measuring the rate of incorporation into plasma proteins of $^{14}$C in two patients on a 20 g protein diet. The values were low in both.

4. Albumin catabolism and albumin synthesis were normal in two patients who had been on regular haemodialysis for 5 and 8 weeks respectively.

5. We conclude that these abnormalities in albumin metabolism were probably due to severe protein depletion, induced either by prolonged anorexia and vomiting or by deliberate restriction of protein in the diet in the course of treatment.

Hypoalbuminaemia commonly occurs in patients with chronic renal failure (Schreiner & Maher, 1961; Mueting, 1961) but the cause of this abnormality is uncertain (Wills, 1968). In view of the widespread use of very low protein diets in the management of chronic renal failure (Giordano, 1963; Giovanetti & Maggiore 1964; Shaw, Bazzard, Booth, Nilwarangkur & Correspondence: Dr G. A. Coles, Medical Unit, Royal Infirmary, Cardiff.)

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the role of dietary protein deficiency is of interest, since hypoalbuminaemia is a late manifestation of human malnutrition (Keys, Brozek, Henschel, Michelson & Taylor, 1950; Brock, 1966).

We report here the results of measurements of albumin catabolism and synthesis in patients with severe chronic renal failure, and the effects of treatment by regular haemodialysis and renal transplantation on plasma albumin concentration.

PATIENTS AND METHODS
Fifty-eight patients with severe chronic renal failure were investigated; all had a creatinine clearance of less than 10 ml/min. Many were in the terminal stages of uraemia and either died or required regular haemodialysis within 1 month. The height and weight of each patient were recorded and total body fat was calculated from fat-fold measurements (Fletcher, 1962). Lean body mass was obtained by subtracting total body fat from body weight; no corrections were made for the presence of oedema. Serum albumin concentration was estimated at regular intervals by the methyl orange method (Keyser, 1961). Blood urea, urinary and serum creatinine were determined by an AutoAnalyser (Auto Technicon). The twelve patients in whom radio-active tracer studies of albumin metabolism were made gave informed consent before participating in these investigations.

Diets
Thirty-six patients were taking a 20 g protein essential amino-acid diet (Shaw et al., 1965), and twelve were on a 40 g protein diet. Ten had had no previous dietary restriction but they had complained of anorexia and vomiting for 1–9 weeks. Patients on regular haemodialysis were eating at least 50 g of protein per day. After renal transplantation (cadaver-donor) a free protein intake was allowed as soon as the urine volume had reached 1·5 l/day and the serum creatinine was falling without dialysis.

Radio-active iodine labelled albumin turnover
Lister human serum albumin, specially prepared for metabolic studies, was labelled with $^{131}$iodine or $^{125}$iodine by a modification of the iodine-monochloride method of McFarlane (1958). Approximately 25 μCi of the labelled albumin was injected intravenously. The syringe was weighed accurately before and after injection and the total amount of radioactivity injected was calculated from the radioactivity of appropriate standards. Care was taken to avoid withdrawal of blood into the syringe, as this could lead to underestimation of the dose of radio-active albumin injected. A blood sample was taken 15 min after the injection and daily thereafter for up to 14 days. Urine collections were made throughout. Thyroid uptake of radioiodine was blocked by giving 10 drops daily of Lugol's iodine in milk.

The radioactivity of serum and urine samples was measured in a Nuclear-Chicago two-channel automatic gamma counter. When measuring free radioactive iodine in the samples the protein-bound radioactivity was precipitated by adding an equal volume of 20% trichloracetic acid. To determine plasma albumin specific activity the albumin was isolated by the alcohol-trichloracetic acid method (Debro, Tarver & Korner, 1957); the protein concentration of the extract was measured by the biuret method (Wolfson, Cohen, Calvary & Ichiba, 1940). Plasma albumin concentration was calculated by isotope-dilution from albumin specific activity and plasma protein-bound radioactivity. The results obtained by this method (x) were slightly
lower than those obtained with the methyl orange method \( (y) \) \( (N = 9; r = 0.82; y = 1.07x + 0.034) \). Initial plasma volume was derived by isotope-dilution from the radioactivity of the 15-min sample. Total intravascular albumin was calculated from plasma volume and plasma albumin concentration.

The total fractional turnover rate (fraction of the intravascular albumin broken down or excreted per day) and the mass ratio of extra- to intra-vascular albumin were calculated by resolution of the plasma specific activity curve into two or more exponential functions of time by the method of Matthews (1957). Total albumin degradation and loss is the product of total fractional turnover rate and intravascular albumin mass. In order to obtain the true (or endogenous) catabolic rate these values were corrected for urinary albumin losses. Urinary albumin was estimated by a modification of the alcohol-trichloracetic acid method (Debro et al., 1957). Faecal collections were made for a period of 5 days in two patients but since less than 1% of the radioactive iodine injected was excreted by this route faecal losses were ignored in subsequent studies.

**Measurement of accumulation of free radioactive iodine in body fluids**

When \( ^{131}I \)-labelled albumin is catabolized the iodine label is released. In normal subjects this is rapidly excreted in the urine but in patients with chronic renal failure excretion is impaired and free radioactive iodine accumulates in the body fluids. Provided the labelled protein is not denatured, measurement of the rate of \( ^{131}I \)iodine release provides an alternative method of measuring albumin catabolism in patients with oliguric renal failure (McFarlane, personal communication). This method was used in two patients. A mixture containing \( ^{125}I \)-labelled human serum albumin and \( ^{131}I \)iodine was injected intravenously and samples of blood were taken at frequent intervals for 2 days. In these experiments 50 \( \mu \)Ci of \( ^{125}I \)albumin (Behring- werke metabolic grade) and 10 \( \mu \)Ci of \( ^{131}I \)iodide were used. The two iodine isotopes in serum, and in the supernatant after precipitation of the serum proteins with an equal volume of 20% trichloracetic acid, were measured separately using a twin channel automatic gamma counter. Because of the retention of iodide in patients with renal failure these doses gave adequate counting rates in the supernatant (the counts were at least three times background in the earliest samples and became higher with catabolism of the labelled protein). The iodine pool-size and iodine excretion were obtained from the plasma \( ^{131}I \)iodine activity and the total amount of \( ^{125}I \)iodine released by degradation of \( ^{125}I \)albumin could then be calculated. This, expressed as a percentage of the amount of \( ^{125}I \)albumin present, represents the fractional catabolic rate.

**Albumin synthesis**

Albumin synthesis was estimated by measuring the rate of incorporation into plasma proteins of \(^{14}\text{C}\)carbon by the method of McFarlane (1963). In this method the hepatic pool of arginine is labelled in the guanidine C by the administration of \(^{14}\text{C}\) sodium carbonate. The specific activity of this precursor pool is obtained by measuring the specific activity of newly formed urea. The rate of urea production was determined with \(^{13}\text{C}\) urea (Jones, Craigie, Tavill, Simon & Rosenoer, 1968). The synthesis rate of albumin is given by the ratio of the specific activities of the \(^{14}\text{C}\) in albumin and urea multiplied by the urea production rate. In these experiments approximately 70 mg of \(^{13}\text{C}\) urea and 200 \( \mu \)Ci of \(^{14}\text{C}\)carbonate were used. All samples were processed in The Division of Biophysics, National Institute for Medical Research, Mill Hill, London.
RESULTS

Incidence of hypoalbuminaemia

The mean plasma albumin concentration in fifty-eight patients with chronic renal failure was 3.27 g/100 ml (SD 0.44 g/100 ml; range 2.44-4.3 g/100 ml). This is significantly lower ($P < 0.001$) than the mean value obtained in normal subjects by Keyser (1961), using the same method.

FIG. 1. Plasma albumin concentration in fifty-eight patients with chronic renal failure.

![Plasma albumin concentration in fifty-eight patients with chronic renal failure.](image)

(mean 3.94 g/100 ml; SD 0.23 g/100 ml; range 3.5-4.4 g/100 ml). In thirty-eight of the fifty-eight patients (65%) plasma albumin concentration was less than the lower limit of normal (Fig. 1).

Albumin catabolism

Radioactive iodine-labelled albumin turnover was investigated in twelve of the fifty-eight patients: the results are shown in Table 1. Ten of the twelve patients were on a 20 g protein essential aminoacid diet during the period of study and had previously been on the diet for up to 32 weeks. There were no significant changes in body weight or plasma albumin concentration during the test.

Plasma albumin concentration was subnormal in eight of the twelve patients but in only two patients did urinary albumin loss exceed 2 g/day (Patients Nos. 7 and 11, Table 1). Plasma half life of the labelled albumin was subnormal in only one of the twelve patients (No. 7) and was only slightly reduced in this patient despite the urinary loss of 5.9 g of albumin per day. Total fractional 'catabolic' rate and total albumin 'degradation' rate (which include urinary albumin loss) were reduced in six and seven patients respectively. Endogenous fractional and absolute albumin degradation rates (which exclude urinary albumin loss) were even more markedly reduced and were within the normal range in only three of the twelve patients. Two
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of these three (Patients Nos. 4 and 9, Table 1) had clinically obvious chest infections. It is of interest that two of the four patients with normal plasma albumin concentrations (Patients Nos. 8 and 10) had reduced fractional catabolic rates.

### Table 1. Albumin turnover in twelve patients with chronic renal failure

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Lean body mass (kg)</th>
<th>Creatinine clearance (ml/min)</th>
<th>Dietary protein (g/day)</th>
<th>Period on diet (weeks)</th>
<th>Plasma albumin (g/100 ml)</th>
<th>Plasma volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>Glomerulonephritis</td>
<td>40-4</td>
<td>1.56</td>
<td>35-6</td>
<td>2-5</td>
<td>20</td>
<td>1</td>
<td>2-6</td>
<td>2063</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>Polycystic disease</td>
<td>71-5</td>
<td>1.87</td>
<td>66-3</td>
<td>&lt;5</td>
<td>20</td>
<td>4</td>
<td>2-6</td>
<td>3590</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>Pyelonephritis</td>
<td>49</td>
<td>1.63</td>
<td>46-5</td>
<td>10</td>
<td>20</td>
<td>18</td>
<td>3-6</td>
<td>2509</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>Polycystic disease</td>
<td>60</td>
<td>1.59</td>
<td>47-0</td>
<td>&lt;5</td>
<td>20</td>
<td>4</td>
<td>2-6</td>
<td>2588</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>Glomerulonephritis</td>
<td>47-7</td>
<td>1.52</td>
<td>43-4</td>
<td>3</td>
<td>20</td>
<td>3</td>
<td>2-0</td>
<td>2343</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>Glomerulonephritis</td>
<td>62</td>
<td>1.69</td>
<td>57-1</td>
<td>2</td>
<td>20</td>
<td>2</td>
<td>2-8</td>
<td>4048</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>Glomerulonephritis</td>
<td>54-7</td>
<td>1.75</td>
<td>50-1</td>
<td>&lt;5</td>
<td>20</td>
<td>6</td>
<td>4-6</td>
<td>3587</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>Pyelonephritis</td>
<td>60-9</td>
<td>1.67</td>
<td>54-4</td>
<td>&lt;5</td>
<td>20</td>
<td>6</td>
<td>3-1</td>
<td>2524</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>Polycystic disease</td>
<td>44-7</td>
<td>1.52</td>
<td>43-3</td>
<td>&lt;5</td>
<td>20</td>
<td>8</td>
<td>3-1</td>
<td>2524</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>Obstructive uropathy</td>
<td>75-9</td>
<td>1.79</td>
<td>70-2</td>
<td>3</td>
<td>40/20</td>
<td>1 day</td>
<td>3-6</td>
<td>4464</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>Amyloid disease</td>
<td>60-0</td>
<td>1.63</td>
<td>50-8</td>
<td>4</td>
<td>40</td>
<td>4</td>
<td>2-2</td>
<td>2541</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>Polycystic disease</td>
<td>50-1</td>
<td>1.55</td>
<td>47-0</td>
<td>6</td>
<td>40</td>
<td>2</td>
<td>3-5</td>
<td>2270</td>
</tr>
</tbody>
</table>

Normal ranges: 90-130, 3-5-4.4

Normal ranges were taken from Cohen, Freeman & McFarlane (1961) and Dykes (1968).
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TABLE 2. Comparison of albumin catabolic rate determined by analysis of plasma specific activity curves and by free radioiodine release

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Plasma specific activity method</th>
<th>% Intravascular albumin per day</th>
<th>Plas$a^{125}$iodine release method</th>
<th>% Intravascular albumin per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>5.2</td>
<td></td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>10.1</td>
<td></td>
<td>10.2</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3. Plasma albumin synthesis rates in chronic renal failure

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>% Intravascular albumin per day (g/day) (mg kg wt$^{-1}$ day$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>4.1 6.6 100</td>
</tr>
<tr>
<td>9</td>
<td>7.1 5.3 120</td>
</tr>
<tr>
<td>Normal*</td>
<td>8–12 135–260</td>
</tr>
</tbody>
</table>

* These values are for albumin catabolism (see Table 1)

FIG. 2. The effects of maintenance haemodialysis on plasma albumin concentration in twenty patients with severe chronic renal failure.
### Table 4. Albumin catabolism and synthesis in patients on regular haemodialysis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Lean body mass (kg)</th>
<th>Plasma albumin albumin/day (g/100 ml)</th>
<th>Fractional catabolic rate (g/day) (mg kg⁻¹ day⁻¹)</th>
<th>% Intravascular albumin/day</th>
<th>Albumin synthesis</th>
<th>Fractional synthesis rate (g/day) (mg kg⁻¹ day⁻¹)</th>
<th>% Intravascular albumin/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>22</td>
<td>Glomerulonephritis</td>
<td>43</td>
<td>1.83</td>
<td>39.2</td>
<td>3.3</td>
<td>11.2*</td>
<td>10.5</td>
<td>244</td>
<td>12.2</td>
<td>11.9</td>
</tr>
<tr>
<td>14</td>
<td>26</td>
<td>Glomerulonephritis</td>
<td>54</td>
<td>1.68</td>
<td>49.0</td>
<td>4.2</td>
<td>11.3</td>
<td>12.8</td>
<td>238</td>
<td>11.9</td>
<td>13.5</td>
</tr>
</tbody>
</table>

* In view of the rising plasma albumin concentration this value probably over-estimates albumin catabolism
Extravascular albumin mass was less than intravascular albumin mass in six of the twelve patients (Table 1).

In two patients (Nos. 8 and 9) albumin catabolism was also estimated by measuring the rate of release of free radio-iodine from radio-iodine labelled albumin. In Patient No. 9 the result (Table 2) was similar to that obtained by the more conventional method of analysis of plasma specific activity curves (Matthews, 1957) but in Patient No. 8 there was a 35% difference between the two methods.

**Albumin synthesis**

Albumin synthesis was estimated in two patients on a 20 g protein diet (Nos. 8 and 9) by measuring the rate of incorporation into plasma proteins of $^{14}$carbon. The values were low in both patients (Table 3). The rates of albumin catabolism, determined concurrently by means of radioactive iodine labelled albumin (Table 1), were significantly higher.

**Regular haemodialysis**

The effect on plasma albumin concentration of twice-weekly, 14-h Kiil haemodialysis is shown in Fig. 2. Fifteen of twenty patients (75%) had hypoalbuminaemia, but on regular haemodialysis plasma albumin concentration increased in all but two; one of these died after 7 weeks and the other had chronic intra-abdominal sepsis.

Albumin catabolism was estimated with $^{125}$I-labelled human serum albumin and albumin synthesis with Na$_2^{14}$CO$_3$ in two patients (Nos. 13 and 14) who had been on regular haemo-
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dialysis for 8 and 5 weeks respectively (Table 4). Patient No. 14 had had bilateral nephrectomy. Albumin synthesis was almost twice that found in two other patients (Nos. 8 and 9, Table 3) not on regular haemodialysis. Plasma albumin concentration increased from 3.3 to 4.0 g/100 ml during the period of study in patient No. 13 (Table 4) confirming protein repletion. In both patients, albumin synthesis was slightly greater than albumin catabolism.

Renal transplantation

The response of plasma albumin concentration to cadaver-donor renal transplantation is shown in Fig. 3. Before transplantation ten of sixteen patients (63%) had hypoalbuminaemia. During the first 2 weeks after transplantation there was often a further fall in plasma albumin concentration but thereafter it gradually increased. Several patients showed marked fluctuations in plasma albumin, probably related to increased dosage of prednisone given for rejection episodes, to intercurrent infection or to urinary fistulae with wound sepsis. Nevertheless, by 12 weeks plasma albumin concentration was normal in all but three of fifteen patients.

DISCUSSION

Hypoalbuminaemia, in patients with chronic renal failure, can be accounted for in several ways. Heavy proteinuria is one of these. However, in the majority of our patients with hypoalbuminaemia urinary protein loss was less than 2 g/day. This degree of proteinuria should not significantly alter plasma albumin concentration (Squire, Hardwicke & Soothill, 1962).

To explain the negative nitrogen balance often found in uraemia McCormick, Shear & Barry (1966) postulated either an increase in the overall rate of protein degradation or that the uraemic liver may make an incomplete or abnormal protein. There is no evidence that plasma albumin in uraemia is abnormal and our results show that the rate of degradation of plasma albumin is decreased.

Plasma protein turnover data may be analysed by several methods and the assumptions inherent in each have been discussed by Freeman & Matthews (1958). Methods based solely on urinary excretion of radioactive iodine are not valid in patients with severe renal failure, because of delay in the excretion of the label and gradual accumulation of free radio-iodine in the body fluids (Solomon, Waldmann, Fahey & McFarlane, 1964). If, however, the rate of accumulation of free radioactive iodine released during catabolism of labelled albumin is actually measured, by using a different iodine isotope to measure volume of distribution, a valid estimate of albumin degradation rate may be obtained. There are no theoretical objections to the use of methods based on analysis of plasma specific activity curves, provided the patients are in a ‘steady-state’. Most of the potential errors inherent in the measurement of albumin catabolism with I-labelled albumin (such as denaturation of the protein during labelling or analyses of plasma curves of too short duration) overestimate catabolic rate. It is unlikely that the low catabolic rates found in these uraemic patients are due to technical errors.

Several possible explanations for the reduced albumin catabolic rate need to be considered. Reduction in renal catabolism of albumin, as a result of chronic renal damage, cannot account for the abnormalities observed. In normal animals less than 10% of total albumin catabolism occurs in the kidney (Schultze & Heremans, 1966) and, indeed, in one of our patients who had had bilateral nephrectomy albumin catabolism was normal. Another possibility is that uraemia,
per se, in some way depresses albumin catabolism. However, if interference with catabolism were the prime factor, plasma albumin concentration should not be reduced. It would appear that uraemia has little or no effect upon the general relationship between intravascular albumin and albumin catabolism (Fig. 4).

![Graph](image)

**Fig. 4.** The relationship between albumin catabolism and intravascular albumin (a) in patients with chronic renal failure (○) and (b) in patients with hypoalbuminaemia due to malabsorption, cirrhosis or malnutrition (●). (Data for (b) taken from Cohen, Freeman & McFarlane, 1961; Wilkinson & Mendenhall, 1963; Jones (1963) and Dykes, 1968).

All our observations can be explained on the basis of protein depletion, induced either by prolonged anorexia and vomiting or by deliberate dietary protein restriction. There is plenty of evidence that protein depletion occurring in the course of disease or induced experimentally leads to a reduction of albumin synthesis, to a fall in albumin catabolic rate (fractional and absolute) and to a shift of albumin from extravascular to intravascular sites, with or without hypoalbuminaemia (Cohen & Hansen, 1962; Picou & Waterlow, 1962; Freeman & Gordon, 1964; Jones 1963; Hoffenberg, Black & Brock, 1966; James & Hay, 1968; Kirsch, Frith, Black & Hoffenberg, 1968). All these phenomena were found in our uraemic patients. It has been suggested that the reduction in catabolic rate and the shift of albumin from extravascular to intravascular sites serve to maintain a normal concentration of albumin in the plasma when albumin synthesis is low (Kirsch et al., 1968; James & Hay 1968). The fact that some uraemic patients with much reduced fractional and absolute catabolic rates nonetheless had normal plasma concentrations of albumin indicates good 'compensation'.

Very low protein diets are widely used in the treatment of advanced renal failure (Giordano, 1963; Giovanetti & Maggiori, 1964; Giordano, de Pascale, de Cristofaro, Capodiscasa, Balestrieri & Baczyk, 1968a; Shaw et al., 1965) but there is disagreement about the minimum
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amount of protein required by such patients. Berlyne & Hocken (1968) concluded that the majority of their patients were probably in positive nitrogen balance on a diet of 0.26 g of protein kg\(^{-1}\) day\(^{-1}\) whereas others consider that the protein intake should be nearer 0.5 g kg\(^{-1}\) day\(^{-1}\) (Ford, Phillips, Toye, Luck & de Wardener, 1969). Patients with chronic renal failure are apparently able to manufacture non-essential amino acids from their own nitrogenous waste products (Giordano, de Pascale, Balestrieri, Cittadino & Crescenzi, 1968b). Ammonia, derived by bacterial breakdown of urea in the colon, can be utilized in the hepatic synthesis of amino acids and proteins, and the lower the protein intake the greater the rate of incorporation of \(^{15}\)N ammonia (Richards, Metcalfe-Gibson, Ward, Wrong & Houghton, 1967). The reduction in albumin catabolism is probably part of a general reduction of protein catabolism. This may be another important factor in maintaining nitrogen balance in uraemia. However, nitrogen balance measurements do not provide a reliable index of nutritional state since it is well established that the greater the degree of protein depletion the less the nitrogen required to maintain nitrogen balance (Allison, 1951; Allison & Bird, 1964). Even if a 20 g protein diet is sufficient to maintain nitrogen balance in uraemia it cannot correct any existing protein depletion. Muscle wasting is often a prominent clinical feature and measurements of lean body mass and fat-free solids indicate severe protein depletion. We believe that hypoalbuminaemia is another manifestation of this, at least in patients with only slight degrees of proteinuria. The increase in plasma albumin and in albumin synthesis rate on regular haemodialysis, or after successful transplantation, is probably due entirely to the higher dietary protein intake; fat-free solids also increase (unpublished data). That the low rate of albumin synthesis might partly be due to some specific effect of uraemia cannot entirely be excluded but this seems an unnecessary hypothesis. To explore this matter further, by continuing to give patients on regular haemodialysis or after transplantation, diets containing only 20 g of protein per day, would be unjustifiable.

There is no conclusive proof that protein depletion is harmful but it appears to reduce the survival rate in experimental animals (Fisher, Green, Shapiro & Ashley, 1964; Allison & Wannemacher 1965) and there is evidence that malnutrition impairs the resistance to infection (Scrimshaw, 1966). While very low protein diets may provide symptomatic relief in patients with severe uraemia it seems reasonable to avoid such diets if facilities for regular haemodialysis or renal transplantation are available. Severe dietary protein restriction should certainly be avoided in patients with mild or moderate degrees of renal failure who are free from symptoms.

ACKNOWLEDGMENTS

We wish to thank Dr A. S. McFarlane, Professor Harold Scarborough and Mr D. I. Crosby for their help. G.A.C. was supported by a Cardiff Royal Infirmary Research Fellowship and D.K.P., in part, by a Medical Research Council Clinical Research Fellowship held at the National Institute for Medical Research, Mill Hill.

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