that the logical extension of the first principle required the provision of full sex education and contraceptive advice for the young. The first principle, too, demands the speedy passage of more liberal abortion laws, in which matter the legislature has been regrettably tardy.

I presented some of the arguments for the acceptance of scientific trials of therapeutic procedures, both medical and surgical, even though these may marginally impair the rights of the individual. Experimenters, in exchange for community cooperation, should be prepared to accept the opinions of their colleagues as to the ethics of their experiments. If we are to sustain the scientific advance of medicine the needs of the community must be accepted as paramount, providing that individuals are not subjected to danger or pain.

In discussing our present care of children, I pleaded for the better integration of our health and welfare services, for their improved organisation, and for the betterment of social conditions, particularly in housing, so that all children might be given a full biological opportunity.

Acknowledgments

This talk has been tried out in the University of Birmingham, the University of Newcastle, the Selly Oak Colleges, and other associations. My grateful acknowledgments must go to those audiences who have listened, and made comments on it. If my basic opinions have not changed, my expression of them has been modified. The theologians (non Roman Catholic) were not concerned with the sanctity of embryonic life, but they were much troubled by the problem of human rights in experiments on man. Some of those who were involved in the training of youth—parsons, teachers, matrons, and so forth—disliked the giving of contraceptive instruction to the young, and were anxious that sex education should not be divorced from ethical and personal advice. The gynæcologists, who must necessarily be the agents of destruction, while in the majority agreeing that the abortion laws should be liberalised, were insistent that the conscience of the individual surgeon must be the final arbiter. The human biologist can do no more than ask that, in the adjudication of these difficult questions, his evidence should not be disregarded. The history of birth-control has demonstrated the error of judging biological and social questions solely by moral and religious considerations.

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A LOW-NITROGEN DIET WITH PROTEINS OF HIGH BIOLOGICAL VALUE FOR SEVERE CHRONIC URÆMIA

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THE diet in chronic uræmia has to fulfil two main and conflicting purposes: to lower the production of protein catabolites, and to prevent wastage of body proteins.

A protein-deficient diet, which could reduce the protein catabolites, is considered unwise because of the protein depletion caused; therefore a high-caloric diet, containing about 0·5 g. of protein per kg. body-weight, is generally advocated as the best compromise between the two opposite requirements (Merrill 1960, Goldman 1962). When renal excretory impairment is severe, however, the administration of even 0·5 g. of protein per kg. per day leads to considerable abnormalities of blood chemistry, and these are usually associated with digestive symptoms which prevent an adequate caloric intake.

We here describe the results of treating patients with severe chronic uræmia with a diet deficient in protein (i.e., containing too little protein to maintain the nitrogen equilibrium) to which are added essential aminoacids or small amounts of protein of high biological value. The purpose of this treatment is to keep the production of protein catabolities low by giving a diet which contains very little protein yet supplies nitrogen in a form which can be completely utilised in the synthesis of body proteins.

Patients and Methods

Eight unselected chronic uræmic patients with uræmic symptoms have so far been treated for periods ranging from 3 to 10 months (table I). All these patients had previously been in our hospital where they had taken a diet containing 0·5 g. of protein per kg. per day until digestive symptoms (nausea and vomiting) appeared, and prevented an adequate caloric intake.

Patients 1–4 (table I) were treated with the diet alone; patients 5 and 6 were first hæmodialysed twice, because nausea and vomiting were so severe as to prevent their feeding at all, and they were then treated with the diet; and patients 7 and 8 were repeatedly hæmodialysed because the diet alone was not sufficient to prevent uræmic symptoms.

The *basal protein-deficient diet* contains 1·0–1·5 g. of nitrogen, 0·25–0·40 mEq. of sodium, and 35–50 mEq. of potassium per day. The bulk of calories (2000–3000 per day) is supplied by unsalted butter, unsalted lard, vegetable oils, sugar, honey, maize starch, and special wheat starch (Energen Food Co., Ashford, Kent). Fruit and vegetables selected from those containing the least nitrogen (pears, apples, peaches, oranges, plums, tomatoes, peppers, aubergines, pumpkins, lettuce, carrots, &c.), are concocted in different ways to give variety to the diet.

As a *bread substitute*, wafers made from maize starch, palm oil, and water are used, while spaghetti is prepared from the special wheat starch. Several types of soup, made with vegetables, tapioca, starch wafers, and butter or vegetable oils, and puddings, made with starch, sugar, butter, and various flavours, are used. Butter is also used, together with starch wafers and sugar, to prepare cakes flavoured with coffee, sweet liquors, or fruit juices. Small amounts of beer and wine are allowed, while water and tea are given ad libitum, and " multivitamins " as a supplement.

Salt is added in an amount to cover its renal excretion except for patients with symptoms suggestive of sodium depletion (some patients are sodium depleted on admission, after repeated vomiting), to whom an additional amount of 40–80 mEq. of sodium is administered, depending on the behaviour of body-weight and blood-pressure. On the other hand, if hypertension appears, sodium is restricted, and the basal protein-deficient diet (almost sodium-free) is given for various periods.

Essential aminoacids are given in the recommended daily amounts according to Rose (1957): L-tryptophan 0·5 g., L-phenylalanine 2·2 g., L-lysine 1·6 g., L-methionine 2·2 g., L-leucine 2·2 g., L-threonine 1·0 g., L-valine 1·6 g., and L-isoleucine 1·4 g. They are administered in a compound powder form enclosed in cachets; the total daily amount is fractionated into 4 or 5 parts, and taken with the meals. Most of the aminoacids used were in the L-form, but the threonine and the valine were in the DL-form, and the administered amount was double the recommended daily intake which refers to the L-form (2·0 g. for DL-threonine and 3·2 g. for DL-valine). (The bulk of the aminoacids used are supplied by Light & Co. Ltd., Colnbrook, Bucks.)

Egg proteins or egg albumen are added to the basal protein-

TABLE I—FINDINGS IN THE EIGHT PATIENTS TREATED

Patient no.	Sex and age (yr.)	Diagnosis	Observation period (mos.)	Body-weight (kg.)		Urea clearance (ml. per min.)		Plasma-urea (mg. per 100 ml.)		Plasma-creatinine (mg. per 100 ml.)		Plasma-urate (mg. per 100 ml.)		Mental symptoms		Neuro-muscular symptoms		Digestive symptoms	
				B*	A*	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	F 38	Chronic pyelonephritis	7	67	71	3·0	2·8	300	60	11·5	12·0	10·6	5·2	+	−	+	−	++	−
2	F 36	„ „	5	64	65	3·2	2·2	225	75	10·6	9·6	8·0	5·7	−	−	+	−	+	−
3	M56	„ „	6	91	87	4·0	4·1	200	60	9·5	9·8	9·2	7·8	−	−	+	−	++	−
4	F 52	„ „	10	51	54	1·8	1·6	240	110	11·8	13·0	9·8	7·2	+	−	++	−	++	−
5	F 45	Chronic glomerulonephritis	6	67	69	2·0	2·5	500	100	16·0	12·2	11·6	9·3	++	−	+	−	+++	−
6	F 27	Chronic pyelonephritis	7	56	64	2·3	3·0	400	60	14·6	12·2	8·9	6·7	+	−	++	−	+++	−
7	M25	„ „	4	68	65	1·2	0·7	360	110	15·6	18·0	11·5	9·8	++	−	+++	−	+++	−
8	M34	Chronic glomerulonephritis	3	65	61	1·0	0·8	400	160	17·9	17·5	14·8	8·7	+++	−	+++	−	+++	−

* B = before (on admission), and A = after treatment.

deficient diet because they are known to have the highest biological value (Allison 1957). These proteins are given in various forms according to the patients' preference, and the amount is weighed at every meal when the patients are in hospital.

Extracorporeal hæmodialyses are performed with the previously described apparatus (Giovannetti et al. 1960) by using the " vein-to-vein system " and a ' Sigmamotor ' pump (model T.6.S). A femoral vein and a suitable vein of the forearm are cannulated percutaneously as described by Shaldon et al. (1961); this technique is particularly advantageous for chronic patients because it is possible to cannulate the same vessel many times without causing permanent damage. When dialyses are performed at short intervals, the cannula is left inside the femoral vein and kept patent by means of a heparin perfuser (Giovannetti et al. 1963); otherwise both the vein of the forearm and the femoral vein are cannulated again.

Blood and urine urea are measured by the hypobromite method, and the total non-protein nitrogen in the urine and fæces is determined by the Kjeldahl method. This technique was also used to determine the total nitrogen content of the food which was checked at least twice for every type of food. The plasma and urine sodium and potassium contents are measured with the flame photometer; the plasma urate and creatinine concentrations are determined respectively by the methods of Pasero and Masini (1958) and of Edwards and White (1958).

Urea clearance is calculated on the 24-hour urine volume by using the formula UV/P in every case, irrespective of the minute urine volume, because this is the only formula which is useful for physiological analysis (Smith, H. W., 1951). We prefer this renal-function test because it is known that the urea/inulin clearance ratio (Chasis and Smith 1938) and the urea/thiosulphate clearance-ratio (Giovannetti 1952) approach 1·0 in severe chronic renal failure. We may thus assume that in our patients the urea-clearance values were only a little lower than the glomerular filtration-rate.

Results

The basal protein-deficient diet was well tolerated by the hæmodialysed patients on the days immediately following dialysis; the other patients tolerated the diet well, and they ingested a sufficient amount of food as soon as their blood abnormalities were significantly reduced (5–10 days after the diet was started). Addition of egg proteins to the diet did not alter its palatability, but the essential amino-acids produced nausea and vomiting in patients 1 and 5.

In the first four patients the blood-urea concentration decreased progressively after the protein-deficient diet was started (fig. 1), and the lowest level reached was, of course, inversely proportional to the residual renal excretory function, as measured by urea clearance. In patients 5 and 6 the blood-urea concentration increased in the days after hæmodialysis, and this was then followed by a slow decrease (fig. 2). Patients 7 and 8 showed a slow increase of the blood-urea concentration after their dialyses, and it was never possible to reduce this blood abnormality by the diet alone (fig. 3).

When essential aminoacids or egg proteins were added to the basal protein-deficient diet, no significant increase of the blood-urea concentration was observed in the first six patients (figs. 1 and 2), and in patients 7 and 8 there were no changes which might be attributed to the supplementary dietary nitrogen (fig. 3). In patients 1, 5, and 6 a decrease in the blood-urea concentration was observed, the renal excretory function being constant when the essential aminoacids were given (figs. 1 and 2).

Plasma-urate and creatinine concentration underwent smaller changes than plasma-urea; a significant decrease was always observed, however, for urate (table I).

The nitrogen balance was obviously negative when the basal protein-deficient diet was followed; but, when essential amino-acids or egg proteins were given, it became soon positive or reached equilibrium (see figures). This equilibrium persisted for several weeks, during which the protein-deficient diet supplemented with egg proteins was followed.

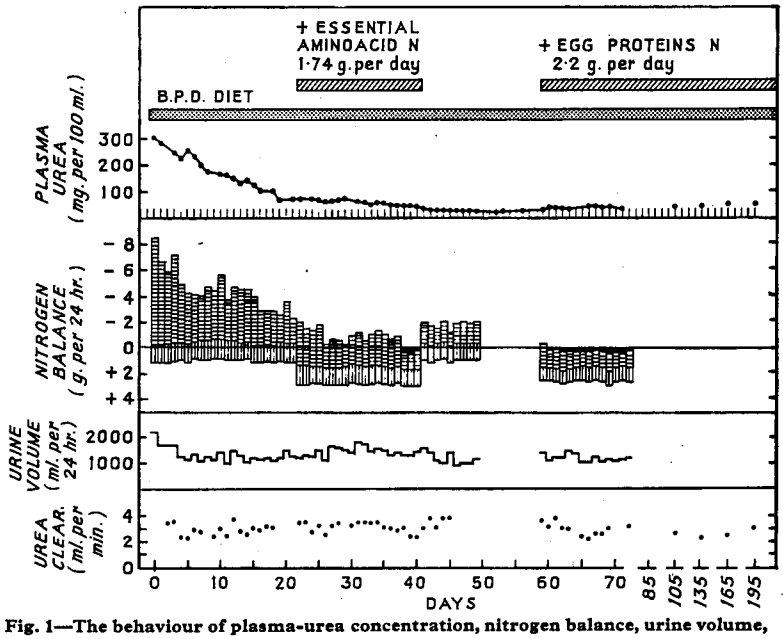

Fig. 1—The behaviour of plasma-urea concentration, nitrogen balance, urine volume, and urea clearance in patient 1.

The nitrogen balance is charted according to Reifenstein et al. (1952): the intake is plotted downwards from the base line, the output is plotted upwards from the bottom of the intake; vertical and horizontal hatching represents fæcal and urinary nitrogen respectively; the black areas indicate the positive nitrogen balance.

No correction has been made for the reduction in the total non-protein nitrogen; therefore, during the initial observation period (when the previously retained protein catabolites were excreted) the tissue balance was less negative than it appears in the figure.

B.P.D. diet = basal protein-deficient diet.

TABLE II—TO SHOW THE ANÆMIA, SERUM-PROTEIN LEVELS, AND LIVER-FUNCTION TESTS

Patient no.	Red-cell count (mill. per c mm.)		Hæmoglobin (g. per 100 ml.)		Serum-proteins (albumin) (g. per 100 ml.)		Bromsulphthalein-retention test (% retention after 30 min.)	
	B*	A*	B	A	B	A	B	A
1	1·85	3·22	6·59	9·35	6·40 (3·04)	6·45 (3·04)	8	8
2	2·53	2·74	8·50	9·64	6·50 (3·10)	6·30 (3·04)	7	9
3	3·02	3·43	8·50	9·65	5·90 (2·79)	6·35 (3·07)	8	10
4	1·98	2·53	4·85	7·25	6·10 (2·81)	6·40 (2·83)	9	12
5	1·85	2·80	5·90	9·75	6·20 (3·03)	6·10 (3·25)	6	9
6	2·33	2·78	7·60	9·25	6·05 (2·93)	6·15 (3·28)	10	11

* B=before (on admission), and A=after the dietetic treatment (when no transfusions had been given for at least 3 mos. Every value represents the mean of at least two determinations.

The uræmic symptoms, such as anorexia, vomiting, fatigue, twitching, and mental changes, disappeared or improved as soon as the blood abnormalities were significantly corrected. Complete rehabilitation has so far been obtained in patients 1–4 and 6, who are now living an almost normal life at home, except for the diet restrictions, antihypertensive therapy (patients 5 and 6), and periodic outpatient visits to hospital. Patient 4 discontinued the diet after about 8 months, and uræmic symptoms soon reappeared. She was readmitted to hospital with a blood-urea of 237 mg. per 100 ml., vomiting, anorexia, and severe fatigue; after 3 weeks of the protein-deficient diet her blood-urea concentration had fallen to 120 mg. per 100 ml., and she is now symptom-free. Patient 5 was also readmitted to hospital for further balance studies; though her blood-urea concentration was 150 mg. per 100 ml. and her arterial blood-pressure was 230/120, she was symptom-free. She is now on the protein-deficient diet, and her sodium supplement has been stopped, and both the blood-urea concentration and the arterial pressure are decreasing.

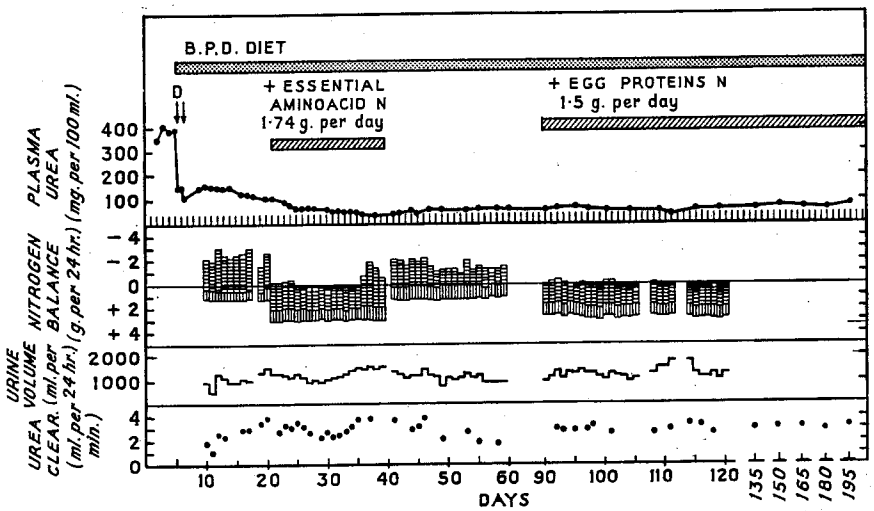

Fig. 2—The behaviour of plasma-urea concentration, nitrogen balance, urine volume, and urea clearance in patient 6, who was hæmodialysed twice (D) before starting dietetic treatment. (For key see legend of fig. 1.)

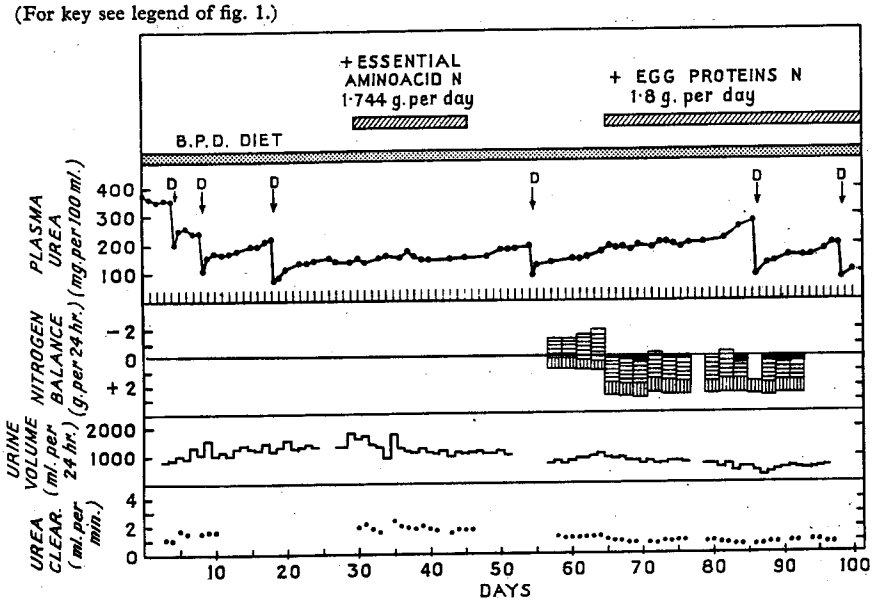

Fig. 3—The behaviour of plasma-urea concentration, nitrogen balance, urine volume, and urea clearance in patient 7.

This patient was repeatedly hæmodialysed because the dietetic treatment alone did not prevent the uræmic symptoms. The nitrogen balance was not corrected for the retention of protein catabolites, and, therefore, when essential aminoacids or egg proteins were given; if the plasma urea concentration was increasing, the nitrogen balance was positive and the tissue-nitrogen balance was less positive than appears in the figure. (For key see legend of fig. 1.)

Patient 7 was discharged 2 days after a hæmodialysis, when he had become free of symptoms; but he discontinued the diet, refused further dialysis, and died 15 days later. Patient 8 died in hospital, after 87 days' observation, of cardiac arrest which appeared after a period of supraventricular tachycardia, when his blood-pressure was 230/140. Postmortem examination revealed an enormous pericardial effusion (despite aspiration of 400 ml. of hæmorrhagic fluid before death) and an enlarged heart weighing 680 g.

Severe anæmia was present in all the patients studied, and packed red cells were repeatedly transfused during the first weeks of observation in hospital. Later, when the first six patients had been discharged and the blood abnormalities had been corrected for several months, the anæmia improved spontaneously (table II). In patients 7 and 8 no significant improvement was noted in the anæmia, and periodic red-cell transfusions were necessary during the whole observation period.

Hypertension was not a problem in the first four patients; in them the arterial pressure was almost normal on admission, and it later showed no significant changes. In patients 5 and 6, whose arterial pressure was also normal on admission, severe hypertension appeared, but it has been possible to control this so far by giving small amounts of guanethidine (5–15 mg.

per day) and by reducing the sodium intake. In patient 7 the arterial pressure progressively increased, and a value of 220/140 was reached; but in this patient guanethidine produced severe side-effects, and it was not possible to control the hypertension satisfactorily. The severe hypertension which appeared in patient 8 after 2 weeks of observation was almost completely resistant to dietary deprivation of sodium, to ultrafiltration performed during dialysis, and to the administration of up to 30 mg. per day of guanethidine, and it persisted up to death. Hypertension was also a problem during dialysis in patients 7 and 8, but no convulsions appeared, and the arterial pressure values progressively decreased when dialyses were discontinued.

With the exception of patient 7, who had an exacerbation of pyelonephritis (fever, lumbar pain, and pyuria) during his stay in hospital, and a simultaneous reduction in urea clearance, no significant changes were observed in the renal excretory function which might be attributed to the dietetic treatment. Oliguria, lasting 2–3 days, was always observed after dialysis, with a corresponding reduction in the urea-clearance values.

No symptoms have been observed as yet which might be attributed to protein depletion. Plasma-protein concentration and electrophoretic pattern (table II), as well as liver-function tests (thymol-turbidity, flocculation, and bromsulphthalein tests) showed no significant abnormalities (table II).

Discussion

The unpalatability and monotony of a protein-free diet, together with the nausea and vomiting which accompany uræmia, are all too often insuperable obstacles to its successful application, even in acute renal failure. Furthermore, the danger of a progressive depletion of body proteins makes such a diet inadvisable for long-term treatment in chronic patients.

In this study hæmodialysis proved to be a very efficient means of eliminating anorexia and vomiting, and of allowing resumption of spontaneous feeding, while the addition of vegetables and fruit to foods of high-caloric value has been helpful in making our protein-deficient diet acceptable. With this diet a reduction of protein catabolism can be obtained which is comparable to that described in normal subjects on a protein-free diet (Smith, M., 1926, Bricker et al. 1949). As for the danger of progressive wastage of the body proteins, it has been proved that very low amounts of dietary nitrogen of high biological value may be sufficient, in chronic uræmia, to maintain nitrogen equilibrium.

The peculiar conditions of the uræmic patients may partly explain the fact that the amount of dietary nitrogen which is necessary for nitrogen equilibrium is lower than in normal people, but the preliminary protein depletion obtained with the basal protein-deficient diet is certainly important. In fact, it is well known that a protein-free diet causes a reduction in the amount of dietary proteins which are necessary for nitrogen equilibrum (Allison 1951), and that it represents a strong stimulus to the synthesis of body proteins (Forsyth et al. 1955, Peters and Van Slyke 1946). Our patients, initially treated with the protein-deficient diet, reached this state (together with a reduction of their blood-urea concentration); and, when essential aminoacids or egg proteins were given, the nitrogen balance became positive or reached equilibrium while there was no significant increase in blood-urea concentration. In the case of the administration of the essential aminoacids alone, a re-utilisation of the protein catabolites (Giordano 1963) may be a contributory explanation.

In conclusion, whatever the explanation of the equilibrium in nitrogen balance which we have observed, it constitutes a reason for persisting in the described dietary treatment of chronic uræmia. This regime reconciles the two opposite requirements of the diet for such patients: it reduces the production of protein catabolites, and prevents wastage of body proteins.

The danger of protein depletion during long-term treatment must be considered, nevertheless, and up to now we have had no experience longer than 10 months. However, because the potential risk of protein depletion must be weighed against the actual and certain danger of the uræmic syndrome, we no longer hesitate but treat with the diet described above all severely uræmic patients who come under our observation.

Summary

A dietetic treatment is described for severe uræmia; to a basal diet grossly deficient in protein, nitrogen of high biological value is added (essential aminoacids alone or egg proteins have been used).

The basal protein-deficient diet consists of vegetable and animal fat, bread substitute, and spaghetti prepared with starch, sugar, honey, jams, fruit, and vegetables selected from those containing the least nitrogen. It furnishes 2000–3000 calories, and contains 1·0–1·5 g. of nitrogen per day.

Eight severe chronic uræmic patients have been treated so far for a preliminary period with the protein-deficient diet to which the egg proteins or the essential aminoacids were subsequently added. An improvement of the uræmic symptoms, together with considerable reduction of the blood abnormalities, was observed in all, and six of them (three in what appeared to be the terminal stage of chronic uræmia) were rehabilitated almost completely. No symptoms have been observed as yet which might be attributed to protein depletion, probably because the nitrogen balance is kept in equilibrium by the essential aminoacids or egg proteins.

Two patients died: one of them discontinued the diet and refused repeated dialysis, and the other went into heart-failure as a result of malignant hypertension.

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" . . . ' must everything pay ? ' . . . my answer is that it need not. Our costing methods are outdated if we think exclusively in terms of pecuniary margins. We should think rather of social accountability. We cannot measure in money the good conferred by hospitals, schools, the postal services, public transport and the rest. . . . In an age of advertised material affluence we ought to be turning our attention away from the nicely calculated less or more of private accountancy, of profit and the profit motive, towards the far more complex matters of social accountancy, to priorities and the old Benthamite doctrine of 'the greatest happiness for the greatest number'. When we ask 'must everything pay ?' we ought to add, surely, 'pay whom ?'"
—BERNARD HULLOWOOD, *Listener*, April 30, 1964, p. 704.