particular individual reacts to and compensates for the various bodily and psychological disabilities from which he may suffer. Selye applies the same concept to organic bodily states. That is why personality studies are so important, as in the differentiation of types as described in the first place by Hoch and Amsden, and, later, notably by Bleuler, Kretschmer, and Sheldon.

Such chronological studies, in terms of life history, are infinitely more illuminating than the cross-section method of the general physician. The latter uses the presenting symptom as his starting-point, and, while skilfully tracing out its ramifications, far too often fails to pay attention to the background, personal or environmental, in which the symptom is occurring. Cabot has given many examples of the fallacy of that method. It is a fault of training, a relic of a too concentrated, mechanistic objective approach, a vain seeking for a specific cause. How seldom we find it, and how much better it is to deal with all the multiple causative factors which may be playing a part. Then we will become much more accurate in our diagnosis, prognosis, and treatment. Very modestly it is suggested that our psychiatric case-taking methods may be of considerable value to our general medical colleagues. They will help them to remember that physical symptoms are often purely a face-saving device to maintain the *amour propre* of the patient. If this is forgotten, then examinations and treatment are introduced which often obscure the clinical picture. This, as I have said already, can be obviated by good history-taking and careful clinical evaluation. If the procedure I advocate was adopted we would hear much less of the failure of orthodox medicine and of the success of the medically untrained.

Our understanding of illness would be greatly increased if the relationship between the doctor and the social worker was drawn a bit closer. The social worker is not used intelligently enough. Social work is not a matter of almsgiving, of arranging loans, of giving financial or other material assistance. But it is the social worker's ability to size up a situation, to sense the atmosphere of the case, and to establish a good liaison between patient and employer, which is one of the most potent factors in successful rehabilitation and preventive medicine. We medical people do not appreciate how much we could gain, and how much more our patients would benefit, if we worked directly with the social workers rather than through the intermediation of the ward sister.

While, therefore, I have been striving to indicate the fields in which all medically trained people may learn to work more co-operatively, yet my main theme has been to show how psychiatry can be more greatly developed in relation to general practice. It is the psychologically oriented general practitioner who can become a much more important force in dealing with the great majority of nervous and mental ailments. The College of General Practitioners, which has just been founded, may be willing to consider how such a development can be most successfully pursued.

Conclusion

To conclude, I might make the following general suggestions :

1. A wider concept of medical education, so that all universities and medical schools recognize that the understanding and treatment of nervous and mental disorders is a matter of paramount national importance and should constitute a major subject in the medical curriculum.

2. Psychiatric clinics for in-patients and out-patients should form an integral part of all large general and paediatric hospitals.

3. Far greater reciprocity and co-ordination should be effected between all groups of medical men and social workers, in the hope that psychiatry will become less of a specialty and more part and parcel of general medicine.

TREATMENT OF RENAL OEDEMA WITH DEXTRAN

BY

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The obstinate oedema characteristic of type II nephritis (nephrosis, nephrotic syndrome, or chronic parenchymatous nephritis) is often difficult to treat. Limitation of salt and fluids seldom does more than mitigate the condition, and often not even that ; the attempt to raise the level of albumin in the plasma with a diet rich in protein is equally unsatisfactory. Among the diuretics, only mersalyl is likely to be outstandingly successful. Even when circumstances appear favourable for administration of mercury—that is, absence of haematuria, normal renal-function tests, and normal blood pressure—many physicians are reluctant to use it in the presence of Bright's disease. More recently, ion exchange resins, A.C.T.H., and cortisone have been used. From the literature the response to these substances appears to be inconstant and the resins are difficult to stomach. The last resort is the removal of oedema by acupuncture or by the insertion of Southey's tubes at the ankles. With the introduction of antibiotics this procedure carries less risk of infection than formerly, but remains an unpleasant one.

Attempts to increase the colloid osmotic pressure of the plasma other than by high protein diet are not new. One of the earliest was by the intravenous injection of 6% gum acacia in normal saline, which was successfully used in the treatment of wound shock in the first world war. As a diuretic, this substance administered in 5% glucose achieved a measure of success, but became unpopular when experiments on animals showed that it remained in the tissues for years, deposited particularly in the liver, where it was said to depress the formation of plasma albumin. Later, blood and plasma were used, usually with little or no diuretic effect. With concentrated plasma, preferably with concentrated human plasma albumin, some diuresis is obtained. These latter blood products are expensive (concentrated plasma albumin is not obtainable in this country), and there is some risk of hepatitis in their use.

More recently the search for a substitute for plasma capable of restoring blood volume in patients suffering from shock has led to the use of gelatin, polyvinylpyrrolidone, and dextran. The last-named has been used as a diuretic in the treatment of renal oedema, and it is this aspect of its use with which this paper deals.

Dextran is a polysaccharide formed by the condensation of the glucose moiety of sucrose by the action of the organism *Leuconostoc mesenteroides*. Commercial dextran is prepared by the controlled hydrolysis and fractional precipitation of this crude dextran. It is thus theoretically possible to produce a dextran of any desired molecular weight, but, in practice, a fairly wide scatter in molecular size results, and it is so far practicable only to make preparations in which a large proportion of the molecules are within the chosen range of molecular size. Not only does the dextran made by

different drug firms vary in molecular distribution, but it is probable that different batches made by the same firm are not identical.

Dextran was introduced in Sweden by Grönwall and Ingelman (1944), who tested its properties in animals, and later in man (1945). They pointed out that an ideal substitute for plasma should be non-toxic, non-antigenic, and either completely excreted or completely metabolized—that is, it should not be stored in the tissues. They considered dextran to have these properties. Bohmansson, Rosenkvist, Thorsén, and Wilander (1946) confirmed the work with large-scale trials in which each batch of dextran was tried first on patients in the last stages of carcinoma. For some years dextran has been used extensively in Sweden for the treatment of shock, and Thorsén (1950) estimated the incidence of reactions to be as low as 0.1%. Bloom (1951) did not find any reactions in 51 patients suffering from shock, or in 50 others who were not suffering from shock.

On the other hand, Turner, Butler, Smith, and Scudder (1949), in America, observed reactions in 10 out of 30 patients. These reactions took the form of fever, headache, and tachycardia, with urticaria in six instances, cyanosis three times, and dyspnoea once. None of their patients was suffering from shock, but 500 ml. of 6% dextran was given in the short time of 30 minutes. More recently, in this country, Maycock (1952) noted reactions in only 1.51% of 1,647 patients who had received dextran at various medical centres, mostly to combat shock. There was one death, in a moribund patient, and the relationship to dextran was uncertain. Pyrexia, headache, urticaria, and pain in the loins and other abnormalities were noted. A severe reaction developed in one patient but none at all in 46 others who received infusions of the same batch of dextran. Accordingly, Maycock thought reactions possibly occurred as a result of sensitization to *L. mesenteroides* or antigenetically related organisms such as pneumococcus type 2 or 20. As Maycock states, it should never be forgotten that large numbers of infusions have been given in the treatment of shock without any reaction whatever.

The fate of injected dextran is still being intensively studied. Thorsén (1949), after infusion into animals of an amount equivalent to one-third of the body weight, found by examination of watery extracts no dextran in the liver, spleen, bone marrow, brain, lungs, heart muscle, or kidney, and observed no morphological changes. On the other hand, Turner and his co-workers (1949) found minimal but in their view irreversible changes in the liver, spleen, kidney, and reticulo-endothelial system. These took the form of giant-cell formation and proliferation. Goldenberg, Crane, and Popper (1947) and Hartman (1951) also noted histological changes in the kidney, the liver, and the reticulo-endothelial system, but considered them to be probably reversible. Using rabbits, to which the equivalent of 1.5 litres of 6% dextran was given daily for seven days, Bull and his colleagues (1949) detected dextran by chemical methods in spleen and lymph nodes up to 21 days later. With a serological method, dextran was found to be still present up to 56 days afterwards.

The amount of dextran excreted in the urine varies considerably with the molecular distribution of the product used. Recent experimental work has shown that up to 40%, presumably of small molecular size, is excreted in the urine—mostly in the first 24 hours and the rest in four to six days. Dextran has also been found in the faeces. Some of the remainder is metabolized, as shown by Gray, Siiteri, and Pulaski (1951), who found the D : N ratio arose when dextran was given to phloridzinized dogs. Work with dextran containing radioactive carbon indicates that some dextran is taken up by the reticulo-endothelial system. It therefore seems highly probable that this fraction also is eventually broken down and metabolized. Some tagged carbon is lost in expired air (Pulaski, 1952).

It is noteworthy that dextran has been approved by the Federal Food and Drug Administration, and that doctors of the American Forces have been authorized to use it wherever they believe it may be suitably employed in place of plasma (Government Services, 1953).

The objects of our investigation were (1) to confirm that dextran is a safe and efficient diuretic for relief of renal oedema ; (2) to attempt to determine the influence of the size of the dextran molecule upon diuresis ; and (3) to study some of the biochemical changes.

Clinical Material and Plan of Treatment

Dextran was given on 81 occasions to eight patients, all of whom showed oedema of long duration, heavy albuminuria, and marked hypo-albuminaemia. Full clinical data are given in the case histories. Throughout the period of treatment the patients were kept in bed and received a constant diet containing less than 2 g. NaCl and a fluid intake of 1,200 or 1,800 ml. in 24 hours. The protein intake in one patient was 60 g. daily, in the others either 100 or 120 g. No other treatment was given. Collections of urine were made over periods of 24 hours, and the patients were weighed daily as a further check on fluctuation in oedema. Dextran was not given until it was reasonably certain that diuresis from the effects of diet or rest in bed was not taking place.

During the period before administration of dextran, observations were made on the protein and cholesterol of the serum, on the blood urea and urea clearance, and on the haemoglobin and packed cell volume. Where possible these observations were repeated at regular intervals.

Salt-free dextran was used, much of which was presented to us by Benger Laboratories Ltd. ; 540 ml. was given by intravenous infusions over a period of not less than four hours. A shorter infusion period was found to be associated with a greater liability to severe headache, nausea, and vomiting. Five infusions were given on consecutive days to Cases 1–6, but in one instance the fifth infusion was omitted altogether because severe dyspnoea occurred after the fourth. Another patient received only 220 ml. at the fourth and fifth infusions (without any reaction), because severe headache had developed after the third. Cases 7 and 8 received single infusions of 540 ml. in order to study more closely the fate of the injected dextran.

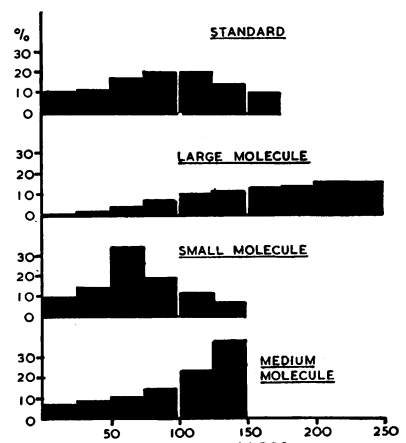

FIG. 1.—Molecular weight distributions of the preparations of dextran used.

Four categories of dextran were used ; the standard commercial salt-free preparation in 6% strength and three preparations of differing molecular distribution (Fig. 1). These

were designated for convenience large, medium, and small molecule, according to the predominant molecular size in each. All were salt-free and were of 10% strength.

Results

Diuresis.—Increase of urinary output was produced by every course of dextran. Outstandingly good results were obtained in Cases 1–3, which became at least temporarily free of oedema, losing 12.3, 13.6, and 18.2 kg. body weight respectively within 7–14 days. On recurrence of oedema, a further course of dextran was again followed by diuresis. In Case 4 a moderate diuresis was produced on five occasions although the patient was never free of pitting oedema. Results in Cases 5 and 6 were less striking, but it is fair to say that in neither was the degree of oedema at all comparable with that present in the other four (Table I). In

TABLE I.—*Effect of Dextran on Oedema*

Case No.	Preparation of Dextran	Weight Loss (kg.)	Weight before Start of Treatment (kg.)	Duration of Diuresis (Days)
1	Standard 6%	12·3	64·5	9
	" "	3·2	60·9	8
2	" "	13·6	92·3	7
	" "	6·4	83·6	6
3	Large molecule 10%	18·2	65·9	14
	Medium " "	10·9	65·9	5
4	Standard 6%	6·4	70·5	9
	Large molecule 10%	7·7	64·5	19
	Medium " "	8·2	69·1	11
	Large " "	6·4	69·5	22
	Small " "	5·9	70·9	6*
5	Large " "	2·7	59·5	13
	Medium " "	4·1	65·6	6
6	Medium " "	2·7		5

* Four infusions only.

Case 7 the administration of a course of small-molecule dextran was begun the day after an apparently spontaneous increase in the output of urine, and the data are therefore excluded from the assessment of dextran as a diuretic.

Effect of Molecular Size of Dextran on Diuresis.—Diuresis occurred with every preparation of dextran irrespective of whether the concentration was 6 or 10%, or whether large or small molecules predominated in the preparation used. With the method of administration employed and the number of observations made, it was not possible to say that one preparation produced a greater loss of oedema

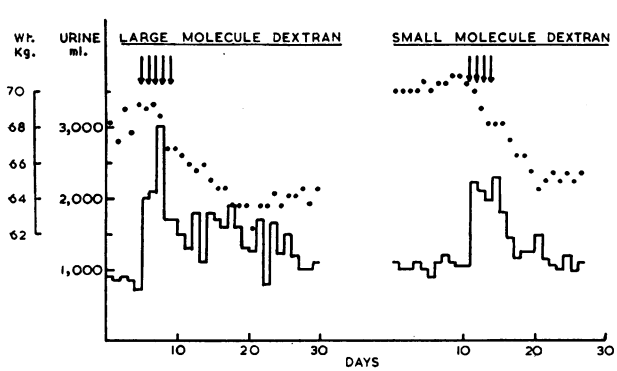

FIG. 2.—The diuretic effect of two preparations of dextran on Case 4.

than another (Table I). It is clear, however, that the diuretic effect of large-molecule dextran is of longer duration than any of the others (Table I). The duration of diuresis with large- and small-molecule dextran in the same patient is shown in Fig. 2. The biochemical findings are in harmony with these clinical observations, which suggest that the larger molecules remain longer in the blood stream.

Effect of Dextran on the Course of Nephritis.—Dextran is an effective agent for dispelling oedema, but its effect is temporary, and there is no evidence that it favourably affects the course of the disease in any other way. On the other hand, three patients (Cases 1, 3, and 6) have died of uraemia 54, 24, and 24 weeks respectively after the last infusion of dextran. In two of these patients the urea clearance was subnormal before the start of treatment. Two were suffering from amyloidosis of the kidneys, a progressive fatal lesion. Periodic observations on renal function for some months after dextran showed nothing to suggest that deterioration was due to its administration, and in our view death occurred in the natural course of the disease and was not accelerated by dextran.

Toxic Effects

Some form of side-effect was shown after most of the infusions, but seldom were there symptoms which gave rise to concern. In Case 4, on the conclusion of the fourth infusion of small-molecule dextran, shivering, marked dyspnoea, and cough developed. The patient complained of nausea and had a temperature of 100.4° F. (38° C.). On examination there were only scanty rales at the lung bases and no wheezing was heard. He was not cyanosed. The blood pressure remained unchanged. The pulse was poor in quality and the rate was 124 per minute. Within four hours these manifestations passed off. This patient had received four courses of dextran (Table I) over 11 months, but there had been an interval of four months since the last course. Accordingly, a skin test was carried out with dextran before the infusion. It was negative. A similar but less severe side-effect occurred in Case 7 during the infusion of small-molecule dextran, which was stopped after 340 ml. had been given.

After the earlier infusions, severe headache lasting for six or more hours was noted. Nausea and vomiting were less common. In one patient a subconjunctival haemorrhage developed and in another bleeding from the gums and nose occurred. Rashes were not seen. These side-effects were less frequent and less severe when the infusion was given more slowly—that is, not faster than four hours for 540 ml. It was not possible to correlate their occurrence with the molecular size of the product used; but it is worth mentioning that the sharpest fall in packed cell volume and in haemoglobin, indicating the greatest increase in blood volume (61%), was seen in association with the severe reaction in Case 4 after administration of small-molecule dextran. Blood-pressure readings before, during, and after infusion showed no change in our cases, but we have not given dextran to anyone with appreciable hypertension.

In two patients hepatic enlargement of two to three fingerbreadths below the costal margin was detected immediately after a course of dextran. This disappeared in two to three weeks, and at necropsy in Case 3 (dying of uraemia six months after administration of dextran) histological observations showed no evidence of damage and, with the method used, no evidence of dextran. We were at this time unaware of the special method required for the detection of dextran advocated by Mowry, Longley, and Millican (1952). This observation would seem to be in agreement with reports of the temporary deposition of dextran in various organs. The absence of other signs of cardiac failure make it unlikely to have been due to engorgement.

Biochemistry

Changes in Blood Volume as Reflected by Changes in Haemoglobin and Haematocrit

Since it was impracticable to make frequent estimations of the blood volume, observations on haemoglobin and haematocrit were made before and at intervals after the administration of dextran. It was thought unlikely that alterations in the total circulating haemoglobin as a result of marrow influence would occur over short periods, and consequently that changes in the haematocrit and haemoglobin level would provide an index of change in the blood volume.

TABLE II.—*Behaviour of Haematocrit and Haemoglobin Levels after Infusion of Dextran*

Preparation of Dextran	No. and Volume of Infusions	Case No.	Haematocrit %				Haemoglobin, g. per 100 ml.			
			Before Dextran	½ Hour After First Infusion	20 Hours After First Infusion	20 Hours After Last Infusion	Before Dextran	½ Hour After First Infusion	20 Hours After First Infusion	20 Hours After Last Infusion
Large molecule	5×540 ml.	3	36·0	26·0	—	27·0	12·2	8·9	—	9·1
	5×540 ,,	3	32·0	—	25·5	21·0	10·2	—	8·3	6·7
	5×540 ,,	4	28·5	22·0	25·5	—	10·8	8·4	9·6	—
	5×540 ,,	4	26·5	21·5	—	19·0	9·6	7·9	—	6·8
	5×540 ,,	5	38·0	33·5	—	29·5	12·0	11·1	10·4	9·7
	1×540 ,,	7	34·0	25·0	29·0	—	9·8	7·2	8·5	—
Medium molecule	5×540 ,,	4	37·0	28·0	29·0	25·0	11·8	10·4	11·0	9·0
	5×540 ,,	5	35·0	—	32·0	30·0	11·1	—	10·7	9·5
	5×540 ,,	6	44·5	39·0	42·0	40·0	13·9	12·2	12·6	12·8
Small molecule	4×540 ,,	4	38·0	26·0	28·5	23·5	12·8	9·0	10·2	8·0
	1×540 ,,	7	43·0	32·0	36·0	—	15·4	11·6	13·0	—
	1×340 ,,	7	41·0	33·0	38·0	—	15·0	11·8	13·4	—
	1×540 ,,	8	37·0	28·0	31·0	—	11·2	8·4	9·6	—
	1×540 ,,	8	32·5	26·5	31·0	—	9·8	7·4	9·6	—

A considerable increase in blood volume was apparent immediately after the first infusion of 540 ml. of dextran, the degree of this increase varying from 13 to 46%. By the following morning a considerable reduction had taken place (Table II). With repeated daily infusions further increases tended to occur and the maximum fall in haemoglobin and haematocrit was usually noted after the final infusion. In general, the rise in plasma dextran was proportional to the fall in haemoglobin and haematocrit. No exact correlation could be determined between them and the preparation of dextran used. However, to Case 4, courses of all four were given and the fall produced by the small-molecule preparation was much the greatest (Table II). It was calculated that the blood volume increased by 61% in this instance, the highest value in the series. The first three cases received 6% commercial dextran. Observations were not made on the haemoglobin and haematocrit; but it is clear that a sharp increase in blood volume also took place as shown by the fall in serum protein. On two occasions restoration of the haemoglobin and haematocrit to the pre-dextran levels lagged behind the rise in serum protein. This was particularly noticeable in Case 4.

Serum Protein.—The serum protein levels showed a sharp drop within half an hour after an infusion of dextran, with gradual return to normal over seven or more days.

Serum Cholesterol.—A striking fall in serum cholesterol was observed within half an hour after the injection of dextran. When considered in relation to the fall in serum protein (Table III) it would seem reasonable to accept this

TABLE III.—*Behaviour of Serum Cholesterol After Infusion of Dextran*

Case No.*	Serum Cholesterol mg./100 ml.	Serum Protein g./100 ml.	Serum Cholesterol mg./100 ml.	Serum Protein g./100 ml.	Serum Cholesterol mg./100 ml.	Serum Protein g./100 ml.
	Before Dextran		*20 hours after 5th infusion*		*Proteins near pre-infusion level*	
3	926	—	204	—	—	—
3	675	3·5	245	1·25	—	—
4	310	4·0	100	1·5	155	4·0
4	235	4·0	114	1·25	159	3·5
4*	316	5·5	92	2·2	177	4·5
5	260	4·5	108	2·0	220	4·5
5	—	5·5	122	2·5	176	5·5
			20 hours after 1st infusion			
7	640	4·25	400	2·8	450	4·0
7	412	4·5	268	3·1	176	4·5
7†	400	5·0	285	3·0	380	4·5
8	175	6·0	110	4·0	134	5·5
8	188	5·75	118	4·0	—	—

* Only 4 infusions. † Only 340 ml.

as further evidence of dilution due to increase of plasma volume. However, even a week or more after the infusion of dextran, when the serum protein had returned to pre-infusion level, the serum cholesterol was usually still well below its original value.

Plasma Dextran.—Values noted 20 hours after the infusion of 540 ml. of 10% dextran ranged from 0.7 to 1.2 g./100 ml. Too few observations were made, however, to determine whether differences could be correlated with the preparations of dextran employed. On subsequent days the values fell more rapidly in those patients who had received small-molecule dextran. When a course of five daily infusions of large-molecule dextran was administered the plasma levels after the final infusion ranged from 2.4 to 3.7 g./100 ml. Fourteen days afterwards plasma levels of 1.2 and 1.3 g./100 ml. were found in Case 3 on two occasions. Only one patient received a course of small-molecule dextran and this was stopped after four infusions of 540 ml. because of a severe reaction. The level of dextran in the plasma was then 1.7 g./100 ml.

Urinary Dextran.—Table IV shows the difference in the amount of dextran excreted in the urine when single infusions of large- and small-molecule dextran were given.

TABLE IV.—*Excretion of Large- and Small-molecule Dextran in the Urine (g. per day)*

Days after Infusion of 540 ml.	Large Molecule		Small Molecule	
	Case 7	Case 8	Case 7	Case 8
1	4·6	1·3	14·8	9·6
2	—	0·8	8·1	1·9
3	2·2	0·7	1·6	1·8
4	1·5	0·5	0·9	0·7
5	1·1	0·5	0·9	0·8
Cumulative ..		3·8	26·3	14·8

While there is no point in comparing these results with the theoretical loss in patients with intact kidneys, it is clear that excretion of dextran is much greater when a preparation containing a high proportion of small molecules is used. The fact that Case 7 excreted 26.3 g. in five days and Case 8 only 14.8 g. in the same period, although both had received small-molecule dextran, may possibly be explained by a difference in the nature of the lesion, the former being an example of type II nephritis and the latter of amyloid nephrosis. The greater excretion of small-molecule dextran was also demonstrated in Case 4, who, in the week following four daily infusions of the small-molecule preparation, excreted 112 g. (52%), whereas only 33 g. (12%) was excreted in a similar period after five pints (2.8 litres) of the large-molecule product.

Case Histories

Case 1.—A woman aged 21 developed oedema of her legs two years before admission to Stobhill Hospital on November 6, 1951. There was no history of preceding infection. On examination oedema was found to be general and the urine contained much albumin; but only scanty casts and red blood corpuscles were found. Serum protein was 4 g./100 ml., serum albumin 1.8 g./100 ml., and serum choles-

terol 552 mg./100 ml. Blood urea was normal (22 mg./100 ml.), but urea clearance was 35% of average normal. Blood pressure was 120/80 mm. Hg. Fundi were normal. The heart, lungs, and nervous system showed no abnormality. Some ascites was present. On a diet rich in protein and poor in salt there was no improvement; but after a course of dextran massive diuresis took place. Oedema gradually reaccumulated and a second course of dextran was again successful. She was discharged improved on December 21. Her urea clearance three months later was 36%. About six months after dismissal renal function began to fail sharply, and she died in her own home on November 29, 1952, of uraemia.

Case 2.—A man aged 34 developed a sore throat in October, 1950, followed a week later by swelling of his feet. When admitted to Stobhill Hospital on January 10, 1951, there was marked general oedema. Blood pressure was 160/112 mm. Hg. The fundi were normal. The urine contained much albumin and numerous hyaline and granular casts. Red blood corpuscles were present, but in numbers too few to give a positive guaiac reaction. The heart, lungs, abdomen, and central nervous system showed no abnormality. Ascites was present. Serum protein was 4.5 g./100 ml., serum albumin 1.6 g./100 ml., and serum cholesterol 384 mg./100 ml. The blood urea was 42 mg./100 ml. and the urea clearance 57%. His condition remained substantially unchanged for 14 months in spite of diet, mersalyl, urea in large doses, A.C.T.H., cortisone, ion-exchange resin, and insertion of Southey's tubes in the legs. Profuse diuresis followed each of two courses of dextran, and he was discharged from hospital much improved in February, 1952; his blood urea being then 35 mg./100 ml. and the urea clearance 72%. Renal function since then has remained good (urea clearance 70% on January 10, 1954) and the blood pressure unchanged.

Case 3.—A woman aged 43 developed oedema insidiously 11 months before admission to Stobhill Hospital on May 2, 1952. For six months ascites had been present. Six years previously she had had pre-eclamptic toxaemia and labour had to be induced at seven and a half months. Eighteen months later there was a normal delivery, and during this pregnancy the urine remained free of albumin and the blood pressure did not rise above 160/110 mm. Hg. On examination in May, 1952, she showed generalized oedema and ascites. In the urine there was much albumin; casts were numerous; but there were no erythrocytes. Serum protein was 4 g./100 ml., serum albumin 1.2 g./100 ml., serum cholesterol 860 mg./100 ml., blood urea 32 mg./100 ml., urea clearance 45%. Blood pressure was 105/85 mm. Hg. The fundi were normal. The heart, lungs, and nervous system showed no abnormality. No improvement followed a protein-rich salt-poor diet. After a course of dextran 18.2 kg. of body weight was lost in 14 days and she was discharged on May 21. On July 5 she was readmitted because of massive oedema. Her serum protein level was 3.5 g./100 ml., albumin 0.8 g./100 ml., blood urea 47 mg./100 ml., and urea clearance 47%. Diuresis again followed a course of dextran. On the day after the fifth injection the liver was noted to be three fingerbreadths below the costal margin and very firm. The serum bilirubin and prothrombin time were within the normal range: the thymol turbidity was two units and the thymol flocculation test negative. When discharged, at her own request, 14 days later the liver was then only just palpable. Renal function was unchanged. She died of uraemia on January 27, 1953. The findings at necropsy were unexpected. There was marked amyloid disease of the kidneys and a large area of necrosis in the cortex of one. No gross or histological evidence of damage due to dextran was made out in the liver, spleen, or kidneys, nor could any focus of sepsis be found except a degree of sinusitis.

Case 4.—A man aged 44 noticed oedema of the legs a month before admission to hospital in December, 1951. There was no history of preceding infection. On examination there was widespread oedema. The urine contained much albumin but only a few red blood corpuscles and casts. Blood pressure was 120/90 mm. Hg. The fundi were normal. Serum protein was 4.8 g./100 ml., serum albumin 1.5 g./100 ml., serum cholesterol 235 mg./100 ml., serum urea 45 mg./100 ml., and urea clearance 33%. The heart, lungs, abdomen, and nervous system showed no abnormality. This patient received no relief from diet. Five courses of dextran were given, each of which produced considerable diuresis, but never enough to make him free of oedema. Renal function was unchanged during the six months he was receiving the first four courses, but is gradually deteriorating: blood pressure 170/110 mm. Hg and blood urea 134 mg./100 ml. on September 15, 1953.

Case 5.—A man aged 49 had suffered from pulmonary tuberculosis for at least five years. In January, 1952, he was admitted to hospital with erysipelas, and a month later swelling of the legs was noted. When admitted to Stobhill Hospital in April there was oedema of the legs only. The urine contained much albumin and many granular casts, but no red blood corpuscles. The blood pressure was 110/60 mm. Hg. The fundi were normal. Serum protein was 5.5 g./100 ml., serum albumin 1.6 g./100 ml., serum cholesterol 350 mg./100 ml., blood urea 47 mg./100 ml., and urea clearance 54%. The heart, abdomen, and nervous system showed no abnormality. There was dullness over the left lung, with deficient respiratory murmur. No adventitious sounds were heard. The trachea was deviated to the left. A skiagram showed collapse of the left lung and a small effusion. At this time no tubercle bacilli were found in the sputum. The fingers showed marked clubbing. A diagnosis of amyloid nephrosis complicating pulmonary tuberculosis was made. With dextran a moderate diuresis which caused reduction in oedema was induced on two occasions. On September 15, 1953, the serum protein was 5.5 g./100 ml., serum urea 37 mg./100 ml., and urea clearance 71%. His condition remains stationary.

Case 6.—A man aged 50 was proved to have pulmonary tuberculosis in 1944. For three months before admission in April, 1952, swelling of the legs had been noted. On examination oedema was found to be moderate only, and confined to the legs. Albuminuria was profuse and casts and erythrocytes were scanty. The blood pressure was 140/85 mm. Hg. The fundi were normal. The heart, abdomen, and nervous system showed no abnormality. There was marked clubbing of the fingers. Over the right upper chest there was extensive dullness, with areas of bronchial respiratory murmur and rales. A skiagram showed cavitation and fibrosis. No tubercle bacilli were found in the sputum at this time. Serum protein was 6 g./100 ml., serum albumin 2 g./100 ml., serum cholesterol 335 mg./100 ml., blood urea 30 mg./100 ml., and urea clearance 90%. A diagnosis of amyloid nephrosis complicating pulmonary tuberculosis was made. Dextran produced slight diuresis. Five months after his discharge from hospital on May 16, 1952, renal function rather suddenly deteriorated and death occurred from uraemia. The clinical diagnosis was confirmed at necropsy.

Case 7.—A boy aged 14 developed generalized oedema in January, 1953, without preceding infection other than boils on the face. When seen on February 20, 1953, he had moderate oedema of the legs and sacrum. The fundi were normal; blood pressure was 130/75 mm. Hg. The heart, lungs, and nervous system showed no abnormality. In the urine there was much albumin; a few granular casts and erythrocytes were found. Serum protein was 3.5 g./100 ml., serum albumin 2 g./100 ml., serum cholesterol 462 mg./100 ml., blood urea 34 mg./100 ml., and urea clearance 56%. When he was last seen his condition was unchanged.

Case 8.—A man aged 62 was admitted to hospital on April 14, 1953, complaining of swelling of the legs and abdomen for two weeks. For many years previously he had had a productive cough which had become worse in the past year and was associated with loss of weight. On examination he was emaciated, but showed gross generalized oedema and also ascites. There was very marked clubbing of the fingers.

In the sputum tubercle bacilli were numerous. The upper zone of the right lung was dull and the breathing bronchial. Rales were numerous and a skiagram confirmed the presence of cavitation. The heart and nervous system showed no abnormality. Blood pressure was 140/80 mm. Hg; the fundi were normal. After withdrawal of 2,700 ml. of fluid from the peritoneal cavity, the liver and spleen were not felt. In the urine there was a large amount of albumin but no casts and no erythrocytes. Serum protein was 5.5 g./100 ml., albumin 1.2 g./100 ml., serum cholesterol 168 mg./100 ml., serum urea 37 mg./100 ml., and urea clearance 37%. A diagnosis of pulmonary tuberculosis complicated by amyloidosis was made. There has been little change in his condition.

Discussion

An earlier publication by Wallenius (1950) indicated that dextran was a diuretic for nephrotic oedema. While Olive, Mills, and Lundy (1953) achieved good results in 7 out of 12 children, Bedford and Broughton (1951) had no success in three attempts on one patient. Both Wallenius (1950) and Olive and co-workers (1953) suggested that single injections are of little or no value.

When we gave five infusions of 540 ml. of 10% dextran on consecutive days, three out of six patients were rendered free of oedema and three were improved. In one instance dextran was successful after a wide variety of measures, including ion-exchange resin, A.C.T.H., cortisone, and even Southey's tubes, had made little impression. The good result was temporary in every instance, but a further course of dextran was again satisfactory on all of 11 occasions. We have found dextran to be consistently effective, and consider it to be a powerful diuretic which is valuable when other measures fail. It is perhaps particularly useful when it is decided not to use mersalyl.

Concerning the mechanism of this diuresis we have little to say. In the treatment of shock the object of administering dextran is to restore the blood volume by infusion of a substance which will remain in the vascular system for a long period. In patients suffering from type II nephritis with hypoproteinaemic oedema, the increase of osmotic pressure of the plasma due to the circulating dextran draws oedema fluid from the tissues into the blood stream. Similar changes followed the intravenous injection of acacia, a plasma volume expander of the first world war, which had a short vogue as a diuretic in nephrotic oedema (Lepore, 1937). Peters (1935) linked increase in blood volume after acacia with the production of diuresis, and, while the mechanism of this is still not understood, more recently MacArthur (1946) found that increase of blood volume was associated with the onset of spontaneous diuresis in nephrotic children. Marked haemodilution without diuresis was observed in the case reported by Bedford and Broughton (1951), who attributed this to the poor state of renal function. None of our cases is comparable with their case in that respect.

When the dextran is excreted or leaves the blood stream the blood volume returns to normal, as shown by the return of the haematocrit, haemoglobin, and total plasma protein to pre-infusion levels. The diuretic effect is therefore of limited duration.

Boyd, Fletcher, and Ratcliffe (1953) showed that dextran containing a high percentage of small molecules left the blood stream more rapidly than a product with a high percentage of larger molecules. The loss occurred into the urine and also, it was stated, into the interstitial fluids. There is not yet general agreement concerning the optimum molecular size to promote diuresis. Wallenius postulated that a preparation of small molecules might prove to be more effective, as they are osmotically more active, and, since they pass freely into the urine, they might also promote diuresis by hindering tubular reabsorption of water. Yet he held that they might pass more freely into the tissue spaces and there exert osmotic pressure against the plasma protein and circulating dextran. This we have not confirmed, in so far as no dextran was detected on examination of oedema fluid. Bedford and Broughton (1951) also failed to find dextran in oedema fluid, and made the point that it may be present in too great dilution to be detected.

A preparation of larger and consequently less osmotically active molecules would, on the other hand, remain longer in the blood stream and so might produce a greater total diuresis. With the preparations used we were, however, unable to detect any material difference in the amount of oedema lost even when the three preparations were given to the same patient with a comparable degree of oedema as judged by body weight.

The findings of this paper cannot easily be compared with those of Wallenius (1950) or of Olive and his co-workers (1953), since both used dextran prepared by Pharmacia, of Sweden, differing in molecular distribution from the dextrans used by us. There is no support from our results for the suggestion made by Wallenius that diuresis might be due to diminished reabsorption of water from the tubules in the presence of a large number of small molecules of dextran, since the diuretic effect was just as good with large-molecule dextran as with the small-molecule preparation.

Hazards of Dextran

The hazards may be considered under two heads. In the first place, those that develop during the period of infusion or very shortly afterwards. Reactions of this type, usually of mild degree, were seen in most of our patients. They included headache and nausea; vomiting and dyspnoea were less common. These, along with rashes and backache, have usually been attributed to sensitivity or to the large molecules of dextran. We are inclined to think, however, that most if not all of these side-effects occurring in patients with oedema are due to overloading of the circulation. We have also seen subconjunctival haemorrhage and bleeding from the gums and nose. Headache, at least, is certainly minimized if the dextran is given slowly. Severe reactions, causing concern, occurred twice, on both occasions when small-molecule dextran was given. The high incidence of reactions in our patients may be explained on the basis that a normal blood volume is suddenly much increased by the attraction of oedema fluid into the blood stream when the plasma osmotic pressure is raised by dextran. Consequently very slow administration is clearly advisable to minimize reactions, and the use of small-molecule dextran is best avoided.

The second potential hazard of dextran administration is the possibility of its retention in the tissues. For a time at least it appears to lodge in the reticulo-endothelial system, particularly of the liver and spleen, and we have twice observed that the haematocrit and haemoglobin values have not returned to the pre-infusion level along with the serum protein. In one patient there was a drop in haemoglobin of over 2 g./100 ml. which was not made good until two months after the dextran was stopped. We can only tentatively interpet this as an indication that marrow function may be temporarily impaired by dextran in some individuals. The evidence gradually accumulating is strongly in favour of the view that all dextran injected is eventually excreted or metabolized. In our work there was no evidence that renal function was adversely affected by its use.

Appendix: Analytical Methods

Haemoglobin, haematocrit, and plasma dextran levels were determined on heparinized blood.

Haemoglobin was estimated as oxyhaemoglobin by photoelectric colorimetry.

Plasma dextran was estimated in the first cases by the method of Hint and Thorsén (1947), but later samples were estimated by a method using anthrone and based on the work of Morris (1948). This method, which was found to give comparable results, was preferred because of its greater rapidity and simplicity. Urinary dextran was also estimated by this procedure.

Serum total protein was estimated by the biuret method. It has been widely reported that the biuret reaction gives falsely high results in the presence of dextran, since dextran combines

with copper in alkaline solution (Jacobsson and Hansen, 1953), but these same authors have pointed out that this occurs only when a method such as that of Lehmann (1944) is used in which there is no initial precipitation of the proteins.

As they have shown, and we have confirmed, the disturbing influence of dextran is, for practical purposes, eliminated by precipitating the protein with trichloracetic acid.

Serum cholesterol was estimated by the modification (King, 1951) of the method of Sackett (1925).

Summary

The diuretic action of dextran in renal oedema has been investigated and confirmed.

Attention is drawn to the large increases in blood volume produced in these patients by intravenous infusions of dextran.

Headache and nausea, usually of slight degree, occurred in most of our patients, and it is postulated that these symptoms were due to overloading of the circulation. Vomiting and dyspnoea were less frequent.

In an attempt to find the optimal molecular size of dextran to promote diuresis four preparations with differing molecular distribution were used. There was little difference in the amount of diuresis produced, but the most severe side-effects, accompanied by the greatest increases in blood volume, occurred after infusion of the preparation containing the greatest proportion of small molecules. The most prolonged diuresis was effected by the large-molecule dextran.

Attention is drawn to the fact that the presence of dextran does not interfere with the estimation of plasma proteins by the biuret reaction provided the proteins are first precipitated by trichloracetic acid.

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THROMBOCYTOPENIC PURPURA AFTER ADMINISTRATION OF GOLD

COMPARISON OF TREATMENT WITH DIMERCAPROL, A.C.T.H., AND CORTISONE

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Various authors, reporting on the incidence of toxic reactions to gold salts, record percentages varying from 20 to 77. Severe reactions occur in approximately 6%. Amongst the most serious are thrombocytopenic purpura, agranulocytosis, and aplastic anaemia. Hartfall *et al.* (1937), in a series of 750 cases of rheumatoid arthritis given gold, noted toxic reactions of greater or lesser severity in 40% of patients, which included nine cases of thrombocytopenic purpura. Three of these patients died. Wintrobe *et al.* (1939), in a review of the literature, reported seven cases of purpura, four of which were fatal. Cecil *et al.* (1942) recorded three cases of purpura, one fatal, in a series of 245 cases given gold. Price and Leichtentritt (1943), in a series of 101 patients, noted three with purpura, one of whom died. Short *et al.* (1946) reported one fatal case of purpura in a series of 47 patients. Nyström (1950) encountered one fatal case of purpura among 572 patients given gold. Mettier *et al.* (1948), on the other hand, recorded four cases of purpura among 160 patients, none of which were fatal. Various other workers have reported isolated cases, but the incidence of this complication of gold therapy has declined in recent years, presumably owing to a better appreciation of the dangers of gold administration.

The introduction of 2,3-dimercaptopropanol (dimercaprol, " B.A.L.") by Peters *et al.* (1947) as a therapeutic agent in the treatment of poisoning by arsenic and other heavy metals quickly led to its use in the treatment of toxic reactions due to gold. Many of the less serious reactions, such as dermatitis, rapidly improved following the use of dimercaprol (Ragan and Boots, 1947; Cohen *et al.*, 1947; Macleod, 1948; Montgomery, 1950; Edström, 1950; Kirsch, 1951). Good results have been recorded in cases of thrombocytopenic purpura, but only a few have been reported in detail. Lockie *et al.* (1947) describe a case of thrombocytopenic purpura due to gold which had shown no response to various methods of treatment over a period of three months and ultimately developed a subarachnoid haemorrhage. Dimercaprol was administered in doses of 180 mg. four-hourly for two days, then twice daily for ten days (total 5.7 g.), and the patient made a good recovery. The platelet level rose from 36,000 to 120,000 in three weeks, and was at approximately the same level three months later. Kroese (1949) described two cases of purpura following gold administration. In one case the response to dimercaprol was excellent. The drug was given immediately the symptoms appeared. The