ON JUNE 9 to 11, 1995, the National Kidney Foundation convened an expert group of investigators and clinicians to consider and develop recommendations on the issue of analgesic-related kidney disease. The rationale for the meeting was based on several disparate facts: (1) the confusion over the definition of analgesic-related renal disease, its manifestations, and health implications; (2) the recent investigative focus on the contribution of acetaminophen to the development of chronic renal failure and its progression to end-stage renal disease (ESRD); (3) the unclear relationship between renal damage and the many analgesic combinations currently available or coming to both the over-the-counter and prescription markets; and (4) the overriding fact that analgesic-related kidney disease should be, in large part, preventable. It had been approximately 10 years since the National Kidney Foundation’s original position paper on the release of nonsteroidal anti-inflammatory drugs (NSAIDs) as an over-the-counter product in the United States, and a more inclusive review of this topic was considered timely.

The organization of the review and format of the meeting was as follows. The group reviewed a database of 556 articles, assembled by James Winchester, MD. This database was supplemented by several hundred additional papers that were added by the individual participants. The general topic of analgesic-related kidney disease was divided into four main subgroups: (1) aspirin-related renal disease; (2) acetaminophen-related renal disease; (3) aspirin/acetaminophen-related renal disease; and (4) NSAID-related renal disease. The issue of analgesic-induced cancer of the kidneys or urinary tract was excluded. Each subgroup consisted of three to four individuals. The participants then divided the subgroup topics into three distinct areas: (1) experimental results and laboratory models of kidney-related damage; (2) acute and chronic effects in humans; and (3) the available evidence linking the drugs to chronic renal disease. A final presentation related to the nongenital side effects of the analgesic agents being considered. Each of these topics was presented to the entire group for discussion. After the discussion period, the subgroups met separately to develop a summary and recommendations for their assigned subgroup topics. The participants then reconvened to finalize the following summary statement and recommendations.
DEFINITIONS

Two main types of analgesic-related renal injury have been well described.

1. "Classic" analgesic nephropathy. This is a disease resulting from the habitual consumption over several years of a mixture containing at least two antipyretic analgesics and usually codeine or caffeine. It is characterized by renal papillary necrosis and chronic interstitial nephritis that leads to the insidious onset of progressive renal failure.

2. NSAID-related renal toxicity. This is a disorder characterized by one of several distinct presentations: acute renal failure secondary to renal vasoconstriction, interstitial nephritis often presenting as nephrotic syndrome due to minimal change glomerulopathy, hyperkalemia, sodium and water retention, and, rarely, papillary necrosis. There is a distinct "at-risk" population for the acute renal failure that develops secondary to renal vasoconstriction: Those individuals with underlying volume depletion from any cause and those individuals with chronic renal disease are particularly susceptible to this effect.

SUMMARY FINDINGS AND RECOMMENDATIONS

Aspirin as a Single Analgesic

Aspirin alone in therapeutic doses does not impair renal function in patients with normal renal function. In patients with renal disease, the acute administration of aspirin alone may cause reversible decrements in renal function. Most studies do not demonstrate an increased risk of ESRD associated with the habitual use of aspirin as a single agent in therapeutic doses. However, aspirin overdosage may impair renal function. There is no risk from the regular use of aspirin in the relatively small doses recommended for prevention of cardiovascular events.

Recommendations Regarding Aspirin as a Single Analgesic

- In patients with normal renal function, aspirin should not be taken within 48 hours of ingestion of any nonnarcotic NSAID, and vice versa.
- In patients with impaired renal function, acute glomerulonephritis, sodium depletion, cirrhosis with ascites, and in children with congestive heart failure, aspirin should be avoided. If use is necessary, careful monitoring of renal function should be undertaken. This would consist, at the least, of following the serum creatinine concentration at baseline and regular intervals.

Acetaminophen as a Single Analgesic

Acetaminophen (as a single agent and in combination products) accounts for approximately 37% of the U.S. over-the-counter analgesic market. The extent of habitual use of acetaminophen as a single agent is unknown. The experimental evidence indicates that very large doses (500 mg to 1 g/kg for weeks to months) can cause renal papillary necrosis. Negligible clinical evidence suggests that the habitual use of acetaminophen alone causes the clinical entity of classic analgesic nephropathy, as defined previously. However, case control studies have suggested a weak association between habitual acetaminophen use and the prevalence of chronic renal failure and ESRD. These studies do not distinguish between acetaminophen used alone and acetaminophen used in combination with other antipyretic analgesics. It should be noted that acetaminophen has been preferentially recommended by physicians to patients with renal failure because of the bleeding complications associated with aspirin in these individuals. There is no evidence that occasional use of acetaminophen causes renal injury.

Recommendations Regarding Acetaminophen as a Single Analgesic

- Acetaminophen remains the nonnarcotic analgesic of choice for episodic use in patients with underlying renal disease.
- The habitual consumption of acetaminophen should be discouraged. If indicated medically, the long-term use of acetaminophen should be supervised by a physician.

Combinations of Aspirin/Acetaminophen

The experimental data provide a biochemical and pathological basis for the enhanced renal toxicity of analgesic mixtures compared with that of single agents. In most circumstances, an "analgesic mixture" refers to a combination of aspirin and acetaminophen combined with caffeine or codeine; however, other combinations are also possible (eg, aspirin/NSAID, aspirin/pyrazolam, acetaminophen/pyrazolam). One prospective cohort study and five satisfactory case control stud-
ies confirm the association between consumption of analgesic mixtures and classic analgesic nephropathy. A positive and direct relationship exists between the local sales of analgesic mixtures and the prevalence of classic analgesic nephropathy. The withdrawal of combination analgesic products from the over-the-counter market in Sweden and Australia has markedly reduced analgesic nephropathy as a cause of ESRD in those countries. In contrast, the isolated removal of phenacetin did not eliminate classic analgesic nephropathy in Australia or Belgium. No data are available regarding the effect of prolonged consumption of analgesic mixtures by children, and there are no data on the safety and efficacy of a single analgesic product mixed with caffeine or codeine.

Recommendations Regarding Aspirin/Acetaminophen Combinations

- The availability of analgesic mixtures as an over-the-counter product should cease.
- Analgesic mixtures as prescription products should have the following language included in the label: "The habitual use of combination analgesics has been associated with an increased prevalence of kidney injury and chronic renal failure."

Nonsteroidal Antiinflammatory Drugs

The use of NSAIDs is safe when the drugs are taken in therapeutic doses for a limited period. Patients with preexisting risk factors, including underlying renal disease and volume depletion, are susceptible to potentially life-threatening nephrotoxicity, including acute renal failure and serious fluid and electrolyte disorders. NSAID-related acute renal failure is usually, but not inevitably, reversible. Renal papillary necrosis and chronic renal failure can occur secondary to the prolonged use of prescription and over-the-counter NSAIDs. No data delineate the exact risk of developing chronic renal failure, papillary necrosis, or ESRD from NSAID use. Neonatal acute renal failure may occur from NSAID use even "as directed" in pregnancy. There are no clinical and experimental data regarding the effect(s) of NSAIDs on the progression of renal disease.

Recommendations Regarding NSAIDs

- There should be an explicit label warning patients taking over-the-counter NSAIDs of the potential renal risks of consuming the drugs. This warning should be similar to the labeling now in place for prescription analgesics and should use understandable language previously recommended by the National Kidney Foundation. This previously suggested warning was as follows: "DO NOT TAKE THIS PRODUCT WITHOUT PHYSICIAN SUPERVISION IF: (1) You are allergic to aspirin; (2) You are under a physician's care for asthma or stomach problems (such as heartburn); (3) You take diuretic medicine; (4) You have heart disease, high blood pressure, kidney disease, or liver disease; (5) You are over 65 years of age." The use of NSAIDs should be avoided in patients with preexisting renal disease or volume depletion; if such use is mandatory, renal function should be monitored carefully.

- The use of NSAIDs during pregnancy should be avoided.

- The prolonged regular use of NSAIDs should be discouraged; if such use is necessary, renal function should be monitored periodically.

- Combinations of NSAIDs with other analgesics or caffeine should be prospectively evaluated for renal safety before the release of any such combination.

Recommendations Regarding Future Research Initiatives in Analgesic-Related Kidney Diseases

As part of its deliberations, the group formulated a series of recommendations regarding new research initiatives. These proposals are listed below.

- The United States Renal Data System (USRDS) should survey the current ESRD population for suspected habitual analgesic consumption and analgesic nephropathy using primary and secondary diagnoses, and perform geographic, age, and gender distribution analyses.

- An incidence study of new-entry ESRD patients in whom the cause of renal failure is "unknown" should be performed (using a computed tomography scan without contrast for diagnosing the disease) to determine the true incidence of analgesic-related renal disease.
• Collaborative studies to learn the true incidence of analgesic-related renal disease should be undertaken in "at-risk" populations (eg, >2 to 3 years of ingestion); these studies should involve nephrologists as well as rheumatologists, and should include adult and pediatric patients.

• Studies that examine the effect(s) of all analgesic agents (alone and in combination) on the progression of chronic renal disease should be performed.

• Basic research that examines the effects of analgesics on kidney differentiation/development, and on the modulation of renal blood flow (eg, prostaglandins, adenosine, nitric oxide), should be performed. Studies that establish a reproducible animal model of analgesic nephropathy together with studies on the biochemical toxicology and the mechanisms of synergistic toxicity should also be encouraged.

• Studies to examine whether analgesics affect pregnancy and whether they are excreted in the milk of lactating breastfeeding mothers should also be performed.

In summary, the intent of the working group has been to provide, based on a critical analysis of the available literature, a clear and useful guideline for physicians and consumers regarding the relationship of analgesics and renal disease. The general concept that any drug purchased over-the-counter is inherently safe, and therefore can be consumed with impunity, is clearly not true. It is hoped that this summary statement and these recommendations will enhance the overall safe use of analgesics and provide some specific insights into areas that require further investigation.

REFERENCES