TREATMENT OF THE NEPHROTIC SYNDROME WITH SERUM TRANSFUSIONS*

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It has been shown that in patients presenting the nephrotic syndrome the degree of oedema depends upon several factors; there is general agreement, however, that hypoproteinaemia is the most important of these. Epstein (1917) first suggested that patients suffering from nephrosis should be given a liberal protein ration, and he claimed successful results from this method of treatment. Nevertheless, Fishberg (1939) has the impression that "apart from cases in which severe protein restriction is practised, the plasma protein level in the nephrotic syndrome is primarily determined by the permeability of the kidneys to protein and is difficult to influence by diet"; and Bing (1936) found that a high protein diet had no appreciable effect on the concentration of serum proteins in Bright's disease.

The theory upon which Epstein based his treatment is very simple—viz., that the hypoproteinaemia is due to loss of protein in the urine and that the protein intake is not sufficient to compensate for this loss. This theory does not provide an adequate explanation for more than some of the manifestations of hypoproteinaemia, as has been emphasized by Casten and Bodenheimer (1941). These authors consider that there is undoubtedly a specific mechanism which controls the formation of serum proteins, and that when this mechanism is impaired it is futile to administer large amounts of protein which cannot be utilized to regenerate serum proteins. In such cases, however, the intravenous injection of human plasma or serum might be expected to have at least a temporary effect on the plasma protein concentration and thus be of real benefit to the patient. Nevertheless, there is the further consideration that a dynamic equilibrium seems to exist between the serum proteins and tissue proteins (Madden and Whipple, 1940), so that we have no guarantee that protein introduced into the blood stream will stay there.

Recently, methods of storage and preparation of human serum have been much developed, and transfusion of this fluid in large amounts has become more practicable. In particular, the introduction of methods of drying human serum has made it possible to prepare easily a concentrated fluid which should be particularly suitable for transfusion in cases of hypoproteinaemia.

Reports so far available upon the results of serum transfusion in cases exhibiting the nephrotic syndrome yield conflicting evidence of the value of this form of treatment. Thus, whilst Aldrich *et al.* (1938) reported complete clearing of oedema in 6 out of 9 cases of nephrosis treated with transfusions of concentrated serum, Weech, Goettsch, and Lytle (1940) found that in a series of 7 similar cases only one responded favourably. Of 2 nephrotic patients treated by Levinson, Rubovits, and Necheles (1940) with serum, only one responded.

The Present Investigation

In view of these very divergent findings, it was proposed to try the effect of transfusion of concentrated serum in the treatment of the nephrotic syndrome and to carry out certain laboratory investigations. War conditions unfortunately made it difficult to adhere to the original programme: many of the patients were lost sight of during the period of treatment, and laboratory facilities were interfered with. The cases, therefore, do not provide conclusive data with regard to the fate of the injected protein, although they do supply some suggestive evidence of the difficulty of raising the plasma protein level by serum transfusions. From the clinical aspect, however, the results support the view that serum transfusions are likely to prove of little value in the treatment of the nephrotic syndrome, at least when the amount of protein transfused is from 20 to 100 g.

Of the 12 patients treated, 8 were considered to be cases of Bright's disease in the nephrotic stage. In the ninth case a diagnosis of lipoid nephrosis was made, and in the tenth of amyloid nephrosis. The eleventh and twelfth cases are examples of malabsorption of protein from the alimentary tract.

Methods

In all but one instance serum was used for transfusion. This serum was reconstituted from the dried product (obtained from the Medical Research Council's Serum Drying Unit). In 25 out of 28 cases the serum was injected in approximately fourfold concentration; actual estimations of the protein content of the fluid injected showed that in fact the concentration was sometimes a little lower—i.e., 18 to 23 g.%. In the descriptions below this fluid is referred to as "concentrated serum." In two other instances normal concentration was used, and in one instance citrate-saline plasma.

The concentrated serum was administered either by syringe (in the case of the smaller quantities) or from an ordinary transfusion bottle. When the latter method was used the rate of flow was found to be slow owing to the high viscosity of the solution, and occasionally the rate was increased by raising the pressure of air inside the transfusion bottle by means of a Higginson syringe.

The rate of administration was variable. In the case of the smaller amounts (50 to 200 c.cm.) of concentrated serum the time of transfusion was 10 to 30 minutes. In the case of the larger amounts (300 to 500 c.cm.) the transfusions were given over a longer period of time—i.e., up to 8 hours were taken over the administration.

Some febrile reactions were noted, and 2 patients developed pain in the back. The development of this symptom during transfusion will not be discussed further in this paper, since its occurrence, together with that of other reactions, following transfusions of concentrated serum, has already been discussed (Brown and Mollison, 1940). However, lest any correlation might be thought to exist between the occurrence of a rigor and subsequent diuresis, cases in which such reactions followed transfusion are shown in Table I.

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TABLE I.—Results of Transfusions

Case	Sex	Age	Diagnosis	Transfusion (c.cm.)	Re-action	Clinical Result
1	F	37	Nephrotic nephritis	{ (1) 100 4N (2) 200 4N (3) 200 4N	+ — —	No diuresis; increase in oedema
2	M	19	"	{ (1) 350 4N (2) 500 4N	+ +	No effect Good diuresis
3	M	25	"	{ (1) 250 4N (2) 500 4N (3) 250 4N (4) 1,500 cit.-sal. plasma	— — — +	Further diuresis; disappearance of oedema Increase in weight No good effect
4	M	45	"	{ (1) 100 4N (2) 200 4N (3) 200 4N	— — —	No effect Diuresis began 4 days later Good further diuresis; disappearance of oedema
5	M	57	"	{ (1) 1,200 N (2) 1,200 N	— —	No reduction in oedema
6	M	46	"	{ (1) 250 4N (2) 300 4N	+ —	Slight increase in urinary output; remission already in progress
7	M	57	"	{ (1) 500 4N (2) 45 4N (3) 75 4N (4) 75 4N	— + — —	No reduction in oedema " " " " " " " " " " " "
8	M	10	"	{ (1) 40 4N (2) 70 4N (3) 70 4N (4) 50 4N (5) 300 4N	— — — — —	No diuresis Some loss of weight Some increase in weight No effect Slight reduction in oedema
9	F	4	Lipoid nephrosis	{ (1) 40 4N (2) 70 4N (3) 70 4N (4) 50 4N (5) 300 4N	— — — — —	No diuresis Some loss of weight Some increase in weight No effect Slight reduction in oedema
10	F	21	Amyloid nephrosis	{ (1) 150 4N (2) 300 4N	— —	No definite clinical effect; slight gain in weight
11	M	15	Hypoproteinaemia due to mal-absorption	{ (1) 150 4N (2) 300 4N	— —	No definite clinical effect
12	F	33	"	{ (1) 200 4N	—	No definite clinical effect

In 6 of the cases changes in weight during the period of transfusion treatment were carefully recorded. Serial estimations of serum proteins were made in the majority of cases and some observations upon alterations in haemoglobin and in haematocrit readings. Haemoglobin was estimated by Haldane's method, using venous samples in most instances; haematocrit estimations were made by Wintrobe's method, the tubes being centrifuged at 3,000 r.p.m. until no further packing occurred. The serum proteins were usually estimated by the Kjeldahl method; in two instances, however, a colorimetric method was employed. These estimations were carried out by several different workers, and we therefore do not feel justified in emphasizing any small changes that were noted. Quantitative estimations of the amount of albumin in the urine were made in some cases by the Kjeldahl method, but mainly the simple Esbach technique was employed. Again only large differences can be considered significant.

Results

Of the 11 oedematous patients only Cases 3 and 4 were completely relieved of their oedema following serum transfusion. In Case 3, however, the oedema had returned within 10 days, and this oedema was unaffected by a further transfusion of concentrated serum. In Cases 6 and 10 there was a slight reduction in oedema. In 5 cases there was no good effect, and in Cases 1 and 8 oedema increased after transfusion. In the case histories given below results in individual cases are described in detail.

Cases with Nephrotic Nephritis

Cases 1 to 8 were all considered to be in the nephrotic stage of diffuse glomerulonephritis. Features common to all were oedema, albuminuria, raised blood pressure, and the finding of red blood corpuscles in increased numbers in the urine at one time or another. Most of the patients were receiving a diet consisting of increased protein, little or no salt, and restricted fluids. In the following case histories the changes following the transfusion of concentrated serum are recorded. Estimations of serum protein before and after transfusion in these cases and in Cases 10 to 12 are listed in Table II.

Case 1.—Female aged 37. First symptoms 4 months previously, during pregnancy; delivered 2 months later. Urea-clearance test showed considerable impairment of renal function. Blood urea 117 mg. per 100 c.cm. Three transfusions of concentrated serum—the equivalent of a total of 130 g. of protein—were given over a period of 8 days, but the serum proteins rose only from 5.0 to 5.8 g.% during this time; no

diuresis occurred, and the patient actually became more oedematous. From rough measurements of the amount of protein passed during this period it seemed very unlikely that more than a small part of the injected protein was lost in the urine. Oedema continued to increase after the last transfusion; the patient died 3 days later.

Case 2.—Male aged 19. Onset of oedema 7 weeks previously after an attack of scarlet fever. A transfusion of concentrated serum produced neither an increase in urinary output nor an increase in serum protein concentration. The patient eventually improved spontaneously and left hospital 5 months later, free from oedema and with apparently normal renal function. Later, however, the oedema recurred and he was readmitted to hospital.

Case 3.—Male aged 25. Onset of oedema 2 months previously. The oedema was increasing in spite of the usual treatment when the first transfusion of concentrated serum was given. The latter produced a very considerable diuresis: within an hour of the end of the transfusion the patient had started to pass large quantities of urine. During the next 5 days over 14 lb. in weight was lost and there was obvious clinical improvement. A second transfusion was given 6 days after the first, with an even better result. A total of 8,820 c.cm. of urine was passed during the following 24 hours (intake 960 c.cm.). Four days after this second transfusion the patient's weight was found to be 42 lb. less than it had been before the first transfusion. As will be seen from Table II the serum protein concentration rose considerably immediately after these transfusions, but 24 hours later was only slightly raised and throughout was below normal. Within a week of the second transfusion the patient's weight started to increase again, and in the course of the next 2 weeks 14 lb. was regained. A third transfusion was then given. Although the serum protein concentration rose following this transfusion, no diuresis occurred and the patient continued to gain weight. After a further 2 weeks a fourth transfusion was given. The previous transfusions had all been of concentrated serum, but on this occasion citrate-saline plasma was used (protein concentration 3 g.% approximately). The response to this transfusion was most unfavourable and no diuresis occurred. The plasma protein concentration decreased significantly and the amount of albuminuria increased. The patient later became well enough to leave hospital, but was readmitted shortly afterwards and died in uraemia.

Case 4.—Male aged 45. Oedema for 3 weeks, unaffected by the usual treatment. Blood urea 50 mg. per 100 c.cm. Three transfusions of concentrated serum were given in a period of 2 weeks. The first transfusion was without effect, but the second and third transfusions resulted in a considerable increase in urinary output without any increase in the daily albumin excretion. The diuresis was followed by complete disappearance of the oedema. The serum protein concentration was scarcely affected by the first 2 transfusions; unfortunately no estimation was made immediately after the third transfusion. Ten days later, however, a considerable increase was found.

Case 5.—Male aged 57. Intermittent generalized oedema for 9 months. Three months after the onset of the oedema the patient had been treated in another hospital with 2 plasma transfusions (of 3 and 6 pints respectively), and the oedema had

TABLE II.—Serum Proteins (G.%) Before and After Transfusions

Case	Time since Previous Transfusion (Days)	Before		Immediately After		24-48 Hours After	
		Total	A/G	Total	A/G	Total	A/G
1	(1) —	5.0				5.0	
	(2) 7	4.6	2.8/1.8	5.4	2.6/2.8	4.8	2.8/2.0
	(3) 1	4.8	2.8/2.0	6.4	3.2/3.2	5.8	2.6/3.2
2	(1) —	4.3	1.8/2.5			4.3	2.0/2.3
	(2) 6	3.6	1.1/2.5	5.1	2.2/2.9	4.0	1.9/2.9
	(3) 21	4.0	2.0/1.9	5.6	3.4/2.2	4.9	2.6/2.3
3	(1) 14	3.8				4.7	
	(2) 6	4.0	2.2/1.8			2.5	
	(3) 8	3.8				3.9	2.1/1.8
4	(1) —	4.0				4.0	2.2/1.8
	(2) 6	3.8				5.4*	
	(3) 8	5.4	2.9/2.5	5.6	3.5/2.1	4.6†	2.9/1.7
5	(1) 2	5.2		5.2	4.0/1.2	5.9‡	4.3/1.6
	(2) 2	4.4		4.6			
	(3) 3	4.7				4.7	
6	(1) —	5.1				4.6	
	(2) 3	4.7				4.3	2.8/1.5
	(3) 9	4.6	3.1/1.6			4.9	2.5/2.3
7	(1) —	4.4	2.2/2.2			5.1	2.2/2.9
	(2) 13	3.2		3.8		4.3‡	
	(3) 4	4.2		4.0		3.6‡	
8	(1) —	3.0	1.2/1.8	2.9	1.6/1.3	2.8	1.7/1.1
	(2) 4						
	(3) —						

* 8 days after

† 8 hours after.

‡ 3-4 days after.

lessened temporarily. After a further 5 weeks, injections of salyrgan had resulted in a similar temporary improvement. Two transfusions of normal concentration serum were given. Both were followed by a temporary increase in urinary output and also by an increase in albuminuria. The degree of oedema was not affected.

Case 6.—Male aged 46. Progressively increasing oedema for the last 7 weeks. Oedema fluid found to contain 0.05% protein. An injection of mersalyl combined with the usual treatment failed to produce a diuresis. Two transfusions of concentrated serum were given at an interval of 3 days. These produced an insignificant increase in serum protein concentration but some increase in urinary output (average before, 650 c.cm./24 hours; average after, 1,250 c.cm./24 hours). Four days after the second transfusion a course of mersalyl injections was begun. Over a period of 5 weeks injections were given approximately every second day. The urinary output steadily increased and the patient lost 56 lb. in weight; he was discharged shortly afterwards, quite free from oedema. Since the daily urinary output had already started to increase before the first injection of mersalyl it is difficult to decide what part, if any, was played by the mersalyl injections and the serum transfusions or whether the remission was completely spontaneous.

Case 7.—Male aged 57. Oedema for 4 months. One transfusion of concentrated serum was given; this was followed by a brief diuresis. 2,800 c.cm. of urine was passed in 24 hours, compared with a previous average daily output of 650 c.cm. No reduction in oedema was observed, however, and, as will be noted, the serum protein concentration decreased slightly.

Case 8.—Male aged 10. Oedema for 2 months. Shortly after the onset of oedema 2 transfusions of 4-times-concentrated serum (25 c.cm. each) were given at another hospital without any good effect. Then, however, an axillary abscess developed, and when this had been incised the oedema cleared rapidly. A few weeks later the oedema recurred and the patient was readmitted to hospital. Two injections of novurit were given, and the oedema was much reduced. At this point 3 transfusions of concentrated serum were given in a period of 7 days. No significant increase in urinary output occurred; on the other hand, the oedema increased and the weight rose by 5½ lb.

Cases of Various Causation

The following cases are examples of hypoproteinaemia of different varieties.

Case 9.—Female aged 4. Diagnosis: lipoid nephrosis. Generalized oedema for 6 weeks. No dietetic deficiency. B.P. 120/90; serum proteins 4.3 g.% (albumin 1.6, globulin 2.7); blood urea 26 mg. per 100 c.cm. Urinary output 170 to 200 c.cm./24 hours; fluid intake 600 to 700 c.cm./24 hours; urinary albumin 3.5 g.%; no excess of red cells in urine. Despite the restriction of fluids and the administration of a salt-free high-protein diet, together with thyroid extract, 1/2 grain twice daily, the oedema was increasing. Three transfusions of concentrated serum were given in a period of 12 days. No diuresis followed the first transfusion; after the second transfusion 1,890 c.cm. was passed in 24 hours, but after the third only 270 c.cm. After this last transfusion oedema and weight increased. Five days later the administration of salyrgan was followed by a diuresis of the same order as that occurring after the second transfusion. The child had then to be evacuated from the hospital to a safer area and could not be followed up.

Case 10.—Female aged 21. Diagnosis: amyloid nephrosis. The patient was first discovered to have pulmonary tuberculosis 6 years previously. For the past year the ankles had been swollen, and during the last 2 weeks the arms, legs, and abdomen also. Examination showed that there was no evidence of recent active extension of the pulmonary tuberculosis. B.P. 110/70; serum proteins 4.9 g.%; blood urea 19 mg. per 100 c.cm. Urinary albumin 1%; only an occasional red cell. An intravenous Congo-red test showed that 50% of the dye disappeared an hour after injection; this is said to justify a diagnosis of amyloidosis. No improvement resulted from the withdrawal of salt from the diet. A preliminary small transfusion of concentrated serum was also without effect. A larger transfusion was therefore given; this was followed by a definite increase in urinary output. The patient became very thirsty during this transfusion and was allowed extra fluid. For this reason probably only a very slight reduction in oedema was observed. A third transfusion was given 2 weeks later, and the urinary output increased slightly in the subsequent few days. During the period of these last two transfusions the weight decreased by 10 lb. and there was a definite diminution in the degree of oedema of the arms and also of the ascites. Within a week of the second transfusion, however, half the lost weight had been regained. During the 24 hours following the second

transfusion only 3.7 g. of albumin was passed in the urine. Although this figure was based upon an Esbach determination it is probably fair to assume that not more than, say, 8 g. was lost in this way. As some 60 g. of serum was transfused it is difficult to see why such a small increase in serum protein concentration occurred without postulating a loss of protein from the blood stream by some route other than the kidney.

Case 11.—Male aged 15. Diagnosis: hypoproteinaemia due to malabsorption from the intestine. Two months' history of diarrhoea and loss of weight. Slight oedema of the ankles had been present for a short period 2 months earlier, but had subsided completely. Serum proteins 3.2 g.% on admission. Two transfusions of concentrated serum were given. As will be seen from Table II, the serum protein concentration rose after the first transfusion. After the second transfusion, however, the level fell again. After both these transfusions the haemoglobin fell temporarily, but reached its previous level 3 to 4 days later. The serum protein changes therefore probably reflect fairly accurately the changes in total serum protein content of the serum. During the period of the transfusions the patient gained 7 lb. Although the urine was tested many times before the transfusions and was always found to be free from albumin, it was unfortunately not tested during the period of the transfusions. Later it was again examined many times, and was always free from albumin. Since there was no evidence of renal damage, we have no reason to suppose that protein was in fact excreted in the urine after the transfusions. As there was no rise in serum protein concentration following the second transfusion it seems practically certain that the transfused protein was either stored or metabolized.

Case 12.—Female aged 33. Diagnosis: oedema due indirectly to malabsorption of protein. Ulcerative colitis for past 2½ years; generalized oedema recently. Serum protein 3.0 g.% (albumin 1.2, globulin 1.8). Blood urea 20 mg. per 100 c.cm. Oedema fluid, 0.16% protein. Urine: trace of albumin; few granular casts and red cells. One transfusion of concentrated serum was given. Although there appeared to be a slight reduction in oedema following the transfusion, there was no diuresis. The reduction in oedema may have been due to dehydration, as the patient was vomiting copiously at the time. The serum protein concentration was lower after transfusion than before, and the haematocrit reading and the haemoglobin were also slightly lower. Quantitative estimations of the amount of proteinuria during this period were made by the Kjeldahl method, and it was found that only a few milligrammes of protein were lost in the urine. Since the protein content of the transfused serum was found to be 18 g.% it seems clear that practically 36 g. of protein must have left the blood stream by some route other than the kidney.

Discussion

The clinical results are clearly in agreement with the experience of Weech *et al.* rather than that of Aldrich *et al.* (see above). In all but one of the cases described by the latter workers a diagnosis of "pure" nephrosis was made, whereas most of the cases here described had clear evidence of glomerulonephritis. It should be noted, however, that the cases recorded by Weech and his co-workers were considered to be examples of "pure" nephrosis, and in these, as has been mentioned, the results were also very disappointing.

Some of the doses given by us were considerably greater than any employed by the authors referred to, even when allowance is made for the fact that their patients were mostly children and ours were adults.

From the laboratory point of view the findings are incomplete and therefore permit only certain tentative conclusions. Changes in serum protein concentrations have been mentioned in the case histories above, and the results are set out in Table II. Immediately after a transfusion of concentrated serum there is usually an increase in the serum protein concentration of the recipient. Since in 13 out of 14 cases in which estimations were made the haemoglobin or the haematocrit reading was found to fall after the transfusion and this in all probability indicates an increase in blood volume, it may be assumed that there is a considerable absolute increase in the total circulating protein immediately after transfusion.

In 17 instances the serum proteins were re-estimated 24 to 48 hours after the transfusion of concentrated serum. In only 8 of these was the concentration found to be significantly greater than before the transfusion. In 6 of these 8 the albumin and globulin fractions were also estimated, and it was found that in only 2 of them was the albumin concentration significantly

greater than before the transfusion. It is interesting to note that these 2 instances were of transfusions resulting in satisfactory diuresis. In the other transfusion resulting in good diuresis (third transfusion, Case 4) serum protein estimations are unfortunately not available.

The rapid fall in serum protein concentration after an initial rise indicates that the injected protein does not remain long in the circulation. It might be thought that this fall is due to dilution of the serum proteins by the drawing in of water from the tissues. Haemoglobin or haematocrit estimations at intervals after transfusion show, however, that the lowest figures are found immediately after transfusion and that there is then a gradual return to the pre-transfusion level, which is usually reached at 24 to 48 hours. The evidence suggests, therefore, that no further increase in plasma volume occurs after the end of transfusion, and that any subsequent fall in serum protein concentration must be due to loss of protein from the blood stream.

In cases in which haemoglobin or haematocrit readings were determined both immediately before and after transfusion, the approximate increase in blood volume can be calculated. Changes in haematocrit readings are probably less reliable than changes in haemoglobin, because alterations in the osmotic pressure of the plasma may cause swelling or shrinking of the recipient's erythrocytes, and thus produce alterations in the red cell volume which make it difficult to interpret the significance of haematocrit changes. If a figure for the initial blood volume is assumed, the approximate increase in the blood volume represented by the fall in haemoglobin can be calculated. In cases in which calculations could be made, it was found that the increase in blood volume was greater than the amount of concentrated serum injected, and this suggests that fluid is drawn into the circulation during transfusion.

[Since writing this article, we observe that Beattie (1942) has recently drawn attention to the fact that after a plasma transfusion some of the transfused plasma may leave the circulation within an hour, and, furthermore, that only about 80% of the volume transfused is available to "dilute" the circulating blood. For both these reasons the observed decrease in haemoglobin concentration may be less than the "expected" figure. Since in the present cases the observed fall in haemoglobin was often much greater than that expected from the volume of concentrated serum transfused, there is further reason to think that fluid is drawn into the circulation during these transfusions.]

Although the available figures are not conclusive, the impression is that the amount of protein lost in the urine is not sufficient to account for the lack of increase in serum protein concentration in many of the cases, and it therefore seems likely that part of the protein is taken up from the blood stream, possibly to fill depleted tissue reserves. Cases 11 and 12 provide the best evidence for this supposition.

Harper, Osterberg, Priestley, and Seldon (1941) also concluded that protein was lost from the circulation following serum transfusions, and in almost all their cases loss in the urine could be excluded. Weech, Goettsch, and Lyttle (1940) have put forward the theory that diuresis, when it occurs, is due to the mechanical effect of a raised blood volume. Our observations, so far as they go, do not support this view, since a considerable fall in haemoglobin or in the haematocrit reading was often found in cases in which no diuresis occurred.

It may be well to point out that concentrated serum is concentrated with regard to salts as well as to protein, and that therefore a considerable amount of salts is administered when a transfusion of concentrated serum is given. This may be an important factor in the prevention of diuresis. If it were possible to obtain by sterile dialysis a protein solution free of salts the resulting fluid might prove of greater value.

Summary

Twelve patients exhibiting hypoproteinaemia have been treated with transfusions; in almost all cases concentrated human serum was used. Dosage ranged from 10 to 15 g. of protein in children and from 20 to 100 g. in adults, and more than one transfusion of these amounts was given in most cases.

Immediately after transfusion the serum protein level was generally found to have risen and the haemoglobin to have fallen; 24 to 48 hours after transfusion, however, the serum protein concentration was usually scarcely greater than before

transfusion, and the haemoglobin had usually returned to the pre-transfusion level. This failure to produce an increase in serum protein cannot have been due to loss of protein in the urine in either Case 12 or, in all probability, in Case 11. In several other cases also it appeared that the amount of albumin passed in the urine was not sufficient to account for the failure of the serum proteins to increase.

Of the 12 patients 11 were suffering from some degree of oedema at the time of the transfusions. In only 2 was a good diuresis produced by administration of serum, and in one of these the oedema returned within 10 days and failed to respond to a further transfusion.

It appears that in the nephrotic stage of glomerulonephritis a transfusion of concentrated serum is as likely to be followed by an adverse as by a favourable effect.

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CANCER OF THE STOMACH A STRIKING CONTRAST IN CLINICAL FEATURES

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The symptoms presented by the patient afflicted with carcinoma of the stomach have been fully described by many writers in recent years, and that they may vary greatly in any considerable group of patients is well recognized. Little attention, however, has been devoted to the factors which influence and determine these variations in the clinical picture, and it is my purpose, by contrasting two very different types of illness produced by primary carcinoma of the stomach, to present at least one factor the importance of which is not sufficiently appreciated.

The Symptomless Type

First we may take the case in which the disease produces no symptoms or appreciable decline in health until a late stage has been reached—so late indeed that a large proportion of such patients are beyond surgical help at the time they first consult their doctor. One example will suffice, though in a series of 145 patients operated upon or observed by me some 13 others would serve just as well.

The patient, an intelligent and industrious man aged 57, complained of epigastric pain of one month's duration. The pain was persistent, but became worse after food. Prior to the onset of pain a month before the examination, he was emphatic in his statement that he had noticed nothing amiss with his digestion, which had always been good, or with his health; but since then he had lost appetite and vigour though he had remained at full work until a fortnight before he visited me.

Examination revealed a large ovoid mass lying across the epigastrium and a gross enlargement of the liver, which presented palpable bosses on its surface. A radiograph showed "an extensive filling defect in the distal half of the stomach." The red cell count was 4,800,000 per c.mm.; the haemoglobin, 98%; and white cells, 7,000. Gastric analysis revealed a lasting achlorhydria. Clearly operation was out of the question, and the man died some four months later, jaundiced and with ascites.