Firstly, and as Jass et al point out, microsatellite instability shows a bimodal distribution, which we interpret as representing microsatellite stable and unstable (MSI-H) populations. This evidence includes the studies cited above^{3,4} and a more recent publication in which mathematical modeling of the distribution of unstable loci in 415 colorectal cancers lead to the conclusion that the MSS/MSI-H model was the best fit for the data set.⁵

Secondly, this and other studies have reported that the MSI-L and MSS groups share many clinical, pathological and genetic properties.^{4,5} In this regard, we have recently completed a study of 312 sporadic colorectal carcinomas (manuscript submitted). We found that the 7% of these tumors that were MSI-L (as measured at loci D2S123, D5S346, D17S250, BAT25, and BAT26) did not differ statistically from the MSS group over a wide range of clinical, pathological and genetic characteristics, including right-sidedness, differentiation, lymphocytic infiltration, or K-ras mutation rate (29% for both MSS and MSI-L). Interestingly, the similarities between MSI-L and MSS groupings has apparently been recognized by Jass et al in their decision to combine these groupings in an excellent recent analysis of the effects of MSI on survival in the setting of Dukes C colorectal cancer.⁶

Thirdly, the MSI-L phenotype has not as yet been linked to any defect in known mismatch repair mechanisms, and the biochemical basis of the phenomenon remains unresolved. While not refuting the argument that MSI-L is a unique biological grouping, this issue remains a major conceptual impediment for the advocates of that viewpoint.

If the alternate hypothesis is to be considered, then plausible reasons must be presented for the finding of instability in a low percentage of markers in some tumors. We suggest that there are a number of factors which may account for this phenomenon. It is recognized that slippage of microsatellite repeat number does occur in cells with no underlying defect in mismatch repair, with estimates at some markers of rates between 0.1 and 1% per cell division in the germline.⁷ Each tumor and the normal cell from which it has arisen have probably undergone at least several hundred divisions since embryogenesis. Assuming that microsatellite slippage must have occurred in the first hundred divisions to be at a detectable level, about 5% of microsatellites would show at least one novel allele at normal mutation rates, easily sufficient to account for MSI-L. Furthermore, a low degree of error is inevitable in any PCR-based assay, particularly where DNA is of suboptimal quality and limited quantity.

In conclusion, we most certainly do not seek to play down the importance of the work of Jass and others in the exploration and elucidation of the MSI-low pathway. To their lasting credit, Jass and his colleagues have pursued the examination of this potential pathway with rigor. However, we stand by our viewpoint that the case for the importance of the MSI-L pathway is not yet proven and that its biological significance and clinicopathological consequences remain largely unknown. We would respectfully disagree with their statement, "It is not sensible to doubt the biological significance of microsatellite-low status." Rather, we will remain prudently skeptical of the biological validity of the MSI-L phenotype until such times

as truly distinctive biological markers or clearly defined pathogenetic mechanisms for this pathway are identified.

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Is Singlet Oxygen Antiatherosclerotic?

To the Editor-in-Chief:

Photoangioplasty is a new therapy of atherothrombosis.^{1,2} An important mediator in photodynamic treatment (PDT) is singlet oxygen (¹O₂). This nonradical oxygen derivative is excited, ie, it emits photons (hν) when returning to ground state oxygen. Physiologically, large concentrations of ¹O₂ are generated by a combined action of NADPH-oxidase and myeloperoxidase, typical enzymes of polymorphonuclear granulocytes (PMN).³ Minor concentrations of ¹O₂ are generated by redox-cycling agents of the quinone type such as phyloquinone (vitamin K), ubiquinone, or tetracycline.⁴

In the pathogenesis of atherothrombosis the pathological and chronic inflammatory action of phagocytes of the monocyte/macrophage type⁵ should be differentiated from the physiological action of PMN: flowing PMN are activated to PMN that roll on the endothelium; once bound to fibrin, depos-

ited on the endothelial layer, the PMN lyse the thrombus.⁴ Therefore, PMN activators and inducers of PMN rolling, such as $^1\text{O}_2$,⁶ might act anti-atherothrombotically. This could be the primary mechanism of anti-atherosclerotic action of certain antibiotics, such as tetracycline or roxithromycin, and not the direct interaction with chlamydia pathogens.^{7,8} $^1\text{O}_2/h\nu$ might also be involved in the mode of action of NO ,⁹ photons induce relaxation of smooth muscle cells similarly to NO .¹⁰ The quenching of physiological amounts of $^1\text{O}_2$ by cholesterol might result in a pathologically decreased anti-atherothrombotic response.⁴ In addition, the present hypothesis on $^1\text{O}_2$ as anti-atherosclerotic agent might explain the so-called dark phenomenon of photoangioplasty, ie, the sensitizer without illumination also acts anti-atherosclerotically, presumably by induction of redox-cycling.

Consequently, physiological PMN activators and/or generators of $^1\text{O}_2$,^{4,11,12} could be of clinical importance for treatment of atherothrombosis.

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