

THE NEPHROTIC SYNDROME

Report of Two Cases

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The outstanding clinical feature of the nephrotic syndrome is a generalized persistent type of edema, frequently of severe degree, associated with remarkably little subjective discomfort. Remissions without obvious cause are characteristic of the syndrome. Frequently, the patient is able to carry on his ordinary occupation without distress or discomfort over long periods of time. The patient's appearance often is strikingly suggestive of severe hypothyroidism, and it is interesting to note that both conditions have the common finding of lowered basal metabolic rates and increased blood cholesterol levels.

The nephrotic patient regularly shows a heavy proteinuria, this being due largely to the increased permeability of the glomerular capillaries to albumen, although all fractions of the protein of the blood plasma participate to some degree. Microscopic examination of the urine regularly reveals the presence of large numbers of granular, hyaline, and epithelial casts which are evidence of the severe tubular damage which is pathologically characteristic of the lesions. A few white blood cells commonly are present. In the majority of instances, red blood cells are lacking. Study of the urinary sediment with the polarizing microscope reveals the presence of doubly refractile lipid bodies which are considered largely pathognomonic of the condition. However, their presence in the urine has been shown in other degenerative lesions of the tubular epithelium.

The most characteristic finding in the laboratory examination is a reduction in total plasma protein which may fall well below the level at which edema occurs. The protein loss is chiefly in the albumen fraction and is considered to be due to the smaller size of the albumin molecule which allows it to pass more readily through the capillary endothelium. Therefore, a reversal of the albumin-globulin ration commonly is seen. The hypoproteinemia results in lowering of the colloid osmotic pressure of the blood, and forms the basis for the severe edema.

Azotemia is not an ordinary feature in the nephrotic syndrome, and occurs only with complications or in terminal stages of the disease. In accordance with this finding the urea clearance test ordinarily shows only minor reductions in the renal reserve as far as the excretion of urea is concerned. Elevation of blood cholesterol to two or three times the normal level is a common finding and is associated with a lowered metabolic rate, even when the increased body weight due to retained fluids is taken into account.

The nephrotic syndrome is seen in any of the types of degenerative

Bright's disease, but more particularly in idiopathic degenerative Bright's disease, or lipid or cryptic nephrosis. In degenerative Bright's disease associated with poisoning from heavy metals, toxemia of eclampsia, or associated with a generalized infection, the complete nephrotic picture rarely develops. In these cases the outlook is much better, as far as the renal lesion is concerned, than in the cases of genuine or lipid nephrosis which, in our experience, have had a uniformly progressive downhill course often over a period of years. In a few instances also, the nephrotic syndrome has been seen in patients who undoubtedly had at the onset a primary hemorrhagic type of nephritis. After a few weeks or months some of these patients have developed the clinical picture which is not distinguishable by clinical and laboratory findings from the true lipid nephrosis of idiopathic origin. However, a persistent microscopic hematuria may be found.

The etiology of the nephrotic syndrome still is obscure. Some have regarded it as being due to a general metabolic disease which causes some alteration in plasma proteins as a result of which they are more readily excreted, rather than to any specific renal lesion. The general conception, however, is that it constitutes a specific pathological renal entity of primary degenerative character. However, a few cases are found in which the nephrotic syndrome appears to be a sequel of ordinary hemorrhagic nephritis.

Treatment of the nephrotic syndrome is entirely symptomatic and, therefore, is applicable no matter what the origin has been. The marked proteinuria and plasma protein deficit logically suggests the desirability of a large protein intake which usually is well tolerated. Attempts also have been made to raise the plasma protein level directly by the use of transfusions of whole blood or blood plasma. Large and repeated transfusions are necessary to cause any appreciable increase in these levels and the results obtained are frequently disappointing because of the constant proteinuria. Some therapeutic success from the use of lyophile serum has been reported by Aldrich et al.¹ An attempt has been made to raise the osmotic pressure of the blood by the use of artificial substances such as acacia. Xanthine diuretics have proved useless. The use of potassium salts alone as a diuretic, and particularly in preparation for the injection of the mercurial diuretics, has been more successful. The oral administration of urea in quantities varying from 15 to 60 grams a day has given marked symptomatic improvements in several patients. However, care must be exercised when using this material in those patients who have suffered glomerular damage as indicated by low values for the urea clearance test. The lowered metabolic rate uniformly found in these patients has suggested the use of thyroid extract. It is well tolerated and large doses may be given with symptomatic benefit,

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but little diuretic effect generally is obtained. The lowered metabolic rate probably is related to general undernutrition rather than to a specific thyroid deficiency.

CASE REPORTS

Case 1: A fifteen year old boy was first seen on January 3, 1940, with a complaint of generalized swelling which had been present for six months. It had developed insidiously without obvious cause, and had persisted steadily with minor fluctuations in degree. Apart from the swelling, the patient felt generally well. His previous history included attacks of what was considered to be scarlet fever in 1933 and in 1934. He had had tonsillitis frequently as a child and tonsillectomy had been performed in 1932. He had had measles, mumps, and chickenpox in childhood.

Examination showed him to be a well-developed, well-nourished boy, with generalized edema of the face, neck, trunk, and extremities. The temperature was 98° F., the pulse rate 100, and blood pressure, 120 systolic, 80 diastolic. Pupillary reactions were normal. The optic discs were outlined clearly and the retinae appeared normal. Dental examination showed the presence of Vincent's infection with marginal gingivitis. The tonsils had been removed cleanly. Two small cervical lymph glands were palpable. The thyroid was not enlarged. The chest was clear to percussion and auscultation. The heart was of moderate size, the rate regular and rhythmical. No abdominal masses were present. Neurological examination showed the reflexes to be normal.

Urinalysis consistently showed a heavy albuminuria with a high specific gravity. Microscopically a few white blood cells were noted regularly, but no red blood cells were seen at any time. A few coarsely granular and hyaline casts were found. Examination of the blood revealed 4,330,000 red cells, 7,350 white cells, and 78 per cent hemoglobin. The differential white count showed no abnormality other than the presence of a high percentage of fragile leukocytes. The fasting blood sugar was 98 mg. per 100 cc. The blood urea was 36 mg. per 100 cc. The total serum proteins were 3.5 mg. per 100 cc. of which the serum albumin constituted 1.6 mg. per 100 cc. and serum globulin 9 mg. per 100 cc. The total urinary protein on one occasion reached 9 mg. per 100 cc. Examination of the urine showed doubly refractile material but no anisotropic bodies. Wassermann and Kahn tests of the blood gave negative reactions. The basal metabolic rate was minus 35 per cent. An electrocardiogram revealed sinus tachycardia with a rate of 114 per minute. Blood cholesterol was 440 mg. per 100 cc.

The patient was given a high protein diet, repeated blood transfusions, and thyroid extract. He also was given a course of six injections of lyophile serum varying between 25 to 50 cc. after a preliminary intradermal test for sensitivity to the material had proved negative. Each injection of the lyophile serum was followed by a chill and febrile reaction which subsided within a short period of time. When discharged from the hospital on February 7, 1940, the edema almost had disappeared. However, the serum proteins were reported as 3 mg. per 100 cc.; the serum albumin, 1.6 mg. per 100 cc.; and serum globulin, 1.7 mg. per 100 cc.

Case 2: A girl, fifteen years of age, was admitted to the Cleveland Clinic on April 4, 1940, with a history of swelling about the face and eyes, and edema of the ankles which had been first noted in October, 1939. From that time until

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the period of admission the patient had gained thirty-five pounds in weight. There had been occasional nausea and vomiting but no headaches. A low fever reaching as high as 100° F. had been experienced intermittently over a period of some months. At times there had been some elevation of blood pressure, but the exact levels were not known. Albumin with casts and occasional blood cells also had been found in the urine regularly. In January, 1940, the patient had a spontaneous remission of all her symptoms and a complete loss of edema. However, a month later the symptoms recurred. She had had an attack of influenza in February, 1939, and apparently had an upper respiratory infection in September of the same year. Recovery apparently had been normal. At the time of admission, the patient's only complaint was that of persistent swelling.

Physical examination showed a well-developed, over-nourished girl with marked generalized edema, particularly about the face. The temperature was 98° F., the pulse 88, and the blood pressure 120 systolic and 90 diastolic. The optic discs were clearly outlined and the retinae appeared normal. The tongue was moist. There was good oral hygiene, and the tonsillar fossae were clean. No lymph glands or thyroid enlargement were palpable. The chest was clear to auscultation and percussion. The heart was not appreciably enlarged and the rate was regular and rhythmical. There was no evidence of enlargement of the abdominal viscera or kidneys. Neurological examination showed the reflexes to be normal with no evidence of sensory or motor disturbance. Routine urinalysis revealed a pH of 6, four plus albumin, no sugar and a specific gravity of 1.038. Microscopically, numerous red and white cells with a few hyaline casts were seen. Blood counts revealed 4,720,000 red cells, 8,800 white cells, and 84 per cent hemoglobin. The total serum proteins were 5 mg. per 100 cc., serum albumin 2.2 mg. per 100 cc., and serum globulin 2.8 mg. per 100 cc. The fasting blood sugar was 77 mg. per 100 cc., blood urea 27 mg. per 100 cc., and blood cholesterol 820 mg. per 100 cc. The urea clearance test showed 50 per cent function the first hour, and 55 per cent the second hour. Wassermann and Kahn tests of the blood gave negative reactions.

The patient was placed upon a high protein, low sodium, high potassium diet. The use of ammonium chloride enteric coated tablets was started. During her hospital stay she received four injections of solyrgan, 0.5 to 1 cc. intravenously. Three transfusions of 500 cc. of blood were given. Urea was given as a diuretic by mouth, 20 gm. three times daily, but its use became inadvisable after a few days because of an increase in the blood urea level to 153 mg. per 100 cc. This urea retention subsided quickly when the material was withdrawn. Three injections of lyophile serum were given during the hospital stay. Each injection was followed by a marked febrile reaction, but without any remarkable diuretic effect. At the time of discharge from the hospital the total blood serum proteins were 4.6 mg. per 100 cc., serum albumin 2.2 mg., and serum globulin 2.4 mg. per 100 cc. The blood cholesterol, however, even though still above normal, had been reduced to 490 mg. per 100 cc.

SUMMARY

The first case represents true degenerative Bright's disease or genuine nephrosis of unknown etiology with characteristic findings. The second case apparently had developed the clinical nephrotic picture in the course of or at least subsequent to a primary hemorrhagic nephritis. Both showed some improvement on intensive therapy but it is obvious that no radi-

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cal improvement has occurred in the underlying renal lesion. In general, such lesions tend to progress gradually with eventual termination from renal failure or intercurrent infection.

The lyophile serum used in the treatment of these cases was supplied through the courtesy of Dr. Joseph Hughes, the Pennsylvania Hospital, Philadelphia, Pennsylvania.

REFERENCE

1. Aldrich, C. A., Stokes, J., Jr., Killingsworth, W. P., and McGuinness, A. C.: Concentrated human blood serum as a diuretic in the treatment of nephrosis, J.A.M.A., 111:129-133, (July 9) 1938.