ANALGESIC NEPHROTOXICITY

MEDICAL GRAND ROUNDS

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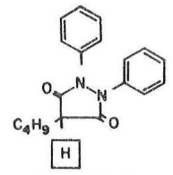
FAMILIES OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS				
ENOLIC ACIDS	CARBOXYLIC ACIDS			
Pyrazolones	Salicylic Acids	Carbo-Hetero Cyclic Acetic Acids	Propionic Acids	Fenamic Acids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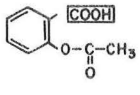
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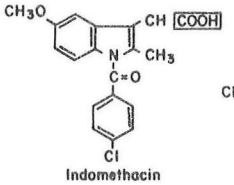
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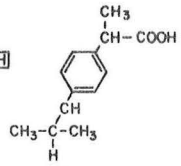
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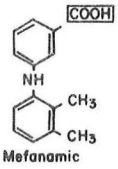
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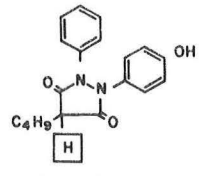
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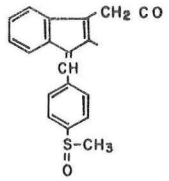
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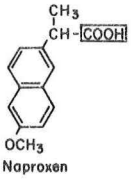
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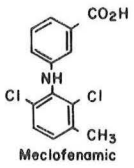
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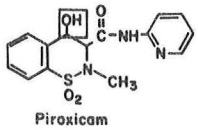
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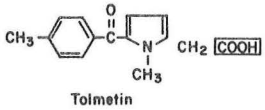
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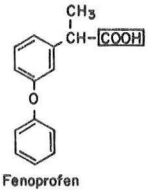
Fenoprofen

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I. INTRODUCTION:

Analgesics are undoubtedly the most widely used, if not prescribed, class of drugs in the world. A diffuse public pre-occupation with relief of minor discomfort and anxiety in concert with very effective advertising by pharmaceutical manufacturers has led to a virtually inestimable consumption of a variety of over-the-counter and prescription analgesics.

The kidney is an important target for toxicity of analgesics as it is for many other drugs. Several factors account for renal susceptability to drug toxicity. First, the kidney has a large blood supply, receiving 25% of the cardiac output. Second, the kidney has the highest oxygen and glucose consumption per gram of any bodily organ. Third, the large surface of the glomerular endothelium presents a considerable area for drug-kidney interaction. Fourth, the kidney concentrates many drugs and these substances may attain extremely high concentrations both in the urine and in renal epithelial cells. Fifth, drugs are often organic acids or bases with high degrees of binding to cellular protein. This results in further increases in concentration of drugs as well as prolongation of their effects. Thus taking into account the frequency of use of analgesics it is not surprising that analgesic nephrotoxicity is a clinical problem of significant proportion.

The following discussion will review the entity well known as analgesic nephropathy as well as other renal functional abnormalities associated with use of the classical analgesics, the salicylates and para-aminophenols and then summarize recent literature (growing at an alarming rate!) describing the nephrotoxic effects of a newer class of drugs, the so-called "non-steroidal anti-inflammatory drugs" (NSAID).

This classification is arbitrary since of course, aspirin is also "non-steroidal".

II. SALICYLATE PARA-AMINOPHENOL GROUP

A. Analgesic Nephropathy

1. GENERAL

In 1950, Zollinger and Spuhler reported the relationship of phenactin abuse and renal papillary necrosis associated with an increased incidence of chronic interstitial nephritis in Switzerland (1-2). Numerous reports over the next decade or so documented the significance of this problem world wide (3-9). Gloor et al. indicated that this disease was indeed a new entity as evidenced by their finding that papillary necrosis was present in only 2.7% of autopsy cases of chronic interstitial nephritis in 1940, but was present in 57% of such cases in 1960 (10). Thirty-two years later despite considerable experimental and clinical efforts and investigations a solution to the problem remains elusive. In the remainder of this discussion the association of papillary necrosis with chronic interstitial nephritis will be referred to as "analgesic nephropathy".

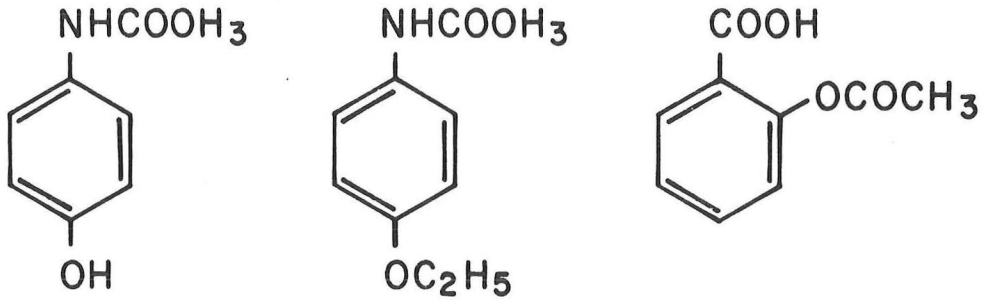
2. PHARMACOLOGY

A. Salicylates: Acetylsalicylic acid (Aspirin) (Fig. 1).

This particular salicylate was introduced into medicine in 1899. It is a potent antipyretic, analgesic and anti-inflammatory substance and probably the single most widely used drug in the world. Aspirin is metabolized primarily in the liver and excreted almost entirely by the

kidneys. Low doses (1-2 gm/d) lower urate excretion and raise the serum uric acid level while doses over 5 gm/d have the opposite effect. Pharmacologic actions of interest include 1) uncoupling of oxidative phosphorylation, resulting in a compensatory increase in oxygen uptake; 2) increase in aerobic metabolism of glucose and glucose-6-phosphotase activity; 3) reduction of synthesis of prostaglandins by prostaglandin synthetase inhibition (11,12).

SALICYLATES AND PARA-AMINOPHENOL



Acetaminophen **Phenacetin** **Aspirin**

B. Para-aminophenol Derivatives: Acetaminophen (paracetemol) and Phenacetin (Fig.1).

These drugs were first used in medicine around 1890. Acetaminophen became the more widely used of the two after 1949, when it was recognized as the major active metabolite of phenacetin. This class of drug has the same antipyretic and analgesic protential as aspirin but has

only weak anti-inflammatory properties compared to aspirin. Phenacetin, is rapidly metabolized to acetaminophen which is then further metabolized and excreted primarily (80%) in the urine (13,14). While acetaminophen is weaker than aspirin in inhibiting prostaglandin synthesis in most tissues, it is 4 1/2 times as potent in renal prostaglandin synthetase inhibition (15). Phenacetin, in particular has abuse potential because it is said to produce relaxation, euphoria and increased efficiency (16). Phenacetin is not generally available to the public at present. Most over-the-counter analgesics now contain aspirin, acetaminophen or both, generally combined with caffeine. The composition of some commonly used analgesics is shown in Table 1 (17).

TABLE 1

Composition of Common Over The Counter Analgesics (mg/tablet)

	ACETAMINOPHEN	ASPIRIN	CAFFEINE
ANACIN	0	400	32
ANACIN-3-MAXIMUM STRENGTH	500	0	32
ANACIN MAXIMUM STRENGTH	0	500	32
BUFFERIN	0	325	0
BUFFERIN EXTRA	0	500	0
DOANS PILLS	0	325[1]	32
ARTHRITIS PAIN FORMULA[2]	0	500	0
ARTHRITIS PAIN FORMULA ASPIRIN FREE[2]	500	0	0
EXCEDRIN EXTRA STRENGTH	250	250	65
EXCEDRIN EXTRA STRENGTH PM[3]	500	0	0
TYLENOL	325	0	0
TYLENOL EXTRA STRENGTH	500	0	0
MIDOL[4]	0	454	32
VANQUISH	194	227	32
PAMPRIN[5]	325	0	0

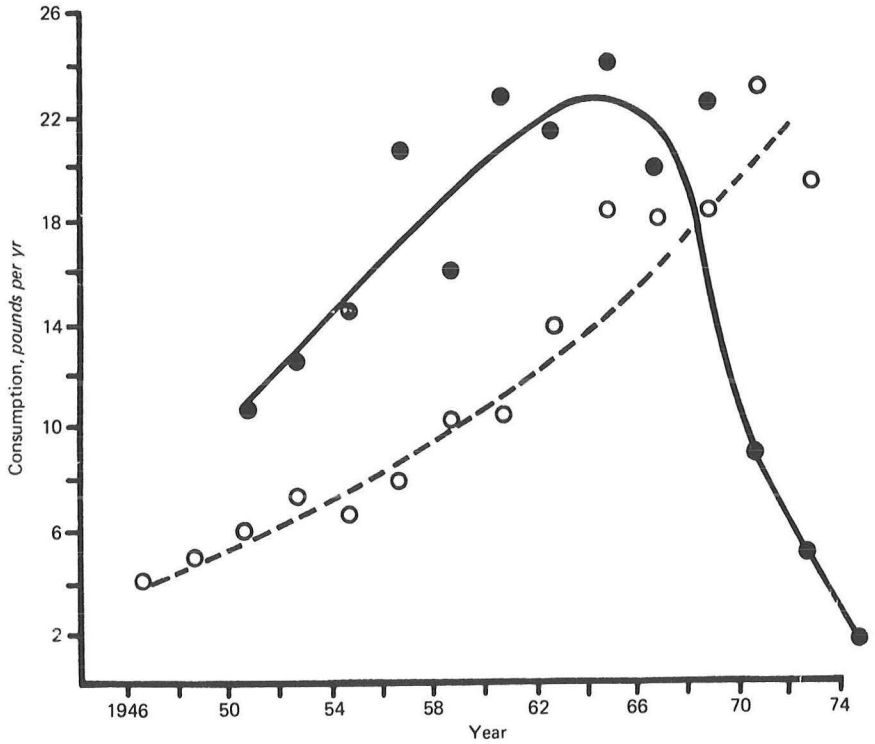
1
2. Magnesium Salicylate
3. Also contains magnesium hydroxide
4. Also contains pyrilamine
. Also contains cinnamedrine

3. INCIDENCE AND EPIDEMIOLOGY

One of the most striking aspects of analgesic nephropathy is the wide variation in geographical incidence of the disease. That this variation is real rather than an artifact related to the vagaries of medical reporting as documented by studies contrasting findings of papillary necrosis in only 0.2% autopsies at Johns Hopkins over a 15 year period with that of 3.7-20% of autopsies in Australian studies over a similar time period (18-19).

Because phenacetin was initially generally implicated as the etiologic agent of analgesic nephropathy in Canada, legislation was enacted resulting in a reduction in its use (20) (Fig. 2).

Analgesic nephropathy in Canada



[redacted] *Estimated Canadian consumption as indicated by two-year means for acetylsalicylic acid* [■, ■] *and phenacetin used by the pharmaceutical industry* [■, ■]. Canadian population increased from 12.3 million in 1946 to 22.4 million in 1974 [■, ■]. The *closed circles and solid line* (•—•) represents phenacetin × 10^4; the *open circles and broken line* (○---○) represent acetytsalicylic acid × 10^5.

This resulted in a subsequent reduction in the apparent incidence of analgesic nephropathy. In 1972, 5.5% of end stage renal disease was said to be related to analgesics (21) while in 1976 only 2.5% of Canadian dialysis patients were said to have analgesic nephropathy (22). Similar reductions in incidence in Scotland and Sweden were initially reported following withdrawal of phenacetin in these countries (23,24) but it is not clear that this reduction has been persistant.

Reports of analgesic nephropathy in the United States were initially slow to surface but, by 1975 numerous case reports began to appear. Murray and Goldberg reported that 20% of cases of chronic interstitial nephritis in Philadelphia were attributable to analgesic abuse. This corresponded to 7% of the cases of chronic renal disease reviewed in their series (25). A subsequent survey of United States nephrologists by the same authors confirmed that 20% of interstitial nephritis throughout the United States is due to analgesic nephropathy but that the incidence in the Southeast is almost twice the national figure (26). It is of interest that this association with warmer climates was also found in Australia, where the disease is much more frequent in the summer and in the warmer states of Queensland and New South Wales than in Victoria (27,28).

In Switzerland where analgesic nephropathy was first recognized, the autopsy incidence of papillary necrosis associated with chronic interstitial nephritis has remained at 1% over 21 years (29), despite a reduction in the use of phenacetin. However, analgesic nephropathy is apparently a problem of major proportion in Australia. As noted above, papillary necrosis is found in up to 20% of autopsies in Australia. The

current estimate of the proportion of Australian patients with end stage renal disease in whom analgesics are the most likely etiology is also approximately 20-25% (30). Regarding the role of phenacetin the incidence of analgesic nephropathy was not reduced by substitution of salicylamide for phenacetin in abusers of "Vincents Powders" a popular Australian compound analgesic (28).

Gault et al. estimated the per capita consumption of phenacetin in a number of countries (Table 2) (31). Although phenacetin may not be the specific etiologic agent of the disease nor can one extrapolate the amount of analgesic consumed by any specific proportion of the population from these data, it suggests that there are country-to-country differences in public consumption of over-the-counter analgesics confirming the observed geographic variations of nephropathy. The estimated incidence of analgesic nephropathy in various countries is summarized in Table 3.

TABLE 2

Per Capita Consumption of Phenacetin

COUNTRY	g/yr
AUSTRALIA	40
SWEDEN	25
SWITZERLAND	22
SCOTLAND	12
USA	10
CANADA	6-7

TABLE 3

Incidence of Analgesic Nephropathy

COUNTRY	AUTOPSIES (%)	ESRD (% patients)
AUSTRALIA	3.7-20	25
SWITZERLAND	1	19.9
SWEDEN	-	10.0
USA	0.2	7.0
CANADA	-	3.5
UNITED KINGDOM	-	1.4

The reason for geographical variations even within countries such as the U.S. and Australia as well as the Australian seasonal variation remain obscure. It has been suggested that analgesics exert nephrotoxicity by attaining high concentrations in the renal medulla and that this is more likely to occur under conditions of "dehydration" in warmer climates. This is a plausible explanation, supported by various experimental studies (CF, Pathogenesis).

As noted below (cf Clinical Features) psychological factors may play an important role in causation of this disease, in so far as analgesics may be "abused" because of subjective perceptions that they provide relief from stress, depression, etc. In this wise, one may speculate that individuals in North America particularly U.S. have had readier access to non-analgesic tranquilizers (Valium remains the most widely prescribed drug in this country) while individuals in Australia have tended, over the years, to use mixtures containing caffeine (combined with analgesics) for this purpose.

The epidemiology issue becomes more complex when one notes that only a minority of individuals who regularly take analgesics develop renal disease (32). This variability may be explained by several unrelated factors. First, toxicity may be due to genetically determined differences in metabolism of these drugs as suggested by association with HLA-A3 (33). Second, the identity of the toxic analgesic or analgesic combinations is not quite clear (CF Pathogenesis). It is possible that various preparations may be contaminated by as yet, unrecognized toxic substances. Third, the frequency of urinary tract infections in many cases of analgesic nephropathy raises the possibility that analgesic toxicity occurs more frequently in the presence of some other pre-disposing physical factor such as bacteruria (cf Clinical Features). Fourth, it has been noted that patients who ingest large quantities of analgesics are very likely to either deny their use or minimize the amount actually taken (34-35). Fifth, it is unknown what effect the use of other substances such as coffee, nicotine etc. has on analgesic nephropathy. Thus, the precise relationship of analgesic ingestion to renal disease will be a difficult question to answer even in carefully designed epidemiologic studies in well-defined populations.

The amount of analgesic required to produce toxicity appears to be considerable. Burry in his series found that mean consumption was 9.8 kg over 13 years. The range in this study was 4.2-30 kg over 5-30 years (36). Another Australian study by Dawborn et al. found a consumption of 2-20 kg over a period of 4-44 years (37). Data derived from these and several other studies (35,38-40) (Table 4) suggests that toxicity is associated with a minimum ingestion of approximately 3 kg of analgesic over 5-15 years.

TABLE 4
Amount* and Duration* of Analgesic Consumption in Patients with Analgesic Nephropathy

SERIES	CUMULATIVE AMOUNT (KG)	DURATION (YRS)
GAULT	7 (2-44)	9 (5-15)
OLAFSSON	7 (4-20)	> 10
BURRY	10 (4-30)	13(5-30)
DAWBORN	6 (2-20)	8 (4-44)

* Mean of Series (Range)

4. PATHOLOGY AND RADIOLOGY

Subsequent to the initial description of Zollinger and Spuhler of chronic interstitial nephritis accompanied by papillary necrosis, considerable controversy arose regarding the cause and effect relationship of these two lesions. That is, does the papillary necrosis cause the interstitial disease or vice versa. Furthermore, it was questioned whether these lesions represented a new clinicopathological entity or whether they were ascribable to already known causes such as diabetes, obstruction etc.. A series of Scandinavian studies suggest that here was indeed an increase in the incidence of papillary necrosis unexplained by previously known causes (Table 5) (7,9,41).

Grossly, the kidneys are often reduced in size, but may be normal. Calcification of cut surfaces is often noted. Histological changes of this disorder are well described and have been divided into early, intermediate and advanced. Early:changes are confined to the inner medulla. Histologic abnormalities are patchy and consist of necrosis of interstitial cells, loops of Henle and capillaries. Intermediate: changes extend to the outer medulla. All elements are necrotic towards

TABLE 5

Relationship of Papillary Necrosis to Diabetes and Obstruction in Three Scandinavian Series

Author	Years Covered	Total No. of Cases of Papillary Necrosis	No. With Diabetes	No. With Chronic Obstruction of Urinary Tract	No. Without Diabetes or Obstruction
Harvald	1957-60	66	5	8	53 (80%)
Lindeneg	1956-58	42	0	1	41 (98%)
Hultengren	1949-59	103	4	6	93 (90%)

the papillary tip but the cortex is often normal suggesting that papillary necrosis causes the interstitial disease rather than vice versa. Advanced:papillary necrosis is total with formation of sinuses or even papillary detachment into the calyx. Extensive calcification may lead to bone formation related to un-detached dead papillae (29-42).

Cortical changes are variable. Extensive cortical thinning associated with scarring and extensive tubular atrophy is often seen and is characteristic of the disorder. Glomeruli may in some occasions appear entirely normal while in other cases they may be completely sclerotic.

It thus appears that the necrotic papilla, by some process, perhaps similar to that of obstructive atrophy is responsible for the cortical changes. Two mechanisms have been postulated. First, atrophy may be caused by interference with drainage by the collecting ducts. Alternatively, atrophy of cortical tubules may result from interruption of long loops of Henle. There is very little experimental data to support or refute either of these possibilities (43).

Radiologic characteristics of renal papillary necrosis are well described. The most characteristic finding is the "ring-sign", caused by the detached papilla dying in the contrast filled calyx (44). As mentioned above, medullary calcification may be noted. Sloughed papillae may also be seen obstructing the ureter. Figure 3 (without contrast) demonstrates that the detached papillae have become calcified while figure 4 with contrast medium reveals the characteristic ring-sign.

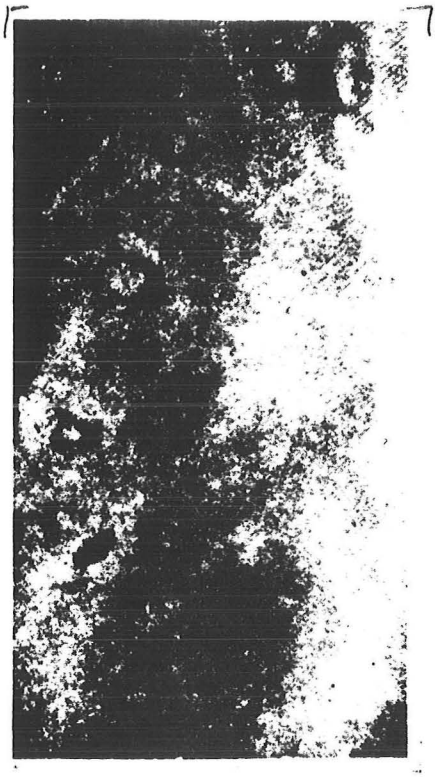


FIGURE 3

FIGURE 4

5. PATHOGENESIS

a. Experimental

Although phenacetin was initially widely regarded as the principal nephrotoxic analgesic, administration of this drug alone to rats has generally failed to produce significant renal lesions (45,46). In some studies doses as high as 1300 mg/kg/day for 51 days failed to induced nephrotoxicity (47) although isolated studies do report toxicity at extremely high doses (48). Similarly acetaminophen, when given alone, generally is not nephrotoxic in experimental animals (45,49,50). Salicylates have been reported to cause papillary necrosis in some studies (51,52). After a single oral dose Calder et al. produced papillary necrosis and acute cortical lesions by intravenous administration of 5 aminosalicylic acid (53). In other studies, even prolonged administration of salicylates has no effect (54).

Combining various agents does cause reproducible nephrotoxicity. Papillary necrosis is readily inducible in rats by giving a mixture of aspirin, phenacetin and caffeine (APC) at doses in the range of 500 mg/kg/day (55-57). Nanra et al. showed that the incidence of papillary necrosis in rats fed 500 mg/kg/day of aspirin was similar to the effect of APC 900 mg/kg/day (52). The incidence of lesions was increased by dehydration and decreased by diuresis. The protective effect of volume has been confirmed by others (58). One should note that the general health of rats given aspirin or APC at these dose levels was said by the authors to be "dreadful". To counter the objection that the industrial strength doses used far exceeded those used clinically the same authors reproduced these lesions with 200 mg/kg/day for 66 weeks (59).

In a study by Whitehouse, guinea pigs pretreated with aspirin 200 mg/kg/day had significantly higher serum levels of acetaminophen after being given a single 150 mg/kg dose of the latter drug. Excretion of acetaminophen by the kidney was reduced while hepatic metabolism was unaltered, suggesting that aspirin competes preferentially for the common anionic secretory mechanism in the renal tubule (60).

The results of a study by Molland comparing individual versus combined analgesic administration over 36-54 weeks in rats is shown in Table 6 (61).

Table 6

Analgesic Toxicity in Rat Kidneys

Drug	Dose	% with Lesions		
		Cortical	Papillary Necrosis	
	mg/kg/d		Intermed.	Total
Phenacetin	137	-	80	-
Phenacetin + Saline	231	-	20	-
Phenacetin, Aspirin + Saline	250+251	100	20	80
Acetaminophen	894	-	60	-
Aspirin and Acetaminophen	360+258	80	20	80

Indicated are the percent of rats that developed papillary necrosis either intermediate or total as well as the percent developing interstitial cortical lesions. The latter are noted only with total papillary necrosis.

This study exemplifies a general consensus that 1. phenacetin or acetaminophen, even in large doses, are only moderately nephrotoxic, when given alone. 2. Aspirin is relatively nephrotoxic when given alone but only at high dosage. 3. The toxicity of aspirin is substantially increased by combining it with either phenacetin or acetamenophen.

Caffeine, sometimes suggested as a possible nephrotoxin, generally causes a diuresis (62). When given with aspirin, it in fact protects against its harmful effects (63). One notes with interest that the addition of bicarbonate to a regimen of aspirin, 500 mg/kg/day reduces toxicity by half, perhaps explanable by the production of an alkaline urine resulting in decreased tubular reabsorption and increased excretion of salicylate (64).

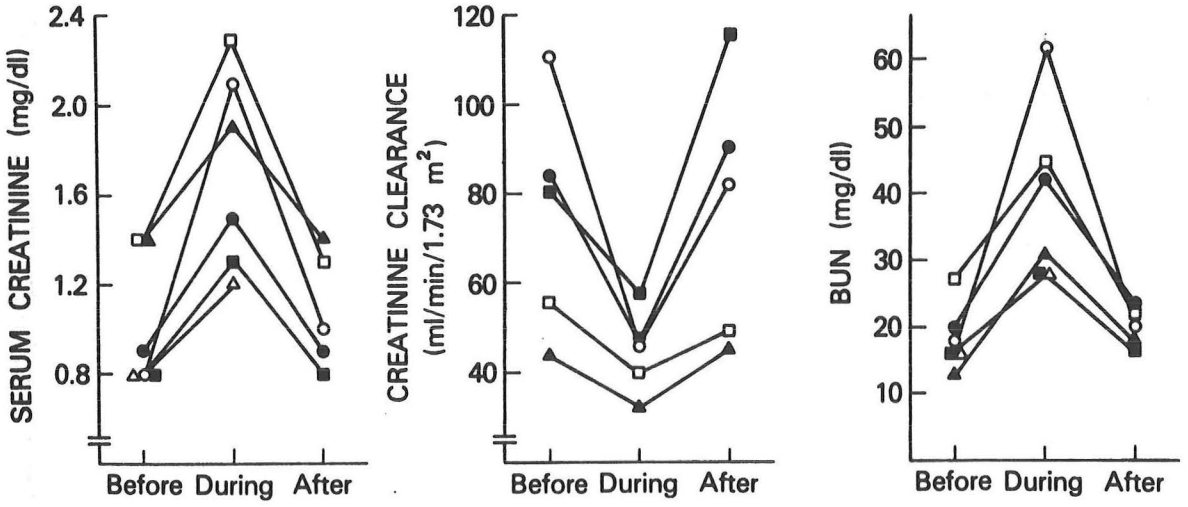
b. Clinical

Ingestion of aspirin has been known to cause shedding of white and red blood cells in the urine, almost since the turn of the century (65,66,67). Salicylates also result in N-acetyl-B glucosaminidase (NAG) enzymuria. NAG is excreted in the urine by renal tubular cells and is a sensitive but not specific indicator of renal injury. Proctor and Cunin have shown that doses of up to 2 gm do not cause significant NAG enzymuria while doses in excess of this amount do (68).

Berg has shown that in normal individuals short term administration of aspirin (5.5 gm/day) results in sodium retention, decreased urine volume and decreased tubular reabsorption of free water without affecting glomerular filtration rate (GFR) as estimated by the creatinine clearance. These effects are more pronounced when plasma renin activity (PRA) is elevated via sodium restriction (69). On the other hand, a number of studies have demonstrated significant reductions in GFR and renal plasma flow (RPF) by aspirin (70,71).

In patients with renal insufficiency sodium retention as well as a 54% decrease in GFR associated with a 66% decrease in RPF has been found (72,73). Kimberly and Plotz described significant reductions in GFR in

a group of patients with systemic lupus erythematosis and in patients with rheumatoid arthritis taking anti-inflammatory doses of aspirin (salicylate levels approximately 26 mg%). Figure 5 demonstrates acute declines in renal function associated with the ingestion of therapeutic doses of aspirin in these patients (74).



Changes in Renal-Function Measurements in Patients with Systemic Lupus Erythematosus during Aspirin Administration.

Six of 13 reactors are shown in detail. Each symbol denotes an individual patient. In all patients except the one designated with the open triangle the reversibility of the aspirin-induced effects was documented. For the sake of clarity, the other seven reactors are not included.

FIGURE 5

In a further study Kimberly and Plotz demonstrated that at doses resulting in serum salicylate levels of 30 mg%, aspirin caused a mean fall in GFR of 16% (baseline 82±0 ml/min) associated with a decrease in RPF of 29% (baseline 434±54 ml/min). These findings were correlated with a 45% reduction in urinary prostaglandin E_2 (PGE) excretion. The abnormalities were readily reversible when aspirin was stopped (75). It is important to note that the baseline urinary PGE was almost 50% greater than normal in these patients prior to the administration of aspirin. There is therefore, evidence that the most dramatic effects of aspirin on renal function are to be found in patients with underlying renal disease.

The results of a study by Muther and Bennet of renal function in normal volunteers after 7 days of aspirin ingestion (3.6 gm/day) are shown in Table 7.

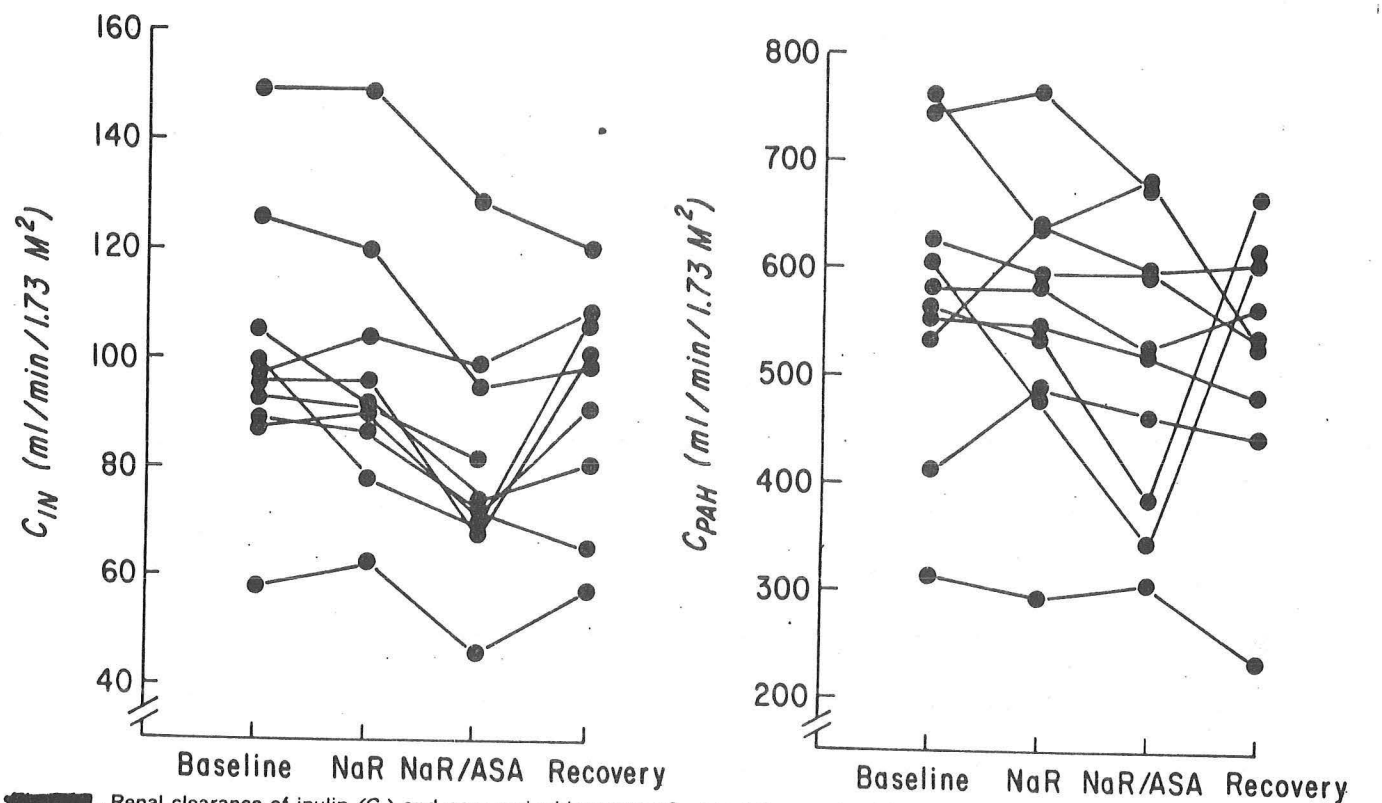
[redacted]. Creatinine and Inulin Clearances Before and After 1 Week of Oral Aspirin Therapy in Nine Normal Humans

Patient	Creatinine Clearance			Inulin Clearance		
	Before	After	Change	Before	After	Change
	← mL/min →					
1	114.5	109.0	−5.5	48.3	75.9	27.6
2	115.8	108.7	−7.1	108.5	83.7	−24.8
3	143.6	118.0	−25.6	145.6	122.4	−23.2
4	118.0	109.8	−8.2	107.5	117.8	10.3
5	115.9	121.9	6.0	104.6	86.0	−18.6
6	117.6	112.0	−5.6	94.0	107.0	13.0
7	167.5	145.3	−22.2	97.0	121.4	24.4
8	130.1	150.6	20.5	161.5	130.5	−31.0
9	78.9	78.7	−0.2	119.0	86.0	−33.0
Mean (±SEM)	122.4 ± 8.0	117.1 ± 7.1	−5.3 ± 10.6	109.6 ± 10.7	103.4 ± 6.8	−6.1 ± 18.9

TABLE 7

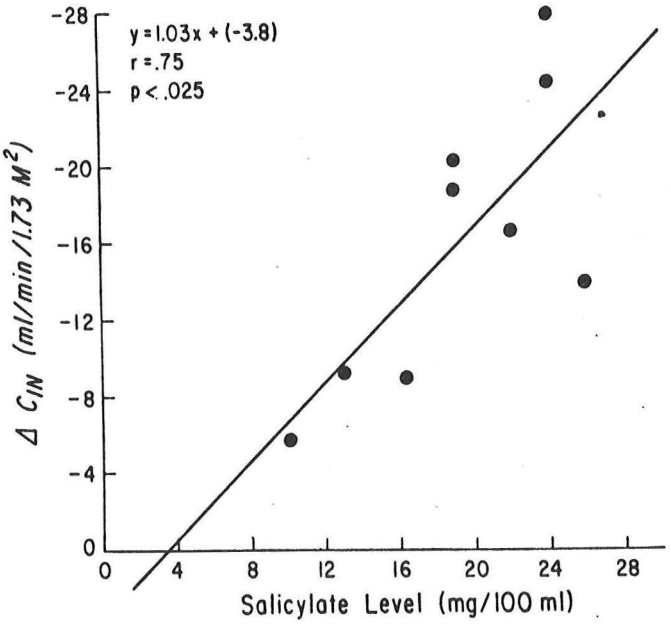
Although modest declines in both creatinine and inulin clearance were found they were not statistically significant (76). These authors and others (77) conclude that usually prescribed doses of aspirin do not alter GFR in healthy individuals and suggest that aspirin may have adverse effects on renal function only in situations where prostaglandins play a central role in maintenance of the GFR. A subsequent study by Muther and Bennet measured effect of aspirin on renal function in healthy volunteers during severe sodium restriction (78). The effects of sodium restriction alone and sodium restriction plus aspirin 3.6 gm/day for 4 days on GFR (inulin clearance) and RPF (PAH clearance) are shown in Fig. 6. Sodium restriction alone had no effect on renal func-

tion while the addition of aspirin resulted in a significant decline in GFR from a mean of 95 to 81 ml/min. The fall in GFR was linearly related to the salicylate level as shown in Fig. 7. There was no significant effect on RPF. These declines in renal function were associated with decreases in urinary PGE (relative to increased values secondary to the sodium restriction). The initial normal increase in plasma renin activity related to sodium restriction was uneffected by aspirin as shown in Fig. 8.



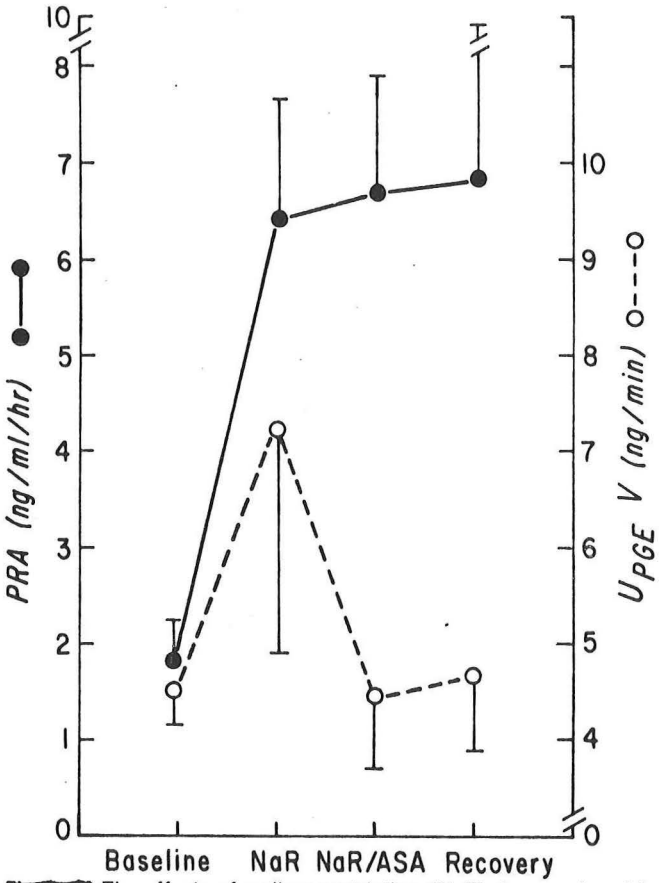
[redacted]. Renal clearance of inulin (C_{in}) and para-aminohippurate (C_{PAH}) in 10 normal subjects in the baseline period and after 5 days of sodium restriction *(NaR)* alone, sodium restriction and aspirin *(NaR/ASA)*, and recovery from aspirin.

FIGURE 6



[redacted]. Regression analysis shows a direct linear relation between the salicylate level and the fall (Δ) in inulin clearance (C_{in}) in sodium restricted, normal subjects taking aspirin.

FIGURE 7



[redacted] The effects of sodium restriction *(NaR)* alone and aspirin *(NaR/ASA)* on the plasma renin activity *(PRA)* and urinary prostaglandin E_2 ($U_{PGE_2}V$) in normal subjects.

A number of mechanisms for pathogenesis of analgesic nephropathy have been proposed. The consensus of opinion is that the first lesion in experimental analgesic nephropathy occurs in the long loops of Henle and the vasa recta, where high concentrations of drug may occur. In many of the above studies in animals maximum concentrating ability is lost before any detectable structural damage occurs (79).

A direct toxic effect on tubular epithelium is suggested by Clausen (80). Anoxia may play a role in the pathogenesis of this order. Anoxia may result from; a) reduction in blood flow by vasoconstriction, b) blood vessel oclusion by interstitial hyperplasia, c) platelet aggregation or d) changes in hemoglobin oxygen affinity. Because aspirin 900 mg/kg/day and acetaminophen 3000 mg/kg/day lower medullary blood flow in experimental animals (51), Kincaid Smith considered the lesion to be ischemic, demonstrating occlusive lesions in the vascular bundles of the outer medulla (81).

Endothelial necrosis and vascular obliteration have been reported in animals after a number of analgesics (52,82). Clausen has demonstrated increase in collagen around the vasa recta (80). Although platelet aggregates in the vasa recta have been reported by some authors (82) the known effect of aspirin in decreasing platelet aggregation and adhesion makes this mechanism implausible. Salicylate administration reduces erythrocyte 2-3 diphosphoglycerate in a dose related manner. This reduction increases the affinity of hemoglobin for oxygen thereby depriving tissues. Kravath et al have shown that salicylates increase venous oxygen saturation by 10-20% in rat and man (83).

Goldberg et al. suggest that the primary lesion is in the interstitium. They showed that aspirin (unlike acetaminophen) inhibits the hexose monphosphate shunt in the renal medulla. Since the main metabolic pathway of the inner medulla consists of anaerobic glucose metabolism this inhibition results in decreased amounts of reduced NADP (NADPH). NADPH normally protects against oxidative injury in the medulla (54). Like acetaminophen, aspirin also depletes cellular glutathione. Both of these effects leave the renal epithelia unprotected against electrophilic attack by chemically reactive intermediate metabolites. These may result from the action of a superoxide anion that generates a semiquinone radical from a quinol metabolite of salicylate.

The recognition that prostaglandins are of considerable importance in the physiology of the kidney has raised the possibility that analgesics exert toxicity via their effects on these vasoregulatory hormones. Prostaglandin PGE_2 is synthesized in the renal medulla and has been said to regulate resting renal blood flow (84). Production of PGE_2

is increased by stimuli which reduce renal blood flow, resulting in partial reversal of the initial reduction (85). Aspirin is a potent inhibitor of prostaglandin synthetase (86) (cyclo-oxygenase), and this effect has been shown to occur at plasma salicylate levels below the peak levels attained after therapeutic dosage in man (87). The recently noted association of papillary necrosis related to other analgesics, the non-steroidal anti-inflammatory agents, notable for their inhibition of protaglandin synthesis strengthens this argument. Nevertheless, it remains unclear why aspirin alone is insufficient to cause clinically significant papillary necrosis in man. For example, patients with rheumatoid arthritis treated almost exclusively with aspirin rather than compound analgesics rarely develop renal failure despite an autopsy incidence of papillary necrosis of roughly 40% (88,89).

It appears that the pathogenesis of analgesic nephropathy is a result of the multiple variables and mechanisms noted above. No single drug or mechanism can account for the clinical disorder.

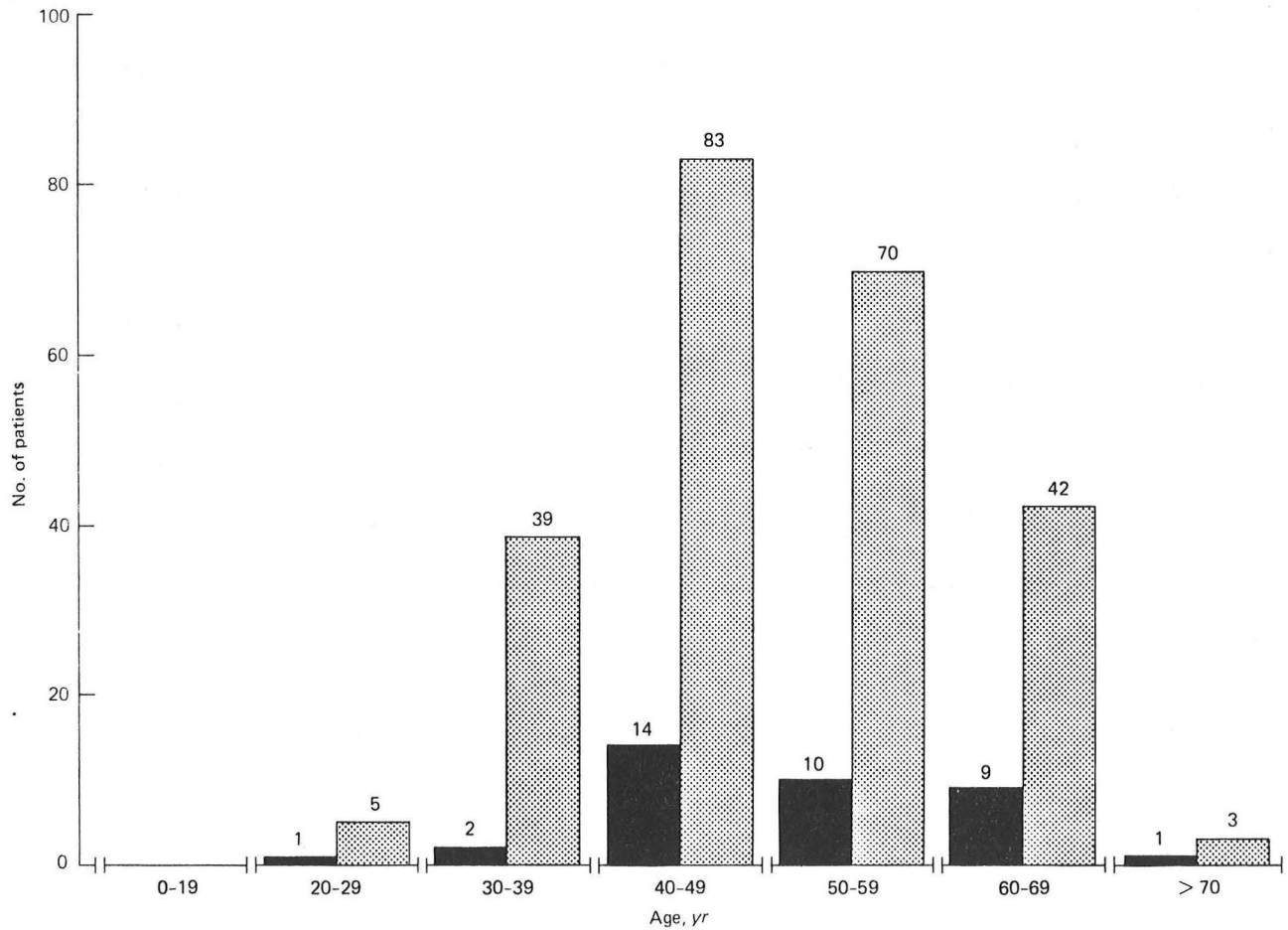
6. Clinical Features

The vast majority of patients who develop analgesic nephropathy abuse compound rather than individual analgesics. It is partially for this reason that there is little information regarding the abuse of single analgesic agents.

The clinical syndrome associated with abuse of analgesic mixtures is reasonably well defined. The six ratio is female/male 5-15/1 (19, 38,90) with peak incidence in the fifth decade. Figure 9 illustrates the age and sex distribution of 279 patients with analgesic nephropathy in Australia (91).

Gastrointestinal complications occur in more than half the patients and peptic ulceration has been reported in up to 35% of patients (37, 92). Anemia related to gastrointestinal blood loss and chronic renal failure is a feature found in 60-90% of these individuals (38,92).

Psychological and psychiatric disturbances are common in analgesic abusers. Headaches are reported by over 90% of these individuals. They frequently demonstrate associated addictive behaviour such as tobacco, laxative, hypnotic and alcohol abuse (93). Several studies recognize an addictive syndrome and cessation of analgesics may result in bizzare withdrawal symptoms (94,95). Pigmentation is a feature of analgesic abuse, due to the 3-amino-7-ethoxy-phenazone metabolite of phenacetin. These patients often present a physiognomy which appears older than their chronological age. This may be aggravated by the onset of renal failure.



A number of experimental and clinical studies suggest that analgesic abuse may be incriminated in a number of possible gonadal and pregnancy-related effects, including post-maturity, toxemia, teratogenicity congenital malformations and infertility (96-98).

Patients with analgesic nephropathy have predominantly tubulomedullary dysfunction characterized by impaired concentrating and acidifying capacity associated with sodium loss (99-102). These abnormalities are responsible for a number of common clinical manifestations of nephropathy including nocturia, polyuria medullary calcification, and renal stones.

Other factors contribute to renal calculus formation in these individuals, such as necrotic papillae, exfoliation of renal tubular cells, urinary tract obstruction and infections by urea splitting organisms such as proteus (22,99, 103). Urinary tract infections are said to occur in 15-60% of patients (104).

Sterile pyuria is frequently observed and may be related to either calculi, occult infection or epithelial celluria.

Persistent microscopic hematuria is an important clue to possible transitional cell carcinoma (see below).

The evolution of these findings was demonstrated by DuBach et al. A 5 year prospective study of 1000 women in Switzerland revealed that an initially normal but subsequently elevated creatinine, impaired urinary concentrating mechanism and bacteruria was significantly more frequent in women who took phenacetin containing analgesics regularly as shown in Table 8 (105).

TABLE 8
Incidence Of Renal Functional Normalities At 5 Year Follow-up

	Controls (percent of cohort)	Phenacetin Users	P
Decreased urine specific gravity	5.3	25.5	<0.0001
Increased serum creatinine	0.8	9.7	<0.001
Bacteriuria	3.3	8.4	0.004
Proteinuria	1.1	2.3	NS
Hematuria	2.4	1.8	NS

The reported incidence of hypertension associated with analgesic nephropathy varies from 15-70% (22,31,37,106). The occurance of significant hypertension in a primarily interstitial disease in which clinical salt and water depletion is common is of interest. Depletion of medullary vasodilator substances has been invoked as a mechanism (106). Clinical gout occurs in 4.6% of patients with normal function and in 26.5% of those with renal insufficiency (107).

Mortality in these individuals once they develop end-stage-renal failure seems to be much greater than for other age matched dialysis patients (21,96).

It has been demonstrated in a number of studies that cessation of analgesics results in improvement or stabilization of renal function (22,26). Figure 10 shows long term follow-up in a series of patients who either ceased or continued analgesic abuse after the diagnosis of renal disease was made (26).

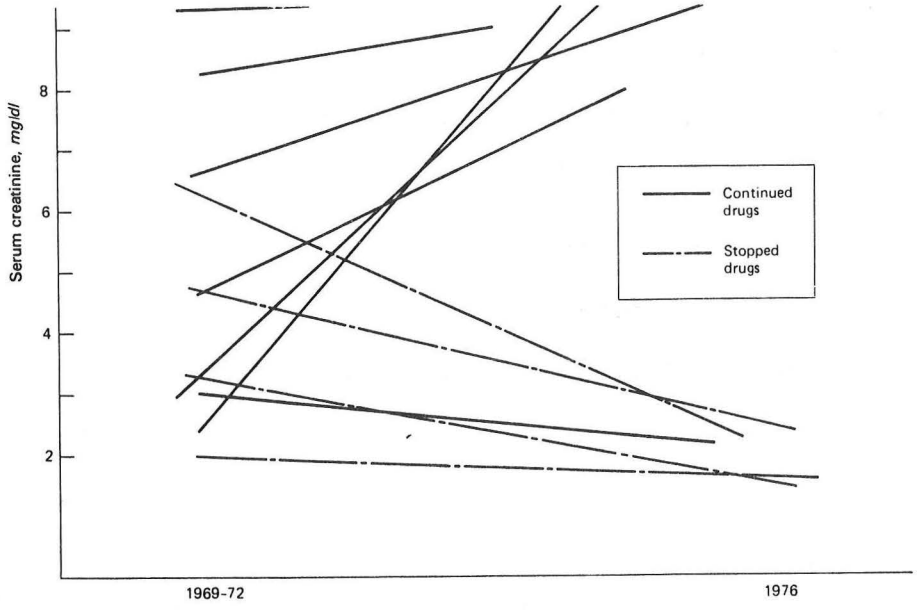


Table 9 summarizes the clinical features of analgesic nephropathy.

TABLE 9

Spectrum of Clinical Features in Patients with Analgesic Abuse Nephropathy from Various Series

FEATURE	SURVEY OF LITERATURE	PATIENTS FROM THE U.S.
AGE	29-72 yr	32-66
FEMALES	50-80%	72-85%
HEADACHE	35-100%	80-85%
ANEMIA	60-90%	65-80%
GASTROINTESTINAL SYMPTOMS	40-60%	40-55%
HYPERTENSION	15-70%	45-50%
URINARY TRACT INFECTION	30-60%	15-60%
ABNORMAL UROGRAM	85-95%	70-95%
PAPILLARY NECROSIS	25-85%	25-40%
PYURIA	50-100%	70-95%

B. Acute Renal Failure

This section deals primarily with the syndrome associated with overdosage, usually deliberate, with large amounts of acetaminophen.

Pathophysiology

Acetaminophen can induce renal failure in experimental animals. Mitchell et al. observed acute necrosis of the inner cortex in rats given acetaminophen (3000 mg/kg) (108).

A number of mechanisms have been postulated. Wilkinson et al. queried whether in fact the hepatic failure generally associated with acetaminophen overdosage was the factor determining renal failure. They observed that in a series of 167 patients with fulminant hepatic failure the incidence of renal failure associated with acetaminophen overdosage was no greater than in those with hepatic failure due to other causes (109). Contradictory findings are reported by Mitchell et al., who

observed azotemia associated with acetaminophen overdosage in the absence of evidence of severe hepatic injury (110).

It is known that the hepatotoxicity of acetaminophen is due to activation of the drug to an arylating metabolite (108). A chemically reactive intermediate, N-hydroxy-acetaminophen is felt to be the toxic metabolite. At ordinary therapeutic concentrations of acetaminophen, this metabolite is bound to glutathione. At high doses of acetaminophen, glutathione rapidly becomes depleted and the reactive metabolite may then bind to cellular proteins causing cell death (111). Studies in the isolated perfused rat kidney support this hypothesis. With toxic doses, the pattern of urinary metabolite excretion changes dramatically. As the plasma level of acetaminophen increases, the proportion excreted as the glucuronide and sulfate conjugate (the primary metabolites at therapeutic levels) becomes limited whereas the excretion of cysteine and mercapturic acid (of which N-hydroxy-acetaminophen is an intermediate metabolite) conjugates increases (112,113). The kidney has been shown to have the capacity to produce these potentially toxic metabolites (114). The cytochrome P450 oxygenase system controls the microsomal oxidation of drugs in the kidney. Further evidence for the above mechanism of acute acetaminophen toxicity is revealed in studies that demonstrate a decrease in both hepato and nephrotoxicity by cobalt chloride, which inhibits the cytochrome P450 system (115). Furthermore, in rats, pretreatment with cysteine, which increases glutathione, decreases acetaminophen toxicity while depletion of glutathiane by diethylmaleate potentiates nephrotoxicity (110).

Wilkinson et al., describe elevated plasma renin activity preceding renal failure associated with acetaminophen dosage. They suggest that renal failure results from inhibition of prostaglandin synthetase in a circumstance (compromised vascular volume) where prostaglandins are crucial to maintenance of function (116).

The pathological lesions described in patients with this disorder is acute tubular necrosis.

Clinical Features:

Acute acetaminophen nephrotoxicity is generally seen accompanying severe hepatic failure, although, as noted above, azotemia can occur without significant hepatic injury. Most cases reported result from ingestion of 5 gm or more of acetaminophen. The clinical picture is that of acute tubular necrosis. A BUN that is low relative to serum creatinine, related to severe hepatic necrosis is usually a poor prognostic sign.

C. Malignancies

The first observations of a relationship between analgesic abuse and transitional cell carcinoma came from Sweden in 1965. Hultgengren et al., described urothelial renal pelvic tumors in six patients who had abused analgesics (117). In 1968, Bengtsson et al., reported on the development of such tumors in 9 of 104 patients with analgesic nephropathy. Two other patients in this series later developed transitional cell bladder tumors, an incidence of malignancy of 11%. All these patients had abused phenacetin, phenazone and caffeine (118), abuse

defined as consumption of 1 gram of phenacetin daily for at least three years. In a third series, review of 29 patients with epithelial renal pelvic cancers revealed that 14 (47%) had abused analgesics. The non-abusers were predominantly elderly men with prostatic hyperplasia while the abusers were primarily younger women (119). Blohme and Johansson found transitional cell carcinoma in 4/84 patients with analgesic nephritis and atypical urothelium in 50% of the total group (120). The total incidence of transitional cell tumors of the renal pelvis in Sweden is 1/156,000 inhabitants. It is predominantly a male disease (male/female - 4/1). Thus the incidence of these malignancies in patients with analgesic abuse is much higher than that noted in the general population (121).

Johansson et al found gross hematuria in 75% of these patients. Microscopic hematuria was noted in an additional 14% of patients. One fourth of the patients had gross hematuria and/or acute pyelonephritis 5-17 years prior to diagnosis of tumor (122).

Most patients had impaired renal function. A history of urinary tract infection was found in 64% of these patients. 92% of patients had papillary necrosis. On average, the consumption of analgesics was 9 kg over 17 years. The duration from initiation of analgesics to discovery of malignancy was about 22 years.

The prognosis seems to be poorer in urothelial malignancies in analgesic abusers than non-abusers and the 5 year survival is half that of non-abusers, possibly related to the high frequency of renal insufficiency in these individuals. Multiple tumors are common, and 35% of the patients had bilateral tumors. Distant metastases were found at autopsy

in 43% of these patients (119). The characteristics of transitional cell carcinoma in analgesic abusers and non-abusers is shown in Table 10.

TABLE 10
Characteristics of Transitional Cell Carcinoma With and Without Analgesic Abuse

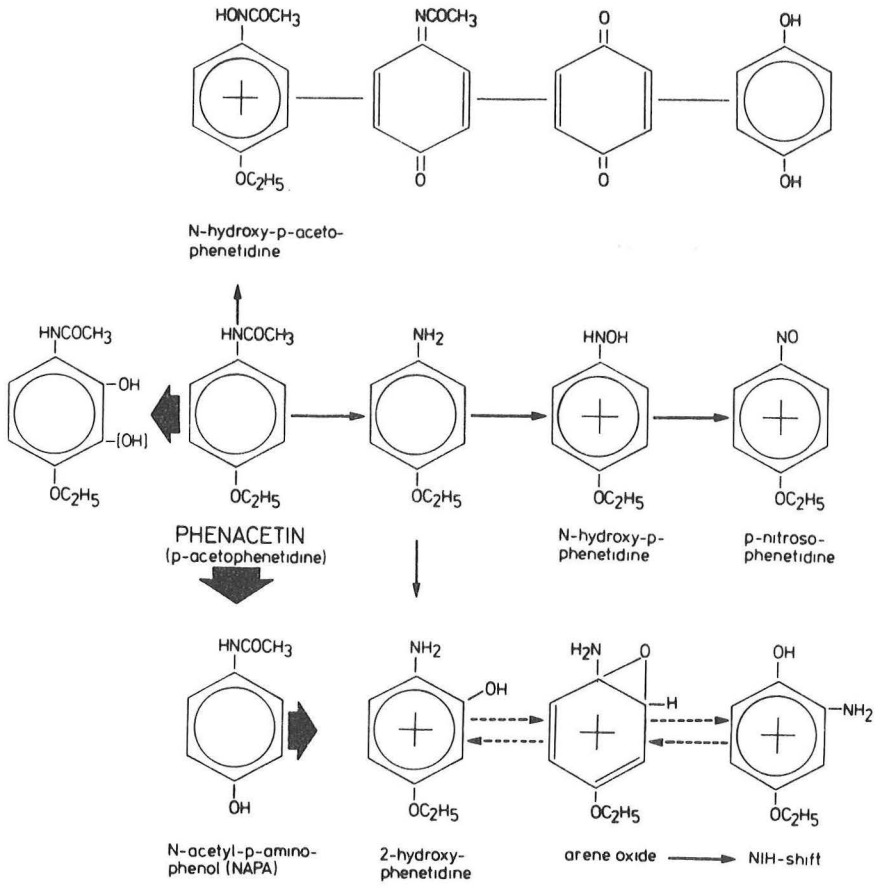
	WITH	WITHOUT
FEMALE %	66	28
AGE AT ONSET	57	67
MORTALITY (person years/1000)	228	56
BLADDER TUMORS (%)	50	98
RENAL PELVIC TUMORS (%)	50	2

Although the bulk of the literature regarding malignancies of the urinary tract in analgesic abuse derives from other countries (117-127) the association is also found in the U.S. (128,129). Gonwa et al., reported on the association of analgesic abuse in a population of 109 patients with transitional cell carcinoma (128). As reported by others, the analgesic abusers had consumed 18 gm on average, of phenacetin over 26 years. The female to male ratio was 2/1 as compared to 3/8 in non-abusers. 66% of the abusers had papillary necrosis on pyelography. The analgesic abusers mean age was 10 years younger than the non-abusers. In a prospective survey of a group of 146 patients with interstitial nephritis followed for 5 years, the etiology was determined to the analgesic abuse in 48. 4 of the 48 developed transitional cell carcinoma while non of the 98 non-abusers developed malignancies (128). Table 11 outlines the important clinical features of these patients.

TABLE 11
Clinical Features of Transitional Cell
Renal Pelvic Tumors in Analgesic Abusers

FEMALE	66%
GROSS HEMATURIA	75%
MICROSCOPIC OR GROSS HEMATURIA	89%
RENAL INSUFFICIENCY	80%
URINARY TRACT INFECTION	64%
PAPILLARY NECROSIS	92%
AMOUNT OF ANALGESIC	9 kg
DURATION OF ANALGESICS	17 yrs
* INDUCTION TIME	22 yrs

* Time from onset of use to discovery of tumor



The carcinogenicity of phenacetin is felt to be related to its N-hydroxylated metabolites, which are closely related to known carcino-

genic amines, such as the naphthylamines, known to be associated with bladder cancers (123,124) (Fig. 11). N-hydroxyphenacetin has been shown to induce hepatomas in rats (125).

III. Non-Steroidal Anti-Inflammatory Drugs (NSAID)

A. GENERAL

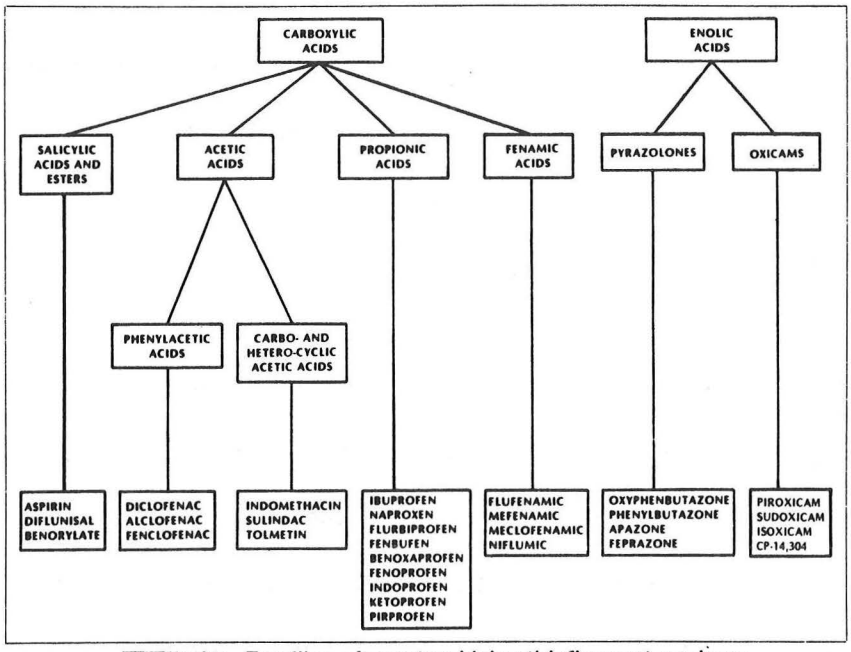
The problem of anti-inflammatory drug toxicity is brought into perspective when one recognizes that 20-40 million people in the United States suffer from various rheumatologic diseases (130). The number of drugs, particularly the NSAID, available for treatment of rheumatologic conditions has increased rapidly in the last decade (Motrin is the fourth most widely prescribed drug in the U.S.) with a promise of an even wider choice in this decade (131). Although initial experimental studies and clinical trials suggested little nephrotoxicity (132-134), as has been the case with almost all drugs, increasing clinical experience reveals that the NSAID are a mixed blessing. Initial enthusiasm abates as the clinical toxicity of these agents becomes apparent.

Parenthetically, I would state that all new drugs are subjected to exhaustive animal testing prior to clinical use. This type of testing, although valuable, often fails to identify subsequent toxic effects in humans. The failure of experimental testing to predict human nephrotoxicity of the NSAID can be explained by several factors. One, human disease is often treated chronically while, animal studies are generally acute and limited in species. More information would be gained from chronic studies in a broader spectrum of species but this is time-consuming and expensive. Second, experiments are often performed in gene-

tically similar or identical animal strains, while human susceptibility to toxicity may be extremely variable, explanable in part by genetic heterogeneity. Third, laboratory animals are subject to controlled conditions. Factors such as tobacco, and alcohol abuse, use of additional drugs, etc. by humans cannot be evaluated in animals. Fourth, many drugs exhibit organ-specific toxicity and this varies from species to species. The rat is a widely used experimental animal but is a poor choice because the rat kidney is extremely resistant to insults such as ischemia, anoxia and drug toxicity. The point to be made is that adding new drugs to one's armamentarium should be accompanied by a high degree of awareness that unanticipated side effects may occur.

B. PHARMACOLOGY AND RENAL EFFECTS

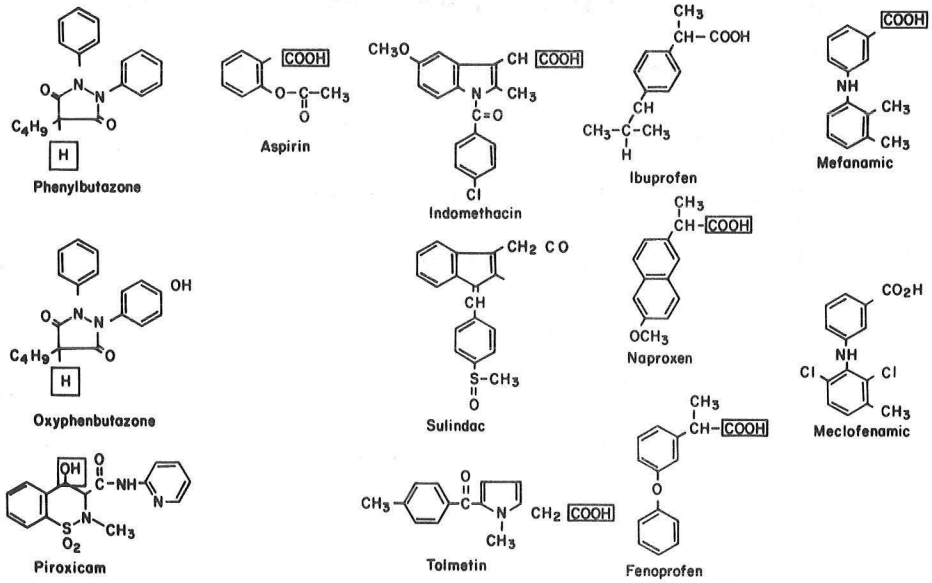
Figure 12 demonstrates the various families of NSAID and Fig. 13 indicates the structures of those more widely used clinically in the U.S. The following discussion reviews these drugs in order of their introduction to clinical use.



[redacted] *Families of nonsteroidal anti-inflammatory drugs.*

FIGURE 12

FAMILIES OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS				
ENOLIC ACIDS	CARBOXYLIC ACIDS			
Pyrazolones	Salicylic Acids	Carbo-Hetero Cyclic Acetic Acids	Propionic Acids	Fenamic Acids



1. Pyrazalones

Phenylbutazone (Butazolidin) (PBZ)

a). Pharmacology

PBZ is a potent prostaglandin synthetase inhibitor. PBZ was introduced into use as a therapeutic agent for rheumatoid arthritis in 1949 (135). This drug is, in general, tolerated poorly by patients, primarily because of a high incidence of gastrointestinal side effects as well as frequent blood disorders. These complications have limited the use of this drug. The structure of PBZ is shown in Figure 13. It is a congener of antipryine and is a pyrazalone derivative. It's primary metabolite is oxyphenbutazone which shares the properties of the parent drug. Metabolites are slowly excreted in the urine because they are highly protein bound limiting filtration and have a high PKa, favoring reabsorption in the distal tubule (136). It also has a uricosuric effect by inhibition of tubular uric acid reabsorption.

b). Experimental

Rats given PBZ exhibit a rapid fall in sodium excretion and free water clearance. In addition, a rise in the corticomedullary concentration gradient is noted (137-140). Williamson et al demonstrated that intravenous administration of PBZ to anesthesized dogs resulted in a 20% fall in renal blood flow (RBF). A 12% fall in GFR as well as a 33% reduction in sodium excretion were also noted. Associated with these renal functional changes was a 75% fall in urinary PGE (Table 12) (141).

Effect of phenylbutazone (2 mg/kg i.v.) on renal function in anesthetized dogs[a]

	Control Period	Phenylbutazone Period	Difference ± S.E.
V (ml/min)	1.1	0.7	−0.4 ± 0.1[b]
$U_{Na}V$ (μEq/min)	144	91	−53 ± 11[b]
GFR (ml/min)	26	22	−4 ± 1.3[b]
RBF (ml/min)	299	245	−54 ± 9[b]
BP (mm Hg)	120	128	+8 ± 2[b]

[a] The mean values for the control and phenylbutazone periods are for 10 animals. Data for the control period are from the clearance period just before administration of phenylbutazone. Data for the phenylbutazone period are from the third clearance period (20–30 minutes) after administration of phenylbutazone.

[b] Significant difference, *t* test, paired comparison.

TABLE 12

A study by Feldman et al showed that PBZ competitively inhibits [^{3}H] aldosterone binding to mineralocorticoid receptors in vitro in homogenates of kidney slices. This effect was confirmed by binding studies in vivo. Furthermore, spirolactone antagonized the salt retaining effect of PBZ (142).

In addition to its effect on renal sodium excretion, PBZ has been shown to induce papillary necrosis in Wistar rats when given in doses of 400 mg/kg (143,144).

c). Clinical

PBZ has been reported to have at least six different adverse renal side effects in humans. Wilkinson et al documented that the sodium retaining effects of PBZ precipitated congestive heart failure in several patients, in the absence of an effect on GFR (145). Several reports indicate that precipitation of uric acid stones or urate crystals has been associated with PBZ (146,147). PBZ has also been noted to be associated with renal papillary necrosis (148,149). Allergic vasculitis (hypersensitivity angitis) has been reported (150). Numerous reports of acute allergic interstitial nephritis can be found in the literature (151-154). Finally, Greenstone, et al have recently reported 2 cases of nephrotic syndrome and biopsy proven glomerulonephritis with subendothelial and mesangial dense deposits (155). These associations are summarized in Table 13.

TABLE 13
Phenylbutazone-Associated Nephrotoxicity

1). Sodium retention and decreased RBF
2). Acute Uric Acid Nephropathy
3). Renal Papillary Necrosis
4). Hypersensitivity Vasculitis
5). Allergic Interstitial Nephritis
6). Acute Glomerulonephritis with subendothelial Deposits

Although the incidence of these various lesions appears to be low it is probably fortunate that this drug is not widely used.

2. Carbo-and Hetero-Cyclic Acetic Acids

Indomethacin (Indocin), Sulindac (Clinoril), Tolmetin (Tolectin).

Indomethacin (IND) is by far the most widely studied of the NSAID with regard to effect on renal function. Only limited data is available regarding the other two clinically used NSAID. Since, however, they are closely related to indomethacin, in terms of their pharmacologic properties, it is likely that they will share to some extent its toxicologic effects:

IND was the product of a laboratory search for a drug with anti-inflammatory properties. It was introduced into clinical use in 1963. The discovery by Vane in 1971 that IND was an inhibitor of prostaglandin synthetase has spawned a decade of remarkably vigorous study of the prostaglandins (PG) and their physiology (86). IND is widely used as a reference compound in numerous PG synthetase systems (see below).

a). Pharmacology

The structure of IND is shown in Figure 13. IND is antipyretic as well as anti-inflammatory. It is rapidly converted by the liver to inactive metabolites, which are slowly excreted in the urine due to a high degree of protein binding. Like salicylate, it uncouples oxidative phospharylation. It may have analgesic properties in addition to its anti-inflammatory effects (156,157). It is the most potent prostaglandin synthetase inhibitor clinically available that is of practical use.

b). Experimental Studies

A number of studies have demonstrated a decrease in RBF with IND (157-160). Administration of IND, 2 mg/kg, results in decreases in sodium excretion, GFR and RBF in anesthesized dogs as shown in Table 14 (141). In addition to causing salt retention it is said to be a competitive inhibitor of aldosterone in the kidney, as demonstrated by both in vitro and in vivo binding studies (158).

Comparison of dogs treated with indomethacin to dogs treated with indomethacin and phenylbutazone[a]

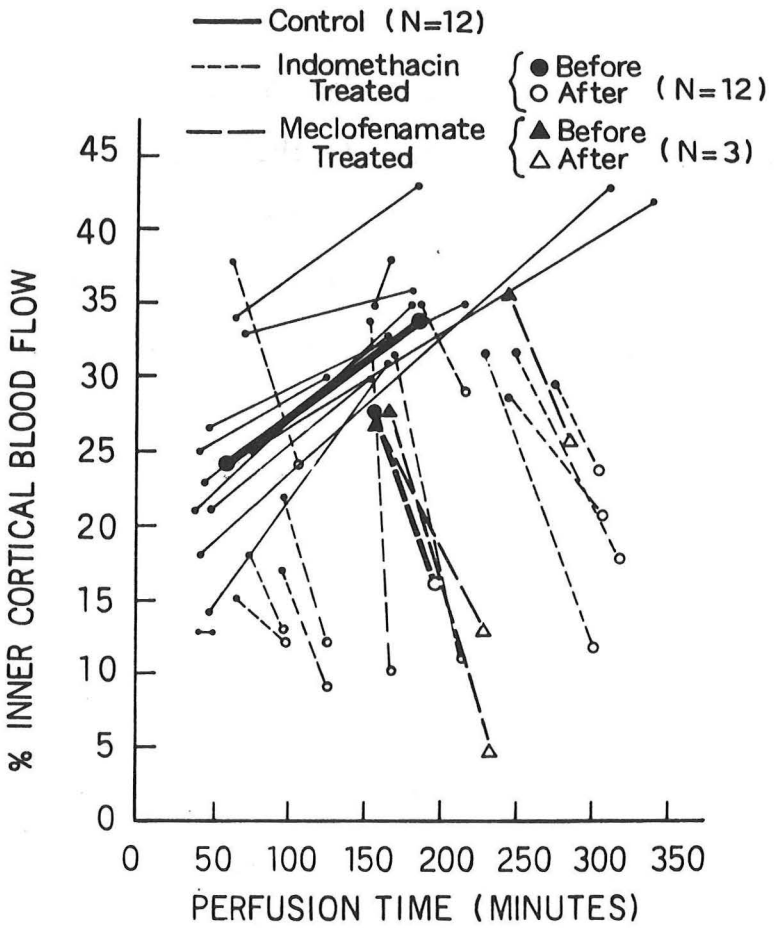
	Indomethacin Group			Indomethacin and Phenylbutazone Group		
	Control Period	Indomethacin Period	Difference	Control Period	Indomethacin + phenylbutazone period	Difference
V (ml/min)	1.5	1.3	−0.2 ± 0.2	1.3	1.0	−0.3 ± 0.2
$U_{Na}V$ (μEq/min)	288	189	−99 ± 23[b]	280	176	−104 ± 32[b]
GFR (ml/min)	40	34	−6 ± 2[b]	35	31	−4 ± 2
RBF (ml/min)	215	181	−34 ± 13[b]	250	210	−40 ± 17[b]
BP (mm Hg)	124	131	+7 ± 2[b]	121	128	+7 ± 3[b]

[a] Mean values are from two groups of animals, each of nine dogs. Values for control periods for both groups are from the clearance period just before administration of indomethacin. Indomethacin was then administered i.v. as two doses, each of 5 mg/kg, 20 minutes apart, to both groups. In the indomethacin and phenylbutazone group, phenylbutazone, 2 mg/kg, was given i.v. 40 minutes after the second dose of indomethacin. The second set of values are from the third clearance period (20-30 minutes) after administration of phenylbutazone. In the indomethacin group, the second set of values are from the comparable clearance period. No significant difference between groups were found (group *t* test).

[b] Significant difference, paired *t* test. (Comparison of control period values to treatment period values.)

TABLE 14

The salt retaining effects of IND are not blocked by spirolactone. McGiff et al, using the blood-perfused isolated canine kidney have shown that IND has a marked effect primarily on inner cortical blood flow (Fig. 14) (161). Other studies however report that IND has no effect on resting RBF in conscious animals (162,163). In rats with chronic unilateral partial ureteric occlusion, IND increased arteriolar resistance and decreased GFR (164).



Fractional distribution of inner cortical blood flow in isolated kidneys as affected by either indomethacin or meclofenamate. In any one experiment the distribution of cortical blood flow was measured twice at intervals ranging from 10 to 270 min by the radioactive microsphere method. The means for control and indomethacin-treated kidneys are shown by heavy uninterrupted and interrupted lines, respectively. Increased fractional blood flow to the inner zone of the cortex, which progresses with time, was reversed by addition of either indomethacin or meclofenamate.

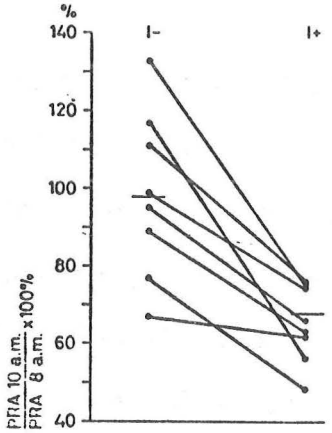
FIGURE 14

There is also no unanimity in the literature regarding the effect of IND on sodium and water excretion. Altsheler at al found a reduction in sodium excretion in dogs after IND (165), confirmed by other studies in rats (141,158,166). A number of other studies fail to detect any effect on sodium excretion (163,167-169). In-as-much as there are considerable differences in the design and methods of the various contradictory studies a conclusion regarding the effect of IND on sodium excretion in experimental animals cannot be made with certainty.

Arnold et al. demonstrated that IND causes papillary necrosis in rats at a dosage of 75 mg/kg (143). In their study, however the dose used caused gastric erosions of such a degree that many of the beasts were probably in hemorrhagic shock. Bokelman et al observed papillary necrosis at lower doses in chronic studies. Interestingly, the lesions occurred only in Manor Farms SPF rats and not in Charles River CD rats studied simultaneously (170).

Clinical Studies

IND, 150 mg/d for 3 days reversibly reduced GFR in normal volunteers who were sodium restricted (50 mg/d for 4 days). Although the GFR fell in all 8 subjects, (mean decline, 9 ml/min) effective renal plasma flow (ERFP) was unchanged. There was in addition a 50% reduction in sodium excretion associated with a change of similar magnitude in plasma renin activity (PRA). In the same study, the effect on PRA 2 hours after a 50 mg oral dose of IND was measured. Significant falls in PRA were noted in 7 of 8 subjects (171) shown in Fig. 15.



Percentual change in PRA 2 h after an oral dose of 50 mg indomethacin (I+) and without indomethacin (I−) ($p \leq 0.01$).

FIGURE 15

Donker et al also studied patients with a variety of renal diseases under the same conditions. In these individuals, a fall in ERPF was noted in addition to fall in GFR, sodium excretion and increase in PRA. Table 15 summarizes the findings of this study.

TABLE 15

Effect of Indomethacin on renal function in normal volunteers and patients with diseased kidneys

	GFR		ERPF		Na^+ Exr		PRA	
	C	IND	C	IND	C	IND	C	IND
NORMALS	100	91	396	385	43	21	942	341
RENAL DISEASE	66	50	235	193	56	29	260	144

C= Control
IND= Indomethacin 150 mg/day x 3 days

Other studies report no effect of IND on renal function in normal subjects despite sodium restriction (169,172).

Zusman et al demonstrated that IND 150 mg/d for 8 days had no effect on GFR in normal volunteers or on urinary sodium excretion and urine volume. Plasma cortisol and urine 17 hydroxy or keto steroid levels were unaffected by IND. Urinary aldosterone excretion was reduced by IND however. This was associated with a significant reduction in plasma renin activity as well as a significant fall in urinary PGE excretion. Administration of ACTH during IND resulted in a significant decline in free water clearance along with a significant elevation of urinary aldosterone as compared to IND alone, with no increase in PRA and no change in urinary PGE (173).

IND has been reported to have detrimental effects on renal function particularly in individuals with compromised circulating extracellular volume. Arisz et al reported that GFR decreased 35% and RBF decreased by 23% in 19 nephrotic patients given IND (174). These changes returned to normal abruptly on cessation of the drug. Interestingly, the proteinuria also decreased by 55% during IND administration. Zipser et al administered IND to 12 patients with severe hepatic disease and ascites. Urinary PGE_2 levels were increased prior to IND. GFR increased from 73 to 32 ml/min for the 12 patients. The patients with the most pronounced hyper-reninism exhibited the most marked falls in GFR (172). IND has also been reported to cause acute decompensation of renal function in patients with congestive heart failure (175). Walshe et al. observed oliguric acute renal failure (ARF) after IND administration to a woman in congestive heart failure. After recovery from ARF, urinary PGE_2 levels were measured and the patient was re-challenged with IND, and mild renal failure again ensued. Urinary PGE_2 excretion of 1068 ng (3 times normal) fell to 58 ng/24 hr during IND. Tan et al. report exacerbation of chronic renal failure in a patient with pyelonephritis given IND 150 mg/d. As shown in Table 16, urinary PGE_2 levels, initially elevated, fell during IND therapy, associated with renal failure and then returned to baseline or cessation of IND therapy (176).

Acute Deterioration of Renal Function Induced by Indomethacin*

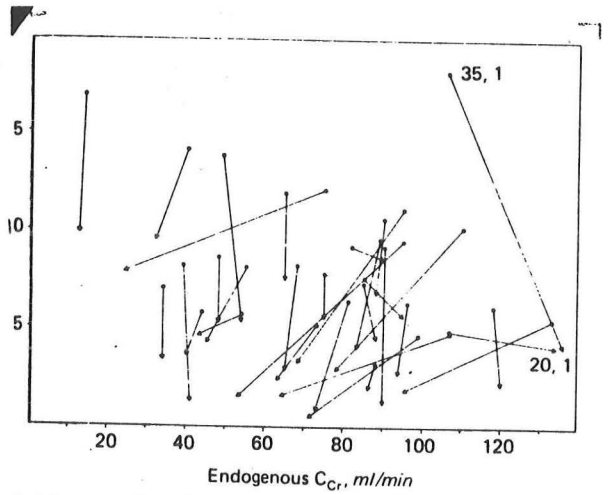
	Before Therapy	During Therapy		After Therapy†		
		Day 3	Day 5	Day 5	Day 17	Day 30
BUN, mg/dL	57	100	111	114	51	48
Creatinine, mg/dL	4.8	5.9	7.3	8.4	4.9	4.5
Creatinine clearance, mL/min	12	4.7	4.2	4	10	11
Urinary prostaglandin E_2, ng/24 hr	521	78	79	98	432	1,147

*Recovery of renal function was accompanied by a return of prostaglandin E_2 level to normal.
†A single hemodialysis treatment was instituted on the tenth day after the discontinuance of indomethacin therapy.

Other case reports of ARF abound in the literature. O'Meara and Eknoyan reported two cases of non-oliguric renal failure during IND. Both patients recovered normal renal function and discontinuation of IND (177). IND has been reported to exacerbate phenylbutazone induced renal failure (178) (not surprising!). Limited histologic evidence of renal failure is available. Gary et al. found interstitial nephritis with normal glomeruli in a 61 year old with oliguric IND-induced ARF (179). Estrup and Ho reported peripheral eosinophilia associated with IND-induced non-oliguric ARF, suggesting that IND may also cause an allergic type of interstitial nephritis, although no histologic evidence was available (180).

A study by Tiggeler et al. addressed the noted effect of IND in reducing proteinuria. They studied the effect of IND, 150 mg/d for 5 days on protein excretion and polyvinylpyrolidine (PVP) clearance (a measurement of glomerular permeability) in 33 nephrotic patients. The mean control 24 hr urinary protein excretion was 9.2 gms. This decreased to 4.6 gms/24 hrs after IND therapy. Sodium restriction did not alter this effect. GFR decreased by a mean of 11% but there was no correlation between reduction in GFR and reduction in protein excretion in individual patients, as shown in Fig. 16.

Glomerular selectively for protein as measured by transferrin, a_2-macroglobulin, albumin and 1_gG clearance was unaffected. PVP clearance was only moderately affected for molecules of 40A radius or greater. Clearance of smaller PVP molecules was not consistently affected. This study strongly suggests that the reduction of proteinuria by IND results from changes in GFR rather than by either anti-inflammatory effects or other direct effects on glomerular basement membrane permeability (181) (Fig. 17). Kleinnrecht et al. reported that IND was effective in reducing proteinuria in steroid resistant nil disease of childhood. They also observed, irreversible (in contrast to other clinical reports) renal failure in six of fifteen children treated with IND 1.5 mg/kg/d for more than 3 months (182).



1. *Absence of a relation between the effect of indomethacin ndogenous creatinine clearance and that on proteinuria.*

FIGURE 16

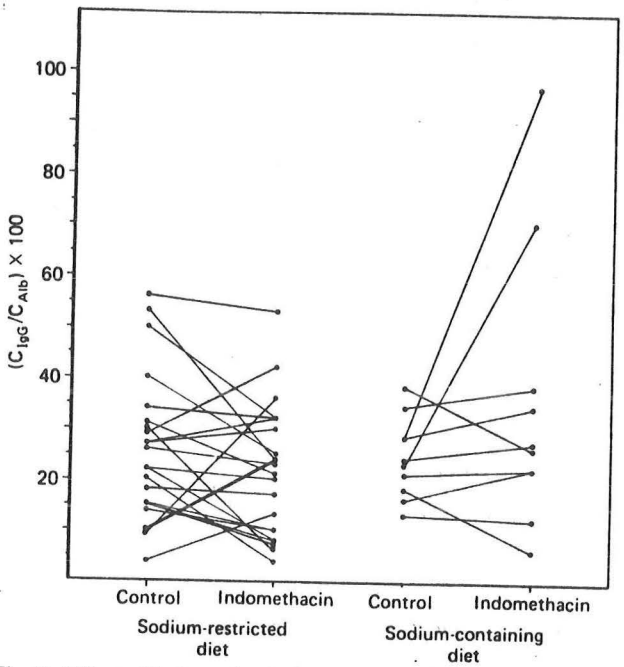


Fig. 2. *Effect of indomethacin on selectivity in 23 patients on a sodium-restricted and 10 on an unrestricted diet.*

FIGURE 17

One final aspect of IND induced renal disease deserves mention. A number of reports cite the occurrence of a syndrome of hyporeninemic hypoaldosteronism in some patients with or without attendant renal failure (182). Tan et al. demonstrated low PRA and plasma aldosterone associated with IND administration in one patient with chronic glomerulonephritis. PRA and aldosterone returned to normal after cessation of IND (183). Findling et al. reported 3 patients with hyperkalemia and renal insufficiency (184), while 5 similar cases were reported by Galler et al (185). Is is suggested that hyporeninemia results in these patients by inhibiting prostaglandin synthesis thereby removing potent stimulus to renin production (186). Papillary necrosis has also been reported in several patients with rheumatoid arthritis treated with IND for several years (187,188).

TABLE 17

Clinical Features of Indomethacin Induced Acute Renal Failure

Dosage > 100 mg/day for 10-180 days.
Oliguria Frequent
Hyperkalemia ± Hyporeninemic Hypoaldosteronism
Predisposing Factors Common
- Advanced Age
-Nephrotic Syndrome
-Congestive Heart Failure (Decreased ECF)
-Cirrhosis
-Underlying Renal Disease
Recovery Is The Rule

Sulindac is structurally similar to IND but is only half as potent as a PG synthetase inhibitor. Despite widespread use, little clinical toxicity has been reported. Lamvardias reported a biopsy documented case of nephrotic syndrome secondary to minimal change disease associated with an allergic reaction to Sulindac. Nephrotic syndrome promptly resolved upon discontinuation of sulindac (189).

Tolmetin, although structurally dissimilar from indomethacin, is also acetic acid derivative. It is about 1/10 as potent an anti-inflammatory agent as indomethacin. Tolmetin causes papillary necrosis and chronic interstitial nephritis in rats. It also reduces RBF in experimental animals (157-159).

Chatterjee has reported a case of nephrotic syndrom associated with Tolmetin 1200 mg/day for 1 1/2 years. Renal biopsy demonstrated marked interstitial nephritis. Nephrotic syndrome resolved after discontinuation of Tolmetin (190). Katz et al. described a case of oliguric interstitial nephritis associated with Tolmetin use. Their patient also regained normal renal function after discontinuation of Tolmetin (191).

3. Propionic Acids

Ibuprofen (Motrin), Fenoprofen (Nalfon), Naproxen (Naprosyn)

These drugs, all phenylpropionic acids were specifically designed as anti-inflammatory agents. Ibuprofen (IBU) was introduced to clinical use in 1974. The latter two, Fenoprofen (FEN) and Naproxen (NAP) have been available for use since 1975. All share similar pharmacologic properties.

A. Pharmacology

These drugs are highly bound to protein and are slowly excreted in the urine as inactive metabolites. They are potent prostaglandin synthetase inhibitors. (see below) (133). They have a much lower incidence of gastro-intestinal side effects than any of the other NSAID perhaps accounting for their rapid rise in use.

B. Experimental

Ibuprofen has been shown to lower GFR and RBF in experimental animals (157-159). IBU and FEN cause papillary necrosis in rats but only at lethal dosage (192). The phenylpropionic acids share with the other NSAID the ability to cause sodium and water retention but to a lesser degree (158). IBU and FEN are competitive aldosterone inhibitors in the kidney but Naproxen is not. In general, these drugs have little experimental nephrotoxicity compared to the other NSAID.

C. Clinical

IBU has been associated with renal papillary necrosis after long-term use (188,193). Husserl et al. reported papillary necrosis and pyelonephritis in a patient with SLE (194) resulting in chronic renal failure. Kimberly et al. demonstrated that IBU, FEN, and NAP all cause reductions in urinary PGE_2 in patients with systemic lupus (195).

A number of reports of IBU associated renal failure have appeared in the literature. Brandstetter and Mar reported oliguric renal failure with IBU, with normal recovery (196). Kimberly et al. reported biopsy documented IBU induced ARF. Histologic changes showed no evidence of drug toxicity and the ARF resolved promptly (197).

Allergic interstitial nephritis appears to be more common than other renal lesions with phenylpropionic acids. Brezin et al. described acute allergic interstitial nephritis in 3 individuals taking either FEN or NAP. All patients presented with nephrotic syndrome and acute renal failure. Fever, rash, and easinophilia were absent in all cases (198). A number of similar cases have been reported (199,200). Curt et

al. described allergic interstitial nephritis in a patient receiving FEN 2400 mg/day. Treatment with prednisone resulted in a gradual return to normal renal function (201). NAP has also been associated with hypersensitivity vasculitis (202).

4. Fenamic Acids

Mefanamic Acid, (Ponstel) Meclofenamate (Meclomen)

These are derivatives of anthranilic acid, the amine analog of salicylic acid. They are not widely used because of numerous side effects, especially diarrhea which can be severe.

A. Pharmacology

These drugs resemble the other NSAID in their high degree of protein binding. They are the most potent prostaglandin synthetase inhibitors clinically available (2-4 times as potent as indomethacin). They also act as prostaglandin antagonists.

B. Experimental

Meclofenamate reduces RBF and GFR in anesthesized animals (157-160, 203) but has little effect on these renal functional parameters in conscious animals (162,163), unless they are sodium depleted (204). They reduce renal sodium and water excretion as do the other NSAID (158,165,166). These drugs regularly cause papillary necrosis in rats (205,206).

C. Clinical

Relatively few reports regarding the human toxicity of these drugs are to be found, probably related to the infrequency of their use.

Robertson et al. reported non-oliguric renal failure with papillary necrosis secondary to mefanamic acid in 6 elderly patients. Volume depletion resulting from diarrhea caused by mefanamic acid appears to have been a pre-disposing factor. Two of the patients in this study developed renal insufficiency (207). Drury et al. reported a similar case of mefanamic acid induced non-oliguric ARF associated with vomiting and diarrhea (208).

Allergic type reactions have also been reported. Venning et al. described biopsy documented allergic interstitial nephritis associated with a rash in a patient taking mefanamic acid (209). Malik et al. described a case of severe vasculitis causing oliguric ARF and death following mefanamic acid (210).

The nephrotoxicity of the NSAID is summarized in Table 18.

TABLE 18

Renal Toxicity Associated with NSAID

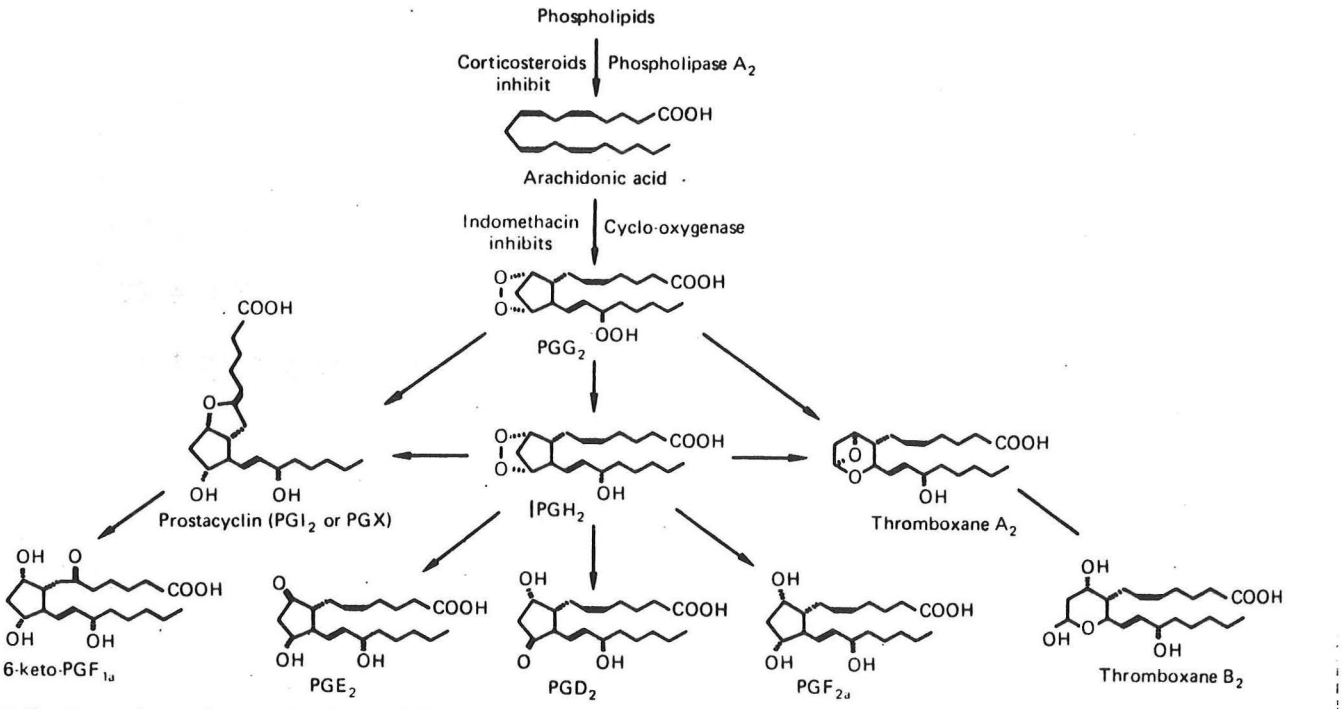
	SODIUM RETENTION	ATN	PAPILLARY NECROSIS	ALLERGIC INTERSTITIAL NEPHRITIS	HYPERSENSITIVITY VASCULITIS	ACUTE GLOMERULONEPHRITIS
PHENYLBUTAZONE	++++	-	+	++	+	+
INDOMETHACIN	++++	+	-	++	-	-
SULINDAC	-	-	-	±	-	±
TOLMETIN	-	-	-	+++	-	-
IBUPROFEN	+	+	+	+++	-	-
FENOPROFEN	-	-	-	++++	-	-
NAPROXEN	-	-	-	+++	+	-
MEFANAMIC ACID	-	++	++	++	±	-

+- Indicates frequency of type of toxicity relative to all types of nephrotoxicity reported for a given drug.

C. Prostaglandins and Renal Disease

The aforegoing has referred to the effect of analgesics on prostaglandin synthesis. What role do protaglandins play in normal renal function and how does interference with them result in renal disease?

The biosynthesis of prostaglandins is depicted in Fig. 18.



[redacted]. *Biosynthesis of prostaglandins and thromboxane.* **All of the products shown in this figure have been found in kidney or urine. Refer to the text for details.**

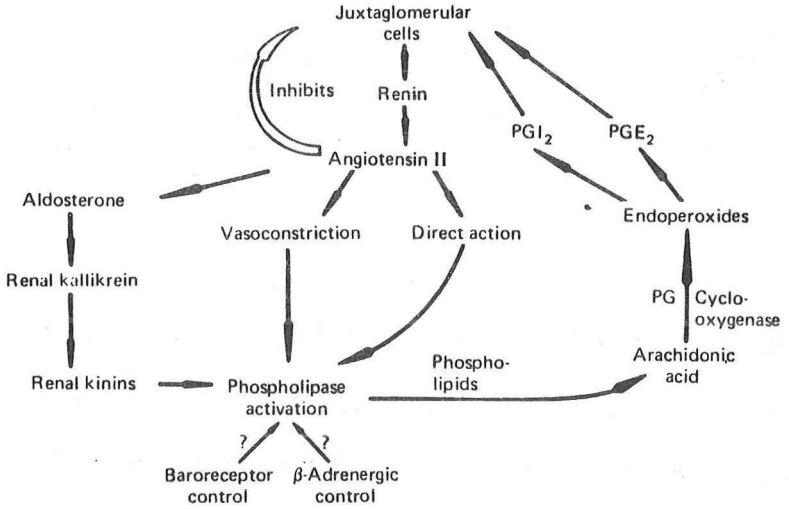
FIGURE 18

They are produced in the kidney from arachidonic acid, a 20 carbon fatty acid. The synthetic enzymes are collectively referred to as prostaglandin synthetase. Table 19 shows some of the components of PG synthetase and the PG formed by these enzymes (211).

TABLE 19
Components of PG Synthetase

ENZYME	PG FORMED
cyclo-oxygenase	PGG_2
endoperoxide isomerase	PGE_2
endoperoxide reductase	PGF_2a
prostacyclin synthetase	PGI_2
thromboxane synthetase	TXA_2

Prostaglandins are formed in both the medulla and the cortex although prostaglandin synthetase activity is 10-fold greater in the medulla. Prostaglandins are metabolized primarily in the renal cortex (212). The specific sites of PG synthesis are illustrated in Table 20. It can be noted that the primary PG product of the medullary structures is PGE_2 a potent vasodilator.



[redacted] *Prostaglandins and renin release.* This schema depicts our understanding of the literature on the subject of the renin-prostaglandin interaction. Other stimuli, besides those shown, do increase prostaglandin synthesis. The site at which baroreceptor and beta adrenergic receptor stimulation trigger prostaglandin synthesis is conjectural. Because indomethacin inhibits the cyclo-oxygenase enzyme, renin secretion is reduced in response to most stimuli.

FIGURE 19

TABLE 20

Renal sites of prostaglandin sythesis

TISSUE	PRODUCTS
Glomeruli	PGF_{2a} > PGE_2 > TxA_2 > PGI_2 > PGD_2
Arterioles	PGI_2
Cortical Tubules	Trace amounts of PGE_2 and PGF_{2a}
Collecting Tubules (papillary)	PGE_2 > PGI_2 > PGF_{2a} > PGD_2
Medullary interstitial cells	PGE_2 >> PGF_{2a}

As noted earlier, studies utilizing PG inhibition have shown no clear role for maintenance of basal RBF by PG. Rather, they appear to play a protective role in maintaining GFR in the face of vasoconstrictor stimuli. Our present understanding of the mechanism of prostaglandin homeostasis of renal function is depicted in Fig. 19.

The relative potency of the NSAID in inhibiting PG synthetase in sheep seminal vesicles SSV (a standard measure of anti-inflammatory activity as well as potency in rabbit kidney synthetase (RKS) activity is shown in Table 21. For comparison, relative sodium and water retaining properties of some NSAID is depicted in Table 22.

TABLE 21

Relative PG synthetase activity of NSAID

	ID_{50} μM	
	SSV	RKS
Indomethacin	0.5	3.7
Mefanamic Acid	0.6	-
Meclofenamate	0.7	1.3
Sulindac	1.0	-
Ibuprofen	1.5	5
Fenoprofen	3	-
Naproxen	6.1	-
Phenylbutazone	12.6	15
Acetaminophen	3900	625
Aspirin	10,000	2800

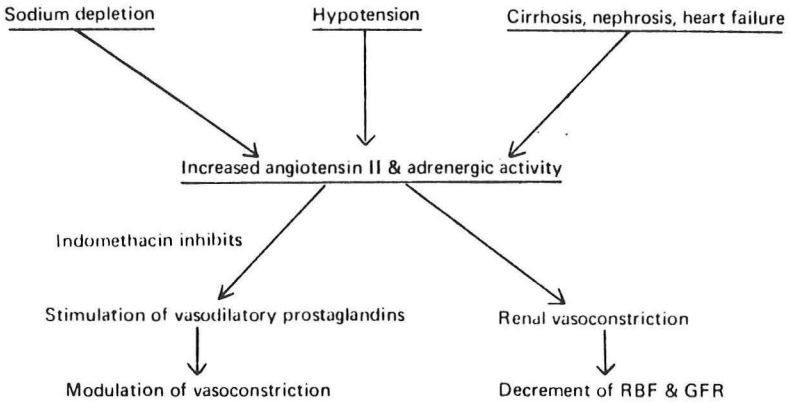
TABLE 22
Effects of NSAID on urinary Na+ and urine volume in the rat

	% of Control	
	Urine Na+	Urine Vol
Indomethacin	21	9
Ibuprofen	30	39
Meclofenamate	40	56
Naproxen	44	39
Aldosterone	42	59

Several points can be made with reference to PG synthetase inhibition. Clinical deterioration of renal function during NSAID (excluding allergic reactions) is seen only under circumstances of compromised circulating volume, when PG are playing a vital role in maintaining RBF and GFR as illustrated by Fig. 20. This is confirmed by the reasonably good correlation between RK synthetase inhibition and sodium and water retaining effects of NSAID's.

Secondly, PG inhibition by aspirin has been posed as a mechanism of analgesic nephropathy. However, the extremely weak RK synthetase inhibition seen with aspirin compared to other NSAID makes this explanation implausible. Furthermore, the sodium and water retention seen with the other potent PG synthetic inhibitors is rarely noted clinically with aspirin even in circumstances of decreased ECF. Alternatively, it is possible that a similar type of analgesic nephropathy will begin to appear in individuals who have taken NSAID for more than 10 years, as this appears to be the lag time for aspirin assocated analgesic nephropathy.

Finally, the interactions of PG, mineralocorticoids and vasopressin must be taken into consideration in treating certain patients with



[redacted]. *Balance between vasoconstrictor and vasodilator factors in the kidney.* Sodium depletion, hypotension, or an ineffective circulatory volume due to cirrhosis, nephrosis, or heart failure exert vasoconstrictor effects on the kidney that are modulated by release of vasodilatory prostaglandins (PGE_2 and PGI_2). If prostaglandin synthesis is inhibited with an antiinflammatory drug, then renal vasoconstriction is exaggerated, and GFR and RBF decrease significantly.

FIGURE 20

NSAID. Prostaglandins antagonize the effects of ADH in the kidney (213,214). As noted above, Zusman et al. demonstrated that in normal volunteers on a 9 meq/d sodium diet, ACTH-stimulated adrenal steroid production superimposed on PG synthetase inhibition by indomethacin resulted in a profound antidiuresis, despite hypo-osmolality (173). This is perhaps related to synergy between the permissive effect imparted to ADH by steroids (215) and the augmented renal response to ADH resulting from PG synthetase inhibition. A clinical example of this may be found in a series of patients reported by Kimberly et al. Three patients with SLE developed deterioration of renal function when treated with NSAID. Two of these patients were also receiving prednisone (195).

IV. Summary and Conclusions

Analgesic nephropathy is a distinct clinical entity associated wth long-term abuse of aspirin and acetaminophen. It often results in chronic renal insufficiency. Because of the nature of the pathogenesis of this disorder, prevention is not possible. However, discontinuation of analgesics often results in improvement or stabilization of renal function and therapeutic efforts should be directed to this goal. Although PG synthetase inhibition has been proposed as a mechanism of injury, it seems more likely that the disease is the result of cytotoxic intermediary oxidizing metabolites. Because of the high incidence of transitional cell carcinoma, patients with suspected analgesic abuse nephropathy should be followed closely for signs to malignancy such as persistent hematuria or urinary tract obstructions.

With respect to the nephrotoxicity of the NSAID several points should be emphasized. First, deterioration of renal function and salt and water retention during NSAID is seen in circumstances associated with reduced effective plasma volume. This is probably related to the key role played by PG in maintaining renal homeostasis in these situations and the abrogation of the beneficial effect of PG by PG synthetase inhibition. Thus, these drugs should be avoided or used sparingly in patients with nephrotic syndrome, cirrhosis and ascites, congestive heart failure and underlying renal disease. Diuretics, because of their potential for volume depletion should be used with caution in patients taking NSAID.

Second, allergic interstitial nephritis, (AIN), a relatively uncommon renal lesion, is seen often with the NSAID. Also noted is hypersensitivity angitis, which is an even rarer nephrotoxic effect of drugs. These side effects are unseemly for drugs notable for their anti-inflammatory potential. A recent report of lipoid nephrosis with a lymphocytic interstitial nephritis associated with fenoprofen raises the possibility that the NSAID cause alterations in cell mediated immunity resulting in these allergic type of lesions (217). AIN should be suspected when a patient taking NSAID present with oliguric or non-oliguric ARF with or without proteinuria, even in the absence of other stigmata of drug reaction such as rash or fever.

Finally, the known effect of steroids in potentiating NSAID induced salt and water retention to produce an inappropriate antidiuresis suggest that concomitant use of NSAID and steroids be avoided particularly in patients with evidence of renal disease.

FOOTNOTE 1: A recent special report in the American Journal of Medicine (Feb., 1982) introduces a new class of NSAID, piroxicam, an oxicam derivative. One is continuously optimistic that the renal side effects are as rare as reported in this special report under Aegis of the Green Journal. Is is reassuring (or is it disconcerting?) that the only reference to renal toxicity in the series of 25 studies in this special report is to "mild occasional rise in serum BUN and creatinine with mild sodium retention".

FOOTNOTE 2: Zomax (Zomepirac McNeil) is being highly touted as a short term general analgesic. Although it is an NSAID, it's long term animal toxicity, including papillary necrosis in rats and interstitial nephritis in primates as well as, frequent dysuria, cystitis, urinary tract infection, pyuria and urinary frequency in humans have precluded marketing it for chronic anti-inflammatory therapy. In addition, the package insert warns of elevations of BUN and creatinine and recommends caution in usage in CHF, hypertension, and renal disease. An intensive advertising campaign has rapidly increased the use of this drug ($ 43,600,000 in sales in 1981). Several anecdotal reports by SWMS nephrology faculty and others (218) associating Zomax with acute renal decompensation should forewarn those who are tempted to use this drug.

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