To the Editor:

We have read with interest the paper of Landolfi et al., "Increased Thromboxane Biosynthesis in Patients With Polycythemia Vera: Evidence for Aspirin-Suppressible Platelet Activation In Vivo." In a recent publication on 11 patients with chronic myeloproliferative disorders (CMPD), 7 with essential thrombocytosis and 4 with polycythemia vera, we have reached a similar conclusion (with respect to enhanced thromboxane generation) in our patients. Yet, the mechanism of this abnormality seems to be different from that suggested by Landolfi et al and, consequently, might have important clinical implications. It seems unlikely that in CMPD patients there is a "biochemical selective alteration in cyclooxygenase/thromboxane synthetase pathway" as stated by Landolfi et al, but rather an increase in platelet aggregation inducer (possibly thrombin) that stimulates platelet thromboxane A$_2$ (TXA$_2$) synthesis. Pertinent is our observation on normal TXB$_2$ generation (corrected to a normal platelet concentration: $2.5 \times 10^9$/mL) in platelet-rich plasma of our patients after stimulation by ADP, collagen, or epinephrine (described also by Landolfi et al), despite a reduced extent of platelet aggregation by these inducers. However, this finding could not explain a pronounced increase in serum TXB$_2$ generation (measured in suboptimal conditions, 22°C, and corrected to a normal platelet concentration) 2.9 to 7.1 times higher than that of controls and the presence of a potent agonist, possibly thrombin, stimulating platelet TXB$_2$ generation was indicated. The latter was also supported by the reported elevated plasma fibrinopeptide A level, a marker of thrombin genera-
tion,\(^4\) in CMPD patients.\(^5\) Moreover, other investigators have observed even a defective signal transduction through the TXA\(_2\) receptor in a CMPD patient,\(^6\) contrary to the conclusion of Landolfi et al.

We agree with Landolfi et al that increased TXA\(_2\) synthesis in CMPD patients may represent an enhanced platelet activation for two reasons. We have obtained a markedly elevated plasma \(\beta\)-thromboglobulin level (corrected to a normal platelet concentration), a marker of platelet activation,\(^6\) in our CMPD patients. In addition, picotamide (a thromboxane synthetase/receptor antagonist) was beneficial in the management of thromboembolic complications and in the reduction of elevated plasma fibrinopeptide A level in CMPD patients.\(^3\)

Finally, and in accordance with Landolfi et al, aspirin might be effective in the suppression of enhanced TXA\(_2\) biosynthesis, but it was ineffective in the management of thrombotic complications (arterial and venous) present in 8 of our 11 CMPD patients. It was therefore substituted with success by heparin-coumadin, compatible with our above-mentioned mechanism.

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REFERENCES

RESPONSE
We are grateful to Drs M. Zahavi and J. Zahavi for their comments. The mechanisms underlying enhanced thromboxane biosynthesis in polycythemia vera\(^1\) and essential thrombocythemia\(^7\) remain elusive. As we reported, it seems likely that thromboxane is produced in response to in vivo stimuli and that the platelet cyclooxygenase/Tx-synthase pathway is involved in their transduction. Unfortunately, the findings of Drs Zahavi do not provide clues for the identification of these stimuli mainly because triggers to platelet activation operating in vivo are unlikely to be detected by ex vivo capacity measurements. As for the role of aspirin in preventing thrombotic complications in this setting, this requires a randomized clinical trial of adequate sample size. One such trial has just started (GISP: Gruppo Italiano di Studio della Polycitemia) with the aim of assessing the long-term efficacy and safety of low-dose aspirin (40 mg/d) in patients with polycythemia vera.

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REFERENCES
Platelet function and thromboxane synthesis in myeloproliferative disorders [letter; comment]

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