initial steep fall, and then the curve declines less steeply; the median survival was 18 months, and the 20% survival four years. For the 125 patients whose blood urea was less than 40 mg/100 ml the median survival was 33 months, and nearly 40% of them were alive at four years. For the 96 patients whose blood urea was between 41 and 79 mg/100 ml the median survival was 20 months, and for the 55 patients whose blood urea was 80 mg/100 ml or higher was only two months.

Of the 35 patients who survived four years there were relatively rather more men than in the whole series; there were also relatively more IgG patients, and fewer IgA patients, and relatively a few more K and a few less L cases. Only 23% of the long survivors had an initial haemoglobin concentration below 10 g/100 ml, compared with 48% in the whole series. Only 13% of the 30 IgG and IgA survivors had urinary Bence Jones protein above 100 mg/100 ml, compared with 32% in the IgG and IgA cases in the whole series. As expected, the proportion of cases with normal blood levels of urea was more than three times higher than in the whole series, and there were more in the high urea group. The proportion of cases with high serum albumin levels was higher and of cases with low levels was lower than in the whole series. Of the 12 patients with moderately raised blood urea levels, four had Bence Jones protein disease (urinary concentrations of 180, 180, 200, and 560 mg/100 ml); the remaining eight did not have Bence Jones proteinuria, but three were hypercalcaemic. Thus the presenting features of the 35 long-survivors were precisely what we should expect from the statistical analysis of the whole series of 276 cases.

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Urea, Albumin, and Response Rates

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The rate at which myeloma responds to a cytotoxic attack has been measured for about half of the series of patients in the first Medical Research Council myeloma trial. The biochemical histories over the first six months of treatment were reviewed for all of the 197 patients who were still alive six months after first admission to estimate the individual percentage paraprotein reduction that had occurred four months after admission. This showed that 79 patients died within six months of admission; 12 survivors had less than 1 g/100 ml of paraprotein initially, which was considered insufficient for the calculation of percentage changes. In 60 survivors the biochemical histories were insufficient for percentage estimations to be possible; while in 36 survivors the paraprotein levels were not finally reduced four months after admission. Finally, in 89 survivors the paraproteins had responded at four months; of these 89, 37 were down by half or more and 52 were down by less than half four months after admission.

On examination of their histories after the sixth month the average death rate among the fast responders was about twice that among the slow responders, confirming Hobbs's suggestion that a myeloma which responds rapidly to cytotoxic therapy is in fact a myeloma with rapidly dividing myeloma cells—and so is dangerous. The Table shows how strongly the death rate depends on two factors—the blood urea and serum albumin levels.

Blood Urea

High blood urea is due either to excessive production or to insufficient excretion. Probably neither high urinary urea nor a high urinary urea/creatinine ratio carry a bad prognosis, so that high blood urea must be associated with a poor prognosis simply because it is an index of renal damage.

Over half the patients who presented with severe uraemia (>80 mg/100 ml) were dead within two months of admission. Two years after admission the death rate among patients who originally presented with mildly raised blood urea levels (40–79 mg/100 ml) remains much higher than among those who presented with normal (10–39 mg/100 ml) blood urea. Renal damage is therefore important and frequently irreversible.

Serum Albumin

Low serum albumin is due to reduced production (such as liver dysfunction or amino-acid starvation), increased excretion (kidney damage), or increased catabolism (some catabolic myeloma activity, for example). Low serum albumin must therefore be of prognostic significance because it measures one or other of these effects. Kidney damage allowing albumin leakage into the urine is an obvious explanation, but if this was the reason for the prognostic importance of albumin we would expect a strong association between low albumin and high urea (which does not in fact exist; see Table), and we would expect urinary

*Estimated Death Rates by Initial Urea and Albumin Levels, Expressed as Proportions of the Overall Average Rate**

	Blood Urea 10–39 mg/100	Blood Urea 40–79 mg/100	Blood Urea >80 mg/100	All Blood Ureas
Albumin <3 g/100	1.40 (19)	1.84 (18)	3.72 (13)	1.89 (50)
Albumin 3.0–3.9 g/100	0.74 (59)	0.99 (46)	4.25 (26)	1.41 (131)
Albumin >4 g/100	0.35 (46)	0.92 (31)	2.00 (17)	0.68 (94)
All Albumins	0.64 (124)	1.07 (95)	3.11 (56)	1.00 (275)

Factors examined and found to be of no statistically significant prognostic importance after adjustment for urea and albumin levels included hypercalcaemia, anaemia, alkaline phosphatase, sex, age, paraprotein type, paraprotein concentration, all radiological findings (lytic lesions, wedging, osteoporosis, or pathological fractures) and all histological findings (staining properties, number, and shape of myeloma cells).

*If the proportion of survivors at time t from first treatment is estimated from a life-table to be $P(t)$, then for a group of patients at risk for times $T_1, T_2, \dots$ in which N deaths occur, the relative death rate is estimated by $-N/\log P(T_1)$.

albumin to be a better index of prognosis than serum albumin, and it is not.

Hence probably a myeloma can somehow catabolize circulating albumin or inhibit its synthesis, and low albumin indicates a very active myeloma. Comparing the data in initial urea and albumin levels with those on initial levels of response in the 89 patients surviving in the six months from admission and responding (so any correlations must be treated with care), we find that 9 of these survivors presented with low (<3 g/100 ml) albumin, and 14 with high (>60 mg/100 ml) urea. Though only 40% of the whole 89 were fast responders and 60% were slow responders, eight of the nine low-albumin patients and 10 of the 14 high-urea patients were fast responders. This can be taken either to mean that a myeloma catabolizes albumin and low albumin indicates an active myeloma (and hence very sensitive to cytotoxic drugs) or that if you have low albumin or high urea your myeloma has to react fast if you are to survive even six months.

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