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THE NEPHROTIC SYNDROME*

BY

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Massive oedema unfits numbers of people, young and old, for their normal daily life. In a fair proportion heavy proteinuria is present, and this group includes the patients to be discussed here. The subject is familiar, but, it must be admitted, a completely successful treatment is not known, so that patients with the nephrotic syndrome often languish for many months or even years in hospital, or closely tied to their homes. The syndrome invites study, not only from the desire to do more to help these patients but on account of its basic scientific interest; further research into the mechanism of the disorder seems likely to extend our knowledge of renal and circulatory physiology and of human protein metabolism.

This account is not to be regarded as a full review, such as the excellent article by Bradley and Tyson (1948); rather it is a preliminary report on some of the work of the last three years undertaken by a team in Birmingham, composed of Drs. J. D. Blainey, D. B. Brewer, J. Hardwicke, D. S. Rowe, Mr. H. J. Yardley, and myself. Though the results are incomplete, the usefulness of certain ideas and techniques can be illustrated. Especially we would emphasize the need for the quantitative collection and analysis of factual data from patients of this kind. We have studied some 20 patients, a few very completely over periods of many months of illness. Other similar studies are needed, and, since the syndrome is not rare, there is no lack of clinical material.

Definitions

There is at present a risk that students of renal disease will use different names for the same condition, or, worse, the same name for different conditions. It seems reasonable to reserve the term "nephrotic syndrome," unqualified, for patients with oedema, definite proteinuria, and hypo-albuminaemia, without hypertension, without electrolyte disorders or retention of non-protein nitrogen, and without an appreciable excess of red blood corpuscles in the urine. These excluding qualifications help, especially in discussions of treatment and prognosis, without denying the possibility that some of these features may appear as late sequelae, at least in certain forms of the syndrome. In addition, the nephrotic syndrome may appear in association with other definite disorders, when one may speak of, say, "constrictive pericarditis with an associated nephrotic syndrome," "hypertension with an associated nephrotic syndrome," etc. This form of description, of course, begs the question of common or dissociated aetiology, which seems advisable in our present state of ignorance.

Other associated disorders included in this series are congestive cardiac failure (often previously treated with mercurial diuretics for long periods), subacute nephritis (i.e., hypertension and some excess of red blood corpuscles in the urine, with a history suggesting previous attacks of more acute renal disease), and femoral thrombosis. In Table I the series is described by diagnosis, sex, and age. Classifications based on the morbid anatomical structure of the kidney have been avoided, since but few of these patients have died, and since, in those that have, our ability to predict the structural changes from studies on living patients has proved to be quite limited.

TABLE I.—*Diagnosis of Patients Studied in Present Series (Common Feature—Proteinuria)*

Diagnosis	Age of Females	Age of Males
Nephrotic syndrome (uncomplicated)	7 years 14 ,, 17 ,, 20 ,, 30 ,, 42 ,, 48 ,,	7 years
Acute nephritis		31 ,, 36 ,,
Subacute nephritis with associated nephrotic syndrome	20 ,,	36 ,, 37 ,,
Hypertension with terminal renal failure, associated nephrotic syndrome		55 ,, 65 ,,
Congestive cardiac failure, associated nephrotic syndrome	35 ,, *59 ,,	
Femoral (and ? caval) thrombosis, associated nephrotic syndrome	55 ,, 58 ,,	

* Constrictive pericarditis.

Prime Cause of Oedema

Various suggestions have been made regarding the prime cause of oedema in the nephrotic syndrome. The most widely held view, following on the publication of Starling's (1896) work, has been that the reduced colloid osmotic pressure of the plasma, a function of the hypo-albuminaemia, is responsible. Our studies support this idea, though some qualifications and extensions are necessary in the light of current knowledge. The evidence in favour of the hypothesis is largely based on the following observations.

*Based on a lecture delivered by invitation of the Academic Council of the University of London on November 30, 1953.

(1) The colloid osmotic pressure (C.O.P.) of nephrotic-syndrome plasma is greatly reduced below the normal average, at least so long as oedema is present. With normal values of 40–50 cm. of water in our measurements, nephrotic plasmas have given readings of 5–25 cm. of water. This evidence is of positive association between a lowering of C.O.P. and oedema formation.

(2) Samples of oedema or ascitic fluid have shown low protein values (less than 0.2 and 0.1 g.% respectively), and, when measured, a negligible C.O.P. (This is true even when pseudo-chylous effusions are found.) This evidence may be regarded as excluding gross capillary permeability to colloid as a cause.

(3) Infusions of salt-free colloid (e.g., 50–100 g. of human albumin, 40–80 g. of transfusion dextran) have almost always led to an increase during the ensuing 24 hours of water and sodium chloride excretion. This is interpreted as a mobilization of oedema fluid with its elimination in the urine. The albumin infusions, for example, cause a rise in C.O.P. (≡from 10 to 20 cm. of water) over this period. (A concomitant increase in plasma volume is usually found.) The diuresis is usually transient, the C.O.P. falling rapidly to the pre-infusion level, though exceptions to this result are noted in a later section. This evidence provides an instance of positive association between rising C.O.P. and oedema reduction.

Two accessory factors operating in oedema production needing discussion are sodium chloride retention and plasma volume reduction. Retention of sodium has been blamed as the primary cause of the oedema by a school of workers, and, indeed, it is a pronounced feature of the disease. Whether on moderate (100 mEq/day) or low (30–40 mEq/day) intakes of sodium, patients are observed who lose less than 10 mEq of sodium daily for week after week. This is a remarkable tribute to the efficiency of at least one component of the tubular reabsorptive capacity of diseased kidneys, for the constancy of the sodium content of the oedema fluid is closely maintained at about 125 mEq/litre. (The plasma level is often about 135–140 mEq/litre, a little below the normal value of 145 mEq/litre. This is probably attributable to the hypo-albuminaemia, since the normal plasma albumin level binds some 10 mEq of sodium/litre.) Clearly, if chemical constancy of the internal environment is to be maintained, retention of sodium must be effected when oedema is forming. It seems, then, that the sodium retention in these patients is a secondary physiological adaptation to meet the situation of oedema formation. This view is strengthened by the immediate response, already mentioned, to colloid infusions when as much as 70–100 mEq of sodium may be released in a day. Chloride metabolism is, of course, similarly affected.

C.O.P. Measurements and their Interpretation

Our measurements of colloid osmotic pressure have been done with an instrument (Fig. 1) with some novel features which make it well adapted to clinical studies. The use of a mechano-electronic transducer valve makes it possible to decide in one minute or less whether fluid is being transferred from the Ringer compartment of the osmometer to the serum sample, or vice versa. By a few successive trials the pressure which has to be applied to the serum to prevent any movement between the compartments is found; this is the C.O.P. Parallel tests on plasma and serum have shown no significant difference, and serum is usually tested as a matter of convenience.

The effect on C.O.P. of diluting a normal serum specimen with Ringer's solution is shown in Fig. 2. It can be seen at once that the relation between C.O.P. and protein concentration is not the simple straight line passing through the origin expected from solutions obeying the simple gas-laws of physical chemistry. The graph is markedly curved, being concave upward, so that at the order of concentrations present in normal serum the C.O.P. is about double that predicted from the molecular weight of its constituents. (Transfusion dextran solutions show a similar or greater

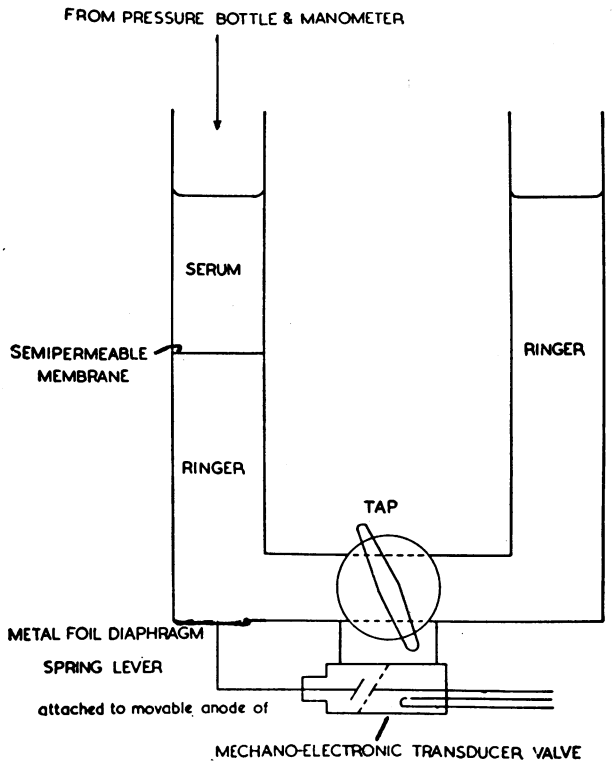

FIG. 1.—Principle of rapidly acting osmometer (D. S. Rowe). When tap is closed osmotic pressure of serum draws fluid through semipermeable membrane, causing upward bulging of diaphragm and changed resistance of transducer valve, which is electrically recorded. The air pressure which has to be applied to the surface of the serum to nullify this effect is equal to the C.O.P. of the serum.

effect.) The accurate determination of this curve is important in several ways. To the chemist the form of the curve at very low concentrations is of interest. From this region, where complications such as intermolecular forces, Donnan effects, etc., are negligible, the mean molecular weight of serum proteins can be calculated. (In Fig. 2 this is shown as the dotted line "limiting gradient.")

The physician is more concerned with two characteristics of the curve at and near the concentrations found in the blood. In the first place, the natural level of C.O.P. is important, for it must be related to the level of hydrostatic pressure at which there is no net movement of fluid through the capillary wall. In addition, the slope of this curve (shown by the dotted line labelled "physiological gradient" in Fig. 2) should be considered. This slope must affect the precision of the homoeostatic mechanism governing the relation between plasma and interstitial fluid volumes. Suppose that a little fluid is ultrafiltered from the plasma into the interstitial space, some haemoconcentration will result and the C.O.P. will rise to an extent depending on the physiological gradient. This rise in C.O.P. will tend to oppose further ultrafiltration and so to maintain homoeostasis. Conversely, haemodilution will be opposed by the fall in C.O.P. induced. Thus the steeper the physiological gradient the more exact the homoeostatic control.

In Fig. 3 the state of affairs with a nephrotic syndrome serum is shown. Again dilutions with Ringer's solution have been prepared and the C.O.P. of each measured. This has made it possible to show that not only is the C.O.P. diminished greatly (to 19.1 cm. of water in this instance),

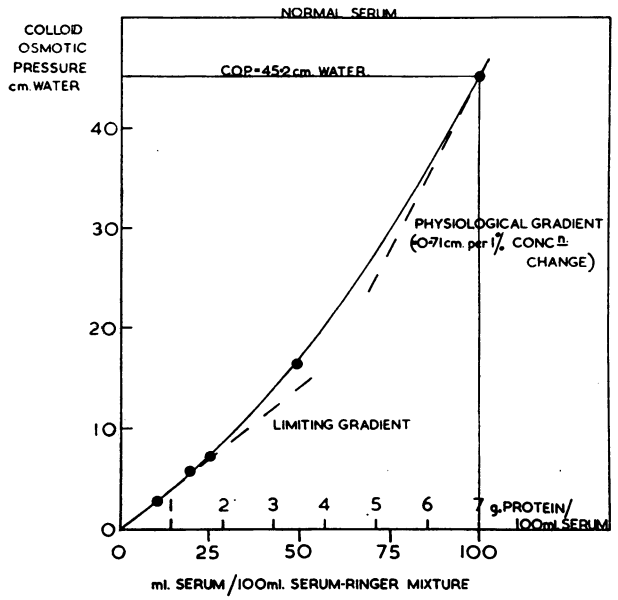

FIG. 2.—C.O.P. of normal serum, full-strength and at various dilutions. The limiting gradient at zero concentration is inversely proportional to the mean molecular weight of the serum colloids. The physiological gradient of full-strength serum is steeper, and is important for the maintenance of constant plasma volume *in vivo*.

but that the physiological gradient is also much less steep. Other factors being equal, not only will the nephrotic-syndrome patient be tending to lose fluid from plasma to interstitial space, but he will also, when some form of balance has been obtained, have a greatly diminished power of regulating the volume of either compartment—a small rise in, say, capillary pressure will tip the balance towards oedema formation, and a much larger fluid shift than normal will occur before a sufficient rise in C.O.P. has occurred to counterbalance the effect. At this stage it may be noted that the measurements here set out are made with semi-permeable membranes completely impervious to the serum colloids. In that the blood capillaries are known to be normally slightly permeable, at any rate to the smaller proteins of the plasma (e.g., albumin), the physiological osmotic pressures will be fractionally less than those shown here.

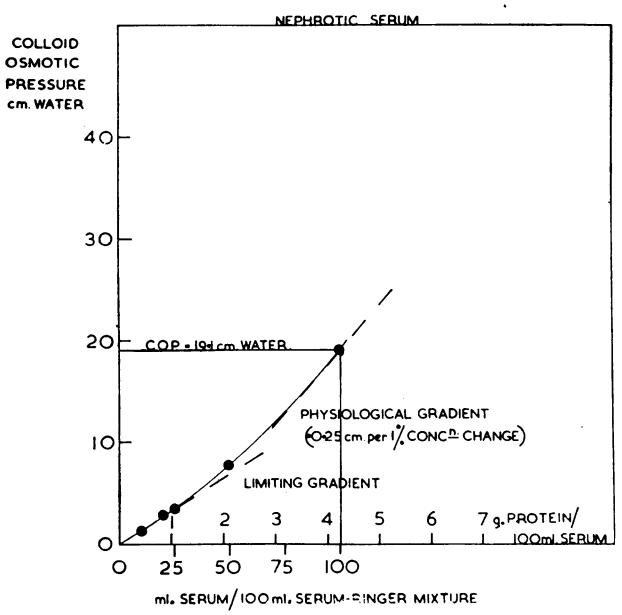

FIG. 3.—C.O.P. of nephrotic serum for comparison with Fig. 2. C.O.P. and physiological gradient considerably reduced. Limiting gradient (cm. water/1 g. protein per 100 ml. serum) somewhat reduced.

It is thought that this difference is not likely to be appreciable, in that the speed of transmission of protein through capillary walls is many thousand times less than the speed of transmission of its Ringer-like solvent.

A further extension of the Starling theory is indicated by the knowledge now current that the interstitial space is occupied by a colloid gel, histologically seen as "ground-substance" lying within a network of collagen and other fibres. In Starling's time the interstitial space separating the vessel wall from the cellular contents tended to be thought of as a potential space analogous to the peritoneal and pleural cavities—assuming appreciable dimensions only in pathological states like oedema, ascites, or pleural effusion. To-day, estimates of the interstitial space in normal subjects suggest a volume perhaps about four times as great as the plasma volume, and that in health this volume is maintained with fair constancy. This state of affairs is inconceivable on the simple Starling hypothesis—the slightest

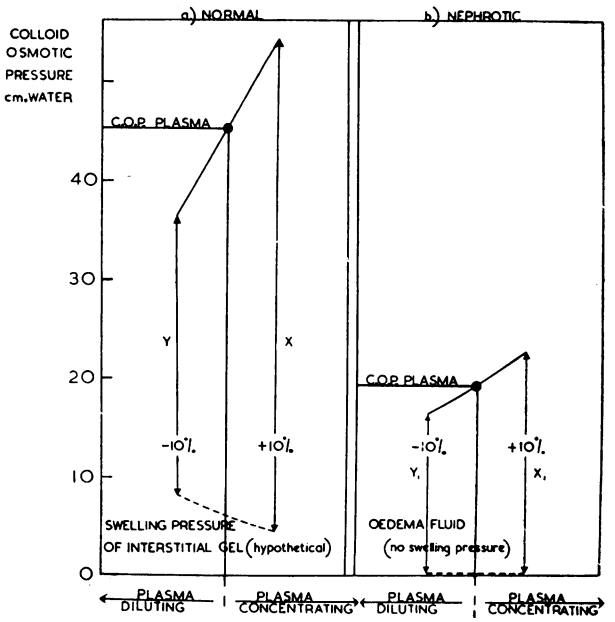

FIG. 4.—Illustration of two factors postulated as minimizing plasma volume alterations in normals (a), with reduced effectiveness in the nephrotic syndrome (b) (for explanation, see text).

discrepancy of mean capillary hydrostatic pressure and mean plasma C.O.P. would produce a progressive alteration in interstitial volume. Mechanical tissue tension in the sense of skin tightness cannot be responsible for interstitial space volume maintenance, as this tension is absent in various anatomical regions. Another factor which must be taken into account in the qualitative difference between oedema fluid and normal interstitial fluid is the tendency of oedema fluid to gravitate and to pit on pressure. This feature is prominent in patients with only, say, 5 litres of oedema—an increase in total interstitial fluid volume of less than 50%.

These difficulties are removed if the interstitial space is regarded as being occupied by a gel. It is known that such gels have a "swelling pressure," analogous to the C.O.P. of a soluble colloid. This swelling pressure tends to attract aqueous solutions into the gel up to a certain limit. At this level the swelling pressure is zero, imbibition ceases, and further addition of water leaves free fluid. This point, it is suggested, corresponds to the level at which oedema is found. Removal of water from a gel is resisted by the swelling pressure, which can be overcome by the exercise of mechanical pressure or by opposing the swelling pressure by C.O.P. In general, swelling pressures tend to rise rather steeply with progressive removal of water. Actual values for the swelling pressure of the interstitial gel have not, so far as is known, been measured. In Fig. 4a the swelling pressure for a normal man has been marked as a hypo-

thetical line. In Fig. 4b the situation in the nephrotic syndrome with oedema present is depicted—no swelling pressure is available to oppose the tendency of fluid to shift to and from the plasma. This, together with the reduced physiological gradient of C.O.P. already described, must make the regulation of plasma volume much more precarious than in the normal subject. In quantitative terms, (X_1-Y_1) is much less than the corresponding normal difference (X–Y) (Fig. 4).

Insufficient measurements have been made of plasma volume or of red-cell mass in the nephrotic syndrome. According to Borst (1948) the plasma volume is usually reduced below normal and the few determinations we have made, using the dye T.1824, confirm this. The reduction is not always great (usually 5–25%), assuming significance only when related to the plasma volume of patients with a comparable degree of anaemia. This is necessary because the plasma volume tends to rise above normal with anaemia (thus tending to lessen the reduction in overall blood volume which would otherwise result). In the anaemia commonly found with the nephrotic syndrome a similar rise occurs, but of less degree. The plasma volume may also be somewhat reduced by salt deprivation even of the degree induced by therapeutic diets.

To conclude this discussion of the relation between the oedema of the nephrotic syndrome and the reduced C.O.P. associated with hypo-albuminaemia, we must agree with other workers that diuresis may occur before any definite rise in serum albumin concentration is found. This is demonstrated in Table II. The patient had been on a low-

TABLE II.—*Factors Concerned in Diuresis*

	1952		1953		
	Nov. 14	Nov. 29	Jan. 7	Jan. 22	Jan. 31
P.C.V.	39	40	25	25	41
Serum albumin, g./100 ml.	0·47	0·51	0·50	0·77	0·99
Plasma volume, ml.	1,780	1,710	3,360	3,360	2,610
Total circulating albumin g.	8·4	8·7	16·8	25·8	26·2
Mean daily weight change g.	+180	+300	−66	−300	−280

Female, 55 kg. High protein intake from November 14, blood transfusion 720 ml. packed cells on January 29, 1953.

In November, 1952, oedema was accumulating. Diuresis began at the beginning of January, 1953 (see weight changes). Note that serum albumin concentration had shown no appreciable change by January 7, but the packed cell volume (P.C.V.) had fallen greatly. This is interpreted as being due to a considerable increase in plasma volume and total circulating albumin.

salt and high-protein diet for many weeks; a markedly positive nitrogen balance was recorded throughout the period shown. Until the middle of December, 1952, steady accumulation of oedema and ascitic fluid continued, making paracentesis repeatedly necessary. This oedema formation is shown for simplicity in Table II by records of weight change: sodium, chloride, and water retention confirmed its nature. Then the trend was gradually reversed, until at the beginning of January a large diuresis occurred. At this point the serum protein concentrations were essentially unchanged. But the packed red cell volume had fallen from 40% to 25% in a matter of weeks, no evidence of haemorrhage or haemolysis being noted. Apparently, therefore, a considerable increase in plasma volume had occurred. The diuresis was not a function of a rise in glomerular filtration rate, as judged by creatinine clearance, which actually appeared to fall, only to rise again when the diuresis was completed. Only towards the end of January, when the diuresis was more than half completed, the serum albumin concentration rose somewhat, no further plasma volume increase being noted.

At this point a transfusion of packed red cells was given for therapeutic purposes, and this enabled the approximate estimate of actual plasma volume, shown in Table II, to be made. It seems that between November and January the total circulating albumin increased about twofold. Unless protein is added very rapidly to the circulation as by transfusion, an increase in plasma volume rather than in protein concentration is what might be expected to follow an increase in total circulating albumin when free oedema is present. When the oedema has been removed, on the other hand, further abstraction of water from the interstitial space into the plasma will result in increased swelling pressure of the interstitial gel, and can only be achieved by reduction in capillary blood pressure or by a rise in serum C.O.P.

In conditions other than the nephrotic syndrome, alterations in interstitial gel may occur. Myxoedema involves its presence in exaggerated amounts (and perhaps in abnormal quality). A reduction in the interstitial gel may be a contributory factor to the production of famine oedema, and perhaps also to oedema in patients with the nephrotic syndrome after prolonged underfeeding.

Changes in Other Serum Proteins Associated with Hypo-albuminaemia

The introduction of paper electrophoresis for the separation of serum proteins has for the first time made possible numerous and repeated examinations of nephrotic syndrome sera and urines. In our department, Dr. Hardwicke has paid particular attention to validating the quantitative results. Differential analysis is made by elution of the dye bromphenol blue from the sites clearly stained by adsorption on to each component. Elution is also carried out from intermediate areas, and allowance is made for tailing of the serum albumin—the fastest-moving component which has travelled over the areas of paper eventually occupied by each globulin fraction. Total serum proteins have been estimated by a biuret method, while the fibrinogen in plasma samples is estimated by the Folin and Ciocalteau method after collection as a clot and redissolving in soda.

Without doubt the protein which is reduced to the greatest extent in the nephrotic syndrome is the serum albumin. As already described, there is fair correspondence between the serum albumin concentration and the C.O.P. Albumin levels have therefore been taken as an index of the severity of the condition from patient to patient and from time to time. Other serum constituents and other features of the syndrome (e.g., the degree of proteinuria) have been compared with the serum albumin level.

In Fig. 5 the total concentration of plasma proteins is plotted graphically against the serum albumin concentra-

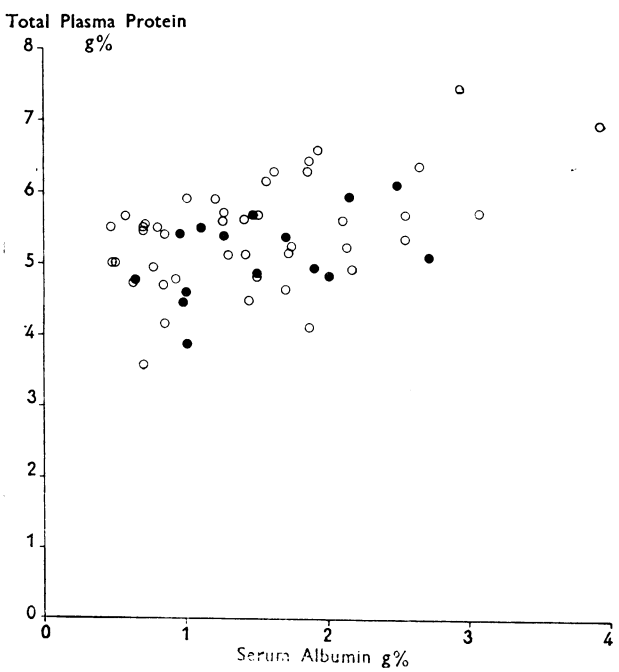

FIG. 5.—Total plasma protein and serum albumin concentrations in patients with proteinuria (J. Hardwicke). For serum albumin levels falling below 2 g./100 ml. there is little further reduction in total plasma protein level. (Contrast findings in malnutrition, liver disease.) In this and subsequent figures the first determination on each patient is shown ●, subsequent readings being shown O.

tion, each being expressed as g.% (15 patients, 59 determinations). The results show that down to a serum albumin concentration of 1.5–2 g.% the level of total serum proteins falls from its normal range of 6.5–8 g.% to about 4.5–6 g.%. Below this value of serum albumin level there is little further fall in total protein, patients with serum albumin levels of below 0.5 g.% maintaining a total protein concentration of 5–5.6 g.%. In this series only one patient showed a total serum protein level of less than 4 g.%—in other words, very low levels of serum albumin concentration are accompanied by a rise in concentration of some globulins. This result contrasts with the findings in other forms of hypoproteinaemia due, for instance, to malabsorption of food from a diseased intestine, when the total protein level may fall to 3 g.%.

In Table III the relation between hypo-albuminaemia of increasing severity and other changes in plasma constituents is shown. Values have been expressed in terms of % of normal averages to facilitate ready appreciation of the relative extents of the changes involved. The ranges observed are also shown beneath each mean. In spite of fairly large variations, some due to experimental error and some to case-to-case variation, all the patients conformed to clear-cut trends. This is notable in view of the probable diversity of aetiological agents concerned. With albumin levels reduced to below 30% of normal, α_2-globulin, fibrinogen, and cholesterol concentrations were invariably raised, increases to 300% of the normal average being the rule with severe hypo-albuminaemia. By contrast, the globulin fractions with smaller molecular weights (α_1- and γ-globulin) tended to fall with (though not so much as) the albumin; usually the α_1-globulin falls to a greater extent that the γ-globulin. The β-globulin rises somewhat, usually to between 100% and 200% of normal. (This finding in particular differs somewhat from the picture described by others using classical free boundary electrophoresis where concentrations are measured by refractometry—a method which estimates the lipids associated with the β-globulin along with the protein.)

TABLE III.—*Relation Between Hypo-albuminaemia of Increasing Severity and Other Plasma Changes*

Plasma Fraction	Molecular Weight	Normal		Nephrotic		
		g./100 ml.	% Normal	Mean Values and Range		
				% Normal	% Normal	% Normal
Albumin ..	69,000	4·0	100	50 (45–53)	26 (23–29)	14 (12–19)
α_1-globulin	45,000	0·3	100	103 (66–140)	84 (33–150)	57 (17–113)
γ-globulin	156,000	0·9	100	86 (44–187)	81 (38–160)	63 (39–72)
β-globulin	90,000 and 1,300,000	0·6	100	129 (80–170)	157 (83–193)	136 (100–183)
α_2-globulin	300,000	0·6	100	152 (100–240)	228 (145–347)	295 (133–400)
Fibrinogen	450,000	0·3	100	197 (123–323)	286 (197–400)	354 (280–460)
Cholesterol	—	0·3	100	170 (104–194)	288 (103–395)	330 (259–478)

Each column is based on 10–15 observations. Note that the smaller proteins (α_1- and γ-globulin) fall with albumin, whereas the other fractions rise.

As, unfortunately, little is still known even of the normal functions of the various serum proteins, these changes cannot be said to cause or to correct any definite abnormality. The plasma viscosity is raised rather than reduced, for the proteins which rise in concentration are large, and in some instances probably asymmetric. It is tempting to associate the fall in γ-globulin with the known tendency of these patients to develop infections. The small degree of fall of the globulin would be unconvincing in this respect were it not known that the γ-globulin fraction is composite, and that some antibodies may perhaps be reduced more than the main γ-globulin fraction. β-globulin is complex also; the small metal-carrying β-globulin is probably reduced more than the larger lipoprotein associated with this fraction. Certain negative conclusions can be drawn. The rises in α_2-globulin, fibrinogen, and total cholesterol are far too great to be accounted for simply in terms of reduced plasma volume with ensuing concentration of some constituents. On the other hand, α_2-globulin and fibrinogen, having molecular weights five times greater than serum albumin, cannot compensate directly for the reduction in colloid osmotic pressure associated with a reduction of serum albumin from, say, 4 g.% to 0.5 g.%. To do this the α_2-globulin and fibrinogen level would need to rise to some 15 g.%—and the resulting solution would resemble treacle in consistency.

Extent of Dependence of Serum Abnormalities on Proteinuria

The clinical association between reduced serum albumin levels and severe proteinuria has often been held to show that the serum abnormality depended directly upon the urinary loss. An alternative view has been that some serum proteins, in particular the albumin, are produced in inadequate amounts in the nephrotic syndrome. These two views are, of course, not mutually exclusive.

Urine samples collected during 24-hour periods and serum obtained on the same day have been subjected to electrophoretic analysis. The same protein fractions—albumin and four globulin components—appear in each, having similar mobilities, and showing only these same fractions when electrophoresis is carried out on a mixture of urine and serum. There seems no reason to doubt, therefore, that the protein found in the urine has "leaked" from the blood via the kidney. The relative amounts of the different fractions, however, is not the same—the urine/serum ratios being always in descending order—albumin, α_1-globulin; β- and γ-globulin; α_2-globulin. (In acute nephritis the ratios may be almost identical, as discussed below.) In other words, the losses of albumin and α_1-globulin tend to be large while that of α_2-globulin is small. No doubt these losses are dependent on molecular weights—the small proteins, like albumin, passing readily through the glomerular wall, the large molecules of α_2-globulin being restrained. It is also tempting to associate the facts that the albumin and α_1-globulin are the proteins most reduced in nephrotic plasma as supporting evidence for the idea that serum changes in the nephrotic syndrome depend largely upon the urinary losses.

More evidence is obtainable from comparing the daily urinary losses of protein with the degree of hypo-albuminaemia on repeated examinations of a number of patients. This comparison is shown in Fig. 6, in which serum albumin concentration is plotted against daily albumin excretion (Fig. 6a) and daily total protein excretion (Fig. 6b). Losses are plotted as g./kg. normal body weight so as to make valid comparisons between large and small patients. A clear association is seen with low serum albumin levels accompanying large urinary losses. Statistical analysis shows this association to be highly significant, and regression lines have been calculated and drawn to show the most likely average relationship in these patients. It should be noted that all the patients from whom these values were derived had long-standing proteinuria; all were on a good hospital diet—in one or two instances only on very high protein diets (over 120 g. of protein a day).

A tentative interpretation may be put forward to explain the relation between albumin excretion and plasma (=serum) albumin level. Normally plasma albumin levels are constant at about 4 g./100 ml., production and utilization being equal. If urinary loss of albumin occurs and production remains steady the plasma level must fall; if utilization also remained steady the fall would continue until no plasma albumin was left. But if utilization is dependent upon plasma albumin concentration in some way, a new balanced state can be envisaged, hypo-albuminaemia being dependent on the degree of albuminuria. Most of these patients showed, in fact, remarkably steady levels of plasma albumin and of albumin excretion in the urine over periods of many weeks. In other words, they were in dynamic equilibrium so far as plasma albumin was concerned—albumin production being equal to the sum of albumin loss by excretion and albumin utilization. In a normal person, with a negligible excretion

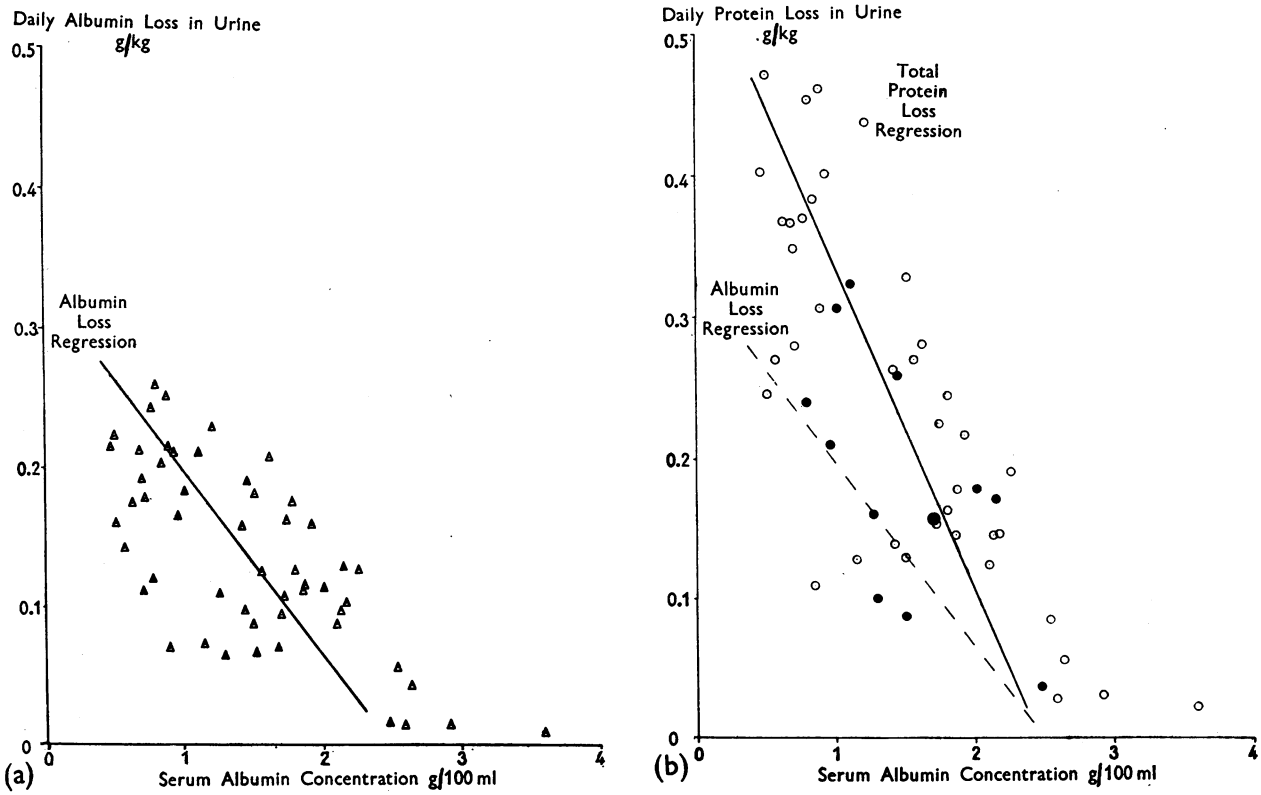

FIG. 6.—Relation between hypo-albuminaemia and daily loss in urine of (a) albumin, and (b) total protein (J. Hardwicke). Regression lines are in each case highly significant, indicating close association of the blood changes and the extent of proteinuria.

of albumin, production is entirely balanced by utilization, which amounts to some 0.25 g./kg./day according to published studies using radioactive techniques (e.g., Sterling, 1951).

Several of the patients excreted 0.25 g./kg./day with constant serum albumin levels; even if utilization had fallen to zero their rate of albumin production was clearly not grossly impaired. If one were to assume that utilization of albumin had remained normal, their production must in every case have been greater than normal, in some instances reaching over 200% of the normal figure. In fact, it seems more plausible to suppose that albumin utilization in hypo-albuminaemia lies between these wide possibilities of zero and normal values. Interesting results are obtained if the assumption is provisionally adopted that albumin utilization is directly proportional to plasma albumin concentration; a similar hypothesis is known to be applicable in various situations with the utilization of glucose at different plasma glucose levels. If albumin utilization is taken as 0.25 g./kg./day with normal plasma albumin levels (4 g./100 ml.), utilization for any level of plasma albumin (P) is given by: (utilization = $\frac{P}{4} \times 0.25$). Production is then calculated from (utilization + excretion). From the 53 determinations charted in Fig. 6a, calculated production levels fall between 48% and 124% of normal, with a mean value of 92% as shown in Table IV.

These figures should be treated with considerable reserve; they are, indeed, little superior to an informed guess. It is perhaps opportune to make such an estimate, for techniques available for accurate estimation in occasional patients are being used in other laboratories. In other words, the figures can be checked. They further emphasize that patients are not constant in this respect; indeed, protein production can apparently vary at least between production levels 60% of normal in severe cases and 120% of normal in convalescence on a liberal protein diet. When quoting experimental determination of albumin production, therefore, it is most desirable to give details of the diet, the daily albumin excretion, and the plasma albumin level.

TABLE IV.—*Albumin Production Values in Nephrotic Patients Calculated from Albumin Excretion and Plasma Albumin Concentrations* (53 *Observations*)

Calculated Albumin Production (% of Normal)	No. of Observations
48– 51	1
52– 59	1
60– 67	3
68– 75	7
76– 83	5
84– 91	7
92– 99	11
100–107	6
108–115	7
116–123	4
124–127	1

(Based on assumptions:—1: Production = utilization + excretion. 2: Utilization = $\frac{\text{plasma albumin}}{4} \times 0{\cdot}25$. 3: Normal production of albumin = 0·25 g./kg./day.) Data as for Fig. 6.

The automatic control of plasma albumin level by means of an albumin utilization rate which rises and falls with this level is presumably the main factor leading to steady levels of hypo-albuminaemia when underproduction occurs without proteinuria (e.g., liver disease). But in renal disease a further factor which determines the plasma albumin level is the marked rise in proteinuria which, without any change in the permeability of the kidney, accompanies any increase in plasma albumin. Such increases may occur naturally with increasing production or be artificially produced with albumin infusions. A rise of plasma albumin by 10% increases protein excretion by about 15%. (Taking into account the increased utilization, the plasma albumin level will rise only 10% in this way if production is stepped up by about 25%.) The effect of such plasma alterations in proteinuria gives useful indications of the exact kind of renal damage in individual patients.

Analysis of Renal Defect which Results in Proteinuria

For many years now there have been debate and confusion about the relative importance of glomerular and tubular lesions in disease processes affecting the kidneys. Histological evidence has focused attention on the glomerular

lesions in acute nephritis, but has shown obvious tubular changes, including pronounced fatty degeneration in patients who showed severe proteinuria and oedema as the chief abnormality before death. In this nephrotic group glomerular changes have been difficult to find; a special form of thickening of the glomerular basement membrane has been described as occurring in what is now often known as Ellis "type II nephritis" (Ellis, 1942), but even these changes are often slight.

The conclusions to be drawn from urinary abnormalities during life have been less definite. The excretion of red blood corpuscles in acute nephritis is reasonably interpreted as severe damage in limited areas of the glomerular membrane. Specific tubular defects are now well recognized in patients able only to a very limited extent to alter the concentrations of certain ions or other substances of low molecular weight in the urine. But the relative contribution of glomerular and tubular defects to severe proteinuria has remained unknown. So long as the normal glomerulus was supposed to produce a protein-free ultrafiltrate, opinion naturally inclined to the view that proteinuria depended entirely on a glomerular defect. If one accepts the evidence from direct sampling of glomerular fluid that both cold- and warm-blooded animals pass some protein into the glomerular filtrate, tubular reabsorption of protein must be recognized as a normal process. Proteinuria therefore could theoretically arise from glomerular damage, allowing so much protein to be filtered that the tubular mechanism was saturated before all protein was reabsorbed, from tubular damage alone or from a combination of glomerular and tubular damage. At present our ability to correct either defect is limited (or in most instances non-existent), but establishing the degree of damage to glomeruli and tubules in each individual patient is a prerequisite of a rational assessment of the problem.

From electrophoretic estimation of proteins in urine and serum, an *"apparent" (or urinary) clearance* can be calculated for each fraction—that is, the ratio of the quantity excreted (expressed as mg./min.) to the serum concentration of the fraction under consideration. Now if no reabsorption of protein occurred in the tubules these *apparent clearances* would represent the *"true" (or glomerular) clearances* of each protein fraction. If reabsorption does occur, these *apparent clearances* will be less than the *true clearances* by an amount depending on the proportion of the protein reabsorbed during any particular test.

Both *true* and *apparent clearances of protein fractions* will depend directly upon the glomerular filtration rate. This has been estimated in all tests on the patients considered here from the clearances of endogenous creatinine. With the precaution of adsorbing serum creatinine on to kaolin to eliminate errors due to other substances giving similar colours with the Jaffé reagent, we believe this test gives a reasonably reliable indication of the glomerular filtration rate, at least with results of over 30 ml./minute. The disadvantage of the small errors which probably remain is offset in clinical studies by the minimal disturbance of the patient, the test requiring only a single venepuncture and an accurately timed collection of urine over a four-hour period. Creatinine clearances are also of considerable value in assessing the progress of patients. In agreement with other workers, we find that clearances of less than 20–30 ml./minute, if maintained over a period of weeks, indicate a poor prognosis.

From the *apparent clearance of a protein fraction* divided by the creatinine clearance, a value can be obtained for the *apparent relative clearance* of each protein fraction. This value will similarly be less than the *true relative clearance* in each case by an amount depending upon the proportion of protein reabsorbed by the tubules. In the absence of knowledge of this proportion, we have adopted certain hypotheses, capable of subsequent testing by measurements. These are:

(*a*) The amount of protein which can be reabsorbed each minute (T_{MP}) in the tubules of each patient is limited and fixed. Over any period of two to three days (except in acute conditions) this amount does not fluctuate. When proteinuria is present this potential reabsorption is fully active.

(*b*) The tubules do not distinguish between different protein fractions—the reabsorptive channels for, say, albumin and for γ-globulin being the same. It follows that if, say, 40% of the total protein in the glomerular filtrate is being reabsorbed, 40% of the albumin and 40% of the γ-globulin present are reabsorbed. The *amount* (as opposed to the proportion) reabsorbed will depend on the amounts of each protein in the glomerular filtrate.

Since the *amount* of protein per minute which can be reabsorbed is fixed, the *proportion* of the protein passed into the glomerular filtrate and then reabsorbed is less the greater the amount passed. It follows that the apparent relative clearance is lower than the true relative clearance of any protein fraction by an amount depending on this proportion reabsorbed; the apparent relative clearance will rise to approach the true value as the amount of protein excreted in the urine per minute is increased—for example, as the result of increasing the concentration of any serum protein. Furthermore, if exact measurements are made of apparent relative clearances of, say, albumin every few hours when total protein excretion changes and is measured, the true relative clearance and the amount of protein reabsorbed per minute can be calculated. This has been achieved by measurements made before and after abruptly increasing the serum albumin level by an infusion of human serum albumin. The calculation depends on the expression:

$$\frac{\text{(True relative clearance of albumin)}}{\text{(Apparent relative clearance of albumin)}}$$

$$= \frac{\text{(Protein passed in glomerular filtrate/min.)}}{\text{(Protein passed in urine/min.)}}$$

$$= \frac{\text{(Protein reabsorbed by tubules/min.} + \text{Protein passed in urine/min.)}}{\text{(Protein passed in urine/min.)}}$$

$$= (T_{MP} + \text{protein passed in urine/min.}) \div \text{(Protein passed in urine/min.)}$$

or by rearrangement:

$$= (T_{MP} + \text{protein passed in urine/min.}) \div \frac{\text{(Protein passed in urine/min.)}}{\text{(True relative clearance of albumin)}}$$

$$\div \frac{\text{(Protein passed in urine/min.)}}{\text{(Apparent relative clearance of albumin)}}$$

Since each clearance estimate is subject to a degree of experimental error, successive clearances and total protein excretions over four-hour or eight-hour periods are measured. The results are shown graphically in Fig. 7, the protein excretions per minute being plotted vertically, and the ratios of (protein passed in urine)/(apparent relative clearances) on the horizontal axis. It can be seen that, in fact, for albumin a straight line is obtained, in agreement

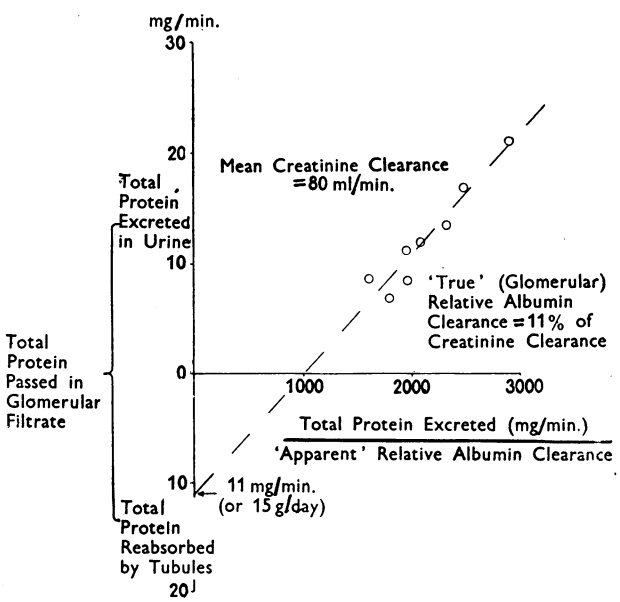

FIG. 7.—Use of albumin infusion to measure glomerular permeability to albumin (calculated from gradient) and rate of protein reabsorption by tubules (from intercept on vertical axis). (Female patient, C. J., 54 kg. Albumin infusion 45 g., June 5, 1952.) Explanation of method is given in text.

with the hypothetical reasoning set out above. The slope of this line represents the true (glomerular) relative clearance of albumin, while the negative intercept on the vertical axis represents the amount of total protein reabsorbed each minute by the tubules.

The general form of result shown in Fig. 7 has been confirmed by five other tests on a total of three patients with the nephrotic syndrome. In all, the relationship has been a straight line within the limits of experimental error, as predicted from the argument already given. In all, a negative intercept has been obtained, indicating that some protein was being reabsorbed by the tubules. When a substantial increase in proteinuria occurred in association with the raised serum albumin, it disappeared with the return of serum albumin to pretransfusion levels—that is, no fresh renal damage followed the infusions. Although the serum globulins showed little tendency to alter after the albumin infusion, during the period of increased proteinuria the apparent relative clearances of these globulins increased in proportion to the increase in apparent relative clearance of albumin. This supports the concept that the tubules' capacity to reabsorb protein is uninfluenced by the nature of the protein presented to them in the glomerular filtrate, as was suggested above. The different proteins compete with each other on equal terms, as it were, for reabsorption.

If this method of investigating the renal defect resulting in proteinuria is accepted, tentative answers may be given to some salient questions. Is the tubular capacity for protein reabsorption affected in the nephrotic syndrome? Is a glomerular defect present? If so, what different forms of glomerular damage occur in different kinds of renal disease? This kind of investigation has not yet been carried out often enough for broad generalizations. In one patient tested, protein reabsorption was very low as compared with the other two patients. Grossly defective tubular reabsorption, on occasion, then, occurs, and it is worth noting that in this patient there was other evidence of tubular dysfunction. Serum electrolyte levels became disordered, and after death, some months later, very severe damage to tubule cells was shown by histological examination. This patient was suffering from subacute nephritis with malignant hypertension, accompanied by the nephrotic syndrome. Slighter degrees of tubular defect are possibly present—for example, in patient C. J., illustrated in Fig. 7—but this remains uncertain until more knowledge of normal tubular reabsorptive capacity for protein is obtained.

Some degree of glomerular defect appears to be present in all of the patients so far studied. If we are correct in assuming that tubular reabsorption of protein is substantially non-selective, and depends only on the relative concentrations of the different proteins in the glomerular filtrate, it follows that the ratios of, say, the apparent α_2-globulin clearance to the apparent albumin clearance is identical with the ratio of the true (glomerular) clearances of these proteins. If the various globulin clearances are expressed as percentages of the albumin clearance in each patient tested, some information is given about the nature of the glomerular defect. In uncomplicated examples of the nephrotic syndrome, typical values found are: α_1-globulin (70–150%), α_2-globulin (2–20%), β-globulin (10–50%), and γ-globulin (5–40%). In acute nephritis, on the other hand, the globulin clearances mostly range from 50 to 150% of the albumin clearance, with slightly lower values for α_2-globulin on occasion. Apparently, therefore, the defective areas of the glomeruli in acute nephritis transmit the different plasma proteins indiscriminately, the larger molecules of, say, γ-globulin being passed into the glomerular filtrate as readily as albumin.

If the glomerular membrane be regarded as a kind of sieve, in acute nephritis a few of the "holes" must be grossly enlarged. From clearance studies with dextran molecules of various sizes, it is known that the holes in the normal glomerular membrane are not all of equal size—all being permeable to molecules of molecular weight 5,000, some 20% transmitting molecules of about 30,000 molecular weight, and very few being capable of transmitting molecules of 60,000–70,000 molecular weight. This state of affairs is apparently largely preserved in the uncomplicated nephrotic syndrome kidney, in that considerable selection is still exerted on the size of molecule which is transmitted. But there is enough "stretching" of many of the holes to permit increased filtration at any rate of the smaller plasma protein molecules such as albumin and α_1-globulin. These

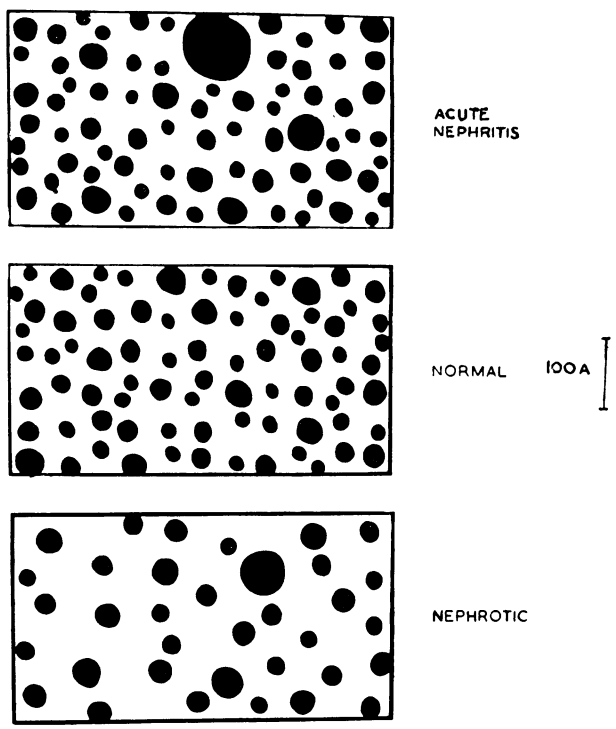

FIG. 8.—Possible glomerular membrane pore sizes as deduced from protein clearance studies. Normal: variations in pore size, but only occasional pores large enough to transmit protein. Acute nephritis: as normal, with occasional pores greatly enlarged. Nephrotic: many pores large enough to transmit smaller plasma proteins, only few transmit larger proteins. Reduced glomerular filtration rate *may* be associated with reduced numbers of pores.

variations in the size of hole in the glomerular sieve are illustrated diagrammatically in Fig. 8. Our findings in patients with subacute nephritis are intermediate between those described for acute nephritis and for the nephrotic syndrome.

Studies of Nitrogenous Metabolism

The patients in this series in whom proteinuria had been present for at least several months were grossly depleted in body protein. This feature of the nephrotic syndrome does not immediately attract attention for several reasons. The depletion develops insidiously, the muscular wasting is masked by oedema, and generally there is no marked loss of fat, so that the contours of the face, arms, and chest are not obviously abnormal. After loss or drainage of oedema, the calf muscles are often seen to be greatly reduced in bulk, and unequivocal evidence of protein depletion can be obtained by nitrogen-balance studies during convalescence. As an example, we have studied a girl of 19 (J. R.) who was severely affected with the nephrotic syndrome in July, 1952. Normally 55 kg. (8 st. 9 lb.) in weight, so much oedema was present by the end of October, 1952, that she weighed 87 kg. (13 st. 10 lb.), further increase being prevented only by repeated paracenteses. At this stage her appetite improved, and by December she was taking a diet containing more than 100 g. of protein each day. Daily nitrogen-balance studies were then carried out until her discharge from hospital 98 days later. During this period she gained over 3.6 kg. of protein (representing

with its associated water and minerals about 11 kg. of "flesh"). Since there was no slackening in this regain of body protein during the latter period of hospital treatment, and since the convalescence continued for several months after return home, this 11 kg. must represent only about two-thirds of the flesh lost at the height of illness, suggesting a maximum loss of 17 kg. In other words, a girl of 55 kg. normally (with no oedema) had wasted at the height of her illness to a person of (55−17 kg.)=38 kg., encumbered by (87−38 kg.)=49 kg. of oedema fluid. Now the normal body of a female of 55 kg. contains about 15%, or 8 kg. of protein. This patient lost and regained at least half and probably nearly two-thirds of this total amount.

Much work has already been devoted to the study of nitrogenous metabolism in the nephrotic syndrome, Farr and MacFadyen's (1940) analysis of their findings in children being specially important. Nevertheless, it seemed worth while adding further studies. For the present, two findings are of interest—the nature and amounts of the nitrogenous metabolites found in the urine, and the effect of various levels of protein intake on these metabolites and on the nitrogen balance.

The daily output of urea is abnormally low in nephrotic syndrome patients of long standing. Whereas a normal person on an average English diet excretes each day about 25 g. of urea (≡ 11.7 g. of urea nitrogen), a severely affected nephrotic patient of similar size excretes only about 10 g. of urea daily (≡ 4.7 g. of urea nitrogen) on an equivalent food intake. This deficient output is not due to inability of the kidneys to excrete urea, for the urea output remains at this level for weeks or months without any *progressive* rise in blood urea concentration. As a practical consequence, simple urinary function tests based on specific gravity or urea content of early morning urines are unreliable in the nephrotic syndrome, especially as it can be shown that extra water taken by mouth does not produce a prompt diuresis in these patients, but tends to be excreted during a period spread over 24–48 hours. The low urea output in the nephrotic syndrome is a manifestation of the need to use all amino-acids derived from food so far as possible to synthesize new protein—especially the plasma proteins being lost in the urine. Even lower outputs of urea have been recorded in experiments when normal subjects have been maintained on diets containing little or no protein for long periods but otherwise adequate in calories and essential supplements. These normal subjects were not, of course, sustaining the same continual loss of specialized protein in the urine. The 10 g. of urea being excreted each day by the nephrotic patient presumably represents the degradation product of certain amino-acids which cannot be used for plasma protein synthesis owing to relative deficiency of other essential components (probably other complex amino-acids).

While making daily measurements of nitrogen excretion by the nephrotic patient (J. R.), an unusually high difference or "gap" was found between the overall non-protein nitrogen values and the nitrogen present as urea+ammonia.

On the same 24-hour urine specimens, total osmolarity estimates disclosed an unusually large departure from the sum of estimated constituents. As these combined discrepancies led to a simple discovery, it seems worth describing the sequence in which they were noted.

In Fig. 9 is shown the Hill–Baldes thermo-electric device for measuring the total osmolarity of a solution. In principle it depends on the lowering of vapour pressure of dilute aqueous solutions in proportion to the number of dissolved particles (molecules such as urea or glucose, and ions such as sodium, sulphate, etc.). In use, the two loops shown are loaded with a drop each of distilled water and urine, and then lowered into the thermostatically controlled chamber with walls lined with filter paper soaked in water. The urine loop, having the lower vapour pressure, allows condensation of minute amounts of water vapour on to itself, and so becomes warmer. This continues for a few seconds until the urine is warm enough to have a vapour pressure equal to that of the water, when equilibrium is restored. This steady temperature difference between the loops, each of which is made up by a small manganin-constantan thermocouple, is measured directly on a specially sensitive galvanometer. The reading is directly proportional to the osmolar strength of the solution on the "urine" loop, so that only simple calibration of the instrument with three or four salt solutions of known strength is required.

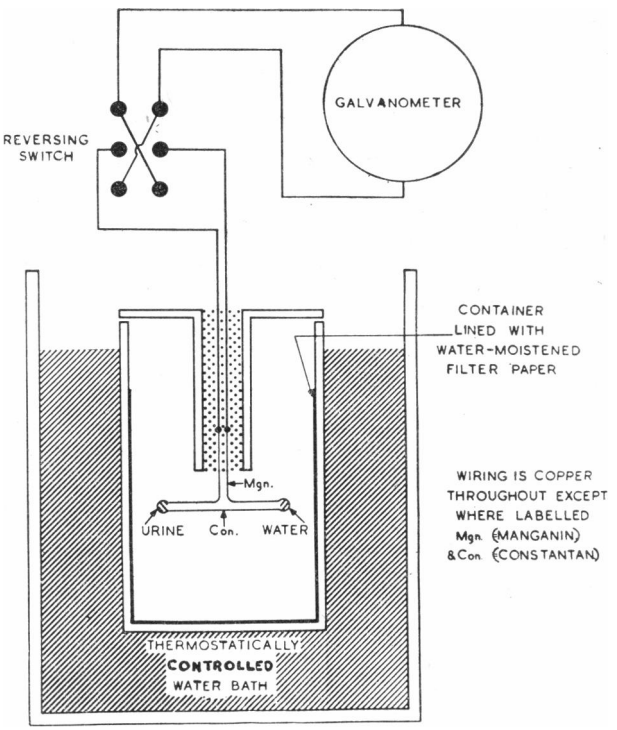

FIG. 9.—Thermo-electric apparatus for measuring total osmolarity, as described by Baldes and Johnson (1939). The loops loaded with urine and water settle to a steady temperature difference which is proportional to the osmolar strength of the urine, and is measured directly with the galvanometer.

In normal urine the main non-electrolyte is urea. Protein has a negligible effect on osmolarity, as such large molecular-weight substances consist of very few particles in solutions of the order of 1 g. or 2 g./100 ml. The electrolyte cations, sodium and potassium, are readily estimated with the flame photometer, and with ammonium, also readily estimated, constitute the main cations. The anions are more various, and in this study were approximately estimated as equivalent to the cations divided by a factor of 1.1, their usual average valency, for conversion from milli-equivalents per litre into milliosmols per litre. In other words, the electrolyte strength in milliosmols due to cations +anions was calculated approximately from :

$$\text{(main cations)}\ \left(1+\frac{1}{1.1}\right)$$

$$\text{or}\quad \text{(main cations)} \times 1.9$$

This sum of (urea) + 1.9 (combined cations) was compared with the total osmolarity measured with the Hill–Baldes instrument, and in normal urine was only about 5% less—a gap which on rough calculation was not unsatisfactory in view of the various minor constituents (creatinine, uric acid, calcium, magnesium, etc.) not considered. In the urine specimen from the nephrotic patient, however, this osmolar gap was much greater, and was found to increase as convalescence advanced. Similarly, the nitrogen gap (non-protein nitrogen−(urea+ammonia)) increased. This is shown in Fig. 10b, the values obtained by the research worker in 24-hour samples of his own urines being shown

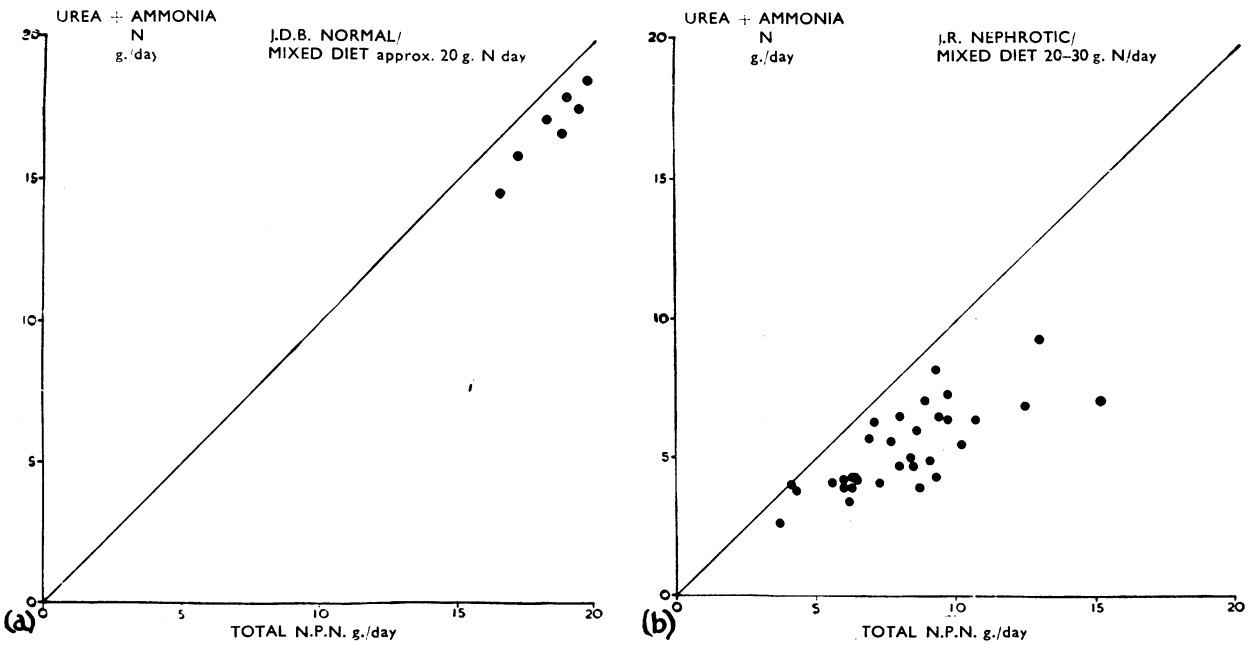

FIG. 10.—"Nitrogen gap" in 72-hour urine specimens between total non-protein nitrogen and its major component (urea+ammonia). The gap (represented by the horizontal distance between the observed points and the line) is small in the normal (a). This confirms other workers' findings with high- and low-protein diets (e.g., Folin, 1905; Deuel and others, 1927). In the nephrotic patient, J. R. (b), the gap is often considerable, especially with larger values of non-protein nitrogen excretion following high-protein feeding.

in Fig. 10a. In Fig. 11 the two forms of gap as found on three-day averages, week after week, are plotted against each other on log. log. scales. There is a considerable scatter, due no doubt in part to errors of estimation, in part to the assumption of a constant valency of 1.1 for the anion constituents of the urine. But the results are consistent with the true relation between the gaps being a straight line rising positively at an angle of 45 degrees. This implies that the two gaps are only separate measurements of the same unidentified constituent or group of constituents. The position of the line accords with molecules each containing between one and four atoms of nitrogen. At this stage amino-acids become suspect as the unanalysed constituents, and paper chromatography recorded their presence in large variety and amount. Nearly all the common amino-acid constituents of protein were found to be present. It may well seem that a rather

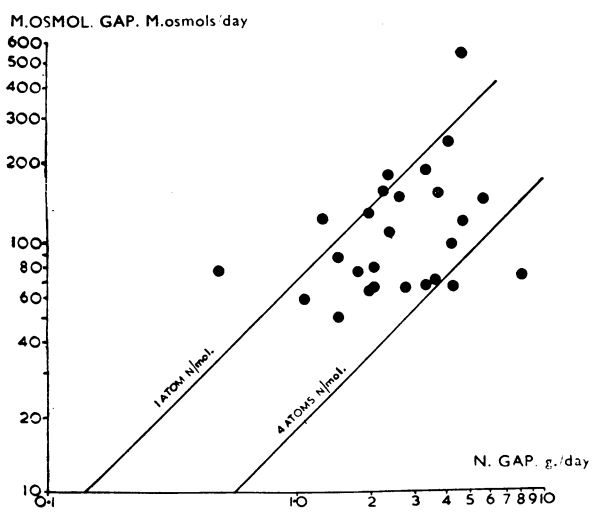

FIG. 11.—Relation between osmolar gap and nitrogen gap in nephrotic patient J. R. (72-hour specimens). Both values are plotted on similar logarithmic scales. The lines indicated show the values expected if the bulk of the unanalysed constituents contained 1 or 4 atoms of nitrogen/molecule—the range observed in 20/26 specimens.

long way round was taken to a simple discovery: the method has been detailed, as it seems to be generally applicable to the search for unknown constituents in the urine in a variety of diseases.

Testing other nephrotic patients for amino-aciduria has shown that its presence is not an isolated occurrence, but that it is not found in every case. In the patient already described, the quantity of amino-acids wasted in the urine was very considerable, increasing on the higher protein diets so that on intakes of about 150 g. of protein daily the equivalent of 20–30 g. was excreted as amino-acids. With severe proteinuria also present this patient was "wasting" about one-third of her protein intake. The amino-aciduria was apparently due to deficient tubular reabsorption resulting in a lowered renal threshold for amino-acids, as the blood amino-acid concentration was not raised above the normal.

Estimation of the nitrogen balance is probably the best criterion on which to choose an optimum diet. High-protein intakes have in the past sometimes been observed to result in increased proteinuria (see Berglund, Scriver, and Medes, 1935), but this is not necessarily a contraindication to their use if it reflects an increase in plasma proteins. Similarly, an increase in amino-aciduria merely seems to reflect an increased absorption of protein. By allowing a patient to take more protein in some balance periods than in others, it is possible to choose the optimum intake for maximum retention of nitrogen. In our studies with adults, the highest intake which we could persuade the patients to take (up to about 180 g. of protein a day in 60 kg. patients, or about 0.5 g. of protein nitrogen per kg.) gave the most strongly

TABLE V.—*Effect of Varying Protein Intake on Nitrogen Excretion and Balance*

	Normal On Protein Intake of:			Nephrotic On Protein Intake of:		
	0·2	0·3	0·4	0·2	0·3	0·4
Excretion of:						
Urea+ammonia	0·19	0·29	0·39	0·09	0·09	1·10
Protein ..	0	0	0	0·06	0·06	0·06
Nitrogen balance	0	0	0	+0·04	+0·11	+0·18

All values expressed as g. nitrogen/kg./day.

positive balance results. Table V summarizes some typical findings. Whereas a normal person put on such a diet increases urea output in a few days and so balances the extra intake by a rise in nitrogen excretion, the nephrotic patient shows very little increase in urea output over periods lasting several weeks. Slowly, however, the urea output does rise somewhat, suggesting that after retention of large amounts of nitrogen the depleted reserves of body protein are restored to more normal levels, and the nitrogen metabolism of the nephrotic approaches that of the normal.

Prognosis and Treatment

Renal diseases associated with sustained hypertension, electrolyte disorders, or rises in blood urea or creatinine levels are known to have a poor prognosis. The outlook seems to be far better for uncomplicated examples of the nephrotic syndrome, especially now that intercurrent infection is so much more readily controlled by the use of antibiotics. These drugs also make reasonably safe the drainage of oedema fluid by paracentesis or Southey's tubes, procedures which may afford symptomatic relief to severely affected patients. Low-sodium diets delay the formation of oedema and, with dialysed milk or animal serum as supplements, can be maintained in conjunction with high levels of protein intake.

Measures aimed at directly raising the colloid osmotic pressure of the plasma seem to meet with varying success. Albumin transfusions (e.g., 50 g. in water) have only a transient diuretic effect, and some of the material administered is rapidly lost into the urine. Salt-free dextran infusions have been given to eight patients on two occasions each, under our observation, in six a similar transient response being observed. In two patients a more satisfactory result was obtained with the second infusion of 1,200 ml., 600 ml. having been administered seven days and ten days previously. Considerable saline diuresis lasting two weeks and three weeks ensued, both patients being entirely cleared of oedema. No relapse followed, the proteinuria diminished, and the chemistry of the plasma slowly reverted towards normal. Certainly, similar results have been obtained in the past with other remedies, gum acacia having been prominent at one period. A task of future research is to discover which patients or what stage of the illness is likely to respond in this fashion.

Gradual recovery may also follow a lengthy period of high-protein intake, diuresis occurring after some two months of positive nitrogen balance. Though the flood of diuresis seems to occur suddenly, a preceding trickle may be detected several weeks earlier in the form of an increased sodium chloride loss. It is possible that the very beneficial results sometimes obtained with colloids like dextran are obtained when patients are in this borderline state, so that, in effect, a hastened convalescence is achieved. In the present state of knowledge it is desirable to emphasize the need for maintaining nephrotic patients on a high-protein intake. Several reports from other centres have suggested that rapid recovery may follow the administration in high dosage of specific food constituents such as methionine or choline. In view of the large overall protein deficit commonly found, it seems very likely that some patients are especially deficient in sulphydryl or labile methyl groups, but more work is needed to find out the relative frequency of general and specific forms of depletion.

Evidently gradual repair of renal defects, glomerular or tubular, can follow conservative treatment. If a drug could be found which reduced proteinuria without diminishing glomerular filtration of substances of smaller molecular weight, much more rapid recovery could be anticipated. Such effects have been claimed for A.C.T.H. and cortisone, though relapse may follow. Again, it seems that favourable results are not universally obtained. Our own experience with these drugs is too limited as yet for useful comment. In one patient an appreciable effect on proteinuria was not obtained with either drug, but cortisone appeared to contribute to an increased appetite, making the institution of high-protein feeding practicable, and so indirectly leading to gradual recovery.

Theoretically, mercurial diuretics seem out of place in the treatment of patients already afflicted with severe proteinuria. In practice, they are used when other measures fail to remove oedema, and may enable a patient to carry on limited activities which would not otherwise be possible.

Summary

The nephrotic syndrome is characterized by oedema, proteinuria, and hypo-albuminaemia without certain signs of other forms of renal disease. Similar syndromes may also occur in association with other diseases.

A reduced colloid osmotic pressure seems to be the prime cause of oedema, and so of saline retention. Plasma volume is also reduced; it may rise and diuresis occur before the colloid osmotic pressure rises. Homoeostasis of fluid volumes is discussed in relation to C.O.P. and interstitial gel swelling pressures.

With proteinuria and hypo-albuminaemia, other plasma constituents show characteristic alterations, the smaller-molecular-weight proteins tending to be reduced, the larger to be increased.

The amount of albuminuria is correlated with the degree of hypo-albuminaemia; albumin synthesis and utilization is discussed in relation to this finding.

The effect of albumin infusion on proteinuria can be used to assess glomerular permeability and tubular reabsorption of protein. The relative clearances of albumin and other plasma proteins differ in various types of disease and imply different disorders of glomerular permeability.

Nitrogen metabolism and balance studies contribute to an understanding of pathogenesis and treatment. Large deficits of body protein have been observed; low urea excretion values are found and interpreted partly as a manifestation of nitrogen conservation. Amino-aciduria of considerable extent may accompany the nephrotic syndrome, especially on high-protein intakes.

The prognosis of uncomplicated nephrotic cases is probably not as bad as is often thought. The achievement of a positive nitrogen balance by high-protein feeding is recommended.

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