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Letters to the Editor

Relations between gastric irritancy/ulcerogenicity and anti-oedemic activity of non-steroidal anti-inflammatory drugs

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Recently, Dearden & Nicholson (1984) reported a study of the relation between gastric irritancy and anti-inflammatory activity for some 25 non-steroidal anti-inflammatory (NSAI) drugs in which they made statements concerning work by Rainsford that require clarification because there appears to be some misinterpretation—viz:

(1) In justifying the purpose of their study in the introduction the authors stated 'It has been postulated (Rainsford 1975) that the gastric irritation induced by non-steroidal anti-inflammatory drugs (NSAIDs) increases as their anti-inflammatory activity increases . . .'. No such statement was made in the review referred to, rather it stressed the differences that exist between responses in different animal models and questioned whether such a comparison (as made at that time by several authors) between anti-inflammatory activity and ulcerogenicity was indeed valid. The view was necessary because of the relatively few NSAI drugs for which comprehensive data were available at that time (1975), and the variable results obtained with different anti-inflammatory assays for individual drugs. In more recent papers, Rainsford has pointed out that more complex aspects exist mitigating against that notion.

(2) In making claims about the greater reliability of the index assessment used by them over that used by Rainsford (1981) Dearden & Nicholson do not seem to have appreciated that Rainsford reported (a) ED 10 values based on *lesion numbers* not an *index* (as they quoted), and (b) that the studies were in cold stress-sensitized rats—a model developed deliberately to enhance specifically the sensitivity of the gastric mucosa towards the ulcerogenic activity of NSAI drugs. Dearden & Nicholson used a complex arbitrary scaling of the type and severity of damage; they summated these scaled values with lesion numbers in such a way that the index derived had virtually no quantitative basis and was incapable of discriminating which individual rating contributed to the overall assessment of mucosal damage. Given these deficiencies in their assessment of mucosal damage, comparison of their data for IC10 values (Table 1; Dearden & Nicholson 1984) with those of Rainsford (1981) showed that far from revealing similar relations as was suggested (equations (1) and (2)), there was wide variability amongst the relative gastric irritancy/ulcerogenicity results for NSAI drugs in these two models. For most, but not all, of the more ulcerogenic NSAI drugs, the IC10 values obtained were markedly higher than those obtained by Rainsford. In contrast the IC10 values for some of the lesser ulcerogenic drugs were slightly lower than those of Rainsford. It might have been more relevant if Dearden & Nicholson had emphasized the possibility that differences do apparently exist in the responses to NSAIDs of carrageenan-injected rats compared with cold-sensitized rats, even though the timing was different (see also (3)). The arbitrary deletion of various drugs which was used in their correlation analyses also may not adequately be justified.

(3) The test procedures used by Dearden & Nicholson were claimed to measure 'short-term irritancy' whereas Rainsford's data measured 'long-term irritancy'. This is incorrect since in Rainsford's study the gastric mucosal damage was assessed at 2 h following oral dosing of the drugs whereas in their own study 4 h was used, a time which for many NSAI drugs is past the peak for lesion development.

(4) An unquoted identical study by Rainsford (1981), showed that a number of NSAI drugs fell outside a relation between anti-inflammatory activity (rat carrageenan assay) and ulcerogenic data when compared with the effective dose range in man. The value of these analyses is that it may be possible to identify NSAI drugs with low ulcerogenic potential relative to their therapeutic potency in either rats or man compared with the traditional NSAI drugs (e.g. aspirin, phenylbutazone, indomethacin). Ulcerogenicity data in rats do show an approximate relation with best estimates in man (gastroscopy, intragastric bleeding). However, there is a range of factors influencing the development of mucosal injury by various formulations of NSAI drugs (see Rainsford 1982, 1984a, b, for reviews) so that it would be naive to regard the value of studies in rats alone as being indicative of what might happen in man. The studies in diseased/stressed animals

may, however, give a reasonable prediction of *intrinsic* ulcerogenicity of NSAI drugs.

(5) Dearden & Nicholson used carrageenan-injected rats in their combined study of ulcerogenicity and anti-inflammatory activity, a model originally developed by Rainsford & Whitehouse (1977). While that acute assay method might have advantages in reducing the cost and numbers of animals (as was originally noted), the large quantity of prostaglandins (PGs) released into the circulation from the injected paws could be sufficient to act as systemic cytoprotective agents despite some lung metabolism of these PGs. Such protection could account for the lower IC50 values obtained, in comparison with those of Rainsford, for the more potent prostaglandin synthesis inhibitors, i.e. aspirin, diclofenac, flubiprofen, indomethacin, naproxen, phenylbutazone, piroxicam and tolmetin.

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Does an endogenous methylpyridinium analogue cause Parkinson's disease?

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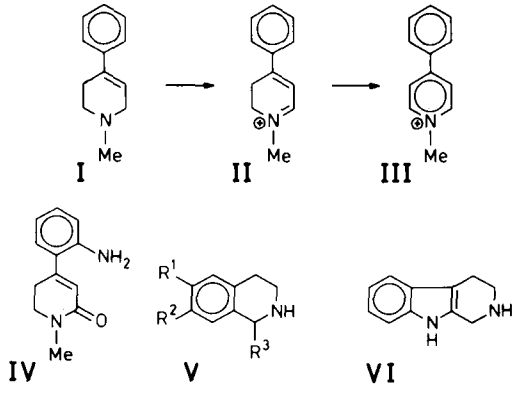
Parkinson's disease affects 1 in 1000 of the general population, and its incidence increases with age, but its cause remains unknown. Twin studies suggest that hereditary factors are not involved (Duvoisin et al 1981). To try to explain the death of dopamine neurons in the brain, the major pathological change in Parkinsonism, attention has been focused on environmental agents or endogenous toxins.

The peripheral administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, I) produces persistent Parkinsonism in human addicts due to selective destruction of the dopamine-containing cells of substantia nigra in brain (Langston et al 1983; Burns et al 1983). The molecular mechanisms underlying this effect are not fully understood, but it is established that MPTP is metabolized by monoamine oxidase B (MAO-B) to 1-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$, II) and then converted to 1-methyl-4-phenylpyridinium (MPP^+, III) (Markey et al 1984; Gessner et al 1984). MPTP-induced toxicity in primates and rodents is prevented by pretreatment with selective MAO-B inhibitors such as deprenyl (Langston et al 1984; Heikkila et al 1984). However, other compounds similar to MPTP may be present in the environment. MPTP itself is not an endogenous molecule nor does it occur naturally in the environment. Another possibility is that some natural toxicant resembling MPTP may be formed endogenously.



With this idea in mind, Ramsden & Williams (1985) proposed a metabolic sequence leading from tryptamine to compound IV, a hypothetical endogenous MPTP-like toxicant. While the proposal has merit, compound IV is not 'a strong contender for the structure of the toxic oxidation product of MPTP . . .' (Ramsden & Williams 1985). Indeed, the postulated metabolic sequence involves some improbable steps such as the *N*-acetylation of a secondary amine, and especially condensation following a nucleophilic attack by a poorly reactive

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