NEPHROSIS.

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Epstein wanted to call nephrosis "diabetes albuminuricus," and although the growth of knowledge has failed to substantiate some of the points in his original thesis, there remain many analogies between the condition we call "nephrosis" and the metabolic disorder named "diabetes mellitus." It would be a hard task even to-day to demonstrate that diabetes mellitus is a disease with a definite morbid anatomical picture; he would be a rash man who pretended to be able to prove that diabetes was purely a disease of the pancreas. But diabetes is nevertheless an entity which can be diagnosed with exactitude, in which an accurate prognosis can usually be given and which responds in a satisfactory manner to treatment.

The same criteria apply in large measure to nephrosis, and the morbid anatomist, who challenges the physician to establish the anatomical basis of nephrosis, should be reminded that modern medical science is possessed of minuter vision than that of the pathologist in the post-mortem room; were this not the case, we should be in almost complete ignorance when faced by such conditions as ketosis, undulant fever, alkaptonuria and a host of others.

The main facts concerning nephrosis may be summarized as follows—there is a group of clinical cases exhibiting constant albuminuria but with no blood or epithelial casts in the urine; the blood pressure is not raised nor is there hypertrophy of the heart or changes in the retinae to suggest any involvement of the cardio-vascular system. These cases tend to exhibit oedema often considerable in degree and of great chronicity. Blood analysis discloses a marked diminution of the plasma proteins, the albumin fraction being frequently even more diminished than the globulin fraction; the urea-content of the blood is unchanged. The prognosis of these cases is relatively good, the main threat to their lives being the risk of infection of the fluid in the subcutaneous tissues or peritoneum; some of them are said to recover completely.

When the conception of nephrosis was first formulated by Müller, Epstein, Munk, and Volhard and Fahr, much of the controversy which arose was occasioned by the inability of clinicians to make immediate distinction between the cases exhibiting the syndrome above described and a much more numerous group in which renal oedema occurs in the course of chronic glomerulo-nephritis and in which cardio-vascular changes and a tendency to gradual evolution towards renal failure are present. It had so long been recognized that the prognosis of such cases could not be considered in any way benign that many physicians were unwilling either to admit the existence of a benign group or to accept the much more generous diets which were advocated in the treatment of such a group.

Further controversy arose when Epstein expressed the belief that nephrosis was a general metabolic disorder without any serious renal lesion. Cases of nephrosis fulfilling all the clinical requirements necessary for inclusion in the group were so rare that post-mortem material, particularly in view of the relatively good prognosis, was exceedingly scarce. Controversy raged, and has continued to rage, as to whether cases of nephrosis showed any histological changes in the kidney or whether if such histological change existed, it was entirely confined to the renal tubules; Epstein used to contend that he could not produce pathological material because all the cases got well.

There was another school of pathologists, such as Bell, who maintained that although no histological change could be demonstrated in the glomeruli by ordinary methods, it could be shown to exist when special types of staining were employed. I think that to-day most of us who have given particular attention to the problem would agree that when an autopsy is carried out on a case of nephrosis the obvious renal changes are to be found in the tubules but that slight morbid change is usually to be found amongst the glomeruli as well, and that even if this is not present we must suppose that the glomeruli are functionally abnormal.

Such a conclusion seems to emerge inevitably from consideration of the origin of the albuminuria which is one of the cardinal features of nephrosis. Attempts to prove that the proteins in the urine are qualitatively different from those in normal blood have always broken down, and we are driven to the conclusion that the albumin must escape through the kidney. With equal certainty we are driven, by accepting the impossibility of such passage through the epithelium of the tubules, to the conclusion that it must pass through the glomerular filter, and this must carry with it the conclusion that the glomerular filter is abnormal. The testimony of Goværts, who has contributed so much to our knowledge of nephrosis and oedema, seems to me to be conclusive on this point.

It may be argued that if it is admitted that nephrosis has an anatomical basis, in the form of an abnormal glomerular filter, there remains no justification for separation of cases into this group as opposed to the group constituted by the victims of subacute or chronic glomerulo-nephritis. As a practising physician, I find such a view both narrow and academic; it seems to me as a physician called upon to treat disease and prophesy the outcome of disease with some exactitude, that it remains possible to pick out with useful precision a group of cases with renal oedema, or threatened with such oedema, in whom the prognosis is relatively good in that they are not threatened with uræmia or hypertension, and to treat such cases with a very good prospect of success. I think it is also possible in the majority of cases accurately to separate from these a very similar group in whom the prognosis is entirely different. To the first group the term "nephrosis" may still, I think, be properly applied.

In the following sections I have dealt with certain of the major aspects of nephrosis in greater detail. What I have written is based chiefly on personal experience, and I would emphasize that I have written with diffidence and without dogmatism because the cases are so rare, and each of them requires study over so many years, that no one man can claim experience of more than a few.

The Ætiology of Nephrosis.

It is of some importance to note that Munk, in writing of nephrosis, was dealing chiefly with syphilitic cases. Syphilis has become so rare a disease that many of us have never seen a case of secondary syphilitic nephritis. I have been told that they were characterized by an intense albuminuria and a tendency to oedema and that with treatment they made an excellent recovery.

In acute mercurial poisoning, such as follows the taking of mercuric sublimate with suicidal intent, an intense necrotic degeneration occurs, which is found on microscopic section to affect the tubules almost exclusively. The morbid anatomy therefore closely resembles what is seen in the kidney of a patient dying with nephrosis. But the clinical picture is entirely different as these patients exhibit suppression of urine and nitrogen retention, and oedema is usually absent.

My own experience of the ætiology of nephrosis is that there is none. The disease appears without explanation; some of my cases have been discovered during routine examination for life assurance; in others the appearance of œdema in a healthy person has led to the discovery of a heavy albuminuria. So impressed have I been by this that when I see a patient with renal œdema, a low blood pressure, and with all the main criteria of nephrosis, if there be a clear history of repeated sore throats, or of some other disease known as a frequent precursor of glomerulo-nephritis, I am always inclined to believe that before very long this case of "nephrosis" will begin to exhibit a rising blood pressure or other stigmata of chronic nephritis with its tendency to proceed towards uræmia.

The Clinical Features of Nephrosis.

On these it is scarcely necessary to dwell. Almost by definition there must be present a heavy albuminuria. Œdema is usually present or has been present in the past; it follows the usual course of a renal œdema, affecting the looser cellular tissues of the body, tending to show itself in the face simultaneously with its appearance in the lower limbs, readily forming a lumbar pad and often affecting the scrotum, particularly in children. When œdema is more severe anasarca is often present in the form of ascites and hydrothorax.

Cardiovascular manifestations are entirely absent, the blood pressure being quite normal or even lower than usual; the retinal fields are perfectly normal.

Biochemistry.

The biochemical findings are also very nearly normal, the exceptions being that the blood cholesterol is usually very high and the plasma proteins markedly diminished. The blood calcium is usually subnormal but not to the extent that is often found in uræmia, and I have never seen or heard of tetany developing in nephrosis.

The following figures give the typical findings of blood analysis in a case of nephrosis as compared with the normal:—

BLOOD ANALYSIS.

	<i>Normal.</i>	<i>Nephrosis.</i>
Urea ...	20-40 mgs. per 100 c.c.	20-30 mgs. per 100 c.c.
N.P.N. ...	20-40 " "	20-30 " "
Cholesterol ...	120-220 " "	250-500 " "
Calcium ...	9-11 " "	7-9 " "
<i>Plasma Proteins.</i>		
Albumin ...	5 g. per 100 c.c.	0.8-2.0 g. per 100 c.c.
Globulin ...	2.0-2.5 g. per 100 c.c.	2.0-2.5 g. per 100 c.c.
Fibrinogen	0.2 g. per 100 c.c.	0.4 g. per 100 c.c.

The Urine.

The urine contains large amounts of protein; many attempts have been made to show that such proteins are different from those found in other types of "albuminuria," but the balance of evidence remains that the albumin and globulin in the urine in nephrosis are indistinguishable from the proteins of the blood plasma. Stress was at one time laid on the fact that doubly-refractile lipoids are to be found in the urine in most cases; this is perfectly true, but it is

also well established that such lipoids are to be found in the urine from cases with chronic glomerulo-nephritis in the stage prior to the appearance of hypertension and renal failure; this applies also to the hyper-cholesterolæmia which is in no way confined to nephrosis but often equally marked in chronic glomerulo-nephritis with œdema. It is for this reason that I have long since abandoned the use of the term "lipoid nephrosis" because it seems misleading to suggest that lipæmia is essentially characteristic of nephrosis.

The Mechanism of Œdema-formation in Nephrosis.

The insistence of Epstein on diminution of the colloid oncotic pressure of the blood, as being the main determining factor in the production of œdema in nephrosis, was one of the important factors in bringing the conception of this condition prominently before the medical world. Prior to this the theory of Widal, who held that in such conditions renal damage was causing salt-retention, and that it was this which led to œdema, had held the field. To-day there are very few opponents of Epstein's theory; we may agree that other factors also come into play, but thanks to the work of Goværts and a number of others there is very general agreement that the loss of protein molecules from the plasma *via* the kidney is the direct cause of such depletion of colloids in the blood that there is a lowering of the capacity to hold water in the circulation and that fluid in consequence tends to lie stagnant in the tissue spaces. Diminution in the total amount of protein in the blood plasma is a very striking feature in all severe cases of nephrosis, and in milder cases one is often able to predict the onset of œdema with precision by noting the steady progressive diminution of these substances. It is notorious that the serum albumin is relatively more reduced than the serum globulin, not infrequently the globulin fraction is even higher than the albumin one (this is an important factor on the bio-physical side, the colloid oncotic pressure of the albumin molecule being very much higher than that of the globulin molecule).

The exact rôle of salt in the mechanism of renal œdema remains obscure; few would demur from the view of Fishberg and others that in nephrosis both water and salt tend to accumulate in the tissue spaces by a process of "pre-renal deviation"; the view of Widal, that the kidney by some alteration of its normal functions prevented the escape of chlorides, has no adherents to-day. But it remains indisputable that œdema can be to a large extent controlled by the withdrawal of salt, and it would seem proper to regard salt rather as a vehicle which, when present, enables large quantities of water to be retained outside the circulation.

The Course and Prognosis of Nephrosis.

It would perhaps be fair to say that if the term "nephrosis" is worthy of retention in medical nomenclature it is because the cases in this group carry a relatively benign prognosis in contrast to cases of established glomerulo-nephritis where the prognosis is bad. I see from time to time a few patients in whom nephrosis has been present for very long periods; one or two of these patients have been alive and well, with no disturbing factor other than an occasional mild œdema, for upwards of fifteen years; I have observed others who have exhibited an intense albuminuria year after year, and in whom the plasma proteins have often been notably diminished, but who have never developed a demonstrable œdema.

Cases of nephrosis with a considerable œdema present great difficulty in that it may be an arduous task to rid them of such œdema, and as long as it is present, particularly if there is much ascites, there is a risk that they may contract a low grade peritonitis or a spreading cellulitis which may kill them. Apart from this risk I have on several occasions seen death occur in nephrotic patients from what appeared to be a sudden syncopal attack. I have reported several such cases to the Association of Physicians of Great Britain and Ireland; they have occurred in patients who had recently been relieved of their œdema but who still exhibited a marked diminution in the plasma proteins but no obvious cardio-vascular manifestations; it seems possible that this little recognized cause of death in nephrosis may be due to the poor cardiac nutrition which probably occurs in any such impoverished state of the blood.

On the other hand, I have from time to time seen cases believed to be examples of nephrosis gradually become transformed, by the appearance of increasing hypertension and renal failure, into typical cases of latent or manifest uræmia; from which condition they have subsequently died. I have believed that in these cases my original diagnosis of nephrosis was incorrect, and in my experience it is usually in cases in whom the nephrotic state has been observed for not more than twelve or eighteen months that such a development occurs. In cases where a heavy albuminuria, with or without œdema, and without cardio-vascular manifestations, has been present for more than three years, I have never known hypertension and uræmia to supervene. It is very difficult to criticize the observations of others, but I cannot help feeling that much of the work which has been published with a view to establishing that nephrosis usually ends in the clinical picture of terminal glomerulo-nephritis is based on faulty initial inquiry and clinical observation.

It seems certain that a favourable prognosis in nephrosis can never be given without the closest and most critical questioning as to the patient's condition during the early months of his illness, and that it is indeed foolish to give anything like a favourable prognosis until the passage of time permits the observer to decide that there is no evidence of the graver forms of renal and cardio-vascular damage.

It has frequently been claimed, particularly by American observers, that cases of nephrosis can make a complete recovery including the total disappearance of albuminuria. The observations supporting this view are nearly always those made on children; my own experience is more with adults and amongst these I have never seen a heavy albuminuria of this type disappear completely.

The Treatment of Nephrosis.

If the prognosis of nephrosis supplies the most important basis for permitting the retention of the label, the treatment of nephrosis is the practical element which makes the condition of supreme interest to the practitioner. The high protein diets which Epstein advocated presented a revolution in the dietetics of renal œdema. Prior to this it had been customary to keep all cases of renal œdema on a régime containing the minimum possible amount of protein.

Before proceeding further with this aspect it is advisable to stress the fact that in practically all cases of œdema, and particularly in cases of nephrotic œdema, the elimination or reduction of salt in the diet is of even greater practical importance than the question of the optimum amount of protein. There can be no question but that in England we have been negligent in our attitude towards

low salt diets; dietetics is a fashionable subject which engages the curiosity of the layman and the pseudo-scientist even more than that of the medical practitioner; the popular press and the beauty parlours engage in friendly rivalry in an endeavour to be the first to propagate the latest fad, and publishers offer attractive rewards to anyone who will provide a new book on food in its relation to health. But it is somewhat remarkable that scarcely any of the numerous volumes published by the "dietitians" who are at present so noisy, deign to mention salt-free diets. In a case of nephrosis such a diet is essential whenever the concentration of the plasma proteins indicates the risk of oedema.

This is not the place to set out such a diet in detail, but it is as well to emphasize the fact that the first principle as regards a low salt diet is to forbid entirely the use of salt at table and at least to restrict its use in the kitchen. It is only when oedema is prominent that the restriction need be pressed to the extent of entirely forbidding the use of salt during the actual cooking. Other important points to bear in mind are that ordinary bread contains a considerable amount of salt and that milk is also not without danger in this respect; the unleavened bread obtainable in Jewish restaurants is of great value, being salt-free. There is no efficient substitute for salt from the gastronomic point of view, and many of the salt substitutes on the market contain sodium although chlorine has been eliminated. The most useful substitute is lemon juice and this may be used with meat and fish with great advantage.

Apart from salt-restriction the great dietetic indication in nephrosis is that protein should not be kept at too low a level. Some of the vegetable foods, such as lentils and peas, are of great value in this respect, and are articles of diet too frequently overlooked. Fat is traditionally kept on the low side because of the hypercholesterolaemia, but here again the restriction should not go beyond the avoidance of cream, oil and butter in excess.

The drugs employed in nephrosis are, in general, of a diuretic nature. Potassium citrate should be placed in the forefront, this salt not only has the benediction of experience, but may to-day be said to be of known value in that its administration assists in the replacement of sodium by potassium. The employment of massive doses of alkali, on the other hand, has not proved to be so valuable as certain workers claimed several years ago. I have myself given up this form of treatment almost entirely, having seen little if any good result from it.

When the oedema proves resistant, stronger diuretics may be used. Of these the first that should be employed is urea; this is unpleasant to take but the taste can to some extent be disguised by lemon juice and by administering it in capsules. It is scarcely necessary to say that careful observations of the blood chemistry should be made to confirm the absence of any degree of nitrogen retention.

If the above measures have failed salyrgan can be used, and I have on several occasions seen an excellent diuresis follow its employment. The evidence to-day goes to show that the action of salyrgan is on the kidney itself, and, if we accept the view that some damage to the kidney is present in all cases of nephrosis, we may not unnaturally hesitate to use a drug having a strong effect upon the renal epithelium; I can only record that I have never seen ill effects from its use, although I have not infrequently been disappointed at its failure to produce an increased secretion of urine, which is in strong contrast to the excellent effects usually seen when it is employed in cases of cardiac failure.

Unfortunately the most careful employment of all the measures indicated above is not infrequently attended by negative result; the patient is kept on a limited fluid intake with a most careful low-salt diet, potassium citrate is administered in appropriate amounts, urea or salyrgan are tried, but the œdema persists or perhaps increases. Knowing the constant danger which hangs over the patient with such an œdema the medical attendant begins to despair, and the patient and his friends become increasingly anxious. In such circumstances mechanical means should be employed and the œdema relieved by incisions in the legs or paracentesis of the abdomen. Southey's tubes are perhaps inferior to direct incision in that they carry a greater risk of local infection; the best method is to clean the skin with surgical spirit, and to make one or two straight incisions above the malleoli or over the subcutaneous surface of the tibiæ. If the fluid is particularly prominent in the abdomen it should be tapped in the usual way. In the majority of cases this procedure is followed by a reassuring improvement in renal secretion.

Conclusion.

Although the word "Nephrosis" remains a talisman to conjure controversy it is a valuable definition of a clinical state. The great danger attendant on its employment is that those unfamiliar with the real complexities of nephritis may use it to describe cases of chronic glomerulo-nephritis in which an attack of acute nephritis is followed by a long period of œdema which waxes and wanes, perhaps with recurrent attacks of the acute condition, and finally passes slowly into the terminal picture of Bright's disease. No great effort has been made in this essay to deal with this latter condition, but it is right that I should conclude by reiterating that not only is there an entire difference between the prognosis and treatment of the two conditions, but that it is a matter of extreme difficulty to select the cases of true nephrosis, with its relative benign prognosis, from those in which there has been severe and permanent renal damage with an onset so insidious that time may be the only factor which reveals the progressive nature of the disease.