Comments on

'Preventive Effect of Dapsone on Renal Scarring following Mannose-Sensitive Piliated Bacterial Infection' by Mochida et al. (Chemotherapy 1998;44:36–41)

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We have read the article 'Preventive effect of dapsone on renal scarring following mannose-sensitive piliated bacterial infection' by Mochida and co-workers [6] with interest. Since a few years we are dealing with the modes of action of dapsone, with aspects of clinical use and side effects [9,11, 12], we are aware of a possibly potential new indication for the sulfone. Indeed we agree with the author's statement that the anti-inflammatory effects of dapsone are exerted, at least partially, by the inhibition of reactive oxygen species (ROS). However, in recent years there are several lines of evidence of additional mechanisms of actions of the sulfone which have been demonstrated using in vitro methods:

- (I) Suppression of the integrin-mediated neutrophilic adherence [2].
- (II) Inhibition of generation of 5-lipoxygenase products (e.g. LTB₄, 12-HETE) [13].
- (III) Inhibition of spontaneous or induced synthesis of prostaglandin E₂ [7].
- (IV) Inhibition of cyclooxygenase I- and II-mediated generation of thromboxane B₂ [5].

(V) Interference with activation or function of the G-protein (Gi-type) resulting in an inhibition of signal transduction [3].

Moreover, it has been shown that dapsone has neuroprotective effects against quinolate- and kainate-induced striatal neurotoxicities in rats [8] and attenuates kainic-induced seizures in rats [4]. Summarizing these different mechanisms, there is growing evidence that dapsone is pharmacodynamically a very active compound.

From the clinical point of view dapsone is especially effective in those disorders in which the polymorphonuclear neutrophil leukocyte (PMN) morphologically and/or functionally seems to play a central role. On the other hand, dapsone is acetylated in the liver to monoacetyldapsone (MADDS), which is genetically determined [15]. The drug is also hydroxylated to hydroxylamine dapsone (DDS-NOH). The latter metabolite has to be seen as being responsible for adverse hematologic effects induced by the drug (e.g. methemoglobinemia, hemolysis) [15].

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To date, however, the anti-inflammatory capacity of dapsone was generally attributed to the parent compound itself. We have therefore addressed the question as to whether these two major metabolites of dapsone DDS-NOH and MADDS have anti-inflammatory properties of their own in vivo. After measurement of the leukotriene B₄-induced accumulation of PMN in healthy skin, we could demonstrate that DDS-NOH has a strong anti-inflammatory effect whereas dapsone and MADDS did not reveal any activity [14]. An additional in vivo study using healthy volunteers revealed an intenser erythema-suppressing effect of DDS-NOH compared to dapsone (unpublished observations). In another investigation, we were again able to show that DDS-NOH is more active in inhib-

iting the generation of 5-lipoxygenase products in comparison to dapsone confirming the anti-inflammatory properties of DDS-NOH [10].

Thus, it is very attractive to speculate that DDS-NOH in vivo has anti-inflammatory potential. As in the investigation of Mochida and co-workers, dapsone systemically was used in rats and it cannot be excluded that in this experiment DDS-NOH might contribute to the effectiveness of dapsone therapy.

It is becoming increasingly clear that dapsone metabolites should be given more notice than they have till now. To obtain a more precise understanding of the mechanisms of action of dapsone therapy, further investigations should confirm our hypothesis.

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