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Antimicrobial Mechanisms of Cranberry Juice

Sir—In their treatment of the potential antimicrobial mechanisms of cranberry juice, Raz and colleagues [1] emphasize its antiadherent activities and discount its significant role in urinary acidification. We would like to highlight a third potential mechanism: the *nonenzymatic* generation of nitric oxide (NO). Nitric oxide possesses potent antimicrobial activities that are both time- and concentration-dependent. Enzymatically, NO can be generated from L-arginine and molecular oxygen by NO synthases; however, NO can also be generated in vivo nonenzymatically by dismutation of nitrite to NO and NO_2 under mildly acidic conditions [2, 3]. In urinary tract infections, acidified nitrite may be a physiologically relevant source of NO produced by bacterial nitrate reductase activity and/or the local induction of inflammation-driven NO synthase activity.

Carlsson and colleagues [1] demonstrated that mild acidification (pH range, 5.0–6.0) of urine containing levels of nitrite comparable to those observed in nitrite-positive urine specimens from patients with urinary tract infection released significant amounts of NO gas [2]. This release was potentiated by the presence of physiologically achievable levels of ascorbic acid. Under the latter conditions, growth of *Escherichia coli, Staphylococcus saprophyticus,* and *Pseudomonas aeruginosa* was significantly attenuated [4, 5]. Of note, the antibacterial effects observed with the addition of ascorbic acid were independent of urine pH. This finding agrees well with numerous prior observations that ascorbic acid is a poor acidifier of urine and supports the notion that the enhanced antibacterial effects of ascorbic acid are due to a reducing capacity that, in turn, facilitates nonenzymatic dismutation of acidified nitrite to NO.

It is plausible, therefore, that the antibacterial effects of cranberry juice may, in part, be explained by the total reducing capacity of its components, including ascorbic acid, which facilitates nonenzymatic generation of NO. Admittedly, the time- and concentration-dependent properties of the antibacterial effects of NO predict a limited role for such a mechanism in both prophylaxis and treatment; these limits are a consequence of variations of both pathogen-specific production of nitrite and the persistence of NO in the urinary tract. Nonetheless, careful evaluation of the *relative* role of such a mechanism may be important for defining the clinical efficacy of cranberry juice as a nonantibiotic alternative for the prophylaxis against urinary tract infections.

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Intracellular Pharmacology of Emtricitabine and Tenofovir

Sir—Anderson et al. [1] are commended for their scholarly review of the cellular pharmacology of nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs) and its relationship to observed toxicities. We wish to provide clarification of the cellular pharmacology data for emtricitabine and tenofovir.

The intracellular half-life in PBMCs for emtricitabine, noted in the review [1] as 20 h, is not accurately reflective of the results reported by Rousseau et al. [2], in which the emtricitabine triphosphate half-life was estimated to be >20 h. Moreover, an additional study involving healthy subjects who received a daily 200-mg dose of emtricitabine for 10 days reported an emtricitabine triphosphate half-life of 39 h [3]. This latter value is from more-rigorous pharmacokinetic analyses and provides a robust estimate of the intracellular half-life, because multiple samples were obtained over a 120-h period following receipt of the last dose of drug.

In addition, the intracellular half-life for tenofovir diphosphate, the active phos-