COMMENTS AND RESPONSES

Where Is the Evidence That the Resurgence of Nomograms Is Harmful?

TO THE EDITOR: The review by Grimes (1) of the history of nomograms was informative. However, his criticism of the "epidemic" of nomogram resurgence was fundamentally unsubstantiated. Grimes states that "nomograms provided speed in calculation at the cost of precision" without providing any evidence that the lost precision mattered. Where is the evidence, for example, that calculating likelihood ratios to additional decimal places improves clinical decision making? Conversely, where is the evidence that calculating medication doses by using a body surface area nomogram adversely affects patient well-being?

An alternative, testable hypothesis is that contemporary reliance on computer-generated values numbs physicians to the meaning of their calculations and blinds them to errors that would have been obvious on a nomogram. Personal computing may be more convenient than nomograms, but inconvenience does not equal inappropriateness ("Hence, the resurgence of this relic is inappropriate").

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Grimes DA. The nomogram epidemic: resurgence of a medical relic. Ann Intern Med. 2008;149:273-5. [PMID: 18711159]

IN RESPONSE: Dr. Zwillich writes that my criticism of the "nomogram epidemic" was "fundamentally unsubstantiated." Moreover, he suggests that use of computers "numbs" physicians. I infer that he would prefer to return to the days of slide rules for physics problems and pencil-and-paper arithmetic for completing income tax returns. When slide rules were used, mistakes by a factor of 10 were easy to make because the placement of the decimal could be unclear. This does not happen with a calculator. Although the utility of electronic versus hand calculations may be a testable hypothesis, some benefits of technology are self-evident (1).

Despite Dr. Zwillich's apparent nostalgia, I do not miss the good old days of hand calculations. Judging from the ubiquitous use of computers and calculators in everyday life, I am not alone.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ. 2003; 327:1459-61. [PMID: 14684649]

Can the SMART Study Data Be Used to Assess Risk Factors for Renal Disease?

TO THE EDITOR: In the recent analysis by the SMART (Strategies for Management of Anti-Retroviral Therapy) Study Group (1), resumption of continuous antiretroviral therapy after structured treatment interruption did not fully abrogate the increased risk for serious adverse events and death associated with initial assignment to the drug conservation group of the trial. This suggests that even short periods of untreated HIV infection may confer a greater overall risk for major complications than that posed by the antiretroviral treatments themselves. However, there was a statistically significant interaction between the study period (premodification vs. postmodification) and the treatment group assignment (continuous virologic suppression vs. drug conservation) for renal disease events. Although the renal event rates were low, this result implies that longer-term, continuous antiretroviral therapy may eventually lead to a higher rate of nephropathy.

We would be interested to see a more thorough description of the medical and antiretroviral treatment histories, including history of treatment with the potentially nephrotoxic antiretroviral drug tenofovir disoproxil fumarate, for the study participants who developed renal disease and a comparison between them and matched control groups, from both study periods, of participants who did not develop such complications. Such an analysis from this well-characterized cohort would be of great value in identifying potential risk factors for renal disease in patients with HIV infection.

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Potential Financial Conflicts of Interest: Dr. Gupta has received advisory and speaking fees from Gilead Sciences (the manufacturer of tenofovir disoproxil fumarate) and is the principal investigator of a phase IV study, sponsored by Gilead Sciences, of renal toxicities associated with antiretroviral therapies.

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1. El-Sadr WM, Grund B, Neuhaus J, Babiker A, Cohen CJ, Darbyshire J, et al; SMART Study Group. Risk for opportunistic disease and death after reinitiating continuous antiretroviral therapy in patients with HIV previously receiving episodic therapy: a randomized trial. Ann Intern Med. 2008;149:289-99. [PMID: 18765698]

IN RESPONSE: We agree with Dr. Gupta that the renal outcomes before and after the protocol modification in SMART are interesting and require further study. The interaction P value corresponding to the treatment hazard ratio comparison before and after the protocol change was significant ($P = 0.014$); however, the number of participants with renal events, defined in SMART as death from renal disease or end-stage renal disease, was too small (a total of 18 across both treatment groups) to reliably study predictors. A careful study of risk factors for renal disease in the SMART study requires more events. Thus, we are exploring the possibility of using stored plasma samples to measure creatinine in SMART participants over the entire follow-up. With these data, an expanded renal outcome (for example, death due to renal failure, end-stage renal disease, or large decline in estimated glomerular filtration rate) would result in more events and would allow reliable assessment of risk factors for renal disease, as suggested by Dr. Gupta.

Our finding that treatment interruption increases risk for renal progression is supported by another recent investigation in SMART (1, 2). Stored samples were used to measure cystatin C, a marker of renal function, during the first year of the study but before the protocol change. Cystatin C levels increased significantly in the treatment interruption group compared with those in patients randomly assigned to receive continuous antiretroviral therapy (2).

Ultimately, we think that the risk and benefits of antiretroviral treatment are best assessed in a randomized trial of early therapy instead of a treatment interruption study, such as SMART. A trial called START (Strategic Timing of AntiRetroviral Therapy) is scheduled to begin next year and is designed to investigate the risks and benefits of early antiretroviral treatment on clinical outcomes, including renal disease, and other serious non-AIDS conditions, such as cardiovascular disease, liver disease, and malignant conditions.

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Potential Financial Conflicts of Interest: None disclosed.

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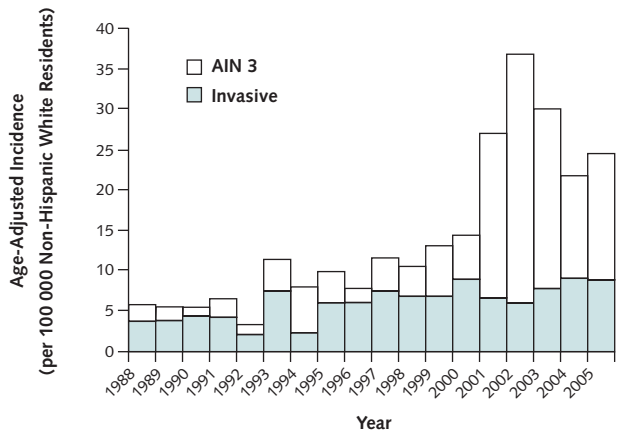
Is There a Proven Link Between Anal Cancer Screening and Reduced Morbidity or Mortality?

TO THE EDITOR: We read with interest the study by Chin-Hong and colleagues (1) comparing techniques to detect anal intraepithelial neoplasia (AIN) among men who have sex with men. A more pressing question is whether sufficient evidence of effectiveness, in terms of reducing anal cancer morbidity or mortality, exists to support anal cancer screening. It does not.

No prospective studies, including randomized, controlled trials, have assessed the effectiveness of anal cancer screening (2). Instead, screening proponents have cited indirect evidence, including analogy to cervical cancer screening, to advocate for routine screening among certain populations, such as men who have sex with men (2, 3). As screening proponents rightly note, randomized, controlled trials of Papanicolaou smears for cervical cancer prevention were never conducted; evidence of effectiveness is based on data correlating increased screening and decreased cancer incidence (2).

In San Francisco, anal cancer screening has been offered at health care provider practices since the late 1990s. Reporting of invasive anal cancer and AIN 3 (sometimes called *in situ carcinoma*) is legally mandated in California. We used data from the California Cancer Registry to examine trends in AIN 3 lesions and invasive anal squamous cell cancer reported among non-Hispanic white male residents of San Francisco County during 1988 to 2005 (4). As shown in the **Figure**, the age-adjusted incidence of invasive anal squamous cell carcinoma was

Figure. **Age-adjusted incidence of AIN 3 and invasive squamous cell carcinoma of the anus* among non-Hispanic white male residents of San Francisco County, 1988–2005.**



AIN 3 = anal intraepithelial neoplasia 3 (including in situ carcinoma). * Anal cancer was defined by using International Classification of Diseases, Oncology, 3rd edition, site codes C210–C212 and C218; AIN 3 by histology code 8077; in situ squamous cell carcinoma by histology codes 8010, 8051–8078, 8081; and invasive squamous cell carcinoma by histology codes 8010, 8051–8076, and 8078.

stable from the mid-1990s, whereas the incidence of AIN 3 substantially increased during 2001 to 2005 compared with previous years. Anal cancer mortality rates are not reliable for this population because fewer than 5 deaths per year occur from anal cancer.

These data demonstrate that screening was associated with increased detection of AIN 3 lesions but not decreased incidence of invasive cancer. Biological or anatomical differences between the anal canal and the cervix might render anal cancer screening less effective than cervical cancer screening. Negative consequences of anal cancer screening, including anxiety, fear, and depression after receiving abnormal results, and procedural complications (5) might also affect the cost–benefit ratio unfavorably.

This ecological analysis does not prove that screening is ineffective. Invasive cancer incidence might have increased without screening; insufficient numbers or types of patients might have been screened; insufficient time might have elapsed to detect a reduction in incidence; or ecological analysis might lack sensitivity to detect incidence changes among specific populations at high risk. Only a randomized, controlled trial involving numerous participants can—and, we hope, ultimately will—provide conclusive effectiveness data (2). Meanwhile, given the costs and consequences of screening, sufficient evidence does not exist to support routine anal cancer screening for men who have sex with men.

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Note: The cancer incidence data used in this study were supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N01-PC-54404 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement 1U58DP00807-01 awarded to the Public Health Institute. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the State of California, the California Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors. Endorsement by any of those agencies is not intended nor should be inferred.

Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: We appreciate Dr. Katz and colleagues' comments and their efforts to draw attention to this important issue. They are correct: The incidence of anal cancer is not decreasing. Indeed, published data show that the incidence of invasive anal cancer is increasing in men and women worldwide. In a recent review of 39 population-based registries in the United States between 1998 and 2003, invasive anal cancer increased 2.6% per year on average (1). Using California Cancer Registry data, Cress and Holly (2) used age-adjusted incidence rates from 1973 to 1999 (beginning before the period analyzed by Dr. Katz and colleagues) to show that, among Hispanic and non-Hispanic white men in San Francisco County, age-adjusted rates of invasive anal cancer tripled from 1.5 per 100 000 persons in 1973 to 1978 to 4.5 per 100 000 persons in 1991 to 1995. Dr. Katz and colleagues' data are consistent with Cress and Holly's data for the period they reviewed (beginning in 1988) and show a further increase in incidence of invasive anal cancer to almost 10 per 100 000 persons by 2004 to 2005.

The increase in anal cancer incidence is even more pronounced in high-risk populations, such as HIV-positive persons, despite the widespread use of highly active antiretroviral therapy (HAART). Matching data from the San Francisco AIDS registry and the California Cancer Registry, Hessol and colleagues (3) demonstrated that after adjustment for age at AIDS diagnosis, race, risk group, sex, calendar year, HAART use, and HAART era, the risk for anal cancer was significantly higher in the HAART era (relative hazard, 2.74). Given that HAART was not associated with a decline in the incidence of invasive anal cancer, even with the limited number of people screened and treated, it is possible—as Dr. Katz and colleagues postulate—that the rates of invasive anal cancer could have been even higher if there was no screening for and treatment of AIN 3 in this population.

However, this is speculative and, as Dr. Katz and colleagues state, "This ecological analysis does not prove that screening is ineffective." One could use ecological data to show a population-level impact of screening on reducing cancer incidence, but this kind of analysis will be less sensitive to demonstrate a true effect if there really was one, unless screening is relatively common in the population at highest risk for disease. Unfortunately, this is not the case. In our community-based sample of men who have sex with men in San Francisco County, a population for which we have advocated systematic screening, only 7% previously underwent anal cancer screening.

Overall, the evidence points to an increase in invasive anal cancer in men and women in the general population. In the absence of widespread systematic anal cancer screening (even in San Francisco), it is difficult to use population-based cancer registry data to discount the benefit of anal cancer screening. We strongly agree that more studies are needed to determine the effect of screening on a population level, similar to what was done with cervical cancer screening. In this case, we would focus on the highest-risk group—those with HIV infection—to most quickly determine the impact of screening. Studies are also needed to determine the acceptability and tolerability of treatment of AIN. If the prophylactic quadrivalent human papillomavirus vaccine is approved for men by the U.S. Food and Drug Administration, additional studies will be needed to determine the effectiveness of the vaccine on anal cancer and associated precursor lesions. In the interim, given the high prevalence of anal human papillomavirus infection and potential anal cancer precursor lesions among men who have sex with men and among HIV-positive men and women, we believe that sufficient evidence already exists for screening populations at high risk for anal cancer. We believe that investment in capacity building is most needed, with continued training of personnel to provide education to patients and providers and to conduct high-resolution anoscopy and treatment.

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Potential Financial Conflicts of Interest: None disclosed.

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Is There a Connection Between High Educational Debt and Suicidal Ideation Among Medical Students?

TO THE EDITOR: We commend Dyrbye and colleagues (1) on their important work linking burnout to suicidal ideation among medical students. To assist educators in addressing this issue, we wondered if there were any observable differences between students who reported "chronic burnout" and those who "recovered from burnout." For example, do more resilient students have marital support or lower educational debt? We also found it especially noteworthy that higher levels of educational debt were associated with increased suicidal ideation in this study (1). It is plausible that high educational debt may act as a chronic stressor, contributing to persistent burnout in certain students. In support of this hypothesis, another recent study observed an association between anticipated debt and perceived financial stress, suggesting that anxieties about future debt also contribute to student stress (2). This highlights the need to consider how to prepare students with higher debt to address this mental stressor.

In addition to these factors, it is also important to understand how much of recovery from burnout is a natural part of completing the stressful, and predominantly clinical, third year. Students in their third year had increased suicidal ideation compared with those in other years (1). In an insightful review (3), 3 of the authors of this study discuss the myriad causes leading to medical student moral distress. During the clinical years, however, moral or ethical distress may play an especially subtle but substantial role in student well-being (4). Using the cardiac stress test as an analogy, clinical clerkships may inadvertently act as an ethical stress test that risk-stratifies those students who are particularly susceptible to poor resilience, cynicism, and burnout as future resident physicians. Given the new accreditation requirement to "periodically assess the learning environment" at U.S. medical schools (5), the extent of burnout and resilience among students might serve as a useful proxy to "risk-stratify" even medical schools—particularly those schools with learning environments that are at high risk for eroding student well-being and promoting burnout.

This study therefore emphasizes the importance of further research on the specific contributions of financial and moral stress in promoting burnout. Through more work like this, medical educators will be better able to target students burdened with high educational debt or those showing poor resiliency from burnout. Early interventions are particularly important before high-risk students become burned-out residents responsible for patient care.

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Potential Financial Conflicts of Interest: None disclosed.

References

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IN RESPONSE: We thank Drs. Yoon and Arora for their thoughtful letter. We agree that debt is a substantial source of stress for today's medical student. As reported, students with more than $100 000 of educational debt were 1.47 times more likely to have suicidal ideation during the previous year than students with less than $50 000 in reported debt on univariate analysis. Despite this association, debt was not independently associated with suicidal ideation during the previous year on multivariate analysis. The amount of debt that students reported was associated with other factors, such as age, relationship status, parental status, year in school, and burnout (all $P < 0.02$). This observation suggests that the relationship between debt and suicidal ideation may be mediated through interactions between debt and burnout or other characteristics rather than directly. This possibility is worthy of further study. We also believe it is important to identify what personal and professional characteristics are associated with recovery from burnout. We hope this information can inform efforts to assist struggling students. We are in the process of performing a comprehensive formal analysis of this aspect, which will be the subject of a future article.

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Potential Financial Conflicts of Interest: None disclosed.

Is Too Much Intervention Recommended in the ACP Osteoporosis Treatment Guidelines?

TO THE EDITOR: We reviewed the American College of Physicians (ACP) guidelines on the treatment of low bone density or osteoporosis to prevent fractures (1). Strengths of these guidelines include

their rigorous methods; their use of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (2); and that they are based on an extensive systematic review. However, we are worried that adherence to these guidelines may not yield the balance of benefits and costs that the authors judged as favorable when they made strong treatment recommendations, and we have a few questions to clarify this issue.

The panel strongly recommended that clinicians offer pharmacologic treatment to everyone with densitometric osteoporosis, as well as those who have experienced fragility fractures. However, they say that "osteoporosis affects an estimated 44 million Americans or 55% of people 50 years of age or older" (1). Do they really mean that one half of U.S. persons older than 50 years should be offered medications? Consider first patients with previous fragility fractures. This is the highest-risk group, and arguably, a strong recommendation to offer medication to reduce the risk for fractures seems compelling.

As the authors acknowledge, bone mineral density (BMD) is not a good fracture predictor (3), and many at-risk patients may choose not to take the medication once informed about their fracture risk and the benefits (fracture risk reduction), risks, burden, and cost of therapy. Offering treatment to a 50-year-old woman with just densitometric osteoporosis will require treating women with a 10-year risk for any fragility fracture of less than 9% (3). The risk for hip fracture, the most morbid fragility fracture, would be under 3%.

Also, the efficacy of osteoporosis treatment programs is lower than expected because of poor patient adherence, which could be improved in at-risk patients who commit to treatment with an understanding of their risk and the potential for risk reduction with medications.

According to the GRADE approach, a weak recommendation indicates an expectation that different patient preferences and circumstances will lead to different optimal management approaches (2). Shouldn't the panel have formulated a weak (grade 2) recommendation for medication for women with densitometric osteoporosis?

Why did the panel decide to set "high risk for fracture" thresholds (for example, 3% for a 50-year-old woman) at levels well below those used for cardiovascular disease? This choice suggests that the panel believes the implications of a fragility fracture to be much greater in magnitude and patient importance than a cardiovascular event, because high-risk thresholds for the latter are usually stated as 20% to 30% at 10 years.

Recommendation 2 suggests treating women with osteopenia (T-score of −1.5 to −2.5) or those older than 62 years. This recommendation is appropriately weak, but did the panel intend to recommend treatment of individuals in this population who are at low risk for fractures? Why not recommend that physicians and patients consider the risk for fractures resulting from risk factors other than BMD by using such models as the one recently developed by the World Health Organization (3)? Why not recommend that clinicians and patients share information about this baseline risk and consider the burdens, side effects, and costs of medications vis-à-vis the expected reduction in this baseline risk? This may lead to decisions that are sensitive to both risk and patient preferences.

Drafting guidelines requires rigor, judgment, consensus, and expertise. In addition to these features of the present guideline, the panel may want to consider making more explicit the values and preferences they used to arrive at these recommendations. Answering these questions may facilitate this process.

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IN RESPONSE: We thank Dr. Alonso-Coello and colleagues for their comments regarding the ACP's recent guideline on pharmacologic treatment of osteoporosis. The Fracture Risk Assessment Tool (FRAX) may be a useful instrument for estimating an individual patient's risk for fracture, and we noted in our guideline that physicians may use such models to help guide their decisions. However, evidence from randomized, controlled trials showing the benefits of treatment in patients who were selected on the basis of their scores from FRAX is currently lacking. Almost all trials demonstrating benefit of treatment enrolled patients on the basis of BMD-determined osteoporosis, as defined by T-score and/or the presence of existing fragility fractures. For example, Liberman and colleagues (1) enrolled postmenopausal women solely on the basis of a BMD T-score of −2.5 or less. This trial showed that treatment with alendronate was associated with a 48% reduction in the proportion of women with new vertebral fractures (3.2% vs. 6.2% in the placebo group; $P = 0.03$), a decreased progression of vertebral deformities (33% vs. 41% in the placebo group; $P = 0.028$), and a reduced loss of height ($P = 0.005$) and was well tolerated. Similarly, Reid and colleagues (2) showed benefits of zoledronic acid in a study population that included women with BMD at the lumbar spine of at least 2.0 SD below the mean value for young adults (a T-score less than −2.0). Thus, our guideline statements define the populations to be considered for treatment to be consistent with the enrollment criteria in the clinical trials that reported benefits. We await evidence from clinical trials showing the benefits of using the FRAX score to make decisions on treatment.

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Clinical Observations

Agranulocytosis After Consumption of Cocaine Adulterated With Levamisole

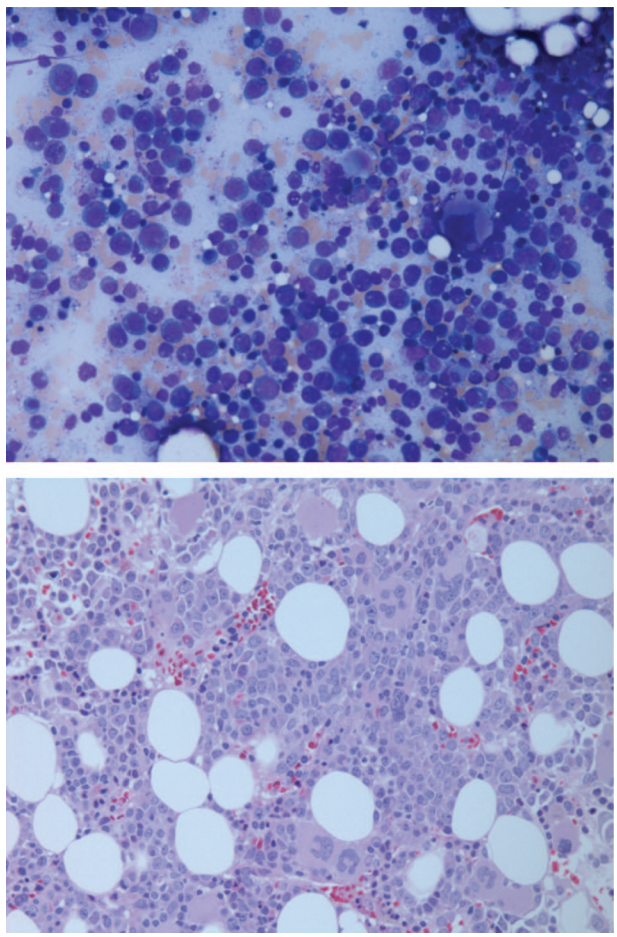
Background: Levamisole is a veterinary antihelminthic previously used as an immunomodulator in rheumatoid arthritis and as adjuvant therapy in the treatment of colorectal cancer. It is no longer available in North America for human use but is available in the United States and South America for veterinary administration.

Since 2004, pharmaceutical agents have been found in cocaine supplies in North America and Europe (1). Levamisole contaminated 30% of cocaine seized by the U.S. Drug Enforcement Agency from July to September 2008 (U.S. Department of Justice, Drug Enforcement Administration. Cocaine Signature Program Report. January–October 2008. Internal document.) and 11% of cocaine samples tested in Alberta, Canada, from April to December 2008 (Office of Research and Surveillance, Health Canada. Personal communication.). Levamisole causes reversible agranulocytosis in up to 20% of cases (2), but the clinical effects of cocaine adulterated with levamisole have not been described.

Objective: To describe 5 patients with severe agranulocytosis after exposure to cocaine and levamisole.

Case Report: Between July and November 2008, 5 patients with a history of cocaine use were hospitalized for agranulocytosis, fever, and a variety of infectious complications in northern Alberta, Canada (**Table**). Two patients had iron deficiency anemia, and 1 had chronic stable hepatitis C. Patients had no history of medication use or nutritional deficiencies, malignant conditions, or rheumatologic disorders that can cause agranulocytosis. Serum vitamin B_{12} and erythrocyte folate levels were normal. Imaging of the chest, abdomen, and pelvis with radiography and ultrasonography or computed tomography did not show any malignant conditions. Bone marrow examination in 2 patients showed reduced granulocytic proliferation and maturation (**Figure**) consistent with past reports of agranulocytosis from levamisole (3).

Figure. **Photographs of bone marrow aspirate (*top*) and trephine biopsy (*bottom*) from a patient with agranulocytosis and levamisole found in the urine.**



Neutrophils and bands are almost completely absent. The abundance of granulocytic precursors suggests toxin-related impairment of granulopoiesis with reduction of neutrophil maturation. The remainder of the bone marrow shows normal heterogeneity. **Top.** Bone marrow aspirate (May-Grünwald–Giemsa stain). **Bottom.** Bone marrow trephine biopsy (hematoxylin–eosin stain).

Urine toxicology testing using gas chromatography/mass spectrometry (GC/MS) detected cocaine or its metabolites and levamisole. The presence of the drugs was verified by injecting urine extracts into the GC/MS and then comparing readings with those from pure standards according to 2 parameters: drug fragmentation pattern (total ion mass spectra) and time for the drug to pass through the system (retention time). Because lupus anticoagulant has been associated with levamisole use (4), we tested for it and detected it in all 5 patients with confirmed levamisole exposure.

All patients fully recovered with use of filgrastim, intravenous antibiotics, and close monitoring. One patient presented with another episode of fevers and agranulocytosis 3 months later, when cocaine and levamisole were again found on urine testing. We treated 6 additional patients with a history of cocaine use who were hospitalized for agranulocytosis and fever. We suspected levamisole-adul-

Table. **Clinical Details of Patients With Febrile Agranulocytosis Associated With Use of Cocaine Adulterated With Levamisole***

Patient	Age, y	Sex	Other Positive Toxicology Findings in Urine	Blood Counts on Presentation		Days Until Neutrophil Count >1 × 10^9 cells/L	Result of Lupus Anticoagulant Testing	Clinical Complications
				Neutrophil, × 10^9 cells/L	Total Leukocyte, × 10^9 cells/L			
Levamisole and cocaine detected								
1	38	Female	Morphine, lidocaine, fluconazole, dimenhydrinate/diphenhydramine	0	0.6	9	Positive	Cellulitis, pneumonia, bacteremia (*Escherichia coli*)
			Methamphetamine, amphetamine, pheniramine, dimenhydrinate/ diphenhydramine, morphine	0	1.2	8	Positive	Cystitis (*Klebsiella pneumoniae*), typhlitis
2	41	Female	Lidocaine, zopiclone, dimenhydrinate/ diphenhydramine	0	2.2	5	Positive	None
3	18	Female	Metoclopramide, benzydamine, ibuprofen	0	0.6	6	Positive	Thrush, peritonsillar abscess, cellulitis
4	44	Female	Acetaminophen, ketorolac, chlorpheniramine metabolite, thymol, polyethylene glycol, dimenhydrinate/diphenhydramine	0	0.7	20	Positive	None
5	48	Male	Clindamycin	0	0.5	7	Positive	Parotitis, face and neck cellulitis, intubation with ICU admission for airway protection
Levamisole not detected, cocaine detected								
1	40	Female	Not done	0	1.1	2	Positive	Sepsis requiring ICU admission (group A streptococcal pharyngitis)
			Not done	0	2.8	5	Not done	Sepsis requiring ICU admission (group G streptococcal pharyngitis)
2	41	Male	Not done	0	0.7	7	Not done	Pharyngitis and epiglottitis
3	30	Male	Not done	0	2.3	4	Positive	Cystitis (*Enterococcus* and *Staphylococcus aureus*)
4	25	Female	Not done	0	2.4	1	Positive	Pharyngitis (*Streptococcus* species)
5	45	Female	Not done	0	0.3	6	Not done	Acute epiglottitis requiring intubation and ICU admission for airway compromise
6	35	Female	Not done	0	0.9	13	Not done	Cellulitis (MRSA), necrotizing granulomatous lymphadenitis

ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*.
* Two patients presented twice. Some urine samples for toxicology testing were obtained after hospital admission and initiation of therapy.

terated cocaine as a cause but could not confirm the presence of the drug by using toxicology testing in these patients.

Discussion: It is unknown why pharmaceutically active agents are added to the cocaine supply; it is possible that cocaine producers or suppliers think that the agents enhance the drug's effects or attenuate its side effects. Cocaine achieves its psychoactive effects by increasing dopamine concentrations in the euphoric centers of the brain, and animal studies have found that levamisole also increases dopamine levels in these regions (5). We speculate that levamisole may potentiate the euphoric effects of cocaine by further increasing brain dopamine levels.

We did not test cocaine samples in the patients' possession for levamisole, so we cannot directly attribute the agranulocytosis to levamisole or prove that the cocaine was adulterated with levamisole. To directly connect levamisole to agranulocytosis, we would have to examine its effects on in vitro stem cell growth (by granulocyte-macrophage colony-forming unit clonogenic assay) (6).

Other nonprescribed medications consumed and not detected on toxicology testing, or other adulterants, might also explain the agranulocytosis. Nevertheless, we advise clinicians to consider the possibility of cocaine use and, specifically, the use of levamisole-adulterated cocaine, in patients with otherwise unexplained fever and agranulocytosis. Prompt urine toxicology testing is essential because levamisole has a short-elimination half-life of 5.6 hours (7) and little of the parent drug (2% to 5%) is detected in urine (8). In addition, cocaine metabolites are detected up to 3.4 days on average after last use (9). Because levamisole is not detected by routine immunoassay toxicology screening tests, other techniques, such as GC/MS, are required.

Conclusion: Cocaine adulterated with levamisole may be a cause of febrile agranulocytosis in cocaine users. Clinicians should consider the possibility of exposure to levamisole-adulterated cocaine in patients with otherwise unexplained fever and agranulocytosis.

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Recurrent Spontaneous Pneumothorax as the Presenting Sign of the Birt–Hogg–Dubé Syndrome

Background: The Birt–Hogg–Dubé syndrome is a rare autosomal dominant disorder, first described in 1977 (1), initially characterized by its chief dermatologic manifestation, cutaneous fibrofolliculoma. We now know that the syndrome is associated with an increased risk for renal tumors and pulmonary cysts. Cysts are found in 90% of patients with the syndrome, resulting in a 24% risk for spontaneous pneumothorax. The underlying pathology is a germline mutation in the tumor suppressor *BHD* gene encoding folliculin (2).

Objective: To report a case of the Birt–Hogg–Dubé syndrome that manifested clinically as recurrent pneumothorax.

Case Report: A 33-year-old white woman presented with several hours of pleuritic chest pain and dyspnea after a long airplane flight. Her medical history included chronic cough, with a normal chest radiograph, a negative sinus computed tomography (CT) scan, normal pulmonary function test results, and a negative methacholine challenge test result. She had a remote, non–clinically significant smoking history and did not report alcohol or drug use. Her only medication at the time was escitalopram.

Chest radiography at presentation revealed left-sided pneumothorax, and a chest tube was placed. A noncontrast CT scan of the chest revealed approximately 5 areas of hypoattenuation outlined by thin walls, consistent with cysts (**Figure**, *A*). After successful reexpansion of the lung, the chest tube was removed and she was discharged. However, she developed a recurrent left-sided pneumothorax and was rehospitalized for video-assisted thoracoscopic lung biopsy and pleurodesis. Given her young age, sex, and the presence of cysts, lymphangioleiomyomatosis (LAM) was suspected. The biopsy sample was stained for HMB-45, a marker of the atypical smooth-muscle cells of LAM, and the results were negative. The biopsy results revealed simple blebs and eosinophilic pleuritis, which are commonly seen in association with pneumothorax of any cause.

On a follow-up office visit, the patient revealed that her mother also had chronic cough. We obtained a chest CT scan of her mother, which showed similar cystic lung lesions (**Figure**, *B*). Furthermore, a maternal first cousin had a reported history of bullous lung disease (**Figure**, *C*) and recently had a radical nephrectomy for renal cell carcinoma. On the basis of the patient's cystic lung lesions and spontaneous pneumothorax, combined with her family history of cystic lung disease and renal cell carcinoma, we suspected a diagnosis of the Birt–Hogg–Dubé syndrome. Mutational analysis of the *BHD* (or *FLCN*) gene confirmed the diagnosis.

Discussion: The Birt–Hogg–Dubé syndrome has traditionally been diagnosed by dermatologists. However, recent studies show that many patients with lung cysts and spontaneous pneumothorax and no dermatologic manifestations or renal tumors have evidence of *BHD* mutations (3). The differential diagnosis of cystic lung disease typically includes LAM, Langerhans cell histiocytosis, lymphocytic interstitial pneumonia, and diseases that mimic cysts (including cystic bronchiectasis and emphysema). This case emphasizes that pulmonologists need to be aware of the Birt–Hogg–Dubé syndrome, which is rare but is probably underdiagnosed, when evaluating patients with cystic lung disease or spontaneous pneumothorax (4). It also emphasizes that a family history is important for providing diagnostic clues to the presence of rare genetic disorders.

Conclusion: The Birt-Hogg-Dubé syndrome is a rare cause of cystic lung disease and recurrent pneumothorax.

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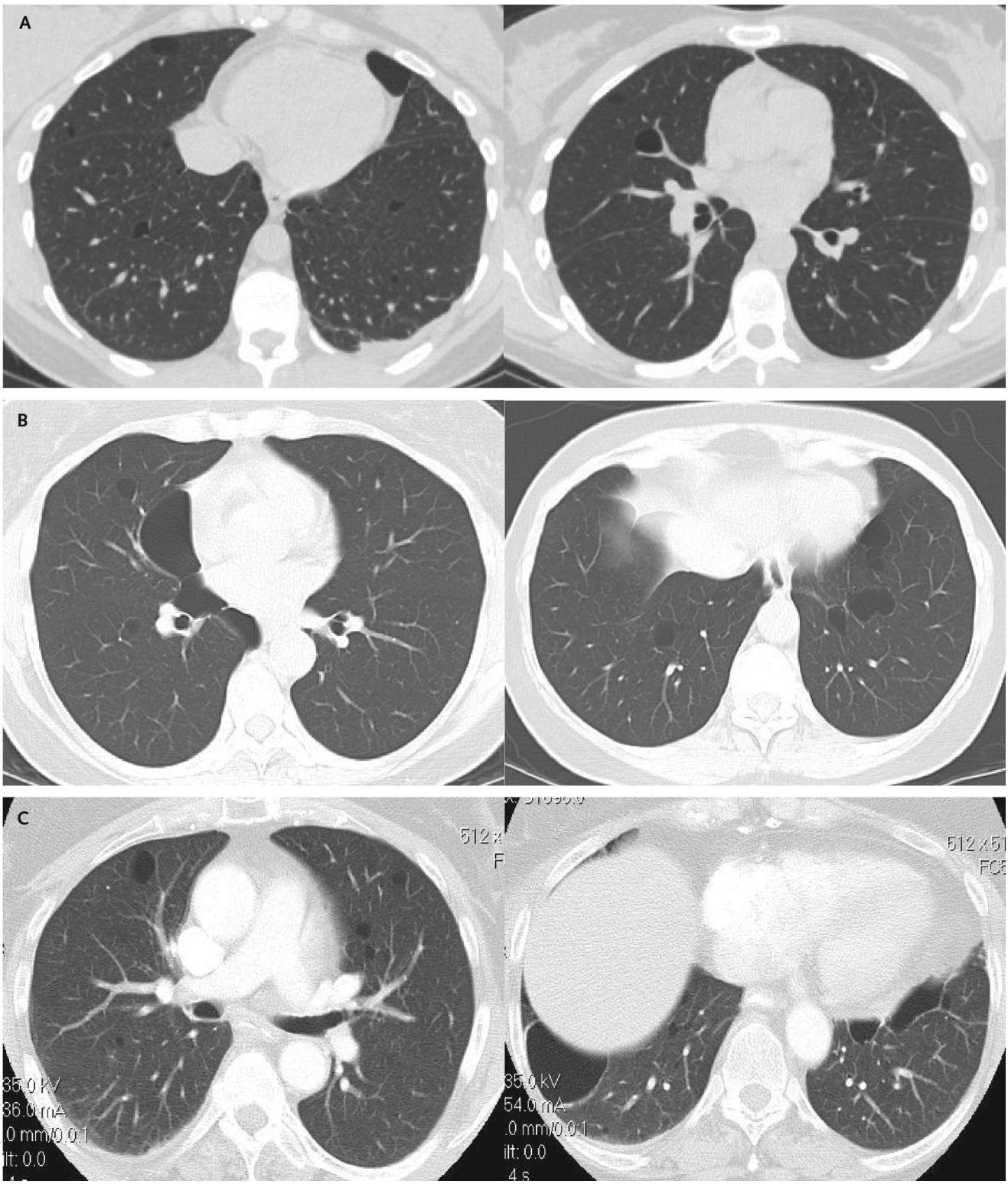
Figure. **Computed tomography scans.**



A. Scans from the index patient. **B.** Scans from the index patient's mother. **C.** Scans from the index patient's cousin.

Table. **Average Caloric Content and Number of Servings in *The Joy of Cooking*, by Publication Year**

Characteristic	Publication Year						
	1936	1946	1951	1963	1975	1997	2006
Mean total calories per recipe (SD)	2123.8 (1050.0)	2122.3 (1002.3)	2089.9 (1009.6)	2250.0 (1078.6)	2234.2 (1089.2)	2249.6 (1094.8)	3051.9 (1496.2)
Mean average calories per serving (SD)	268.1 (124.8)	271.1 (124.2)	280.9 (116.2)	294.7 (117.7)	285.6 (118.3)	288.6 (122.0)	384.4 (168.3)
Mean number of servings per recipe (SD)	12.9 (13.3)	12.9 (13.3)	13.0 (14.5)	12.7 (14.6)	12.4 (14.3)	12.4 (14.3)	12.7 (13.0)

Continued on following page

The Joy of Cooking Too Much: 70 Years of Calorie Increases in Classic Recipes

Background: Obesity has been associated with the expanding portion sizes of away-from-home foods (1). Although portion size norms and calorie density have increased outside the home, they could also have a parallel or referred impact on serving sizes in the home (2, 3). Cookbook recipes might provide a longitudinal gauge of how serving sizes and calorie density have changed inside homes. One cookbook, *The Joy of Cooking*, has been updated approximately every 10 years since 1936 (4) and could provide a glimpse into the changing norms of U.S. food preparation and serving sizes over the past 70 years (5).

Objective: To assess changes in calorie density and serving sizes of household meals since 1936, as reflected in recipes in *The Joy of Cooking.*

Methods: We content-analyzed the 7 editions of *The Joy of Cooking* (1936, 1946, 1951, 1963, 1975, 1997, and 2006) to determine how serving sizes and calorie density have changed over the past 70 years (**Table**). Since the first edition in 1936, only 18 recipes have been continuously published in each subsequent edition. By using standard nutritional analysis techniques, we determined serving size calorie levels for each recipe in each edition.

We performed all analyses of variance by using SPSS statistical software, version 12.0 (SPSS, Chicago, Illinois). We considered a P value less than 0.05 to be statistically significant.

Results: Over the past 70 years, the total caloric content increased for 14 of the 18 recipes. Because of changes in ingredients, the mean average calories in a recipe increased by 928.1 (from 2123.8 calories [95% CI, 1638.7 to 2608.9 calories] to 3051.9 calories [CI, 2360.7 to 3743.1 calories]), representing a 43.7% increase ($P < 0.001$). As the **Table** indicates, mean average calories per serving increased for 17 of 18 recipes and was influenced by both changes in ingredients and changes in serving size. The resulting increase of 168.8 calories (from 268.1 calories [CI, 210.4 to 325.8 calories] to 436.9 calories [CI, 359.1 to 514.7 calories]) represents a 63.0% increase ($P < 0.001$) in calories per serving. Given that the average 2006 recipe had 1.1 fewer servings than in 1936, the average calorie density per serving size has increased by 37.4% ($P < 0.001$).

Over the 70-year history of *The Joy of Cooking*, the recommended serving sizes were altered at 3 points. Between 1946 and 1951, 3 of 18 recipes increased their serving size by an average of 32.5%. Between 1951 and 1963, 4 recipes increased their serving size by an average of 20.0%. Between 1997 and 2006, 5 recipes increased their serving size by an average of 21.1%. Only 3 recipes decreased their serving size at any point in the past 70 years, but all 3 were compensated by subsequent increases in later years.

Discussion: The mean average calorie density in 18 classic recipes has increased 35.2% per serving over the past 70 years. This is due mostly to the use of higher-calorie ingredients and partly to serving sizes that showed small increases in the late 1940s and early 1960s and a 33.2% increase since 1996.

The calories and portion sizes of classic recipes may reflect prevailing tastes and norms. Yet, they may also establish or reinforce exaggerated norms in other settings, such as new families. Although this study is largely descriptive, it implies a prescriptive recommendation for families. The serving size and calorie composition of classic recipes need to be downsized to counteract growing waistlines.

Conclusion: Calorie density and serving sizes in recipes from *The Joy of Cooking* have increased since 1936.

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CORRECTIONS

Correction: What Do You Do When Your Loved One Is Ill?

In a recent article by Fromme and colleagues (1), the questions listed in Table 1 are excerpted, not modified, from reference 1 of the article (2). The online version of the article has been corrected.

Table—Continued

F Value (*P* Value)	Change from 1936 to 2006, %
402.3 (0.000)	43.70
436.9 (0.000)	63.00
0.01 (0.999)	−2.0

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Correction: Radiographic Contrast Infusion and Catecholamine Release in Patients With Pheochromocytoma

There are 2 errors in the recent article by Baid and colleagues (1). First, on page 29, in the paragraph starting with "Nine patients . . . ", the last sentence should say "The between-group differences in diastolic blood pressure *became* non–statistically significant . . ." Second, the figure legend should include the following: "Number of patients with available data shown at each time point; there are no obvious outliers within the data." The online version of the article has been corrected.

Reference

1. Baid SK, Lai EW, Wesley RA, Ling A, Timmers HJ, Adams KT, et al. Brief communication: radiographic contrast infusion and catecholamine release in patients with pheochromocytoma. Ann Intern Med. 2009;150:27-32. [PMID: 19124817]