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Lipoid nephrosis

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LIPOID NEPHROSIS

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INTRODUCTION

In 1905 Müller (71) brought forth the name "nephrosis" to differentiate the degenerative from the inflamatory lesions of the kidney. Since its original conception, the term nephrosis has been broken down to signify more specific types of kidney disease. These types include lipoid or pure nephrosis, febrile nephrosis, diabetic nephrosis, nephrosis of pregnancy and nephrosis of necrotizing origin such as found in heavy metal poisoning.

This paper will deal with the true or lipoid nephrosis. The other types of nephrosis mentioned above do not present the problems found in the pure nephrosis and they are more generally understood.

During the past 39 years, the disease has been investigated extensively as to its etiology, pathology, pathogenesis, clinical and laboratory findings and treatment. While none of these have been clarified to the satisfaction of all other investigators, the treatment of the disease has been the most difficult problem confronting the clinician. Because of these difficulties, this paper will deal principally with therapeutic problems of the disease. The other facts and findings of the disease will be presented to lay a foundation for the types of therapy.

DEFINITION AND ETIOLOGY

Lipoid nephrosis is a chronic disease of variable duration, characterized by massive edema, albuminuria and lipemia. It is a syndrome that exists without evidence of glomerulonephritis or amyloid disease.

The etiology of nephrosis is a problem which has never been satisfactorily explained.

Patients suffering with nephrosis have been examined thoroughly and repeatedly. Their histories have been checked and rechecked. In spite of all of this investigation, no definite points have been brought out which further throw light upon the complexity of the problem.

McElroy (67) believes that there are certain predisposing factors involved in the etiology of nephrosis. Of these factors, one of the foremost appears to be youth. Nephrosis is generally considered to be a disease of youth, and, in fact, its incidence in adults is rather rare. He also believes the diet to be a very important item, and states that the malnourished, frail individual is much more liable to have the disease than the healthy robust child. It appears, however, that a child in such a condition of malnourishment is not only predisposed to nephrosis, but also to many

other types of illnesses and diseases. A third factor brought forth by McElroy is that of constitutional inferiority. This condition, like that of malnutrition, may only indicate a decreased resistance to any type of illness.

Clausen (10) in 1925 presented his theory as to the definite etiological cause of nephrosis. He believed the disease to be the result of staphlococcus infection of the para-nasal sinuses. He also found that exacerbations of these infections were accompanied by an exaggeration of the symptoms of nephrosis. By the successful treatment of these infections, he found that improvement or cure of the nephrosis followed, whereas other types of therapy were of a temporary benefit only. Clausen went on to explain that the manner in which this was brought about was by the liberation of toxins from the foci of infection. Septicemia is not necessary. This liberated toxin acts upon the kidneys in such a manner that albuminuria ensues, followed by the other common clinical findings.

The method of action is explained by the fact that the toxins cause a decrease in the surface tension of the body fluids. He isolated this

substance and found it changes the permeability of both living and dead membranes. This surface tension lowering substance was found to disappear when the sinus infection had cleared up. Marriot (66) published results very similar to Clausens and substantiated them.

Davison and Salinger (12) were unable to get any demonstrable results from treating sinuses with traces of infections in patients with the nephrotic syndrome.

It seems that if the work of Clausen were as exacting and effective as he claims, it would be in much wider use today than it is. It is noticed that very little reference or attention is now given it by the more prominent investigators. In view of this, the conclusion must be drawn that para-nasal sinus infection is not the etiological cause of the disease in any appreciable number of cases.

Aside from the above mentioned work, little has been done to prove the etiology of nephrosis. The etiology is now, as it was when Müller first presented the name, nephrosis, still unknown. There has been a connection between nephrosis and syphilis brought forth. In some cases this may be the causitive

agent, but the actual cause in the vast majority of cases of nephrosis is at present obscure.

In incidence, nephrosis is a rare disease. Those working with renal diseases for years, and seeing many thousands of cases involving the kidneys, report very few cases of nephrosis. Leiter (57) states that the incidence is probably between 1 to 5 per cent of all patients with bilateral non-suppurative renal disease.

Age is important because the largest per cent of cases occur in children. Sex apparently has no effect upon the incidence or distribution of the disease.

CLINICAL PICTURE

The disease, nephrosis, presents a definite clinical picture. There are, however, a few of the more prominent findings which are very similar to findings in other diseases. The disease is most commonly confused with glomerulonephritis. Their similarities and differences will be discussed in another section.

The clinical picture is at this time a fairly well settled syndrome, and for that reason will only be given briefly that it may lead to a better understanding of those questions and problems which are still unexplained, and which will be discussed later.

Onset The onset of nephrosis is usually very insidious. The patient may feel weak, and tire very easily over a long period of time. The patient endures this usually, and pays little heed until the edema makes its appearance, at which time he consults his physician.

General Symptoms Following the symptoms of onset, the patient suffers general malaise, fatigubility, weakness, backache and headache. Some are free from symptoms other than edema. Undernutrition may develop, but may be masked by edema. Anorexia may

be present, and may be due to abdominal conditions such as ascites. Dyspnea too, may occur due to the accumulation of ascitic fluid in the pleural spaces. These patients also present a peculiar waxy pallor, but seldom have an anemia. In general, they are more comfortable than their appearance suggests.

Edema The most prominent and characteristic finding in nephrosis is edema. "Without edema there is no nephrosis". Leiter (57) As mentioned before, the symptom that leads the patient to consult his physician is edema. The edema, in the larger proportion of cases, usually appears very insidiously. It may spread slowly and progressively, or appear intermittently. The edema is nearly always a dependent type, appearing first in the feet and ankles. This progresses up the legs and thighs and to the scrotum or labia. The eyelids, cheeks and parotid region are usually effected early. This edema gives the face a waxy, white pallor. After a nights sleep the eyelids appear bluish-white. This is a pathognomonic appearance. The edema may, however, shift with position. In severe cases it may also involve the abdominal and thoracic wall, arms, hands, and scalp. Ascites and hydrothorax are also quite common.

The edema is also very persistant, and does not respond well to diuretics. The condition may remain stationary, or grow slightly worse for weeks or months. A peculiar factor regarding this edema is that it may dramatically, and for some unexplainable reason, suddenly be relieved by diuresis, and go down until the edema has disappeared. The cause for this is not known, and when certain therapeutic measures have just preceded it, it often leads to undue optimism.

Gainsbourgh (42) believed edema essential as the original symptom of the disease, but thought that it soon gave way to the more important cardiac signs and symptoms. It is apparent that he was in reality studying nephritis rather than nephrosis.

Albuminuria Albuminuria is as constant a finding in nephrosis as edema. As a rule the quantity of protein lost in the urine is very great. There is probably no other disease in which there is a greater loss of protein in the urine according to Fishberg (40). Bell (4) found up to fifty grams of protein per day in the urine of nephrotic patients. Hiller and coworkers (46) found this urinary protein to be largely albumin, usually over ninety per cent. It is thought that albuminuria probably precedes the edema for a

long period before the edema becomes evident. Albuminuria also is known to exist long after the edema has disappeared, and may even continue for years before remission occurs. After the edema is gone, and the albuminuria disappears, and remains so for a period of months; it is presumptive but not positive evidence that the disease has been cured or has spontaneously recovered.

Urinary Findings The urine in nephrosis is greatly diminished in volume when the edema is increasing, or during periods when edema is present and fluid restricted. The daily output for days at a time may not exceed 300 to 400 cc. As the edema decreases, the urinary volume increases.

The specific gravity of urine during these periods of oliguria is usually high and values of 1.040 are not uncommon. It is at this time usually a dirty brown color, and may have a heavy sediment on standing.

The examination of the urinary sediment usually reveals the presence of many casts of hyaline and epithelial type. The outstanding feature of the urinary sediment is the presence of a considerable amount of doubly refractile lipoids. These must be

determined by a polarizing device which is attached to the microscope, as otherwise, they cannot be distinguished from fat or may also pass for a cast. Leucocytes are usually found in the sediment, but not in great numbers. Contrary to inflammatory types of kidney disease, there are no or very few red blood cells found in the urinary sediment.

Blood The study of the blood in this disease reveals several characteristic findings. These changes involve the colloids, crystalloids, and lipoids of the blood. The loss of protein from the plasma, due to albuminuria, tends to cause compensatory changes in the proteins, fat and lipids of the plasma. The changes may be set forth as follows:

(1) Decrease in total blood protein, chiefly albumin, with inversion of albumin/globulin ratio.

(2) Decrease in colloidal osmotic pressure of plasma.

(3) Increase in erythrocyte sedimentation rate.

(4) Increase in fat and lipid concentration in the plasma.

(5) Relatively little change in blood crystalloids.

(6) Nitrogenous products of blood little effected.

The total protein content of the blood is usually greatly decreased as mentioned above. The proteins may decrease from a normal level of about 7 per cent to about 4 or 5 per cent, and often to 3 per cent or less in severe cases. This is mostly a decrease in the albumin fraction which may fall as low as one per cent. The globulin may show an absolute, as well as a relative increase. As a result of this, the albumin/globulin ratio which is usually 1.5 to 2.5 to one is inverted.

Epstein (17) pointed out that the colloidal osmotic pressure was markedly decreased in nephrosis. The relationship between the colloidal osmotic pressure and edema has been established by direct measurements.

Salomen (85) has shown that the sedimentation rate of red blood cells is increased in chronic nephrosis. This is probably a result of changes in plasma colloids. He has also shown that a relative rise in the globulin fraction is always accompanied by an increased sedimentation rate.

The blood serum of the nephrotic patient presents an almost milky picture. This appearance is due to the presence of fats in the blood. Chauffard (13)

first pointed out the presence of fats and cholesterol in the blood. Schwarz and Kohn (80) found a definite increase in fats and cholesterol in the blood in every one of 17 cases they followed. This finding was also confirmed by Lichtenstein and Epstein (58) in their study of 15 cases. The amount of increase has been found to be from 500 to 1000 mgm. per cent over the normal of 250 to 350 mgm. per cent. Schwarz and Kohn (82) found that as the serum protein decreased, there was usually an increase in serum cholesterol.

The change in inorganic constituents of the blood is relatively small. Kahn (49) found in a series of twelve cases that there was no great variation in calcium. In cases of quite evident decrease in serum protein, there was a slight decrease in calcium content in the blood. The potassium content was found to be remarkably constant.

The sodium chloride was likewise found to vary little from normal.

The inorganic phosphorus was determined in only two cases and found normal in both.

Kohn (54) and Salvesen and Linder (78) also made studies of serum electrolytes and found

them to be little affected. A normal acid-base balance was found, giving evidence of a normal renal function.

The non-protein nitrogen substances of the blood are uniformly within normal limits except during sudden increases in edema, when not enough urine is available to carry all these products away, and in sudden diuresis when the body is literally washed out. Blackman (6) states he has seen the levels at a low, normal and slightly elevated reading. These facts, together with renal function tests, tend to rule out the possibility of a renal insufficiency, complicating or interrelated with the process of this disease.

Blood Volume and Anemia Brown and Roundtree (8), after examining the blood in nephrosis, found that 50 per cent of the cases did not show any anemia, with the remainder showing only milder grades of anemia. In the non-anemic type the volume of plasma and blood were found to be normal. In cases with diminished hemoglobin and cell values, the volume of blood and plasma are increased. Schwarz and Kohn (80) also state that the anemia of this disease is of a very mild type if present. They say that it is only at the end of the disease that the hemoglobin

may fall below 50 per cent, and erythrocytes fall below three million. Wilbur and Brown (88) found only one case in 25 in which the red blood cells and hemoglobin values approached those of anemia.

Cardio-vascular System The cardio-vascular system in nephrosis is only to a very slight degree involved. Blackman (6) found rather widespread capillary damage which he believed due to edema not to mechanical injury. The heart shows no clinical evidence of enlargement, nor of any other abnormalities. There is not found an increase in blood pressure at any time during the course of this disease. Bell (4) states that if the blood pressure is over 140, systolic, it is not a true lipoid nephrosis. Eye ground examinations are negative, and the peripheral arteries are soft and pliable.

Renal Function Tests The renal function tests in nephrosis reveal that there is no impairment in uncomplicated cases. Hiller and co-workers (46) and Linder and co-workers (59) in conducting kidney tests, found normal concentration tests, normal phenosulphonphthalein outputs, normal acid-base balances in the blood. Emerson (22) found elevated urea clearances,

as did Blackfan and Davis (7). Emerson also found an increased inulin and diodrast clearance. Lyttle (63) found patients with nephrosis cleared plasma amino acids as quickly as normal controls. In view of the above findings, it appears that the kidney functions quite normally, and the question arises as to whether this is primarily a kidney disease, or a disturbance in protein-lipoid metabolism, a kind of lipoid-protein diabetes as Shapiro (84) believes.

Basal Metabolic Rate Epstein (23) found a lowered basal metabolic rate in 60 per cent of people with nephrosis. He used the surface area standard of DuBois with the height-weight form. When edema was present, the weight used was that just preceding its formation or just following its elimination. Farr (28) also found a decreased basal metabolic rate and used the DuBois formula but used the ideal weight per age and height in his calculations. Hiller and associates (47) had similar findings.

Course The course of nephrosis may be long or short, and it may be smooth or complicated. Davison and Salinger (12) have found the disease to last from two to thirty six months with an average of eight. Nephrosis may go along with massive edema and present

the clinical picture for months on end, and then diuresis may suddenly set in, as mentioned before, and the patient may be edema free for another period of months. An exacerbation may occur at any time, and then another remission may occur. It is truly a chronic disease. During periods of remission, the patient may appear to be only skin and bones, and may present a serious malnutrition problem. Other cases, after clearing up, may be up and around and carry on in an almost normal manner. As a rule, some degree of albuminuria persists for many months.

Emerson and Van Slyke (23) describe a peculiar occurrence during the course of the disease which they call a "nephrotic crisis". This is the occurrence of an acute febrile episode with symptoms of peritonitis. The attack may take place without warning, and with dramatic suddenness. It is ushered in by an abrupt rise in temperature which may go up as high as 106°F. in three to four hours, and is often accompanied by a chill. There is always a general abdominal pain, some rigidity, nausea, vomiting, distention and prostration. They may have grunting on expiration, and there is an increase in pallor. The leucocyte count may rise to 20,000 to 40,000.

Blood cultures frequently reveal pathogenic organisms. The attack usually lasts about 36 to 48 hours, and may leave as abruptly as it came. Death often occurs as a result of the crisis in about 10 days to two weeks.

Farr (30) made a study of the nephrotic crisis, and correlated blood findings with its onset and duration. He found that for several days preceding the onset of the crisis there was an increase in the loss of urinary non-protein nitrogen causing a negative nitrogen balance. There was also a decrease in albumin in plasma to about 1 per cent or lower. The plasma amino acids were studied by Farr and MacFayden (33) who found that a chronic deficit in plasma amino acids often accompanies the disease. The normal amino acid level was found to be over 5 mgm. per cent. They found the level to be about 3 to 4 mgm. per cent in nephrotic children. They state that with a decline of plasma amino acids to a level of 2.5 mgm. per cent or less, the patient suffered with a nephrotic crisis. Recovery is accompanied by a rise in amino acid blood values. As the severity of the crisis is roughly proportional to the decrease in plasma amino acid level,

recovery is roughly proportional to their rise toward normal. These changes occur simultaneously.

Complications Of the complications of nephrosis, pneumococcal peritonitis is probably the most frequent and the most serious. The chief clinical features are abdominal pain and vomiting. Diarrhea is often present. Distention may occur. There may be an accompanying upper respiratory disease. Farr and co-workers (32) also found a hypoaminoacidemia in this complication, and stated that their blood level decreased in proportion to its acuteness and increased as it improved. Pahmer (75) found that in his series, the longer the patient had suffered from nephrosis, the greater his resistance to this type of complication. In spite of this he found a mortality of about 76 per cent in patients with nephrosis. In addition to the usual therapeutic measures, serum or chemotherapy must be given and sometimes surgery and drainage. The cause of this complication is not known, but theories have been expressed that infection reaches the abdomen by the blood stream, gastrointestinal tract, lymphatics and possibly by the vaginal route in girls.

Schwarz and Kohn (81) in a study of many cases, saw

and to respiratory disease of various types and severity. Death occurs quite often after nephrotic crisis unless appropriate measures are taken. Death does not occur because of impaired renal function or uremia.

PATHOLOGY

The pathology of nephrosis has been the point around which much of the controversy has waged as to the definitness of nephrosis as a disease entity. Some authors have described the kidney of what they termed nephrosis, but which was in reality not the pure nephrosis. Fahr (24) in an extensive study of the pathological anatomy of the disease has contributed much to our present day understanding.

According to Fahr, the kidneys are the only organs of the body showing significant changes in spite of evidence that the disease may be more widespread and generalized in nature. Shapiro (84), on the other hand, believes the liver to be involved, because of changes in protein metabolism, water imbalance, and decreased anti-bacterial activity by blood serum in nephrosis.

Kidney Grossly--The kidneys are usually normal or moderately enlarged in size, although Bell (4) records kidneys which weigh up to 812 grams per pair. The kidney capsule strips readily, and leaves a smooth yellowish to greyish surface upon which the stellate venules stand out conspicuously. On cut section the cortex is widened and the same color

as the surface, while the pyramids are deep brown. The gross appearance is quite characteristic, but is not diagnostic.

Microscopic--It is upon the microscopic picture that the basis of the diagnosis of nephrosis is made. The convoluted tubules offer the greatest degree of variation from the normal. The proximal convoluted tubules are involved to the greatest degree, and may show all degrees of degeneration from slight cloudiness to complete necrosis. The distal convoluted tubules and loops of Henle are to a less extent affected and the collecting tubules are but little affected. A prominent feature, to be seen, is the desqumation of cells into the lumen of the tubule. Some parts of the tubule may be quite seriously affected, while other parts remain quite normal in appearance. In areas where marked degeneration is occurring, there are also evidences of regeneration in the form of a lining of flat, endothelioid cells. Many hyaline casts are found, chiefly in the loops of Henle and in the collecting tubules. Fahr also states that doubly refracting lipoid bodies are found in the tubules. Wolback and Blackfan (89) state that fat is a conspicuous feature in the tubular epithelium,

but is not doubly refractile, as found in the patients urine. Fuller (41) found that a histological diagnosis of nephrosis cannot be made on the finding of lipoid deposits in the kidney. He found the highest incidence of lipoids found in the kidney to be associated with evidence of inflammatory or degenerative changes in the glomeruli.

Fahr (25) found after careful examination, that there were some slight changes in the glomeruli. There was some widening and thicking of the capillary loops in some glomeruli. There were also some fatty or lipoid drops in the glomerular endo- and epithelium with swelling of the parietal cells of the capsule. Stolz (86) reported the presence of polymorphonuclear leucocytes in many of the glomeruli. Bell (4) found that sections appearing normal with hematoxylin and eosin can be shown to have definite abnormalities when stained with anilin blue. The capillaries are laden with swollen endothelial cells heavily laden with lipoid droplets and corresponding with clinical glomerulonephritis except for the absence of hyaline fibers in the capillaries. Some glomeruli showed increases in endothelium and a patchy thickening of the basement membrane. It is thought that these above cases however, were

probably not pure lipoid nephrosis, but a form of nephrotic glomerulonephritis, although proof is lacking. This is given to show that even the most prominent of pathologists are not sure whether they are describing nephrosis or chronic glomerulonephritis. Lohlein (62) after examining glomeruli in this disease, found no changes which resembled recent, or old pictures of glomerulonephritis.

Murphy and co-workers (72) found that early in the disease no glomerular disturbances were found. In later stages, however, changes in the basement membrane, the capillary endothelial cells and epithelial cells of the glomerulus occured. This involvement was not uniform and was not of the same nature as the lesion seen in glomerulonephritis. Shapiro (84) found the glomeruli of kidneys in nephrosis to be entirely normal. Schwarz, Kohn and Weiner (83) found the glomeruli to be normal and believed the disease to be a distinct entity. It is now most commonly believed that the glomeruli show little if any change and what changes that may be present are not those found in glomerulonephritis. Hitzrot (48) substantiates these views.

The arteries and arterioles do not show any pathological changes in this disease.

Shapiro (84) states that the most characteristic change in the nephrotic kidney is the reaction of the interstitial tissue. The sessile histiocytes of the stroma proliferate. These cells draw in their branches, swell up and become packed with singly and doubly refractile lipoid. These cells serve as waste piles in the slow epithelial cell exhaustion. He believes it to be the most definite and positive histological criterion of nephrosis. Other cells of the reticulo-endothelial system also show singly and doubly refractile lipoids. Wolback and Blackfan (89) also describe the presence of many small cicatrices which were probably the end result of a previously necrosed tubule. It was thought that this complete healing occured during remissions as the patient had had the disease over a long period of time. It is conceivable that should this occur over a long enough period of time it would eventually lead to a disarrangement in the normal kidney structure and possibly to a contracted kidney.

Wolback and Blackfan (89) also report that they found definite changes in the thyroid gland. They

found absence of colloid, atrophy and desquamation of the epithelial cells and extreme vascular engorgement. These changes may have followed excessive functional performance. It is the writers opinion that it occured at the same time and is associated with tubular degeneration. This may be true in light of the fact that the basal matabolic rate is often low during the course of the disease and the gland may be overworked in an attempt to maintain a normal basal rate. More investigation, however, is required as to the thyroids relationship with nephrosis.

Liver--The above workers also found the liver worthy of consideration in this disease. There was rather uniform increase in liver weight, which they thought due to engorgement of the sinusoids. The parenchyma cells of the liver were reduced in size in all cases. Other findings were changes in staining properties, fine vacuolization of cells, and granular debris. Shapiro (84) also found the presence of fatty degeneration and cloudy swelling in liver cells. As he has pointed out, certain metabolic changes in the disease indicate the possibility of the liver playing a more important role than hitherto thought.

PATHOGENESIS

The pathogenesis of nephrosis is rather complex and involves an analysis of the pathogenesis of the various symptoms found in the disease. The symptoms and signs involved, and which we will discuss here, are albuminuria, changes in plasma protein, edema, oliguria, hypercholesterolemia, lipoid deposits in cells, and lowered basal metabolic rate.

The pathogenesis of the above mentioned conditions are each very involved and lengthy if one were to go into them thoroughly. Because of this fact, and because the emphasis of this paper is to be placed on treatment, the following section will not be a complete discussion of the problems, but the ideas most prevalent at the present time.

Albuminuria Albuminuria, as stated before, is one of the principle findings of this disease. The question has come up as to whether the proteins in the urine were the same as in the serum, or were they in the urine as a result of some changes they had undergone during the course of the disease. Elwyn (14) states that proteins found in urine are identical with proteins found in the blood, serum albumin and serum globulin.

Linder and associates (59) and Hiller and co-workers (46) working with the proteins found in urine, found that 85 to 95 per cent of the urinary protein was albumin; the remaining 5 to 15 per cent being globulin. This would give an albumin/globulin ratio of 5 to 20 to one. In the majority of cases the ratio was greater than ten. These workers also noted that this differed considerably from the findings in nephritis, where the ratio falls between 2 to 5 and one, and where the globulin excreted was much increased.

The escape of proteins from the blood serum to urine is believed to be through the glomerular membrane of the kidneys. The reason for the loss is unknown in the absence of any inflammatory disease, unless it could have some relation to the surface tension lowering substance which Clausen (10) explained was from bacterial toxins from infection. His explanations, however, have not been widely accepted by subsequent workers.

The reason for the larger amounts of albumin escaping, as compared with globulin, is believed to be due to the fact that there is a difference in their molecular size. The albumin molecule is smaller

than the globulin molecule and as a consequence it escapes easier and in larger numbers.

In analysis, we find the first serious consideration to be the loss of serum proteins through the kidneys.

Plasma proteins As a result of continued proteinuria, the plasma content of protein falls. The normal levels for plasma protein are from 5 to 7 grams per cent. Epstein (15) studying patients with nephrosis found the plasma proteins to be from 2.73 to 5.12 grams per cent with the albumin/globulin ratios 0.133 to 0.80. His results were widely confirmed. Schwarz and Kohn (80) found serum protein values between 4 and 6 per cent in a series of nephrotic children. Linder and his associates (59) found that plasma levels ranged from 3.5 to 5.5 grams per cent, but found that the patients still had normal plasma volumes. This proved that plasma proteins were absolutely diminished in amount, as well as concentration per given volume. With these facts, it was definitely proved that there was a direct relationship between the albuminuria of nephrosis and the reduction of plasma proteins. Linder and co-workers (59) found low plasma protein figures

when the output of protein in the urine reached one gram or more; and when albuminuria decreased to a trace, the plasma proteins rose to almost 7 grams per cent.

Another factor to be regarded in relation to plasma proteins is the presence of an absolute, as well as relative increase in the globulin fraction. It is believed this is due to an effort by the body to compensate for such a large loss of plasma protein. Elwyn (14)

There is like-wise some loss of plasma proteins in the transudates. This is very small in comparison with that lost in the urine, but the two seem to account for the levels found in the blood plasma.

Edema The edema of nephrosis is peculiar in that it does not appear to be of renal origin in the sense of salt and fluid retention or insufficiency, nor is it similar to cardiac edema. This agrees with the findings of normal renal function, and negative findings in the cardio-vascular system.

Epstein (17) believed that the continual loss of albumin in urine caused a decrease in the osmotic pressure of the blood, with a resultant absorbtion of fluids by the tissues, due to an inability to

counterbalance the hydrostatic pressure in the capillaries. Thus, more fluid was pushed into the tissues than pulled back by the osmotic effect of the plasma proteins. His theory was later substantiated by the findings of the capillary blood pressure to be 150 mm. of water, while the colloidal osmotic pressure was only 100 mm. of water compared with a normal of 450 mm. of water. The work was followed up with many similar findings, and in spite of small variations here and there it was quite generally conceded that the total osmotic pressure of the serum proteins is markedly reduced in nephrotic edema and in relation to the low plasma proteins. According to Leiter (56) who found that the surface tension tended to decrease, the capillary permiability tended to increase helping cause the edema. Leiter (57) also states that the fall in osmotic pressure was out of proportion to the fall of total serum proteins. This was later explained by the fact that the larger proportion of protein lost was albumin, and that albumin because of its smaller molecular size had a higher osmotic pressure per gram of protein.

It is thus concluded, from this brief summary, that the edema is due to loss of plasma proteins

in the urine with a consequent decrease in plasma osmotic pressure.

Oliguria The cause of oliguria in nephrosis is not definite, but it is thought to be, according to Elwyn (14), a compensatory mechanism. The body decreases the amount of urine output, and thereby reduces the amount of protein lost.

Lipemia The term lipoid nephrosis arose from the fact that there was a great increase in the amount of lipids in the blood stream as well as lipoid droplets in the kidney and urine. The lipids in the blood stream, upon examination, have proved to be, for the most part, cholesterol and cholesterol esters. Epstein (19) found a case in which the blood cholesterol was over 1200 mgm. per cent. It is also of note that in spite of this high level in the blood, there is not an abnormal increase in the urine in most cases.

Epstein (16) in 1917 was of the opinion that the lipemia appeared in a manner similar to that of diabetes. He believed it was due to non-utilization of lipoids from the food, and from break down of the tissues due to under nutrition. In 1922, Epstein (19) and Page and Farr (74) were all of the opinion that the fat in the diet had no effect upon the

lipemia. Epstein, in the same article, believed that the degree of hypercholesterolemia was an index to the severity of the disease.

Hiller and co-workers (47) after studying diets in cases of nephrosis, thought that lipemia was a disturbed mechanism for the transfer of fat from the blood to tissue depots. This would tend to suggest that the liver was incapable of carrying on its work.

Fishberg (39) believed that lipids were mobilized in the blood stream to off-set protein decreases, and by so doing to retain the plasma osmotic pressure and prevent edema.

Fishberg (38) found that by bleeding a rabbit and decreasing protein content of the blood, the osmotic pressure would be lowered and a lipemia would result. He believed the lipemia to come from fat deposits. He also believed it helped retain the osmotic pressure in bled rabbits.

The above work represents many experiments that have been carried out, mostly with diets, and at present it is believed the most probable cause of lipemia is a disturbance in the transfer of fat from the blood stream to the fat deposits found over the body.

Low basal metabolic rate Epstein found the basal metabolic rates, by methods explained previously, to be lower than normal in about 60 per cent of patients with nephrosis. Hiller and coworkers (47) and Farr (28) reported similar findings. The cause of this is obscure. Under nutrition has been advanced as one cause. Moschowitz (70) believes the low basal rate to be due to the edema which acts like a suit of clothes and prevents dissipation of body heat. Epstein (31) brought forth a relationship between nephrosis and hypothyroidism, and at the same time advocated thyroid therapy. It must be remembered that this is not a necessary and constant finding in the disease, and for that reason theories involving it must be limited to the individual type or case, not to the disease as a whole, and it must not be considered as part of the regular pathogenesis. It is known that metabolic changes similar to this may occur in debilitating diseases associated with under nutrition and prolonged bed rest. It would seem that the lower basal rate may be only a secondary involvement of the disease due to these above mentioned factors rather than a primary element of the disease.

Elwyn (14) has a theory of pathogenesis that differs somewhat from the above theories. He believes that the albuminuria is to some extent compensated for by the oliguria to cut down the proteins lost in the urine. He believes the absolute increase in globulin is to compensate for the loss of albumin from the plasma. He thinks the edema is due to an effort on the part of the organism to maintain a normal blood volume. He explains this by the fact that the blood volume must be kept constant by either the kidneys or the tissues, and as the kidneys have decreased their output to conserve albumin, the tissues must necessarily take up the excess which soon results in edema. He disclaims the more commonly held theories by the fact, that varying states of edema, and even absence of edema, may occur in spite of low plasma proteins. He goes on to state that the transudates contain about 0.1 per cent of proteins or less. He believes this to be due to a regulative mechanism to conserve to proteins in the blood stream. This mechanism is the increased contraction of capillary walls which tends to withstand the passage of protein, letting only fluids and salts pass through. This contraction would also explain the marked pallor

in these patients which has been found not to be due to anemia. As a result of the contraction of the capillaries, the tissues receive less blood and less nourishment and oxygen. This decrease in oxygen and nourishment will lead to starvation of the tissues, and consequently to a decrease in the basal metabolic rate, loss of weight and lessened resistance to infection. The dimunition of oxygen also causes a decrease in intracellular oxidation which leads to lipoid deposits. Cells are unable to completely utilize the nutritive supply and and lipoids appear in the blood.

While Elwyn's theory has some convincing ideas, it is not widely accepted in view of the much greater amount of work done and substantiated along other lines.

In summarizing this brief account of pathogenesis, it must be stated that, in spite of the fact, that most of the problems have been worked out to a fairly satisfactory and acceptable solution, much more work and investigation needs to be done before we have the true picture of the pathogenesis of the disease as a whole.

NEPHROSIS AND NEPHRITIS

Since its conception in 1905, the term nephrosis, has been the subject of controversy in the medical world as to whether it, in itself, was a distinct clinical entity, or whether it was a manifestation of glomerulonephritis.

Nephrosis and glomerulonephritis are alike clinically in that each has some degree of edema, albuminuria and lipemia, to such an extent that it is almost impossible, at times, to differentiate one from another. The edema of both is similar in pathogenesis, as far as can be determined in either case. The loss of kidney power to excrete nitrogenous wastes and the presence of hematuria are the chief differences in the two diseases. They are often similar to such a degree that it is only possible to differentiate by necropsy reports. As stated previously, the pathology of nephrosis is chiefly in the tubules and parenchyma; whereas, the pathology of nephritis lies in the glomeruli. It is generally concluded that the disease must be observed over long periods of time in these cases before a definite diagnosis can be made.

With these facts in mind, many investigators have decided in favor of nephrosis as an entity. Murphy and Warfield (72) after observing cases from beginning to end, and after necropsy reports, state that it is a definite entity involving tubular degeneration, and can occur without any glomerular lesion. Bell (5) gives a classification of the nephritides in which he includes lipoid nephrosis under chronic glomerulonephritis, because the kidneys are large, and there are abundant lipoid droplets in the tubules. He says that the glomeruli are supposed to be normal, but reports they are not when stained with his special anilin dye. In all probability the majority of cases he studied were of chronic glomerulonephritis although it is not possible state for sure.

Shapiro (84) deviates widely from the accepted views in explaining why nephrosis is a separate disease entity. He states that it is not primarily a kidney disease, but a disturbance in protein-lipoid metabolism. The kidney is involved only because of its role of an active excretory organ for the products of this disturbed metabolism. He believes renal changes start with hyper-activity

of renal epithelium. This proceeds slowly to exhaustion, atrophy and degeneration of the tubule cells.

In spite of conflicting views on the subject, most of which are ten or fifteen years old, it now appears that nephrosis exists as such. It must be remembered that nephritis is a much more common disease and therefore, must be carefully ruled out before a definite diagnosis of nephrosis is made.

TREATMENT

The treatment of nephrosis leaves much to be desired. Many and varied methods of therapy have been applied to the disease. Some have treated symptoms, others have treated what they thought was the basis of the symptoms. In the forty years since the disease was first described as an entity, no definite therapeutic regime has been advocated and widely accepted as the correct one. As a consequence our present day trends are to relieve symptoms and to promote the better general well being in the patient, so that nature itself may act more efficiently and may proceed to effect a recovery, which a large proportion of patients may now expect.

The general principles of treatment of this disease are similar to those of any long standing chronic disease. The first consideration is to bring about the best possible physical well being of the patient and to be sure that no harm is being effected by the type of treatment being used.

In the patient who is suffering only mildly from the disease, i.e. slight edema of the ankles,

at the end of day or who is disabled only slightly, the major objectives are to build up the resistance to infection, and treat malnourishment. He is allowed moderate activity and a normal diet. He should, however, be under regular scrutiny.

It is with the patient who has the more acute symptoms and complications of the disease that more strict and definite measures are taken. As has been previously stated, there exists a copious albuminuria in this disease. These patients, as a result, need protein to replace that lost in the urine in addition to that protein broken down in tissue metabolism. These losses may amount to 20 to 30 grams per day for month after month. Epstein (18) seeing this depletion of body protein, and knowing that plasma contains less protein as a result, and very probably causing edema, deviated from the ancient rule of decreasing protein in the diet in renal disease. He advocated a high protein diet, stating that it would increase plasma protein. In addition to high protein intake, he advocated an almost total exclusion of fats and a minimum of carbohydrates. He restricted fluids to 1200-1500 cc. per day, and allowed salt only to palatability. This diet

provided for protein 120 to 240 grams; fat 20 to 40 grams; and carbohydrate 150 to 300 grams per day. In connection with this he also advised phlebotomy and transfusion of normal blood. Epstein (20) published further studies along the same lines, and substantiated his results in 1922.

This form of treatment was quite revolutionary as far as renal diseases go, and was put to test almost immediately by other clinicians.

Wordley (90) stated that he found variations in the amount of protein in the diet have no effect on the amount of protein excreted in the urine. Increases in protein do not increase albuminuria and may decrease it relatively owing to diuresis produced by rich protein diets.

Aldrich (1) and Schwarz and Kohn (80) reported that they could find no instance of favorable effects upon edema, but added that patients looked and acted better on high protein diets.

McLean and Wessel (68) claimed that a rich protein diet did not increase the plasma proteins, but that some beneficial effect was received in that the urea content of the blood was raised thus helping induce a diuresis.

These reports seemed to show that a high protein diet, while not a cure for the disease, was a definite advance in treatment, and soon it was under more widespread use and observation.

Peters and Bulger (76), after careful metabolic studies, concluded that patients actually suffer from protein starvation, and that if more than enough protein is given to replace the amount lost in the urine, they would store the excess within certain limits. In this manner, some of the effects of the previous nitrogen wastage were repaired.

In spite of many reports stating that the plasma protein level was not changed, and therefore the edema was not effected, Fishberg (40) has had cases in which the edema was diminished greatly while on high protein diet in spite of the fact that the plasma proteins did not change appreciably. He also noted cases in which plasma protein was increased with high protein diets following periods of protein starvation.

The protein diet has been incorporated in almost every dietary regimen, and even if it does not act dramatically, it is generally accepted as of some beneficial effect and tends to alliviate the patients critical condition. One must be sure, however, that

there is no kidney damage, and that renal function is intact before proceeding with the high protein diet.

Liu and Chu (61) found in 1935 that the maximum protein storage was obtained on a diet with 2.5 grams of protein per kilogram of body weight for children, and 1.8 grams per kilogram of body weight most satisfactory in adults.

This led to more investigation regarding the nitrogen balance in nephrotic patients. Farr (29) (34) found that to avoid a negative nitrogen balance in children, their daily protein ration should contain more than 2.5 grams per kilogram of ideal body weight. He also stressed that protein intake should not exceed 3.0 grams per kilogram to gain the maximum retention. He concluded the caloric intake, when increased, had little effect upon the assimilation of nitrogen.

The ideal diet for patients with the nephrotic syndrome is, therefore, one rich in protein containing 2.5 to 3.0 grams per kilogram of ideal weight for children and about 1.8 grams per kilogram for adults. It is rich in energy but poor in salt and water. Keith and associates (51) have also found that diets low in mineral and water content

are both practical and effective in treatment of edema and ascites. In view of the fact that diets high in protein are sometimes apt to grow tiresome with children, this diet by Keith may be substituted from time to time for variety.

In addition to diet, there have been many medicinal measures taken for the alleviation and treatment of this disease.

An effort was made to find a diuretic that would satisfactorily relieve the edema of this disease. As a consequence, many and varied types of diuretics were brought forth and advocated.

Thyroid treatment was first advocated and brought into use by Epstein (19) (20) in 1926. He was directed by the fact that there is an associated lowering of the basal metabolic rate in many cases of nephrosis. He also noted a similarity between the clinical pictures of myxedema and chronic nephrosis. He believed that if the lowered rate could be increased, through stimulation of protein metabolism, the bodily mechanisms would also act more efficiently and a resultant diuresis would occur. After administration, he found that patients with nephrosis had enormous tolerance for thyroid, and rarely

exhibited toxic symptoms or elevation of the basal metabolic rate as long as lipemia was present. His results after administering thyroid extract, were a dimunition in albuminuria, and the production of diuresis with a consequent decrease in edema and a reduction in lipemia. They thyroid was given in conjunction with his high protein diet. He started with small doses, one half to one grain given three times per day. As a rule, larger doses are required, and the dosage may be increased until daily doses of 15 grains are given. If this fails, the dosage may be doubled and given for 5 to 7 days. If this too fails, thyroxin may be given. Thyroxin may be given intravenously with an initial dose of 5 to 10 mgm., and repeated at intervals of 5 to 10 days until definite effects are observed. His guide to treatment is the degree of lipemia of the blood. As long as a hypercholesterolemia exists, it may be given without fear. He states that it may take up to a year to bring about a cure.

Liu (60) a year later achieved results which confirmed Epstein's findings.

Davison and Salinger (12) after using thyroid, report that edema is decreased, but the effect of

such is only transitory. It may be that they did not continue their therapy over a long enough period of time.

Schwarz and Kohn (82) followed Epstein's methods and concluded that the patient was helped by the high protein diet, but did not agree that the thyroid was beneficial.

In summarizing the value of thyroid therapy, it cannot be stated that it will positively bring about a cure, but it is pretty generally accepted that some benefits are to be received. It should be remembered that in cases that stubbornly resist therapeutic and dietary measures might derive some benefit from thyroid therapy.

Urea has been used to good results in cases of nephrotic edema by Wordley (91) It is not effective in all cases but sometimes patients may be kept edema free for long periods of time by its administration. Some believe that the helpful effect of the high protein diet is due to the formation of urea and consequent diuresis. Urea must be given in large doses, 20 to 100 grams per day. The diuresis usually takes several days to a week to appear, and is of a moderate degree. It ceases, however, whenever the urea is discontinued.

The purine diuretics are generally useless in the nephrotic type of edema.

Saline diuretics likewise have little effect on this type of edema.

Acid forming diuretics, calcium chloride, ammonium chloride, ammonium nitrate and similar substances may be given by mouth in doses varying from 5 to 20 grams daily. They may lead to a definite diuresis, but their effect is usually not prolonged.

Keith, Barrier and Whelan (50) showed that with carefully controlled low salt diets and adequate ammonium chloride followed by novursal, the immediate results were satisfactory, but the three must all be combined. The results obtained were better than any previously reached. They also found sodium to be secreted in increased amounts. In follow up articles Keith and Whelan (51) (52) substantiated their findings with the above treatment, and stated it could effectively be followed over a long period of time with good results.

Other mercurials such as salyrgan and mercupurin often produce copious diuresis in chronic nephrosis. They too work best after producing diuresis with some acid forming salt as mentioned above. In most cases

there seems to be little danger connected with the use of these diuretics. Fishberg (40) states that he has seen increased proteinuria and the appearance of red blood cells in the sediment after their administration.

Another type of treatment was advanced wherein the objective was to raise the colloidal osmotic pressure of the blood stream. To bring this about a colloid, acacia, was injected in the blood stream. It was thought that by increasing the colloidal osmotic pressure, fluids could be drawn from the tissues into the blood stream and thus eliminated by the kidneys. Clausen first used it in 1920, but his results were not satisfactory and it is believed he used inadequate amounts. Hartmann and associates (45) administered acacia in amounts sufficient to raise the osmotic pressure of the plasma from a level of 12 to 15 cm. of water to a level of 21 to 23 cm. of water. This was still considerably below the normal level of 30 to 35 cm. of water but they found that if administered long enough, the edema would completely reside. The amount given was 1 gram per kilogram, of a 2 per cent solution of acacia, in plasma solution until the desired osmotic

pressure is obtained. They found that 25 per cent was lost in 2 days, and 60 per cent in seven days. They produced satisfactory results in 5 out of 6 cases.

Goudsmit and Binger (43) received good results by using intravenous acacia solution in conjunction with oral potassium nitrate which they thought increased the sodium chloride output. This type of treatment was given in conjunction with a high protein diet and limitation of sodium chloride.

Two years after Hartmann's work, Dick and coworkers (13) found that acacia had only a transient effect upon the edema. They found that continual use led to a marked lowering of the serum protein, and to development of an enlarged tender liver. When acacia is discontinued, the serum protein tends to remain low. Later at necropsy, they found deposits of acacia in the liver, bone marrow, lymph nodes, lungs, kidneys and spleen.

Landis (55) believed in giving acacia in daily doses of not more than 30 grams up to 180 grams, and accompanied by a low fluid intake and rigid salt restriction. He found no deleterious actions. He states, however, that the effect is only symptomatic,

and should be given only in the absence of complications. It should be tried after other measures have failed.

Studdiford (87) found liver damage in some cases after acacia administration. He also thought that acacia may interfere with the gaseous interchanges of the red blood cells, and may as a consequence give severe anoxemia.

It appears from the forgoing, that the use of acacia is not advisable, and may be linked with serious consequences. This was further emphasized by the findings of Falkenstein and Jackson (26) who found considerable amounts of acacia in parenchymatous tissue six years after its intravenous administration. During this six year period the patient was unable to raise the serum protein to a normal level. He concluded that acacia seems to hinder protein synthesis, possibly because of its residual action on the liver. He also believes this interference with serum protein greatly outweighs the transitory benefit resulting from its use.

In view of this work and also Yuile's (91) work with intravenous injections of acacia in dogs, which showed a lowered plasma protein level which

remained low, it would appear that acacia is not the treatment of choice in attempting to alleviate the edema. If it is true that these detrimental effects usually occur, acacia should be discarded as an effective means of treatment of nephrosis.

Aldrich and co-workers (2) have treated nephrosis by the intravenous injection of concentrated human blood serum. They used the Flosdorf and Mudd lyophile process to concentrate the human serum five times. They injected this solution very slowly, not more than 5 cc. per minute, and not more than 80 cc. at one time. In six of nine patients they had complete and immediate diuresis, incomplete diuresis in one case, and failure in two. In 1940 Aldrich and Boyle (3) using a 4 times concentrated human blood serum solution, found diuresis usually occured and went on to complete elimination of edema fluid, and as a rule, went on to complete recovery. They believe it should be used at the earliest possible time, and not as a last resort. If other results will substantiate this, it will be one of the most effective measures of treatment we have. They caution, however, that it is of no good in the presence of acute infection.

Keith and workers (53) have tried the use of redissolved dried blood plasma intravenously. It did not always cause diuresis, but a satisfactory response is to be expected when the loss of serum protein in the urine is small. They do not know the manner in which benefits are derived, but advise its use when other therapeutic measures fail. It is possible that it acts by increasing osmotic pressure in the blood stream.

The use of pectin solution, which had the same viscosity and osmotic pressure as blood, has been tried in surgery, and its users suggest that it may be of value in nephrosis. No work has yet been done on this. Hartman (44)

Major and Helwig (64) and Major (65) used anterior pituitary extract in treatment of nephrosis, but found it did not alter the course of the disease. He also tried adrenal cortex hormones with no striking or definite results. Farr (34) also tried the growth promoting hormone of the anterior pituitary with no effects. They believed that possibly the disease was in some way correlated with a disturbance in hormonal production and function, and that this brought about many of the manifestations of the disease.

Schlutz and Collier (79) in 1927 followed the alkali treatment first published by Osman (73). The rational of this type of therapy was to bring about a change in the acid-base balance which would in turn bring about an alteration of the blood medium and changes in the iso-electric point. The change in iso-electric point would result in a change in cellular water content and its distribution in the body. They gave large doses of potassium citrate, potassium bicarbonate, sodium citrate and sodium bicarbonate in equal amounts plus water and flavoring agent. The potassium is more effective in decreasing edema and in increasing diuresis, but cannot be given in too large amounts, because of the danger to the heart. The amount given is based on the bicarbonate level in the plasma. They started in children with 2 to 3 grams three times a day initially. The next day the dose was increased to four times per day. They then increase the dosage by 2 to 3 grams per day until the urine has a pH of 7.0 to 7.6. The plasma level of bicarbonate should be constantly watched, and should not deviate from normal. Diuresis occurs after the desired urinary pH is reached. This diuresis continues until complete loss of edema occurs.

The albuminuria and lipemia also leave. These are rather heroic measures, and are advised in cases not yielding to less drastic measures.

Aldrich (1) also tried alkali, and got diuresis in 12 cases and none in 6. He concluded that he found it impossible to tell whether it was beneficial or not, but that it probably was not.

Caldwell (9) tried the use of Vitamin A and unsaturated fatty acids in treatment of nephrosis. He based his work on the fact that when some animals are deprived of Vitamin A and on an otherwise normal diet, some developed edema, albuminuria, increased suseptibility to infection and an inversion of the albumin/globulin ratio. With the administration of Vitamin A and unsaturated fatty acids, these animals returned to health. Caldwell gave his 7 year old patient 100,000 units of Vitamin A every day for three days, 80,000 units every day for 2 days, and 60,000 units per day thereafter. Unsaturated fatty acids were given, 2 tablespoons three times per day. The patient improved, and was cured at the time the article was reported. The underlying mechanism is not explained and no similar findings have been reported to substantiate these.

In 1940 Farr (35) used intravenous amino acids in the treatment of nephrosis. As mentioned previously, Farr observed that patients with nephrosis had a hypoaminoacidemia. He studied nitrogen balance in these patients, and found a negative balance in acute stages of the disease. (40) (36) In 1939, Farr and McFayden (31) gave children with nephrosis a 10 per cent solution of amino acids intravenously, and tested the urine immediately afterwards. There was no significant increase in non-protein nitrogen, in urea and ammonia nitrogen or amino acid retention. Therefore, it appeared probable that the injected amino acids were utilized for the nutritional needs of the patient. Farr (37) (35) gave amino acids in a form called casein hydrolysate. He used a 10 per cent solution of casein hydrolysate in a 10 per cent glucose solution. He gave 30 to 40 grams on alternate weeks for four injection periods. He found that the amino acids were assimilated, and retained as well or better than similar amounts of protein fed as protein. After injection the capacity to assimilate a high protein diet was markedly increased.

In view of these finding, Farr recommended that casein hydrolysate be given as a primary therapeutic

procedure in the treatment of nephrosis. He also stated that such administration prevented the occurrence of the nephrotic crisis described earlier. It is to be noted also that the injection of amino acids causes no untoward reactions with the patient except slight flushing and nausea if given rapidly. There were no febrile reactions.

Farr has not advocated this treatment to cure the disease, but it puts the patient in a better condition to combat infection and puts the body in a better position to overcome the disease and achieve recovery. This therapeutic measure is one of the newest and to date one of the best methods of treatment we have. It holds much promise, but it requires more investigation before it can be widely acclaimed in the treatment of nephrosis.

There have also been advocated some mechanical and surgical measures in the treatment of nephrosis.

Clausen (10), in accordance with his theory that nephrosis is caused by foci of infection in the para-nasal sinuses, advocates removal of the infection. He states that the prodedure he finds most beneficial is to irrigate and remove the infection and to increase the protein in the diet. He restricts fluids

to 1000 cc. and gives a low salt diet. He does not think tonsillectomy or adenoidectomy are helpful. Marriot (66) has made similar studies and agrees with Clausen and advocates the same methods of treatment. It may be that the dietary regimen, rather than the clearing of the infection, is responsible for their encouraging results.

Another treatment of a surgical nature is paracentesis of extensive effusions into serous cavities. This is only a palliative measure to relieve dyspnea and discomfort.

This group of therapeutic measures, some of which hold promise and others which appear to be of no value, represent the efforts of almost half a century of trying to cure the specific disease, nephrosis. It appears as though we are making progress, but due to the rarity of the disease, progress is slow.

CONCLUSIONS

There has been a great deal of investigation into the problems arising from nephrosis. As a result of this investigation, many points have been established which lead to a better understanding of the disease.

The etiology of nephrosis has, however, very persistantly remained obscure. Theories have been presented and rejected and many of our foremost investigators are still of the opinion that the etiology is unknown.

The clinical findings of nephrosis are at this time fairly well established. Nephrosis is now associated with a definite disease picture that is more or less accepted by all workers in the field.

The pathology of nephrosis has not been definitely established. Some cases show rather marked glomerular changes. Many men think that when evidence of this glomerular change is present, it represents a previous glomerulonephritis. These men disclaim any glomerular damage and state that cases presenting it are not the true nephrosis. Other men just as vigorously state that there is some glomerular damage and the disease is not a disease entity, but a

derivative of glomerulonephritis. Increasing evidence seems to point to the belief that there may be some glomerular damage, but also indicates that nephrosis is a disease entity.

The pathogenesis of nephrosis involves investtigation into its symptoms. The albuminuria and edema are generally considered to be interrelated in the respect that that albuminuria causes a decrease in plasma proteins which leads to a decrease in plasma osmotic pressure and a consequent edema. The pathogenesis of the other great factor in nephrosis, the lipemia, is not generally understood. Some men are of the opinion that it is due to a disturbance in metabolism wherein the fat is not properly deposited in the body fat depots. Others believe it compensitory in action and is brought about to raise the the plasma osmotic pressure and decrease the edema. It may be that the disease is not a kidney condition primarily, but a disorder of the protein-lipoid metabolism as proposed by some investigators. The nitrogen balance in the body has been shown to be abnormal. The mechanism of this abnormality has not been satisfactorily explained and more investigation into this problem is desireable.

The whole picture of the pathogenesis is not clear, and until it is worked out to a greater extent than it now is, progress in its treatment will not advance greatly.

In the treatment of the disease, we have seen encouraging results in the last few years. Farr's work involving the nitrogen balance in patients with nephrosis is enlightening and the effects brought about by the injection of intravenous amino acids in nephrotic patients indicate that we are making definite progress in the problem of treatment.

The diuretic problem is not completely satisfactory. The protein diet, ammonium chloride and mercurial diuretic program of Keith and Whelan seems to work well in many cases but is not dependable for all. Likewise the work of Aldrich with concentrated human blood plasma is encouraging in bringing about diuresis and even cure, but it is not always effective. They appear to be, however, the best that we have today and in all probability will be used until a better method appears.

The patient can now be kept in a positive nitrogen balance by the use of intravenous amino acids. This is a definite step from the position of a few

years ago. In many cases with the use of the appropriate diuretic for the particular case, the patient may be kept almost edema free at the same time.

Nephrosis is still a disease requiring much more investigation. Definite advances are being made, and we are steadily, if slowly, progressing toward a more clear cut understanding of the processes involved and therapeutic requirements. The disease is difficult to study because of its rarity.

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