syndrome. The observations of Ziegler *et al.* (1969) indicate that there is no general fundamental abnormality of the lymphoreticular responses in patients who develop the syndrome. This suggests that either persistence or alteration of malarial antigen, or both, may be of prime importance. Dacie *et al.* (1969) suggested that an altered endogenous antigen may be the aetiological factor in non-tropical cases. If this is correct, persistent antigenic stimulus might explain the pathogenesis of both the tropical and the non-tropical cases.

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REFERENCES

- British Medical Journal, 1969, 4, 4.
- Charmot, G., and Vargues, R. (1963). *Semaine des Hôpitaux de Paris*, 39, 1421.
- Chaudhuri, R. N., Saha, T. K., Basu, S. P., Mukherjee, A. M., and Chaudhuri, M. N. R. (1956). *Indian Journal of Medical Research*, 44, 305.
- Dacie, J. V., Brain, M. C., Harrison, C. V., Lewis, S. M., and Worledge, S. M. (1969). *British Journal of Haematology*, 17, 317.
- Fawdry, A. L. (1955). *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 49, 387.
- Fisher, G. U., and Schultz, M. G. (1969). *Lancet*, 2, 716.
- Lanzo, A. (1969). *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 63, 150.
- Lowenthal, M. N., Hamilton, P. J. S., Hutt, M. S. R., and Wilks, N. E. (1966). *Central African Journal of Medicine*, 12, 99.
- Marsden, P. D., *et al.* (1965). *British Medical Journal*, 1, 89.
- Marsden, P. D., *et al.* (1967). *Bulletin of the World Health Organization*, 36, 901.
- Marsden, P. D., and Hamilton, P. J. S. (1969). *British Medical Journal*, 1, 99.
- Mustafa, D. (1965). *Journal of Tropical Medicine and Hygiene*, 68, 183.
- Pitney, W. R. (1968). *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 62, 717.
- Pryor, D. S. (1967). *Quarterly Journal of Medicine*, 36, 321.
- Ratnesar, V. C., Hathorn, M., Lahiri, H., Younn, S., and Kovi, J. (1966). *Ghana Medical Journal*, 5, 109.
- Voller, A., and Bray, R. S. (1962). *Proceedings of the Society for Experimental Biology and Medicine*, 110, 907.
- Watson-Williams, E. J., and Allan, N. C. (1968). *British Medical Journal*, 4, 793.
- Wilks, N. E., Turner, P. P., Somers, K., and Markandya, O. P. (1965). *East African Medical Journal*, 42, 580.
- Ziegler, J. L., Cohen, M. H., and Hutt, M. S. R. (1969). *British Medical Journal*, 4, 15.

Preliminary Communications

Urographic Changes in Acute Papillary Necrosis in the Rat

British Medical Journal, 1970, 3, 263-265

Summary: Intravenous high-dosage urography was performed in rats which had renal papillary necrosis induced with ethyleneimine or renal tubular necrosis produced with mercuric chloride. In both groups, nephrograms were abnormally persistent. In animals treated with ethyleneimine dense selective opacification of the necrotic renal pyramid occurred. It is suggested that this selective opacification may be a valuable radiological sign of recent renal papillary necrosis.

INTRODUCTION

Until recently intravenous urography was thought to be contraindicated in acute renal failure because it was considered dangerous and of little clinical value (Emmett, 1964). By using contrast media such as diatrizoate in high doses, however, information of diagnostic and prognostic significance may be obtained by this technique in renal failure (Schwartz *et al.*, 1963; Chrispin, 1968; Mahaffy *et al.*, 1968; Kelsey Fry and Cattell, 1970).

The present study stems from finding urographic abnormalities in infants suffering acute renal damage following severe gastroenteritis (Chrispin *et al.*, 1970). In these three patients intravenous urography revealed nephrograms that were abnormally persistent and prolonged selective opacification of the renal pyramids. Repeat urograms on two of these infants some months later showed loss of renal papillae. To investigate this matter further we decided to induce renal papillary necrosis in rats to see if similar

urographic changes could be produced. Our findings confirm that persistent opacification of the renal papilla occurs as a result of renal papillary necrosis. No such abnormal opacification of the renal papilla occurs where there is acute tubular necrosis alone.

MATERIALS AND METHODS

White male Wistar rats weighing between 250 and 300 g. were used throughout. The animals were divided into two groups and treated as follows:

Group A (eight animals).—Ethyleneimine (between 0.6 and 1.0 ml./kg. body weight of a 1% solution) was administered by intraperitoneal injection to each animal once only.

Group B (seven animals).—Mercuric chloride (between 1.5 and 1.8 mg./kg. body weight of the mercuric ion) was administered by intraperitoneal injection to each animal once only.

Several untreated animals were used as controls.

Radiological studies were performed at one- and four-day intervals after injection of the nephrotoxins. The animals were anaesthetized with sodium pentobarbitone (25 mg./kg. body weight) given by intraperitoneal injection and augmented by ether inhalation. Hypaque 65% (sodium and methylglucamine diatrizoate, Bayer) in a dose of between 2 and 2.4 ml./kg. body weight was injected into a femoral vein, radiographs being taken at 1, 3, 10, and 45 minutes after the injection. In addition further films were made at 90 minutes in some of the animals in group A. Each animal was subsequently killed and the kidneys were removed. These were examined macroscopically and then fixed in buffered formalin (pH 7.0) for 48 hours and secondarily fixed in mercuric chloride-formalin for six hours. The tissue was then embedded in paraffin wax and sections of 3-4 μ thickness were prepared. These were stained by Ehrlich's haematoxylin and eosin, periodic acid-Schiff, and Martius scarlet blue (M.S.B.).

PATHOLOGICAL CHANGES IN THE KIDNEYS

ANIMALS TREATED WITH MERCURIC CHLORIDE

Macroscopic.—The kidneys were swollen and there was pronounced yellowish-brown pallor of the cortex, with considerable congestion of the medulla.

Microscopical.—In animals killed one and four days after administration of mercuric chloride extensive areas of acute tubular necrosis were observed in the renal cortex. These principally affected the proximal convoluted tubules and were more pronounced in the rats killed at four days; the changes did not affect the tubules in the medulla. The glomeruli were engorged but showed no other abnormality.

ANIMALS TREATED WITH ETHYLENEIMINE

Macroscopic.—The kidneys were swollen and intensely congested. In animals killed one day after injection of ethyleneimine transection of the kidney showed the renal pyramid to be dark red and haemorrhagic. At four days necrosis of the pyramid was obvious macroscopically. The renal papilla was a pale creamy buff colour, and at the base of the pyramid there was a sharp line of demarcation outlining the necrotic zone.

Microscopical.—The changes were confined to the medulla; the cells lining the collecting ducts and loops of Henle were frankly necrotic in the kidneys removed both one and four days after the administration of ethyleneimine. At four days the majority of cells were desquamated, and at the edge of the infarcted area there was a zone of acute inflammation.

RADIOLOGICAL FINDINGS

These are summarized in the Table. In rats treated with mercuric chloride excretion of contrast medium was not visible one day after injection of the nephrotoxin. At four days a nephrogram of even intensity was evident in films taken one minute after injection of diatrizoate, and this was still easily seen in the films taken at 45 minutes; no opacification of the ureter or urinary bladder was observed. This was in contrast to the findings in the untreated animals, in which the nephrogram had faded at 45 minutes.

In rats treated with ethyleneimine there was a persistent nephrogram as well as selective opacification of the renal pyramid. This was apparent in films taken at 3 and 10 minutes after injection of diatrizoate, was intensified at 45 minutes, and persisted until 90 minutes in some animals. Filling of the urinary bladder was occasionally seen in films taken at 10 minutes, but more often it was not apparent until 45 minutes.

DISCUSSION

Our radiographic findings in the control rats and in those treated with mercuric chloride are essentially similar to those of Chamberlain and Sherwood (1967). In the animals treated

with ethyleneimine there was also a persistent nephrogram, but dense selective opacification of the renal pyramid also occurred (Fig. 1). These results are very similar to those we described in young infants with renal impairment following acute gastroenteritis (Chrispin *et al.*, 1970), and it seems reasonable, particularly in view of later urograms showing loss of renal papillae, to attribute the radiological appearances in these children to recent papillary necrosis.

FIG. 1.—Film taken 45 minutes after injection of diatrizoate in an animal 4 days after treatment with ethyleneimine. Note selective opacification of renal pyramid.

The selectively opacified area in the urogram exactly matches the zone of necrosis in the renal pyramid seen in the excised kidney (Fig. 2). The increased density in the pyramid reflects an increase in the amount of contrast medium it contains. The necrotic tubules are denuded of lining epithelial cells, thus increasing their cross-sectional area and the volume of contrast medium they contain at any given moment. The persistent nephrogram effect in the ethyleneimine-treated animals probably results from a "leakage" of contrast medium from the damaged tubules in the pyramid into the interstitial tissues, where a constant reabsorption into the blood vessels at the edge of the necrotic zone would lead to its subsequent recirculation and re-excretion by the kidney (see Fig. 3).

Summary of Radiological Findings

	Days After Injection of Nephrotoxin	Time Radiographs Taken After Injection of Diatrizoate				
		1 Minute	3 Minutes	10 Minutes	45 Minutes	90 Minutes
Normal		Nephrogram	Nephrogram with outlining of tip of renal papilla and ureter	Nephrogram beginning to fade. Filling of bladder	Nephrogram gone. Faint outlining of renal papilla and ureter	
Mercuric chloride	1	No excretion of contrast medium				
	4	Nephrogram	Uniform nephrogram with no filling of ureter	Persistent nephrogram	Nephrogram still apparent. No filling of bladder	
Ethyleneimine	1	Nephrogram	Nephrogram	Nephrogram persisting. Some selective opacification of renal pyramid	Selective opacification of renal pyramid. Filling of bladder	
	4	Nephrogram	Nephrogram with slight selective opacification of renal pyramid	Nephrogram persisting. Selective opacification of renal pyramid	Nephrogram persisting. Dense selective opacification of renal pyramid. Filling of urinary bladder	Opacification of renal pyramid still present though faded. Filling of urinary bladder

FIG. 2.—Left: Isolated rat kidneys 4 days after administration of ethylenimine. Kidneys were removed and x-rayed after animal had received diatrizoate by intravenous injection. Right: Transected kidney from same animal. Note how area of opacification in radiograph corresponds to area of necrosis in renal pyramid.

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FIG. 3.—Diagram showing continuous recirculation of proportion of contrast medium excreted by kidney after it has "leaked" from damaged tubules in necrotic renal papilla.

REFERENCES

- Chamberlain, M. J., and Sherwood, T. (1967). *Nephron*, **4**, 65.
 Chrispin, A. R. (1968). In *Paediatric Urology*, ed. D. Innes Williams, p. 533. London, Butterworths.
 Chrispin, A. R., Hull, D., Lillie, J. G., and Risdon, R. A. (1970). *British Medical Journal*, **1**, 410.
 Emmett, J. L. (1964). *Clinical Urography*, 2nd edn., Vol. 1, p. 26. Saunders, Philadelphia.
 Fry, I. K., and Cattell, W. R. (1970). *British Journal of Hospital Medicine*, **3**, 67.
 Mahaffy, R. G., Caridis, D. T., and Matheson, N. A. (1968). In *Dialysis and Renal Transplantation: Proceedings of the 4th Conference of the European Dialysis and Transplant Association*, ed. D. N. S. Kerr, p. 437. Amsterdam, Excerpta Medica.
 Schwartz, W. B., Hurwit, A., and Ettinger, A. (1963). *New England Journal of Medicine*, **269**, 277.

Medical Memoranda

Polyuria after Cardiac Surgery

British Medical Journal, 1970, **3**, 265-266

Diabetes insipidus is of interest as a rare disease which may be difficult to diagnose. Study of this condition in man and animals has contributed to our understanding of water balance. We present a case of what is believed to be transitory diabetes insipidus.

CASE REPORT

The patient was born in January 1954 after a normal pregnancy and delivery. At age 1 she was found to have a cardiac murmur. Subsequent investigation confirmed the diagnosis of acyanotic Fallot's tetralogy with a right to left shunt of 2:1. On 6 May 1969 she was admitted to Guy's Hospital for further investigation and surgery.

On examination she was short (height on the 3rd percentile), with normal secondary sexual characteristics but a rather distinctive facies with an absent epicanthic fold. The only other abnormal findings were those consistent with Fallot's tetralogy. Investigations were: haemoglobin 13.0 g./100 ml.; platelets 133,000/cu. mm.; coagulation normal; 24-hour urine volume 500 ml., with corrected creatinine clearance of 64 ml./min.; skull x-ray picture normal.

Operation was performed on 13 May under normothermic 36–37°C.) cardiopulmonary bypass (3.5–8 l./min.). The total bypass time was 58 minutes. The diagnosis was confirmed, the ventricular septal defect closed, and the stenosis relieved. There was immediate restoration of normal cardiac rhythm with a negligible gradient between right ventricle and pulmonary artery. Post-

operatively the blood pressure was 90/70. The hypotension was not thought to be hypovolaemic as there was a difference of only 2°C. between the peripheral and central temperatures, and the central venous pressure of 10 cm. of water was adequate.

After 10 hours isoprenaline was infused at 0.4 µg./min. This produced a satisfactory rise of blood pressure. Subsequent attempts to wean her off the isoprenaline were unsuccessful, and at 36 hours the combination of a falling blood pressure and urine output with a rising central venous pressure led to a diagnosis of cardiac tamponade. This was relieved by one of us with immediate return of blood pressure, urine output, and peripheral circulation to normal limits.

There were no further complications until the sudden onset of a diuresis on the afternoon of the fifth postoperative day. This continued for 42 hours during which time she passed about 10 litres of urine with a specific gravity of 1000–1008. Diuretics had not been given. She was not hypokalaemic, hypercalcaemic, or hyperglycaemic. There were no signs of adrenal failure. She was otherwise symptomless. The blood urea was 18 mg./100 ml. and the urea clearance 59 ml./min. At this time the differential diagnosis lay between hysterical polydipsia (or its iatrogenic counterpart of excessive intravenous therapy causing a solute and/or water diuresis) and failure in production of antidiuretic hormone.

She was given one unit of the short-acting aqueous preparation of vasopressin injection (Pitressin). This suppressed the urine flow rate from 8.8 to 0.5 ml./min. for one hour. The urine flow rate then increased again to 8.4 ml./min. until the long-acting oily preparation was given (see Fig. 1). This effect lasted for 24 hours during which time she was allowed unrestricted access to oral fluids and received a further 2.5 litres of fluid intravenously. At no time did she show any signs of water intoxication, as might have been the case had she been suffering from compulsive polydipsia. For the next four days she received 5 units of the preparation in oil daily. Her requirements subsequently rapidly