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Analgesic nephropathy: Etiology, clinical syndrome, and clinicopathologic correlations in Australia

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The abuse of analgesics in the Australian community and its role in disease of the heart and alimentary canal has been recognized since 1907 [1] when it was noted that "what the drink habit is among men in Australia, the headache powder is among women." The initial reports of analgesic nephropathy from Australia appeared in the early 1960's [2–5], almost ten years after Spühler and Zollinger in 1953 [6] drew attention to the association between abuse of phenacetin-containing compounds and a form of renal disease characterized by renal papillary necrosis (RPN) and chronic interstitial nephritis.

The habit of analgesic abuse and the serious consequences of renal disease and renal failure is a major public health problem in the Australian community. Between 4.6% and 45.1% of different subpopulations in the community consume analgesics daily, often for inappropriate reasons [7–16].

At the Royal Newcastle Hospital, 407 patients with analgesic nephropathy have presented over four years. This represents a third of all patients presenting to the renal unit. In Australia, analgesic abuse causes terminal renal failure in 20% of those treated by dialysis and transplantation [17], compared to 5.5% in Canada [19] and 3.1% in Europe [20]. In the U.S.A., analgesic nephropathy was found to be responsible for 7% of chronic renal disease in one survey [18]. The autopsy incidence of RPN in major Australian hospitals is between 3.6 and 20% [2,21–25] and is much higher than that reported from elsewhere in the world (0.1 to 4%) [27–35].

Etiology

There is considerable evidence that compound analgesics are toxic in man, and analgesic nephropathy has been reported from most countries in the world, including such unlikely places as the Middle East and Japan [36]. In addition to the 407 cases seen by one of us, more than 3,000 cases of analgesic nephropathy have been reported in the literature. The characteristic analgesic syndrome [25, 37–39], the specific pathology [26, 40, 41], the repeated observation that continued analgesic abuse leads to renal disease and that renal function improves when patients stop taking analgesics [19, 42–48], and the association between *per capita* analgesic consumption and the incidence of analgesic nephropathy in various countries [38], all support the view that analgesics have very significant nephrotoxicity. The prospective study that was begun in Switzerland in 1963 by Dubach and colleagues shows a small but significant risk to the urinary tract from phenacetin-containing mixtures [49]. Experimentally, RPN is readily produced by compound analgesics containing aspirin [50]. Some investigators, nonetheless, still question the existence of analgesic-related renal disease [51–53].

The analgesics commonly abused in Australia are shown in Table 1 [54]. 94.7% of patients take compound analgesics, but a small proportion of patients with RPN had only taken individual analgesics (Table 1). The analgesic compounds associated with renal disease in some European countries are different in that aspirin is commonly replaced by phenazone or amidopyrine in analgesic mixtures.

Early reports of analgesic nephropathy blamed phenacetin as the nephrotoxic agent on the basis that it was the "common denominator" in the compound mixtures abused by patients. Some workers cautioned that serious consideration should be given to the other components in the analgesic mixtures, particularly aspirin, as they were also potentially nephrotoxic [55–57].

Direct evidence of the clinical nephrotoxicity of individual analgesic compounds such as aspirin, phenacetin, paracetamol, and caffeine is not available, because single analgesic agents are rarely

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Table 1. Pattern of analgesic intake in 190 consecutive patients with analgesic nephropathy

Analgesic compounds	No. of patients	%
Bex Powder®[a]	71	37.4
Vincents Powder®[b]	47	24.7
Miltiple compounds	62	32.6
Bex		
Vincents		
paracetamol		
aspirin		
indomethacin		
phenylbutazone		
Individual compounds[c]	10	5.3
aspirin (4)		
paracetamol (2)		
aspirin + paracetamol (1)		
aspirin + indomethacin (1)		
indomethacin + phenylbutazone (2)		
Total	190	100

[a] Bex® = 500 mg of aspirin + 250 mg of phenacetin + 150 mg of caffeine.

[b] Vincents® = 504 mg of aspirin + 168 mg of salicylamide + 168 mg of caffeine.

[c] Numbers in parentheses denote the number of patients taking the compounds.

abused. With the possible exception of one case [58], RPN has not been reported due to phenacetin abuse alone. In addition to the cases in Table 1, there are, however, a number of reports of RPN and renal failure in patients taking aspirin alone [39, 45, 47, 59–66] (NANRA RS: unpublished observations) and a lesser number of reports attributed to paracetamol alone [67, 68] (MAHONEY JF: personal communication). Paracetamol is the major metabolite of phenacetin [69] and is concentrated in the renal papilla when animals are fed phenacetin [70]. Additional evidence suggesting that aspirin and paracetamol are nephrotoxic is the occasional acute deterioration in renal function and fresh RPN observed in patients with analgesic nephropathy who stop abusing compound analgesics but continue to take aspirin or paracetamol [65].

Following withdrawal of phenacetin, Murray in Glasgow reported a decline in new cases of analgesic nephropathy [64], Gault in Canada suggested an arrest in the progression of the renal disease [48], and Nordenfelt in Sweden claimed a reduction in the annual mortality from analgesic nephropathy in a county hospital [71]. Burry in Australia attributed a decline in the autopsy incidence of RPN to the change in formulation of compound analgesics [24], but has since stated that continuing damage is occurring in the absence of phenacetin [72]. The influence of dialysis and transplantation on mortality and autopsy rates has not been fully recognized in some of these studies, and the Scandinavian data cannot be applied to Australia or other Anglo-Saxon countries because the nephrotoxicity and analgesic syndrome associated with the phenazone-phenacetin-caffeine mixtures in Sweden differs significantly from that seen with the aspirin-phenacetin-caffeine mixture [25].

In Australia, abuse of analgesics is largely confined to two aspirin containing headache powders, Bex® and Vincents® (Table 1). In Vincents compound, phenacetin was replaced by salicylamide in 1967, while Bex contained phenacetin until 1976, when it was replaced by paracetamol. This afforded an opportunity to study two consecutive groups of patients who had exclusively abused either Bex (aspirin, 500 mg; phenacetin, 250 mg; caffeine, 150 mg), or Vincents (aspirin, 504 mg; salicylamide, 168 mg; caffeine, 168 mg) [54]. Their data is summarized in Table 2. The absence of phenacetin over an eight-year period from Vincents powder did not appear to influence the degree of frequency of renal insufficiency in patients. Similar conclusions were also reached by Burry, Axelsen, and Trolove [24].

Patients with rheumatoid arthritis are commonly treated with large amounts of salicylates over many years and, therefore, provide an opportunity to assess the clinical nephrotoxicity of aspirin. The autopsy and biopsy incidence of RPN and chronic interstitial nephritis in rheumatoid arthritis is high and varies from 7.8% to 100% (mean, 40.3%) [24, 66, 73–78]; the renal lesions are identical to those seen in patients with analgesic nephropathy. The renal lesion in rheumatoid arthritis related to aspirin alone, however, is milder than that seen in patients who abuse compound analgesics, and rheumatoid arthritis patients rarely present with severe renal failure. Attempts to evaluate the nephrotoxicity of aspirin by renal function tests have been conflicting and inconclusive [51, 78–82]. The results of function studies, however, depend upon the timing and sensitivity of the tests used [66].

Animal studies have provided considerable information regarding the relative nephrotoxicity of analgesics. Abrahams et al [83,84] and Saker and Kincaid-Smith [85] reported the development of typical RPN in rats that were gavage-fed with an aspirin-phenacetin-caffeine (APC) mixture. Saker and Kincaid-Smith [85] had used a dose of APC (500 mg/kg/day), which on a weight-for-weight basis, was equivalent to that consumed by some patients with analgesic nephropathy. To extend these studies, we developed a short experimental model of analgesic-induced RPN in rats [86, 87]. The results from a number of studies in rats are summarized in Table 3

Table 2. Comparison of Bex® and Vincents® powder abusers[a]

	Bex® abusers	Vincents® abusers
	Analgesic consumption > 8 yrs	
No. of pts	54	33
Estimated consumption:		
aspirin, *kg*	11 ± 10	10 ± 7
phenacetin, *kg*	11 ± 10	5 ± 3
salicylamide, *kg*	—	5 ± 4
caffeine, *kg*	4 ± 4	4 ± 4
Age, *yr*	50.9 ± 10.0	51.6 ± 10.3
Female:male ratio	6.4:1	5.6:1
Serum creatinine, *mmoles/liter*	0.39 ± 0.32	0.32 ± 0.35
No. of pts. with renal insufficiency[b]	42 (77.8%)	24 (72.7%)
	Analgesic Consumption > 8 yrs	
No. of pts.	17	14
Estimated consumption:		
aspirin, *kg*	4 ± 4	3.5 ± 3.5
phenacetin, *kg*	4 ± 4	—
salicylamide, *kg*	—	3 ± 3
caffeine, *kg*	1.5 ± 1.5	1.5 ± 1.5
Age, *yr*	43.7 ± 11.5	50.9 ± 9.7
Female:male ratio	16:1	1.8:1
Serum creatinine, *mmoles/liter*	0.18 ± 0.14	0.18 ± 0.14
No. of pts. with renal insufficiency[b]	11 (64.7%)	8 (57.1%)

[a] Values are mean ± SD. Analgesic consumption is adjusted to the nearest 0.5 kg.
[b] Renal insufficiency = serum creatinine > 0.11mmoles/liter.

Table 3. Experimental renal papillary necrosis (RPN) with individual and compound analgesics

Analgesic[a]	Dose, *mg/kg/day*	Duration feeding, *weeks*	RPN	
			dehydration	water diuresis
APC (Impure)[b]	900	8—20	13/31 (37.5%)	0/9
APC (Pure)[c]	900	8—20	6/10 (60%)	
A + NAPA + C	900	12—30	3/8 (37.5%)	2/9 (22.2%)
A	500	8—20	9/27 (33.3%)	
A[d]	200	10—66	7/13 (54.8%)	
P	3,000	8—20	3/8 (37.5%)	0/10
NAPA	3,000	8—20	3/7 (42.9%)	
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%)	
Phenazone	1,000	12—30	1/8 (12.5%)	

[a] Abbreviations used are: A, aspirin; P, phenacetin; NAPA, paracetamol; C, caffeine. A:P (NAPA) :C = 21:21:8.
[b] Impure = 0.1% *p*-chloracetanilide.
[c] Pure = 0.01 *p*-chloracetanilide in P.
[d] Cortical scars in 3/13 (23.1%).

[65, 86–89]. The RPN, medullary calcification, and cortical scarring produced in the animals were identical to those seen in patients with analgesic nephropathy.

RPN was readily produced by an APC mixture in more than a third of animals. The presence of *p*-chloracetanilide did not appear to influence the medullary lesion, confirming a previous study by Schnitzer, Smith, and Golden [90]. When phenacetin was replaced by paracetamol in an equivalent dose, the nephrotoxicity of the analgesic mixture was not reduced, and 37.5% of animals developed frank RPN. The nephrotoxicity of phenacetin may be related, therefore, to the concentration of paracetamol, its major metabolite, in the renal papilla [69, 70]. Experimental RPN with combinations of aspirin and phenacetin has also been reported by Goldberg et al [91] and Molland [92]. The nephrotoxicity of phenacetin and paracetamol appear to be similar. Massive doses of phenacetin and paracetamol (3,000 mg/kg/

day) were used in the studies, and the lesions produced were minor compared with those seen with APC or aspirin alone. Similar results have been reported by Clausen [93] and Fordham, Huffines, and Welt [94]. There have been more than 30 other studies in a variety of animals designed to assess the nephrotoxicity of phenacetin and paracetamol, but they have been uniformly unsuccessful (reviewed by Nanra and Kincaid-Smith [50]). The doses of phenacetin and paracetamol used in these studies ranged from 200 to 3,000 mg/kg/day, and the period of feeding ranged from 2 to 24 months, whereas aspirin alone in a dose of 500 mg/kg/day over 8 to 20 weeks produced severe RPN in 9 out of 27 animals. To evaluate the nephrotoxicity of low doses of aspirin, rats were gavage-fed 200 mg/kg/day of aspirin for 10 to 66 weeks. More than half the animals developed frank RPN; medullary calcification was noted in 5/13 rats and cortical scars, typical of chronic interstitial nephritis, in 3/13 rats. No toxicity attributable to caffeine was found in these studies.

Experimental RPN and medullary damage was also seen with a variety of other nonsteroid antiinflammatory agents (Table 3). It has been suggested that medullary necrosis is a toxic effect common to nonsteroid antiinflammatory drugs [50, 87], and that this form of tissue damage is mediated through suppression of prostaglandin synthesis in the renal medulla [95]. RPN with these drugs has also been reported by other investigators [96–98].

Acute clinical and animal studies with analgesics and related chemical substances have been shown to induce tubular epithelial celluria and hematuria, aminoaciduria, enzymuria, depression of glomerular and tubular function, acute tubular necrosis, and renal failure [99–122]. In all of these studies, aspirin appears to be much more nephrotoxic than either phenacetin or paracetamol. The relevance of these acute experiments and somewhat related chemical substances to the chronic lesion of RPN associated with the continuous long term ingestion of analgesic compounds is, however, questionable.

Clinical syndrome and clinicopathological correlations

The clinical syndrome associated with abuse of analgesic mixtures is now well recognized. With the exception of one report in which there were more males than females [123], analgesic nephropathy has been recognized as a predominantly female disease [25, 37–39, 47]. The age and sex distribution of 279 patients with analgesic nephropathy is shown in Figure 1. Analgesic nephropathy may have a familial tendency [18, 71, 124]. The recent observation that there is an association between analgesic nephropathy and HLA antigens suggests the presence of an additional genetic factor [125].

Nonrenal manifestations of the analgesic syndrome. Analgesic nephropathy is part of a much wider clinical syndrome seen in patients who abuse analgesic mixtures [25].

Gastrointestinal manifestations occur in more than half the patients, and peptic ulceration, particularly a giant gastric ulcer, has been reported in up to 35% of patients [19, 37–39, 126–129]. Peptic ulcer disease occurs exclusively in patients who abuse aspirin-containing compounds and is, therefore, absent from the clinical syndrome in Europe.

Hepatocellular injury with single cell necrosis and abnormal liver function tests may be associated with large doses of aspirin [131–132].

Approximately 60 to 90% of analgesic nephropathy patients have anemia commonly due to gastrointestinal blood loss and chronic renal failure, but other forms of anemia have also been described [19, 126, 127, 133–137]. Splenomegaly is found in about 10% of patients [39, 138, 139]. The presence of a cyanotic tinge due to methemoglobinemia and sulfhemoglobinemia is related to *p*-phenetidine, a metabolite of phenacetin, and *p*-chloracetinilide, a contaminant [90, 133, 140, 141].

Psychological and psychiatric manifestations are common in patients who abuse analgesics. This is reflected in the frequency of associated addictive habits such as purgative abuse [142, 143], smoking, [127, 142, 144], alcoholism [127, 142], and use of psychotrophic drugs and sleeping tablets [9, 142]. Using recognized psychological techniques, certain personality traits and inadequacies have been identified, and these include introversion and neuroticism on the background of disturbed family and social circumstances [145, 146]. Many workers [144, 147, 148] recognize an addictive syndrome [149], and cessation of analgesic abuse often leads to withdrawal features. Organic features also occur, and bizarre headaches, migraine, dementia, psychosis, hallucinations, and reversible electroencephalographic abnormalities have all been described [45, 150–155].

Ischemic heart disease occurs in over a third of the patients with nephropathy [39, 156]. It appears to be related to the duration of the disease, degree of renal insufficiency, and severity of hypertension and is commonly associated with generalized atherosclerosis.

Pigmentation is a feature in patients with analgesic nephropathy and is aggravated by uremia and a sodium-wasting state. The brownish-black appearance of the necrotic papillae and the brown appearance of urine in analgesic abusers is related to

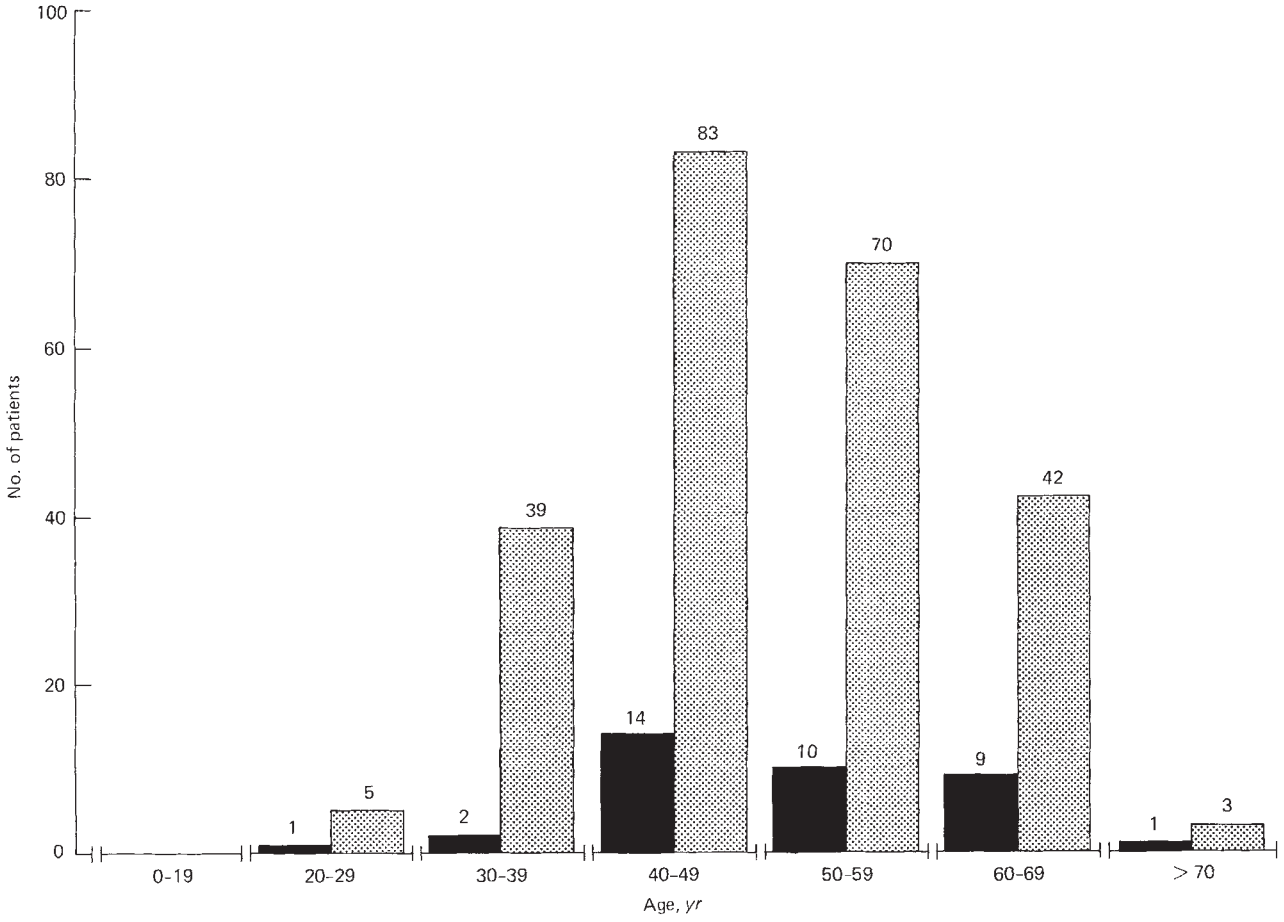

Fig. 1. *Age and sex distribution of 279 patients with analgesic nephropathy.* The female to male ratio is 6.5:1. Analgesic nephropathy is rare under the age of 30 years, the peak occurrence being in the 4th and 5th decades of life. *Dotted bars* denote female patients; *solid bars* denote male patients.

3-amino-7-ethoxyphenazone, a breakdown product of phenacetin [157, 158]. A golden-brown lipofuchsin-like pigment is widely distributed in the brain, heart, liver, joint cartilage (like ochronosis), skin, kidney, and lower urinary tract [159–163]. Lipofuchsin is a highly oxidized polymer of unsaturated fatty acids [164], and its accumulation in organs is probably related to the oxidant effect of phenacetin.

Experimental and clinical studies suggest that analgesic abuse may be incriminated in a number of possible gonadal- and pregnancy-related effects; these include postmaturity, due to reduced uterine prostaglandin, toxemia of pregnancy, teratogenicity, and congenital malformations and infertility [165–171].

The prematurely aged appearance in patients with analgesic nephropathy has been emphasized [25, 38]. The multiorgan dysfunction occurring at an early age with the prominent presence of wear-and-tear pigment may reflect premature biologic aging.

Renal manifestations of the analgesic syndrome. Patients with analgesic nephropathy have a predominant tubulomedullary dysfunction characterized by an impaired concentrating and acidifying capacity and a sodium-losing state [163, 172–178]. The functional abnormalities in 33 patients with analgesic nephropathy, 24 patients with glomerulonephritis, and 30 control subjects, all with normal creatinine clearances [178] are summarized in Table 4. Frank renal tubular acidosis with a minimum urinary pH > 5.7 is only seen in analgesic nephropathy patients when renal function is impaired. These functional defects are responsible for a number of common clinical manifestations in patients—nocturia, polyuria, cramps, medullary calcification [25, 45, 163, 179–183], calculus disease [184, 185], uremic bone disease [186], and systemic acidosis. Dystrophic calcification of necrotic tissue and excessive ingestion of milk-alkalis because of gastric disturbances contribute to the nephrocalcinosis. The other factors

Table 4. Renal function tests in patients with analgesic nephropathy and glomerulonephritis[a]

	Control	Analgesic nephropathy	Glomerulonephritis
No. of patients	30	33	24
Age, *yr*	34.6 ± 10.1	45.4 ± 9.9	31.0 ± 11.2
C_{Cr}, *ml/min/1.73 m²*	112.9 ± 21.3	98.2 ± 20.3	114.5 ± 28.3
Max. U_{Osm}, *mOsm/kg H_2O*	971.5 ± 133.4	655.0[b] ± 152.3	909.0 ± 110.4
Acidification:			
Min. urine pH > 5.2	0	3/30 (10.0%)	1[c]/24 (4.2%)
Titratable acid, *μEq/ml/min/1.73 m²*	35.0 ± 8.7	26.1[b] ± 5.7	31.6 ± 4.9
Ammonium, *μEq/ml/min/1.73 m²*	53.1 ± 9.1	44.3 ± 11.2	56.4 ± 19.5
Bicarbonate, *μEq/ml/min/1.73 m²*	1.2 ± 1.4	0.4 ± 1.7	0.6 ± 1.0

[a] Values are mean ± SD.
[b] Significant reduction, $P < 0.01$.
[c] Patient with lupus nephritis.

that contribute to stone formation are necrotic papillae, exfoliation of tubular epithelial cells by analgesics, urinary tract obstruction, and infection by urea-splitting organisms, such as proteus.

Urinary tract infections have been reported in 15 to 60% of patients [19, 38, 39, 46, 47, 127, 144, 163] and may be asymptomatic. A sterile pyuria is seen in more than three quarters of the patients and may be related to either occult infection, calculi, or epithelial celluria. Instrumentation or obstruction in analgesic nephropathy may lead to septicemia.

Persistent microscopic hematuria is an important clue to the development of a transitional cell carcinoma. Although the reports of the association between analgesic abuse and papillary carcinoma have come mainly from Europe [187–192], this serious complication is also recognized in Australia [193–196] (ORELL S: personal communication, 1976).

Proteinuria has recently been recognized as a significant and serious prognostic feature of analgesic nephropathy [197]. The incidence of proteinuria rises with a decline in renal function, and there is a significant inverse correlation between proteinuria and the creatinine clearance ($y = 1.93 - 0.15x$, $P < 0.01$). Renal biopsies were available in 23 patients with analgesic nephropathy and proteinuria; all biopsies showed changes of chronic interstitial nephritis. However, significant glomerular lesions were seen in 16 patients, membranous nephritis was seen in two patients, focal glomerular sclerosis was seen in nine patients, and focal glomerular hyalinosis was seen in 14 patients.

The reported incidence of hypertension in analgesic nephropathy varies from 15 to 70% [19, 37–39, 46, 47, 126, 127, 144, 145, 198]. Malignant hypertension has been observed in 6.9% cases of analgesic nephropathy, and the common occurrence of significant clinical salt- and water-depletion in patients with severe hypertension is of interest (Fig. 2). The mechanism of this physiological paradox is not clear, but depletion of renal medullary vasodilator substances [199, 200] and activation of the renin-angiotensin system may be involved. Atheromatous renal artery stenosis may also contribute to severe hypertension, and correction of such a lesion may lead to improvement in blood pressure control and renal function.

Clinical gout has been observed in 4.6% of analgesic nephropathy patients with normal renal function and in 26.5% patients when there is renal insufficiency [202]; the secondary gout appears to be more common in males.

RPN is the primary event in analgesic nephropathy [29, 41, 95] and results from ischemic and toxic damage to the interstitial cells, vasae rectae, and loops of Henle [40, 92, 95, 202, 203] due to concentration of analgesics by the countercurrent mechanism [70,205,206]. The roles of medullary ischemia, probably via suppression of prostaglandin synthesis [95], and the concentration mechanism have been emphasized in a number of experimental studies [50, 65, 86–89, 207]. Aspirin has a number of intracellular toxic effects, including interference with the tricarboxylic cycle, oxidative phosphorylation, and mucopolysaccharide synthesis [107, 208]. Phenacetin and paracetamol cause potent oxidative damage to all membranes, leading to glucose-6-phosphate dehydrogenase, glutathione, and dihydronicotinamide adenine dinucleotide phosphate (NADPH) deficiency, and it has been suggested that the synergism between aspirin and phenacetin nephrotoxicity may be explained on the basis of salicylate inhibition of NADPH supply through the hexose-monophosphate shunt [91, 209].

Chronic interstitial nephritis is a nonspecific cortical change resulting from obstruction to tubules in

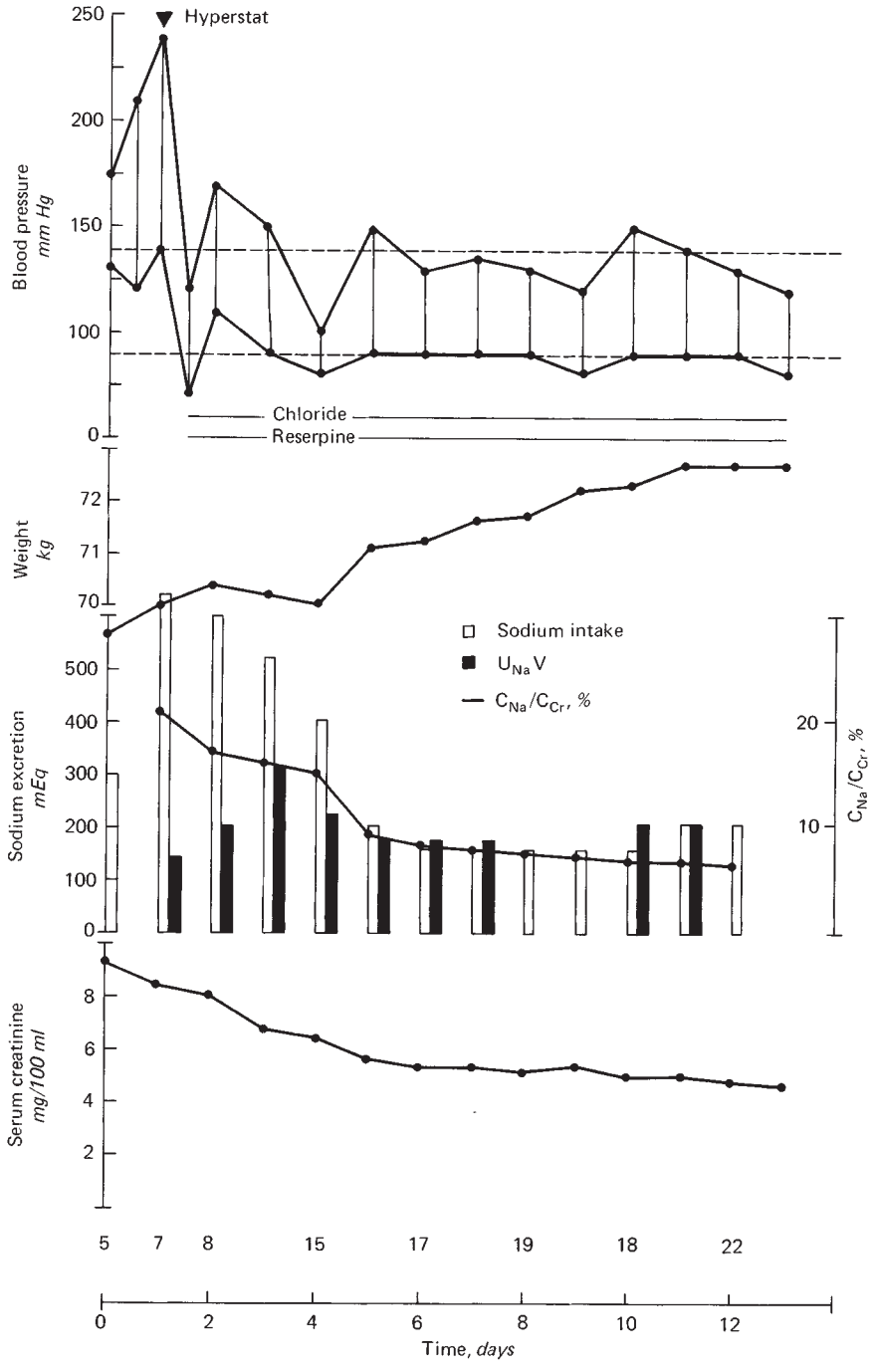

Fig. 2. *Association between salt and water balance, hypertension, and renal function in analgesic nephropathy.* The figure shows a patient admitted with severe hypertension (BP, 175/130 mm Hg). There was salt- and water-depletion, indicated by a fall in weight (68.5 kg) and low sodium excretion, and deterioration in renal function (serum creatinine, 9.2 mg/100 ml; serum bicarbonate, 5 mEq/liter). Acute reduction of blood pressure with parenteral diazoxide and rapid volume expansion with i.v. saline led to a weight gain (72.4 kg), improvement of renal function (serum creatinine, 4.8 mg/100 ml; serum bicarbonate, 22 mEq/liter), and stabilization of blood pressure which now required minimal therapy with chlorothiazide and reserpine.

the necrotic medulla [29, 40, 41, 50, 95, 202], and similar changes may result form experimental papillectomy or ureteric ligation [210, 211]. In the early stages, chronic interstitial nephritis may only be seen in the cortex overlying the necrotic papilla, while the intervening cortex which is an extension of the column of Bertin may be entirely normal.

Diagnosis of analgesic nephropathy. The diagnosis of analgesic nephropathy is based on a history of analgesic abuse and demonstration of RPN.

Analgesic abuse may be defined as an intake of 2 kg of aspirin or phenacetin or paracetamol in the form of an analgesic mixture [25]; the actual consumption of analgesics may be as high as 30 kg of aspirin or phenacetin. Precise quantitation of analgesics may be difficult, and many patients attempt to conceal and minimize the extent of abuse [13, 38, 127, 142, 144].

The typical features of RPN are usually identified on an i.v. urogram or by retrograde pyelography. A normal pelvicalyceal system may be due to early and mild papillary damage or RPN *in situ* [212–214]. The relationship between renal function, radiological, and renal biopsy abnormalities are summarized in Table 5.

RPN is occasionally confirmed by the demonstration of a necrotic papilla voided in urine. When the radiological features are not diagnostic, the demonstration of cortical changes of chronic interstitial nephritis with the prominent presence of lipofuchsin-like pigment on renal biopsy assists in the confirmation of diagnosis. Occasionally necrotic medulla may be present in the biopsy tissue.

The radiological features of RPN may be of the papillary or the medullary types, and the important features which assist in diagnosis are ring shadows, medullary cavities, and medullary calcifications [179–184, 215, 216]. These changes, however, cannot be distinguished from RPN in conditions such as diabetes mellitus or sickle cell disease and have to be differentiated from chronic nonobstructive atrophic pyelonephritis or "reflux" nephropathy, tuberculosis, obstructive uropathy, pyelogenic cysts, and medullary sponge kidney. The radiological differentiation between analgesic nephropathy and chronic pyelonephritis is important, and the criteria that may assist in this differentiation are detailed elsewhere [183].

Management and outcome of analgesic nephropathy. The management of acute renal failure due to RPN involves the immediate control of life-threatening complications such as hyperkalemia, severe systemic acidosis, and septicemia, and it involves the establishment of an adequate urine flow by rapid correction of intravascular volume-depletion and the use of large doses of a potent diuretic, such as frusemide; dialysis may be necessary. Severe hypertension which may be present is managed independently of the negative salt and water balance and responds satisfactorily to parenteral administration of diazoxide or clonidine. Attempts to control hypertension by sodium restriction may lead to persisting oliguria and terminal renal failure. Ureteric catheterization is undertaken early to exclude obstruction from necrotic papillae. Recovery from an episode of acute RPN is commonly followed by a severe salt-losing phase.

Urological procedures are frequently necessary [217, 218] (Table 6); 86 procedures were carried out in 70 patients (30.2%). The indications in our series were diagnostic (31), unexplained reduction in renal function (14), renal colic (8), hematuria (8), and persistent urinary tract infection (2).

The therapeutic urological procedures in 17 patients (7.3%) were not associated with any mortality or significant morbidity. Endoscopic extraction of papillae were more successful with the dormia basket, and occasionally ureteric catheter drainage of the renal pelvis for several days was necessary [219–222]. Contrary to the experience of Johnson [218], pyelolithiotomy was not performed for free nonobstructing papillae in the renal pelvis, and on several occasions large papillae disintegrated and were

Table 5. Relationships between renal function, radiological, and renal biopsy abnormalities in analgesic nephropathy[a]

GFR	Concentration capacity	Acidification	IVP		Chronic interstitial nephritis
			Size	Pelvicalyceal abnormality	
−	+	−	−	−	−/±
+	++	+	−/+	+	+/±
++	+++	++ RTA	++	++	+
++	+++	++ RTA	++	− (RPN *in situ*)	+++

[a] Abbreviations used are: GFR, glomerular filtration rate; RTA, renal tubular acidosis; RPN, renal papillary necrosis; IVP, intravenous pyelography.

Table 6. Urological procedures in the management of 232 patients with analgesic nephropathy

	No. of patients	No. of procedures
Diagnostic procedures		
Cystoscopy	6	6
Cystoscopy + retrograde pyelography	42	57
Open renal biopsy	5	5
Therapeutic procedures		
Cystoscopy + ureteric catheterization	6	6
Cystoscopy + extraction of papillae from ureter	4	5
Ureterolithotomy	1	1
Pyelolithotomy	4	4
Nephroureterectomy	2	2
Total	70	86

passed uneventfully. The two cases of transitional cell carcinoma detected in the 232 patients were successfully treated by nephroureterectomy.

The main principles in the management of chronic analgesic nephropathy are total avoidance of all nonsteroid antiinflammatory drugs, careful long-term supervision of hypertension, salt and water balance and urinary tract infections, and a constant awareness and early detection of serious complications such as silent urinary tract obstruction and transitional cell carcinoma. Evidence of cessation of analgesic abuse should be obtained by routine screening of urine and serum of patients for aspirin, phenacetin, and paracetamol, and their metabolites [223–225].

Outcome. The long-term outlook of patients with analgesic nephropathy is optimistic if patients stop abusing analgesics, and a 73.8% five-year cumulative survival in a group of 43 patients with severe renal failure has been reported [43]. With the exception of a very small number with severe personality defects, most patients with analgesic nephropathy can be persuaded to stop the regular use of analgesics if an aggressive and positive attitude is adopted in follow-up management. The factors which contribute to deterioration in renal function are uncontrolled malignant hypertension, persistent proteinuria indicative of a glomerular lesion, nephrectomy necessitated by pyonephrosis or renal papillary carcinoma, ischemic heart disease with cardiac failure, and continuing analgesic abuse.

Over a five-year period, 110 patients with terminal renal failure were accepted for maintenance dialysis and transplantation, from a population of 500,000; 61 patients (55.5%) had analgesic nephropathy, and 19 patients (17.3%) had glomerulonephritis. This is in striking contrast to similar data from Europe [20]. The analgesic nephropathy group appeared to be extemely poor risk patients; the overall mortality in patients with analgesic nephropathy accepted for dialysis was 50.8%. This was much higher than the mortality in patients with glomerulonephritis, which was 15.8% ($x^2 = 5.9$, $P < 0.025$). The causes of death in the 31 patients with analgesic nephropathy are shown in Table 7 and appear to be mainly related to vascular complications.

Table 7. Causes of death in 31 patients accepted for dialysis with analgesic nephropathy and terminal renal failure

	No. of patients	%
Ischemic heart disease	19	61.3
Septicemia	6	19.4
Cerebrovascular accidents	6	19.4
Dissecting aneurysm	1	
Hemopericardium	1	
Carcinoma stomach	1	
Total	34[a]	

[a] There were two causes in three patients.

Summary

Analgesic abuse is a major public health hazard in Australia, and analgesic nephropathy with consequent terminal renal failure is the underlying cause in 20% of the patients requiring dialysis and transplantation. Analgesics are invariably taken in the form of compounds and mixtures. In the aspirin-phenacetin-caffeine (APC) mixture, aspirin appears to be the major nephrotoxic agent and phenacetin appears to play a secondary and synergistic role. The renal disease associated with abuse of analgesics is characteristic and is part of a much wider clinical syndrome, the analgesic syndrome, which includes peptic ulcer disease (35%), anemia (60 to 90%), hypertension (15 to 70%), ischemic heart disease (35%), psychological and psychiatric manifestations, pigmentation, and possible gonadal- and pregnancy-related effects. The primary lesion in analgesic nephropathy is renal papillary necrosis (RPN), and this is a nephrotoxic effect common to all nonsteroid antiinflammatory agents. The most important factor in the management of patients with analgesic nephropathy is the cessation of analgesic abuse, and this leads to improvement and stabilization of renal function. A small proportion of patients will, however, deteriorate in relation to accelerated hypertension, persistent proteinuria, ischemic heart disease, and complications leading to nephrectomy. Patients with analgesic nephropathy are poor risk patients and

have a poor prognosis, even after dialysis and transplantation.

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