PHENINDIONE NEPHROPATHY WITH RECOVERY: STUDIES OF MORPHOLOGY AND RENAL FUNCTION

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VARIOUS hypersensitivity reactions secondary to phenindione therapy have been described since its introduction in 1947. Amongst the most severe reactions are those involving the kidney. Transient albuminuria is not uncommon following phenindione therapy (Coon, Hodgson and Dennis, 1953; Goodman and Gilman, 1955). There have been seven reported cases of more severe renal involvement, in four of which the renal morphology has been known (Barritt and Jordan, 1960; Postgraduate Medical School of London, 1960; Galea, Young and Bell, 1963; Baker and Williams, 1963). Only in the last case was renal function investigated fully and correlated with the morphological changes. A further example of phenindione nephropathy, with a successful outcome of medical management, is reported to illustrate a type of renal lesion and change in renal function due to phenindione and to compare it with the case reported by Baker and Williams (1963).

Case Report

A fit civil servant, aged 55, fell off a ladder on March 27, 1963, and sustained a fracture of the left tibia. On March 30 an open reduction of the fracture was performed, and the leg was immobilized in an above-knee plaster. Although the post-operative course was satisfactory it was decided on April 7 to treat the patient with phenindione to prevent phlebo-thrombosis.

On May 1 the patient, then at home, felt unwell, was pyrexial and developed a widespread erythematous skin rash. He was given antihistamines but with little effect. On May 4, because of continuing rash, fever and general malaise, the patient's general practitioner discontinued the phenindione therapy. The patient had been taking the drug for 28 days and had received a total dosage of 2.83 g. On May 7 the patient was seen by a dermatologist who considered that the rash was probably due to phenindione sensitivity and prescribed cortisone and further antihistamines.

However, the patient continued to experience malaise, had shivering attacks and the rash become more extensive. He was admitted to a nursing home on May 13, when he had a temperature of 103°F. (39.5°C.). The rash was an extensive erythematous maculo-papular one, becoming scaly over the face, neck and arms. His urine output at that time was normal and his blood urea 37 mg./100 ml. Other investigations were:— ESR 23 mm./hour; Hb. 15 g./100 ml.; PCV 46%; MCHC

34%; wbc 12,200/cu. mm.; neutrophils 80%, lymphocytes 12%, eosinophils 5%, and monocytes 3%. Some lymphocytes were noted to have unduly prominent cytoplasm. Total serum protein 6.1 g./100 ml., with normal albumin: globulin ratio. Liver function tests were normal. Serum glutamic-pyruvic transaminase 55 i.u./ml.

By May 15 the patient had developed a frank exfoliative dermatitis and was having frequent rigors. His urine output was 500 ml./24 hours in spite of adequate fluid intake.

Investigations now showed:— Hb 11.2 g./100 ml., PCV 36%, wbc 13,500/cu. mm., neutrophils 75%, lymphocytes 13%, eosinophils 8%, monocytes 4%, plasma cells 4%. Again unusual lymphocytes, with abundant basophilic cytoplasm and large reticulated nuclei were seen. Turk cells were also seen. Serum glutamic-pyruvic transaminase was now 203 i.u./ml.

On May 17 urine output fell to 390 ml./24 hours and blood urea was 160 mg./100 ml. Urine microscopy showed 3 leucocytes per high power field, no red blood cells or organisms. There was moderate albuminuria. Urine urea was 660 mg./100 ml.

On May 18 he was transferred to this Unit. Examination showed an obese, anxious man with widespread exfoliative dermatitis. He was not jaundiced, nor was there any lymphadenopathy. Blood pressure was 130/80 mm. Hg, the JVP was raised 1 cm., and the pulse 80/min. and regular. There were bilateral basal medium crepitations in the chest and a sacral pad of oedema. The liver edge was palpable one inch below the right costal margin. There was no splenomegaly.

Investigations.—Hb 9.8 g./100 ml., PCV 38%, wbc 13,600/cu. mm., neutrophils 59%, lymphocytes 26%, eosinophils 11%, monocytes 4%, with again many abnormal mononuclear cells; ESR 68 mm./hour; prothrombin time 19 seconds (control 16 seconds); serum glutamic-pyruvic transaminase 25 units/ml.; serum glutamic-oxaloacetic transaminase 41 units/ml.; blood urea 235 mg./100 ml.; serum sodium 120m Eq./l.; serum potassium 5.1 mEq./l.; serum chloride 90 mEq./l.; serum bicarbonate 16 mEq./l.; liver function tests normal; serum bilirubin 0.5 mg./100 ml.

Urine examination showed moderate proteinuria with numerous red and white cells. There were no casts. Urine urea concentration 920 mg./100 ml. Urine sodium 26 mEq./l, potassium 24 mEq./l, osmolality 156 mOsm/kg. Plasma osmolality 256 mOsm/kg. Plain X-rays of the abdomen showed the kidneys to be of normal shape, size and outline. Chest X-ray normal. ECG normal.

Progress

Artificial haemodialysis was performed using the Kolff

FIG. 1.—Urine and serum osmolality values and urinary electrolytes during the onset and recovery of the oliguric renal failure.

twin coil apparatus, on May 20, because of rising blood urea, falling serum bicarbonate, virtual anuria (22 ml./24 hours) and the known seriousness of this condition. Treatment with prednisone, 40 mg. daily, was begun on May 21 on the basis that the skin and the renal lesions were the result of a hypersensitivity reaction to phenindione and was continued in diminishing dosage until June 8 when a good urine output had been achieved.

Following the first haemodialysis the blood urea fell to 130 mg./100 ml., the bicarbonate rose to 25 mEq./l and the serum potassium fell to 3.3 mEq./l (See Fig. 2).

A second haemodialysis was required on May 24 and thereafter the blood urea gradually fell and reached almost normal levels by June 15. By June 7 the patient's skin had returned to normal. Although abnormal mononuclear cells had disappeared from the blood films by May 29, there was still an eosinophilia of 12% (990/cu. mm.), a normochromic anaemia (9.7 g./100 ml.) and an ESR of 68 mm./hour on June 15 when he was discharged. These findings showed continued activity of the hypersensitivity reaction.

A renal biopsy was performed on June 14 to gauge the degree of renal recovery. This had not been done earlier as the urine biochemistry had been characteristic of acute renal tubular necrosis.

The patient was readmitted on two more occasions for follow-up studies. On July 8 he still complained of occasional irritating rashes developing over various parts of his body. He was otherwise well. Examination revealed a maculo-papular rash on the arms, back and buttocks. He was clinically anaemic. When finally admitted on August 13 he was symptom free and there

FIG. 2.—Blood urea, plasma bicarbonate and urine output during the onset and recovery of the oliguric renal failure.

were no abnormal physical findings. His blood pressure has remained at 140/90 mm. Hg.

The results of investigations during these two admissions are shown in Table 1. The haematological findings, particularly the falling ESR and disappearance of the eosinophilia, are consistent with the slow subsidence of a hypersensitivity reaction.

Renal Function

The changes in urine and serum findings throughout the recovery phase are shown in Figs. 1 and 2. It is seen that the osmolality of the urine in the early stages was below that of the plasma, while the urine sodium concentration approached that of the serum and the urine potassium concentration was low. These findings together with the low urine/plasma (U/P) ratio of urea, are characteristic of acute tubular necrosis (Bull, Joekes and Lowe, 1950; Meroney and Rubini, 1959; Merrill, 1956; Sevitt, 1959). With recovery, the urine osmolality rose above that of plasma, the urine sodium concentration fell and the urine potassium concentration rose. The U/P urea ratio rose slowly but there was a much longer delay before there was any change in the plasma/urine (P/U) ratio of sodium. The slow approach of the urine electrolytes towards normality and likewise of the U/P urea and P/U sodium ratios long after the onset of the diuretic phase is typical of the recovery phase of acute tubular necrosis (Bull and others, 1950).

TABLE I
FOLLOW-UP STUDIES

	July 8-10, 1963	August 13-15, 1963
ESR	50 mm./hour	18 mm./hour
Hæmatology Hæmoglobin ..	8.9 g./100 ml.	10.8 g./100 ml.
MCHC	33%	34%
WBC	9,300/cu. mm.	5,900/cu. mm.
	Eosinophils 11%	Eosinophils 0%
Mid-stream urine specimen ..	Sterile. No protein cells or casts	Sterile. No protein, occasional casts
Glomerular filtration rate ..	54 ml./min.	90 ml./min.
Urea clearance	38%	38%
Urine acidification test ..	pH 5.6	pH 4.8
Maximum concentration power	510 mOsm./kg.	700 mOsm./kg.
Maximum diluting power ..	90 mOsm./kg.	90 mOsm./kg.
Blood urea	47 mg. %	48 mg. %
Serum electrolytes	Na 137, Cl 105 K 4.2, bicarbonate 27 mEq./l.	Na 138, Cl 108 K 4.4, bicarbonate 29 mEq./l.
Urine urea concentration ..	740 mg./100 ml.	1,240 mg./100 ml.
U/P urea	15	26
Urine sodium	74 mEq./l.	66 mEq./l.
Urine potassium	17 mEq./l.	29 mEq./l.
Liver function tests	Normal	Normal
Renal biopsy		See text

Mild to moderate albuminuria persisted until June 6, after which none was found. There was never any glycosuria. Throughout his stay in hospital there were a few red and white cells in his urine but no casts were seen, and no organisms were ever cultured. The urine acidity as measured in immediately voided urine (under paraffin oil) never fell below pH 6.1 when measured between May 23 and 28. A urine acidification test (Wrong and Davies, 1959) performed on July 9 showed a fall in urine pH to 5.6 after the oral administration of ammonium chloride. This showed further improvement by August (Table 1).

The glomerular filtration rate (GFR) using the inulin clearance method by continuous infusion was estimated on May 28. However, during the early phases of tubular dysfunction it is not possible to be sure that the inulin clearance represents glomerular filtration because some of the inulin may be passively reabsorbed across the walls of damaged tubules. Therefore, the early rising GFR values we obtained probably reflect tubular recovery. However, the later GFR values obtained when there was tubular recovery, are likely to be near correct indices of glomerular filtration (Bull and others, 1950). A urea clearance test carried out on June 11 gave a result of 29% (urine flow 15 ml./min.).

The follow-up renal function studies (see Table 1) all showed improvement though they had not reached normality and the evidence is that a very long interval elapses before they do (Lowe, 1952). The greatest deficit is still seen in renal tubular function tests (e.g. maximum concentrating power, urine electrolyte values) and this

is in agreement with the findings of the second renal biopsy.

Renal Biopsy was performed on June 14 by the percutaneous method using a Menghini needle. The biopsy report showed that the specimen contained seven glomeruli. There was a small cortical scar present which included a single hyalinized glomerulus. The remaining glomeruli were normal. There was some thickening of the glomerular capsules. No crescents were seen. The epithelium of both the distal and proximal tubules was swollen and granular or, in some instances, necrotic. A few mitotic figures were seen suggesting that some of the epithelium was regenerating (Fig. 3). The tubular basement membranes were difficult to define in some areas, but most of them were intact. The most striking feature was a cellular infiltration, with a predominance of plasma cells, of the interstitial tissue, where there was some early fibrosis. A few eosinophils were seen.

The second renal biopsy, performed on August 13, showed the following. The cellular infiltrate in the interstitial tissue persisted but it now consisted predominantly of lymphocytes. No eosinophils were seen and the plasma cells were fewer than in the previous biopsy. Changes in the tubules were less marked than before but dilated tubules containing hyaline casts were still seen and there was a deposit of calcium in relation to a tubule. The glomerular basement membranes were probably thicker than before and less well defined (Fig. 4).

FIG. 3.—First biopsy, showing intense cellular infiltration of interstitial tissue and tubular necrosis. (5μ section. Hæmatoxylin and eosin $\times 140$).

Discussion

There can be little doubt that this patient's illness was due to phenindione hypersensitivity. He showed features typical of such a reaction:—fever, exfoliative dermatitis, raised serum transaminase levels, eosinophilia and atypical mononuclear cells (Perkins, 1962). The patient had not received any other medication likely to have produced such a picture. The fact that the renal complications did not occur until some five weeks after commencement of phenindione seems consistent with the delay noted in previously reported cases (Kirkby, 1954; Barritt and Jordan, 1960; Galea and others, 1963; Postgraduate Medical School of London, 1960). The albuminuria, which was never severe in this patient, only persisted for 21 days although there was still considerable impairment of renal function 53 days later.

There have now been eight cases reported of severe renal complications following phenindione sensitivity (see Table 2). In five of these details of renal histology are available. The features of severe, acute tubular necrosis and reactive inflammation were seen in the case reported by Barritt and Jordan (1960). In the case from the Postgrad-

FIG. 4.—Second biopsy, showing considerable reduction in cellular infiltrate. There is less tubular damage and hyaline casts are seen in some tubules. Deposit of calcium in relation to one tubule. (5μ section. Hæmatoxylin and eosin $\times 140$).

uate Medical School of London (1960), the histology was that of tubular necrosis with a more diffuse cellular infiltration by plasma cells and lymphocytes. The post mortem histology in the case reported by Galea and others (1963) showed tubular necrosis, interstitial oedema with plasma cell and lymphocyte infiltration and glomerular changes. The latter consisted of thickening of the basement membrane, swelling of the endothelial cells and the presence of neutrophils, plasma cells and occasional eosinophils in the glomerular tufts. The histology in the case reported by Baker and Williams (1963) was again that of patchy tubular necrosis and considerable inflammatory cell infiltration, mainly plasma cells and eosinophils with some foci of neutrophils. These authors stressed that their case was one of interstitial nephritis rather than tubular necrosis and presented biochemical data to support this contention.

This present case is in many respects similar to that of Baker and Williams (1963). The striking finding in the renal biopsy was that in addition to tubular necrosis there was a gross interstitial infiltration of plasma cells and eosinophils

TABLE 2
ABSTRACTS OF PREVIOUS CASE REPORTS

Reference	Primary condition requiring anti-coagulants	Duration and dosage of Phenindione	Associated reactions	Evidence of renal involvement	End result
Kirkby, 1954	Myocardial infarction	5 weeks 3g +	Fever, rash, jaundice, agranulocytosis	Acute renal failure. No histology	Death from renal failure
Barritt and Jordan, 1960	Pulmonary embolism	30 days	Rash, fever, diarrhoea	Oliguric renal failure. Necropsy showed acute renal necrosis	Death from renal failure
Tait, 1960	Myocardial infarction	3 months 10g +	Diarrhoea	Nephrotic syndrome. No histology	Persistent albuminuria
Brooks and Calleja, 1960	Myocardial infarction	26 days 2.4g	Fever, rash and jaundice	Proteinuria, R.B.C., W.B.C., casts. No histology	Recovery
Postgraduate Medical School, London, 1960	Pulmonary hypertension	2 months		Oliguric renal failure. Both biopsy and necropsy showed acute tubular necrosis and interstitial plasma cell infiltration	Death from pulmonary hypertension
Galea et al., 1963	Angina pectoris	31 days 3.8g	Rash, jaundice	Acute oliguric renal failure. Thickening of glomerular basement membrane	Death from renal failure
Baker and Williams, 1963	Angina pectoris	19 days	Fever, rash, jaundice, atypical lymphocytes	Acute renal failure. Biopsy showed interstitial nephritis and tubular necrosis	Recovery, biopsy showed some residual fibrosis
Present case	Fractured tibia	28 days 2.8g	Fever, exfoliative dermatitis	Acute renal failure. Tubular necrosis. Plasma cell infiltration	Recovery. Some permanent tubular damage

The biochemical data were characteristic of renal tubular necrosis.

We suggest that in these cases the renal tubular cells predominantly have become sensitized to phenindione and subsequently necrose and that the interstitial infiltration represents the histological picture of a sensitivity reaction. Thus, depending upon the severity and the particular site of this reaction in the kidneys, i.e. whether in tubules, interstitial tissue or glomeruli, one will find varying histological pictures. There may be a mild interstitial nephritis (Burns and Desmond, 1958), a severe interstitial nephritis with some tubular necrosis (Baker and Williams, 1963), or a severe interstitial nephritis, acute tubular necrosis and glomerular involvement as in this case and that recorded by Galea and others (1963). In the case of Baker and Williams the urine investigations were not wholly characteristic of tubular necrosis,

agreeing with their renal biopsy, but a minority of tubules may have been involved. It is, therefore, seen that interstitial nephritis and tubular necrosis are part of the same pattern of hypersensitivity reactions in the kidney (Kimmelstiel, 1938; Melnick, 1943).

The reason for the oliguria is speculative. Probably multiple factors operate such as acute interstitial oedema compressing tubules (Peters, 1945) already narrowed by their contained debris (Maluf, 1949; Harrison, Bunting, Ordway and Albrink, 1947) or tubular necrosis allowing back diffusion of water and perhaps reduced glomerular filtration subsequent upon glomerular membrane or capillary changes. Compression of the tubules by interstitial oedema may also cause considerable local anoxia.

It would appear logical to use steroid therapy in such patients since the renal and skin lesions are

due to marked cellular infiltration secondary to a hypersensitivity reaction. In this case the urine output began to increase the day following commencement of prednisone therapy but this may have been coincidence. Baker and Williams also thought it was coincidental that their patient passed urine four hours after his first dose of prednisolone. In the present case it might have been better to continue steroid therapy longer in view of the persistently raised ESR and continuing eosinophilia and the abnormal renal function studies.

The second renal biopsy shows that there will be some permanent renal damage but nevertheless the degree of recovery has been remarkable. It is interesting to note how closely the renal biopsy findings have mimicked those of chronic pyelonephritis. Baker and Williams (1963) have put forward the possibility that some cases of chronic pyelonephritis may take origin in a kidney which has been the site of a hypersensitivity reaction to some unidentified allergen. As they rightly point out, the only solution will be found in the long-term follow-up of cases where hypersensitivity was clearly established.

Phenindione nephropathies seem to occur after prolonged use of the drug and even after it has been stopped. The drug must, therefore, be stopped and steroid therapy begun at the earliest

indication that a sensitivity reaction is developing. Since the renal complications are so severe, it would seem expedient to teach patients on phenindione therapy to test their urine daily for albumin with the simple 'Albustix' method. They should be instructed to report back to hospital should the test become positive as this is probably the earliest sign of renal involvement. Healing of the renal tissue is slow and steroid therapy may need to be prolonged.

Summary

A 55-year-old male was given post-operative prophylactic phenindione therapy after an open reduction of a fractured left tibia. He developed fever, rigors and skin rashes 28 days after starting the drug. Eleven days later he developed oliguric renal failure and required artificial hæmodialysis on two occasions. Follow-up renal function studies have shown a fairly good recovery although some permanent renal damage has occurred. Correlation between morphological and biochemical changes has been discussed. The management of such cases is briefly considered.

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