

seroconversion. This analysis found CD4 slope to be significantly associated with time to clinical AIDS. To exclude potent ART use, only visits prior to 1990 were included. Other studies have confirmed the prognostic value of CD4 slope; however, they also have confirmed its high variability and relatively weak prognostic value relative to pretreatment plasma HIV RNA or CD4 cell count.^{2,3}

The analysis by Wolbers et al⁴ from the CASCADE collaborative included treatment-naïve persons with documented seroconversion who started cART in 1996 or later. The primary outcome was time to progression to AIDS or death following initiation of cART. Using a variety of carefully considered statistical methods, the authors found no association of CD4 slope with outcome for the full analysis cohort or for a subset with CD4 cell counts above 350/μL prior to treatment. However, a supplementary analysis from the pre-cART era confirmed a small but statistically significant association of CD4 slope with outcome (not present in a subset with CD4 cell count above 350/μL). This implies that the beneficial effect of ART overwhelms the relatively weak prognostic value of CD4+ slope.

Yet, as Wolbers et al⁴ point out, the small number of outcomes at higher baseline CD4 cell counts diminishes the power of all surrogate markers, and the analysis may be confounded by individuals with rapid CD4 declines beginning ART earlier, as suggested by existing guidelines, potentially leading to better outcomes. Both MACS and CASCADE analyses are relevant to seroconverters; therefore, the validity of extrapolation to the larger population of persons without known seroconversion dates remains unproven.

We agree that as treatment is recommended at higher CD4 cell counts, CD4 slope becomes less relevant. The recommendation to begin therapy at CD4 cell count of 500/μL, as well as to treat many subgroups regardless of CD4 cell count, captures most patients with substantial CD4 decline. Yet, because of the consistent though small association with disease progression in untreated patients, and the potential confounding factors associated with the timing of initiation of therapy in cohort studies, CD4 slope may still be valid and useful in a small subset of patients.

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1. Lyles RH, Muñoz A, Yamashita TE, et al. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men: Multicenter AIDS Cohort Study. *J Infect Dis.* 2000; 181(3):872-880.
2. Mellors JW, Muñoz AM, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med.* 1997;126(12):946-954.
3. Cozzi Lepri A, Sabin CA, Phillips AN, Lee CA, Pezzotti P, Rezza G. The rate of CD4 decline as a determinant of progression to AIDS independent of the most recent CD4 count: the Italian Seroconversion Study. *Epidemiol Infect.* 1998; 121(2):369-376.
4. Wolbers M, Babiker A, Sabin C, et al; CASCADE Collaboration Members. Pre-treatment CD4 cell slope and progression to AIDS or death in HIV-infected patients initiating antiretroviral therapy: the CASCADE collaboration: a collaboration of 23 cohort studies. *PLoS Med.* 2010;7(2):e1000239.

RESEARCH LETTER

Biochemical Misdiagnosis of Pheochromocytoma in Patients Treated With Sulfasalazine

To the Editor: The excessive secretion of catecholamines by pheochromocytoma can have serious medical consequences.¹ Adrenal incidentaloma is becoming an important public health challenge in aging populations.² Initial evaluation for possible pheochromocytoma or adrenal incidentaloma generally includes measurements of fractionated metanephrines in urine, plasma, or both.^{1,3} We report 3 cases of biochemical misdiagnosis of pheochromocytoma in patients being treated with sulfasalazine.

Methods. Between 2006 and 2009, 3 women were admitted to the hospital with suspected pheochromocytoma (in 2) or adrenal incidentaloma (in 1) (TABLE). All were receiving sulfasalazine (1500 mg or 2000 mg daily) for either rheumatoid arthritis or ankylosing spondylitis. The 24-hour urinary normetanephrine (UNM) levels, measured several times by high-performance liquid chromatography with electrochemical detection (HPLC-EC), were extremely high (mean [SD], 12 064 [7993], 12 708 [4220], and 10 946 [1435] μg/d, respectively; normal range, 105-600 μg/d). Urinary and plasma metanephrine and norepinephrine levels remained normal. Anatomical as well as functional imaging did not show any evidence of a pheochromocytoma or paraganglioma (Table). After a false-positive result in UNM assay due to sulfasalazine was suspected, sulfasalazine treatment was stopped.

Approximately 1 month later, UNM levels had returned to normal in all 3 patients (310, 501, and 249 $\mu\text{g}/\text{d}$, respectively). The first patient decided to take sulfasalazine again, and UNM levels checked twice 1 month later returned to high levels (mean [SD], 17 209 [6231] $\mu\text{g}/\text{d}$).

To assess for interference by sulfasalazine, the UNM levels of the patients were analyzed by mass spectrometry (LCQ Finnigan MAT, San Jose, California). The results with the UNM levels obtained by both techniques were compared in 3 patients with pheochromocytoma and 3 healthy control participants. Because sulfasalazine is a prodrug, to assess whether interference could be due to 5-aminosalicylic acid (mesalamine, an active breakdown product of sulfasalazine formed in the gut), chromatograms of pure samples of sulfasalazine (S0883; Sigma, St Louis, Missouri), mesalamine (A3537; Sigma), and normetanephrine (Sigma) were directly compared for coelution.

The institutional review board of the University Hospital Rangueil approved this study, and all participants provided written informed consent.

Results. Mean (SD) UNM concentration measured by HPLC-EC was 6477 (3184) $\mu\text{g}/\text{L}$ in patients using sulfasalazine, 3096 (1713) $\mu\text{g}/\text{L}$ in patients with pheochromocytoma, and 300 (134) $\mu\text{g}/\text{L}$ in healthy controls. Mean (SD) UNM abundance measured by mass spectrometer was 2.34×10^5 (7.39×10^4) for sulfasalazine patients, 1.99×10^6 (1.47×10^6) for patients with pheochromocytoma, and 2.08×10^5 (9.81×10^4) for healthy controls. By HPLC-EC, the patients treated with sulfasalazine had UNM values 2159% of control values, whereas the pheochromocytoma patients had UNM values 1032% of control values. A urine chromatogram from patient 1 compared with a standard normetanephrine sample is shown in FIGURE A. However, by mass spectrometry, the patients treated with sulfasalazine had only 113% of con-

Table. Characteristics of 3 Women With False-Positive Results for Pheochromocytoma

	Patient 1	Patient 2	Patient 3
	Clinical Characteristics		
Age, y	51	54	69
Weight, kg	83	76	50
Height, cm	167	163	150
Blood pressure, mm Hg	115/85	116/74	160/80
Sulfasalazine dose, mg/d	1500	2000	2000
Indication for sulfasalazine	Rheumatoid arthritis	Ulcerative colitis, ankylosing spondylitis	Ankylosing spondylitis
Other comorbidities	Hypothyroidism	Hypothyroidism, chronic hypokalemia	Hypertension, acute atrial fibrillation
Other medications	Prednisone, levothyroxine	Levothyroxine, potassium chloride	Acebutolol, spironolactone, thiazide diuretic, aspirin
Reason for testing urinary meta/normetanephrines	Paroxysmal hypertension, palpitations, anxiety	Adrenal incidentaloma found on CT scan for abdominal pain	Uncontrolled hypertension, anxiety
	Investigations		
Imaging	CT: no adrenal or other tumor Cranial/neck MRI: normal MIBG scintigraphy, somatostatin receptor scintigraphy, and FDG PET: no abnormal accumulation	CT: adrenal nodular hyperplasia, bladder lipoma Cranial/neck MRI: normal MIBG scintigraphy and somatostatin receptor scintigraphy: no abnormal accumulation	CT: no adrenal tumor
Urinary normetanephrine level, range, $\mu\text{g}/\text{d}$ (normal, 105-600)			
Before stopping sulfasalazine	5151-21 575	7836-18 060	9931-11 960
After stopping sulfasalazine ^a	Day 45: 310 Day 395: 320	Day 30: 501	Day 30: 249
Urinary metanephrine level, range, $\mu\text{g}/\text{d}$ (normal, 70-350)			
Before stopping sulfasalazine	44-115	76-214	100-102
After stopping sulfasalazine ^a	Day 45: 70 Day 395: 72	Day 30: 91	Day 30: 110
Plasma normetanephrine level, pg/mL (normal <200)			
Before stopping sulfasalazine	42	74	51
After stopping sulfasalazine ^a	Day 45: 36	Day 30: 69	Day 30: 42
Plasma metanephrine level, pg/mL (normal <90)			
Before stopping sulfasalazine	2	28	6
After stopping sulfasalazine ^a	Day 45: 10	Day 30: 106	Day 30: 4

Abbreviations: CT, computed tomography; FDG PET, fluorodeoxyglucose positron emission tomography; MIBG, meta-iodobenzylguanidine; MRI, magnetic resonance imaging.
^aDay 0 is the date of stopping sulfasalazine.

tol values, whereas patients with pheochromocytoma had 958% of control values. Pure mesalamine and pure sulfasalazine did not interfere with normetanephrine (Figure B).

Comment. The mass spectrometry analysis demonstrates that the urinary HPLC-EC UMN assay routinely used in the clinic may experience interference by a molecule released into the urine during sulfasalazine treatment. This interference has been observed in patients treated with mesalamine.^{4,5} However, because pure mesalamine did not coelute with normetanephrine in HPLC-EC (Figure B), the interfering compound in urine of sulfasalazine-treated patients might be a metabolite of mesalamine.

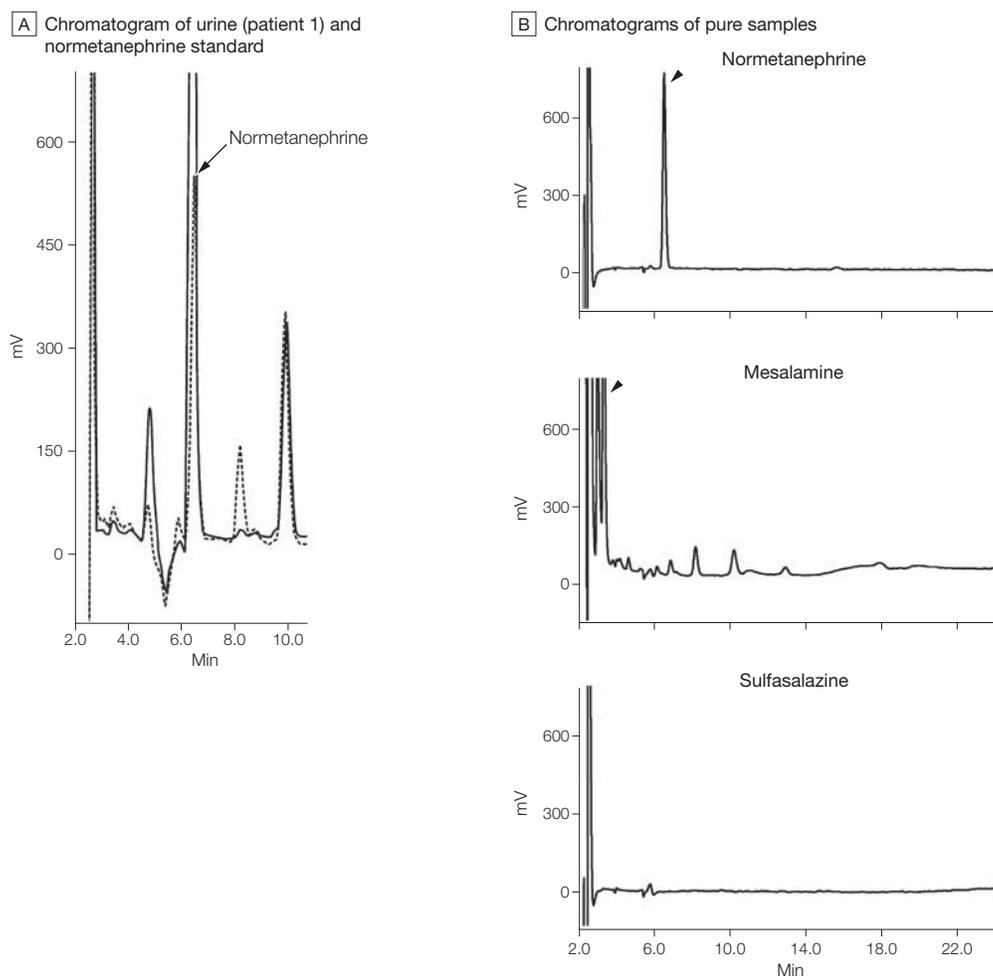
Although plasma metanephrine testing may be more specific,¹ urinary testing is included in guidelines and remains very common globally.³ Our findings would support using plasma metanephrines instead of urinary metanephrines to

detect pheochromocytoma, particularly when patients use medications that could interfere with the urinary assay.^{1,6} Recognition of sulfasalazine as a medication that interferes with assays for UNM can avoid the unnecessary exposure of patients to radiation and the cost of additional investigation for neuroendocrine tumors.

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Figure. Chromatograms Showing Association Between a Metabolite of Mesalamine and Urinary Assay of Normetanephrine



A: Chromatogram of urine from patient 1 treated with sulfasalazine (solid line) and chromatogram of a normetanephrine standard sample (dotted line). A high peak was observed in the position of normetanephrine (arrow); this peak was the interfering molecule coeluting with normetanephrine. B: Chromatogram of pure normetanephrine, pure mesalamine, and pure sulfasalazine. The retention time of mesalamine is lower than the retention time of normetanephrine, and sulfasalazine was not detected. Arrowheads indicate peaks of normetanephrine (top chromatogram) and mesalamine (middle).

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Author Contributions: Dr Pont had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bouhanick, Pont.

Acquisition of data: Bouhanick, Fauvel, Pont.

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1. Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA*. 2002;287(11):1427-1434.

2. Terzolo M, Bovio S, Pia A, Reimondo G, Angeli A. Management of adrenal incidentaloma. *Best Pract Res Clin Endocrinol Metab*. 2009;23(2):233-243.

3. Pacak K, Eisenhofer G, Ahlman H, et al; International Symposium on Pheochromocytoma. Pheochromocytoma: recommendations for clinical practice from the First International Symposium: October 2005. *Nat Clin Pract Endocrinol Metab*. 2007;3(2):92-102.

4. Walsh N. Sulfasalazine induced falsely positive urinary catecholamines. *Rheumatology News*. 2006;5(8):11.

5. Ito T, Imai T, Kikumori T, et al. Adrenal incidentaloma: review of 197 patients and report of a drug-related false-positive urinary normetanephrine result. *Surg Today*. 2006;36(11):961-965.

6. Peaston RT, Graham KS, Chambers E, van der Molen JC, Ball S. Performance of plasma free metanephrines measured by liquid chromatography-tandem mass spectrometry in the diagnosis of pheochromocytoma. *Clin Chim Acta*. 2010;411(7-8):546-552.

CORRECTIONS

Text Errors: In the Original Contribution entitled "Association of Telomere Length of Peripheral Blood Leukocytes With Hematopoietic Relapse, Malignant Transformation, and Survival in Severe Aplastic Anemia," published in the September 22/29, 2010, issue of *JAMA* (2010;304[12]:1358-1364), incorrect data identification was published in the "Results" section of the abstract on page 1358. The clause that reads "evolution to monosomy 7 or complex cytogenetics was more common in the first quartile (HR, 18.8%; 95% CI, 3.5%-31.6%) than in quartiles 2 through 4 (HR, 4.5%; 95% CI, 0.5%-8.2%; $P=.002$)" should not have included either "HR."

In the Figure 3 legend on page 1362, the words "was observed" in the penultimate sentence should not have been included. The sentence should read: "A group with intermediate survival was defined by either a low ARC and longer telomere (quartiles 2 through 4) or a high ARC and with the shortest telomere length (first quartile)."

Numerical Error: In the Original Contribution entitled "Use of Advanced Radiology During Visits to US Emergency Departments for Injury-Related Conditions, 1998-2007," published in the October 6, 2010, issue of *JAMA* (2010;304[13]:1465-1471), a numerical error appeared in the "Results" section of the abstract and in the text. On page 1465, in the "Results" section of the abstract, the second sentence should be "There was a small increase in the prevalence of life-threatening conditions (1.7% [95% CI, 1.2%-2.2%; 89 of 5237 visits] in 1998 and 2.0% [95% CI, 1.6%-2.5%; 142 of 6567 visits] in 2007; $P=.04$ for trend)." On page 1468, in the first column, first full paragraph, the first sentence should be "A life-threatening condition was diagnosed in 89 of 5237 sampled visits (1.7%; 95% CI, 1.2%-2.2%) in 1998 compared with 142 of 6567 visits (2.0%; 95% CI, 1.6%-2.5%) in 2007 ($P=.04$ for trend; AOR for 2007 vs 1998, 1.20 [95% CI, 0.81-1.79])."

Nobody grows old by merely living a number of years.
People grow old by deserting their ideals. Years may
wrinkle the skin, but to give up interest wrinkles the
soul. . . . You are as young as your faith, as old as your
doubt; as young as your self-confidence, as old as your
fear; as young as your hope, as old as your despair.

—Douglas MacArthur (1880-1964)