CLINICAL AND PATHOLOGICAL ASPECTS OF ANALGESIC NEPHROPATHY

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- 1 Analgesic nephropathy is part of the analgesic syndrome which has gastrointestinal, haematological, cardiovascular, psychological and psychiatric, and pregnancy and gonadal manifestations; premature ageing may also be a feature.
- 2 Analgesic nephropathy is a form of renal disease characterized by renal papillary necrosis, secondary chronic interstitial nephritis and renal failure with features of predominant tubulointerstitial dysfunction.
- 3 The percentage of patients with analgesic nephropathy who present with terminal renal failure is 12%. With appropriate management, 17% of analgesic nephropathy patients improve, 50% remain stable and 23% deteriorate. The 6 year cumulative survival is 70%. The major factors influencing deterioration are malignant hypertension, persistent proteinuria and small initial renal size.
- 4 The risk of renal papillary carcinoma in patients who regularly take analgesics is 8 per 100,000 patients per year.
- 5 Renal papillary necrosis is a consequence of the chronic toxicity of all non-steroidal anti-inflammatory drugs and results from medullary ischaemia secondary to suppression of prostaglandin E_2 synthesis and from direct cellular toxicity.
- 6 Analgesic nephropathy is a preventable form of renal disease and renal failure. It can be prevented by limiting the abuse potential of analgesics rather than by making minor modifications in the composition of analgesic mixtures.

Introduction

ANALGESIC nephropathy is a form of renal disease characterized by renal papillary necrosis (RPN) which results from the chronic ingestion of non-steroidal anti-inflammatory drugs usually in the form of common analgesic mixtures. The association between this form of renal disease and the abuse of analgesic mixtures, usually containing phenacetin, was first recognized by Spühler & Zollinger in Europe (1953). Analgesic nephropathy has now been reported from most parts of the world including countries such as the Middle East and Japan (Prescott, 1976); the disease, however, is particularly common in developed countries such as Australia, Europe, United Kingdom, United States, Canada and South Africa.

In Australia, the problem of analgesic abuse and analgesic nephropathy seems to be a major community problem. Between 4.6% and 45.1% of different subpopulations in the community consume analgesics daily, often for inappropriate reasons (Report from Senate Standing Committee on Social Welfare, 1977). The community habit was recognized as early as 1907 (*The Lone Hand*, 1907) when it was

noted that “what the drink habit is among men in Australia, the headache powder is among women”. Terminal renal failure from analgesic nephropathy is responsible for 20% of the national dialysis and transplantation programme (Australia and New Zealand Dialysis and Transplant Registry, 1979) and this is much higher than figures reported from other parts of the world — Europe 3.7% (Wing *et al.*, 1978) and Canada 5.5% (Linton, 1972).

Clinical aspects

Analgesic nephropathy is part of a much wider clinical syndrome, the analgesic syndrome (Duggan, 1974; Nanra, 1976) (Table 1), which is seen in patients who chronically abuse analgesics.

Non-renal manifestations of the analgesic syndrome

Gastric manifestations occur in more than half of the patients who abuse analgesics, and peptic ulceration (particularly giant gastric ulcer) has been reported in

up to 35% of patients (Duggan, 1976). Peptic ulcers occur only with aspirin-containing analgesic mixtures and are therefore largely absent in the analgesic syndrome in Europe (Dawborn, Fairley, Kincaid-Smith & King, 1966; Gault, Rudwal, Engles & Dosseter, 1968; Nanra, Stuart-Taylor, De Leon & White, 1978a).

Sixty to ninety per cent of patients have anaemia which is mainly related to chronic renal failure and iron deficiency secondary to aspirin-related gastrointestinal blood loss. However, haemolytic and sideroblastic anaemias have also been described (Dacie & Mollin, 1966; Beutler, 1969; Linton, 1972). Cyanosis, which is associated with methaemoglobinemia and sulphaemoglobinemia, is mainly related to a metabolite of phenacetin, *p*-phenetidine, and a contaminant, *p*-chloracetanilide (Schnitzer, Smith & Golden, 1965; Gault, Shahidi & Barber, 1974). Methaemoglobinemia and sulphaemoglobinemia have become uncommon in recent years with the withdrawal of phenacetin from analgesic mixtures. Splenomegaly has been reported in about 10% of patients (Fordham & Huffines, 1967).

Patients with analgesic nephropathy seem to have premature and severe atherosclerosis (Nanra, 1976). Ischaemic heart disease has been reported in over a third of patients with analgesic nephropathy (Krishnaswamy, Wallace & Nanra, 1974) and seems to be related to the severity of hypertension and duration of renal failure. The fact that it is frequently observed in young women is highly significant.

Headaches occur in more than 90% of patients and are the most common reason given for analgesic abuse. Psychological disturbances are common and are reflected in the frequency of associated addictive habits such as smoking, alcoholism, use of

psychotropic drugs and laxative abuse (Clarkson & Lawrence, 1970; Murray, 1973; Wainscoat & Finn, 1974). The personality inadequacies described are introversion and neuroticism on the background of disturbed family and social circumstances (Murray, 1974). However, organic features such as migraine, dementia, psychosis, hallucinations and electroencephalographic abnormalities have all been described (Kasanen & Valleala, 1963; Murray, Green & Adams, 1971; Drtil, 1972).

Clinical and experimental studies suggest that analgesic abuse may be associated with a number of gonadal and pregnancy-related complications; these include postmaturity due to reduced uterine prostaglandin activity, toxemia of pregnancy, teratogenicity, congenital malformations and infertility (Editorial, 1970; Boyd, 1971; Lewis & Schulman, 1973; Nanra, 1976).

The prematurely aged appearance of analgesic nephropathy patients has been emphasized (Gault *et al.*, 1968; Nanra, 1976). The multiorgan dysfunction, the relatively severe atherosclerosis and the widespread presence of the wear-and-tear pigment, lipofuscin, at a relatively early age may reflect premature biological ageing (Nanra *et al.*, 1978a).

Analgesic nephropathy

With the exception of a single report in which there were more males (Nordenfelt & Ringertz, 1961) analgesic nephropathy is a predominantly female disease. In a large series reported by Nanra *et al.* (1978a), the female to male sex ratio was 6.5 to 1 and this is in accord with other published data (Dawborn *et al.*, 1966; Gault *et al.*, 1968; Duggan, 1974; Bailey, Neale & Little, 1974). Most patients with analgesic nephropathy present between the ages of 30 yr and 70 yr, with a peak in the fourth decade. The disease is rare under the age of 30 yr and in patients presenting under that age an alternate diagnosis should be considered (Nanra, 1976). Analgesic nephropathy may have a familial tendency (Nordenfelt, 1972).

Analgesic nephropathy is a tubular-interstitial disorder and features of tubular-medullary dysfunction such as an impaired concentrating and acidifying capacity and a sodium-losing state predominate (Steele, Gyory & Edwards, 1969; Cove-Smith & Knapp, 1973; Krishnaswamy, Kuna & Nanra, 1976). A failure to concentrate urine is present in all patients with analgesic nephropathy, and it is the earliest functional defect which is identifiable; thus, nocturia is a prominent and early symptom. Although a defect in urinary acidification may be detected in 25% of analgesic nephropathy patients, frank renal tubular acidosis with a minimum urinary pH greater than 5.7 only occurs when the glomerular filtration rate is reduced and is seen in about 10% of such patients (Krishnaswamy *et al.*, 1976). The defect in urinary

Table 1 The analgesic syndrome

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- 1 Analgesic nephropathy
  - 2 Gastric ulcer and complications
  - 3 Haematological manifestations
    - (a) Anaemia
    - (b) Met- and sulphaemoglobinemia
  - 4 Cardiovascular manifestations
    - (a) Hypertension
    - (b) Ischaemic heart disease
    - (c) Cerebrovascular accidents
    - (d) Peripheral vascular disease
  - 5 Psychological and psychiatric manifestations
    - (a) Headaches
    - (b) Dependant personality
    - (c) Dementia
  - 6 Pregnancy and gonadal manifestations
    - (a) Toxaemia of pregnancy
    - (b) Postmaturity
    - (c) Infertility
  - 7 Premature ageing

acidification contributes to the prominent systemic acidosis usually seen with severe renal failure, medullary calcification, renal calculus formation and uraemic bone disease (Blackman, Gibson, Lavan, Learoyd & Posen, 1967; Murphy, 1968; Ingham, Kleerekoper, Stewart & Posen, 1974; Nanra, 1976; De Leon & Nanra, 1976).

Urine abnormalities are common. These include urinary tract infections (15–60%) (Gault *et al.*, 1968; Clarkson & Lawrence, 1970; Linton, 1972; Duggan, 1974; Bailey *et al.*, 1974), sterile pyuria (95%), tubular epithelial celluria, microscopic haematuria (35%) and significant proteinuria (greater than 0.3 g daily) (40%) (Mehta, White & Nanra, 1977). The spectrum of urinary pathogens and their pattern of antibiotic sensitivities are similar to those seen in hospitalized patients. Urinary tract infections rarely, if ever, cause renal deterioration except by the development of mixed infection staghorn calculi, usually with urea splitting organisms, such as *Proteus* and *Pseudomonas*. The combination of active urinary tract infection and potential obstruction from calculi or sloughed papillae, or investigative instrumentation, is associated with a high risk of septicaemia. Urinary tract obstruction may lead to hydronephrosis or pyonephrosis.

Renal tubular celluria is related to the exfoliation of epithelial cells by analgesics (Prescott, 1965) and may be differentiated from a true sterile pyuria by urinary staining (Prescott & Brodie, 1964). Persistent tubular epithelial celluria may provide the nidus for calculus formation and is often a reflection of continuing analgesic intake.

Haematuria, which is seen in a third of patients is usually related to continuing analgesic abuse, recent RPN; calculus disease, interstitial cystitis, malignant hypertension and the development of glomerular lesions, or transitional cell tumours of the urothelium.

The association between abuse of phenacetin-containing analgesic mixtures and transitional cell tumours of the urothelium has been recognized since 1965 (Hultengren, Lagergren & Ljungqvist, 1965) and there are a number of recent reports which have confirmed this association (Taylor, 1972; Johansson, Angervall, Bengtsson & Wahlqvist, 1974; Mahony, Storey, Ibanez & Stewart, 1977). In a recent 7 yr study at the Royal Newcastle Hospital (Orell, Nanra & Ferguson, 1980), 40 new cases of renal papillary carcinoma were seen and the overall crude incidence rate was 1.6 tumours per 100,000 population per year. Forty-nine per cent of the tumours were associated with analgesic abuse and analgesic nephropathy and the estimated risk of tumours in analgesic users was 8 tumours per 100,000 population per year. The renal papillary carcinoma had a female to male ratio of 2.6 to 1 in the 'analgesic group' compared with 1 to 2 in the 'non-analgesic' group. Also the tumour was more often poorly

differentiated and at an advanced stage at the time of diagnosis with a tendency to multiple tumours and coexistent flat carcinoma *in situ*.

Significant proteinuria has been found in 40% of patients with analgesic nephropathy, and its incidence and severity have a significant inverse relationship with glomerular filtration rate (Mehta *et al.*, 1977); when the creatinine clearance is less than 10 ml/min per 1.73m² surface area, more than 90% of patients have persistent proteinuria. Renal biopsies in these patients have revealed glomerular lesions (see pathology).

Hypertension has been reported in 15–70% of analgesic nephropathy patients (Dawborn *et al.*, 1966; Gault *et al.*, 1968; Clarkson & Lawrence, 1970; Linton, 1972; Duggan, 1974; Bailey *et al.*, 1974). Malignant hypertension occurs in 7% of patients and the association between sodium and water depletion and severe hypertension is of interest (Nanra *et al.*, 1978a). In a recent study in analgesic-fed rats, significant hypertension was found to be associated with RPN, impaired concentrating capacity, reduced total body sodium and renal vein prostaglandin E₂, and elevated renal vein plasma renin activity (R.S. Nanra, V. Daniel & M. Howard, unpublished). Severe, resistant or labile hypertension may be related to atheromatous renal artery stenosis.

Over 85% of patients with analgesic nephropathy present with varying degrees of renal failure. Acute renal failure associated with recent RPN is often associated with severe systemic acidosis, hypertension, salt and water depletion, oliguria and septicaemia. However, many patients with analgesic nephropathy and chronic renal failure may be relatively asymptomatic because of the insidious nature of the disease and may only be recognized as a result of a routine medical examination. Clinical gout occurs in 5% of patients with analgesic nephropathy and normal glomerular filtration rate but the incidence of secondary gout increases to 25% when there is renal insufficiency (Nanra, Howard & Daniel, 1978b).

Diagnosis of analgesic nephropathy

The diagnosis of analgesic nephropathy is based on a history of significant ingestion of analgesics and the demonstration of RPN. Analgesic abuse may be defined as an intake of a minimum of 2 kg aspirin or phenacetin. Patients often consume large quantities (up to 10 g to 30 kg) of aspirin or phenacetin over many years (Nanra, 1976). Precise quantification of analgesic abuse may be difficult because patients tend to conceal or minimize the habit (Gault *et al.*, 1968; Clarkson & Lawrence, 1970). RPN is usually demonstrated on an intravenous urogram and in patients with renal insufficiency, retrograde

Figure 1 Retrograde pyelogram showing changes typical of renal papillary necrosis. 'Ring shadows', medullary cavities and blunted calyces can be seen.

pyelography is necessary for adequate visualization of calyceal detail. The diagnostic radiological features of RPN have been fully described (Lindvall, 1960; Hare, 1970; De Leon & Nanra, 1976) and include medullary calcification, medullary cavities and ring shadows (Figure 1). A 'normal' intravenous urogram does not exclude RPN because it may represent early or mild papillary damage or RPN *in situ* (Fairley & Kincaid-Smith, 1968; Poynter & Hare, 1974). RPN, however, may result from other causes which include diabetes mellitus, obstructive uropathy, sickle-cell disease and acute vascular lesions of the kidneys. Although tuberculosis of the kidney, medullary sponge kidney, pyelogenic cysts and obstructive or postobstructive uropathy should be considered in the differential diagnosis of RPN (Hare, 1970), the most important disease to be differentiated is chronic nonobstructive atrophic pyelonephritis secondary to vesicoureteric reflux (De Leon & Nanra, 1976).

RPN is occasionally confirmed by the histological demonstration of necrotic papillae voided in urine or in medullary tissue obtained by renal biopsy or from autopsies. When a patient admits to analgesic abuse and the radiology is inconclusive, the diagnosis of analgesic nephropathy may be confirmed by the

demonstration of chronic interstitial nephritis on renal biopsy or by a disproportionate reduction of the concentration capacity.

Management

The management of acute severe oliguric renal failure due to analgesic nephropathy may require control of severe hypertension with intravenous diazoxide or clonidine, correction of volume depletion by normal saline administration, appropriate parenteral doses of frusemide, correction of electrolyte disturbances and systemic acidosis and the use of broad spectrum antibiotics if septicaemia is suspected. Acute dialysis may be necessary. At the earliest opportunity, retrograde catheterization and pyelography is usually indicated to exclude obstruction and to define the anatomy of the urinary tract.

The long-term management of patients with analgesic nephropathy should include (1) the avoidance of all non-steroidal anti-inflammatory drugs as they are potentially nephrotoxic (Nanra & Kincaid-Smith, 1972); (2) the management of the manifestations and complications of renal dysfunction, particularly hypertension and sodium and water balance; and (3) the careful review of the patient with view to early detection and treatment of complications such as ischaemic heart disease, silent obstructive uropathy, urinary tract infections, persistent proteinuria (indicating the possible development of a glomerular lesion) and transitional cell tumour of the urothelium. Patients should be regularly checked for evidence of continuing analgesic abuse by screening of the urine for aspirin and phenacetin metabolites (Dubach, 1967; Duggan, 1972). Unexplained deterioration of renal function and persistent microscopic haematuria and proteinuria should be carefully assessed and this may include repeat intravenous urography, urinary cytology, endoscopy with retrograde pyelography and a renal biopsy. Renal arteriography is indicated if hypertension control is difficult. Urological procedures are frequently necessary; in a review of 232 patients with analgesic nephropathy, 86 urological procedures were carried out in 70 patients (Nanra *et al.*, 1978a).

Outcome

Nanra (1978) has analyzed the outcome of 323 patients with analgesic nephropathy followed for up to 66 months; 12% of patients died or commenced maintenance dialysis within 6 months of presentation; 17% improved; 50% remained stable; and 23% deteriorated. The 6 yr cumulative survival was 70%. The major factors associated with deterioration were malignant hypertension, persistent proteinuria and

Figure 2 Natural history of a hypothetical patient with the analgesic syndrome. The renal manifestations usually occur after the age of 30 years. GIH, UTI and RPCa represent gastrointestinal haemorrhage, urinary tract infection and renal pelvic carcinoma, respectively.

initial renal size and glomerular filtration rate. Overall, 21% of patients died and the main causes of mortality were ischaemic heart disease, septicaemia and cerebrovascular accidents. The long-term outlook of analgesic nephropathy patients is optimistic if patients stop abusing analgesics. In another study involving 43 patients with severe renal failure, the 5-yr cumulative survival was 73.8% (Kincaid-Smith, Nanra & Fairley, 1970).

Analgesic nephropathy patients who are treated by dialysis and transplantation seem to fare poorly in comparison to patients with glomerulonephritis (Nanra, 1977; Nanra *et al.*, 1978a) and this has been related mainly to the aggressive degenerative vascular disease seen in these patients.

Natural history of the analgesic syndrome

Figure 2 illustrates the natural history of a hypothetical patient with the analgesic syndrome. The habit of analgesic intake commences in secondary school and by school leaving age analgesic consumption is at adult level (Egger & Champion, 1978). The obstetric and gastrointestinal manifestations are usually seen between the ages of 20 yr and 40 yr, whereas the renal and other complications tend to occur after the age of 30 years.

Pathological aspects

Macroscopic appearance

Characteristically, the kidney in a patient who dies with terminal uraemia is markedly shrunken. The capsule is adherent and the stripped surface usually shows multiple small cysts. In patients who stop analgesic abuse there is an opportunity for surviving nephrons to hypertrophy and pale, raised, tumour-like nodules may be seen on the surface of stripped kidney. When the kidney is bisected, the nodules can be identified as representing hypertrophied cortical tissue corresponding to the columns of Bertin. The scars seen on the surface of the kidney correspond to atrophic cortical tissue overlying necrotic papillae. The necrotic papillae are often readily identified and have a shrunken greyish-black appearance (Figure 3). The brownish-black appearance of the papillae is related to breakdown products of phenacetin (Prescott & Brown, 1970). The mucosal lining of the renal pelvis and the urinary tract may also show golden-brown streaks.

Microscopic appearance

RPN is a bland form of coagulative necrosis involving all elements of the medulla, vasa rectae, loops of Henle, collecting tubules and interstitial cells, and is usually maximal towards the tip of the papilla. There is a clear line of demarcation between necrotic and viable tissue and invariably a total absence of an inflammatory infiltrate. In patchy RPN, the collecting tubules are not involved. The earliest lesions are usually seen at the tips of the vasa rectae and loops of Henle. There is a 'drop-out' of the nuclei of the cells of the vasa rectae and loops of Henle giving a 'ghost-like' appearance of these structures: this change is referred to as necrobiosis (Burry, 1967). On a periodic-acid-Schiff stain, the basement membrane of the necrobiotic lesions appears thickened. At this early stage of analgesic nephrotoxicity there is degeneration of, and a marked reduction in the number of interstitial cells.

Calcification is commonly seen in the necrotic medulla both in the interstitium as well as in casts in the collecting tubules. Ossification rarely occurs.

The changes in the cortex of chronic interstitial nephritis are non-specific and may be seen in any obstructive lesion involving the urinary drainage system (Figure 4). The prominent changes are tubular atrophy and dilatation, interstitial fibrosis and a non-specific round cell infiltrate. A golden-brown lipofuchsin pigment is usually readily identified within the cells. The glomerular changes are variable, ranging from completely normal to global sclerosis.

Figure 3 A sagittal section through an analgesic nephropathy kidney. The greyish-black separated and necrotic papillae can easily be recognized. There is marked thinning of the cortex overlying the necrotic papillae.

Periglomerular fibrosis is common. In most advanced cases, the glomeruli invariably show focal and segmental glomerular sclerosis and hyalinosis; uncommonly, a typical membranous glomerular lesion has been identified with typical basement spikes on silver methenamine stain (Mehta *et al.*, 1977; Nanra *et al.*, 1978a). On immunofluorescent microscopy, the segmental lesions commonly have coarse blobs of C3, whereas the membranous lesions show the characteristic granular deposits of IgG and C3 along glomerular capillary loops in an epimembranous distribution. The vascular changes are variable and the arteries may be normal or show changes typical of benign or malignant nephrosclerosis.

Pathogenesis

RPN is the primary lesion in analgesic nephropathy and results from medullary ischaemia and toxic

damage to the interstitial cells, vasa rectae and loops of Henle (Kincaid-Smith, 1967; Burry, 1967; Nanra, Chirawong & Kincaid-Smith, 1973; Molland, 1976). Medullary ischaemia probably occurs as a result of suppression of prostaglandin E₂ synthesis by non-steroidal anti-inflammatory agents; the demonstration of reduced medullary perfusion and reduced renal vein prostaglandin E₂ in experimental analgesic nephropathy supports this hypothesis (Nanra *et al.*, 1973; Nanra, R.S., Daniel, V. & Howard, M., unpublished observations).

The concentration and countercurrent multiplier mechanisms of the kidney also play a dominant role in the pathogenesis of RPN and this is emphasized in a number of experimental studies (reviewed by Nanra & Kincaid-Smith, 1972) and by the demonstration that some drugs and their metabolites achieve high renal papillary tissue concentration in hydropenic animals (Bleumle & Goldberg, 1968; Gault, 1970; Duggin & Mudge, 1976). Both phenacetin and

Figure 4 Renal biopsy showing severe chronic interstitial nephritis. There is severe tubular atrophy, interstitial fibrosis and a round cell infiltrate. One glomerulus shows global sclerosis and another has typical periglomerular fibrosis with an otherwise normal tuft.

paracetamol acutely enhance the efficacy of antidiuretic hormone in promoting urinary concentration (Lozada, Gouaux & Hayes, 1971) and this may be a significant factor in concentrating toxic metabolites in the medulla (Nanra *et al.*, 1973).

At a cellular level, aspirin interferes with the tricarboxylic cycle, oxidative phosphorylation and mucopolysaccharide synthesis, covalently acetylates renal tissue proteins and depletes cellular glutathione (Smith, 1966; Wheldrake, 1975; Caterson *et al.*, quoted in Duggin, 1977; Mudge, Gemborys & Duggin, 1978). Paracetamol is the major metabolite of phenacetin and unlike phenacetin concentrates in the renal medulla. It is believed to be converted to a cytotoxic metabolite which covalently binds to tissue proteins and causes damage leading to glucose-6-phosphate dehydrogenase, glutathione and dihydronicotinamide adenine dinucleotide phosphate (NADPH) depletion and cellular necrosis. It has been suggested that the synergism between

aspirin and phenacetin or paracetamol nephrotoxicity may be explained on the basis of inactivation of intracellular enzyme systems and salicylate inhibition of NADPH supply through the hexose monophosphate shunt (Goldberg, Myers, Peshel, McCarron & Morrison, 1971; Murray & Goldberg, 1975; Mitchell, McMurtry, Statham & Nelson, 1977; Mudge *et al.*, 1978).

The combination of medullary ischaemia and cellular necrosis leads to RPN which has all the histological features of an infarct (Nanra *et al.*, 1973). The chronic interstitial nephritis is a non specific lesion which results from obstruction to tubules in the necrotic medulla (Burry, 1967; Kincaid-Smith, 1967; Nanra & Kincaid-Smith, 1972). The golden-brown lipofuchsin-like pigment which is readily seen in the kidney is also widely distributed in most organs of the body and is probably a highly oxidized polymer of unsaturated fatty acids related to the oxidant effect of phenacetin (Pearse, 1960).

Aetiological factors

There is considerable clinical, epidemiological and experimental evidence that chronic analgesic consumption leads to renal disease and renal failure, and the subject has been extensively reviewed (Haley, 1966; Shelley, 1967; Abel, 1971; Nanra & Kincaid-Smith, 1972; Murray & Goldberg, 1975; Nanra *et al.*, 1978a). Animal experiments suggest that RPN may result from the chronic toxicity of all non-steroid anti-inflammatory drugs; the results from a number of studies in rats are summarized in Table 2 (reviewed in Nanra *et al.*, 1978a; R.S. Nanra, V. Daniel & M. Howard, unpublished). In man, analgesic nephropathy is usually associated with abuse of popular analgesic mixtures containing proprietary combinations of aspirin, phenacetin, paracetamol, phenazone (antipyrine), caffeine or codeine. Occasional examples of RPN with individual analgesics such as aspirin, paracetamol, indomethacin or phenylbutazone have been described but these are uncommon because individual analgesics are rarely addictive. These data have been recently reviewed elsewhere (Nanra & Kincaid-Smith, 1972; Nanra *et al.*, 1978a).

Although the association between analgesic abuse and RPN is well established, other factors probably exist and are not fully recognized. A genetic predisposition has recently been given some support by the demonstration of an increased frequency of the HLA-B12 antigen in analgesic nephropathy (MacDonald *et al.*, 1978). Women seem to be at an increased risk of renal damage from analgesics;

although the female to male ratio of analgesic abusers in the Australian community is 2 to 1, the female to male ratio of analgesic nephropathy is approximately 7 to 1. Climatic factors and fluid intake have also been incriminated. Of great interest are patients who give a history of massive analgesic abuse but who surprisingly show absent or minimal evidence of tubulomedullary dysfunction.

Conclusions

Analgesic nephropathy is a totally preventable form of progressive renal disease which would be eradicated by legislation to control the availability of addicting analgesic mixtures. Community studies are also required to define the factors that lead to the regular use of pain-killers for inappropriate reasons. Individual analgesics are almost never abused and there are good reasons to believe that renal damage results from the synergistic nephrotoxicity of the different components of the analgesic mixtures — aspirin, phenacetin, paracetamol and phenazone. RPN is an expression of nephrotoxicity common to all non-steroidal anti-inflammatory agents and, therefore, modification of the composition of analgesic mixtures is unlikely to lead to a significant reduction in analgesic-related renal failure (Nanra *et al.*, 1978a). Even in patients with established analgesic nephropathy, long term survival may be anticipated if patients can stop the abuse of analgesics.

In Australia, the unabated sale of analgesic

Table 2 Experimental RPN with individual and compound analgesics

<i>Analgesic*</i>	<i>Dose (mg/kg daily)</i>	<i>Duration (weeks)</i>	<i>RPN</i>	
APC (impure)†	900	8–20	13/31	(37.5%)
APC (pure)‡	900	8–72	13/20	(65.0%)
A + APAP + C	900	12–72	9/16	(56.3%)
A + salicylamide + C	840	12–72	7/13	(53.9%)
Phenazone + P + C	840	12–72	4/11	(36.4%)
A	500	8–20	9/27	(33.3%)
A§	200	10–66	7/13	(54.8%)
P	3,000	8–20	3/8	(37.5%)
APAP	3,000	8–20	3/7	(42.9%)
Phenazone	1,000	12–30	1/8	(12.5%)
C	150	8–20	0/10	
Phenylbutazone	10	8–20	1/9	(11.1%)
Indomethacin	12	12–30	2/7	(28.6%)
Mefenamic acid	100	8–20	6/9	(66.7%)

* Abbreviations used: A, aspirin; P, phenacetin; APAP, paracetamol; C, caffeine.

† Impure = 0.1% *p*-chloroacetanilide in P.

‡ Pure = 0.01% *p*-chloroacetanilide in P.

§ Cortical scars in 3/13 (23.1%).

mixtures is likely to lead to terminal renal failure in 300 new patients per year, with an estimated cost in excess of A\$10,000,000 per annum for their treatment (Duggin, 1977). Legislation to limit analgesic mixtures to prescription might lead to a reduction in the incidence of terminal renal failure

but the results of this intervention will probably not be recognized for another decade.

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