stenosis and are improved by valve replacement. Along with Heyde[1] and Schwartz,[2] I called attention to this association, in an article published in 1961.[3] For some time after my article appeared, colleagues began to call the association Williams's syndrome. Later, when direct upper and lower endoscopies became common practice, the association between gastrointestinal bleeding and aortic stenosis was ascribed to arteriovenous ectasias and similar vascular abnormalities presumably associated with aging, in the same vein as aortic stenosis.

The observation by Vincentelli and coworkers only proves to me that if a physician lives long enough, a few things he or she has reported will turn out to be true.

Ralph C. Williams, Jr., M.D.

University of New Mexico
Albuquerque, NM 87131
rcwilliams@salud.unm.edu

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THE AUTHORS REPLY: Dr. Sucker and colleagues confirm the high frequency of hemostatic abnormalities in severe aortic stenosis but point out that the frequency of bleeding symptoms is low. Such a discrepancy was also found in our series and is usual in the von Willebrand syndrome as well as in other hemostatic diseases, since bleeding symptoms depend on the presence of bleeding-prone lesions (such as angiodysplasias or traumatic or surgical lesions). It is well known that the clinical expression of acquired von Willebrand syndrome is highly variable.[1] However, the diagnosis of this syndrome relies on biologic data.[2] We believe that in circumstances involving trauma, such as noncardiac surgery, the risk of bleeding is present in patients with severe aortic stenosis, even if they do not have any spontaneous bleeding. Moreover, this risk could be especially high in patients who are not eligible for surgical valve replacement: in a prospective survey of 123 patients with asymptomatic aortic stenosis, 8 of the patients who did not undergo surgery died, 4 of them from cardiac causes and 2 from gastrointestinal bleeding, suggesting that the risk of bleeding is not negligible as compared with classic cardiac causes of death.[3] In our opinion, the high probability of von Willebrand factor abnormalities should be taken into account in the management of severe aortic stenosis, even in the absence of bleeding symptoms.

Drs. Hansen and Hassager observed the association between bleeding symptoms and hypertrophic obstructive cardiomyopathy and suspect that similar proteolysis of high-molecular-weight multimers can occur in this disease, which is associated with high shear stress. Such a hypothesis is in good accordance with our findings and also with previously reported data and should be confirmed by specific exploration of von Willebrand factor in such cases.[4]

Finally, we would like to thank Dr. Williams for his perspicacity and for his continued interest in this issue, from 1958 to this day.

Sophie Susen, M.D.
André Vincentelli, M.D.
Brigitte Jude, M.D., Ph.D.

University Hospital
59037 Lille, France

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Microsatellite Instability in Colon Cancer

TO THE EDITOR: Ribic et al. (July 17 issue)[1] investigated microsatellite instability as a predictor of a benefit from adjuvant chemotherapy in patients with stage II or stage III colon cancer, and their findings confirm that microsatellite instability portends a better prognosis than microsatellite-stable cancer.[1-3] However, this research differs from that of Elsaleh et al., in which patients whose stage III colorectal cancer demonstrated microsatellite instability derived the greatest benefit from adjuvant chemotherapy.[4] In contrast, Ribic et al. found that patients with microsatellite instability did not benefit from adjuvant chemotherapy and may have been harmed by it (P=0.01). We wish to bring attention to a Na-

tional Cancer Institute–National Surgical Adjuvant Breast and Bowel Project (NCI–NSABP) collaborative investigation involving 542 patients with stage II or III colon cancer (173 of whom underwent surgery only and 369 of whom received adjuvant therapy). Patients with microsatellite instability (18 percent) and patients with microsatellite-stable cancers were found to benefit equally from the use of adjuvant chemotherapy. Thus, although the described investigations consistently show that adjuvant chemotherapy benefits patients with microsatellite-stable colon cancer, the relation between microsatellite instability and adjuvant chemotherapy differs among studies. We agree with Ribic et al. that the microsatellite-instability status should not be used in making therapeutic decisions outside of clinical trials at the present time.

Carmen J. Allegra, M.D.

National Surgical Adjuvant Breast and Bowel Project
Pittsburgh, PA 15212
callegra@nmcr.com

George Kim, M.D.

Mayo Clinic Jacksonville
Jacksonville, FL 32224

Ilan R. Kirsch, M.D.

National Cancer Institute
Bethesda, MD 20889

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TO THE EDITOR: Ribic et al. report that patients with stage II or III colorectal cancer do not benefit from adjuvant chemotherapy if their tumors show microsatellite instability, in contrast with our findings in patients with stage III disease[1] and the findings of others in patients with stage IV disease.[2] A possible explanation for these discrepancies might be that tumors with microsatellite instability have different properties, including prognosis and response to chemotherapy, depending on the underlying cause of their microsatellite-instability phenotype. Patients with sporadic colorectal cancer in whom microsatellite instability is caused by *MLH1* gene-promoter methylation are on average 18 years older than patients with microsatellite instability who do not have methylation of this gene.[3] A variety of mechanisms that are not related to methylation cause microsatellite instability in the majority of younger patients, including germ-line and somatic mutations and the loss of heterozygosity of mismatch-repair genes.[4] The patients studied by Ribic et al. were enrolled in clinical trials and hence were considerably younger than those in our population-based series.[1] We suggest that it may be premature to discount the predictive value of microsatellite instability without further characterization of tumors with this phenotype, particularly in terms of their DNA-methylation status.

Barry Iacopetta, Ph.D.

University of Western Australia
Nedlands 6009, Australia
bjiac@cyllene.uwa.edu.au

Hany Elsaleh, M.B., B.S., Ph.D.

University of California, Los Angeles
Los Angeles, CA 90095-6951

Nik Zeps, Ph.D.

Sir Charles Gairdner Hospital
Nedlands 6009, Australia

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TO THE EDITOR: Microsatellite instability helps predict the treatment response in patients with colorectal carcinoma.[1-3] In our studies of microsatellite instability, we found that intratumor heterogeneity for a given marker may bias the stratification of patients. In analyzing 90 sporadic colorectal adenocarcinomas for microsatellite instability and *MLH1*–*MSH2* expression according to the topographic compartment of the tumor, we found significant differences between the superficial compartment (tumor cells above the muscularis propria) and the deep compartment (tumor cells infiltrating the muscularis propria), with down-regulation of protein expression and increased microsatellite instability in the deep compartment. At least one third of tumors that

are unstable in the deep compartment can be expected to be stable in the superficial compartment.

Juan J. Jimenez, M.D., Ph.D.
Alfredo Blanes, M.D., Ph.D.
University of Malaga School of Medicine
29071 Malaga, Spain
Salvador J. Diaz-Cano, M.D., Ph.D.
Barts and the London NHS Trust
London E1 1BB, United Kingdom
s.j.diaz-cano@qmul.ac.uk

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THE AUTHORS REPLY: Our findings that patients who have stage II or stage III colon cancer with high-frequency microsatellite instability do not benefit from and may be harmed by fluorouracil-based adjuvant chemotherapy were based on analyses of tumors from patients who were randomly assigned prospectively to surgery alone or to fluorouracil-based adjuvant chemotherapy after surgery. In contrast, the unpublished results described by Allegra and colleagues were derived through the comparison of patients participating in two NSABP trials (trials C-01 and C-02) who had undergone surgical resection with patients from two other NSABP trials (C-03 and C-04) who were assigned to surgery plus fluorouracil-based adjuvant chemotherapy.[1] The observations of Iacopetta and colleagues were derived from a nonrandomized, hospital-based cohort study[2] in which the choice of whether to deliver adjuvant treatment was made by the physician. Age, coexisting conditions, and performance status were all possible factors in determining whether patients were offered or accepted adjuvant chemotherapy after surgery. Thus, the findings described by both Allegra et al. and Iacopetta et al. are susceptible to measurable and unmeasurable differences in the treated and untreated patients among the study populations they analyzed. In addition, the findings of Elsaleh et al.[2] regarding differential efficacy of treatment according to sex and the location of the cancer within the colon have recently been contradicted by a pooled analysis of data from more than 3300 patients, raising additional issues about the representativeness of the population of patients they studied.[3] Nonetheless, we agree that further studies are needed before the current recommendations for the use of fluorouracil-based adjuvant chemotherapy in patients with colon cancer are changed.

The observations, described by Jimenez and colleagues, of topographic differences in high-frequency microsatellite-instability status within cancer specimens are interesting but appear to be inconsistent with the presence of high-frequency microsatellite instability in the benign lesions that are precursors to colorectal cancer: aberrant crypt foci and adenomatous polyps.[4,5] Furthermore, the consistent association of distinct clinicopathological phenotypes with colorectal cancers with high-frequency microsatellite instability (right-sided predominance, exophytic growth, poor differentiation, lymphocytic infiltrates, and "pushing" margins of invasion)[6] and the routine use of tumor microsatellite instability to identify patients with hereditary nonpolyposis colorectal cancer argue that microsatellite instability does indeed reflect a reliable tumor genotype, as defined by most investigators, and is probably not influenced by methodologic factors.

We agree that the tumor-methylation status or the specific mismatch-repair deficiency present in any cancer may further influence the observed response to chemotherapy. We hope that large, multicenter, collaborative efforts or meta-analyses will soon be able to address these important issues in order to optimize the care of patients with colon cancer.

Robert Gryfe, M.D., Ph.D.
Christine M. Ribic, M.Sc.
Mount Sinai Hospital
Toronto, ON M5G 1X5, Canada
gryfe@mshri.on.ca
Daniel J. Sargent, Ph.D.
Mayo Foundation
Rochester, MN 55905

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