Nicotinamide and neutrophilia

To the Editor:

The authors of an article appearing in the February 2009 issue of *Nature Medicine* reporting that nicotinamide induces neutrophilia in humans¹ should have acknowledged that this observation is not new. The marked neutrophilia induced by nicotinamide was previously reported by me in a larger and more detailed clinical study² than the one reported in *Nature Medicine*. Both nicotinamide and nicotinic acid (which is metabolized to nicotinamide) induce neutrophilia in normal people, although, interest-

ingly, nicotinic acid acts more promptly than nicotinamide. This effect of nicotinic acid disappears after 30 days of therapy³.

Abram Hoffer¹

Victoria, British Columbia, Canada. ¹Deceased.

1. Skokowa, J. *et al. Nat. Med.* **15**, 139–158 (2009).

2. Hoffer, A. *Can. Med. Assoc. J.* **74**, 448–451 (1956).

3. Hoffer, A. & Callbeck, M.J. *Can. Med. Assoc. J.* **80**, 736–737 (1959).

Skokowa *et al.* reply:

When we performed our experiments and wrote our manuscript¹, we were not aware of the papers published by Hoffer and his colleagues^{2–4} that he mentions in his correspondence⁵. Indeed, according to the ISI Web of Knowledge, none of these three papers, published in 1956 or 1959, seems to have been previously cited in the biomedical literature. Because no follow-up research or clinical trials have been performed, it is hard for us to appreciate the value of his data, which we feel provide only incidental evidence to support the notion that nicotinamide induces neutrophilia in humans and are in fact not clearly related to our own *in vivo* findings¹. Moreover, we think that the findings of Hoffer are of a preliminary nature, in that no mechanism was proposed for the induction of granulopoiesis: the leukocytosis induced by nicotinic acid and by nicotinamide was ascribed to only “some physiological activity of the vitamin”² and the effects of nicotinic acid on eosinophilia to the plastic coating of the tablets⁴.

Hoffer reported that both nicotinamide and nicotinic acid induced an increase in neutrophil counts at two and four hours but not 24 hours after administration² and that nicotinic acid did not induce substantial changes in leukocyte or neutrophil counts over a 30-day period of administration at a dosage of 3 g per day (and may even have induced a decrease in eosinophil counts)³. After four hours of nicotinamide treatment, neutrophil counts increased by only 28% (with 1 g of nicotinamide) or 44% (with 2 g of nicotinamide) (which we would not consider to be “dramatic neutrophilia”), with a decline to initial levels after 24 hours of treatment². In contrast, we administered nicotinamide at a dosage of 10–20 mg per kg body weight per day (for a total dosage of between 1 and 1.5 g per day per person) and observed that neutrophil counts were elevated by more than 100% after one day of treatment; these counts did not decline over the seven-day course of treatment and normalized only after its discontinuation¹.

In addition, we feel that Hoffer’s data regarding the action of nicotinic acid are internally inconsistent. In his first publication, he claimed to see an intense neutrophilia after treatment with nicotinic acid for two hours², but his later publications showed no changes in leukocyte,

neutrophil or eosinophil counts after one week, two weeks or 30 days of nicotinic acid treatment^{3,4}.

Most importantly, the main aim of our work was the elucidation of an autoregulatory loop in which granulocyte colony-stimulating factor (G-CSF) induced expression of its own receptor. We found that the molecular events triggered by nicotinamide phosphoribosyl-transferase (Nampt) include NAD⁺-dependent sirtuin-1 activation, subsequent induction of CCAAT-enhancer binding proteins and, ultimately, upregulation of G-CSF synthesis and G-CSF receptor expression. G-CSF, in turn, further increases Nampt levels. We performed the experiments in which we administered nicotinamide, the substrate of Nampt, to healthy individuals principally to provide evidence for the *in vivo* relevance of this mechanism in humans. In addition to seeing increased neutrophil counts, we found that the amounts of NAD⁺, CCAAT-enhancer-binding proteins and G-CSF in myeloid cells were increased, providing further evidence that nicotinamide stimulates this autoregulatory loop. Our most noteworthy finding was that G-CSF signaling is dependent on Nampt and NAD⁺. Neither G-CSF nor Nampt were known to exist at the time when Hoffer published his papers.

Another key issue is that, in mammals, nicotinamide but not nicotinic acid serves as a substrate for Nampt^{6,7}. We, therefore, did not use nicotinic acid in our experiments, and the biological effects of nicotinamide would be expected to differ from those of nicotinic acid.

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1. Skokowa, J. *et al. Nat. Med.* **15**, 151–158 (2009).

2. Hoffer, A. *Can. Med. Assoc. J.* **74**, 448–451 (1956).

3. Hoffer, A. & Callbeck, M.J. *Can. Med. Assoc. J.* **80**, 736–737 (1959).

4. O’Reilly, P.O., Callbeck, M.J. & Hoffer, A. *Can. Med. Assoc. J.* **80**, 359–362 (1959).

5. Hoffer, A. *Nat. Med.* **15**, aaa–bbb (2009).

6. Rongvaux, A., *et al. Eur. J. Immunol.* **32**, 3225–3234 (2002).

7. Rongvaux, A., Andris, F., Van Gool, F. & Leo, O. *Bioessays* **25**, 683–690 (2003).