

## Editorial Comment

# In memoriam ‘analgesic nephropathy’ (circa 1972–2006)

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Throughout the last decades, analgesic nephropathy (AN) has remained a subject for controversy, leading to a series of epidemiological studies, reviews, statements by more or less officially appointed committees and appeals to public health authorities. In contrast, the ‘Obituary to Analgesic Nephropathy’ which appeared in the November issue of *NDT* [1] reports only a decisive new fact: 20 years after the removal of phenacetin from the freely available analgesics, the typical lesions of AN are no longer found at autopsy in Basel. How does this new evidence fit into the other available pieces of the puzzle?

It all started in the 50s, with localized epidemics of chronic renal failure in Sweden, in Swiss watch factories, in the Flanders region of Belgium and in Australia. All had in common a compulsive craving for analgesic mixtures, usually powders containing phenacetin combined with other antipyretic analgesics, caffeine and sometimes codeine. The description of capillary sclerosis as a pathognomonic lesion later completed the picture. As phenacetin was the only ‘common’ ingredient present in all the mixtures, the new disease became known as *phenacetin nephropathy*. As a consequence, phenacetin was progressively removed from most popular mixed analgesics and usually replaced by its principal metabolite, paracetamol.

In the 70s, the exclusive role of phenacetin became increasingly questioned when it appeared that paracetamol and not phenacetin accumulated in the papilla [2]. In addition, phenacetin had always been used in combination with other analgesics. Moreover, in animal experiments, phenacetin appeared less nephrotoxic than the other analgesics, especially acetylsalicylic acid [3]. The turning point was the claim that in Australia, the withdrawal of phenacetin from some brands of analgesics had not prevented the disease [4]. This interpretation, which is at variance

with the new data of Mihatsch *et al.* [1], can be explained by a too short observation period and the use of inadequate criteria. In many subsequent publications, it remained a pillar for the suggestion of alternative aetiologies, and the name of the disease was changed to *analgesic nephropathy*, leaving open which analgesics were the ‘culprits’. The new name, actively supported by the group of Kincaid-Smith, has remained in general use until today. At first, the clinical and pathological description of the disease remained unchanged but the content of the term ‘analgesic’ surreptitiously evolved. In the beginning, it was meant to include only the classical APC mixtures, in which phenacetin was replaced by paracetamol. The Position Paper of the National Kidney Foundation defines AN as ‘a disease resulting from the habitual consumption over several years of a mixture containing at least two antipyretic analgesics and usually codeine or caffeine’ [5]. The statement published the same year in *NDT* is less specific, mentioning only: ‘... prolonged and excessive consumption of analgesic mixtures containing addictive substances’ [6]. In all these studies and statements, a recurring leitmotiv is that the phenacetin ban in Belgium had failed, as opposed to the success of the total ban on all mixed analgesics in Australia. As mentioned before, on disputable grounds, Nanra *et al.* [4] had already claimed the failure of the phenacetin ban in Australia and, as the ban on all mixed analgesics was already introduced 2 years after the phenacetin ban, it became impossible to verify this allegation.

In Belgium, phenacetin was removed from the two most frequently ‘abused’ combination preparations in 1972 and 1981, followed by a legal ban in 1988. The failure of these measures was claimed on the basis of a persisting high prevalence of AN among the patients on dialysis [7–9]. It was ignored that the increasing number of elderly patients admitted to dialysis had introduced an important bias, as AN was prominently present in these older age groups [10]. This could result in the finding of a stable or even an increased prevalence of AN cases, while the incidence per age category actually decreased. When not the prevalence but the incidence of AN is used, subdivided according to age and expressed as a percentage of the total

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number of patients admitted per category, it becomes clear that in Belgium the time trend of the incidence of AN decreases progressively in all age categories from 40% in 1976 to 5% in 1998. Furthermore, these data from Flanders are similar to those obtained in comparable groups in Australia [11]. When the data are correctly analysed, the time trend of the evolution of the incidence of AN in Belgium and Australia is identical, and in agreement with the conclusions of the recent autopsy study of Mihatsch *et al.* [1].

In the meantime, the decreasing incidence of AN was obvious in most dialysis centres [10]. In countries with limited phenacetin abuse, the incidence of AN remained extremely low, which was surprising if not phenacetin but other mixed analgesics were to be incriminated. It was suggested that a large number of cases were overlooked. Elseviers *et al.* proposed CT without contrast as a sensitive and specific method of diagnosing AN and suggested that this could lead to the detection of a number of undiagnosed cases [12,13]. As renal imaging was already part of the diagnostic work-up of cases suspected of AN and as the CT image of classic AN in the terminal phase corresponds to the criteria described in [12,13], a good sensitivity can be expected for the detection of classic AN. A recent large-scale NIH-sponsored observational study [14] demonstrated that, among the patients who did not take phenacetin, prevalence of CT-positive cases was low. The association of heavy analgesic ingestion and typical CT changes seemed to be accounted for mostly by phenacetin-containing products. This is exactly what was to be expected if classical AN is due to phenacetin and not to any other antipyretic analgesics, mixed or not.

In summary, whatever the method used for the diagnosis, be it the clinical diagnosis at admission in haemodialysis, the non-contrast-enhanced CT or the histopathological diagnosis at autopsy, all available data indicate a correlation of AN with the intake of phenacetin. There are no consistent data favouring another hypothesis.

Epidemiological studies are in high standing and popular, notwithstanding their high cost. AN was investigated in a few cohort studies and many case control or observational studies. All these studies were confronted with the difficulty in defining the outcome. Outside rarely available autopsy data, clinical diagnosis of AN is not consistent and reliable enough to be used as outcome in epidemiological studies. Therefore, ESRD or a decrease in glomerular filtration rate have been used. However, this lacks specificity and has led to a reformulation of the diagnosis as ‘analgesic associated nephropathy’ (AAN) or, more recently, ‘analgesic-related kidney disease’, further subdivided into ‘classical analgesic nephropathy’ (AN) and an ‘aspecific contribution to the development or the progression of chronic renal diseases, of whatever aetiology, towards end-stage renal failure’ [15]. In these studies, all analgesics or combinations have been

considered as possible causal factors, and they are sometimes lumped together with the NSAIDs under the denominator ‘analgesics’. This has added to the confusion as, besides AN, other specific causal associations exist between some analgesic drugs and renal injury, e.g. tubular necrosis after massive paracetamol ingestion, or diffuse interstitial lymphocytic infiltration with heavy proteinuria sometimes seen after treatment with indomethacin, or a dramatic decrease of the glomerular filtration observed during administration of NSAIDs (but not antipyretic analgesics) to dehydrated elderly patients. Notwithstanding these shortcomings, the epidemiological studies have been expected to bring the final answer in analgesic nephropathy. Unfortunately, the evidence they present is usually weak and the results are conflicting. An in-depth review by Delzell and Shapiro [16] concluded that all these studies presented major flaws and have not established that analgesics, other than phenacetin, cause chronic renal disease. A peer review committee, jointly selected by the regulatory authorities of Germany, Switzerland and Austria and the pharmaceutical industry, came to the same conclusion [17]. This does not preclude grossly flawed studies being quoted over and over again, as supporting the role of mixed analgesics.

Maybe one should remember a quote from Douglas Black, the initiator of many MRC trials ‘...if a controlled trial is practicable and can produce a result, it is a most valuable contribution to progress; but it seems to me unrealistic to suggest that nothing should be done without a controlled trial and that any issue can be settled for all times, even by a randomized controlled trial...’ [18].

The present study of Mihatsch *et al.* [1] puts an end to this analgesic saga. Let us hope that it will remind clinicians that, even in this era of computerized evidence-based medicine, clinical judgment and common sense are still the basis of good medical practice.

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