indeed, it may be one of her most important decisions. The full psychological implications of sterilisation are still not clear. It is not a notifiable operation, and we are ignorant about how many are done annually. Perhaps only national surveys will provide a basis for solving many of these urgent problems.

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Today's Treatment

Diseases of the Urinary system

Proteinuria

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Proteinuria may arise as an isolated clinical finding or as part of a clinical picture of disease. Minor degrees of proteinuria may be overlooked in dilute urine. It is, therefore, advisable, when testing for protein, to examine an early morning urine specimen. In patients with normal renal function this will be the most concentrated urine passed. Ideally, the specific gravity should be above 1015. The most reliable method of testing for proteinuria is to use sulphosalicylic acid rather than the impregnated paper strip techniques.

An early morning urine sample may also help to establish whether an orthostatic proteinuria is present. Mild proteinuria may be intermittent, and more than one specimen of urine should be examined if there is any doubt.

A fresh, clean urine specimen should be sent to the laboratory and examined, with a standard culture, for sugar, protein, and the presence of red and white cells, casts, and bacteria. Fat bodies may be seen in the urine of patients with the nephrotic syndrome.

A urinary tract infection may entirely explain the presence of proteinuria. It should be remembered, however, that patients with various renal diseases may have a urinary tract infection, and care must be taken in interpreting the results.

Measurement of the protein loss in the urine is of great help in elucidating whether the proteinuria is appreciable and in defining the cause of the protein loss. Protein losses over 0.5 g in 24 hours are important. Protein losses below this figure may still be considered important if one is investigating a condition in which renal disease is suspected. It is unusual, however, to have glomerular disease with protein losses below this figure. A protein loss of over 3 g in 24 hours is within the range of a nephrotic syndrome and makes the likelihood of a glomerulonephritis probable.

Proteins of low molecular weight (about 50 000) cross the glomerular filter and are absorbed and catabolised by the renal

tubules. Thus there is quite an appreciable quantity of low-molecular-weight protein in the glomerular filtrate, but usually this does not appear in the urine in any quantity. Small light-chain globulins constitute some of these molecules and may be present in various conditions associated with renal tubular abnormality. In the Fanconi syndrome, for example, low-molecular-weight globulins may be seen in the urine as well as aminoaciduria. They have also been described in various "interstitial nephropathies" and in tubular damage as a result of tubular toxins such as heavy metals or nephrotoxic drugs.

Identification of various types of protein in the urine needs special physicochemical and immunochemical techniques. Using these methods investigators have been studying the clearance of low-molecular-weight proteins to try to associate them with particular disease processes. The presence of abnormal proteins, such as Bence Jones protein, is best identified using these more refined techniques, while routine plasma protein electrophoresis will often succeed in showing a myeloma protein band.

The clinical picture associated with the proteinuria is important in guiding the direction of the investigations. It is unlikely that there will be oedema or overt signs of a nephrotic syndrome unless the protein loss is greater than 3 g in 24 hours.

Proteinuria may occur on exercise and with fever, but as with postural proteinuria this is unlikely to exceed 0.5 g daily. In many nephrotics there is a postural element affecting the degree of protein loss, but even if the patient rests it is unlikely that the proteinuria will disappear altogether. Postural or orthostatic proteinuria is often considered a benign condition. Nevertheless, several series have been studied using renal biopsy in such cases and have shown various glomerular lesions,¹ including different types of glomerular nephritis, amyloid and non-specific histological change.

Experimental studies have shown that proteinuria may occur as a result of glomerular blood flow changes, without necessarily structural abnormality.² It is seen in congestive cardiac failure, but the quantity of protein lost is again not usually greater than 0.5 g daily. Hypertension associated with proteinuria may pose the problem of a primary renal lesion as the basis of the condition, as opposed to hypertension being the primary cause. This is often difficult to establish, but it is unlikely that with protein losses greater than 2 to 3 g daily the underlying cause is primarily hypertension.

Investigations

The presence of diabetes mellitus usually implies the existence of a diabetic nephropathy. Diabetic retinopathy may help to establish this. The retinal vasculature often reflects the renal vasculature, and fluorescent techniques used in studying the retina may help to establish any abnormality.

Specific inquiry about a history of sore throats, rashes, and joint pains may suggest a glomerular nephritis or a systemic autoimmune disease. A history of rheumatoid arthritis or chronic osteomyelitis may point to the presence of amyloidosis. If the patient has lived in a tropical climate and suffered from malaria this may give a clue to the renal disease.

A personal and family medical history to exclude a previous renal disease or hereditary renal disease, such as polycystic kidneys or familial nephritis, are part of the standard inquiry.

BIOCHEMICAL FACTORS

Specific biochemical factors may be looked for in the plasma. Hypercalcaemia may underlie the presence of multiple myeloma, hyperparathyroidism, sarcoidosis, and malignancies. All of these conditions may be associated with renal disease. Hyperuricaemia, although a feature of renal failure, may be primary and signify a gouty nephropathy.

Hypoalbuminaemia, with a low α_1 -globulin and gamma-globulin, is consistent with heavy albumin loss in the urine. An associated increase of α_2 -globulin, beta-globulin, and fibrinogen is seen in the nephrotic syndrome. Increase in plasma phospholipids and hypercholesterolaemia and increase of lipoproteins further support the diagnosis of a nephrotic syndrome.

Some evidence of renal disease may be gained from the routine blood film. If renal failure is present a normochromic normocytic anaemia may be found. The presence of fragmented red cells may point to a microangiopathic anaemia, while a high erythrocyte sedimentation rate, although non-specific, may suggest myeloma, an autoimmune disease, or retroperitoneal fibrosis.

The serum complement is of great help in studying patients with proteinuria. If the patient has a low serum complement then the possibility of a glomerulonephritis is very high. It is helpful to measure all the complement fractions, especially C_3 fraction, which is the fraction most specifically lowered in glomerulonephritis of various types. Anti-deoxyribonucleic acid titres or lupus erythematosus cell phenomenon may also help to establish the presence of an autoimmune disease.

INTRAVENOUS UROGRAPHY

Intravenous urography is of primary importance for it will help to exclude abnormalities of the urinary tract and the kidneys themselves. Although it is unlikely that protein losses of over 2 g daily are due to abnormalities of the urinary tract, unless chronic pyelonephritis is present, it may help to explain lesser degrees of proteinuria. Undoubtedly, it can exclude polycystic disease, unilateral renal lesions, and small contracted kidneys. Before embarking on intravenous urography the doctor must ascertain the renal function, and this is where the 24-hour urinary protein loss can be combined to give a 24-hour creatinine clearance. It will determine early on whether there is renal functional impairment, which is, of course, important in any investigation of renal disease. The radiologist needs to know the degree of renal function, for if this is impaired he may want to use a high-dose technique for urography and will also need to take late films.

RADIOGRAPHY

A chest radiograph will help to exclude a bronchial neoplasm as a cause of nephritis and evidence of quiescent or active pulmonary tuberculosis, which may suggest there is a renal

tuberculous lesion or amyloidosis to explain the proteinuria. The shape of the heart shadow will help to establish the presence of long-standing hypertension or the possibility of valvular disease if subacute bacterial endocarditis is suspected.

Radiographs of the hands, skull, and spine will distinguish the presence of hyperparathyroid disease, alone or as part of renal osteodystrophy, and also the presence of multiple myeloma.

DIFFERENTIAL PROTEIN EXCRETION INDEX

When the protein loss is over 3 g daily a differential protein excretion index can be determined. The basis of this test is to establish the degree of selectivity of the protein leak. In a highly selective protein leak—that is, when the protein loss is due to a narrow range of molecular protein size—the likely kidney lesion is one of minimal change on light microscopy, like that associated with lipid nephrosis, and has a good response to steroid treatment and generally a good prognosis. In a non-selective protein loss, however, with a greater range of protein molecular size leakage, the likely lesion is that of a proliferative, membranous, or membranoproliferative type. The prognosis is correspondingly worse as is the response to any immunosuppressive treatment.

To arrive at this index of selectivity there are many tests—for example, infusing various macromolecules, such as dextrans, and studying their clearance; a simpler clinical test is to study the endogenous clearance of transferrin and IgG; these clearances are expressed as a ratio. If the ratio is below 0.2 there is a selective protein loss, whereas above that figure it is considered an unselective proteinuria with the implications as stated above. This particular test is of great use in children with proteinuria associated with glomerular disease and correlates well with the biopsy findings, often obviating the need for renal biopsy. In adults its reliability is not so good, and the index may change from initially suggesting a selective to one suggesting a non-selective proteinuria. Nevertheless, its degree of correlation with renal biopsy findings is sufficiently good to make it a useful test.

RENAL BIOPSY

After all the preceding investigations have been performed, a renal biopsy is often necessary. The renal biopsy may be examined in three ways—by standard light microscopy using various stains, by immunofluorescence, and by electron microscopy.

The first two techniques are generally available and give much information about the type of lesion underlying the proteinuria and help in prognosis.

Light microscopy—Obvious abnormalities to be seen with light microscopy are the presence of amyloid or myeloma protein or classical diabetic nephropathy. The other lesions generally fall into diffuse or focal types, both showing endothelial, mesangial, or epithelial cell proliferation or membranous changes. There may be a combination of both membranous and proliferative changes.

Immunofluorescence—Immunofluorescence is helpful on two counts. Firstly, mild proliferative changes are often debatable and quite subjective. Immunoglobulin and complement deposition will therefore be more objective. Secondly, specific patterns of immunoglobulin, complement, and fibrin deposition are emerging in relation to particular types of glomerulonephritis and aid in their classification. Some guidance in proposed treatment may also emerge.

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