ANALGESIC NEPHROPATHY

MEDICAL GRAND ROUNDS

WILLIAM L. HENRICH, M.D.

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL

DALLAS, TEXAS

October 15, 1987

Table of Contents

This review covers the problem of analgesic nephropathy (AN) in two sections: Part I describes the features of "classical" AN which has been observed with over-the-counter combination analgesics. In Part II, the nephrotoxic syndromes recognized to be associated with the non-steroidal anti-inflammatory drugs (NSAIDs) are discussed.

I. "CLASSICAL" AN

A. General Comments

Nonprescription antipyretic analgesics have been in use for over a century. The first report linking habitual analgesic consumption came from Switzerland in 1953 and was written by Spuhler and Zollinger (1). This report noted that 14 of 44 patients with chronic interstitial nephritis had a history of consumption of combination analgesics containing phenacetin, amidopyrine, isopropylantipherine, caffeine, and persedon. Similar reports form Scandinavia and Australia soon followed, and a general trend toward increasing consumption of analgesics was noted. Initially, the syndrome was described as a chronic interstitial nephritis, but in subsequent reports this lesion was recognized to occur with papillary necrosis. Papillary necrosis has become recognized as the characteristic pathologic finding in the syndrome.

The early reports linking analgesics and renal disease were generally found in patients who consumed combination products containing phenacetin. This fact focused attention on phenacetin as the primary cause of the syndrome, and phenacetin was officially removed from non-prescription analgesics in Sweden and Denmark (1961), Finland (1965), Canada (1973), United Kingdom (1975), and the U.S (1975). Phenacetin was removed from prescription products in the U.S. in 1986. Significantly, the removal of phenacetin has not been usually followed by the expected reduction in the incidence of AN.

B. Syndrome of Habitual Analgesic Consumption

AN occurs in patients who consume analgesics daily (usually for headaches or to improve work productivity), is more common in women (by a factor of 2 to 6 fold), and has a peak incidence at age 53. Moderate to low proteinuria and "sterile pyuria" are common; tubulointerstitial nephritis is seen on renal biopsy (possibly secondary to renal papillary damage). Occasionally hematuria and loin pain are noted, but non-specific complaints and findings such as malaise, weight loss, anemia, peptic ulcer, and hypertension occur. Loss of maximum urinary concentrating ability, renal tubular acidosis, and a salt-losing state are occasionally described. These clinical findings are summarized in Table 1.

Table 1: Clinical Features of AN

	% Affected
Urinary Tract Symptoms	70
Sterile Pyuria	47
Bacteruria	36
Renal Colic or Hematuria	32
GFR Reduction	92
IVP Changes	90
Hypertension	32
Dyspepsia	86
Prior GI Bleeding/Operation	36
Anemia	60
Hemolytic	17
Iron Deficiency	20

Several lines of epidemiologic evidence point to analgesics as a causative factor in the syndrome. In one study of 698 patients (2), daily consumption of phenacetin in combination products resulted in a higher incidence of renal impairment, particularly in patients who consumed daily analgesics for over 10 years (Table 2).

Table 2: Analgesic Consumption and Renal Function

a.

	No. of patients	% of total	No. of patients with reduced renal function (%)
No phenacetin consumption	337	48.3	29 (8.6)
Periodic consumption of phenacetin	156	22.3	17 (10.9)
Daily consumption of phenacetin	205	29.4	68 (33.2)

b.

Daily consumption of phenacetin	Duration (y)	No. of patients	No. of patients with reduced renal function (%)
Under 1g	0-5	56	9 (16.1)
1g or more	0-5	51	14 (27.3)
Under 1g	6-10	18	5 (27.8)
1g or more	6-10	31	10 (32.3)
Under 1g	Over 10	30	15 (50.0)
1g or more	Over 10	19	15 (78.9)

Retrospective analyses indicate that a cumulative dose of 2 to 3 kg has been ingested prior to developing the syndrome. In general, there is a correlation between the prevalence of habitual consumption and the prevalence of nephropathy as shown in Figure 1 and Table 3 (3). Table 3 also points out the enormous variability in incidence of the syndrome worldwide.

Figure 1: Consumption vs Nephropathy

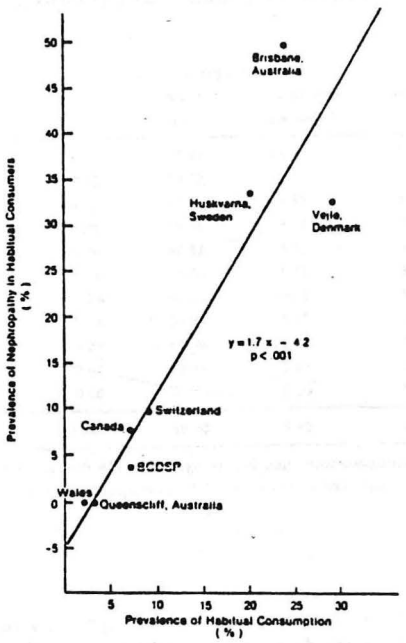


Table 3: Consumption vs Nephropathy

Country	Estimated Per Capita Consumption Phenacetin (g/yr)	RPN (% of Cases Resulting From Analgesic Abuse)	Analgesic Nephropathy (% of Cases With RPN)	% of Cases With ESRD Resulting From AN
Australia	40	57–94	63	15-20
Sweden	25	79	60–86	10
Switzerland	22	30	—	20
Scotland	12	—	30	4–8
USA	10	15	26	2–10
Canada	6–7	—	68	3.5

From Reference 3

Similarly, there is also a clear-cut regional frequency of the prevalence of AN and uroepithelial tumors which correlates with the consumption of analgesics. Pommer et al have recently surveyed analgesic consumption in West Germany and have shown a marked difference in the incidence of tumors depending upon geographical region. The northern regions of Germany have far greater-combination analgesic consumption and a much greater incidence of uroepithelial abnormalities. (Table 4).

Table 4: Analgesic Consumption and Incidence of Tumors

	Analgesic nephropathy[a]				Urinary bladder tumors[b]
	pmp[c]	%[c]	mean age	% of new patients[c,**]	incidence
Berlin (W)	37.37	10.26	59.84	16.1	9.21
Hamburg	26.25	7.12	59.72	12.0	9.15
Bremen	20.00	4.22	57.96	4.55	8.03
Niedersachsen	17.95	6.85	59.46	4.61	7.06
Hessen	14.64	4.94	60.52	5.32	6.50
Nordrhein-Westfalen	13.59	4.96	58.36	6.42	8.97
Baden-Württemberg	10.22	3.38	60.28	41.8	5.43
Schleswig-Holstein	8.08	5.18	57.95	5.45	8.10
Rheinland-Pfalz	7.22	3.39	60.86	1.42	7.63
Bayern	5.55	2.27	58.54	2.63	5.77
Saarland	0.00	0.00	–	0.00	5.69
All patients with AN (N = 774)	12.57	4.66	59.30	5.40	7.40

[c] per million population, [c] percentage of patients with AN in the regional end-stage renal population, [c,**] incidence, based on all patients accepted for treatment in 1983. [a] EDTA-registry [1983 unpublished], [b] Becker et al. [1982] data in standard mortality rates (per 100.000 inhabitants).

Only one study surveying this problem has been performed prospectively (5). In this study, the authors screened 7,311 women (ages 30-49) in northwest Switzerland for regular intake of phenacetin by chemical examination of the urine for N-acetyl-para-aminophenol (NAPA), the major phenacetin metabolite. High and low NAPA groups were identified based on the absolute amounts of NAPA in the urine; the high group was shown to ingest greater than 1.25 g/d of phenacetin. An initial study revealed that phenacetin consumers are more likely to have a history of proteinuria, kidney disorders, and abnormal concentrating ability than controls, but the serum creatinines were similar in both groups. However, the high NAPA group had a higher prevalance of elevated creatinine compared to the low NAPA and control group (Tables 3 and 4). These 623 working women were assessed 6 times over an 11 year period. The conclusion from this study was that heavy users of analgesics have a higher incidence of both abnormal kidney function and kidney-related mortality than do casual users and nonusers.

Table 5: Tests of Specific Gravity

Distribution of Subjects with Normal Urinary Specific Gravity on Initial Examination, According to Number of Abnormal Results on Subsequent Examinations.

Group	No. of Abnormal Results			
	Total	0	1	≥2
	no. of subjects (per cent with ≥2 abnormal findings)			
Study group	423	220	105	98 (23.2 *)
High-NAPAP subgroup	206	72	61	73 (35.4 †)
Low-NAPAP subgroup	217	148	44	25 (11.5 ‡)
Control group	476	355	89	32 (6.7)

*Significantly different from controls (P<0.001).
†Significantly different from controls (P<0.001) and value for low-NAPAP subgroup (P<0.001).
‡Significantly different from controls (P = 0.047).

Table 6: Serum Creatinine

Distribution of Subjects with Normal Serum Creatinine on Initial Examination, According to Number of Abnormal Results (Elevated Levels) on Subsequent Examinations.

Group	No. of Abnormal Results			
	Total	0	1	≥2
	no. of subjects (per cent with ≥2 abnormal findings)			
Study group	431	360	42	29 (6.7 *)
High-NAPAP subgroup	217	163	28	26 (12.0 †)
Low-NAPAP subgroup	214	197	14	3 (1.4 ‡)
Control group	452	407	41	4 (0.9)

*Significantly different from controls (P<0.001).
†Significantly different from controls (P<0.001) and value for low-NAPAP subgroup (P<0.001).
‡Not significantly different from controls.

Relatively little information exists regarding AN prevalence in the U.S. In one study performed in Philadelphia (6), 6% of a hospital population consumed analgesics daily for more than a year, although an additional 4% had consumed analgesics daily for periods of 30 days to one year. Two recent studies which surveyed the U.S. concluded between 20 and 32% of patients with interstitial nephritis had analgesic consumption as the cause (7,8). Just as noted above in the West German study, significant regional differences of incidence also appear to exist in the U.S. For example, the use of combination analgesics is more common in the Southeastern U.S., and the incidence of AN is 3-5 times as common a cause of end-stage-renal-disease in North Carolina compared to Philadelphia. A recent NIH concensus panel (9) concluded that the overall incidence of AN in the U.S. was more congruent with the Northeastern sector of the country than with the patterns of consumption noted in the Southeast in general and North Carolina in particular. Overall estimates for the country are that between 2 and 4% of all ESRD may be attributable to habitual analgesic consumption. The NIH concensus panel also recommended that serious consideration be given to the elimination of combination analgesic preparations (9).

C. Which Analgesic is Responsible for AN?

Pommer has recently pointed out (10) that beginning in the 1960's in West Germany phenacetin has been gradually replaced with acetaminophen in combination products. Further, the per

capita consumption of phenacetin has decreased from 3.43 grams (in 1976) to 1.73 grams (in 1983). In the same period, acetaminophen consumption increased from 2.19 to 4.48 grams. About two-thirds of analgesic consumption is self-medication, and 80% of the more than 400 available analgesic compounds are mixture products. Despite the replacement of phenacetin with acetamenophen, the incidence of AN in the ESRD population is about 13% (up to 50% in some northern regions) in Germany, suggesting that the use of combination products is as important as whether the compound contains phenacetin. A similar finding has been reported from Australia (Table 7).

Other recent epidemiologic incidence has favored a specific role for compound analgesic mixtures in the AN syndrome. Korcok (11) reports that the overall incidence of AN has fallen by about 50% after a 1972 ruling which removed phenacetin and mixture compounds from over-the-counter sales.

Table 7: Trends in Prevalence of AN in ESRD in Australia

Dates	Prevalence (1%)
1967*-68	33
1968-69	23
1969-70	27
1970-71	29
1971-72	30
1972-73	36
1973-74	30

* The year Phenacetin was restricted

The above data from Australia are difficult to interpret. On the one hand, these studies show a failure of phenacetin restriction to lower the prevalence of AN as a cause of ESRD. However; the incidence of renal papillary necrosis at autopsy has been diminished by the phenacetin restriction. Further studies are required to clarify this issue.

Phenacetin has historically always been used in combination products, and no cases of AN have been reported with solo use of the product. That phenacetin compounds can clearly affect renal function over time is illustrated by a summary of studies which have compared phenacetin compounds vs. aspirin alone in rheumatology populations (3). These results are shown in Table 7A.

Table 7A: Rheumatology Clinic Studies

Comparison	Prevalence % Consumers	Controls‖
Renal score >8*		
Phenacetin compounds vs. aspirin alone		
Brisbane, Australia	26.7	7.8†
New Zealand	6.25	4.6
Autopsy diagnosis of papillary necrosis		
Phenacetin vs. phenacetin-free compounds	29.7	8.3†
Clinical diagnosis of papillary necrosis		
Phenacetin compounds vs. aspirin alone		
New Zealand	9.4	0.30†
Brisbane, Australia	13.3	0.97†
Autopsy diagnosis of non-obstructive pyelonephritis		
Phenacetin vs. phenacetin-free compounds	64.9	20.8†
Aspirin alone vs. controls‡	21.7	9.0§

* Scoring system (1-10) for specificity of clinical evidence of AN.
† Significantly different by chi square ($p < 0.05$).
‡ Control population without rheumatoid arthritis whose analgesic consumption was unknown.
§ Significantly different when 7 patients with diabetic renal disease were removed from the control population.
‖ Consumers of aspirin alone or phenacetin-free compounds except where indicated.

While these studies highlight the key role of combination products as a cause of AN, they also suggest a more central role for phenacetin as a pathogenic factor. As phenacetin continues to become less common worldwide, the precise importance of the compound in classical AN will become clearer.

Attempts to produce renal lesions with phenacetin alone have been largely unsuccessful. Rats given 300 to 600 mg/kg/d have developed only tubular degenerative changes. The use of 1,000 to 3,000 mg/kg/d for periods of two to 15 months has led to more severe tubulointerstitial nephritis with frank papillary necrosis in one-third (particulary if the rats were dehydrated). Similarly, large doses of acetaminophen (900 to 3,000 mg/kg/d) produce papillary necrosis in 40 to 60% of animals. Studies in the dog have shown that dehydration produces extremely high concentrations of acetaminophen in the papillary tip. Summaries of the experimental results of studies with phenacetin, acetaminophen (paracetamol), and aspirin alone are shown in Tables 8,9, and 10 below (14).

Table 8: Experimental Analgesic Nephropathy-Phenacetin

Animal	Dose mg/kg/day	Duration (mo)	Renal Lesion
Cat	50	5.5	None
Dog	225	21.0	None
Rabbit	1,000–2,000	12.0	None
Rat	300	1.0	TIN
Rat	500	5.0	TIN in 35%
Rat	1,000	15.0	TIN in 100%, RPN
Rat	400	10.0	TIN
Rat	300–600	1.0	TIN, RPN in 8%
Rat	2% Diet	4.0	None
Rat	750–1,300	1.8	None
Rat	500	6–9	None
Rat-De	3,000	2–5	RPN in 37.5%
Rat-Hy	3,000	2–5	None
Rat-De	130–250	9–12	RPN in 80%
Rat-Hy	230	2–5	None

Abbreviations: TIN, tubulointerstitial nephritis; De, dehydrated rats; Hy, hydrated rats.

Table 9: Experimental Analgesic Nephropathy-Paracetamol

Animal	Dose mg/kg/day	Duration (mo)	Renal Lesion
Rat	100–300	1.0	TIN in 30%
Cat	50	5.5	None
Rat	2% Diet	4.0	None
Rat-De	3,000	2–5	RPN in 43%
Rat-Hy	3,000	2–5	None
Rat-De	900	9–12	RPN in 60%
Rat-Hy	900	12.0	None

Table 10: Experimental Analgesic Nephropathy-Aspirin

Animal	Dose mg/kg/day	Duration (mo)	Renal Lesion
Cat	50	5.5	None
Rat	250	5.0	None
Rabbit	1,000	12.0	TIN
Rat	500	6–9	TIN, RPN in 33%
Rat	500	6.0	None
Pig	1,000	10.0	None
Rat	25–175	5.0	None
Rat	300	9–12	TIN in 33%, RPN in 75%
Rat-De	200	2.5–16.5	RPN in 54.8%
Rat-Hy	200	2.5–16.5	None

One feature of experimental AN is that mixtures containing aspirin, phenacetin, or acetamenophen result in a higher incidence of papillary necrosis than when each drug is administered individually. In contrast to the data in the prior tables the doses of analgesics in the mixture preparations shown below are closer to the therapeutic range. These data are shown in Table 11 below.

Table 11: Experimental Analgesic Nephropathy-Analgesic Mixtures

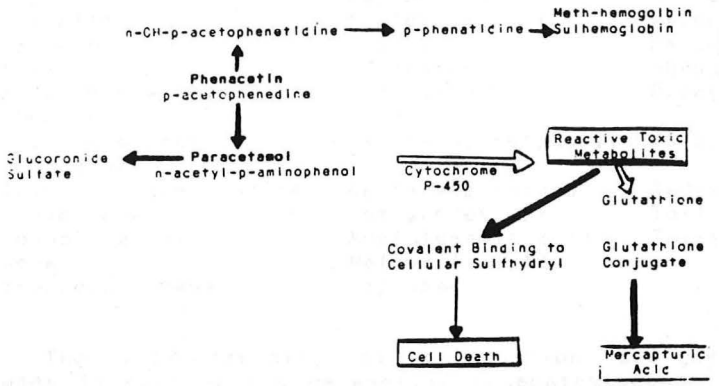
Mixture	Animal	Duration (mo)	Renal Lesion
A & Ph	Rat	15.0	TIN, RPN
A & Ph	Rat	6–9	TIN, RPN in 60%
A & Ph	Rat	9–12	TIN in 80%, RPN in 100%
A & P	Rat	9–12	TIN in 100%, RPN in 100%
A & Ph	Rat-De	2–5	RPN in 37.5%
A & Ph	Rat-Hy	2–5	None
A & P	Rat-De	3–7.5	RPN in 37.5%
A & P	Rat-Hy	3–7.5	RPN in 22%

A, aspirin; P, paracetamol; Ph, phenacetin.

D. Mechanisms of AN and of Renal Papillary Necrosis

The appearances of AN and papillary necrosis are said to be consistant with an ischemic process and endothelial necrosis, vascular obliteration and narrowing, platelet aggregation in the vasa recta, and generalized microangiopathy. Necrosis of the ascending limb of Henle and the associated peritubular capillaries has also been described. Clearly, dehydration potentiates the nephrotoxicity of combination analgesics in experimental studies. As mentioned above, combination analgesics have far greater renal toxicity than any individual agent. An important ingredient in the toxicity of mixed analgesics is n-acetyl-p-aminophenol (NAPAP), a major metabolite of phenacetin. Phenacetin is no longer available as an over the counter agent or prescription drug in the U.S., having been replaced usually with acetaminophen. Phanacetin undergoes extensive (79%) and rapid first pass metabolism in the liver to paracetamial (acetaminophen), which is then further metabolized and excreted in the urine. Phenacetin is only weakly bound to plasma protein, undergoes glomerular filtration, and is passively reabsorbed by tubules. No corticomedullary concentration gradient for phenacetin is achieved in kidney. Only a small percentage of acetaminophen is excreted as the parent compound. Over 80% is excreted as the glucuronide or sulphate conjugate. The conjugates of mercapturic acid and cysteine are small and depend on the dose administered. The outline of this metabolic pathway is shown below.

Figure 2



Acetaminophen metabolism. Major pathways of phenacetin metabolism. The renal activity of cytochrome P 450 is localized to the cortex and possibly the outer medulla.

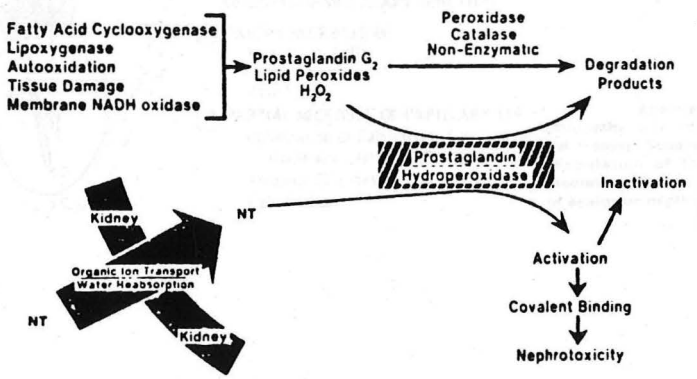
Evidence has been accumulated which relates the toxic effects of acetaminophen to oxidation and its activation to a reactive intermediate in the renal cortex and medulla. If glutathione supply is depleted, these metabolites become cytotoxic by virtue of their ability to induce free radical or oxidative injury. Oxidation of acetaminophen by the cytochrome P450 mixed function oxidases has been shown to be responsible for hepatic toxicity. The renal activity of cytochrome P450 is located in the renal cortex and (possibly) outer medulla. The renal papilla contains no cytochrome P450. Thus, metabolism of acetaminophen to an activated compound by prostaglandin endoperoxidase synthetase has been proposed as a mechanism for acetaminophen activation to an as yet unidentified nephrotoxic radical in the papilla. Aspirin may have a further deleterious effect on acetaminophen toxicity because: 1) aspirin does not slow acetaminophen metabolism; 2) aspirin acetylates a variety of renal proteins; 3) the ability of salicylate to reduce renal glutathione levels. Several recent studies have been congruent with this mechanism. There are a number of compounds now identified with the ability to cause renal papillary necrosis in vivo, and these are listed below:

Table 12: Therapeutically administered analgesics, NSAID and other drugs implicated with a direct papillotoxic potential

Aclofenac	Fenoprofen	Niflumic acid
Aminopyrine	Flufenamic acid	Oxyphenbutazone
Antipyrine	Glaphenine	Paracetamol
Aspirin	Ibuprofen	Phenacetin
Aspirin, Phenacetin and Codeine	Indomethacin	Phenylalkanate
Aspirin, Phenacetin and Caffeine	4-Isopropylbiphenyl	Phenylbutazone
Aspirin, and Pentazocine	Ketophenbutazone	Sudoxicam
Bucloxic acid	Ketoprofen	Tolfenamic acid
Cyclophosphamide	Meclofenamic acid	Tolmetin
Dapsone	Mefanamic acid	
Dextropropoxyphene	Naproxen	

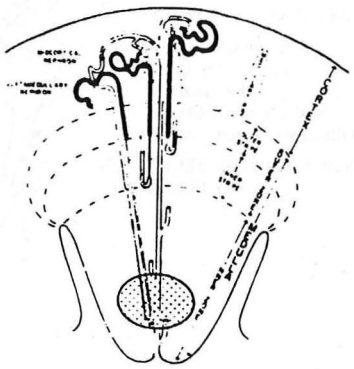
The nephrotoxicity of combination analgesics probably depends in part on the metabolism of acetaminophen to free radicals, strongly electrophilic intermediates, or to chemically unstable metabolites which give rise to reactive intermediates. Normally the intracellular presence of excessive amounts of nucleophiles (reduced glutathione among others) combine with these reactive intermediates and prevent the disruption of cellular functions. If, however, these scavengers are not present in sufficient supply to buffer the reactive intermediates, they will bind to other nucleophilic regions (including sites on macromolecules much as proteins and nucleic acids) leading to biochemical dysfunction or even cell death. The generation of lipid free radicals (lipid peroxidation) may lead to the generation of other lipid-free radicals and an autocatalytic chain reaction. A scheme integrating several of these concepts is illustrated below:

Figure 3: Hypothetical Scheme for Nephrotoxicity From Reference 14



The evolving stages of renal papillary necrosis are illustrated in Figures 4 through 6:

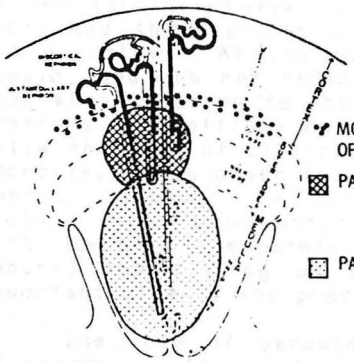
Figure 4: Early Papillary Necrosis
From Reference 14



PATCHY NECROSIS OF
Interstitial Cells
Loops of Henle
Capillaries
↑ BASEMENT MEMBRANE
↑ GROUND SUBSTANCE
COLLECTING DUCTS SPARED

Analgesic nephropathy: early renal lesions. Schematic representation of the early pathologic lesions of analgesic nephrotoxicity.

Figure 5: Mid-stage Papillary Necrosis
From Reference 14



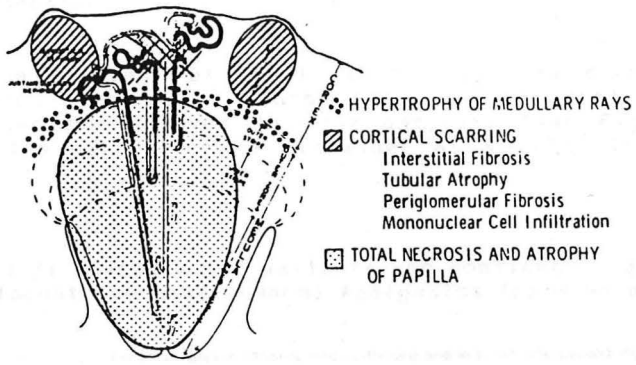
MONONUCLEAR CELLULAR INFILTRATE
OF CORTICO-MEDULLARY JUNCTION

PATCHY NECROSIS OF
Interstitial Cells
Loops of Henle
Vasa Recta

PARTIAL NECROSIS OF PAPILLARY TIP
Obliteration of Capillaries, Loops of Henle and Collecting Ducts
Atrophic Changes
Calcification

Analgesic nephropathy: intermediate renal lesions. Schematic representation of the intermediate pathologic lesions of analgesic nephrotoxicity.

Figure 6: Late Papillary Necrosis
From Reference 14



Analgesic nephropathy: advanced renal lesions. Schematic representation of the late pathologic lesions of analgesic nephrotoxicity.

The concentration of salicylate and acetaminophen is 2 to 5-fold that of cortex. The initial lesions are patchy and consist of necrosis of interstitial cells, thin loops of Henle, and capillaries. Later, cortical scarring, characterized by interstitial fibrosis, tubular atrophy, and periglomerular fibrosis develop over necrotic medullary segments. The fact that the lesions begin in the papillary tip is believed to be due to the concentration of the drugs and their metabolites. Also, the blood supply of the terminal calyx is provided by progressively thinner vasa recti and the branches of arteries from the terminal portion of the pyramids. At the papillary tip only single blood vessels remain, and the net effect is that the papillary blood supply is poor when compared to the rest of the medulla. Excellent illustrations of papillary necrosis by radiographs are available (19). While the bulk of clinical cases associated with AN and papillary necrosis, it is clear that NSAIDs may also be associated with the lesion, although far less frequently. One particularly disturbing report documented papillary necrosis in children treated with juvenile rheumatoid arthritis with NSAIDs (20). In this report, the finding of microscopic or gross hematuria was an important clue to the presence of renal papillary necrosis.

The role of peroxidase-mediated carcinogenesis is unclear at present. It has been shown that NSAID pretreatment can inhibit metabolism of benzidine in dog bladder (21). Several important carcinogens are metabolized to form protein, DNA, and tRNA in the presence of an arachidonic acid-dependent microsomal sys-

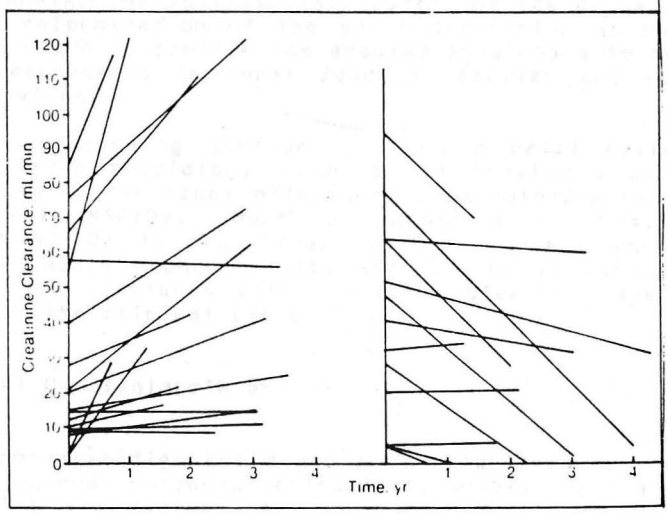
tem. The prostaglandin endoperoxidase system has also been shown to be capable of generating mutagenic products in the Ames test (22,23).

E. Prognosis

The response of renal function to the discontinuation of analgesics is mixed. Linton (24) reported that renal function stabilized or improved in most patients (see Figure 7). Certainly the experience of Schreiner et al (25) is mixed in this regard.

Figure 7: Outlook for patients who continue (right pance) and discontinue (left pance) Analgesics (From Reference 24)

—Filtration rates in patients who continued and in those who ceased ingestion of analgesics (adapted from Linton[24]).



II NEPHROTOXICITY ASSOCIATED WITH NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

A. General Comments Anti-Inflammatory Drugs

Reports of adverse renal effects of nonsteroidal anti-inflammatory drugs (NSAIDs) have grown remarkably in recent years. Nephrologists report that NSAIDs are among the most frequent reasons for a renal consultation regarding an acute reduction in renal function. In fact in one recent European study (26) NSAID-associated renal failure accounted for 37% of the drug-associated acute renal failure and about 7% of all cases of acute renal failure. The recognition that NSAIDs are a major cause of acute renal failure in the U.S. is due to several factors: (1) it has been estimated that between 20 and 40 million people in the United States have a potential therapeutic indication for the drugs (27), so the population at potential risk is huge; (2) many of the NSAIDs are relatively new to the market and the reporting of adverse clinical experiences has naturally lagged behind the initial distribution of the drugs; and (3) the routine determination of the serum creatinine as a part of the SMA 12 or SMA 18 profile has enabled physicians to detect significant decrements in renal function earlier and more reliably than previously.

The following section provides a brief review of renal prostaglandin physiology in order to provide a background for understanding the renal effects of prostaglandin synthesis inhibition with NSAIDs. Next, a pharmacologic classification and list of NSAIDs is presented, followed by a discussion of the types of NSAID nephrotoxicity encountered in humans. Finally, the section concludes with specific guidelines and recommendations for the clinical use of NSAIDs.

B. Renal Prostaglandin System

Prostaglandins are a group of ubiquitous substances formed from endogenous polyunsaturated fatty acids. In the kidney prostaglandins are synthesized from arachidonic acid, a 20 carbon fatty acid. Prostaglandins are synthesized in both the renal medulla and cortex. A greater amount of prostaglandins are synthesized in the renal medulla while metabolism of prostaglandins occurs primarily in the renal cortex (28). The major prostaglandins made in the kidney are PGE_2 and $PGF_{2\alpha}$. Thromboxane A_2 (a vasoconstrictor) and PGI_2 (a vasodilator) are also synthesized in the kidney in lesser quantities.

Renal prostaglandins (notably PGE_2) are acknowledged to be potent vasodilators in the renal circulation. When infused directly into the kidney, renal blood flow sharply increases as

renal vascular resistance declines. When a vasoconstrictive stimulus (norepinephrine infusion, angiotensin II infusion, or renal nerve stimulation) is directed to the renal circulation, the synthesis and release of renal prostaglandins dramatically increase, and act to oppose the vasoconstrictive stimulus. The importance of this vasoconstrictor-vasodilator (prostaglandin) relationship has been demonstrated in a number of experimental studies **in vivo** in which renal vasoconstrictive stimuli have been applied first in the presence of intact prostaglandin synthesis and then following prostaglandin synthesis inhibition with a NSAID prostaglandin synthesis inhibitor. In these experimental models of renal ischemic stress, the inhibition of prostaglandin synthesis results in enhanced renal ischemia since vasoconstrictive forces are unopposed by the vasodilatory influence of prostaglandins. This sequence of events has occurred during experimental acute reductions in cardiac output (29), hemorrhage (30,31), endotoxemia (32), and cirrhosis (33). Each of these pathophysiologic conditions have in common the ability to induce renal ischemia and produce renal vasoconstriction.

Several examples of a compensatory vasodilatory role for renal prostaglandins also exist in humans. For example Zia and colleagues have documented a close correlation between plasma renin activity, an index of relative renal ischemia, and 24-hr urinary PGE excretion (34). In their study, the highest PGE excretions were observed in patients with cirrhosis and ascites (34). A similar evaluation of the 24-hr urinary PGE excretion has been reported in a patient with congestive heart failure by Walsh and Venuto (35). In this case indomethacin treatments resulted in a decline in renal function. Further studies in cirrhotic patients have demonstrated that augmentation of PGE and sodium excretion occurs during the central blood volume expansion maneuver of water immersion to the neck (36). These studies suggest that PGE is a determinant of renal function in patients with compromised blood volumes. Further support for this relationship is provided by other neck immersion studies in which the administration of indomethacin blunted the natriuresis associated with neck immersion in sodium depleted but not sodium repleted subjects. Taken together, these studies suggest that PGE excretion is markedly enhanced under conditions of effective volume depletion, sodium restriction or other high-renin conditions. Under these conditions prostaglandin synthesis inhibition results in an antinatriuretic effect. Under euvolemic conditions with normal renal function, little or no change in renal function occurs following prostaglandin synthesis inhibition (37,38). Only where a vasoconstrictive stress or underlying renal disease is present has prostaglandin synthesis inhibition resulted in decrements in renal function.

Other known effects of prostaglandins on renal function include marked effects on the renin-angiotensin system as well as alterations in renal water excretion. Prostaglandin infusions are known to stimulate renin release in man and prosta-

glandin inhibition is associated with a lowering of basal plasma renin activity, probably via effects on the renal baroreceptor and macula densa pathways to renin release (39-41). Prostaglandins also play a role in renal water excretion by exerting a negative feedback on the hydro-osmotic effect of an antidiuretic hormone. Thus, in the presence of prostaglandin synthesis inhibition, the water reabsorption stimulated by AVP has been demonstrated to be enhanced **in vivo** (42).

Finally, renal prostaglandins may modulate renal blood flow during the development of acute renal failure suggesting that the hemodynamic effects of prostaglandins are of more than theoretical importance. Studies by Mauk et al demonstrated no protective effect of PGE administration to alter acute renal failure induced by the nephrotoxin uranyl nitrate (43). In contrast, the administration of PGE prior to intra-arterial norepinephrine as associated with preservation of glomerular filtration rate compared to kidneys not infused with PGE. Subsequent studies by Patak et al (44) implicated the increase in osmolar excretion secondary to PGE_2 infusion as a mechanism of primary protective importance in this ischemic model of acute renal failure. PGE_2 infusions have also been shown to protect against the development of acute renal failure in other experimental models such as glycerol (45). Conversely, inhibition of prostaglandin synthesis may enhance the incidence of and severity of glycerol-induced renal failure (46).

C. Classification of NSAIDs

Table 13 provides a list of NSAIDs according to the chemical derivative structure of the agents. Of particular clinical interest on the list are the carbo- and heterocyclic acetic acid derivatives which include indomethacin (Indocin), sulindac (Clinoril), and tolmetin (Tolectin). The most extensive clinical experience exists with indomethacin, which is antipyretic, anti-inflammatory, and may have analgesic effects as well. It is rapidly converted by the liver to inactive metabolites. Indomethacin is the most potent prostaglandin synthesis inhibitor in this group of drugs.

Table 13: Families of Nonsteroidal Anti-Inflammatory Drugs

I. Carboxylic Acids

A. Salicylic Acids and Esters

1) Aspirin
2) Diflunisal
3) Benorylate

Table 13 Continued

B. Acetic AcidS

1) Phyenylacetic Acids

a) Diclofenac
b) Alclofenac
c) Fenclofenac

2) Carbo-and Heterocyclic Acetic Acids

a) Indomethacin
b) Sulindac
c) Tolmetin
d) Zomepirac

3) Proprionic Acids

1) Ibuprofen
2) Naproxen
3) Flurbiprofen
4) Fenbufen
5) Benoxaprofen
6) Fenoprofen
7) Indoprofen
8) Ketoprofen
9) Pirprofen
10) Suprofen

D) Fenamic acids

1) Flufenamic
2) Mefenamic
3) Meclofenamic
4) Niflumic

II. Enolic Acids

A.Pyrazolones

1) Oxypenbutazone
2) Phenylbutazone
3) Apazone
4) Feprazone

B.1) Piroxicam
2) Sudoxicam
3) Isoxicam
4) CP-14, 304

The group of phenyl-proprionic acids consisting of ibuprofen (motrin), fenaprofen (nalfon), and naproxen (naprosyn) were introduced as anti-inflammatory agents in 1974 and 1975. These drugs are highly bound to protein and are slowly excreted in the urine as inactive metabolites. All are potent prostaglandin synthetase inhibitors, but have been reported to have lower incidences of gastrointestinal side effects. The anthranilic acid derivatives include mefanamic acid (ponstel) and meclofenemate (medomen). They are derived from the ancine analog of salicylic acid. These drugs have been less popular clinically because of the higher incidence of gastrointestinal side effects, notably diarrhea.

D. Nephrotoxicity of NSAIDs

The most commonly recognized clinical syndromes of nephrotoxicity of NSAIDs are listed in Table 14. The most important of these recognized syndromes are renal insufficiency due to PG synthesis inhibition and drug-associated interstitial nephritis. These disorders are discussed herein.

Table 14: Clinical Syndromes of Nephrotoxicity with NSAIDs

1) **Renal Insufficiency:** PG synthesis inhibition leads to enhanced renal vasoconstriction often in the context of diminished basal renal blood flow (e.g., congestive heart failure, volume depletion, cirrhosis, nephrotoxic syndrome, shock states, pre-existent renal disease, advanced age).

2) **Interstitial Nephritis:** Direct nephrotoxicity; often results in heavy, nephrotic-range proteinuria.

3) **Hyperkalemia:** PG synthesis inhibition leads to suppression of renin release which leads to hyporeninemic hypoaldosteronism and resultant hyperkalemia.

4) **Sodium and Water Retention:** Diuretic resistance due to aldosterone-like effect of NSAID as well as antinatriuretic effect of PG synthesis inhibition; water retention in part secondary to PG synthesis inhibition and enhanced effect of arginine vasopressin.

5) **Anaphylaxis:** Often after a second exposure; anaphylactoid reaction; more likely to occur in individuals with aspirin sensitivity and nasal polyps.

D-1. Renal Insufficiency

The greatest number of reported cases of renal insufficiency have occurred with indomethacin, which is probably related in part to the length of time the drug has been available for use compared to new preparations. Several of the most frequent features of NSAID-induced acute renal failure are listed in Table 15. Several of the most convincing reports have documented urinary prostaglandin levels (40-47). However, numerous other persuasive ancedotes exist (48-54). As noted in Table 15, the population of patients at greatest risk to develop renal failure from indomethacin therapy share a number of predisposing factors. The greatest of these risk factors appear to be a high

renin state and/or a decrease in renal function. As noted previously, this clinical finding is analagous to the experimental work which provided evidence that renal prostaglandins are important protective physiologic factors during ischemic stress.

Table 15: Clinical Features of NSAID-Induced Renal Failure

1) Dosage of NSAID often high

2) Oliguria initially, then an oliguric or non-oliguric course possible

3) Predisposing factors:

   a) Volume depletion, shock, sepsis
   b) Concommitant diuretic therapy
   c) Congestive heart failure
   d) Cirrhosis
   e) Underlying renal disease
   f) Post-op patients with "third-space" fluid sequestration
   g) Advanced age (possibly)

4) Usually reversible, does not require dialysis in the majority of cases.

Reversible acute renal failure syndrome has been associated with other drugs in the carbo-hetero-cyclic acetic acid class as well as drugs in other chemical derivative classes of NSAIDs. For example, zomepirac (53), proprionic acid derivatives such as ibuprofen (54-32), fenoprofen (58) and the fenamic acid derivative meclofenamic acid have all been associated with acute renal failure syndromes. It is also of interest that salicylic acids (aspirin) and the enolic acid derivative phenylbutazone are capable of inducing renal ischemic lesions, particularly in patients with pre-existent renal disease (59-71). In some patients, it may be argued that phenacetin or other analgesic use in addition to aspirin is required to produce ischemic lesions, particularly in patients without underlying renal disease (72,73).

Suprofen (suprol) is a new phenylpropionic acid derivative NSAID released in January of 1986 which requires special mention. Since its release this drug has been associated with a peculiar syndrome of flank pain and acute renal failure (74,75). This syndrome has led some to postulate that the drug precipitates an acute uric acid nephropathy because of the uricosuric actions of the drug. At least 16 patients have been reported to develop this syndrome within the first several months of the drug's release. These reports have led the FDA (76) to make a labelling change with suprofen so that the drug is no

longer considered as initial treatment for either of its primary indications: mild to moderate pain and dysmenorrhea.

An area of continuing debate centers on the "renal-sparing" effect of sulindac. Several investigators have reported a diminished renal effect of the drug as compared to other NSAIDs (77,78,79). The metabolism of sulindac is unique among the NSAID's (80) requiring activation of a prodrug (sulfoxide) to the active (i.e., cyclooxygenase inhibitor) sulfide in the liver. The kidney converts the sulfide back to the sulfoxide or to another inactive product (sulfone) via mixed function oxidases which reside in the renal cortex. Thus, the medulla of the kidney may not be exposed to high concentrations of active sulfide in every case. Caution with the use of sulindac is still warrented, however, since some studies have shown an ability of the drug to exascerbate renal ischemia (81).

Another interesting aspect of this problem regarding renal failure and NSAIDs is the fact that ibuprofen was released as an over-the-counter drug in 1984. This drug was released as a 200 mg (in contrast to the usual 400 mg dosage) tablet, with a maximum recommended dose of 1200 mg per day. The drug is to be used for shorter lengths of time. Since its release, very few adverse reports have been returned to the FDA regarding kidney toxicity (personal communication, Dr. John Harter). However, three recent communications (82,83,84) have pointed out that toxicity is still possible with this formulation of ibuprofen, and that caution is still indicated. Whether or not long-term renal sequelae will result is unknown.

D-2: Interstitial Nephritis

Most of the NSAIDs have been associated with a reversible clinical syndrome of heavy proteinuria and renal insufficiency. The incidence of this syndrome is unknown, but it is much less common than renal insufficiency in high-renin conditions. Clinical features of this disorder are provided in Table 16. Of interest is the fact that the glomeruli are relatively normal on biopsy in the majority of these cases despite heavy proteinuria. In some cases, corticosteroids have aided in the resolution of renal failure and proteinuria. Exposure to the drugs has been over a variable length of time in most cases; flank pain has been a prominent feature in several cases. While the pathogenesis of the lesion is not known, Torres has recently postulated that prostaglandin inhibition may lead to a cycle of immunologic events culminating in enhanced lymphokine production and thereby allow a delayed hypersensitivity reaction to proceed unchecked (85).

Table 16: Interstitial Nephritis Associated With NSAIDs; Clinical Features

1) Heavy proteinuria.

2) Tubulo-interstitial nephritis on biopsy; glomeruli often have only minimal changes.

3) Nonoliguric course commonly.

4) Flank pain, hematuria and eosinophilia in some cases.

5) Rapid decline in renal function; steroids may have aided resolution in some cases.

6) Time to development highly variable.

Drugs frequently associated with this type of renal insufficiency include indomethacin (86), tolmetin (87,88), sulindac (89), fenoprofen (90-94), naproxen (90), benoxaprofen (95), and zomepirac (96-97). The interstitial nephritis reaction and the previously noted ischemic acute renal insufficiency account for the majority of morbidity reported thus far with the use of NSAIDs. A recent review of interstitial nephritis (98) has pointed out that fenoprofen accounts for about 60% of the cases described in the literature. Tables 17 and 18 list the associated drugs and clinical presentations from that study.

Table 17: Agents Associated with Nonsteroidal Anti-Inflammatory Drug-Induced Interstitital Disease

	Number (%)
Proprionic acid derivatives	
Fenoprofen	22 (61)
Ibuprofen	2
Naproxen	3
	27 (75)
Other agents	
Zomepirac	3
Sulindac	1
Tolmetin sodium	2
Indomethacin	2
Phenylbutazone	1
	9 (25)
Total	**36 (100)**

Only those agents currently available in the U.S. are included in this analysis.

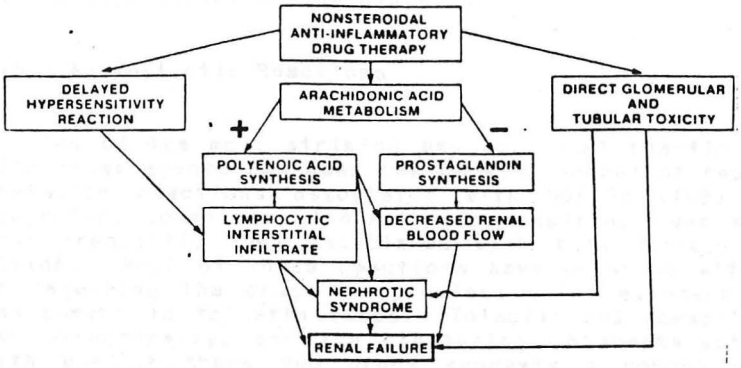
Table 18: Clinical Presentation of Nonsteroidal Anti-Inflammatory Drug-Induced Glomerular and Interstitial Disease

	Number	Age years	Drug exposure months	Peak serum creatinine mg/dl	Urinary protein g/24 h	Systemic hypersensitivity reaction[2]
A) Nephrotic syndrome and renal failure [3, 8, 12, 16, 18, 52–57]	26	65 ± 1.98	5.7 ± 0.8	6.1 ± 0.65	13.2 ± 1.48	3
B) Nephrotic syndrome without renal failure [18, 54, 58, 59]	4	64.8 ± 5.1	11.3 ± 6.4	1.05 ± 0.12	7.35 ± 2.76	0
C) Renal failure without nephrotic syndrome[3] [13, 19, 60–63]	6	62.7 ± 9.7	1.2 ± 0.5	7.0 ± 1.3	–	4

[1] Data expressed as mean ± SEM where appropriate.
[2] Drug fever, skin rash, blood eosinophilia, or eosinophiluria.
[3] Documented by renal biopsy [4] or associated systemic hypersensitivity response [2].

The pathogenesis of an interstitial nephritis which is manifest as a heavy proteinuric syndrome is obscure. Normal serum complement levels and negative immunofluorescence and electron microscopy accompany the syndrome. A direct toxic effect of the NSAID is possible, but is unlikely. The ability of NSAIDs to alter arachidonic acid metabolism has been suggested as a potential contributor to the syndrome by affecting renal blood flow or renal blood flow distribution. A delayed hypersensitivity response to an NSAID may be pathogenic in some, and may be suggested by the predominately T cell infiltrate in the interstitium. Infiltrating lymphocytes may release a variety of substances including lymphokines and vascular permeability factor. Both of these substances may participate in glomerular proteinuria. In addition to causing prostaglandin synthesis inhibition, NSAIDs may alter production of other metabolites of arachidonic acid metabolism of arachidonic acid via the lipooxygenase pathway to polyenoic acid, including leukotrines. Synthesis of polyenoic acids and leukotrines may be increased by some NSAIDs. These lipooxygenase metabolites are potent mediators of inflammation and may also induce vasoconstriction, increase vascular permeability to macromolecules, and increase chemotaxis for white blood cells including T lymphocytes and eosinophils. Whether or not these lipooxygenase metabolites are produced locally or are produced by infiltrating T lymphocytes is unknown. At present, the role of cell mediated immunity is unknonw in this syndrome. A diagram depicting this overall scheme is shown in Figure 8.

Figure 8
From Reference 98



Potential pathogenetic mechanisms of nonsteroidal anti-inflammatory drug glomerular and interstitial disease.
+ = facilitation: - = inhibition

D-3: Hyperkalemia

The inhibition of prostaglandin synthesis results in a decrement in renin release. This decrease in renin has lead to hypoaldosteronism and hyperkalemia in susceptible patients, particularly those with pre-existent renal insufficiency. Most of the reports have focused attention on indomethacin with respect to this side effect (54,99,102), but hyperkalemia remains a potential adverse effect in patients exposed to any of the NSAIDs.

D-4: Sodium and Water Retention

This side effect of NSAIDs is of lesser severity in most patients. However, in patients with tenuous sodium balance susceptible to congestive heart failure, the use of NSAIDs may precipitate symptoms (103). These effects on sodium excretion may be related to an aldosterone-like effect (considered unlikely by some), to redistribution of renal medullary blood flow, or to a direct antinatriuretic effect on prostaglandin synthesis inhibition. The enhanced end-organ effects of AVP and resultant water retention tendency associated with NSAIDs should be considered in the differential diagnosis of hyponatremia in affected patients. Nies and colleagues have also described a mechanism to explain the diuretic resistance seen with NSAID's (104). These authors postulate that NSAIDs ablate the increase in renal

blood flow seen with potent loop diuretics, and that this is most pronounced under circumstances in which the kidney is avid for sodium. The loss of renal vasodilation leads to a blunted natriuretic effect of the diuretic.

D-5: Anaphylactic Reactions

One of the most striking and worrisome reactions associated with these agents has been the growing number of reports of anaphylactic reactions associated with NSAIDs (105). Tolmetin, ibuprofen, zomepirac, indomethacin, aspirin, and sulindac have most frequently been associated with this serious adverse reaction. Most of these reactions have occurred within one hour of ingesting the drug. A previous brief exposure to the drug was common in tolmetin cases. Tolmetin and zomepirac are similar structurally, and the clustering of anaphylactic reactions with use of these two drugs suggests a common pathogenesis. Prior aspirin sensitivity and the presence of nasal polyps are further clues to patients at risk for this effect.

E: Summary and Recommendations

With regard to the classical type of AN, it is clear that the elimination of phenacetin from the over the counter and prescription markets has not significantly reduced the incidence of the disease in many instances. Most of the experimental evidence implicates the habitual use of combination analgesics (usually containing acetaminophen, aspirin, and possibly caffeine) as the most important predictive risk factor. If future epidemiologic studies confirm the work showing that 20-30% of interstitial nephritis is secondary to combination analgesic consumption, then it is likely the combination products will be either restricted or eliminated.

It is also clear that the spectrum of adverse renal reactions to NSAIDs is rapidly evolving. Investigations in experimental animals have accurately predicted the observed clinical occurrence of exacerbated acute reductions in renal blood flow and glomerular filtration rate when prostaglandin synthesis inhibition occurs during any renal ischemic stress. The interstitial nephritis and renal failure noted with these agents may also be a prostaglandin metabolism-related process, although the exact pathogenesis is unclear as yet.

In view of these considerations, a logical approach to patients requiring exposure to these drugs would dictate that patients at risk to developing renal insufficiency have renal function assessed prior to and after starting the agents. Accordingly, patients with high renin states (i.e., heart failure, volume depletion, nephrotic syndrome, cirrhosis, or taking high

diuretic doses etc.), pre-existent renal insufficiency or taking other analgesics should have serum creatinine monitored during therapy. Second, patients should be advised of the symptoms of the interstitial nephropathy (i.e., back pain, polyuria, a change in urine color, and edema) so that the drug may be stopped immediately should these symptoms occur and renal function assessed. Finally, physicians need to be cognizant of the possibility of anaphylactic reactions associated with these drugs, particularly when restarting the drugs after a nontreatment interval.

REFERENCES

1. Spuhler D: Zeitschrift fur Klinische Medizin 151:1-50, 1953
2. Larsen K: Acta Medica Scand 164:53-71, 1959
3. Buchalew VM: Medicine 11:291-303, 1986
4. Pommer W: Clin Nephrol 26:273-278, 1986
5. Duback UC: New Engl J Med 308:357-362, 1983
6. Murray TG: Arch Int Med 143:1687-1693, 1983
7. Murry TG: Kidney Int 13:64-71, 1978
8. Gonwa TA: Arch Int Med 141:462-465, 1981
9. JAMA 251:3123-3125, 1984
10. Pommer W: Lancet 1:40, 7/5/86
11. Korcok M: JAMA 246:2008, 1981
12. Norderfelt O: Acta Medica Scand 191:11-16, 1972
13. Stewart JH: Br Med J 1:440-443, 1975
14. Eknoyan G: Sem In Nephrol 4:65-76, 1984
15. Mohandas J: Toxicol and Appl Pharmacol 61:252-259, 1981
16. Newton JF: Toxicol and Appl Pharmacol 81:416-430, 1985
17. Bach PH: Prostaglandins Leukotrieves and Med 15:251-274, 1984
18. Zenser TV: J Lab Clin Med 101:58-65, 1983
19. Ellis PS: Sem In Nephrol 4:77-87, 1984
20. Allen RC: Am J Dis Child 140:20-22, 1986
21. Zenser TV: Cancer Res 40:2839-2845, 1980
22. Marnett LJ: Life Sci 29:531-546, 1981
23. Marnett LJ: Biochem 18:2923-2329, 1979
24. Linton AL: Can Med Asso J 107:749-751, 1972
25. Schreiner GE: Arch Int Med 141:349-357, 1981

26. Kleinknecht D: Clin Nephrol 25:275-281, 1986.

27. Wiseman EH: Am J Med (Special Report) 72(2A):2-8, 1982.

28. Larson C: Eur J Pharmacol 21:30-36, 1973.

29. Oliver JA: J Clin Invest 64:229-237,1 982.

30. Vatner SF: J Clin Invest 54:225-235, 1974.

31. Henrich WL: J Clin Invest 61:744-750, 1978.

32. Henrich WL: J Clin Invest 69:691-699, 1982.

33. Zambraski EJ: Kidney Int 19:218, 1981.

34. Zia P: J Lab Clin Med 92:415-422, 1978.

35. Walshe JJ: Ann Int Med 91:47-49, 1979.

36. Epstein M: Proc Am Soc Nephrol (Abstr) 150A, 1979.

37. Muther RS: Ann Int Med 92:386-387, 1980.

38. Gullner H-G: AJM 69:718-724, 1980.

39. Henrich WL: Kidney Int 19:822-830, 1981.

40. Keeton TK: Physiol Rev 31:81-227, 1981.

41. Berl T: Am J Physiol 236:F472-477, 1979.

42. Anderson RJ: J Clin Invest 56:420-426, 1975.

43. Mauk RH: Kidney Int 12:122-130, 1977.

44. Patak RV: Kidney Int 15:227-237, 1979.

45. Werb R: Clin Sci Mol Med 55:505-507, 1978.

46. Torres VE: Kidney Int 7:170-178, 1975.

47. McCarthy JT: Mayo Clin Proc 57:289-296, 1982.

48. Koren JF: Drug Intell and Clin Pharmacy 14:711-714,1 980.

49. Fawaz-Estrup: Arch Int Med 141:1670-1671, 1981.

50. Kleinknecht C: New Engl J Med 302:691, 1980.

51. Tan SY: JAMA 241:2732-2333, 1979.

52. O'Mera ME: S Med J 73:587-589, 1980.

53. Fellner SK: Arch Int Med 141:1846, 1981.

54. Galler M: JAMA 246:154-155, 1981.

55. Fong HJ: Am J Nephrol 2:28-31, 1982.

56. Brandsetter RD: Br Med J 2:1194-1155, 1978.

57. Kimberly RP: Arth Rheum 22:281-285, 1979.

58. Husserl FE: JAMA 242:1896-1898, 1979.

59. Stewart IC: Scottish Med J 26:183, 1981.

60. Woods KL: Br Med J 282:1471, 1981.

61. Drury PL: Br Med J 282:865, 1981.

62. Venning V: Lancet 1:745-746, 1980.

63. Robertson CE: Lancet 1:232-233, 1980.

64. Kimberly RP: Am J Med 64:804-807, 1978.

65. Mulhalwas KK: JAMA 246:867-868, 1981.

66. Edwards KDG: Med J Australia 1:492, 1972.

67. Nanra RS: Med J Australia 1:194-197, 1975.

68. Kimberly RP: Ann Intern Med 89:336-341, 1978.

69. Gokal R: Br Med J 1:1517-1518, 1977.

70. Morales P: Arch Surg 103:420, 1971.

71. Wilkinson EL: Am J Med Sci 225:153, 1953.

72. Ferguson I: Med J Australia 1:950-954, 1977.

73. Emkey RD: JAMA 247:55-57, 1982.

74. Hart D: Ann Intern Med 106:235-238, 1982.

75. Davis NS: Ann Intern Med 105:976-977, 1986.

76. Suprofen Labelling Revised: FDA Drug Bulletin 16;15-16, 1986.

77. Bunning RD: JAMA 248:2864-2867, 1982.

78. Ciabattoni G: Eur J Rheumatol Inflam 3:210-2

79. Ciabattoni G: N Engl J Med 310:279-283, 1984

80. Miller MJS: J Pharmacol Ther 231:449-456, 1984.

81. Henrich WL: Kidney Int 29:484-489, 1986

82. Justiniani FR: Ann Intern Med 105:303, 1986.

83. Moss AH: Ann Int Med 105:303, 1986

84. Schneider PD: Ann Int Med 105:303, 1986

85. Torres VE: Mayo Clin Proc 57:389-393, 1982.

86. Gary NE: Am J Med 69:135-136, 1980.

87. Chatterjee GP: JAMA 246:1589, 1981.

88. Katz SM: JAMA 246:253-254, 1981.

89. Lomvardias S: N Engl J Med 305:424, 1981.

90. Brezin JH: N Engl J Med 301:1271-1273, 1979.

91. Finkelstein A: Am J Med 72:81-87, 1982.

92. Wendland ML: Mayo Clin Proc 55:103-107, 1980.

93. Curt GA: Ann Intern Med 92:72-73, 1980.

94. Handa SP: Ann Intern Med 93:508, 1980.

95. Fine W: Postgrad Med J 58:317-318, 1982.

96. Ratner SJ: Ann Intern Med 96:793, 1982.

97. McCarthy JT: Mayo Clin Proc 57:351-354, 1982.

98. Abraham PA: Am J Nephrol 4:1-6, 1984.

99. Findling JW: JAMA 244:1127-1128, 1980.

100. MacCarthy EP: Med J Australia 1:550, 1979.

101. Goldszer RC: Arch Intern Med 141:802-804, 1981.

102. Tan SY: Ann Intern Med 90:783-785, 1979.

103. Wilkinson EL: Am J Med Sci 225:153, 1985.

104. Nies AS: J Pharmacol Exp Ther 226:27, 1983

105. Rossi AC: N Engl J Med 307:499-500, 1982.