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EXPERIMENTAL AND CLINICAL NEPHROSIS

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DR. MANSON

In our last basic science seminar, Drs. Caldwell, Neher and Hamilton Smith dealt with the ultrastructure of the nephron which constituted a fitting introduction to our consideration this afternoon of the experimental and clinical aspects of nephrosis. Nephrosis is a systemic disease with disturbances in many areas of metabolism. In the broad sense of the word, there are many causes of the clinical syndrome we call nephrosis. These have been reviewed at length by Adams1 in his excellent monograph. For the present seminar, however, we shall confine our discussion to consideration of a clinical entity characterized by proteinuria, hypoproteinemia and hyperlipemia. In the pediatric age group, this syndrome often is associated with one of four diseases: acute glomerulonephritis, it may occur during the course of chronic glomerulonephritis, it may be seen as a sequel to Schonlein-Henoch Purpura (historically more correctly referred to as Heberden’s Purpura2) and it may occur as a familial disease. It is referred to variously as nephrosis, childhood nephrosis, or lipoid nephrosis. It is sometimes regarded as occurring in “pure” or “mixed” varieties.

Inasmuch as a major clinical manifestation of this disease consists of massive proteinuria and associated hypoproteinemia, we will ask Dr. O’Neill to deal with the disturbances seen in protein metabolism.

DR. O’NEILL

Nephrosis is a distinct clinical and biochemical entity. It is characterized by: edema, proteinuria, hypoproteinemia and hyperlipemia. Occasionally one sees hematuria, hypertension or azotemia. The pathogenesis of nephrosis is unknown, but it is commonly thought to be the result of an antibody reaction to unknown stimuli in a susceptible person.

While the causes of the disease in children are somewhat limited, in older age groups other causes are seen:

1. Intrinsic renal disease
   a. Membranous glomerulonephritis
   b. Mixed glomerulonephritis

2. Infection
   a. Syphilis
   b. Malaria

3. Poisons
   a. Heavy metals
   b. Organic solvents
   c. Drugs

*Basic Science Seminar presented at the Henry Ford Hospital by the Department of Pediatrics, October 24, 1960.
4. Hypersensitivity reactions
   a. Insect stings
   b. Serum sickness
   c. “Anaphylactoid” purpura
5. Mechanical
   a. Renal vein thrombosis
   b. Pericarditis
   c. Tricuspid insufficiency
6. Systemic disease
   a. Systemic lupus erythematosus
   b. Amyloidosis
   c. Multiple Myeloma
   d. Diabetes mellitus
7. Heredofamilial Nephrosis

Historically, “classical nephrosis” or membranous nephrosis, studied by light microscopy showed lipoid tubular degeneration, occasional increased cellularity of the glomerulus and splitting of the basement membrane. The lipoid granules in the tubules were considered the primary lesions of nephrosis. Actually, the lipoid granules of the tubules are the result of reabsorption of lipids that are the product of abnormal glomerular function rather than the primary defect in the disease. Elucidation of the primary lesion had to wait until the studies of the normal glomerulus were done by electron microscopy. Agreement on the histology of the glomerulus was no small struggle. Due to different staining techniques, artifacts and studies of various sections of the glomerulus, there was much controversy over normal glomerular histology. Now it is pretty well agreed that there are three layers in the normal glomerulus; endothelium, basement membrane and epithelium with podocytes. Farquhar, Vernier and Good studied sections of the kidney from patients with various primary diseases having in common the presence of nephrosis. One lesion, other than the changes of the primary disease process, common in the glomeruli was the presence of degenerative changes in the podocytes. This lesion seems related quantitively to the severity of proteinuria. With the healing of the podocytes, proteinuria decreases. Hall has proposed that the spaces or pores between the podocytes normally limit the molecular size of glomerular filtrate and that podocyte changes allowed larger protein particles to pass through and be lost in urine. Others have taken exception to this, postulating that it is not just a geometrical problem of pore size, but rather that there exists an enzymatic aspect to glomerular permeability and upon degeneration of the podocytes, there exists a biochemical defect allowing large protein particles to pass.

Before discussing the pathophysiology of nephrosis, a few comments as to age incidence of onset may be of interest. Acute glomerulonephritis has its highest incidence between four to ten years of age with a peak at about six to eight years.
Nephrosis

Nephrosis has its highest incidence from six months to six years with a peak of about 18 to 30 months. An episode of acute upper respiratory infection or acute tonsillitis is found to precede acute glomerulonephritis by two weeks in about 60 to 80 percent of cases, but in nephrosis this occurs only in 25 to 30 percent of cases. Some workers have suggested that infection is related to the onset of obvious edema in nephrotic patients only in that infection produces water retention in any child. However, in the yet unrecognized nephrotic child with inapparent edema, the added insult of infection may make the patient's nephrotic edema apparent for the first time. About 40 percent of nephrotics have a past history or family history of allergy, while this is much lower in the patients with acute glomerulonephritis.

Turning to the pathogenesis of nephrosis, two general views exist in regard to the primary defect; first, that nephrosis is a primary renal disease, more specifically a disorder of the epithelial podocytes. The second view is that nephrosis is a generalized metabolic disease with glomerular lesions being but a part of the process. The second view seemed a little vague until many excellent observations of a generalized capillary, metabolic, immunological, electrolyte, and hormonal disturbances of nephrosis are reviewed, then the theory of a systemic disease existing seems more logical. Without defending or trying to propagate any given viewpoint, let us try to evaluate each theory objectively.

Proteinuria is one of the most striking findings in nephrosis and may reach 20 to 60 grams per day. Proteinuria could be due to excretion of an abnormal protein, reduced tubular reabsorption of normally filtered proteins, or increased glomerular filtration. Immunological, chemical, and electrophoretic studies of urinary proteins rule out the first theory of abnormal protein production. The proteins excreted are normal serum albumin and globulins. Regarding the second theory, if 30 to 40 percent of serum proteins normally filtered by the glomerulus were not absorbed, one could account for all of the albuminuria. However, tubular reabsorption studies of albumin in normal and nephrotic patients is about equal. Microcannulation and Evan's Blue dye studies on experimental animals also confirmed the fact that protein absorption in normal and nephrotic animals was about equal. A third theory is that of increased glomerular permeability to serum protein. By micropuncture techniques, it has been shown that nephrotic kidneys have increased protein clearance. In human studies, infusion of nephrotic patients with dextran particles of molecular weights of from 10,000 to 150,000 with simultaneous fusion of tagged albumin and globulin, it has been shown that the dextrans of the molecular size of the various serum albumin and globulin molecules have been excreted in equal proportion to the concentration of albumin and globulin present. To add more support to this theory of increased glomerular permeability, one would expect the large molecules to pass less easily and the smaller molecules to pass more easily. This is borne out by the fact that the larger globulin molecules are found in lower concentration in the urine.

The source of the amount of proteins lost in the urine by the nephrotic patients is controversial in regard to the symptomatology and total body nitrogen balance. Metabolic balance studies in nephrosis in the active stage showed markedly negative
nitrogen balance. However, such patients synthesize two to five times the usual amount of albumin and globulins; the total turnover of serum proteins is therefore greatly exaggerated. This has also been demonstrated with the use of albumin tagged with I-131 and tagged glycine molecules. The net result of proteinuria and greatly increased protein synthesis is reflected in serum by a low albumin, low alpha I gamma globulin, and low metal carrying globulins. Globulins of larger molecular size, the beta lipoglobalins and the alpha I lipoglobalins, due to an increased rate of synthesis and a decreased or at least not a very high rate of excretion, are actually increased in nephrosis, accounting for part of the hyperlipemia. Along with low beta lipoglobalin levels, one sees a low serum iron, low serum copper and low iron binding capacity. The protein-bound iodine is excreted in large amounts resulting in a low serum protein bound iodine value. However, normal I-131 uptake is present, excluding hypothyroidism as a factor in nephrosis. Gamma globulin synthesis is markedly increased and so is gamma globulin excretion; the net result is that the nephrotic usually has a very low gamma globulin. The role of protein intake on overall mortality is difficult to evaluate, but Blainey and others have shown straight line correlations between nitrogen intake and storage. It is not possible to predict on the basis of patients' nitrogen balance whether or not recovery will occur.

DR. MANSON

No disturbance of metabolism in nephrosis is independent of other metabolic pathways. This is clearly illustrated by the observation that the infusion of 50 grams of salt-free human albumin is generally completely lost by the kidney within 24 to 72 hours from the time of infusion. Thus, albumin infusion is of more value to the physician's peace of mind than to the patient's nephrosis. An interesting observation in this regard is that such an infusion tends to produce a concomitant transitory decrease and subsequent rise in serum cholesterol level. Moreover, we note that in the nephrotic patient on steroid therapy, one generally must achieve a rise in serum albumin before the serum lipid level tends to fall. For a discussion of lipid metabolism and some of its inter-relationships with protein metabolism we shall hear Dr. Bandera.

DR. BANDERA

One of the metabolic disturbances found in nephrosis is hyperlipemia; the extent of the total lipids infrequently may reach a level of five grams. Although many of the metabolic inter-relationships of lipid and protein metabolism are known, an adequate explanation for the hyperlipemia has not yet been established.

In aqueous medium; that is, serum, lipids exist as joined colloidal lipid-protein complexes known as lipo-proteins. When the serum is analyzed electrophoretically, lipo-proteins are grouped into two fractions: (1) Alpha lipoproteins which are of lower molecular weight, high density, low lipid content lipo-proteins and (2) Beta lipoproteins which are high molecular weight, high lipid content lipo-proteins. Beta lipo-proteins normally transport about 70 percent of all plasma lipids in a normal fasting person. The fate of lipids in body fluids could be told in this simplified way: in the succus entericus the lipids exist as chylomicrons. Upon entering venous blood, by action of "clearing factor", there is loss of triglycerides from the chylomicrons and the lipids are found as low density beta lipo-proteins. These in turn are transformed
Nephrosis

to high density alpha or beta lipo-proteins. The “clearing factor” is thought to be a lipo-protein lipase. The following factors are thought to influence the activity or effectiveness of lipo-protein lipase: heparin, plasma proteins, and “tissue factor.”

In trying to explain the hyperlipemia of the nephrotic serum, certain observations are useful. Although it is established that infusion of plasma protein will decrease the hyperlipemia of the nephrotic sera, the infusion of plasma protein has no effect on normal plasma systems. There is no diminution of lipemia. In experimental nephrosis, hyperlipemia precedes the diminution of serum proteins. Another pertinent observation is that in idiopathic hypoalbuminemia, serum lipids are normal but one can diminish serum lipids with infusion of albumin.

It is known that heparin will clear the lactescent nephrotic serum. At least in certain experimental situations it has been established that the degradation of heparin is not increased. When heparin is injected into nephrotic rats and the rat’s serum titrated with protamine sulfate, the prolongation of clotting time is similar in nephrotic serum as compared with normal control. Infusion of heparin to nephrotic rats with hyperlipemia does not diminish the extent of their hyperlipemia. These observations would exclude heparin, or lack of it, as the sole cause of hyperlipemia.

Despite low protein bound iodine and basal metabolic rate values in nephrotic patients, there is no evidence to suggest that the nephrotic patients are hypometabolic. The hyperlipemia of the nephrosis, although similar to that found in hypothyroidism cannot be influenced by the administration of thyroid extract. Marsh and Drabkin have proposed a very interesting theory of hyperlipemia. They suggested that in nephrosis the body’s main and most important effort must be to regenerate serum proteins lost in the urine. Since proteins are excluded from the metabolic functions they would normally participate in, such as gluconeogenesis, fats are called upon to carry the metabolic burden. Thus, the picture that one sees in nephrosis might represent mobilization of body lipid stores and the increased quantity in serum reflect an increased demand for them in the metabolic economy of the body. This situation could be rightly called “lipid diabetes.”

The role of albumin in the hyperlipemia of nephrosis cannot be overlooked. Although it is thought that albumin serves as a ‘carrying horse” for serum lipids, it is unlikely that its function is that simple. In this connection, the observation that the hyperlipemia persists despite the correction of serum albumin, as seen in clinical remission, supports the impression that there are other factors operating in the disturbances of lipid metabolism in the nephrotic patient. It is thus pertinent to remember that in acute glomerulonephritis, one sees hyperlipemia with normal serum proteins. The question of what constitutes the “clearing factor” cannot be answered as yet.

DR. MANSON

Disturbances in protein metabolism with their inevitable consequences in the area of lipoid metabolism also have a rather direct bearing on electrolyte and water metabolism. From the patient’s point of view, edema may be his most distressing clinical manifestation. Edema formation, however, is not simply a matter of hypo-proteinemia but also involves certain other factors. Dr. O’Neill will discuss these factors.
Bandera, O'Neill and Manson

DR. O'NEILL

Edema is one of the major clinical findings of nephrosis and to parents this is one of the most distressing, ominous signs encountered. The clinician, however, must keep in mind that massive edema of nephrosis is but a reflection of many metabolic processes going on simultaneously to produce the net result — edema. Many factors operate to produce edema in any disease; in nephrosis, low protein, hormonal disturbances, water and electrolyte derangements contribute to the production of edema. Low protein is a result of increased protein catabolism and urinary loss. However, in other diseases with equally low serum protein concentrations, one does not see the massive edema of nephrosis; therefore, there must be other factors. Nephrotic patients have diminished plasma volume and occasionally this results in decreased renal blood flow with a shock-like picture which could account for edema on the basis of renal failure. However, this would not explain all cases of massive edema. Another possibility is the increased amount of antidiuretic hormone that has been found in nephrotic patients. This, however, is not a constant finding and could not explain all the cases of edema. In 1953 British investigators observed that various extracts of urine from nephrotic patients showed marked sodium retaining activity and produced a potassium diuresis. These urinary extracts caused changes similar to those produced by crude adrenal extract; the active compound being later identified as aldosterone. This compound is present in increased quantities in nephrotic patients and is believed to play a large part in the often massive edema of nephrosis accompanied by extreme sodium and water retention and potassium excretion. The nephrotic patient can tolerate much larger excretory loads of potassium than the normal person but does not tolerate sodium and water as well. However, a major mistake made in treating nephrosis is to assume that limitation of sodium is essential to prevent edema. It is true that limiting sodium intake to some extent is necessary; however, a nephrotic patient seems to have a certain threshold level of edema which is the sum total of the hormonal and protein factors. When given more salt, the patient will increase his threshold for edema but beyond that point any excess salt is excreted. In treating nephrosis, acute limiting of sodium and the misery it causes these children, is certainly inexcusable on the basis of metabolic studies. Moreover significant sodium restriction is impossible, if good nutrition is to be provided. The mechanism for increased aldosterone production is probably on a basis of low plasma volume and as the sodium is diluted by the edema from other causes, osmo-receptors stimulate aldosterone production causing more sodium retention. Hydrocortisone will cause a rapid drop in aldosterone levels and the interesting observation is that in a spontaneous or induced remission, one sees a marked drop in aldosterone before diuresis occurs. One other possibility in nephrotic edema has been studied, that of generalized capillary permeability. Perfusion with Evans Blue tagged albumin substantiates the idea that, not only do glomerular capillaries have increased permeability, but the capillaries in other parts of the body as well. The actual quantitation of this phenomenon as to particle size has been very difficult, but there is clear indication that at least in part, the edema of nephrosis is due to generalized increased capillary permeability.

DR. BANDERA

As a clinical “rule of thumb," it is usually accepted that edema will appear when
Nephrosis

the serum albumin in an adult falls to a level of 2.5 grams percent or less; or in a child under 10 years of age, the serum albumin level reaches 1.2 grams percent. In nephrotic patients, however, one often sees no discernable edema when the serum albumin is less than 1 gram percent. The analysis of the tissue specimens of edematous rats shows that the skin and subcutaneous tissues are the most avid acceptors of water. An excess of 1.9 grams of water per gram of tissue is retained in a nephrotic rat’s skin. One gram of muscle tissue of a nephrotic rat has an excess of 0.5 grams of water as compared to the tissue of a normal rat. The analysis of electrolytes of a nephrotic rat’s tissue shows that there is marked increase in sodium and chloride and decrease in potassium content when compared to the tissue of healthy rats.

DR. MANSON

So we see that a number of metabolic disturbances are involved in the clinical picture we know as nephrosis. These aberrations have been rather well worked out to date. Much work has been done and much remains to be done in elucidating the basic reason of why these disturbances occur. This brings us then to a consideration of experimental nephrosis and nephritis and the relationship of these experimental models to human disease. For this we shall call on Dr. Bandera.

DR. BANDERA

Experimentally, one can produce in animals a whole spectrum of renal diseases. These range from lesions clinically resembling human acute glomerulonephritis, to lesions resembling nephrosis and serum sickness. Many agents have been used: amino-nucleosides, nephrotoxic sera, intravenous saccharated ferrous oxide, trimethadione, just to mention a few. From these studies much knowledge has accumulated. Our correlation of anatomical lesions and clinical picture has become clearer; the biochemical aberrations and their sequence of appearance, inter-relationship and pathogenesis has been intensively investigated. Although the crowning of these experimental investigations would be definition of etiology (or etiologies) of human nephrosis, the fact that some renal lesions experimentally produced so closely resemble human nephrotic syndrome helps us to understand and manage the patients with the disease. It has been clearly established that, at least in the rats, nephrosis and nephritis can be diseases of hypersensitivity. Some investigators have followed a different path of investigation. They have been able to produce experimental nephrosis with subcutaneous injections of an amino-nucleoside, 6-dimethylamine-9 purine. This experimental approach has been studied by Bartlett at this hospital. It has been shown by experiments using mitochondria prepared from pooled kidney tissue that there is a loss of mitochondrial activity in respect to both substrate oxidation, and concomitant phosphorylation, when succinate is used as a substrate. The following sequence of histologic changes has been established in experimentally produced nephrosis. Within one hour after administration of nephrotoxic sera to experimental animals, there occurs swelling of foot processes and increase in the amount of epithelial cytoplasm. In three hours swelling of epithelial cells takes place and in six hours there is coalescence of foot process. By 24 hours one finds proteinuria and the clinical picture of nephrosis follows soon after that. Amino-nucleoside induced nephrosis is somewhat different: the rat is the only susceptible animal. Although one is able to produce a full-blown picture of nephrosis with elevation of the BUN with this
agent, upon the discontinuation of amino-nucleoside induced nephrosis appears on the sixth day, edema and ascites appears on the tenth day, and uremia on the twelfth day. The main histologic change, which is somewhat different than in “hypersensitivity” nephrosis, is vacuolization of mitochondria within the distal tubules and breaking up of cristae.

Not only has production of experimental nephrosis been extensively investigated, but the modification and prevention of the disease has produced some interesting results. For instance, total body radiation, cortisone in a dose of 5 mg. per kilogram per day will produce significant suppression of disease. Marked or complete suppression can be attained by giving cortison in a dosage of 20 mg. per kilogram per day. Nitrogen mustards given in adequate doses will also prevent production of nephrosis by the use of nephrotoxic sera. It is significant that all these agents; radiation, steroids and nitrogen mustards are agents which we associate with inhibition of immunologic systems. In this connection it is worth pointing out that amino-nucleoside nephrosis is not influenced by pre-treatment with steroids.

The immunologic concept is frequently challenged by the fact that infants, who are usually considered “immunologically immature,” will develop nephrosis. In this connection, it is worth pointing out that maternal antibodies against infants' kidneys have not been found.

Certain questions might be raised regarding the relationship of experimental nephrosis to the clinical nephrosis: a. Is there an abnormal nucleoside or nucleotide which functions as an antimetabolite and inhibits renal enzyme systems? b. Is there a “substance” which might be a by-product of an antigen antibody reaction which is responsible for the clinical picture of nephrosis? Although in azotemic patients abnormally high levels of nucleotides have been found, the relationship of those substances to nephrosis has not been established.

DR. MANSON

The possible role of the immune mechanism in the production of human nephrosis has been long apparent. Further substantiation of this concept has been emphasized by the discussion of experimental nephrosis by Dr. Bandera.

Clinically, it has been noted that atopic allergy is more common in families of nephrotic patients than in normal controls. Eosinophilia in these patients is not infrequent. It is equally clear, however, that atopic allergy together with a positive family history, hardly provides an adequate explanation of the pathogenesis of the disease. Other evidence of the role of the immune mechanism in this disease is to be found in the observation that complement is diminished in these patients. Serum complement also falls in experimental nephrosis. Furthermore, it has been demonstrated that this reduction in serum complement in both situations is not due to urinary loss in a manner analogous to serum iron, serum copper, protein-bound iodine, etc., as discussed previously. Localization of antibodies on glomerular components has been demonstrated in experimental disease but this observation has not been made in specimens from human nephrotic patients. However, in experimental disease these antibodies may remain attached to the glomerulus for months.
Nephrosis

Antibodies to human kidney tissue have been studied but their presence in nephrotic patients has not been consistently demonstrated and the observation is open to considerable question. Boyden has studied the sera of nephrotic patients by means of her tanned red blood cell technique. She reported that the sera of nephrotic patients produced agglutination of these specially treated red cells and showed that steroid therapy prevents this response. Other workers, however, have been unable to duplicate these results and so this observation remains open to some question.

Occasional isolated case reports of nephrosis in early infancy have been interpreted by some to imply that the immune mechanism is not as important as some have suggested inasmuch as the young infant is regarded as an immunologically immature individual. Though this is in general true, it should be remembered that the immune response of young infants to test antigens is a complex problem because of the influence of passive maternal immunity to a wide variety of antigens. Furthermore, young infants may show a striking response to some antigens when maternal titers to these antigens are low.

In any event, similarities between human nephrosis and experimental immunologic disease are sufficient in number and nature to provide a rationale for the ablation of such a pathogenetic response by the use of steroid therapy. It might be pointed out in this regard that, utilizing the same rationale, nitrogen mustards have been used for the same purpose in the role of antireticuloendothelial agents. We shall ask Dr. Bandera to discuss the present day therapeutic approaches to nephrosis.

DR. BANDERA

In planning a therapeutic regimen there are some considerations which influence the therapeutic success of a regimen. It has been found that in the case of nephrotic patients less than one year of age, the disease is usually not influenced by any therapeutic regimen. The duration of the disease has bearing on the responsiveness; the purity of clinical picture is rather important since, if one has complications such as positive tuberculin reaction or exposure to tuberculosis, prolonged disease with impaired renal function, or hypertension the approach is somewhat different.

Historically, one is impressed by the great mortality of nephrotic patients in the pre-antibiotic era. Barnes, et. al., in 1950 reported 42% of patients out of his series of 107 patients died when followed two or more years. Although antibiotic therapy lessened the mortality, the survival figure still left much to be desired.

Many articles have been written on efficacy of steroids or corticotropin and the clinical course of nephrosis. Most articles have reported favorable influence on the course of the disease and very little influence on the growth if the steroids are used intermittently. Some investigators feel that corticotropin is the preparation to use; others have praised one steroid in preference to another as far as the side effects, hypertension and the percentage of remissions is concerned. Certain serious side effects of steroid therapy have been seen in nephrotic patients. Consensus, however, is that steroids should be used intensively and not merely as diuretic agents to be stopped as soon as diuresis ensues, but to be continued until the biochemical abnormalities, hypoalbuminemia and albuminuria, disappear and there is a cessation of hyperlipemia.
Some investigators report chlorothiazide will produce substantial diuresis. Threshold substances, such as Vitamin C, are occasionally used to induce diuresis. Although albumin will frequently produce temporary diuresis, it is worth pointing out that the pre-infusion level is usually reached within 24 to 72 hours and the course of the disease is not influenced by any such infusion even repeated daily. When after an adequate trial of steroids or corticotropin no response is obtained, frequently the nitrogen mustards are used with some success. In a resistant case one can use spironolactones, but our experience in this phase of treatment has been limited. Although steroids are thought to be rather specific, there are reports that nephrosis will return after remission of four years or more when the steroids are discontinued.

One should not forget that supportive treatment such as adequate diet, reasonable isolation, and prevention of exposure to infections, especially viral, should be practiced when the patient is on high doses of steroids. Antibiotics, of course, do not influence the course of nephrosis but antibiotic treatment of bacterial infections has markedly reduced mortality from that major cause. Some also consider it good taste to put the patient on "prophylactic" antibiotics when long term steroid treatment is employed. This practice is open to serious question and we no longer follow it in this clinic.

One should keep in mind that nephrosis is not the only thing that we are concerned with: the family, their attitude toward the manifestation of the disease, such as edema, profoundly influence our approach to it. Parents are often disturbed by the acneiform eruption or moon-face of the steroid treated patient. It is hard for them to accept that more than appearance is at stake when the patient is receiving steroids. Sympathy and an understanding attitude, combined with adequate explanation of what one is aiming at frequently is enough to change the parents' attitudes toward the disease, our management and the child's acceptance of necessary hospitalization and unpleasant venipuncture. In this regard, we must acknowledge the blessings of microchemical technics. The frequent criticism that we have no controls for the present regimen of steroid therapy is eloquently rebutted by the observation that our controls were all buried before the dawn of antibiotic therapy and may probably be used as an indication of the effectiveness of therapeutic antibiotics together with long term steroid therapy.

DR. MANSON

Thank you, Dr. Bandera and Dr. O'Neill. Our time is drawing to a close and before it is up, I should like to emphasize a few points on which I think we all agree. The first is that nephrosis in childhood is a disease of unknown etiology whose prognosis has been vastly improved by two well established forms of therapy. It has been stated that with the use of antibiotics to treat bacterial infections, 40-60% of nephrotic children will ultimately recover. Most observers are of the opinion that with the use of adequate steroid therapy, as many as 70-80% of such patients will recover. Secondly, if steroid therapy is to be used, and we feel strongly that it should be, these agents should be used in large enough doses for a long enough period of time. It has been established that adequate steroid therapy will reverse the abnormalities of the podocytes which are found on electron microscopy of needle biopsy specimens of the kidney from affected children and produce clinical remission. Thus we have objective evidence of the value of corticoid therapy in this difficult disease of childhood.
Nephrosis

In our clinic, we have followed a prescribed program of treatment, in conjunction with the Children’s Hospital of Michigan and the Department of Pediatrics and Communicable Diseases of the University Hospitals at Ann Arbor, which is part of a national study, designed to evaluate the long term results of therapy in this disease. The fact that this study involves three institutions in the same corner of Michigan brings me to the third point on which we find agreement. Nephrosis is a disease which taxes the patience and confidence of parents and physician alike because of its natural history of remissions and exacerbations and its chronicity... the average case lasting two to three years, sometimes longer. The tendency is strong for parents of affected children to seek help at one institution and then another. This is clearly shown by comparing the rosters of nephrotic patients at one center with the other two. However, by a joint effort of the three hospitals involved, we have obtained a good follow-up on virtually all of the nephrotic children in this area for the past several years. The results obtained to date are presently under study and the project continues. The fact that nephrosis is such a trying disease to treat, brings into bold relief the importance of ancillary measures in the management of the patient. These include: orientation of the parents regarding nephrosis; prompt treatment of bacterial infections when they occur; minimizing exposure to infection, both bacterial and viral; education for the patient; maintenance of nutrition, especially insuring that the child gets as much protein food as possible; appreciation of the fact that steroid therapy is not without risk and careful evaluation of steroid induced complications when they occur, bearing in mind that nephrosis is a serious disease in which the side effects of steroid therapy must often be balanced against the implications of the disease.

Thank you gentlemen — we stand adjourned.

REFERENCES


