was nothing to be made out in any system except as stated below.

Alimentary System.—"Barium outlined a small high stomach from which the food was leaving rapidly through the gastro-enterostomy opening, which appeared well formed and over which there was no tenderness. No barium was leaving by the pylorus, but no filling defect of distal portion of the stomach could be made out which might suggest new growth. *Six hours:* Residual flakes of barium round stroma. Stomach was refilled and previous examination confirmed. No evidence of a gastric lesion was found." (Report from Radiological Department.)

Haemopoietic System.—No enlargement of glands anywhere. A blood count taken on July 25th showed: red blood cells 1,320,000 per c.mm., white cells 7,000 per c.mm., haemoglobin 32 per cent., colour index 1.2. This was confirmed on July 26th and on August 4th, except that on the latter date his white blood cells numbered 10,000 per c.mm. The blood picture showed marked megalocytosis and anisocytosis, and was absolutely typical of pernicious anaemia except for the absence of leucopenia. The white blood cells varied from 7,000 to 10,000 per c.mm. on different occasions, 80 per cent. of which were polymorphonuclear leucocytes. Except when there has been concomitant disease of the kidneys, I have never found a white count so high as this in any case of pernicious anaemia. The fragility test was normal. The van den Bergh test showed direct reaction—weak delayed reaction; indirect reaction—positive reaction. This was indicative of haemolytic (non-obstructive) jaundice. The Wassermann reaction was negative.

Test Meals.—Three test meals were given at different times. The first two showed no free hydrochloric acid. This was not surprising since the fluid tested was a greenish bile-stained mixture of gastric and duodenal contents. The third test, made just previous to discharge from hospital, consisted mainly of stomach contents which turned red litmus blue, Congo red blue, and gave a positive Gunzberg reaction. Titration showed: free acidity=25; total acidity=51.

Treatment.

The patient was placed on light diet and given alkalis and liver by the mouth. Following this treatment the gastric pain disappeared and the patient put on weight rapidly. He gained $1\frac{1}{2}$ st. in six weeks. The symptoms and signs of anaemia quickly disappeared, and his blood count rose from 1,350,000 red cells per c.mm. and haemoglobin 28 per cent. on August 4th, to 3,690,000 red cells per c.mm. and haemoglobin 60 per cent. on August 27th. The white blood corpuscles remained at 8,000 per c.mm. A typical reticulocyte rise occurred, and the response to treatment was exactly what one is accustomed to get in a case of pernicious anaemia, but not in secondary anaemias. The enlarged spleen remained unchanged.

The patient was discharged from hospital looking and feeling very well.

Summary.

It is interesting to obtain a long history of epigastric pain which the patient consistently denies is affected by the taking of food, and yet find he is suffering from duodenal ulcer. The presence of marked megalocytosis and anisocytosis, a colour index over unity, and a van den Bergh reaction characteristic of haemolytic jaundice, are all classical signs of pernicious anaemia. On the other hand, the presence of free hydrochloric acid in the stomach and the absence of leucopenia contraindicate the diagnosis. Moreover, there is considerable evidence to show that pernicious anaemia patients conform to a constitutional type or build. Thus Addison noted that the disease occurred chiefly in persons of a somewhat large and bulky frame. More recently Draper,¹ by his laborious method of anthropological measurements of 45 cases, confirmed this observation, and showed that the pernicious anaemia group tended in their measurements very decidedly to approach the acromegaly. My own clinical experience agrees with these views. My first visual impression of the patient described in this paper was of a small, badly developed, emaciated, haggard man, who was probably suffering from a simple or malignant ulcer of the stomach. Without many blood examinations I would have been loath to diagnose the case as pernicious anaemia.

Hurst² and Hartman³ have reported pernicious anaemia occurring after gastrectomy in a very few cases. Conybeare⁴ has reported a case following gastro-enterostomy.

In the case reported here the blood condition was present previous to operation, and, so far as I am aware, the coexistence of duodenal ulcer and pernicious anaemia in a patient has never previously been reported.

I have to thank Professor Edwin Bramwell for the early notes of this case during the patient's stay in his ward, and Dr. Alexander Goodall for his assistance and his permission to publish the case.

REFERENCES.

- ¹ Draper, G.: *Human Constitution*. Saunders Company, Philadelphia, 1924.
- ² Hurst, A. F.: *Medical Essays and Addresses*. London, 1924, p. 81.
- ³ Hartman, J. T.: *Amer. Journ. Med. Sci.*, 1921, 162, 201.
- ⁴ Conybeare, J. J.: *Guy's Hospital Reports*, 1922, 62, 166.
- ⁵ Castle, W. B., and Locke, E. A.: *Journ. Clin. Investigation*, 1928, vi, 2.

CHRONIC NEPHRITIS IN CHILDHOOD.*

BY

J. C. SPENCE, M.D.,

Honorary Assistant Physician and Chemical Pathologist,
Royal Victoria Infirmary, Newcastle-upon-Tyne.

From the standpoint of morbid anatomy there are no forms of chronic nephritis which are peculiar to childhood, and conversely, even an arterio-sclerotic granular kidney may occasionally be found in children. There are, however, certain clinical features about the disease in children which deserve attention. So in this discussion it will be profitable both to describe our experiences of the various forms of the disease in children and also to consider if there be anything peculiar or characteristic about them in childhood which will throw light on some of the obscure problems of the subject. It is in this light that the study of disease in childhood may be looked upon as an important branch of comparative medicine; and as such should concern us no less than the study of actual "children's diseases," of which, *sensu stricto*, there are very few examples.

For the convenience of description and discussion a classification of the various forms of chronic nephritis must be attempted. It is usual to deplore the fact that the various clinical types of the disease are difficult to correlate with the classifications given to us by the morbid anatomists, but I think that we can agree that there are at least three groups of the condition which occur in childhood, and that in the main they are widely different and best considered as separate diseases. These are: (a) chronic interstitial nephritis; (b) chronic parenchymatous nephritis, including nephrosis; and (c) chronic ascending pyelo-nephritis.

It is probable that each of these three groups can be further differentiated into types which in themselves are distinct diseases, but for the present they will serve our purpose, being clinical entities which we are accustomed to recognize and content to diagnose.

I have purposely included chronic ascending pyelo-nephritis for discussion. Truly it is not a primary disease of the kidney, but the same may perhaps be said of nephrosis, and it has this clinical importance, that it may impair the renal function in the same way as chronic interstitial nephritis, and so is likely to be mistaken for it. Moreover, it deserves some comment, for occasionally the ascending infection is due to an obstruction of the urinary tract which can be treated successfully; this is more than can be said for most other forms of chronic nephritis.

My classification does not include two conditions which are sometimes spoken of as forms of chronic nephritis—namely, chronic haemorrhagic nephritis, and a syndrome to which Heubner gave the name "paedo-nephritis." The first of these is characterized by attacks of haematuria without oedema, which usually follow throat infections. I am inclined to look upon them as examples of recurrent attacks of slight acute glomerular nephritis. It is true that some of these cases do ultimately develop chronic interstitial nephritis with hypertension, but I know of at least two cases which have suffered from these attacks for more than ten years, and so far there has been no impairment of general health or of the renal function. "Paedo-nephritis" is a term which could now be discarded. Heubner coined it thirty years ago to describe doubtful forms of chronic nephritis in children who showed no other signs than albuminuria and anaemia. It is probably no distinct entity, but includes conditions such as latent chronic nephritis, toxic albuminuria, and orthostatic albuminuria.

CHRONIC INTERSTITIAL NEPHRITIS.

It is this form of chronic nephritis in childhood which will yield some of the most interesting points for discussion. At one time it was considered a great clinical rarity, and in 1896 Leonard Guthrie, while writing a wonderful description of its signs and symptoms, was able to collect from the literature only seven cases under the age of 14. By 1903 Sawyer was able to collect twenty-four cases. But

* Read in opening a discussion in the Section of Diseases of Children of the Annual Meeting of the British Medical Association, Cardiff, 1928.

still the subject attracted no great attention apart from the possibility of its being a result of congenital syphilis, a view widely held at that time. In 1911, however, Morley Fletcher, Parsons, and Miller drew attention to the fact that the disease might result in peculiar bony changes and dwarfism, and since that time a great number of cases have been recognized. More recently biochemical methods of examination have added further interest, giving us readier means of diagnosis.

Now of this disease, which we call chronic interstitial nephritis, I believe that we can recognize three clinical types in children, in whom they are more easily distinguishable than they are in adults. Each of these types has probably its own mode of origin and evolution as a separate disease, although proof of this may be lacking when we attempt it by examining the end-results in the kidneys after these diseases have run their course.

Taking them first as a group it will suffice briefly to mention some of the common clinical features and their variations which are found during the

course of the disease. The symptoms may arise at any age from infancy onwards, and usually advice is not sought for several years, by which time a history of thirst, polyuria, anaemia, and arrested development can be obtained. On the other hand, an attack of uraemia, of one sort or another, may be the first warning of the disease.

In the majority of cases there is no history of an initial acute nephritis or of any illness which would be likely to cause it. On the other hand, in the minority the disease can be traced to an attack of acute nephritis, or more commonly to a preceding illness of prolonged sepsis; and I think that it is on this point that two of the types I shall mention can be distinguished.

In the well-established cases the patients are usually emaciated, with coarse, dry, and pigmented skins. The general health is poor and they are liable to recurrent attacks of uraemic vomiting and headache. There is no mental defect; indeed, the patients seem to be shrewd, precocious, and intelligent beyond their years. One of my patients at the age of 6 was a regular performer on the music-hall stage as an infant prodigy at the piano. To the eye he looked no more than the age of 2 as he sat singing in a high shrill voice to his own accompaniment. To describe such cases, Guthrie quoted W. S. Gilbert's precocious child "who died an enfeebled old dotard at five."

When the dwarfism and bony changes are present they may be extreme, as will be seen from the accompanying illustrations (Figs. 1 and 2). Fractures are common, and the gait becomes slow and uncertain. These bony changes are not likely to appear in those cases which run a rapid course towards their terminal uraemia. In studying the disease the bone deformities are of great clinical importance, since they give us a valuable means of assessing the duration of the nephritis. They do not occur unless renal function is much impaired; so, for example, if a child with chronic nephritis has had bone deformities and failed to grow for ten years, we can presume that he has been sorely afflicted with the disease for at least ten years.

Polyuria is one of the most prominent symptoms, and in one of my cases it was for this that advice was sought by the mother, who remarked, "He passes urine night and day just like tap water." The amount of albumin is variable, and may be so slight at times as to be easily overlooked. Casts, leucocytes, and red cells are to be found in the urine as in the chronic nephritis of adults. The blood pressure may be normal throughout, high throughout, or become high in the course of the disease. This is an important point, to which I shall refer again in classifying the different types.

FIG. 1.—Renal dwarfism in a girl aged 10.

Renal retinitis may be absent throughout, even though the patient die in uraemia. In my experience it is present only in those cases with high blood pressure. The renal function tests will demonstrate great loss of function in all cases of "renal dwarfism" and "renal rickets." In these the blood urea lies usually between 50 and 100 mg. per 100 c.cm. of blood, rising beyond that with each attack of uraemia.

It is on certain combinations of these various symptoms and signs that I would propose to subdivide the cases of chronic interstitial nephritis into the three following types.

TYPE I.—Chronic Interstitial Nephritis—Primary Renal Type without History of Acute Nephritis or Preceding Sepsis.

(Chief features: Unrecognizable onset, marked azotaemic nephritis, slow course with renal dwarfism developing, normal blood pressure, no retinitis, true uraemia. "Small white kidneys" at necropsy.)

These are the cases which start insidiously without any preceding acute nephritis, oedema, or prolonged septic illness. They are usually first seen when dwarfism or bone deformities are developed. By this time the blood urea is already high, and they present all the symptoms of the "syndrome de rétention azotée" of Widal and Javal—dry-skinned and shrunken, with foul breath, stomatitis, subnormal temperature, and evident uraemic digestive symptoms. In the majority the blood pressure remains normal to the end, or, if raised, is rarely above 150 mm., and no retinitis appears. Attacks of tetany, though not common, may occur with this type. The terminal uraemia is of the sort best described as true azotaemic uraemia, an undramatic picture of muscular twitchings, vomiting, and coma. There may be a terminal convulsion, but striking cerebral phenomena such as transient amaurosis or monoplegia do not occur. It is the type of uraemia which we see with calculous anuria in adults, and I am inclined to think this is the picture of true uraemia when uncomplicated by hypertension—although the textbooks call it "latent uraemia," because it lacks certain dramatic features. The following typical case illustrates this type.

J. S. (see Fig. 2) was under close observation from the age of 15 to 18, when he died in uraemia. He had been in chronic ill health from the age of 4, with maldevelopment of the bones and severe rickets. Prior to that he had not thrived well. In infancy he had measles and chicken-pox. There was no history of scarlet fever, of skin sepsis, or of oedema. At the age of 8 an osteotomy was performed for the correction of his deformities, and again about the age of 10. At the age of 15 he was found to have albumin in his urine, and he then came under my care. At this time a history of polyuria and thirst since the age of 4 was elicited.

On examination he was found to be 18 inches below the normal height for his age. There was marked genu valgum and active rachitic changes at the radial epiphyses. Albumin and casts were in the urine. Blood urea was 59 mg. per cent. and the highest urea concentration in the urine was 0.90 per cent. The systolic blood pressure was 105 mm. and the optic discs and retinae were normal. There was no enlargement of the heart. During the next three years he led the life of an invalid, scarcely able to walk about. His blood urea was constantly raised, and varied from 52 to 341 mg. per cent. He had several attacks of tetany during this time. His blood phosphorus varied from 4.1 to 12 mg., and his serum calcium from 10.4 to 6.2 mg. per cent. He died in a uraemic attack of thirty-six hours' duration, which was ushered in by vomiting and muscular twitchings and ended in coma. During the whole of the time he was under observation his blood pressure remained below 110 mm., and renal retinitis did not appear, although frequent examinations were made up to the hour of his death.

At the post-mortem examination both kidneys were small (right 19 grams, left 25 grams). The capsule was not thickened, and stripped fairly readily. After examination they were described:

FIG. 2.—Renal dwarfism in a lad, aged 18, with chronic interstitial nephritis.

"Both kidneys have an embryonic appearance although the changes are those of chronic interstitial nephritis." The heart was not enlarged.

This is a typical example of renal dwarfism due to chronic interstitial nephritis of this type. It is reasonable to presume that he had suffered from it for at least fourteen years; yet during this time there was no rise in blood pressure. During recent years I have had five other similar cases under observation. Four of these are already dead in uraemia. The highest systolic blood pressures in these have been 95 (age 6), 100 (age 4), 100 (age 10), 105 (age 7), 160 (age 12). In none of these could I obtain a history of preceding acute nephritis or sepsis.

The type of kidneys which are found on *post-mortem* examination in these cases is always the same—small, pale, and shrunken, weighing usually about 1 oz. The capsule strips fairly readily, and in cortex are often to be found small nodular areas of local hypertrophy of kidney tissue. They are "small white kidneys."

TYPE 2.—Chronic Interstitial Nephritis—Primary Renal Type with a History of Acute Glomerular Nephritis or Prolonged Sepsis.

(Chief features: Within a few years of the initial illness high blood pressure (150 to 200 mm.), cardiac hypertrophy, albuminuria, numbers of red cells in urine, retinitis; the course of the disease is usually rapid. Dwarfism and rickets may develop.)

It is well recognized that transient tonsillar sepsis from streptococcal infection is a cause of acute glomerular nephritis. Other forms of sepsis are equally important, and in my own series of cases I have found that skin sepsis, whitlows, and gland abscesses are more common causes than tonsillar sepsis.

It is true that the majority of these cases of acute nephritis are cured completely, but on *a priori* grounds it is reasonable to presume that when the kidney damage has resulted from sepsis of a more prolonged character, such as might occur in cellulitis and osteitis, a chronic nephritis would be more likely to ensue. This is in accord with my experience of certain cases of severe chronic nephritis in young adults, with blood pressures of about 180 to 200 mm., albuminuria, red cells in the urine, and azotaemia. In many of these I have been able to obtain a history of cellulitis or "blood poisoning" a year or two before the first serious symptoms of chronic nephritis. Very often there has been no evident oedema or gross haematuria in the early stages to draw attention to the kidneys and to invite a close examination of the urine, and the presence of red blood cells in the urine—which is the chief and most important sign of acute glomerular nephritis—may have been overlooked. The following is an example of a case of this type in a child.

A schoolboy, aged 10, was admitted to hospital with appendix abscess. Prior to that he had been in perfect health without any history of previous illnesses. The abscess was drained, but was followed by a period of extreme illness for four weeks with high swinging temperature. At this stage an empyema was diagnosed, and rib resection was performed, with the evacuation of a quantity of thin pus. For two weeks afterwards the patient was in a critical condition with septic fever, which slowly subsided. Convalescence was prolonged, and it was six months before recovery was complete enough to allow him out of bed. Then followed a period of two years in apparent good health. The next striking symptom was a complaint of slight visual impairment believed to be an error of refraction, for which advice was sought from an ophthalmological surgeon. Examination revealed a retinal haemorrhage.

On examination at this stage the urine was found to contain a large quantity of albumin, casts, and some red cells, and the blood pressure was 195 mm. The heart was enlarged. Urine urea concentration was 1.4 per cent., and blood urea 92 mg. per 100 c.cm. of blood. After this the course of the disease was rapid. Headaches were a prominent symptom, and he died eight months later after a "uraemic phase," which lasted off and on for three weeks. In this uraemia, headache, restlessness, and convulsions were the most prominent features. Towards the end some oedema over the sacrum appeared.

This is a clinical example of a malignant type of chronic interstitial nephritis not common among children, but fairly frequent in early adult life.

TYPE 3.—Chronic Interstitial Nephritis—Primary Arterio-sclerotic Type with Secondary Contraction of the Kidneys.

(Chief features: A preliminary stage of high blood pressure—often over 200 mm. at first examination—cardiac hypertrophy, retinitis, tendency to "uraemia of cerebral type" with transient amaurosis, monoplegia, and convulsions. Later albuminuria and some azotaemia develop. Death from heart failure or apoplexy.)

It is not uncommon to see a young adult with a blood pressure over 200 mm., with a normal blood urea, with kidneys capable of concentrating efficiently, and with a mere trace of albumin in the urine. He is subject to headaches, but is capable of work. In this state he may continue for a few years with the blood pressure slowly rising. I know of such a case—a bricklayer, who had been working on scaffolding with a blood pressure of 305 mm. Sooner or later the albuminuria becomes severe and constant, and death takes place in apoplexy or as a result of heart failure. So long as there is no gross albuminuria these patients have a fair chance of survival, but when it appears their term of life is short. The primary disease in this condition is that form of arterio-sclerosis which Gull and Sutton named "arterio-capillary fibrosis," and which Evans and others name "diffuse hyperplastic sclerosis." The patients usually live long enough for the kidneys to become small and contracted, and after death they are commonly called granular kidneys or small red kidneys.

These are well-known clinical facts, which I mention only to ask if this arterio-sclerotic disease, primary diffuse hyperplastic sclerosis, is recognizable in a young child apart from severe chronic interstitial nephritis or at a stage before the kidneys become affected. It appears to be extremely rare. Evans' in his article on "Arterio-sclerosis in children" quotes a case (No. 2) of a boy who, at the age of 7, had a blood pressure of 195, with a trace of protein (0.001 per cent.) in the urine, which gave all the reactions of globulin. Seven years later he had a blood pressure of 265 mm. systolic, 200 mm. diastolic, with a blood urea of 67 mg. per 100 c.cm. and 0.025 per cent. of albumin in the urine. He died of cerebral haemorrhage, the kidneys showing advanced chronic nephritis. But in this case there was evident dwarfism at the age of 7 with genu valgum, so it is probable that he had chronic nephritis already at that stage.

From my own experience I can quote the following case, of a child with high blood pressure and normal renal function who had an attack which was thought to be uraemia, which appears to be a true example of the type mentioned.

A girl, aged 10, was admitted to hospital with a history of generalized convulsions and some mental disturbance in which she was restless and noisy. On admission she was thought to be suffering from encephalitis. She was well nourished and of normal stature. The next morning the mental condition was clearer, but there was complete amaurosis and palsy of the left arm. There was no muscular twitching and no vomiting. The retinae showed some haemorrhages, but no papilloedema. The aortic second sound was very loud, and when the blood pressure was taken it was found to be 220 mm. systolic. The urine contained a trace of albumin, but no deposit. The cerebro-spinal fluid was clear without pleocytosis. In two or three days the amaurosis and the monoplegia disappeared and no more convulsions occurred. This was looked upon as a case of uraemia because of the symptoms, blood pressure, retinitis, and albuminuria. When, however, the blood urea was examined, it was found to be only 26 mg. per 100 c.cm., and urea concentration was normal. The child passed on towards recovery. Seen two years later, there was commencing deterioration of renal function. Albumin was more evident, the blood urea was 45 mg. per 100 c.cm., renal retinitis was again present, and the blood pressure was 210 mm.

The chief importance of such a case as this is the light it throws on what is called uraemia. Here we have a child with normal renal function showing such classical uraemic manifestations as transient amaurosis and monoplegia, whereas in the first type I have described, where a typical severe interstitial nephritis is combined with extreme impairment of renal function and azotaemia, the chief symptoms are vomiting and muscular twitchings. The former is, I think, a mere cerebral vascular syndrome, due to hypertension, and it is the latter which is true uraemia. In the second clinical type I described, in which high blood pressure and severe renal damage advance together, the uraemic picture is likely to be a confusion of the cerebral vascular syndrome with true uraemia, and it is that which is most frequently seen in adults.

I would like to stress the fact that these three types of chronic interstitial nephritis are merely a convenient clinical subdivision of the cases. They may suggest, but do not explain, the association of chronic nephritis and arterio-sclerosis, or other problems of pathology. Evans' studies have led him to the conclusion that the form of arterio-sclerosis we have been discussing is an inflammatory and not a degenerative lesion. If that be so, these three types may be different manifestations of the same disease,

in which the variation depends on the site of the damage—the kidney alone in the first type, the systemic vessels in the third type.

Etiology of Chronic Interstitial Nephritis.

It is the cases of the first type I have described—slowly advancing azotaemic nephritis with little or no rise in blood pressure—which are commonest in children. In many of these the history suggests that the symptoms of the disease started in the first year of life. Fletcher,² when discussing his original case, was of the opinion that the disease dated from intrauterine existence, and many others have supported a view of some congenital infection. This is probably not true in all instances, however. Barber's³ cases occurred mainly in adolescence, and Rose Bradford⁴ has described young adults who die in uraemia with small white kidneys without cardiac hypertrophy or arterio-sclerosis (aplastic Bright's disease some people called them in those days), which is probably the same condition. Both sexes are equally affected (26 males and 25 females in a series collected by Hunt⁵), and there is no recognizable familial tendency. Syphilis can now be ruled out as a cause. In more than 90 per cent. of cases there is no evidence of infection of mother or child. It must be concluded that we know nothing positive of the etiology of these cases.

In the second type of case I have described I have already suggested that a severe septic illness, even though it produced no recognizable acute nephritis, may be the cause.

In the third type the cause of the arterio-sclerosis is unknown, but it must be borne in mind that it is probably an inflammatory and not a degenerative agent.

Renal Dwarfism and Tetany in Chronic Nephritis.

When a chronic interstitial nephritis has existed for some years bone growth and development are usually affected. The changes in the bones have been fully described by Parsons,⁶ Paterson,⁷ and others, and are commonly spoken of as "renal rickets" or "renal dwarfism." They are the result of a metabolic disturbance which accompanies azotaemic nephritis, but they do not yield to the usual antirachitic remedies. Indeed, it occurred that one of my cases was thrown into uraemia after exposure to ultra-violet ray treatment. X-ray and histological examinations have shown that the changes are as follows: (a) actual cessation of growth and development at the epiphyseal line, producing dwarfism; (b) a rachitic change at the epiphyseal line, best seen at the lower end of the radius; (c) atrophy and osteoporosis of the shafts of the bones. One or other, or a combination of these, is to be found in most cases, and clinically they may present themselves as examples of late rickets or, as in Barber's cases, of adolescent genu valgum. If the course is prolonged there may be periods of temporary improvement with a healing line, which can be seen in a radiograph of the epiphyses as a narrow dense striation. It must be mentioned that in some cases of short duration the bones remain quite normal.

Frank tetany is not a common symptom. As far as I know it has not been recorded in any of the published cases, but in two of my own it was a prominent feature. In many cases, however, latent tetany can be shown to be present by Chrostek's sign, and this should be sought for whenever chronic interstitial nephritis is suspected.

The changes in the calcium and phosphorus content of the blood throw some light both on the bony changes and the tetany. From the work of Greenwald,⁸ de Wesselow,⁹ and others it is known that in the azotaemic forms of nephritis there is a retention of phosphorus, which may rise from its normal level of 3 or 4 mg. to 15 or 20 mg. per cent. in uraemic cases. With or as a result of this, there is often a corresponding fall of calcium in the blood. I have been able to confirm this in some of my own cases of chronic interstitial nephritis with renal dwarfism, but in others there has been a rise of blood phosphorus only, without any fall in blood calcium. When one considers that ordinary infantile rickets is associated with a diminished amount of phosphorus in the blood, and tetany with a diminished amount of calcium, it is reasonable to believe that the bony changes and the tetany which may be present in chronic interstitial nephritis are also dependent on a disturbance of the phosphorus-calcium ratio of the blood and tissue fluids. On this point Parsons has advanced an interesting theory, which some of you may wish to comment

on. Speaking of those cases which have a high blood phosphorus but normal blood calcium, he says:

"It seems conceivable that the serum calcium is maintained at this level to prevent the occurrence of tetany, which is such a very serious complication, and to which the young and growing child is much more prone than the adult. . . . It is therefore not improbable that in renal rickets there is a washing out of calcium from the bones with resulting osteoporosis and rickets."

If Parsons's suggestion be correct, it is probable that the parathyroids would be the organs concerned in producing this effect. Now this may explain cases of parathyroid hyperplasia in chronic renal disease described by Bergstrand, Thomas, and Wentworth, which Box and de Wesselow¹⁰ refer to in their published case of chronic nephritis with a possible parathyroid syndrome.

Renal Retinitis and Blood Pressure.

In all the cases which I have seen of chronic interstitial nephritis in children with normal or low blood pressures no retinitis has been observed, even during or after their attacks of uraemia. To confirm this experience I have looked over 29 published cases in which the blood pressure was recorded. In 21 of these it was normal, in one 130 mm., in one 138 mm., in one 165 mm., and in 4 over 200 mm. The state of the retinae and discs was mentioned in 15 of these. They were normal in 9 cases, which all had blood pressures below 150 mm.; and renal retinitis was present in 5 cases, in which the systolic pressures were 260, 250, 210, 165, and 100 mm. The remaining case had primary optic atrophy but no retinitis. Thus I could find only one case of chronic interstitial nephritis (Glaser¹¹) in which retinitis was present with a normal blood pressure of 100 mm., and that child was dying of acute diphtheria at the time. From this I would conclude that so-called albuminuric or renal retinitis in children is not a manifestation of albuminuria or uraemia, but of hypertension or vascular disease, a view that has long been held by many.

Treatment.

The treatment of chronic interstitial nephritis in children leaves little scope for discussion. It is well to bear in mind that some of the reported cases have died in uraemia immediately after an operation for the correction of the deformities. The best that can be done is to preserve what health they have by conservative methods. No success has been achieved by the use of glandular extracts.

CHRONIC PARENCHYMATOUS NEPHRITIS OR NEPHROSIS.

This is the commonest form of chronic nephritis in childhood, and, taking year for year, it is more prevalent among children than among adults. In a series of 23 cases reported by Clausen,¹² 15 were below the age of 7 years and 8 between the ages of 8 and 15, and this can be taken as a fairly typical age distribution.

Whether we call the disease "chronic parenchymatous nephritis" or "nephrosis" matters little. Müller¹³ coined and uttered the latter term in 1905, maintaining that the lesion of the kidney was a degeneration and not an inflammation. An opposite school of pathologists replied that that type of degeneration was the result of an inflammation, and refused to accept the term. Now it appears that the disease is not primarily a disease of the kidney at all, but a general disease with "an abnormal permeability of the cutaneous and renal vessels for albumins and lipoids referable to changes of metabolism"; so the most recent fashion is to call it "lipoid dystrophy of the kidneys." A fairly clear conception of the malady can be obtained if we use the word "nephrosis," and look upon it as a general disorder in which the kidneys are large and pale with tubular degeneration, and recognize that in this state the kidneys may be further damaged by a superimposed infection which produces an actual nephritis and complicates the picture.

Clinically there are certain clear features of the disease by which we may recognize it: obstinate oedema with effusions into the serous cavities, marked albuminuria, absence of haematuria, normal blood pressure, normal renal function, increase of cholesterol in the blood, diminution of the plasma proteins, and a peculiar susceptibility to secondary infections, especially to pneumococcal peritonitis.

The only evidence that the clinical condition is due to a disease of the kidneys is the albuminuria and the casts in the urine. Marriott¹⁴ refers to cases in which the oedema preceded the albuminuria and the appearance

of casts. If this is so, there are good grounds for the belief that it is not primarily a kidney disease, but that the kidney becomes large and white with tubular degeneration, as do other tissues in the body. By some it is held that the oedema is due to the retention of chlorides by a diseased kidney, but de Wesselow¹⁵ has shown that the absence of chlorides from the urine is not due to this. The kidneys are quite capable of passing and concentrating chlorides, but they do not get the opportunity, for chlorides are retained in the tissue fluids for other reasons.

Without going further into the definition and description of the disease and its pathology, there are certain practical problems which may be considered for discussion. The first of these concerns the diagnosis. Can it be taken for granted that an absence of red cells from the urine and a normal blood urea are essential before making a diagnosis? I do not think so myself, but I agree with the view that in a classical uncomplicated case there are no red blood cells in the urine, and the blood urea is normal, and that this is sufficient evidence that there is no inflammatory lesion, at least in the glomeruli. Rarely, however, do cases run an uncomplicated course. They are peculiarly liable to secondary infections, and at such times a glomerulitis with haematuria and nitrogen retention is superimposed. Linder, Maxwell, and Green¹⁶ have given a very excellent description of prolonged observation of a patient who had intermittent periods of nitrogen retention, and died ultimately with broncho-pneumonia, when the non-protein nitrogen of the blood was 187 mg. per cent. On the other hand, I had the rare opportunity last year of following a case in a young child in whom the disease ran its course, while the blood urea was normal and there were no red cells in the urine. A very careful histological examination showed that there were no glomerular lesions and no red cells in the tubules—only a marked tubular degeneration with the typical lipid substance present.

The next point concerns treatment. Marriott, a great authority on the disease, is a strong advocate of the view that it is due to a toxin which damages the tissue cells, and causes them to absorb more chloride from the blood, so producing oedema. The toxin is usually from a staphylococcal infection of the mastoid or paranasal sinuses. He advises a very thorough examination and exploration of these sites, and reports cases of rapid cure after drainage by operation. Is this a view with which most of us agree, and if we do not agree with it, is it because we have failed to recognize the local staphylococcal infections in our cases? Another form of treatment which Osman¹⁷ has revived is the use of large doses of alkali. On occasions its use is followed by the disappearance of oedema, but the same can be said for almost any other form of treatment. It should be tried in obstinate cases, but it is to be remembered that it often produces severe vomiting and tetany.

It is difficult to assess the value of any form of treatment, for the disease is liable to incalculable fluctuations, and spontaneous cure may take place. Some of the most remarkable cases of cure are those in which the symptoms have disappeared after the patient has weathered the storm of an acute intercurrent illness such as influenzal pneumonia. There are other points in treatment on which it is easier to agree—namely, that a high protein diet is beneficial; that decapsulation of the kidney is useless; and that it is imperative that every patient with nephrosis should be guarded rigidly against the danger of intercurrent infections in case he develops an acute lesion in the glomeruli and haemorrhagic nephritis.

The prognosis is a matter on which it would be useful to collate our experiences. Of Clausen's 23 cases in children, 10 died, 9 of infection and one of alkalosis due to an overdose of sodium bicarbonate. Of Schwarz and Kohn's¹⁸ 17 cases, 6 died "and none of the others can be declared well." My impression is that, although the oedema may disappear, albuminuria and ill health remain, for such was the result in 5 patients I have been able to trace who have survived for more than three years. I would like to ask if anyone can record cases of nephrosis which, after an initial stage of oedema lasting more than ten weeks, have been cured and remained in permanent good health free from oedema and albuminuria.

CHRONIC ASCENDING PYELONEPHRITIS.

Urinary infections are so common in infancy and early childhood that it is appropriate to consider what chronic renal damage may result therefrom, and whether some of the unexplained types of chronic interstitial nephritis do not have their origin in an ascending infection.

Most cases of acute pyelitis, if promptly diagnosed and treated, make a satisfactory recovery. There are others, more chronic, which remain in ill health and liable to recurrences of fever and pyuria. In a few of these a permanent damage to the kidneys ensues, and the failure in renal function shows itself as an advancing azotaemic nephritis ending in uraemia. If the condition is sufficiently prolonged, these patients become chronic invalids and develop renal dwarfism, and to all appearances look like the stunted dry-skinned child with the primary renal type of chronic interstitial nephritis. In such circumstances it should be asked if there is not some chronic obstruction or deformity of the urinary tract which is the cause of the infection, for in children, as in adults, imperfect urinary drainage plays an important role in this.

One of the most striking examples of ascending pyelonephritis is due to the valvular obstruction in the posterior urethra of male children described so well by Young, Frontz, and Baldwin.¹⁹ This is a valvular obstruction amenable to surgical treatment, but if neglected it leads to hypertrophy of the bladder, dilatation of the ureters, pyonephrosis, and uraemia.

A review of the literature of the subject prior to 1919 shows that there had been reported only two cases of valvular urethral obstruction in which a diagnosis had been made during life. Since then a large number of cases have been recognized and successfully treated. In Hugh Young's clinic at Johns Hopkins Hospital, 12 such cases were seen in six years. In this country a case has been recently treated and reported by Gilmour.²⁰ In one case which I have seen, a small boy in a chronic uraemic state was apparently cured and completely restored to health by operation.

I have mentioned briefly this type of case merely to invite attention to the possibility of the condition as a cause of chronic renal disease. It should at least be considered in every case of chronic pyelitis and uraemia in a young boy. When the subject is looked at conversely, however, there are few of the cases of chronic nephritis or renal dwarfism which can be traced back to an acute or chronic pyelitis.

I have attempted the task of describing and suggesting certain aspects of chronic nephritis in childhood which lend themselves to discussion, but I realize how truly Müller spoke when, in the address in which he introduced the term "nephrosis," he described the kidney as "ein heimtückisches Organ." For I also have found its diseases too spiteful satisfactorily to be described and confined within the limits of this address. But from a study of these diseases in children there emerge two significant facts to which I would direct your particular attention: (1) the "small white kidney" is the commonest form of chronic interstitial nephritis in children, and it does not appear to result from any preceding acute nephritis or infection; and (2) this disease, though resulting in uraemia, does not produce any rise in blood pressure or retinitis.

REFERENCES.

Papers by Hunt⁵ and Greene²¹ have full bibliographies on the subject of chronic interstitial nephritis and renal dwarfism.

- Evans, G.: *Quart. Journ. Med.*, 1922-23, xvi, 33.
- Fletcher, H. M.: *Proc. Roy. Soc. Med.*, 1911, iv (Sect. Dis. Child.), 95.
- Barber, H.: *Quart. Journ. Med.*, 1922-23, xiv, 205.
- Bradford, Rose: *Lancet*, 1904, ii, 354.
- Hunt, F. C.: *Amer. Journ. Dis. Child.*, 1927, xxxiv, 234.
- Parsons, L. G.: *Arch. Dis. Child.*, 1927, ii, 1.
- Paterson, D.: *Proc. Roy. Soc. Med.*, 1920, xiii (Sect. Dis. Child.), 107.
- Greenwald: *Journ. Biol. Chem.*, 1915, xxi, 29.
- de Wesselow: *Quart. Journ. Med.*, 1922-23, xvi, 347.
- Box, C. E., and de Wesselow: *Lancet*, 1925, ii, 543.
- Glaser: *Jahrb. f. Kinderh.*, 1918, lxxvii, 95.
- Clausen, S. W.: *Amer. Journ. Dis. Child.*, 1925, xxix, 582.
- Müller: *Verhandl. des Deut. Path. Gesellsch.*, 1906, 64.
- Marriott: *Amer. Journ. Dis. Child.*, 1925, xxix, 578, and *Med. Clin. N. Amer.*, 1924, vii, 1413.
- de Wesselow, O. L. V.: *Quart. Journ. Med.*, 1925-26, xix, 53.
- Linder, Maxwell, and Green: *Arch. Dis. Child.*, 1927, ii, 220.
- Osman, A. A.: *Guy's Hospital Reports*, 1927, lxxvii, 385.
- Schwarz and Kohn: *Amer. Journ. Dis. Child.*, 1922, xxiv, 125.
- Young, H., Frontz, and Baldwin: *Journ. Urol.*, 1919, iii, 289.
- Gilmour, J.: *Newcastle Med. Journ.*, 1928, viii, 125.
- Greene, C.: *Amer. Journ. Dis. Child.*, 1922, xxiii, 183.