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RENAL LESIONS IN A CASE OF EXCESSIVE VOMITING

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(Plate IX)

The observations of Dunn, Gillespie and Niven (1941) and of Bywaters and Dible (1942) on the renal lesions of the crush syndrome have aroused interest in the problem of the localisation of damage in renal tubular nephritis. Tubular lesions similar to what they have described in the crush syndrome have been found in a patient who had impaired renal function associated with the excessive vomiting of pyloric stenosis. We consider that the findings may be of some significance in the general problem of the pathogenesis of tubular damage.

Case report

Summary of clinical history

The patient, a male aged 33, had a history of peptic ulcer for the preceding eight years. In the last two years vomiting was frequent and radiological examination revealed pyloric stenosis. Four days before admission to hospital the patient felt worse than usual, having severe abdominal pain and frequent vomiting. He took large quantities of alkaline powders for relief. On the day before admission vomiting became severe and almost continuous and muscular cramps developed in the feet and hands.

The patient was admitted to hospital in a collapsed state and extremely dehydrated and having tetanic contractions of the muscles of the feet. His reflexes were exaggerated. Trousseau's sign was positive. The temperature and pulse were normal; respirations were shallow but of normal rate. Intravenous glucose saline, rectal saline and intravenous calcium gluconate were administered on the day of admission, with relief from the manifestations of tetany. This treatment, with the addition of sedatives and ammonium chloride orally, was continued. During the first three days after admission the patient had anuria; 1 oz. of urine was recovered by catheter on two occasions during this period; it was acid and contained albumin. After the third day the patient passed urine in varying quantity. On the fourth and fifth days he was incontinent. Thereafter small quantities of urine (8-16 oz. per day) were passed throughout the illness. The urine was acid to litmus and contained albumin and the chlorides were diminished. Albuminuria ceased on the tenth day but the reaction of the urine was not

recorded from this point. The blood urea was high—0·360 per cent. on the ninth day and 0·230 per cent. on the tenth day. Thirteen days after admission, a posterior gastro-enterostomy was performed. The patient never rallied after the operation. The pulse and respiratory rate gradually rose and the patient died on the third day.

Post-mortem findings

There was extensive suppurative bronchopneumonia with large abscesses near the hilum of each lung. In contrast to the extreme emaciation, the liver was large (2000 g.). The stomach was greatly distended and the musculature, especially of the pyloric portion, hypertrophied. The pylorus was greatly narrowed—2·5 mm. diameter. Abutting on the pylorus, on the lesser curvature of the stomach, there was a large chronic ulcer 3 cm. in diameter, with fibrous induration around. The gastro-enterostomy was in good condition. Apart from the kidneys, no other abnormality was found in the organs.

Both kidneys were large (200 and 190 g.), very pale and softer than normal. The capsule stripped easily, revealing a very pale smooth surface. The cut surface was blanched and wetter than normal. The general architecture was indistinct.

Histological examination of kidneys

Apart from an occasional sclerosed tuft there is no evidence of old renal disease. The glomeruli appear normal. There is widespread tubular damage accompanied by interstitial œdema and early fibrous interstitial proliferation. Foci of more marked interstitial proliferation and round cell infiltration are associated with areas of tubular collapse. The majority of the affected tubules show changes at a reparative stage ; in a few the changes are more recent. The tubular damage is mainly if not entirely in the ascending limbs of Henle, the second convoluted tubules and a few of the collecting tubules. Thus in the cortex the many normal tubules are all first convoluted tubules, while no normal second convoluted tubules are seen. The damaged tubules are recognised as straight segments in the rays of the cortex and also appear amidst the cortical labyrinth in wide angulations which come into contact with a glomerulus at one point ; this is characteristic of the distribution of the ascending limbs of Henle and the second convoluted tubules. The straight descending limbs of first convoluted tubules in the medullary rays of the cortex are normal.

The changes in the altered tubules take the following forms.

1. *Acute changes.* These are represented by necrosis and partial desquamation of epithelium, with occasional early epithelial regeneration and the appearance of mitotic figures. This acute damage is invariably associated with highly fuchsinophil casts

RENAL LESIONS IN EXCESSIVE VOMITING

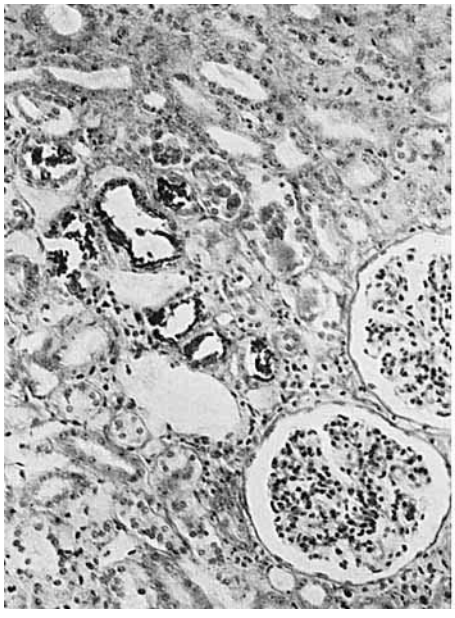

FIG. 1.—Cortex showing fuchsinophil ribbon casts (black) closely applied to the necrotic epithelium of segments of a second convoluted tubule. Lumina of tubules immediately to right of this contain desquamated necrotic epithelial cells; remainder of cortex normal. Picro-Mallory. ×120.

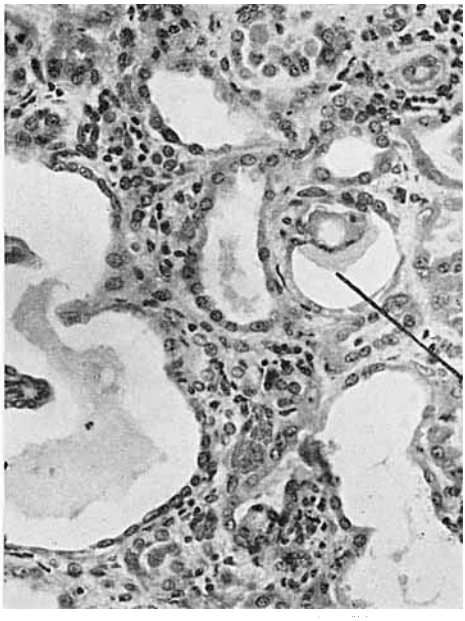

FIG. 2.—Ascending limbs of Henle in boundary zone, showing dilatation and a regenerative type of epithelial lining. A fatty cast with early calcification (indicated by a line) is seen partially covered by new epithelium. H. and E. ×210.

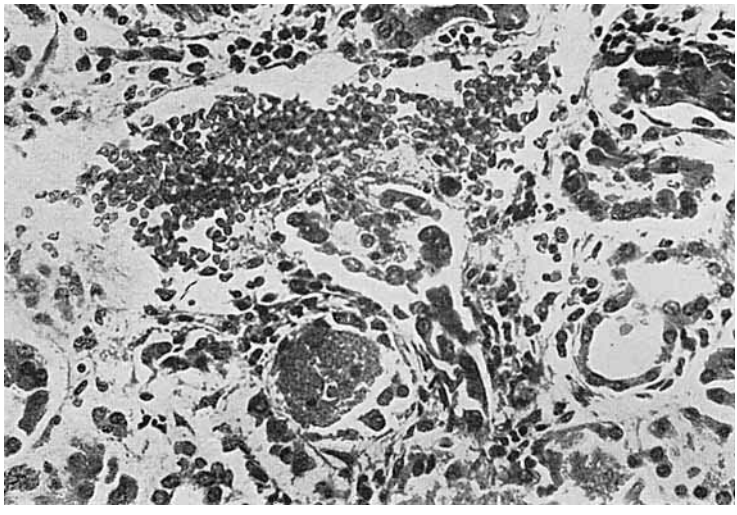

FIG. 3.—Tubulo-venous lesion. The affected tubule pouts into a venule filled with red blood cells. Fibrin threads entangling blood cells are seen to pass through an opening in the wall of the venule. H. and E. ×210.

which are often " ribbon-like " in form and closely applied to the damaged epithelium. The fuchsinophil casts are Gram-positive but do not give the benzidine reaction ; in unstained sections they are refractile and colourless (fig. 1). The lumen of a few of the damaged tubule segments is packed with red blood cells.

2. *Regenerative changes.* The great majority of the ascending limbs of Henle and second convoluted tubules show varying degrees of dilatation with flattening of the epithelium. Their lining epithelium also has an excess of nuclei, which are hyperchromatic, while the protoplasm is distinctly basophilic. Mitotic figures are rarely seen but the appearances are indicative of recent proliferation and re-lining (fig. 2). There are abundant hyaline and some granular casts in these tubules but they bear a striking contrast to the fuchsinophil ribbon casts associated with more recent damage. They are neither fuchsinophil nor Gram-positive, but stain deep blue with Mallory's stain. They may be free in the lumen but are often in contact with the tubule wall at one point. There the tubular epithelium grows over the casts, forming characteristic buds which project into the lumen. When the epithelial covering is complete the casts, now interstitial, have undergone fatty change and early calcification (fig. 2). Scattered zones in a few of the collecting tubules show focal changes (acute degenerative and regenerative) similar to those in the second convoluted tubules. A few of the basophilic hyaline casts are being invaded by polymorphs, but there is no evidence of bacterial infection in the kidneys.

3. *Tubulo-venous communications.* At some points in the majority of the larger thin-walled venules in both cortex and medulla, there are fibrin aggregations, entangled in the meshes of which are a few blood cells and often larger cells resembling renal tubular epithelium. These aggregations are not associated with complete thrombosis or occlusion of the venules. Serial sections show that they are associated with tubulo-venous fistulæ. In each instance the tubule, unlike others nearby which also lie close on the venule wall, shows recent damage and active regeneration of cells ; at the point of rupture strands of fibrin may be seen to extend through from the venule into the lumen of the tubule, while frequently a band of proliferated epithelial cells projects into the lumen of the venule (fig. 3). These lesions, which all appear to be of recent origin, are in all respects similar to those described by Dunn *et al.* in the kidneys of the crush syndrome. In addition there are many partially healed tubulo-venous lesions. In some the affected tubule has collapsed ; in a few a basophil hyaline cast protrudes from the tubule lumen into the interstitium.

Scattered zones in a few of the collecting tubules show focal changes (acute degenerative and regenerative) similar to those in the second convoluted tubules.

Discussion

Attention has already been drawn by a number of observers to renal damage in cases of excessive vomiting from pyloric stenosis associated with dehydration, alkalæmia, azotæmia and often tetany (Brown *et al.*, 1923 ; Zeman *et al.*, 1924 ; Cooke, 1933). The renal signs in the present case were unusually severe in that there was an initial period of anuria ; in the other recorded cases there were only oliguria, albuminuria and cylindruria. The fact that an acid urine was excreted for a period might appear unlikely in a subject who presumably had alkalæmia ; this, however, was also the finding of Cooke in such cases. Cooke also showed that if, with large saline transfusions, the oliguria and albuminuria cease, the urine promptly becomes alkaline.

Brown *et al.* and Cooke have given brief pathological descriptions of the renal changes in cases of alkalæmia from excessive vomiting in pyloric stenosis. They are agreed on the finding of alterations in the tubules but do not indicate which segments are involved. The changes appear to have been regenerative rather than necrotic and Cooke lays stress upon the occurrence of calcification ; his illustrations depict a distribution of lesions corresponding to those in the present case. Zeman *et al.* on the other hand (p. 41) describe damage " in the spiral and terminal straight portions of the first convoluted tubules ". These authors also produced tubular lesions in the kidneys of cats by tying the pylorus so as to ensure loss of chloride from the body ; the same tubule segments were believed to be affected as in the human cases with, in addition, tubules " adjacent to glomeruli ".

In the present case it is considered certain that the lesions involve the more distal part of the nephron and that they are morphologically similar to those constantly found in the kidneys of cases of the crush syndrome as described by Dunn *et al.* and by Bywaters and Dible in a larger series, except that pigmented (myohæmoglobin) casts are not present. In this case acute tubulovenous lesions are a striking feature and they have the peculiarly focal character which Dunn *et al.* described.

The specific localisation of damage in the lower segments of the nephrons has been referred by Bywaters and Dible, in cases of crush syndrome, to concentration of the tubular contents at this level, while Dunn *et al.* have attributed importance to change in reaction of the filtrate. In the cases which they describe, casts of myohæmoglobin are so commonly associated with the lesions as to suggest that this substance may have toxic effects, though it remains possible that the cellular damage is caused by some other unrecognised agent. In the present case, myohæmoglobin does not come into consideration as a possible toxic agent but there are

good grounds for assuming considerable departure from normal in the blood/filtrate exchanges owing to excessive loss of chloride by vomiting. There can be no doubt that at most times, and particularly when highly concentrated urine is being formed, the osmotic difference between the filtrate in the tubules and the blood in the vessels around them is very great, while the two fluids are separated only by a very narrow layer of highly specialised epithelium which may still be presumed to exert some modifying influence on the filtrate at this level. The mechanism by which this epithelium is normally preserved intact in these circumstances is at present conjectural, but it would appear to be a possibility that this could at times be overwhelmed by some alteration in the natural process of exchange. The epithelial damage described may have been produced in this way and we consider that the tubulo-venous fistulæ, which are much too frequent to be regarded as fortuitous, are determined on a functional basis and depend on blood/filtrate readjustment being particularly active at these points.

Bywaters and Dible mention a number of other conditions (intravascular hæmolysis, blackwater fever) in which renal lesions are produced similar to those in the crush syndrome. The experimental approach to the crush syndrome and these other conditions is difficult owing to the obscurity of the ætiological factors involved. In the type of case which we have described the initial cause—loss of fluid and chlorides from the body—is simple and clearly defined and capable of being produced experimentally. It may well open up an avenue in experimentation which will be of value in the elucidation of the pathogenesis of lesions in the distal part of the nephron.

It is recognised that in the present case a severe infective pulmonary lesion in the form of bronchopneumonia with abscess formation was present terminally, but we do not consider this had any part in the production of the renal changes. A renal lesion of this description is not known as an accompaniment of bronchopneumonia, which is a common disease, and in addition there is no evidence in the kidneys that infection had played any part in the genesis of the lesions.

Summary

1. Renal tubular lesions are described in a case of excessive vomiting due to pyloric stenosis.

2. The changes, which are both degenerative and regenerative in type, are confined to the ascending limbs of Henle, the second convoluted tubules and the collecting tubules, and are similar to those described by Dunn *et al.* and Bywaters and Dible in the crush syndrome.

3. The acute tubular damage includes formation of communications between the tubules and adjacent venules. We consider that these tubulo-venous fistulæ are determined on a functional basis and have a special significance in relation to the morbid process rather than being fortuitous manifestations of tubular damage.

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REFERENCES

BROWN, G. E., EUSTERMAN, G. B., HARTMAN, H. R., AND ROWNTREE, L. G.	1923.	*Arch. Int. Med.*, xxxii, 425.
BYWATERS, E. G. L., AND DIBLE, J. H.	1942.	This *Journal*, liv, 111.
COOKE, A. M.	1933.	*Quart. J. Med.*, N.S. ii, 539.
DUNN, J. S., GILLESPIE, M., AND NIVEN, J. S. F.	1941.	*Lancet*, ii, 549.
ZEMAN, F. D., FRIEDMAN, W., AND MANN, L. T.	1924.	*Proc. New York Path. Soc.*, xxiv, 41.