

Trends of Analgesic Nephropathy in Two High-Endemic Regions with Different Legislation

PAUL MICHIENSEN* and PAUL DE SCHEPPER†

Departments of *Medicine and †Pharmacology, University of Leuven, Leuven, Belgium.

Abstract. Analgesic abuse is related to a specific form of interstitial nephritis, but the exact nature of the causal agent remains controversial and this has resulted in differences in regulation. In Flanders, the free sale of phenacetin was banned, but the consumption of other combined analgesics remained free. In New South Wales, phenacetin was also banned, but 2 yr later the sales of all combined analgesics were also prohibited. This study compared the evolution of end-stage renal disease as a result of analgesic nephropathy (AN) in these two

high-endemic regions with different legislation. In both regions, the time trend of the age-specific incidence of end-stage renal disease as a result of AN is similar in the age group 45 to 54 yr. In all age groups combined, the time trend of the percentage of AN among the patients admitted for renal replacement therapy is also similar. This finding does not support the hypothesis that non-phenacetin mixed analgesics play a significant role in the occurrence of AN.

On the basis of clinical evidence, over-the-counter sales of phenacetin-containing analgesics have been legally prohibited in most countries. The epidemiologic studies that have attempted to confirm the causal relationship between regular analgesic intake and analgesic nephropathy (AN) present a number of limitations and potential biases (1). A recent review (2) concluded that despite methodological flaws, these studies suggest a causal relationship between AN and chronic intake of phenacetin but no convincing evidence for a causal relationship between chronic intake of non-phenacetin analgesics and AN. However, the specific role of phenacetin remains a matter of controversy, and renal toxicity has been attributed to paracetamol, one of its metabolites, or even to any non-phenacetin mixed analgesic combination (3,4).

A recent position paper of the National Kidney Foundation recommended that the over-the-counter availability of analgesic mixtures without phenacetin should cease (5). On methodological grounds the validity of the epidemiologic studies underlying this recommendation has been questioned (6). However, the recommendation of the position paper was strongly influenced by the widely disseminated view that an isolated ban on phenacetin failed to control the epidemic of AN in Australia and Belgium, whereas a later ban on all mixed analgesics in Australia seemed more successful (5,7). To settle this crucial issue, we examined the now available long-term data on the evolution of AN in Australia and Belgium.

Materials and Methods

The distribution of AN is uneven, and regions with high prevalence have been described, usually related to local factors (8,9). The time trend of the incidence in specific high-endemic regions is more likely to be sensitive to changes in the legislation on analgesics than data based on larger registries including low-endemic regions. In Belgium, the problem of analgesic nephropathy is largely limited to Flanders (population 5.6 million) (9,10). We therefore reviewed the consumption of popular analgesics in Flanders and all relevant data on the time trend of the new cases of AN among the patients who were admitted for renal replacement therapy (RRT). When appropriate, the results were compared with similar data obtained in New South Wales (NSW; population 6 million), a state of Australia with a comparable number of new cases of AN.

Detailed data on the patients who had end-stage renal failure and who were receiving RRT in the Flemish part of Belgium were obtained from the European Dialysis and Transplant Association–European Renal Association (EDTA-ERA) Registry. For the period between 1973 and 1989, the mean response rate of the Belgian centers was 92% (range, 83 to 100%). From 1990 on, the data were collected by the Flemish Nephrology Association (NBVN), and the retrieval rate approximates 100%. Data for NSW were retrieved from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry (11).

Age-specific incidences for Flanders were calculated using the population data obtained from the National Institute of Statistics (Leuvenseweg 44, B1000 Brussels, Belgium). For Australia, age-specific incidences were obtained from the ANZDATA Registry.

The detailed sales between 1965 and 1998 of Perdolan (Jansen-Cilag NV, Antwerp, Belgium), Mann (S.M.B. Laboratoria, Brussels, Belgium), and Witte Kruis (S.M.B. Laboratoria), the three analgesic brands most popular in Flanders, were obtained from IMS Belgium (Informations Médicales et Statistiques), an international institution that collects sales data for the industry.

Results

Trends of AN Occurrence

The following data were retrieved or calculated from the registry data for Flanders and when available for NSW. All of these data concern exclusively the patients accepted for RRT:

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Correspondence to Dr. Paul Michielsen, Kuleuven, Acacialaan 54, Herent B-3020, Belgium. Phone: 32-16-228345; Fax: 32-16-290946; E-mail: paul.michielsen@med.kuleuven.ac.be

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1. *Number and age distribution of new patients with ESRD admitted per year and per million population, all primary renal diseases (PRD) included.* As more facilities for RRT progressively became available, the number of new patients admitted for treatment increased progressively. Until 1985, this number increased at the same pace in Flanders and in NSW; thereafter, the increase was faster in Flanders (Figure 1). In 1997, 80 patients per million were admitted in NSW, compared with 140 in Flanders. As shown in Figure 2, this increase resulted mainly from the increased admission of elderly patients. In the 1970s, patients older than 65 rarely were admitted; presently, they make up more than half of those starting treatment in Flanders.
2. *Number of new AN patients admitted per year and per million population.* The time trend of the number of new AN patients must be interpreted against the increasing number of patients with ESRD who are accepted for treatment. In Flanders, the number of new AN patients has remained relatively stable since the 1980s (Figure 3), in contrast to the persistent increase in the number of admissions (Figure 1). In NSW, however, the increase in the acceptance rate of new patients (Figure 1) was more limited, and the number of new AN patients has declined since 1985 (Figure 3).
3. *Age-specific incidence of new AN patients in selected subgroups of age.* This time-trend of the number of new AN patients is different when age subgroups are considered. In the age group 45 to 54 yr in Flanders, the number of new AN patients has decreased since 1977; for the age group 55 to 64 yr, this decrease started 10 years later; and in the age group 65 to 74 yr, the number of new AN patients continued to increase until recently (Figure 4). For NSW, data on these age subgroups are available only since 1980. For the age group 45 to 54 yr, the age-specific incidence of AN initially

was higher than in Flanders. From 1984 on, the incidence became comparable, and the further decrease was identical in both regions (Figure 5).

4. *Percentage of AN among new ESRD patients admitted to RRT.* When the number of new AN patients is expressed as a percentage of the total number of patients admitted to RRT (Figure 6), the difference in time trend between the age groups (Figure 4) disappears. In all age groups, the highest percentage is observed in 1976 to 1977 and the subsequent decline is similar. When overall percentages of AN are considered irrespective of age, the trend with time in Flanders and NSW is identical (Figure 7).

Trends in Analgesic Composition and Consumption

In Flanders, the three most popular analgesic drugs were Mann and Witte Kruis powders and Perdolan tablets (10,12). The changing composition of these three most popular analgesic drugs is reported in Table 1. Phenacetin had been removed from Perdolan as early as in 1967. Phenacetin was removed from Witte Kruis powders in 1972 and from Mann powders in 1981. Warnings of possible renal damage in case of prolonged use were put on the packages in 1967 and in 1972, but their influence seems to have been limited. The withdrawal of phenacetin thus has been progressive, and it started long before the legal ban in 1987.

The mean number of doses of these three most popular analgesics sold per year in Belgium is listed in Table 2. Although these numbers correspond to the total sales in Belgium, the majority were sold in Flanders, where these products were manufactured (9,10). These numbers do not include the powders sold outside the pharmacies, which was a common practice for Mann and Witte Kruis. Between 1965 and 1971, more than 70 million phenacetin-containing doses were sold

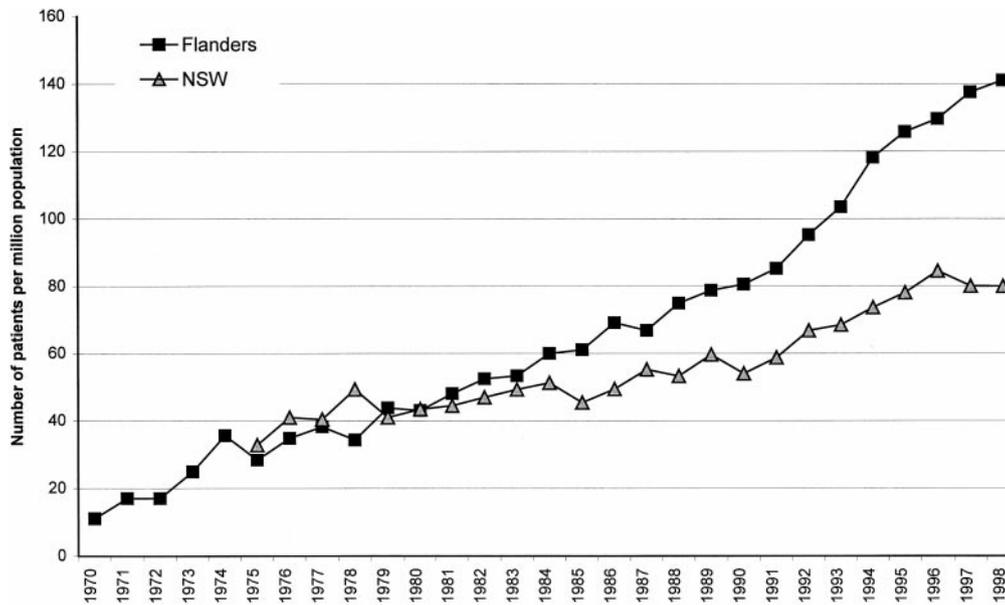


Figure 1. Number of patients with end-stage renal disease (ESRD) admitted renal replacement therapy (RRT) in Flanders and in New South Wales (NSW). (Data from European Dialysis and Transplant Association–European Renal Association, the Flemish Nephrology Association, and Australia and New Zealand Dialysis and Transplant Registry.)

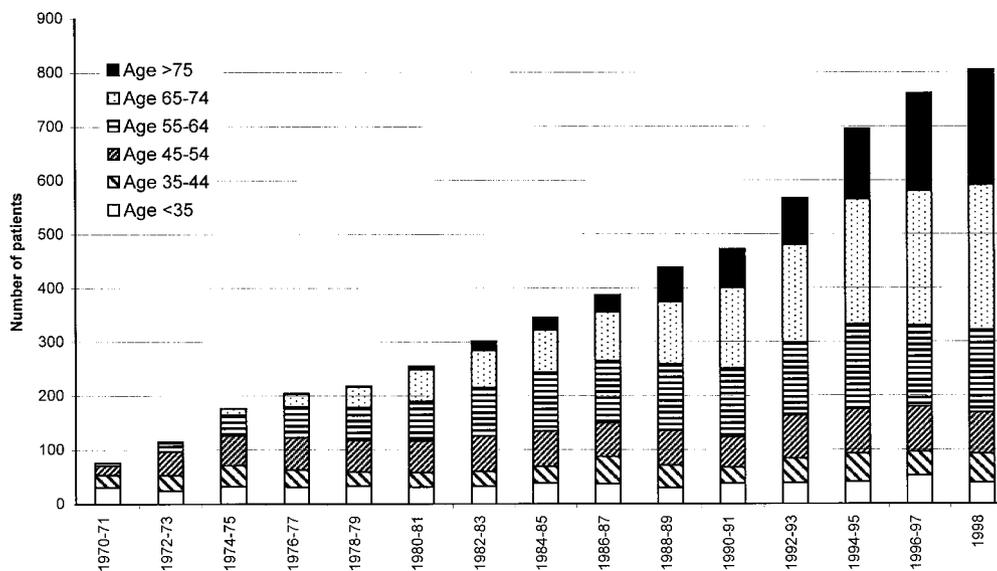


Figure 2. Age distribution of ESRD patients admitted to RRT in Flanders (mean of two consecutive years).

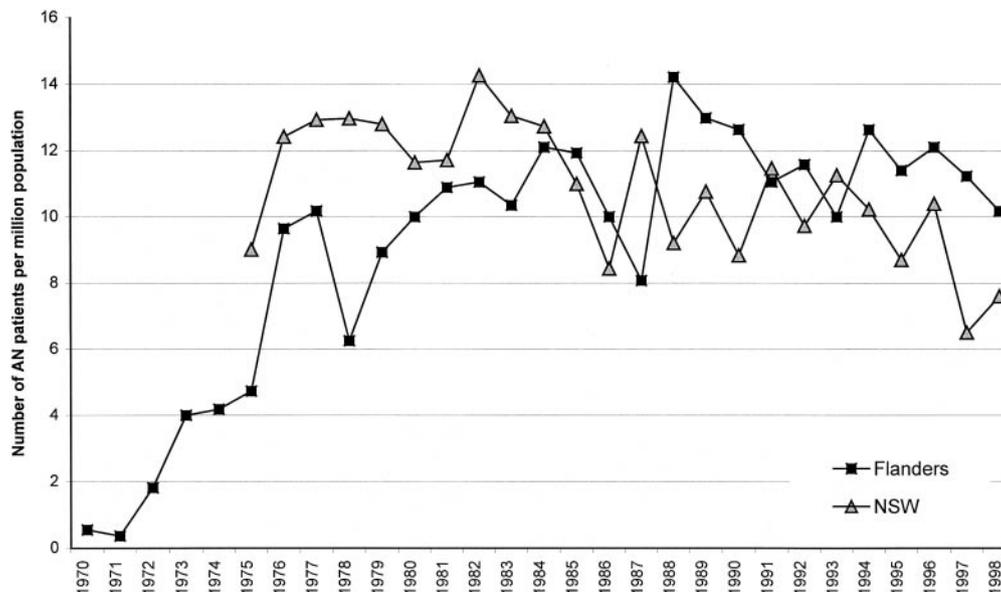


Figure 3. Number of analgesic nephropathy (AN) patients admitted to RRT in Flanders and in NSW data per million population.

per year. The abrupt decrease in phenacetin sales in 1972 and 1981 corresponds to the withdrawal of phenacetin from Witte Kruis and Mann. The consumption of mixed analgesics with phenacetin then was shifted to mixed analgesics without phenacetin. Since the change of Mann and Witte Kruis to the mono formula in 1988, the sales of mixed analgesics have remained at 52 million doses per year. When the sales of only these three most popular analgesic mixtures are considered, these data indicate that the crucial dates for a decrease of the consumption of phenacetin are 1972 and 1981. After the ban of phenacetin, the consumption of mixed analgesics persisted at a high level.

Discussion

The main objective of this study was to test the assumption that the incidence of AN was reduced to a greater extent in

Australia than in Belgium. The major possible bias when using registry data to compare the incidence of AN between countries is the progressive change in the admission criteria. Two solutions have been proposed to circumvent this difficulty. The first is based on the assumption that below the age of 54 yr, no patients with AN were denied treatment, and the incidence of AN in these patients therefore has been considered as indicating the real incidence of the disease (13). Our data (Figure 2) indicate, however, that even in this younger age group the number of admissions has increased somewhat, suggesting that some changes in selection criteria could have occurred. It is possible that when facilities were still limited, some patients with behavioral problems, frequently observed among AN patients, could have been denied RRT. A major disadvantage of the restriction of the analysis to younger patients, however,

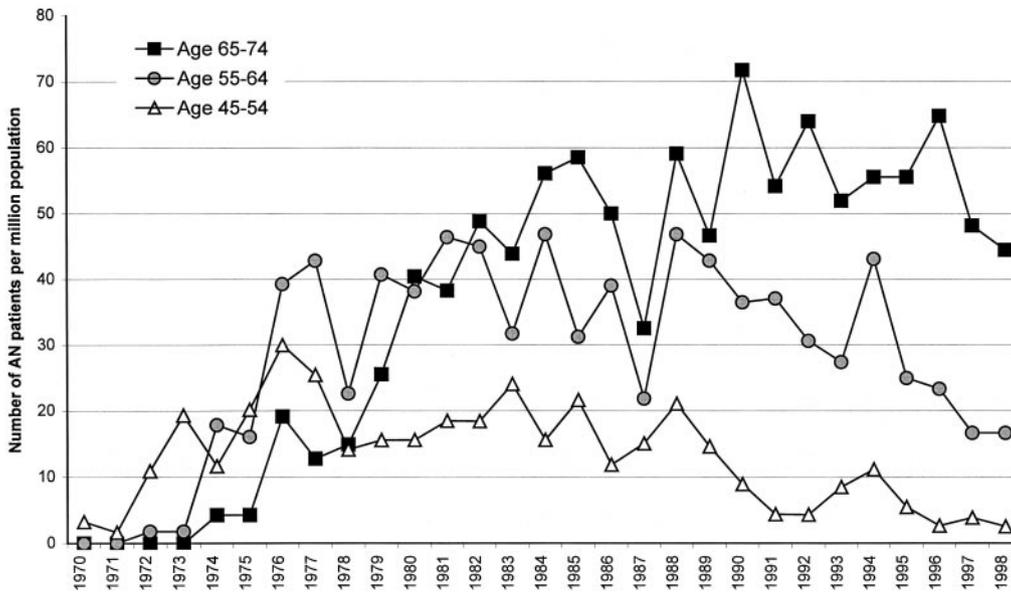


Figure 4. Age-specific incidence of AN among different age groups in Flanders.

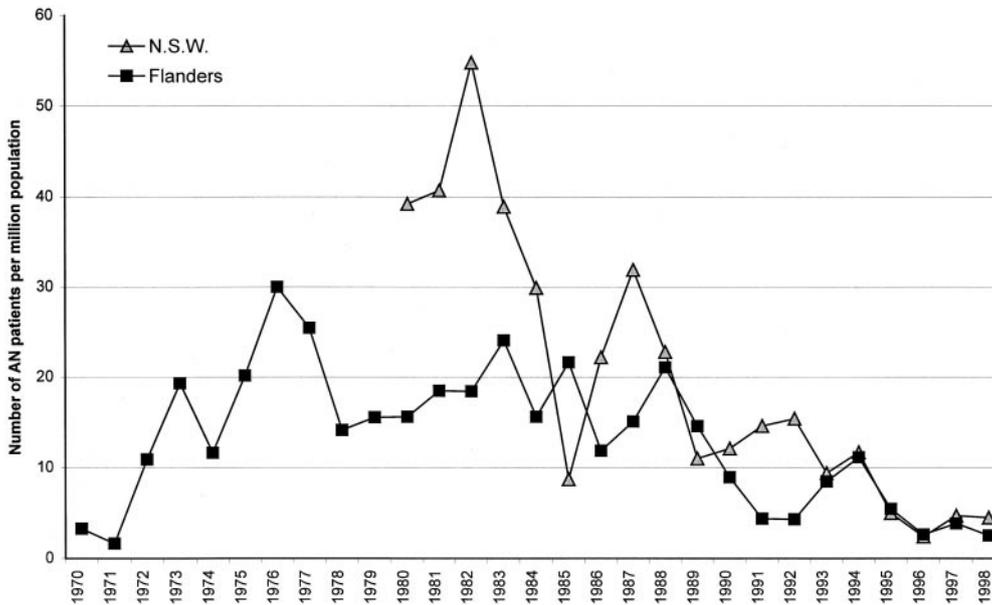


Figure 5. Age-specific incidence of AN in the age group 45 to 54 yr in Flanders and in NSW.

is the limited number of patients. This results in an increased year-to-year variation, which makes evaluation of the time trend difficult. The second solution is to express the results as the proportion of AN patients among the total group accepted for treatment. A major objection is that bias will occur if changes are made in the exclusion criteria for well-defined diseases, other than AN. The similarity in the time trend of the proportion of AN in all age groups (Figure 6), however, makes unlikely a relevant bias as a result of age-related diseases. An increase in the number of diabetic patients admitted to RRT has been observed in most countries and could result in a decrease in the proportion of AN patients. However, exclusion of diabetics from the calculation only marginally increases the per-

centage of AN in the recent years, as shown for Flanders in Figure 7. The same applies to NSW (data not shown). For our comparison between regions, the importance of this bias is limited further, as the number of diabetic patients admitted to RRT increased in Flanders as well as in NSW and therefore the proportion of AN is modified in the same way. Whatever the parameter used, age-specific incidence of AN in the age group 45 to 54 yr (Figure 5) or proportion of AN patients (Figure 7), the incidence of AN was found to decline at the same rate in Flanders and in NSW.

Earlier studies concluded that the phenacetin ban in Belgium and Australia had no effect on the incidence of AN (5). The discrepancy between our findings and those of others is ex-

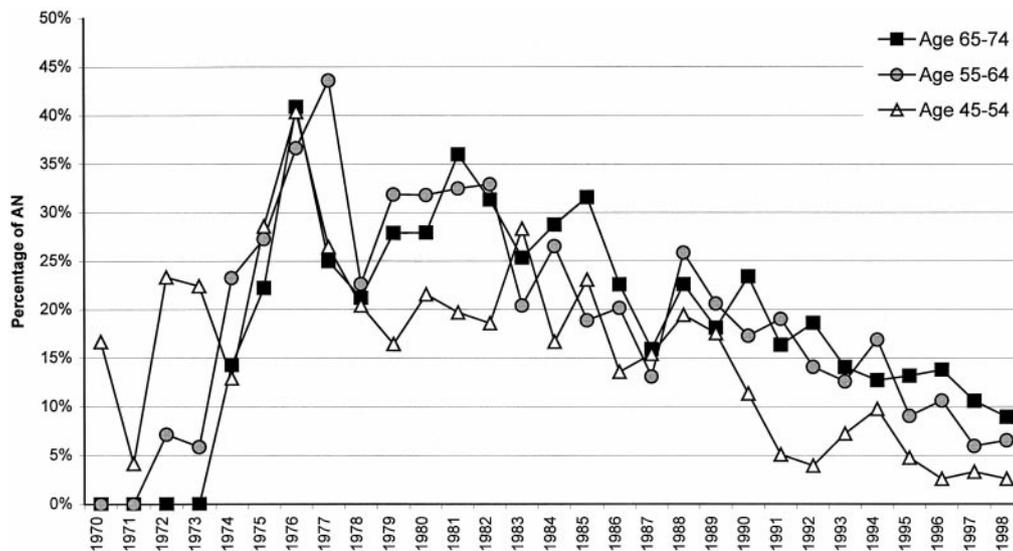


Figure 6. Number of AN patients expressed as percentage of all patients admitted for RRT (data for Flanders). The time trend of the percentage is similar in all age groups.

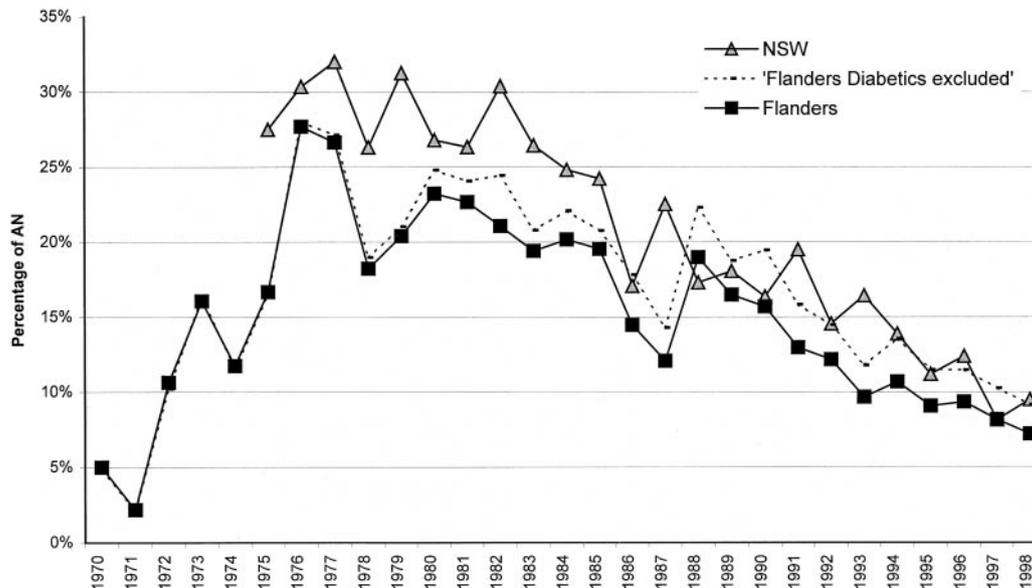


Figure 7. All age groups combined. Identical time trend of the percentage of AN in Flanders and in NSW. Exclusion of diabetic patients in Flanders does not significantly modify the trend of the curve.

plained by the criteria used to estimate success or failure. The validity of the conclusion will depend on three factors: (1) adequacy of the parameter used to estimate the time trend, (2) correct estimation of the time at which the consumption of the abused drug(s) changed, and (3) correct estimation of the time interval between withdrawal of the drug and the expected effect on the time trend of AN.

In Belgium, the conclusion that analgesic nephropathy did not decrease significantly was based on a comparison between AN prevalence in the dialysis units in 1982, 1984, and 1990 (12,14). The absence of improvement in the prevalence of AN in Belgium is still mentioned in a recent review as indicating the failure of phenacetin withdrawal (4). Prevalence of AN

among dialysis patients, however, cannot be considered an adequate parameter, as it not only will reflect a change in the incidence with a considerable delay but also will be biased by the transplantation policy. In the early years, patients from the younger age group were preferentially selected for transplantation, and as the incidence of AN is lower below 40 yr of age, this will increase the prevalence of AN among those remaining in dialysis. In addition, data indicate that AN patients have been discriminated against in selection for transplantation (12,15). The importance of this bias is illustrated by the fact that the prevalence of AN in dialysis can be nearly twice as high as the prevalence calculated on the total number of survivors with RRT (including the patients with a functioning

Table 1. Composition of the three most popular analgesics in Flanders

Years	Perdolan							Witte Kruis							Mann										
	Phenacetin	Paracetamol	Salicylic acid	Phenazone	Phenazonesalic	Other	Caffeine	Codeine	Phenacetin	Paracetamol	Salicylic acid	Phenazone	Phenazonesalic	Other	Caffeine	Codeine	Phenacetin	Paracetamol	Salicylic acid	Phenazone	Phenazonesal	Other	Caffeine	Codeine	
1961 to 1966	+	+	+			+	+	+	+								+								+
1967 to 1971		+	+			+	+	+	+								+								+
1972 to 1980		+	+			+	+	+				+	+	+	+		+								+
1981 to 1986		+	+			+	+	+				+	+	+	+					+	+				+
1987		+	+				+	+				+	+	+	+					+	+				+
1988 to 1999		+	+				+	+	+								+								+

transplant) (12). Similar differences were reported for Switzerland, Austria, and Germany (10).

A recent review mentioned that the “frequency” of AN started to decrease in Belgium in 1992 only and in Australia in 1985 (3). The authors clearly are referring to the decline in the number of AN patients admitted to RRT (Figure 3). As this number is biased by the increased admission to RRT (Figure 1), it is not suitable for estimating a change in incidence of the disease.

In Australia, interpretation of the data is more difficult than in Belgium. This is due to a short time interval of only 2 yr between the legal ban on phenacetin and on all mixed analgesics, making it difficult or even impossible to assess the respective influences of the two measures (16). In Australia, phenacetin was legally banned in 1977, but phenacetin had been withdrawn from many analgesics much earlier. The most frequently abused powders were Vincents and Bex, from which phenacetin was removed in 1967 and 1976, respectively (17–19). We have no quantitative data on the consumption of these powders, but 1967 and 1976 can be considered as crucial dates for a decrease of phenacetin consumption among addicts. The absence of a decline in the percentage of AN among the Australian patients who started RRT between 1971 and 1978 was interpreted as indicating a failure of the phenacetin withdrawal (20). Obviously, it was the absence of an immediate decrease in the incidence of ESRD as a result of AN that was interpreted as a failure of the phenacetin ban. With the long-term data now available, it is clear that even in the younger age groups, the first change in the trend of the incidence of AN can

be observed only several years after the withdrawal of phenacetin and the proportion of AN among patients starting dialysis becomes negligible only after 20 yr or more (Figure 6). In the older age groups, this decrease is even slower. This is consistent with the view that cessation of phenacetin intake in patients with reduced renal function has not led to a reversal but only to a slowing of the progression to terminal renal failure. Brunner and Selwood (21) concluded on the basis of EDTA Registry data that it took some 20 yr after withdrawal of phenacetin for AN to disappear as a cause of ESRD. Our data indicate that in countries such as Belgium, where a high proportion of elderly patients are accepted for treatment, this interval could even be longer.

On the basis of a short-term study that involved a limited number of patients who were not yet in the end stage of their nephropathy, Nanra *et al.* (18) claimed that withdrawal of phenacetin had failed to reduce the incidence of AN. They compared the incidence of renal insufficiency in patients who had taken Bex and Vincents powders between 1967 and 1976. At that time, Bex still contained phenacetin and Vincents did not. Renal insufficiency, defined by a serum creatinine exceeding 0.11 mmol/L, was found in 64.7% of the Bex abusers, compared with 57.1% in the Vincents abusers. Here also, the absence of a rapid improvement in renal function was interpreted as showing the failure of the withdrawal of phenacetin (19). It can be concluded that the claim for the failure of the phenacetin withdrawal in Australia is not supported by convincing data. On the basis of the Australian data, the progressive disappearance of AN in the long run could as well be due

Table 2. Mean yearly sales of three most popular analgesic brands in Flanders (Data from I.M.S.)

Composition	Mean No. of Doses Sold Per Year (in million)			
	1965–71	1972–80	1981–87	1988–98
Mixed with phenacetin	77.5	40	0	0
Mixed no phenacetin	12.5	95.1	97.2	52.1
Mono	0	0	0	31.2

to the phenacetin withdrawal as to the withdrawal of combined analgesics.

Conclusion

In Australia, the most significant decrease in phenacetin consumption by addicts can be estimated to have occurred in 1967 and 1976 and in Flanders in 1972 and 1981. In contrast to Australia, where all mixed analgesics have been prohibited since 1979, the decrease of phenacetin consumption in Belgium was largely compensated by an increase in the consumption of mixed analgesics without phenacetin. This persisting high consumption of mixed analgesics did not preclude a similar decrease with time of the frequency of AN in Flanders and in NSW. These findings make unlikely a significant role of non-phenacetin mixed analgesics in the genesis of AN.

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