we have little evidence on this point. In only one of our cases were the serum proteins estimated before the onset of the nephrotic syndrome, and in this instance they were normal; the estimation was, however, carried out four years before the appearance of the nephrotic syndrome.

In the prophylaxis of this condition close supervision of patients treated with mercurial diuretics, including regular examination of the urine, is essential. It is noteworthy that two of our three fatal cases had no hospital supervision in the three years preceding death, and the third patient travelled round the Continent for long periods with a supply of mercloran tablets.

The principal warning signs of the onset of the nephrotic syndrome complicating mercurial diuretic therapy are: (1) Failure of albuminuria to decrease after a satisfactory diuresis. This, we think, is by far the most valuable indication of tubular damage. Case 4 undoubtedly had congestive cardiac failure, and this alone might have been responsible for the proteinuria. Mersalyl produced a satisfactory diuresis, but in spite of this the heavy proteinuria persisted (see Chart), indicating serious tubular damage. (2) Increasing oedema, especially of the arms and face, in the absence of other signs of cardiac failure. (3) Absence of diuresis after mercurial therapy. This has been ascribed to tubular damage, but in our experience it is a late and unreliable sign.

Treatment of the fully developed syndrome is unsatisfactory. BAL (dimercaprol), corticotrophin, ion-exchange resins, and decapsulation of the kidneys have all been tried without benefit.

The survival of one of our patients who received no specific therapy indicates that in some circumstances the condition is reversible. Early recognition of the condition and cessation of mercurial therapy before irreparable renal damage has occurred offer the best chance of recovery.

Summary

The nephrotic syndrome complicating congestive heart failure is reported in five patients who received mercurial diuretics for long periods.

The clinical features, and the pathological findings in three fatal cases, suggest that the renal lesion was due to mercury. Possible contributory factors are considered.

Early recognition of the condition is of the utmost importance if a fatal outcome is to be avoided.

The most useful evidence of tubular damage is persistence of albuminuria despite a satisfactory diuresis in response to mercurial therapy.

Our thanks are due to Dr. Una Ledingham and Dr. Wallace Brigden for permission to publish Cases 1 and 5 respectively.

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Middlesex had its record lowest infant mortality rate in 1957. There were 561 deaths of infants under 1 year old, giving a rate of 17.7 per thousand live births. This is 5.3 below the rate for England and Wales as a whole. As elsewhere, deaths from lung cancer increased, being 1,166, or 76 more than in 1956. Despite an excess of live births over deaths amounting to more than 9,000, the population of the county again fell owing to removal from it. At about 2¼m. the population was 2,000 lower than in 1956.

NEPHROSIS DUE TO MERCURIAL DIURETICS

BY

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Following the work of Saxl and Heilig in 1920 on the diuretic effect of organic compounds of mercury, mercurial diuretics have been used extensively to control oedema in cardiac failure and less extensively to control oedema secondary to renal disease. At first these drugs were used with considerable caution, for it was well known that inorganic mercuric salts were apt to cause renal damage. However, these fears were soon overcome, since cases of renal damage due to mercurial diuretics have been infrequent. The first case was reported by Sprunt in 1930, although others have since come to light (Tarr and Jacobson, 1932; Rosenthal, 1933; Waife and Pratt, 1946; Bruno, 1948; Preedy and Russell, 1953). The use of mercurial diuretics is now so widespread that perhaps the danger is being overlooked. The purpose of this report is to record a case in which a mercurial diuretic is thought to have produced the renal damage, and to show by microdissection the site of the lesions, which is similar to that described for inorganic mercury.

Clinical Course

A woman of 69 was admitted to hospital on April 18, 1957, with a four-months history of progressive heart failure together with angina of effort for two months. Her health prior to this was excellent. On examination she was found to have a trace of ankle oedema. Her pulse was 85 and regular, and B.P. 140/90. The apex beat was in the fifth intercostal space 3½ in. (9 cm.) from the midline; a harsh systolic murmur was audible to the left of the sternum, maximal in the fourth interspace, and a systolic thrill was palpable in this area. Crepitations were heard at both lung bases and the liver was palpable. The urine contained no albumin.

A diagnosis of ischaemic heart disease was made and the patient was given weekly injections of 2 ml. of mersalyl. The response was satisfactory and the patient was discharged home after three weeks. The urine was protein-free on discharge.

Weekly injections of 2 ml. of mersalyl were continued at home and her condition remained satisfactory for two months. Oedema then reappeared and she was readmitted on September 15. On examination on admission there was gross oedema of the legs, of the trunk to the level of the mid-dorsal region, and of the forearms and hands. The pulse rate was 96 and regular, the B.P. 140/80. The jugular venous pressure was raised 1 in. (2.5 cm.). The systolic murmur was unchanged. There were small effusions at each base and moist adventitia in the lungs. The urine was found to contain a considerable quantity of protein, and later determinations revealed a daily urinary excretion of 11.5 to 35 g. Plasma proteins on admission were as follows: total 5.3 g./100 ml. (albumin 1.5 g., globulin 2.96 g., fibrinogen, 0.84 g.). The blood urea was 46 mg./100 ml.; sodium, 134 mEq/l.; potassium, 4.7 mEq/l.; chloride, 91 mEq/l.; CO_2 combining power, 26 mEq/l.; bilirubin, 0.2 mg./100 ml.

Because of these findings the mersalyl was stopped and acetazolamide substituted. Neither this nor intravenous dextran produced a diuresis, and the patient died on September 27.

Necropsy Report

At necropsy the gross oedema noted on admission was unchanged. The heart was found to be slightly enlarged owing to left ventricular hypertrophy, and just above the midpoint of the interventricular septum there was a defect 2 mm. in diameter. The heart valves were normal. There was extensive atherosclerosis of the coronary arteries with patchy calcification, and the aorta and major arteries throughout the body were atherosclerotic. Each pleural cavity contained half a pint (284 ml.) of clear straw-coloured fluid, and the lungs were congested and oedematous. The liver and spleen showed the changes of chronic passive congestion.

The kidneys were of normal size (left 160 g., right 170 g.) and there was persistence of foetal lobulation. The capsules stripped easily and the subcapsular surface was smooth. The parenchyma was congested and the corticomedullary junction was indistinct.

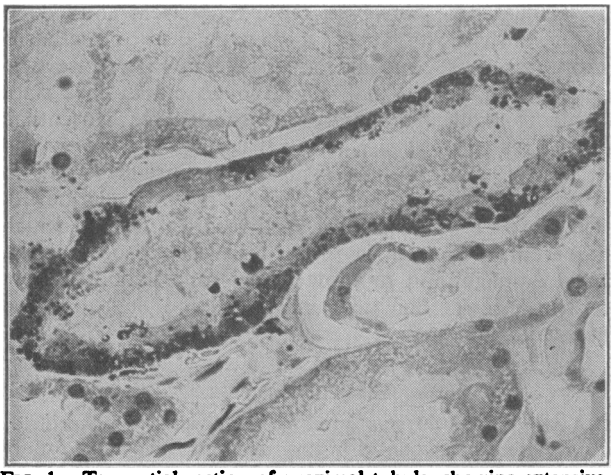

FIG. 1.—Tangential section of proximal tubule, showing extensive epithelial intracellular deposits of fatty material. (Fettrot. ×360.)

Histological examination of the tissues confirmed the presence of widespread vascular congestion, but the chief interest lay in the kidneys. Sections from the kidneys were stained with H. and E., with P.A.S., and by von Kossa's method. Gelatin-embedded tissue was stained for fat by the method of Fettrot. The glomeruli were substantially normal apart from the presence of eosinophilic granular material in Bowman's space, though occasional glomeruli were shrunken. The capillaries were bloodless and there was no thickening of the basement membrane or proliferation of epithelium. Tubular damage was prominent, with flattening and desquamation of the epithelium in the proximal and distal convoluted tubules. The lumen of the tubules which were dilated was filled with eosinophilic granular debris and necrotic cells. The remaining damaged cells lining the convoluted tubules had a foamy and vacuolated cytoplasm. The nuclei were often pyknotic. Though some of this appearance may be due to post-mortem autolysis, there was an undoubted increase in the intracellular fat (Fig. 1). Regenerating epithelium was not seen in any of the material studied. Nowhere was there evidence of calcification of either the tubular epithelium or the debris in the lumen. There was marked oedema of the interstitial tissue, with scattered chronic inflammatory cell-infiltration. Apart from the congestion the vasculature was normal.

Microdissection of the nephrons was carried out by the method previously described by Darmady and Stranack (1957). The total number of nephrons appeared to be within normal limits. The glomeruli showed no anatomical abnormality. (By this technique it is not possible to identify with accuracy glomerular abnormalities.) The proximal tubules, although normal in outline, showed localized and, in places, extensive deposits of fat-containing material, giving a strongly positive result with Nile blue (Fig. 2A). The position of these lesions corresponded in general with those described by Oliver, MacDowell, and Tracy (1951) for mercuric chloride. In other areas the arrangement of the epithelium was normal; the loop of Henle showed no damage. In the distal tubules, however, there were extensive and focal areas of epithelial fat replacement, with distortion of the epithelium arrangement (Fig. 2B). The atrophy seen might have been accounted for by the age of the patient.

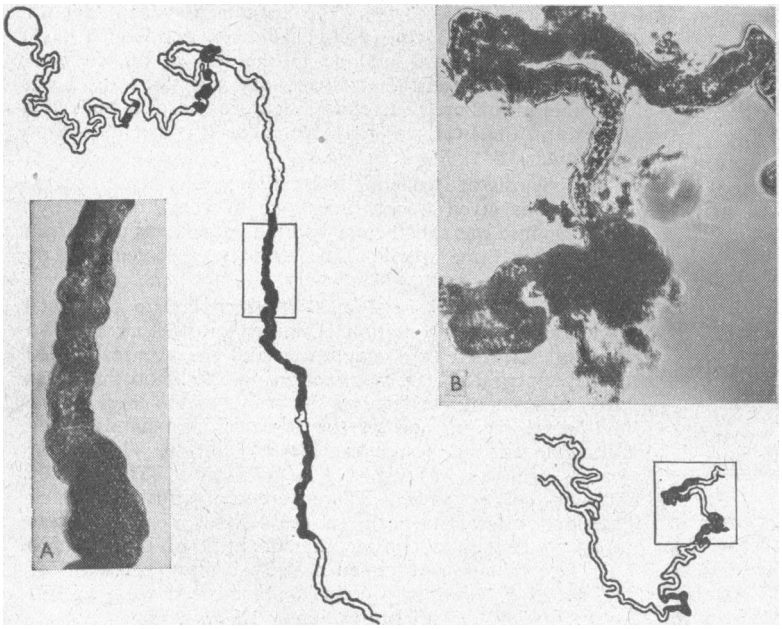

FIG. 2.—Semi-diagrammatic line drawing of proximal tubule and distal tubule to indicate areas of fat replacement, seen in black. A, Portion of proximal tubule showing focal areas of fat replacement. (Phase contrast. ×100.) B, Portion of distal tubule showing focal areas of fat replacement. (Phase contrast. ×100.)

Comment

The appearances here described are in agreement with the gross and microscopical findings in cases of renal damage due to inorganic and organic mercurials. Damage in the convoluted tubules is the salient feature, and it is most probable that damage in this section of the nephron is a function of the absorptive activity of the convoluted tubules raising the local concentration of mercury. The localized areas of cell necrosis and fatty degeneration suggest that this was due to the direct effects of mercury, which is a powerful protoplasmic poison. In the case described fatty degeneration of the renal epithelium was a prominent feature. This finding has been reported in only two cases (Waife and Pratt, 1946; Preedy and Russell 1953). However, in the cases described earlier in this issue (p. 1274) microdissection in two of the cases also showed fatty epithelial degenerative change mostly confined to the proximal tubules, but also to a lesser extent in the distal tubules. Calcification of the damaged cells and luminal debris, though absent in this case, has been a prominent feature in some cases of poisoning with inorganic mercury (Tarr and Jacobson, 1932; Allen, 1947; Bruno, 1948). In cases reported by these authors the deposits of

"calcium" appeared within a few days of the administration of mercury. This is in marked contrast with our experience in producing experimental nephrocalcinosis, which was usually found to take 10 to 14 days. Since von Kossa's stain for calcium is not specific it is possible that at least some of the stainable "calcium" reported by these authors was in fact a phosphate mercury complex.

Specific glomerular changes other than the accumulation of eosinophilic material in Bowman's space have not been described following the administration of mercurial diuretics. However, shrunken glomeruli of the type described earlier were found in the kidneys of rabbits which had received mercuric chloride (Edwards, 1942). These shrunken glomeruli may be of considerable importance in this case, since it is recognized that in the nephrotic syndrome there is not only tubular dysfunction with some resultant failure to reabsorb protein, but also increased permeability of the capillary tufts in the glomerulus (Hardwicke and Squire, 1955). The nephrotic syndrome has not been a feature of previously recorded cases of fatal renal damage following mercurial diuretics, and this might be explained by the fact that the glomerular lesion is not a constant feature in these cases.

From the clinical angle mercurial diuretics are now widely used. The possible action of this drug as a nephrotoxin does not seem to be as fully recognized as it should. In this case the renal tubular damage had apparently become irreversible before steps to institute an alternative diuretic could be arranged. It is not easy to suggest methods for the recognition of the onset of renal failure. The one sign which may be of value is the onset of increasing proteinuria.

Summary

A case of the nephrotic syndrome following the administration of a mercurial diuretic is described.

The salient histological feature was necrosis and fatty degeneration without calcification of the epithelium in the convoluted tubules. In addition a number of the glomeruli were shrunken.

The significance of the dual lesion in the production of the nephrotic syndrome is discussed.

The observation of increasing proteinuria in patients under treatment with mercurial diuretics suggests that renal damage may be occurring, and that prompt steps should be taken to institute alternative diuretics.

Our thanks are due to the Medical Research Council for an expenses grant. We are grateful to Dr. J. C. Prestwich, under whose care the patient was for her final illness, for his permission to publish this case. We are also grateful to Mrs. S. J. W. East for the line drawing and to Mr. A. E. Clarke, F.I.M.L.T., for the photomicrograph.

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The Medical Research Council's medical mycology committee has recently revised *Nomenclature of Fungi Pathogenic to Man and Animals* (M.R.C. Memorandum No. 23, H.M.S.O., price 1s. 3d. net.). The memorandum lists the names for fungi and for fungal diseases which the committee recommends should be used in Britain; it also includes notes on why some of the names are preferred and a list of rejected names.

LARYNGEAL STRIDOR IN RHEUMATOID ARTHRITIS

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[WITH SPECIAL PLATE]

Arthritis of the cricoarytenoid joint is one of the more unusual manifestations of rheumatoid arthritis and has been accepted by most observers as the cause of laryngeal stridor which sometimes occurs late in the disease. We have recently encountered five patients with unmistakable evidence of advanced rheumatoid arthritis who presented with stridor. The onset of this complication occurred when the generalized joint disease appeared to be quiescent, and tracheotomy became necessary in four cases. Clinical examination in three of the cases indicated a bilateral abductor paralysis of the vocal cords. As the difficulty of differentiating between an arthritis of the cricoarytenoid joint and a bilateral abductor paralysis with disuse fixation is well recognized, the death of two of our patients provided material for a detailed microscopical study of this problem.

Case 1

The patient worked in a rolling mill until the age of 57, when he developed rheumatoid arthritis. He received a variety of physical treatments at a local spa, but these did not include gold or other injections. Gradually the disability increased so that he had to find lighter work. In December, 1953, at the age of 62, and two years before his death, he developed a respiratory infection with hoarseness. At no time in the past had there been any laryngeal symptoms, and there was no local pain or dysphagia on this occasion. Three weeks later his breathing became very distressed owing to respiratory obstruction. Both vocal cords were touching, and an emergency tracheotomy was performed. After recovery from the operation the nature of the laryngeal lesion was more fully investigated. Indirect laryngoscopy showed a symmetrical appearance with a vocal gap of 2–3 mm. posteriorly. No movement occurred on inspiration or expiration, but the cords met on phonation. On straining, the larynx as a whole contracted. Direct laryngoscopy was performed under thiopentone and succinylcholine chloride anaesthesia, and the mobility of the arytenoids tested by grasping them in a pair of Paterson's forceps. Movement of the cricoarytenoid joint was found to be unrestricted. Because of these findings the lesion was regarded as a bilateral abductor paralysis rather than a cricoarytenoid arthritis. Neurological examination showed no cause for a paralysis of the vocal cords, so the case was finally diagnosed as idiopathic bilateral abductor paralysis of the larynx.

The patient managed to get about at home fairly well for the next 18 months until his dyspnoea returned, eventually being present even at rest. When examined at this time he showed undoubted changes of advanced burnt-out rheumatoid arthritis, with permanent deformities in the hands. In addi-