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Nephritis in children

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NEPHRITIS IN CHILDREN

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TABLE OF CONTENTS

INTRODUCTION

In a partial review of the literature, the author has attempted to discuss the common forms of nephritis that occur in childhood, and the more rare, but very interesting chronic kidney disease associated with stunted growth, ricket-like changes in the bones, and infantilism.

An attempt has been made to arrive at a workable classification of nephritis as it occurs in childhood, a rational treatment, complications, and after effects on the life of the individual.

Nephritis in children, is quite different from nephritis in adults. In the adult, one has to consider the wear and tear of life, the condition of the circulatory system, or the type of life the patient led, etc. as possible etiological factors. (55) The etiological role of nephritis in children is dominated by infection, which is in marked contrast to those slow degenerative processes that are the main causative factors in nephritis in adults. (53)

Acute nephritis is the most frequent type seen in children. A correlation of the history of onset and the prominent clinical symptoms with the laboratory

findings enables one to predict with a fair degree of accuracy the underlying pathological processes. This is especially true in the glomerular and tubular forms. (13) In other words, nephritis tends to occur in more pure forms in children than in adults.

Aldrich (2) states that "Since nephritis occurs in a peculiarly pure form in childhood, uncomplicated by confusing symptoms due to degenerative changes, cardiac disease or any of the other chronic ailments of adults, perhaps only by the study of the disease in youth may it be possible to discover the nature of uncomplicated nephritis."

HISTORY

Certain clinical signs and symptoms associated with pathological changes in the kidneys have been known for centuries.

Gugliclmo Salicetti, professor at Bologna, about 1268, described hardened kidneys associated with scanty urine and dropsy. (79)

In 1798, Cruickshank noted that in certain cases of dropsy, the urine could be coagulated by heat. (85)

However, Dr. Richard Bright, in 1827 was the first to point out the importance of the association of albumin in the urine and disease of the kidneys. (29) (79) This initiated the study of kidney disease, and the name Bright's Disease was introduced in honor of Dr. Bright.

With the development of the microscope and chemical methods of studying the blood and urine, an enormous amount of research and clinical study have been carried on concerning Bright's Disease, and the literature on the subject is voluminous.

General interest in nephritis in children appears

to have developed during the latter part of the first, and the second, decades of this century, and now occupies an important place in medical literature.

THE CLASSIFICATION OF NEPHRITIS IN CHILDREN

There are many classifications of nephritis in children. Almost everyone who prepares a paper on this subject gives his own classification or a modification of some other classification given by someone else. These classifications for the most part are based upon the symptomatology, clinical findings, urinary findings, kidney function tests, pathological changes, and the subsequent course of the disease in the various groups studied. In reviewing the literature on this subject, one finds that different descriptive terms are used by different authors in describing essentially the same condition. A possible explanation for this is that the symptomatology and pathological findings vary in different individuals and in different stages of the disease, and because there is not always a constant correlation between the pathology and the clinical findings.

Acute nephritis following an infection in the upper respiratory tract is by far the most common type seen in children. It is agreed by most observers that the primary part of the kidney injured in this type is

the glomerulus. This condition is referred to as acute glomerulonephritis, acute hemorrhagic nephritis, acute hemorrhagic glomerulonephritis, and acute post-infectious hemorrhagic nephritis.

The following types are included in most of the classifications, acute glomerulonephritis, acute tubular nephritis or nephroses, chronic nephritis, and chronic nephritis with infantilism.

Before discussing the various classifications and their criteria that is found in the literature, it might be well to say that it is rarely if ever found that the injury is sharply localized to one portion of the histological unit of the kidney. The vascular arrangement of the kidney is such that practically all the blood supplying the tubules must first pass through the glomerular capillaries. Therefore if obliteration of a glomerular tuft occurs, a disturbance of the function of the dependent tubular epithelium will follow. If a tubule is destroyed and collapsed, the function of the glomerulus attached to it must be interferred with. If the interstitial tissue is primarily damaged, the parenchyma may be secondarily compressed or injured in the process of the inflammatory reaction. Death of the parenchyma may initiate proliferative changes in the interstitial

tissue. Therefore one can assume that a pure form of the different types is probably present only during the initial stage, and mixed forms occur as the disease progresses. (36)

An etiological classification would be the most satisfactory. In the absence of an accurate etiological basis for the classification of the disease, most terminologies are of a descriptive clinical or anatomical nature. Classifications based upon the anatomical changes in the kidneys are more generally accepted. These have their drawbacks however, because often the pathologist is not able to determine the nature or picture the course of the antecedent disease on the basis of the gross or microscopical findings present at death. (28)

Davison and Salinger (36) feel that a pathological classification is the most reliable. They give the three main pathological types of nephritis as glomerular, tubular, and interstitial, in which, glomeruli, or tubules, or connective tissue, respectively are the primary seat of the damage. The glomeruli are damaged if red blood cells appear in the urine at any time, and the patient is suffering from glomerular nephritis. The damage is primarily in the tubules or interstitial tissue if no red blood cells, or at most only a few,

appear in the urine.

Boyd (19) gives the following classification; glomerulonephrites - first, second, and third stages; nephrosis, and arteriosclerotic kidney. Holt and McIntosh(59) give acute glomerular nephritis, nephrosis or tubular nephritis, subacute parenchmatous nephritis or mixed nephritis which presents a clinical picture that combines the outstanding characteristics of an acute glomerular nephritis and nephroses, and chronic nephritis.

Lyttle and Rosenberg (73) classified their cases into three groups: (1) Acute tubular nephrites, (2) acute diffuse (glomerulo-tubular nephritis), and, (3) acute glomerulo-nephrites. They maintain that a pure acute glomerular nephritis without tubular damage rarely ever exists. These cases seen clincally probably have a varying amount of tubular damage, but the damage is minimal and not reflected in the clinical or laboratory results. The cirteria given for classification were hematuria and hypertension for glomerular nephritis and generalized edema, marked albuminuria, normal blood pressure and absence of nitrogen retention for acute tubular nephritis.

Morse (86) believes that a classification based on a combination of the symptomatology and the findings

in the urine is more simple and more rational than one based on the pathological changes, or on the findings of the modern tests for kidney function.

He gave the following classification which was developed by Hill (55): acute hemorrhagic nephritis; acute exudative nephritis; subacute nephritis; chronic nephritis, mild or severe; chronic nephritis with infantilism. The criteria for this classification: (1) Acute hemorrhagic nephritis - amount of urine little if any reduced, usually no edema, moderate amount of albumin, never many casts, usually moderate amount of round epithelial cells, many red blood cells, usually not very ill. Most recover fairly quickly. Blood pressure little if at all elevated, no enlargement of the heart. Very little diminution in the functional capacity of the kidneys. (2) Acute exudative nephritis - the urine always diminished in the acute stage. Edema always present. Many casts and epithelial cells in the urine. Moderate to large amount of albumin. Red blood cells in the urine never as numerous as in the above type. (3) Subacute nephritis - usually develops from the hemorrhagic type. However, in some instances the symptoms are so slight from the beginning that the disease is apparently always of this type. The diagnosis is probably justified by the persistence of red blood

cells and casts after three months without any marked symptoms. The red blood cells, epithelial cells, and casts are not very great in amount. The patient usually looks well and feels well. No elevation of the blood pressure, no enlargement of the heart, and little or no interference with the function of the kidney. Almost all recover although it may take up to two to three months for the urine to clear up. Occasionally one becomes chronic. (4) Chronic hephritis - this type is uncommon and is the sequelae of the acute type. It is not the type seen in adults. The urine may be normal or greatly reduced in amount and may contain a large or small amount of albumin. Casts and cells of all sorts are found in the urine, but no blood is present unless there is an acute exacerbation. The blood pressure is usually somewhat elevated, and the enlargement of the heart varies with the blood pressure. The kidney function is impaired. The final outcome is always death, although it may be delayed for a considerable period of time. (5) Chronic nephritis with infantilism - findings of chronic nephritis plus infantilism.

Aldrich (2) made observations on 186 consecutive children with nephritis, and placed the cases in the following groups: (1) Acute post-infectious hemorrhagic nephritis. The criteria for diagnosis is essentially

the same as that described in the acute hemorrhagic given above. (2) Chronic nonspecific nephritis. The diagnostic criteria - edema, hematuria, hypertension, increase in blood non protien nitrogen, and chronic course or death. This is about the same as the chronic nephritis described above. (3) Nephrosis. Except for the fact that if any blood was found in the urine it was not considered as nephrosis, this is essentially the same as the acute exudative nephritis in the above classification. Other groups given in this article were subacute bacterial endocarditis with nephritis, Syphilis with nephritis, and tuberculosis with nephritis, with nephritis, which resembled chronic nonspecific nephritis except for the other disease.

Boyd (16) in a study of a series of 26 cases divided them into three main groups; (1) the acute - 24 cases (2) chronic glomerulonephritis - 2 cases and (3) nephrosis - 1 case. The acute cases were further subdivided into those which progress toward recovery was rapid and steady, a resolving group, and those which tended to become chronic - a nonresolving group.

After observing 155 patients at the Hospital for sick children, Tronto, between 1920 and 1926, Boyd (18) gives another classification which she believes as being the simplest clinically and showing agreement with

with the pathological diagnosis in most instances.

1. Acute hemorrhagid nephritis.
2. Acute tubular or hydremic nephritis (also known as acute exudative, acute parenchymatous, or nephrosis).
3. Mixed type or acute glomerulo-tubular nephphritis.

Gould (45) says that the forms generally recognized in children are; (1) Glomerular or hemorrhagic nephritis, (2) Tubular nephritis or nephrosis, and (3) the mixed forms. Acute glomerular and acute tubular nephritis are the most common form of nephritis occurring in children, according to Blackfan (14), chronic nephritis is relatively rare.

Addis (1) (74) divides kidney diseases into three large groups: (1) Hemorrhagic Bright's disease (acute glomerulo-nephritis), (2) Degenerative Bright's disease (nephrosis) and, (3) Arteriosclerotic Bright's disease.

Bierman (12) gives four stages of glomerulonephritis which were first established by Addis. (1) (a) initial stage - follows an acute infection. It may be mild or severe, and may be too mild to be recognized, (b) Latent stage - is asymptomatic and is diagnosed only by the aid of the Addis tests which show a continued excretion of abnormal amounts of red blood cells, casts, and albumin in the urine, (c) Degenerative (nephrosis), and (d) the terminal stage.

Bruce (22) states that "a simple but adequate classification of nephritis in childhood is: acute nephritis, chronic nephritis, and nephrosis. The addition of descriptive anatomical terms such as glomerular, tubular, interstitial or exudative are misleading because pure examples of these conditions rarely, if ever, occur. Also descriptive clinical terms such as post infectious and non specific requires considerable definition and while helpful need much wide spread usage to be understood."

Graubarth (47) writes that "the classification of nephritis in childhood has been variously proposed by different writers, but they are essentially the same. The classification of Volhard and Fahr, and Addis are used herein as a basis. Their classification is hemorrhagic Bright's disease or glomerulonephritis, degenerative Bright's disease or nephrosis, arteriosclerotic Bright's disease or nephrosclerosis.

The varieties of true nephritis may be classified as follows:

1. (a) Acute hemorrhagic Bright's disease (Addis)
   (b) Acute post-infectious nephritis (Aldrich)
   (c) Acute glomerulo-nephritis (Volhard and Fahr)
   (d) Acute hemorrhagic nephritis.

2. (a) Parenchymatous nephritis.
   (b) Tubular nephritis
   (c) Nephrosis (Volhard and Fahr)
   (d) Degenerative Bright's disease (Addis)

3. (a) Arteriosclerotic nephritis
   (b) Nephrosclerosis (Volhard and Fahr)
   (c) Chronic interstitial nephritis
   (d) Renal rickets or infantilism "

ETIOLOGY

Acute Glomerular Nephritis

Acute nephritis in children is almost always secondary to infective processes elsewhere in the body. Practically every article that discusses the etiology of nephritis gives the upper respiratory tract as the most frequent site of the antecedent infection. Acute nephritis may accompany or follow any acute infectious disease such as diphtheris, or scarlet fever. (86)

L. W. Hill (53) says that "nephritis is really an extremely common condition in childhood, following, particularly, the various acute infections to which children are so susceptible." The seasonal incidence of the disease closely follows the incidence of respiratory disease. (73)

The hemolytic streptococcus is the most frequent pathogenic organism causing these infections in the upper respiratory tract. (31) This organism elaborates a toxin which is carried by the blood stream to the kidneys. (59)

The seasonal and geographical incidence of acute nephritis in children quite closely parallels that of streptococcal infections. (76) Dr. J. D. Lyttle and associates (76) studied the anti-streptolysin titer of the blood stream in acute nephritis in 116 consecutive

cases. They found that in a great majority of normal individuals that the anti-streptolysin titer was less than 125 units. They showed that 90% of the patients with nephritis had an abnormally high anti-streptolysin titer. His conclusion was that in New York City (where the experiment was performed) the great majority of the patients with nephritis have a streptococcal infection preceding the nephritis.

It is not known just how the streptococcal infection produces nephritis. It is not by direct bacterial invasion of the kidney. Escherich and Shick (quoted from Lyttle (75)) suggested as early as 1915 that it "might be a case of hypersensitivity of the organism which is expressed in the ability of small amounts of pathogenic substance to elicit clinical symptoms which at another time would be tolerated without any reaction." They pointed out the analogy between the sequence of events in post scarletinal nephritis and that in the group of allergic reactions. This is the theory held by most observers today. (76)

Many other authors state that acute nephritis in children usually follows infections with the hemolytic streptococci in the respiratory tract. (95) (101) (13) (42)

Many authors have found that tonsillitis is the most frequent cause of nephritis in childhood. G. Boyd

(16) found that in a series of 26 cases tonsillitis was the cause in 42.2%. In some of the cases the presence of tonsillitis was revealed only by the examination of the tonsils, there being no complaint of sore throat, In a series of 235 cases A. A. Osman (88) found that 36.5% followed acute tonsillitis. These were both adults and children. J. L. Morse (86) and L. W. Hill (56) state that most cases are secondary to tonsillitis. In the majority of cases reported by R. F. James (63) the onset was preceded by tonsillitis.

There are many other conditions that are considered as being the antecedent disease in nephritis in children. Among these are chronic sinus infection, scarlet fever, acute mastoiditis, pneumonia, otitis media, nasal pharyngitis, umbilical infections, diphtheria, influenza, erysiplas, impetigo contagiosa, purpura, measles, etc. The following is a table from G. Boyd's (16) 26 cases that shows the number of cases preceded by certain conditions:

Disease	Number of Cases	Per Cent
Tonsillitis	11	42.2%
Scarlet fever	4	15.4%
Otitis media	3	11.6%
Nasopharyngitis	3	11.6%
Umbilical infection	1	3.9%
Mercuric chlorid	1	3.9%
Unknown	3	11.6%

Clausen (31) prepared the following table from his series of cases:

Disease	Number of Cases
Chronic upper respiratory infection	33
Chronic sinus infection	4
Scarlet fever	26
Acute upper respiratory infections	12
Acute mastoiditis	5
Pneumonia	10
Diphtheria	4
Osteomyelitis of Jaw	1
Influenza	1
Erysipelas	1
Congenital defects causing obstruction	2
No infection localized	3

L. W. Hill (56) in a series of 51 cases listed the following conditions as preceding the nephritis in certain cases:

Disease	Nephritis Acute	Nephritis Chronic
Tonsillitis	22	4
Otitis media	5	
Unknown etiology	11	
Scarlet fever	4	4
Impetigo	1	
Influenza	2	
Measles	1	1
Lobar pneumonia	3	
Cervical adenitis	3	
Turpentine given for worms	1	
Gastro-intestinal	1	
Following appendectomy	1	1
Pyorrhea	1	
Purpura	2	2

Total Cases - 70

These tables show that nephritis in childhood may

occur secondary to many infectious conditions, the most common site being in the upper respiratory tract and adjacent structures.

It was formerly thought that scarlet fever was the most important etiologic factor in acute nephritis in children. Hutinel (reported by Hill (53)) believed that nephritis following scarlet fever is the most common type of nephritis in childhood. The above tables show that not many cases are listed as secondary to scarlet fever. Hill (55) says that not many cases secondary to scarlet fever are seen in a general hospital, because most of them get well entirely, or die while in a contagious hospital. In A. A. Osman's (88) series of 56 cases only 7 had had scarlet fever, and the nephritis did not follow directly upon the fever in any of these. He states that the "incidence of nephritis in scarlet fever varies in different epidemics, but is usually given as from 6 to 11% of cases."

The importance of scarlet fever in the etiology of nephritis has probably been overestimated. However, it is definitely a predisposing factor. This is shown in Aldrich's (2) series of 159 cases in which 15% were preceded by scarlet fever. Morse (86) states that "it may be true that scarlet fever is more often accompanied by nephritis than any other disease, but the number of

due to scarlet fever is absolutely much smaller than that due to infection of the throat."

Several investigators have noted that impetigo contagiosa is not infrequently followed by acute nephritis. (5) Sutton (103) writing in the Southern Medical Journal reports five cases of acute nephritis following impetigo. Several other cases came under his observation during that time but only five were reported. However, it was not definitely established that there were no other causes of the nephritis such as infections in the tonsils or the sinuses in some of the cases. Impetigo is quite common in the south.

Other causes and predisposing factors of acute nephritis in children mentioned in the literature are exposure and chilling. (88) (52) (101) (42) (56) toxic agents such as turpentine or carbolic acid may rarely be etiologic factors. (42) Morse (86) gives suppurative processes involving the gums of teeth as another common cause of acute nephritis. S. Maggiore (78) describes a few cases of malarial nephritis in children.

The seasonal incidence of acute nephritis closely fllows that of repiratory diseases. About 75% of the cases occurring between December and May. The greatest incidence is between the second and eighth years, being rare under the age of 2. Males are slightly

more often affected than females. (73) In Clausen's (31) series of 102 cases the greatest incidence of acute nephritis was between the ages of 5 and 7.

Although acute nephritis is not very common under the age of two , it has been observed in very young infants. Tyson (107) reports a case of a five weeks old baby that developed edema following influenza and bronchopneumonia. The baby was dead in less than 24 hours after the onset of the edema. Autopsy showed acute hemorrhagic nephritis. Conrad (33) reports three cases of neonatal nephritis. The deliveries in these three cases were normal, but all three showed generalized edema at birth. The urine contained albumin red blood cells, and casts; pus was present in two of the cases. All were cyanotic at times and had convulsions. Two recovered and one died. Lapage (67) reports a case of acute hemorrhagic nephritis in an eleven day old infant. The diagnosis being confirmed at autopsy. Harvey (51) reports a case in a baby of nine and one half weeks.

A hereditary tendency in Bright's disease has often been referred to. Hurst (62) reports hemorrhagic nephritis occurring in 16 individuals in 3 generations. Three or four out of eight members of the first generation, eight out of twelve of the second generation,

and at least 5 out of 8 of the third generation suffered from nephritis.

The Seegals and Jost (98) made a comparative study of the geographic distribution of rheumatic fever, and acute glomerulonephritis in North America. They studied the incidence of acute glomerulonephritis in 24 hospitals in North America from 1910 through 1931. They found that the incidence of acute glomerulonephritis did not diminish in frequency in the souther latitudes, while the opposite was true for rheumatic fever and scarlet fever. They concluded "that the failure of acute glomerulonephritis to diminish in frequency in the southern latitudes might be interputed as supporting the hypothesis that agents other than the hemolytic streptococcus play the chief etiologic role in this disease. This does not seem likely, however, since considerable evidence is available incriminating the hemolytic streptococcus as the main incitant of the disease".

NEPHROSIS

The term nephrosis was introduced by Von Muller to disignate a primary degenerative process of the tubular epithelium in contrast to inflammatory changes in interstitial tissue and glomeruli. These changes may vary from cloudy swelling to necrosis of the cells(6)

Some think that nephrosis is a metabolic disease with an abnormal fat and protein metabolism i which the kidney change is only one manifestation of the underlying disease. To others it is a synonym for parenchymatous or tubular nephritis. (73),(59)

Nephrosis closely resembles the nephrotic component of chronic glomerulonephritis. It is differeintiated by the absence of signs of glomerulonephritis, especially hematuria or renal insufficiency over a period of years.(27)

The cause of nephrosis is presumably toxic substances which are absorbed in the focus of infection and affect the kidney and the body as a whole. Sinus infection is often the apparent cause in children. A close association seems to be present between the activity of the infection and the symptoms. (31)

The following is a table presented by Clausen (31) showing the number of cases that were presumably caused by certain conditions i his series.

DISEASE	NUMBER OF CASES
Nasal sinusitis	13
Probably sinusitis	4
Unknown	4
Diphtheria	3
Burns, infected	1
Empyema (Staph)	1
Amyloid disease	1
Influenza	1
Total - 28	

The age incidence is between 8 months and 11 years, and is more common in males. (36)

Tuberculosis and leues have been claimed to be causes, but this is probably not true. (36)

Clausen working in Marriott's laboratory was able to demonstrate a substance in the blood that was capable of changing the surface tension of the blood and changes in permeability. It changed the permeability of the renal tubules as well as the blood vessels, so that albumin passed from the blood into the urine. This substance disappeared with the subsidence of infection which was most commonly located in the nasal accessory sinuses, especially the maxillary antra. The edema and other symptoms disappeared too. The infecting organism was usually a hemolytic staphlococcus. The symptoms disappeared with clearing up on the infection, but was apt to recur with reinfection. Staphlococci infections in other places than the sinuses resulted in nephrosis in a few instances. They believe that infection leads to a production of the toxic substance which in turn damages the cells throughout the body, including those of the renal tubules. (81)

The etiology of chronic nephritis will be discussed in the secion on renal rickets.

PATHOLOGY

Acute Glomerular Nephritis

Grossly, the kidneys are usually enlarged, deeply congested, and rather pasty. The capsule is thin and strips easily from the smooth congested surface. On section there is marked congestion. The cortex is swollen, thicker than normal, and can be easily differentiated from the medulla. Sometimes the cortex is gray in color and frequently flecked with small hemorrhages. The glomeruli are prominent. (16) (42) (50) (59)

Microscopic appearance: Boyd (16) describes the glomeruli as being swollen, congested and the seat of cellular proliferation. Foster (42) found a proliferation and desquamation of the epithelial lining of Bowman's capsule, also thrombosis of the capillaries forming the glomerular tuft. Degenerative changes are often found in the tubular epithelium, and the tubules may be filled with blood and casts. (42) (16) Guthrie (50) performed autopsies on 46 cases of nephritis and found widespead hemorrhage into Bowman's capsule and into the tubules. This varied from a few cells to massive hemorrhage. The renal vessels were all intensely engorged. The glomeruli were moderately enlarged with slight proliferation of the capillary endothelium in the tuft. The

changes in the tubules was a mild degeneration in the tubule cells, chiefly cloudy swelling. The interstitial tissue was slightly edematous in 2 cases, and one case showed early fibrosis and very slight polymorphonuclear cellular emigration around the individual glomeruli. Boyd(16) found little abnormality in the interstitial tissue. Foster (42) frequently found an exudate in the interstitial tissue.

Aldrich (2) preformed 21 autopsies and observed that the changes were not very constant, some kidneys showed tremendous changes and some almost negligible ones.

Clausen (31) describes a systemic pathology in which the essential changes is a wide spread injury of the capillaries. This is seen by viewing the capillaries at the base of the finger nail. Here the vessels are more numerous and more tortuous than normal. They may show aneurysmal dilatation, may be branched, and show segmentation due to spasm. The arterial limb is often much narrower than normal, and the venous limb much wider. Similar changes are seen in vasomotor neurosis in which no nephritis is present, but in nephritis progressive and regressive changes are observed from day to day. Probably these changes are associated with hypertension, and when occurring inthe brain, may be the cause of ~~eclampsia~~.

NEPHROSIS

The kidneys are enlarged and pale yellow in color. The capsule is not adherent and the surface is smooth. On cut section the cortex is thick and the color is grey, tinged with yellow. Many bright flecks are scattered throughout the cortices. Microscopically the most striking changes are in the tubules. The tubules are dilated and lined with a very flat atrophic epithelium containing large amounts of doubly refractile lipoid. The glomeruli in some cases are entirely normal in appearance. In others, the glomeruli may contain hyalin thrombi. The interstitial tissue is usually normal except for slight scarring. There are hyalin casts and much albuminous material in the tubules. Cases of long standing may show anatomical changes in the glomeruli. (36) (59) (6) (16) (81) (110)

The liver may show slight atrophy and degeneration of the hepatic cells. This may be interpeted as as effects of overtaxed functional activity consequent to loss of blood protein. (110)

Acute Interstitial Nephritis: This is a relatively uncommon condition. It is seen as a complication of s sepsis, occasionally in association with diphtheria or other infectious diseases. (59) The kidneys are enlarged pale, and rather soft. On cut section there is partial

obliteration of the normal markings. There is marked cellular infiltration of the interstitial tissue. Holt and McIntosh (59) describe this cellular infiltration as being of mononuclear cells in foci throughout the interstitial tissue. Guthrie (50) found that the type of cellular infiltration differed, polymorphonuclear cells being fairly abundant in one, and lymphocytes and large mononuclear cells in others. The glomeruli may be quite uneffected, except in the most cellular areas. The same is true of the tubules, although some show degenerative changes, and those caught in the inflammatory area suffer from pressure atrophy. Extensive interstitial lesions may escape detection during life because the excretory function of the kidney may be unimpaired and little information concern-the lesion can be acquired from a study of the urine. (59)(50)

Since there are many more functional units in the kidney than are necessary for the maintenance of life, and the cells of the tubules have a remarkable capacity for regeneration and compensatory hyperplasia, enough units are usually left intact to maintain life after any one of the three acute processes or until new tissues is formed to compensate for that destroyed beyond repair. Destroyed glomeruli can ot be restored

to normal. Therefore they are partially or entirely replaced by connective tissue. Slight glomerular injuries can heal perfectly. Tubular epithelium can regenerate perfectly. Inflammatory exudate can be completely removed from the interstitial tissue, leaving no trace. However, a severe enough damage to the tubules or the interstitial tissue will result in its replacement by scars. (59)

The pathology of chronic nephritis will be discussed in the section on renal rickets.

PATHOGENESIS OF EDEMA IN NEPHROSIS

Relation between plasma protein level and edema;

Farr and Van Slyke (40) made 114 observations on ten children of various ages who had edema of the nephrotic type. The duration of the illness when the patients were admitted to the hospital varied from 3 days to 3 years. The periods of observation varied from 9 months to 3 years. They found that edema was quite regularly absent when the plasma albumin level was above the critical point of 1.2 grams per 100 cc. This is markedly lower than the critical level for adults which has been reported as 2.5 grams per 100 cc.

When the plasma albumin was below the level of about 1.2 grams per 100 cc., salt restriction caused no diuresis and had no marked effect in controlling the edema. In a small group of patients where the plasma albumin level ranged between 0.81 and 0.97 grams per 100 cc., mercurial diuretics and urea used for a diuretic were not effective.

Relation between colloidal osmotic pressure of blood plasma, protein level and edema:

The colloidal osmotic pressure of the blood plasma which is 25 to 30 mm. of mercury, is maintained largely by the plasma proteins. The individual plasma proteins

have a different osmotic pressure. That exerted by the smaller molecular complex of albumin is much greater than that exerted by the larger globulin and fibrinogen. A change in the relative proportions of the different proteins may change the osmotic pressure of the plasma, yet the total amount of protein may remain the same. The normal capillary wall is impermeable to the plasma proteins. The colloidal osmotic pressure of the plasma proteins which is their attraction for water, tends to counteract transudation from the capillaries and aids absorption from the tissue spaces. The hydrostatic pressure, which is higher in the arterolar than in the venous end of the capillary, tends to force fluids out into the tissue spaces. Normally there is an equilibrium between these two processes. A decrease in the protein osmotic pressure in the plasma would likely result in fluid passing out into the tissues. In nephrosis the protein lost in the urine is almost entirely albumin. This may be explained by the fact that the albumin molecular complex is smaller and would pass through the renal filter more readily. This would result in lowering of the protein osmotic pressure, even though the globulin and fibrinogem content of the plasma is little if any diminished. (25) Calvin and Goldberg (25) studied the plasma proteins in 12 cases of

nephrosis and the nephrotic syndrome. They found the albumin usually markedly decreased. The globulin was little decreased and even often increased so that there was a reversal of the albumin-globulin ratio. The total content of the proteins in the blood was always decreased somewhat, but often very little because of the increased globulin content. The reduction in the serum albumin and edema very frequently occurred together. However, sometimes the edema appeared and disappeared more rapidly than the changes in the blood proteins, which suggests some other unknown factor.

Cholesterol and edema:

Marked lipemia and lipoidemia (cholesterolemia) are practically always found in the nephrotic syndrome, whether in the rarer true nephrosis or in the more common nephrotic type of glomerulonephritis. The blood cholesterol is often over 500 mg.%. Fatty acids are increased in the blood even more markedly than cholesterol. The cause of hypercholesterolemia in renal disease may be that there is a primary or secondary disturbance of the fat metabolism, independent of the kidney, resulting in lipoidemia, and the excretion of excessive amounts of cholesterol through the kidneys causes a deposition of lipoids and damage in the renal tissue. The hypercholesterolemia may be compensatory factor for the low

protein level of the blood. The primary disturbance may be in the liver which results in a retention of cholesterol in the blood and resultant damage to the kidneys. (26)

Calvin and Goldberg (26) studied 12 patients with reference to changes in blood cholesterol and edema. They found that in general, the values of cholesterol varied directly with the degree of edema, being highest during the greatest period of edema and falling as the edema disappeared. There were several outstanding exceptions to this rule, however. In 3 cases the values for cholesterol actually rose about 200 mg.% higher as the edema disappeared which was not due to the blood becoming more concentrated because values of the other blood constituents did not change to any extent.

Other findings by these investigators were: the patients were markedly emaciated when the edema disappeared, especially an absence of subcutaneous fat even though the blood cholesterol was high, which is evidence that the cholesterol is mobilized from fat deposits in the body; the amount of cholesterol in the diet did not apparently influence the hypercholesterolemia; cholesterol can readily pass through the kidney; cholesterol has difficulty in passing from the blood to

the tissue fluids because it was very low in the tissue fluids; and a low blood sugar was noted which favors disturbed liver function as a factor.

They concluded that the hypercholesterolemia is probably due to a disturbance in the fat metabolism accompanying the nephrotic syndrome and is not the cause or the result of edema.

SYMPTOMS AND SIGNS

Acute Glomerulonephritis

Acute glomerulonephritis is the form most frequently seen in children. It is usually preceded by an acute illness commonly associated with the hemolytic streptococcus. A period of from a few days to two or three weeks following the recovery from an attack of acute tonsillitis, acute pharyngitis, or other febrile diseases may elapse before the onset of the renal symptoms. The child may be up and about and may even have returned to school. The signs that usually first attract attention to the condition are puffiness about eyes, especially in the mornings, and a bloody tinge to the urine. Either one may be noted first. In many cases a certain amount of pallor and the continued presence of blood in the urine are the presenting signs. These may persist for a period varying from 4 to 6 weeks, or even longer. (15) It is not uncommon for a mother to come to a physician saying that the child had an acute upper respiratory infection, two weeks later a bloody urine was noticed, and finally a swollen face developed. (5)

Edema;

The edema may be so slight that only the use of

scales or the observation of the urinary output will indicate it. Ocasionally there is extreme ansarca. The altered water balance in the tissues is indicated by the increased speed of absorption of salt solution injected intradermally and by the decrease of sensible persperation. (31) Boyd (16) found that slight edema of the eyelids and about the ankles was common. This tended to disappear in a few days and was not accompanied by marked diuresis but there was a persistent increase in excretion.

Rennie (90) studied ten cases of nephritis in infants under 18 months of age in the Royal Hospital for Sick Children, and found that edema of the face was the most frequent site. Other sites included the legs, sacrum, chest wall lumbar region, some cases showed generalized edema and a few had ascites. Other cases reported in young infants showed generalized edema as one of the first symptoms. (107) (33) Most quthors state that there is a slight amount of edema, usually slight puffiness of the eyelids or face, in acute glomerulonephritis, or that edema may or may not be present. (108) (54) (95) (2) (14) (86)

Hypertension

Normal blood pressure ranges from 89 at 4 years to 112 at 15 years (systolic). (31)

The blood pressure is usually not increased in acute glomerulonephritis in children. (59) (95) (54) (86) (10) However, some authors report a slight elevation.(14)(31) and Aldrich (2) found the systolic pressure elevated above 130 mm. of mercury in 26 per cent of his cases. Ahigh blood pressure or a rising blood pressure is generally a danger sign of cerebral complications.

Urinary Findings

The terms used to describe this condition, acute hemorrhagic nephritis or acute glomerular nephritis indicate that there is glomerular damage and blood in the urine. Blood cells in the urine indicate that the glomeruli are damaged. (36) The mount of blood varies from enough to give the urine a slight smaky color to a marked red color. Most writers state that the urine is bloody, or hematuria is present. (16)(49)(95)(54)(14) The hematuria is macroscopic in the majority of cases.(2)

Other urinary findings include albumin, white blood cells and casts. The casts are of all varieties, hyaline, granular, epithelial and blood casts. The albumin is usually moderate in amount. The urine may be reduced in amount. This is usually not marked. (86) Anuria is rare.(59) Occasionally the suppression of urine is quite marked. (16)

Kidney function tests.

Hill (52) divided the renal function tests into 2 groups. One dealing with the tests which measure the power of the kidney to excrete chemical substances that are not ordinarily contained in the food: and one which tests the ability of the kidney to excrete substances contained in the food. He states that the excretion of nitrogen, salt, and water are the three most important functions of the kidney. The phenolsulphonephthalein test measures the power of the kidney to excrete chemical substances not ordinarily found in the food. The technique of this test is as follows; 6mg of the dye is injected intramuscularly, the urine is save for 2 hours, is made alkaline with soda hydrate to bring out the color of the dye, the volume is diluted to 100cc. and the color intensity compared with that of a standard solution. The results are expressed in the percentage of dye excreted in 2 hours. For the adult 50 to 80 per cent excreted in 2 hours, is considered as normal. Below 50% is abnormal. There is a considerable variation from this in children Hill tested 27 normal children between the ages of $2\frac{1}{2}$ years and 11 years. The highest figure obtained was 100 per cent excretion in 2 hours and the lowest was 64 per cent. The average was 76 per cent. He concludes that the average phenol-

sulphonephthalein test is about 75 per cent and one below 60 would be considered as abnormal.

In 21 acute cases of nephritis the average as 59% which is 17% below the normal This test was not infrequently found high in children in which there was unquestionable severe kidney damage. However, a low test in acute cases was condiered as indicative of severe damage.

Other tests designed to determine the functional capacity of the kidney were discussed by Hill(52) in the same article. These tests were: the added salt and urea test; the "two hour" renal test; and the blood urea-nitrogen. The added salt and urea test consisted of the addition of a known amount of urea to the diet and the determination of how much was excreted in a given period of time. It was found that the response varied widely in normal children, so was not of much value. The "two hour" renal test consisted of giving a full diet, containing a considerable amount of purin bases, nitrogen and salt. The noon meal contained mor of these than the other meals. The fluid taken with each meal was the same in amount, and none was taken between meals or at night. The test takes one day. Two hour urine specimens were collected. A normal response is shown by a considerable variation if the amount,

specific gravity, nitrogen, and salt concentration in the two hour specimens, and a relatively small amount of night urine of high specific gravity, and high nitrogen concentration. An impaired function shows little variation in the specific gravity and nitrogen and salt concentration. The night urine is apt to be large and the nitrogen concentration and the specific gravity low. The fixation of the specific gravity being the most important thing to watch. The results of 15 normal children studied showed the same results as normal adults do. Sixteen nephritics were studied and in nearly all a definite fixation of the specific gravity was noted. It was not stated whether these were acute or chronic cases. Hill thought that it might be possible that relatively marked fixation of the specific gravity may mean that there is only slight functional damage, and that a good deal of caution is necessary in the interputation of this test. The blood urea nitrogen: Leopold and Bernhard found a considerable variation in normal children, from 8 to 15 mg.%. A figure above 15 is considered as abnormal. Twelve nephritic children were studied by Hill and found that there was urea retention in chronic cases. He concluded that this test was not of much value.

Crawford (340) Boyd (16) and Morse (86) found

little diminition of the functional capacity of the kidney in acute glomerulonephritis.

Cutter and Morse (35) studied two cases of acute nephritis in children, and found that retention of creatinin and creatin nitrogen is a matter of less than 24 hours. The excretion of these substances varied from day to day and the amounts were not correlative with any known condition. Their results showed a wide divergence from that reported for adults in which retention of creatin and creatinin is described.

The bacteriology of the urine is acute nephritis in childhood: Hill, Hunt and Brown (58) took urine cultures from 21 cases of acute nephritis. The results indicated that there were no bacteria in the urine and probably none in the kidneys after the disease has once been established.

Rennie (91) Aldrich (2) and Blackfan (4) found an elevation in the blood non protein nitrogen in the majority of cases. This was not marked.

Other symptoms: There is some headache, languor, lack of appetite, occasionally vomiting and generally marked anemia. There is usually little or no fever. (59)

NEPHROSIS

The patients are usually brought in because of the presence of edema which may develop without any preced-

ing infection or may appear after an acute infection, usually of the upper respiratory tract. The onset of the edema is usually gradual however, at times it is very rapid. It may be progressive or may present daily fluctuations. Occasionally an attack is ushered in by nausea and vomiting which may be accompanied by suppresiion of urine. The edema may be extreme, the eyes being swollen shut, legs swollen, marked ascites and the scrotum distended with fluid. However, the patient often feels well and has a good appetite in spite of the edema. The tendency to collection of fluid in the serous cavities is quite different in different children.

The volume of urine may be decreased or increased. It usually is decreased with the development of edema and increased with the subsidence of edema.

There is no fixation of the specific gravity of the urine. No hematuria. A large amount of albumin is found in the urine. Large quantities of doubly refractile lipoid bodies are sometimes found in the urine, also numerous hyaline and occasional granular casts.

The chlorides and cholesterol of the blood are increased . There is a low value of the plasma proteins with the reversal of the albumin-globumin ratio.

The non protein nitrogen and blooe urea are usually normal. The blood pressure is usually normal. (36) (59) (27) (99) The total fixed base is nearly always markedly decreased. (14) The edema is cyclic, of a soft, pitting, easily shifting type. The edema fluid is very low in protein content and is easily obtained by puncture of the skin. It is apparently an extracellular, noninflammatory edema. (25) (27)

Subacute Parenchymatous Nephritis, or mixed type:

This is a group in which it is not possible to tell at the time of observation whether the disease started as an acute hemorrhagic nephritis or as a nephrose. There are outstanding characteristics of both types.

The onset is usually insidious. Edema is usually the outstanding complaint. The history often reveals that there was some puffiness of the eyes several months before the edema became striking. The blood pressure is slightly elevated, and there is a moderate grade of anemia. The urine contains may red blood cells, often frank hematuria. There are large quantities of albumin in the urine. The serum protein is low with a reversal of the albumin globulin ratio. The non protein nitrogen of the blood in slightly elevated, and a slight diminution of the phenolsulphonephthalein test is often present. The disease is characterized by remissions and exacerbations of the edema and hematuria. (59)

CHRONIC NEPHRITIS

This condition is not frequently seen in children. A few result from acute nephritis. Some are due to back pressure destroying the kidney tissue due to congenital malformations, and some are the result of chronic infection. Acute nephritis is sometimes superimposed on a pre existing chronic nephritis. The symptoms of chronic renal insufficiency are present in all cases.

Edema: Lindsay (69) reports a case in a girl of 13 years in which there was no edema. Calvin and Rosenblum (24) report two cases in which no edema was present. Edema is present at some time in all cases according to Aldrich. (2) Holt and McIntosh say that in some patients the edema is nearly constant in degree, and in others it fluctuates greatly from time to time.

Loss of weight, anoxeria, abdominal pain, and vomiting are frequent symptoms. (97) (69) Also weakness and pallor (24). These symptoms come on gradually. Headache and anemia is always marked.

Eye Symptoms and findings: Lindsay (69) reports the following ophthalmoscopic findings; typical signs of albuminuric retinitis - large tortuous vessels and white spots, also swelling of the retina and papilla edema.

Cabot (23) describes a case in a nin year old child whose first symptoms were pain in the eyes and loss of vision. Examination of the eyegrounds showed albuminuric retinitis. Pain in the eyes and diplopia is described by Scobey (97). Holt and McIntosh (59) say that marked changes are often seen in the eyegrounds - edema of the disc and of the entire retina, retinitis, hemorrhages, and even detachment of the retina.

The cardiovascular system: In some cases the heart is not enlarged nor the blood pressure greatly elevated. (59) However, Scobey (97) reports a case in which the cardiovascular changes were very marked. There was palpitation and dyspnea on exertion. All palpable blood vessels were hard and resistent. The blood pressure was 250/320. The X-Ray showed enlargement of the heart to the left with mitral configuration. This marked degree of arteriosclerosis is a rare finding in early life. The case was written about because it is unusual, and because of its similarity to the adult picture of chronic nephritis.

Bierring (11) reports 2 cases of chronic nephritis in a girl of 11 and one of 15 which were attended by severe cardiovascular changes.

Calvin and Rosenblum (24) report two cases in which there was no elevation of the blood pressure, and

but slight enlargement of the heart. In Lindsay's (69) case the heart was enlarged to the left and the blood pressure was 239/212. Berkley and Lee (10) found a definite increase in the blood pressure. The average was about 20 mm. of mercury systolic and about 10 for diastolic above normal.

Urinary findings: Albumin, red blood cells, casts, and leukocytes are the usual findings. The amount varies in different cases and in different stages of the disease. A small amount indicates the disease process is in a mild stage. (57)

The specific gravity is fixed at a low level. (69)(24)(97) A large amount of urine is passed. The night urine is equal in amount to the day urine. Nocturia and enuresis is common. (97)(24)

Blood.

The nitrogen retention increases as the time goes on. (59). There is marked anemia in advanced cases. The blood urea and creatinin levels are high. (2)(69)

Kidney Tests

Hill (52) found that the phenolsulphonephthalein excretion in chronic cases was likely to behigher than in acute cases which is the reverse in adults. Even in the very severe cases the phthalein excretion was not as low as would be expected. He not uncommonly

saw normal excretion in a child who had had nephritis for 2 or more years, was edematous and anemic, increased blood pressure and urine loaded with albumin and casts.

Crawford (34) found an average of 57% excretion in chronic cases as compared to 67% in normal children. However, some were as low as 2%.

DIFFERENTIAL DIAGNOSIS OF ACUTE GLOMERULONEPHRITIS

1. Other causes of albuminuria: Albumin may be found in the urine in conditions other than nephritis. Albumin in the urine is often seen in febrile states. It is probably due to coudy swelling of the kidneys in such instances. It clears up soon after convalesence. Albumin may be found in perfectly healthy children. It may be found after exercise, over eating, and exposure to cold. It is sometimes seen in rapidly growing children, and in adolescence. Then ther is the condition known as orthostatic albuminuria.

2. Vesical calculus rarely causes so much blood and is nearly always accompanied by severe pain. Vesical polyps are extremely rare in children. (49)

3. Nephrosis: Generalized edema, normal blood pressure, marked albuminuria, no elevation of the non protein nitrogen, low serum albumin, and high cholesterol are factors in favor of nephrosis.

4. Acute exacerbation of chronic nephritis: This question would arise in older children. A history of long continued ill health with malnutrition, anemia, dyspnea, and fatigue along with a history of polyuria with examination showing hypertension, heart enlargement fundi changes and evidence of advanced kidney lesion would all point to chronic nephritis.

COMPLICATIONS OF ACUTE GLOMERULONEPHRITIS

Probably the most frequent complication of acute hemorrhagic nephritis, and the most alarming one is the development of cerebral manifestations. This complication is characterized by headache, vomiting, visual disturbances, frequently a slowing of the heart and respiratory rates, coma, convulsion, and finally death. (15) (76) (4) (38) A rising blood pressure in children with acute glomerular nephritis is a danger sign of the development of crebral complications. A rise above the level of 120 mm. Hg systolic, practically a steady rise, usually denotes the onset of cerebral symptoms. When the blood pressure rises above 140 the patient may vomit or complain of a headache. A further rise indicates the danger of coma or convulsion. The rapidity of the rise is as important as the degree of elevation. (15) This complication has been termed uremia, pseudo-uremia, or convulsive uremia. The development of these symptoms is not related to the nitrogenous end products and may occur in the presence of normal kidney function, so the term uremia is a misleading one. The term cerebral manifestations of acute glomerularnephritis is a better one. At autopsy the brain has found to be firm and found to weigh 20-30% more than the normal for the age.

The dura is tense, the convulutions flattened, and at the base is found the so called medullary cone phase which was produced when the medulla was forced into the foramen magnium as the result of rapid increase in the brain volume.

Cerebral edema, which has been confirmed at autopsy, seems to be the cause of the development of the cerebral manifestations. (15) (76)

Rennie (92) states that convulsions associated with acute nephritis in children is not uncommon. The onset of the cerebral manifestation is indicated by headache, persistent vomiting and drowsiness. The blood pressure is raised. Convulsions and coma may then follow, and the patient may die as the result of heart failure, pulmonary edema, or bronchopneumonia. The convulsions are usually generalized, and they are indistinguishable from fits due to other causes.

Rennie (92) discussed the incidence, cerebral symptoms, pathogenesis, and diagnosis of acute nephritis in which convulsions occurred.

Incidence: Of 9310 acute cases of nephritis admitted to the Royal Hospital for Sick Children at Glasgow in 5½ years, 23 had convulsions, or 7.4%. This figure is probably high since cases with convulsions would be more frequently admitted to the hospital. Sixteen were

males and seven were females.

Cerebral Symptoms: The duration of the nephritis ranged from 4-23 days before the onset of cerebral symptoms. Vomiting and headache were the usual features. All of the patients were drowsy and nineteen were more or less comatose. Blindness was present in four patients, and three complained of dimness of vision. The cerebral spinal fluid was under high pressure, but otherwise was normal. The blood pressure was invariably raised. There seemed to be no relationship between the presence of edema and the cerebral symptoms. The same was true for the blood non protein nitrogen.

Pathogenesis: Autopsies on three cases that died showed edema of the brain and nothing else. The cerebral symptoms and cerebral edema may be due to the constriction of the cerebral arterioles. This would lead to ischemia of the brain which would account for the temporary attacks of paralysis and amaurosis. It is believed that cerebral edema can be produced by prolonged cerebral ischemia.

Diagnosis: The diagnosis in a case of acute nephritis with a history of hematuria and showing edema would not be so difficult. However, if there is an indefinite story of being "out of sorts", followed by drowsiness, convulsions, and coma in a patient showing little or no edema it would be more difficult. The possibility of other causes of convulsion should be kept in mind, such

as meningitis, epilepsy, polio-encephalitis, spontaneous intracranial hemorrhage. A high blood pressure in a comatose child with a history of convulsions is almost pathognomic of cerebral manifestation of acute glomerular nephritis. Examination of the urine would yield important confirmatory evidence. (92)

Anuria, or renal shutdown, as termed by Lyttle, (76) is another serious complication of acute glomerulonephritis. It is best explained by arteriolar spasm and decreased blood flow through the kidney. This idea is supported by the fact that termination of the anuria and the appearance of sudden duiresis is too sudden to be explained by the subsidence of inflammatory lesions.

This and the cerebral manifestations seem to be further evidence that acute glomerulonephritis is but one manifestation widespread capillary injury.

Cardiac involvment may occur during acute glomerulonephritis in children. According to Lyttle (76) there is clinical, X-Ray, or electrocardiographic evidence of cardiac involvement in over 60% of the cases. The signs being dyspnea or dizzyness when the patient sits up, hypertension, a low pulse pressure, or the poor quality of the heart sounds and a systolic murmur.

Rubin and Rapoport (94) in 55 cases of acute hemorrhagic nephritis studied at the Children's Hospital at Philadelphia found 14 cases with varying degrees of cardiac involvement during the acute stage of the disease. Involvement of the heart was the most frequent complication observed in these 55 cases. The clinical evidence of cardiac involvement and failure observed in these cases were: (a) dyspnea, tachycardia, and cough, (b) enlargement of the heart, as demonstrated by physical examination and x-ray, (c) muffled heart tones, (d) rapid heart rate, (e) murmurs, usually a mitral systolic murmur, which was often the last evidence of cardiac damage to disappear as the patient recovered, (f) enlargement and tenderness of the liver, (g) engorgement of the venous system, (h) pulmonary edema, (i) peripheral edema, (j) electrocardiographic changes indicative of varying degrees of myocardial damage.

Moycardial damage and increased peripheral vascular resistance are factors which may effect the heart. The myocardial damage may be due to the same agent causing the kidney damage, since it has been shown that the occurrence of myocardial damage during the course of an acute streptococcal infection is fairly common, and acute hemorrhagic nephritis is closely associated with hemolytic streptococci. The heart responds to increased

peripheral resistance by dilatation of the left ventricle, and ultimate hypertrophy. In cases where the heart has been primarily involved with the disease, it is likely to fail under the added strain of a sudden increase in peripheral resistence. Therefore, the development of heart failure depends on the extent of the myocardial damage and the degree of hypertension. (94)

A small group of cases develop extensive vascular changes. Hyalin degeneration in the muscularis of the arteries and a general capillary fibrosis develops. They have "pipe stem" arteries, and the blood pressure is permanently elevated, often to extreme degrees. (38)

The development of chronic nephritis from the acute variety is not very common. Rennie(92) followed over 90% of the cases admitted to the Royal Hospital for Sick Children in Glasgow and found no evidence of chronic nephritis.

PROGNOSIS

Acute Glomerulonephritis

In the individual case the prognosis is difficult because mild cases may go on to chronicity and death, and severe cases often improve suddenly and recover. (86) However, the prognosis as a rule is good in acute hemorrhagic nephritis. The greater percentage of the cases recover absolutely, leaving a perfectly good kidney behind. However, a few develop into chronic nephritis. (63) (56)

The prognosis is considered from two points of view. First the immediated danger to life, and secondly the development of chronic nephritis. (59) The mortality figures during the acute stage of the illness, and the percentage that develop chronic nephritis, are somewhat different as given by the different authors. In Hill's (55) series of 52 cases of acute nephritis, there were two deaths, and four developed chronic nephritis. He believes that the kidneys in the cases that recover are no more susceptible to damage later than are any other kidneys, and states that Ernberg in 1911 located and examined forty adults who had had acute nephritis before the age of 15 and found normal urines in all.

Aldrich (3) had a mortality of 6.2% in a series of 186 cases. Tallerman (105) in a series of 27 consecutive cases reexamined 18 months to 3½ years after discharge from the hospital found that 2 had died (7.4%) 18 completely recovered (66.6%) and of the remaining 7, only 4 showed any evidence of persisting renal damage. Boyle and others (20) examined 25 children who were clinically recovered from acute nephritis for a period of from one half to eight years. They found that the results of the Addis tests corresponded very closely to those obtained on normal children. They feel that this is evidence that children who have clinically recovered from acute hemorrhagic nephritis do not have subacute or latent nephritis.

The following table shows the cause of death in acute nephritis in children as reported by different observers. The total deaths was 68 out of a total of 722 cases, or 9.4%. (76)

Cause of Death	Number
Infection	28
Cerebral edema	9
Renal failure	12
Uremia (type not stated)	13
Cardiac failure	6

The duration from the time of onset until the urine is free from albumin, blood, and casts, is usually from 6 to 12 weeks. (55) If the initial infection is an accessible pus pocket where free drainage

can be established, such as a maxillary sinusitis, or retropharyngeal abscess, the duration of the nephritis is usually short, otherwise the nephritis is apt to be prolonged for many weeks. (42)

Recovery occurs sooner in the younger patients. (45) (59)

The development of subacute and chronic nephritis is relatively infrequent considering the frequency of acute nephritis.

In those cases that develop cerebral manifestations and recover the ultimate prognosis is not adversely affected. (92)

NEPHROSIS

The prognosis of nephrosis is good from the standpoint of the kidneys themselves. However, these patients are very susceptible to secondary infection. The usual cause of death is some intercurrent infection, which is quite often a pneumoccocus infection either generalized or in the form of a peritonitis. (59) The reason why these patients are so susceptible to pneumococcus peritonitis is not known. (36) Hemolytic streptococcal peritonitis and septicemia are also quite frequent causes of death. (110) This low resistence to infection makes the prognosis uncertain in any case.

Ascites may develop quite suddenly, also pleural effusions which may displace the heart sufficiently to

cause cardiac embarrassment. Edema of the prepuce may cause difficulty in urination, and edema of the glottis or brain may cause death. (27)

In the twenty cases studied by Davison and Salinger (36) 6 died giving a mortality of 30%. Clausen got a mortality of 43%. According to Bruce (22) about 50% recover.

Complete recovery does occur. The disease runs a chronic course and it may be several years before the patient is completely free of edema and albuminuria.

CHRONIC NEPHRITIS

The prognosis in chronic nephritis is almost always bad. Death may occur during some intercurrent infection, or the child will ultimately die in uremia. The duration of life cannot be stated definitely. Under proper care the child may live for many years. A rising blood non protein nitrogen, fixation of the specific gravity of the urine, and poor dye excretion are signs of a bad prognosis. (16) (59)

TREATMENT

Acute Glomerulonephritis

Prophalaxis: The preventive treatment consists of the use of measures that would tend to shorten the febrile period of any acute infection, especially of the upper respiratory tract. These measures would be keeping the child in bed, giving adequate fluids, avoidance of chilling, and prevention of infection. (5) There seem to be more cases of nephritis in the poorly cared for children than in the ones that are properly cared for. These measures are practically always used in any illness, yet some cases develop nephritis. Lyttle (74) believes "that it is settled early in the course of the disease which cases will get nephritis."

Addis (reported by Lyttle (74)) tells a story which appears to be good evidence that chilling is an important factor in acute glomerular nephritis. There was one bed on a scarlet fever ward that was called the "nephritis bed" because many of the children that occupied this bed developed nephritis. Finally it was discovered that a ventilator was near the bed which directed a draft of cold air against the backs of the patients if they sat up. The ventilator was closed and the nephritic rate dropped to normal.

Peters (89) found that the occurrence of renal complications following scarlet fever could be materially reduced by giving slkalies until the urine was alkaline to litmus. He gained an 80% reduction by this method.

It has been claimed that scarlet fever antitoxin will reduce the incidence of nephritis following scarlet fever, but there is no good basis for this idea.(74) A high protein diet has been thought to increase the per centage of post scarlatinal nephritis. This was disproven by Aldrich.(5)

Morse (86) advocates the removal of of adenoids and clinically diseased tonsils before they have a chance to cause trouble. This operation may prevent some cases of acute glomerulonephritis, but it would be difficult to prove. Lyttle (74) sites a series of 44 patients with nephritis, fifteen of which had the tonsils and adenoids removed before the onset of the nephritis.

Since acute glomerulonephritis is so frequently associated with infections with the hemolytic streptococci the use of sulfanilamide will doubtlessly be a valuable aid in the prevention of acute nephritis. No reports were found in the literature concerning its importance as a preventive measures.

The proper treatment of acute diseases that might develop into acute nephritis is no doubt a very important factor of the preventive treatment of acute nephritis. The urine should be examined frequently during these diseases, also during the convalescence of these diseases because if nephritis is recognized early and properly treated, it rarely becomes severe.(86)

Drugs

The use of drugs is not an important factor in the treatment of acute glomerulonephritis in children. The use of diuretics is considered by most quthors to be of no value and may even do harm in some cases, therefore they are contraindicated. (55) (86) (56) (31) (95) (5)

Asprin may be used for symptomatic relief.(5) (44) Many authors recommend the use of small quantities of alkalies to counteract the tendency to acidosis. (109)(5) Grulee (49) used sodium bicarbonate or potassium citrate in sufficient doses to keep the urine slightly alkaline.

Magnesium sulphate is a very valuable aid in combatting the cerebral manifestations of acute glomerulonephritis. Its use will be discussed under the treatment of complications.

Goodwin (44) and Lyttle (76) mention the use of sulfanilamide in the treatment of acute glomerulonephritis

but make no conclusions as to its value. Goodwin states that "so far no one has demonstrated any harmful effects on the kidney from this drug in therapeutic doses. Therefore, it seems reasonable if there is a coincident infection with the hemolytic streptococci to employ it even during the presence of nephritis". Lyttle used the drug in a few cases on nephritis with actibe streptococcus infections. He states that "the only thing I can say about it is that if renal function is impaired the level of sulfanilamide in the blood must be carefully watched". Goodwin also cautions about the use of the substance in the presence of impaired renal function.

Bed rest

Bed rest is a very important part of the treatment. This is of the utmost importance even if the attack is mild. The child should be kept warm and free from exposure to drafts. (44) (56) (49) (54) The period of complete bed rest is usually from six to ten weeks. The child may be allowed up when the kidney function is normal, the blood pressure normal, the infection subsided and when the urine shows only a trace of albumin with few casts and cells. This process of getting up should be gradual. There may be moderate urinary changes with no other clinical findings for

a period of six to twelve months. However, this does not necessitate a rigid restriction of the child's activity. If allowing the child to be up increases the urinary changes, he should be put back to bed. (74)(75)(54)

Diet and Fluid Intake.

The generalconsensus of opinion is that fluids should be given freely and that a rigid restriction of the diet is not necessary. Fluids were given freely irrespectively of the edema by Aldrich (2) and the patients were less toxic and more comfortable when given adequate fluids. He suggests that the edema may be a protective measure to dilute toxins. Grulee (49) Schultz, (95) Aldrich (4) Holt and McIntosh (59) and Foster (42) advocate a large fluid intake. Others advocate a restricted fluid intake, especially in the presence of edema, or a close paralellism between the intake and output. The more recent articles discussing this subject recommend a large amount of fluids, or as much as the patient desires.

For the first few days of the illness, the patient should be kept on a bland diet consisting of chiefly milk and cereal food. (59) Lyttle (75) recommends a diet low in protein and salt and high in carbohydrates and fats disregarding the caloric requirement for the first four to seven days. An adequate diet should be provided as soon as the appetite returns and the clinical picture

improves. (75) This type of dietary regime is advocated by most of the recent authors.

Surgery

A rapid improvement of the clinical picture often follows the treatment of foci of infection such as the drainage of an ear infection or of abcesses in the pharynx or cervical regions. Surgical procedures are indicated rather than contraindicated in nephritis even if a small amount of ether has to be given. (5) Major surgical problems such as mastoiditis or peritonsillar or retropharyngeal abscesses should be met with otherwise the patient will become weaker as the nephritis and complications progress.(76) The foci of infection is usually in the tonsils. Their removal should be postponed until the hematuria and albuminuria have diminished, hypertension has subsided, and when the throat is not inflammed. This is usually reached in the first two to four months after the onset of the acute nephritis. (76) (10)

Aldrich (2) removed the tonsils and adenoids as a preventive measure before the patients left the hospital. He found that ether did not hurt these patients.

Jepson(64) reports a case of acute nephritis in a child aged three years in which a pair of unhealthy, inflammed tonsils were removed as a last hope. The patient improved and was well four years later.

Edebohls' Operation. This consists of decapsulation of the kidneys. This operation is not performed often at the present time. Hill(56) states that the operation should only be considered in extreme cases where ther is a large amount of edema that wont respond to ordinary measures or when the patient is in such a severe state of uremia or anuria that the prognosis is very bad. It was used in three cases and undoubtedly saved life on one and temporarily in another. In another article, Hill (55) reports eight cases in which the operation was performed as a last resort. In one acute case it probably saved a life but did not prevent the development of a chronic process. It helped a great deal in one chronic case and in one acute and one chronic case it probably saved life and apparently cured.

Morse (86) believes that this operation should be tried in every case of acute nephritis with suppression of urine and a threatened death from uremia.

No mention of this operation was noted in the recent literature.

Miscellaneous

Clausen (31) reports that persistent hematuria, in absence of serious symptoms, is frequently benefited by one or two "sugar days" in which the ordinary diet is discontinued and the patient is encouraged to drink as

much as he wishes of a mixture of ten grams of cane sugar per pilogram of body weight, dissolved in one or one and one half liters of fruit juice.

Purgation, hot applications to the loins, sweating, and hot colonic flushings have been advocated to help relieve renal congestion. (16) (86) However, these procedures are usually considered as being ineffectual. (5) (31)

Treatment of Complications of Acute Glomerulonephritis

Cerebral manifestations: A steadily rising blood pressure, headache, vomiting, and visual disturbances are signs indicating the development of cerebral manifestations. Later coma or delirium, and convulsions occur. This is the most dangerous complication of acute glomerulonephritis. Blackfan (13) treated this complication with the intravenous injection of a 1% solution of magnesium sulphate and large doses of magnesium sulphate by mouth and rectum. This lowered the blood pressure and relieved the cerebral symptoms. In five to twelve hours the dose was repeated if the blood pressure became elevated again. One to one and one-half ounces of a 50% solution of magnesium sulphate by mouth every four to six hours, and two to three ounces by rectum every six hours were active measures used to control generalized edema.

Since Blackfan's discovery, other authors report good results with the use of magnesium sulphate. Among these include Aldrich (5) (4), Rubin and Rapoport (94) Rennie (92) Lyttle (76).

The above dosage of magnesium sulphate by mouth and rectum is usually enough to produce relief of the cerebral symptoms and a fall in the blood pressure. This does not cause diarrhea in children with the hemorrhagic type of nephritis. The action appears to be one of gradual dehydration, with resultant diminution of cerebral edema. The improvement is gradual and is usually accompanied by a loss in body weight. The administration of the magnesium sulphate should be continued until the blood pressure approaches a normal level. If the patient is comatose or has convulsive twitchings, magnesium sulphate by mouth and rectum is not rapid in action enough to prevent a fatal outcome. In such an instance, prompt relief from the cerebral symptoms and a rapid fall in the blood pressure can be obtained by the intravenous injection of a 1% solution of anhydrous magnesium sulphate. The injection should be slow, from three to four cc. per minute into the vein of the arm. At the same time the blood pressure should be followed on the other arm. The patient may perspire freely, vasomotor flushes run over the body, the twitchings stop, and the blood pressure gradually falls as the

injection is continued. The amount of solution necessary for the desired results is usually about ten percent of the body weight. Signs of respiratory depression may develop if the injection of the salt is too rapid. If this happens, the injection should be stopped for a few minutes, or if it is alarming, it can be relieved by paraenteral injection of five to ten cc of a two or five percent calcium chloride solution. A 25% solution of magnesium sulphate injected intramuscularly has almost as prompt an effect in relieving the cerebral symptoms and lowering the blood pressure as does the intravenous injections. It is seldom necessary to use more than 0.2 cc per kilogram of body weight. If results don't follow the first injection, a second one can be made after two to three hours with relative safety. In some cases it might have to be repeated several times. These injection procedures are emergency measures and do not take the place of the large doses of magnesium sulphate by mouth or rectum. If the blood pressure rises again and the cerebral symptoms recur, the injections will have to be repeated. (15)

Spinal puncture is not without danger in these cases because the sudden withdrawal of fluid may induce the medullary cone phase and death. (76)

Rubin and Rapoport (94) produced vasospasm in rats by feeding them ergotamine tartrate, and were able to

relieve this by including magnesium in their diets. This experimental evidence supports the theory that the cerebral edema is due to spasm of the small arteries of the brain producing eschemia then edema.

Aldrich (5) believes that giving plenty of fluids to patients with acute glomerulonephritis will reduce the number showing cerebral complications. This is based on the theory that the primary causes of edema is a toxin or chemical substance which causes the tissues to absorb more fluid than normally. This fluid and toxins are held in chemical combination with the colloids of the body. With the free administration of fluids, a simple dilution of toxins would follow, resulting in a lowered affinity of the tissue colloids for water, and a liberation of some of the chemically bound fluids. This water would then be free for elimination, and when excreted would carry with it some of the toxins. This would explain the clinical improvement following fluid administration and the subsidence of symptoms preceding a demonstrable loss in weight. (5)

<u>Cardiac Complications:</u> Hypertension is the agent immediately responsible for impairment of cardiac function. The usual response of the heart to increased peripheral resistence is dilatation of the left ventricles, followed by hypertrophy. If the blood pressure is not elevated and the heart is normal the therapy might include the

forcing of fluids in an attempt to dilute the toxins. If the blood pressure rises and signs of myocardial damage develop fluids would have to be restricted because they may further elevate the blood pressure and precipitate a heart catastrophe. Magnesium sulphate will bring down the blood pressure. In case of heart failure rest, restricted fluids, and digitalis would be the treatment. Morphine and chloral are good sedatives to use. (94) (76)

Renal Failure: Renal failure with resultant anuria is very rare. Two cases out of ~~six out~~ of sixty nephritics admitted to the Children's Hospital, Philedelphia, over a period of three years developed it. (93) The treatment employed was forcing fluids given as isotonic glucose and saline intravenously. Hypertonic succrose solution (50) and magnesium sulphate aids diuresis.(93) (76)

TREATMENT OF NEPHROSIS

The treatment should be first directed to the source of infection and foci of infection should be cleared up. Marriott (80) reports a cure following removal of the tonsils and adenoids, and drainage of infected sinuses. The nasal accessory sinuses are often the foci of infection.

The condition is best treated as a deficiency disease with abundant proteins, minerals and vitamines(220

A high protein diet is advocated because of the marked proteinuria which leads to the diminution of protein in the plasma. However, a high protein diet has not been found to increase the protein level in the plasma.(59) One way to increase the level of protein in the plasma is by transfusions which have been found to be followed by good results. (70) (59) (81)

Marked edema is the most prominent symptom of nephrosis. This may be quite distressing to the patient especially if it hinders freedom of movement or causes pain due to stretching of structures. The patient often feels better when the body is not water logged. (27)

Dick and others (37) tried the use of acacia in the treatment of nephrosis. The rationale of this treatment was based on the fact that acacia is an inert colloid which when introduced into the blood stream will raise the osmotic pressure of the blood above levels at which edema occurs. This treatment was tried in four cases,the results were disappointing. The first administration (one gram per kilo of ideal body weight) was markedly effective in reducing edema. The succeeding injections were less effective in reducing the edema and were followed by untoward results. The liver became quite enlarged and tender and the serum protein

became very low and remained very low as long as the use of acacia was continued.

Bruce (22) got several severe reactions with the use of acacia solution, and the results were not favorable.

Schultz and Collier (95) and Lowenberg and Freedman (71) treated nephrosis in children with the alkali method as was first advocated by Osman. The preparation used was equal parts of potassium citrate, potassium bicarbonate, sodium citrate and sodium bicarbonate. Water, and enough flavoring agent were added to disguise the taste. The initial dose was two to three grams three times a day for the first day. This was increased to four times a day on the second day, and thereafter the dose was increased by two to three grams a day until the pH of the urine was from 7 to 7.6. Dosages of from thirty to forty grams a day and even higher were reached with safety. Diuresis usually occurred after the maximum dose was reached. This treatment was followed by marked improvement both clinically and in the laboratory studies. The edema disappeared and the blood protein, albumin, and globulin approached the normal figures. This treatment does not restore a structurally damaged kidney, but a marked improvement or even complete regression of some of the distressing symptoms such as excessive edema,

oliguria, anuria, or excessive proteinuria can be expected. The alkalies are given to restore the plasma bicarbonate to a normal level and to maintain it there. There is some danger of overdosage of the alkalies. This is guarded against by periodic checking of the plasma bicarbonate.

There are three dangerous manifestations watched for in carrying out this treatment. These are tetany, diarrhea, and myocardial weakness. Tetany is prevented or usually relieved by the repeated intramuscular injection of calcium chloride in dosages of 0.05 grams. Diarrhea may occur as a result of the large doses of citrate. Should this occur, the citrates can be withdrawn from the alkali combination. Myocardial weakness may result from the large doses of the potassium salt, and should this occur, the potassium portion may be eliminated.

Schultz and Collier advise that the maximum doses be continued until the edema has completely disappeared and the urinary volume has returned to normal.

Diuretics will sometimes cause loss of the edema, but it usually accumulates again after the drugs are discontinued. Great care must be exercised to prevent superimposed infections. Sometimes the edema disappears with a febrile illness, which led to the use of artificial fever. However, the results have not been satisfactory.

Chronic Nephritis

The treatment of chronic nephritis consists for the most part in relieving the symptoms as they arise and staying the course of the disease as much as possible. Acute exacerbations are treated the same as in acute nephritis.

The patient must be carefully guarded against infection and exposure to cold. He should never be allowed to exercise to the point of fatigue, and adequate rest is important. (59)

Formerly these patients were given a diet low in protein and salt with consistently bad results. This was revolutionized in 1930 by Aldrich who began giving abundant proteins, minerals and vitamins. (22)

Edebohl's operation has been reported as producing temporary benefit. A short discussion of the operation is given under Treatment of Acute Nephritis. Cases due to malformation in the lower urinary tract is mentioned under the section of Renal Rickets.

RENAL RICKETS

Definition

The terms renal dwarfism, renal infantilism, and renal rickets are applied to the same condition, which is a symptom complex of disease of the kidneys and bones with dwarfism and infantilism. The disease is characterized by reduced kidney function, ricket-like change in the bones, and delayed sexual development. (30) The term renal dwarfism is used to denote small stature and stunted growth almost always associated with the chronic kidney disease. Renal rickets, as the term implies, refers to the ricket-like changes in the bones which occurs in about two-thirds of the cases. Renal infantilism denotes the lack of sexual development that occurs in patients who reach the age of puberty. (82) (65) The condition is sometimes associated with congenital changes in the kidneys, such as congenital cystic kidneys. (39) (46) Obstructive lower urinary tract pathology may be associated with it. (66)

Chronic renal insufficiency due to chronic interstitial nephritis is the usual condition of the kidneys (39) (100). This is a very rare disease entity and is practically always seen before or at the age of puberty; very few cases live long enough to become adults.

History

The association of chronic kidney disease with dwarfism, ricket-like changes in the bones, and lack of development of the secondary sexual characteristics occasionally seen in children was not fully appreciated until the early part of this century. Case reports appear in the British literature of the 1870's and 1880's presenting signs and symptoms that are quite suggestive of the condition. Greene (48) states that "the possibility of its occurrence was first suggested in 1872 when Gull and Sutton described a case of contracted kidneys in a nine year old girl". Its actual occurrence was confirmed in 1874 by W. H. Barlow (9) who described what he called Granular Contracted Kidney, in a child of 5 years and 11 months. Since then, a number of cases have been reported in England where the term renal infantilism was given to the condition.

In 1883 Lucas (72) described several cases in which ricketic changes were associated with albuminuria. He stages that "the phenomenon of late rickets and albuminuria are too frequently connected to be matters of chance." Morley Fletcher in 1911 was the first to clearly point out the close association between the kidney and the bony lesions occasionally seen in children. (48)

Reports of cases and discussions of the various aspects of the disease have appeared fairly frequently in the American literature since 1911.

It seems that the condition is more frequently seen in the British Isles than in this country. Whether this is due to the fact that the ordinary type of infantile rickets is of more common occurrence in that country, or perhaps to the different living conditions of the inhabitants, or because the condition was first described in that country, making the profession more aware of the diagnostic signs of the disease, is largely a matter of conjecture.

ETIOLOGY

The cause of this rare disease entity variously known as renal rickets, renal infantilism, and renal swarfism, is not definitely known. The bone changes, the dwarfism, the infantilism are always preceded by changes in the kidneys. The occurrence of congenital malformation of the kidneys and lower urinary tract as the primary cause of the condition were mentioned under the definition. Apparently, the damage to the kidneys occurs early in the life of the individual, and is of a chronic nature, since chronic interstitial nephritis is the usual finding in the kidneys.

Mitchell and Guest (84) suggest the possibility of nephritis occurring during intrauterine life, or very early in infancy. In such a case, the damage is not sufficient to cause death at once, and enough functioning tissue remains to carry on for a time. When greater demands are made on the kidney by such factors as increased body growth, or the increased functional demand for the excretion of waste products which are the end results of tissue destruction by bacterial toxins occurring during infections, symptoms of renal insufficiency develop. (83) (84) There are cases reported in which death occurred in the first few

months of life, and chronic kidney changes were found, and no reasons could be discovered during the life of the infant which would account for these findings. The nature of the pathologic changes in many cases indicate a process of greater duration than the life of the patient. These observations strengthen the idea of intrauterine nephritis. (82) Fletcher (41) supports the idea that renal changes can begin in intrauterine life or in early infancy.

Goldberg and Candido (43) report a case in which a chronic urinary infection produced a bilateral pyohydronephrosis with hydro-ureters and secondary renal insufficiency, which so disturbed the mineral metabolism that the symptom complex of renal rickets developed.

Cases are reported in which renal rickets followed attacks of acute nephritis in children who were apparently healthy and of normal size before the attacks of acute nephritis. (39) (32) However, there was no evidence that there was not any preexisting kidney damage in these cases.

Acute bacterial infections, especially of streptococcal nature, may cause chronic as well as acute nephritis in some cases. An hereditary predisposition to kidney disease may influence this. (83)

Chronic interstitial nephritis and renal rickets

occurring in more than one member of a family as well as in preceding and succeeding generations have been reported in the literature. (77) (82)

Since the advent of the Wassermann test, syphilis is considered as rarely, if ever, an etiologic factor. (77) (82) (100)

Exogenous and endogenous poisons and toxins are seldom etiologic factors. (84)

The majority of cases occur between the ages of 3 and 10 years (61) and the sexes are about equally affected. (100) (83)

The primary cause of renal rickets is chronic interstitial nephritis. The etiology of the primary condition has been discussed and the causes of the other manifestations of the disease will be taken up.

The etiology of the skeletal changes: With the progression of the kidney changes, the excretory function of the kidneys is diminished, which results in a piling up of waste substances in the blood and tissues. This, in turn, may interfere increasingly with the chemical reactions necessary for the normal activity and growth of the body. (84) The kidney normally eliminates phosphorous, but, with a poorly functioning kidney, phosphorous elimination is retarded, and a retention of phosphorous occurs. In such a case, the phosphorous elimin-

ation is shifted to the gastro-intestinal tract, the phosphorous comes in contact with the food calcium, and an insoluble calcium phosphate is formed, which prevents calcium from entering the blood stream, and causes a serious calcium depletion. In order to maintain a normal calcium level in the blood, bone calcium is drafted. This loss of calcium from the bones results in bone changes. (60)

Maddox (77) says that in chronic nephritis, there is a retention of acid phosphates which theoretically should cause a corresponding diminution in the calcium ions in the blood. In renal rickets there is present a chronic nephritis, frequently a normal blood calcium, and a raised plasma phosphorous and phosphotase and a very definite acidosis. The spproximately normal level in the calcium of the blood is maintained by the continuous mobilization of calcium of the bones, which exists under the influence of the raised blood phosphate.

The role of the parathyroid glands in the disease of renal rickets has been discussed by several authors. The parathyroids apparently have some effect on the renal threshold for phosphorous. In the presence of chronic renal damage, there is an elevation of the level for phosphorous which may call forth parathyroid activity just as hyperglycemia apparently is the stimulus

for insulin activity in the normal pancreas. In the presence of chronic renal impairment, the parathyroid stimulation establishes a vicious cycle,and the primary effect of the parathyroid hormone on the renal threshold for phosphorous is defeated by the impaired function of the kidney. (104) Howard (60) believes that this type of rickets is due to a hyperplasia of the parathyroid glands. The hyperactivity of the flands is the factor that mobilizes the bone calcium in order to keep a sufficient level of serum calcium to prevent convulsions, which otherwise would occur early in the disease.

Comp (66) believes that parathyrroid hyperplasia is a secondary phenomenon in renal rickets rather than a primary factor in the etiology of the disease, since renal rickets is a disease of the first decade of life while primary hyperthyroidism is a disease of the fifth decade. Also hyperplasia of the parathyroid glands is observed in bone diseases such as true ruckets, multiple myioloma, and metastitic carcinoma.

The undernutrition seen in these patients is probably to a large extent dependent on a partial starvation due to the anorexia which is present to a varying degree. The faulty synthesis of glycogen by the liver has been suggested by Mitchell (84) as an important factor in the poor development and growth in young nephritic patients.

PATHOLOGY

Kidneys: The pathological changes in the kidneys seen at autopsy are those ascribed to chronic interstitial nephritis. The pathological changes differ slightly in cases that are due to obstructive lower urinary tract pathology, and in cases due to other causes. Howard (60) describes the microscopical changes seen in the kidneys of a case in which bladder neck obstruction was found. There were sclerotic changes in the interstitial tissue which before death had affected the majority of the tubules and glomeruli. The tubules that were active showed very large lumena, due to dilation from back pressure or a compensatory hypertrophy. Many of the glomeruli were hyalinized, and those that were not seemed to show a hyperplasia as though they had made an extra attempt to carry the work after the changes in the interstitial tissue had destroyed the majority of them. In some glomeruli Bowman's space appeared to be dilated, as though it became so in attempting to excrete urine through a tubular system that had become partially blocked by connective tissue and back pressure.

The microscopic picture is generally that of advanced chronic interstitial nephritis. Diffuse round cell infiltration with overgrowth of fibrous tissue is characteristic in the medullary portion. Many tubules

are tortuous and compressed, some are dilated and contain hyaline cysts, granular casts, and cellular debris. The glomeruli show extensive changes, depending upon the degree of kidney damage. The less affected glomeruli are enlarged and hypertrophied. Others show infiltration of connective tissue around them that first led to fusion of the different loops of the tufts, or to adhesion between the tuft and capsule causing the final condition of atrophy of the glomeruli with subsequent hyaline change. Proliferation of the endothelial cells of Bowman's capsule is seen. Increase of interstitial tissue is uniformly present. In some cases, the vessels show thickening of the walls.

Grossly, the kidneys are small and pale, both being equally affected. They are usually more contracted and fibriotic than in the most extreme grade of chronic interstitial nephritis seen in the adult. The capsule is usually thick and strips with some difficulty, leaving a rough granular surface. On section, the tissue is firm and cuts with resistance. The color is often pale or yellowish red, and the cortex is poorly defined and quite thin. (77) (48) (61)

A moderate degree of cardiac hypertrophy is often seen. Arteriosclerosis usually limited to the larger vessels has been found in 10% of the patients coming

to necropsy according to Hunt (61).

Bones: The changes are usually more marked in the weight bearing bones of the body, or in the distal extremities of the radius and ulna.. All bones are affected, including even the ribs and skull (77). The bones may be soft enough to be bent easily with the hand; and may be cut with a scalpel (21) (77). The medullary cavity shows a large increase in its fat content.

A separation and displacement of the epiphsis is usually seen, the displacement being most marked at the lower ends of the femur, tibia, radius and ulna. The direction in which the epiphysis are displaced may be governed, by the pull of the muscles in relation to them. (21)

Brockman (21) studied sections taken through the growth disc at the upper end of the tibia. His findings were:(1) The red marrow replaced entirely by fat; (2) An almost entire destruction of the regular column of cartilage cells; (3) Active absorption of bone by osteoclasts; (4) Little formation of new bone; (5) The whole area which normally should be occupied by columns of cartilage cells and bony trabeculae was filled with fibrous tissue; (6) An increase above normal in the number of blood capillaries in this area. Longitudinal section through the shaft of the tibia showed the presence of large numbers of well formed osteoclasts lying beneath the periosteum and between it and the bone

which were actively absorbing bones.

SYMPTOMS AND SIGNS

The outstanding features of this disease which are most commonly seen when the child is first brought under medical observation are: the marked diminution in the stature of the child; bony deformities such as genu volgum and enlargement of the epiphysis of the wrists and ankles; a history of lack of appetite and, occasionally, vomiting, polydipsia and polyuria; and failure of the child to increase in height and weight at the normal rate. Examination of the urine reveals changes characteristic of renal insufficiency. The blood often shows a retention of the vitrogenous waste products, and radiographic studies of the bones show ricket-like changes.

Onset: The onset may be insidious (84). Seven years is about the average age of onset of the symptoms, but many cases have symptoms in early infancy. (84) (77) Graham and Oakley (46) report a case that was small from birth in which the legs started to bend at 18 months, and the child could not stand until three years old. Karelitz and Kolmoyzeff (65) reported the case of a child that was normal and could walk at the age of one year. A waddling gait developed at 18 months, and at the age of two years the child weighed the same as it did at the age of one year - 22 pounds.

These patients are often weak and delicate from the time of their birth. They are often feeding problems in early infancy; however, this may not appear until the time of weaning, with the change to solid food. Some show a distaste for solid foods, preferring liquid foods, such as soups and milk. (48)

The insidious onset of the disease is exemplified by a case reported by Graham and Oakley (46) that was normal until the age of 4 when growing at the usual rate ceased. The child was well, but grew slowly, and at the age of 15, the signs of renal rickets developed.

Occasionally, the symptoms develop a few years after an attack of acute nephritis.

Genu Valgum commonly first appears between the age of 12 and 14 years. (77) (7)

According to Barber, (8) the clinical picture may be met with in three stages. (1) Lack of development with increased thirst and polyuria becoming noticeable about the sixth or seventh year. (2) Deformities of the bones appearing toward the age of puberty. (3) A few live until the epiphyses are joined.

Growth and Mentality

The retarded development is a characteristic part of the disease. All of the case reports and articles pertaining to the disease that were reviewed by the author listed the lack of normal development as one of the features of the disease. A few of these are: Greene (48) Choun and Lee (30), Taylor (106), Karelitz and

Kolomoyzeff (65), Graham and Oakley (46), Hunt (61), Maddox (77), and Mitchell and Grant (84). The term renal dwarfism would imply a lack of normal development.

The smallness of stature is often the chief complaint for which the child is brought under medical observation. Hunt found that the average height of 28 patients whose measurements were recorded was 24.2% below the standard normal figures as published by the American Child Health Association of the Childrens Bureau, Unites States Department of Labor. In 25 cases The average weight was 45.2% below the normal figures for their ages. Graham and Oakley (46) report a case of a five hear old child that was 28 pounds underweight and 8 inches underheight. The presence of genu valgum is often a factor causing the decreased height. Some cases reported show a decrease in height as the disease progresses, especially when the genu valgum progressed to a marked degree. However, the slow growth of the is the main factor.(77)

There is some disagreement as to the mentality of these patients. Some authors report a normal or above normal intelligence in their patients. Others report a mentality of below normal. Maddox (77) states that "the intelligence is very gair, being proportional to the toxemia and to the degree of interference of education caused by the invalidism". Hunt (6) says

that the "general consensus of opinion now is that up to the age of puberty the mental faculties are normal, but that with the retarded development of the secondary sexual characteristics there is a tendency to mental sluggishness".

Sexual Development: The retardation or absence of the secondary sexual characteristics is a very frequent finding in cases that reach the age of puberty. Maddox (77) states that "infantilism in some degree, but never complete is usually apparent in cases beyond the age of puberty". The lack of development or absence of the usual secondary sexual characteristics is reported by Fletcher (41) Choun and Lee (30) and Barber (7) and Mitchell and Guest (84).

Polydipsia and Polyuria: These are very frequent and often very early symptoms (84) (65) (106) (7). Polyuria was noted in 40 out of 72 cases by Maddox. (77) Polydipsia is often the first symptom, often appearing at the age of weaning, and increasing in severity as the disease progresses. (61) The increased thirst may be very extreme. Choun and Lee (30) report a case that was often so thirsty that it would drink out of the bathroom stool. The polyuria usually becomes progressively greater. It may be quite extreme - 1200 - 3700 cc of urine being not uncommon. Nocturia is almost always present, and enuresis is not uncommon. (61) (77) (65)

Bone deformation: Genu Valgum is the most common deformity seen. It is mentioned in practically all of the cases reported. It usually develops gradually, interferring with walking to such a degree that the individual often has to use crutches, and often becomes extreme so that the child cannot walk at all. It sometimes develops suddenly. (84) Pain in the knees often accompanies genu valgum, and is probably due to abnormal ligament strain. (77) (65)

Other deformities frequently noted are: enlargement of the epiphyses of the wrists and ankles; enlargement of the costo-chondral junctions; pigeon shape chest; Harrison's sulcees; bossing of the frontal and parietal bones of the skull; fontenelles may remain open; anterior and lateral bowing of the femora and tibiae; and malacia of the long bones in advanced cases. (84) (77) (61) (102) (65) (105) (48) (7)

Urinary findings and kidney function: The urninary findings as reported by various observers are quite similar. The urine is usually described as being large in amount, pale, in color, acid in reaction, and of a low specific gravity. (48) There is usually a constant low fixation of the specific gravity, and an increase in the amount of urine passed during the night. (77) Albumin is always present sometime during the course of the disease. It is usually present in small amounts.

Casts of the hyaline and granular variety are usually not very numerous, are not found constantly, but are always present at one time or another. (77) (61) (48) Red blood cells and white blood cells are not numerous. The ability of the kidneys to secrete dye, urea and chlorides is greatly impaired. (87) (77) (46) (48)

Edema: Edema is not a very frequent finding. If it is present, it is usually very slight. (84) When edema is present it is usually a terminal manifestation and is associated with cardiac failure rather than with the renal disturbances. (48)

Eye grounds: The usual abnormalities are papilledema, albuminuric retinitis, or hemorrhages. The fundi appear normal quite frequently. The sight is not much impaired except in cases showing hemorrhages. (61)

Cardiovascular: A moderate degree of enlargement of the heart is usually found. (84) (61) This finding is usually not present before the age of five, however. (48) The condition of the vessels and the blood pressure is a variable finding. Mitchell and Guest (84) frequently found a high blood pressure, and sometimes found sclerosis of the superficial vessels. Hunt (61) found that the blood pressure may be slightly elevated, and arteriosclerosis, which was limited to the large vessels, in 10% of the patients coming to necropsy. Barber (7) states that "a normal blood pressure and absence of any

degree of cardiovascular changes are usual."

Lightwood (68) reports a case that was associated with widespread arterial degeneration and deposition of calcium in the tissues. The cardiovascular changes when present, are, no doubt, secondary to the renal changes, and perhaps in many cases observed have not yet become evident.

Headache, anorexia, and vomiting are frequently seen. (84) (61) (65) Anorexia may be a marked symptom, and is sometimes accompanied by abdominal pain, occurring in attacks. (61)

A pale, dry, wrinkled skin is common. The facies and expression are often surprisingly mature. Pigmentation of the skin often occurs sometime during the course of the disease. This is apt to be of a dirty brownish-yellow color, varying in intensity from time to time, and not always having the same distribution. It is usually most marked on the exposed surfaces. (77) (61)

Symth and Goldman (104) observed a case of renal rickets associated with metastatic calcification. There were over growths of irregularly calcified masses at the ends of nearly all the ribs, at both end of the right clavicle, and on both acromial processes. Also, small calcified tumors were seen on the medial and lateral sides of some of the digits. These appeared to be joined

to the bone by small pedicules. The falx cerebia and tentorium were densely calcified.

Blood: The blood urea, total non-protein nitrogen, uric acid, and creatinin are elevated to various degrees during the course of the disease. These show a progressive rise as the disease progresses, and death approaches. Lipemia may occur, and sometimes is extreme. The blood phosphorous is usually high and the calcium low or normal. A very high phosphorous reading such as 14 mg % or more is apparently found only within a short time of death, but sudden falls can occur. Acidosis is usually a common occurrence. (77) Hunt (61) found a urea value ranging from 11.5 to 400 mg% with an average of 140 in eight cases. Barber (8) finds that when the rachitic changes appear, the average reading for the blood urea is about 100 mg.% and that this is compatible with another five years of life.

A persistent secondary anemia is usually described as being associated with the disease (84) (77) (65) (48)

Radiographic findings of the bones: The characteristic findings are thinning of the cortex of the long bones. Irregular calcification at the epiphyseal lines. Many epiphyses become so disorganized that there appears to be slight epiphyseal slippings. The bones have a general hazy, porotic, appearance. (46) (104)

Parsons (reported by Kennedy (66)) describes three different types of bone changes: (1) the atrophic (2) the florid type (3) the woolly or stippled or honey comb type. In the atrophic type, the bones are fragile atrophic, and osteoporotic. The cortex is thin and atrophic and fractures of the shaft may be present. Lines of cancellous tissue are present at the epiphyseal ends of the diaphysis.

In the florid type the changes are not distinguishable from nutritional rickets. In the woolly type the typical changes occur in the region of proximal border of the epiphyseal cartilage. The edge is irregularly serrated and has a ragged, rat-eaten appearance extending right across the widened metaphysis. Rounded areas of rarifaction are present, giving a honey combed stippled or woolly appearance. The metaphysis is wider than normal and has a moth eaten appearance. The shaft as a rule is not quite so atrophic as in the florid type, and shows a coarse stippling or honey combed appearance.

In the x-ray of the calvarium, osteoporosis is definite. There is marked coarse stippling, and the inner and outer tables are ill defined. (87) The changes in the skull often resemble closely the changes in Paget's disease. (65)

DIAGNOSIS

The diagnosis of renal rickets is based upon the failure of the child to develop at the normal rate; the general appearance; the bone changes; the blood changes; the sexual development, and renal changes.

The lack of normal growth may date from birth or early infancy, or may appear sometime in the early years of life. The general appearance often consists of a pale, dry, wrinkled skin, with patches of dirty, yellow pigment. The facies are often surprisingly mature, or they may be expressionless, resembling those of a Mongolian idiot. Genu valgum is usually the first bone change noted, which is followed by other skeletal changes listed under symptoms and signs. The x-ray findings are usually conclusive of the disease. The blood changes consist of changes in the calcium and phosphorous levels and a retention of the nitrogenous waste products. In normal children the blood calcium is between 9 and 11 mg% and the phosphorous between 3.5 and 5 mg%. In renal rickets, this ratio changes, the phosphorous increasing and the calcium decreasing. (60) The evidence of renal insufficiency are listed under symptoms and signs.

The following conditions may be confused with the disease: tumor of the parthyroid glands; late rickets, diabetes insipidus; other causes of dwarfism; juvenile diabetes mellitus; hereditary ectodermal dysplasia; and, Addison's disease. (84) (77) (102)

In differentiating renal rickets from tumors of the parathyroid glands, one does not find palpable tumors in the parathyroid glands or cysts and tumors in the bone in renal rickets. Also, the epiphyseal changes are different than in the hyperparathyroidism. (102) The headache and vomiting present in some cases might suggest brain tumor, but the bone changes, urinary findings, etc., would differentiate this. (84) Polydipsia and polyuria are common to both renal rickets and diabetes insipidus, but in diabetes insipidus there is no dwarfism, no albuminuria, no bone changes, no cardiovascular hypertrophy or retinitis. On injection of an active extract of the posterior lobe of the pituitary gland will immediately lessen the polyuria in cases of diabetes insipidus. (77) The shafts of the long bones and the flat bones have a greater translucence and a more spongy appearance, by x-ray than in infantile rickets. (84) Other causes of dwarfism include: cretinism; achondroplasia; congenital heart disease; pancreatic

disease; cocliac disease; osteogenesis imperfecta; progeria; ateleisis; and the Lorain and Brissand types of dyspituitarism. The urine tests, renal efficiency tests, and the x-ray and blood phosphorous will rule these out. A sugar tolerance test would at once rule out the question of juvenile diabetes mellitus. The urinary and bone changes would rule out hereditary ectodermal dysplasia. Addison's disease can be ruled out because the asthenia is not present to the same degree, the blood pressure is not so low, does not respond so well to epiniephrine, and pigmentation of the mucous membranes has not bee described in renal dwarfism. (77)

The x-ray picture might be confused with ordinary rickets of the florid type, syphilitic diaphysitis, chronic osteomyelitis, scurvy, and other types of rickets such as coeliac rickets. (77).

COURSE AND PROGNOSIS

The final outcome of this condition is always death. No cures have been reported. The individuals either die in uremia, or succumb to some intercurrent infection. (43) (46) (104)

According to Maddox (77) death usually occurs within two or three years after bone deformities appear. However, some live for 10 years. Hunt (61) says that the average duration of life is less than two years after the appearance of these deformities. Very rarely does a case reach adult life. (43) In many cases, it appears that the condition originated in early childhood or even in infancy. The rapidity of the process of the kidney lesion determines whether death will occur during the first few years of life or whether life will be sustained until past puberty. (61)

TREATMENT

The treatment of this disease is chiefly protective and symtomatic. Nothing has been found to arrest the course of the disease, once it has become established. Secondary infections should be closely guarded against. The patient should be put to bed if there is an acute exacerbation of the disease. Surgical procedures to correct the deformities are of no avail because the deformity tends to recur, and they are not desirable because of the danger of uremia following the anesthetic. (21) (77) (43)

Light, supporting or correcting irons may help until the growth period is over. (77)

Anti-rachitic treatment, such as vitamin D and irradiation therapy, have been of no value and are usually considered to be harmful in renal rickets. (43) (104) (65)

In cases where the primary pathology is some obstructive lesion in the lower urinary tract, such as bladder neck obstruction, early diagnosis and treatment might prevent the development of the disease entity. (60)

Karelitz and Kolomoyzeff (65) and Grahm and Oakley (46) treated a few cases along anti-rachitic lines. They noted some improvement in the general condition, some improvement in bone lesions, but the state of the

kidney was little if any improved. All of the cases died within a short time.

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