TO THE EDITOR: In the study by Collins and colleagues (1), the initial group of 3100 became 2600 analytic case-patients. Some of these may represent nonadherent patients who did not complete the fecal occult blood test (FOBT) process. The authors should have used the intention-to-study population for the denominator. Second, clinicians may be performing the single FOBT with the rectal examination yearly. Thus, this study might also have considered the question, “How does the health outcome of a single FOBT test (6 samples) compare with 6 annual rectal examinations including a single FOBT test each year?” Given that these were asymptomatic patients who would need a colonoscopy only every 10 years (assuming no interval findings), a single FOBT annually as part of the rectal examination might have merit and circumvent the nonadherent “home tester.”

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Potential Financial Conflicts of Interest: None disclosed.

Reference

TO THE EDITOR: Regarding the articles (1, 2) and editorial (3) on fecal occult blood testing (FOBT), I believe the lesson you have drawn is flawed, as illustrated in Nadel and colleagues’ article (2): Physicians do not consistently follow recommendations. Although we can decry the poor practices of our colleagues, we must face the reality of the situation.

Specifically, my concern is that locking up the guaiac cards, as Dr. Sox suggested (3), will provide a further excuse for excluding the digital examination of the prostate or performance of an appropriate cul-de-sac examination. It is likely that, even in emergencies, physicians will neglect to consider gastrointestinal blood loss as a cause of hypotension or fatigue.

The likelihood ratio of 1.68 for in-office FOBT is preferable to 1.0, and that ratio applies only to neoplasms of 10 mm or greater, as in Collins and colleagues’ study (1). We do detect more neoplasms of smaller size. Also, the reality is that patients adhere poorly to home sampling recommendations, so the office FOBT may be the only opportunity for sampling.

The message to our trainees and to our colleagues should be to do both a digital rectal examination and 6-specimen FOBT, while encouraging colonoscopic screening and surveillance as appropriate.

Let’s not flush the baby with the toilet water.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: The recent paper (1) denigrating the use of single-specimen FOBT done at an office visit compared with a mail-in multiple-specimen test failed to take into account an important factor: adherence. It would appear to be only common sense that a test with relatively low sensitivity (and also specificity!) would have a higher yield when done on multiple specimens, as was the main point of the paper.

I switched to in-office testing when I realized that most of my patients who were given take-home kits failed to return the kits. The sensitivity of a test never done is zero. As Dr. Sox is also doubtless aware, the value of FOBT itself is questionable, and in 2005 we should be recommending colonoscopies regardless of the stool results.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

TO THE EDITOR: We read with interest the article by Collins and colleagues (1) and the accompanying editorial by Dr. Sox (2). We share Dr. Sox’s concern that colorectal cancer mortality rates have not decreased more rapidly, considering the emphasis on increased screening over the past 10 years. We think this is multifactorial, and we would like to respond to these observations before the office-based FOBT is abandoned.

One reason for the slow decline might be the replacement of flexible sigmoidoscopy with total colonoscopy for people at low risk for colorectal cancer. With the exception of the Veterans Administration health system, this practice has produced a chasm between those who can afford total colonoscopy or insist on it versus those who cannot. A paucity of any screening intervention in the African-American and Hispanic populations is troubling because available data show that colon cancer is diagnosed more frequently in African-American and Hispanic persons than in white persons (3, 4).

One reason for this failure in these populations may be the abandonment of FOBT. Collins and colleagues stressed that a single analysis of stool obtained by rectal examination showed a very low
sensitivity for the detection of advanced neoplasia when compared with analysis of 3 stools spontaneously passed. The authors do not stress the fact that FOBT is done annually and that many of these advanced neoplasms would be picked up on subsequent annual examinations, no matter what type of stool is tested. We therefore support any and all FOBT, with the caveat that a digital rectal examination should be considered sufficient for screening only if stool is obtained and that stool obtained by using this method should not be tested if visible blood is present. Some screening is better than no screening at all.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: In response to Dr. Wolff and Dr. Hoffer, I can but elaborate on my editorial. One concern is using office guaiac in lieu of other, better tests, which is common practice, according to Nadel and colleagues’ survey (1). A second concern is placing too much weight on a negative result on a test that misses 95% of colonic neoplasia. The third concern is inefficient use of invasive follow-up tests. The office guaiac has a positive likelihood ratio of 1.68 (2), which means that the probability of high-risk neoplasia rises from 7.0% to 12% after a positive test result, which means doing 8.5 negative follow-up colonoscopies for every positive colonoscopy. When the 6-sample home test is used, the probability would rise from 7.0% to 35%, which would require fewer than 3 colonoscopies to detect an important lesion. Ultimately, physicians must develop better office systems to support home testing and identify nonadherent patients.

I only partially agree with Drs. Jackson and Craig. Fecal occult blood testing using 6 samples obtained at home is an important test because, coupled with colonoscopy when results are positive, it reduces mortality from colorectal cancer from 8.83 deaths per 1000 over 13 years to 5.88 deaths per 1000 (3). It’s not a perfect test. Its sensitivity of 23.5% is very poor, so that it generates many negative colonoscopies. But it does reduce colorectal cancer death rates, which is more than you can say for sure about any other colorectal cancer screening test, least of all the office guaiac. We should advocate home testing, and we should develop office systems to help us raise adherence rates to a test that reduces colorectal cancer rates substantially.

Is a bad screening test better than none at all? Now there’s a good subject for debate!

Harold C. Sox, MD
Editor

Potential Financial Conflicts of Interest: None disclosed.

References

My Right Knee

TO THE EDITOR: Dr. Berwick (1) writes with insight on some of the important inefficiencies and flaws in our system, but I fear his attitude speaks louder than his words. Gandhi appears several times in the article as if to provide an approving stamp of compassion, and Berwick calls for better care not only for his knee but for a “Thai with dengue or an African with AIDS.” But his is not a universal prescription for care; it is a prescription for grease to the squeaky wheel. He needs an appointment “any day [he] want[s] it” because he is “really busy” and cannot wait, yet at the same time he wants all his questions answered to his full satisfaction. He is like the patient who stomps his foot angrily when the doctor is running late but then stays in the examining room for 1 hour dissecting his concerns while other patients—perhaps including the Thai and the African— languish in the waiting room. This is part of human nature, but it does not lend itself to a just and universal health care system. To add injury to injury, Berwick asks for no needless deaths or pain, yet in his own nonmedical life he has courted both by climbing Mount Rainier 5 times. Woe to the poor knees.

Berwick seems to be one of the many medical consultants who believe that aping business models is the only way to save U.S. medicine. He quotes glowingly Paul O’Neill and his idea of a “habit of excellence,” the same O’Neill who has presided over the decline of the U.S. economy over the past several years. Medicine can never be truly run like a business: One does not refuse to serve the customer with dengue or an African with AIDS.” But his is not a universal prescription for care; it is a prescription for grease to the squeaky wheel. He needs an appointment “any day [he] want[s] it” because he is “really busy” and cannot wait, yet at the same time he wants all his questions answered to his full satisfaction. He is like the patient who stomps his foot angrily when the doctor is running late but then stays in the examining room for 1 hour dissecting his concerns while other patients—perhaps including the Thai and the African—languish in the waiting room. This is part of human nature, but it does not lend itself to a just and universal health care system. To add injury to injury, Berwick asks for no needless deaths or pain, yet in his own nonmedical life he has courted both by climbing Mount Rainier 5 times. Woe to the poor knees.

Berwick seems to be one of the many medical consultants who believe that aping business models is the only way to save U.S. medicine. He quotes glowingly Paul O’Neill and his idea of a “habit of excellence,” the same O’Neill who has presided over the decline of the U.S. economy over the past several years. Medicine can never be truly run like a business: One does not refuse to serve the customer in the emergency department because he cannot pay. Berwick’s hybrid model, which to me looks something like a Wal-Mart staffed by Gandhis, may appear to be an answer to him, but I remain unconvinced.

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Potential Financial Conflicts of Interest: None disclosed.
TO THE EDITOR: Although the application of the “total quality” method might seem appropriate to medicine, one fundamental problem exists. The “quality movement” is, of course, a concept borrowed from business models, which can be traced back to Deming’s seminal work (1). However, there is a critical difference between U.S. medicine and other businesses that makes Dr. Berwick’s search (2) a fool’s errand. Specifically, “total quality” was primarily intended as a method to increase sales and profits in a business operating in the free market, and U.S. health care is simply not a free market.

According to 2001 data from the Organisation for Economic Co-operation and Development data, health care accounts for 13.9% of the gross domestic product, and 44.6% of health care expenditures in the United States were paid by public systems such as Medicare, Medicaid, the Veterans Administration and other military care, public health clinics, and other programs (3). However, when one includes tax subsidies and public employee benefits, the current tax-financed share of health spending is nearly 60% (4). Government mandates and regulations add another layer of public expense to health care in the United States. From 1970 to 1996, state and federal mandates increased 25-fold, an annual growth rate of 15% (5). Thus public spending, not private outlays, already pays the majority of U.S. health costs.

This is an important distinction because the U.S. government sets prices (from doctor’s fees to hospital stays) for its Medicare and Medicaid programs. Fixing prices for an industry, while intended to reduce outlays, removes the essential information provided by prices, which best reflect supply and demand. This imposes “the impossible burden” of replacing the intricate information available through prices with a centralized bureaucracy that must somehow learn what people want and provide it by orders and protocols (6). In contrast to price rationing present in the free market, health care outlays under Medicare and Medicaid are rationed by means other than price, such as waiting lists, drug formularies, limited treatment options, and discrimination by age or disease. Additional effects of nonprice rationing (that is, fixed prices) include underfunding, shortages, delayed diagnosis and treatment, reduced quality, and health worker strikes (7). As a result, investment and rewards are not determined by meeting patient needs but instead by surviving the below-cost payments offered by the government, achieved by shifting those costs onto younger insured patients (a method becoming less and less available).

For the health care competition that does exist in the United States, the incentives are skewed to favor innovations that raise costs or increase quality regardless of expense. These incentives discourage cost sensitivity for patients while providers are encouraged to increase services, maximize reimbursement, make expensive referrals, and practice defensive medicine.

In short, incentives matter, and the incentives of the current U.S. health care system are unable to create the “total quality” system desired by the author. The problem is one of basic economics, not a lack of “energy, insight, and courage.” Attempts to change human behavior through rousing admonitions rather than improved incentives are doomed to failure.

References

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: I understand Dr. Sapers’ skepticism, given how poorly designed health care is today. My vision, however, is hardly that of a “Wal-Mart.” It is of a health care system that seeks to address each individual patient on his or her own terms, as far as possible. I believe that dedicated clinicians indeed try to do that as a matter of personal mission, and I also believe that modern understandings of health care as a system (not “aping business models”) with open-minded, scientific redesigns, can go a long way toward that vision. For example, waiting times can be reduced dramatically with relatively simple changes in time-honored, but illogical, scheduling systems (1). Much safer care is within our reach, if only we will commit to new levels of reliability in our processes.

Dr. Fleming accurately notes the toxicity of current financing systems with respect to the changes we need for truly patient-centered, reliable care (2). I disagree, however, about the promise of making patients more “cost sensitive,” which usually means shifting costs to individuals. I find little evidence that that helps, and besides, illness and poverty are too closely correlated to make that ethical social policy (3). Indeed, nations with globally funded, often government-sponsored health care with universal access seem in important dimensions to outperform our system at far lower cost (4). “Total quality,” in my view, will be found sooner in a health care system with clear mandates, policy guidance, universality, flexible funding, and public accountability than in one relying on the invisible hand of a market to care for the sick.

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Potential Financial Conflicts of Interest: None disclosed.

References

**CLINICAL OBSERVATION**

Editor’s Note: The lead author of the following Clinical Observation was one of a dozen Associates of the American College of Physicians selected to present a clinical vignette at the 2003 Annual Session in San Diego. We are proud to present this case report through a special arrangement with the Council of Associates of the College.

Regulation of Body Weight by Proopiomelanocortin Peptides in Humans: Lessons from the Nelson Syndrome

TO THE EDITOR: Background: Melanocortins (α-melanocyte-stimulating hormone [MSH] and adrenocorticotropic hormone [ACTH]), in addition to their melanocyte-stimulating actions, may regulate energy balance through hypothalamic melanocortin-4 receptors (MC4Rs). In mice, deletion of the proopiomelanocortin (POMC) or MC4R genes leads to obesity, whereas administration of MC4R agonists (for example, MSH) causes weight loss (1). In humans, inactivating mutations of the POMC (2) or MC4R (3) genes can cause obesity, but there is no evidence that increased melanocortin action can cause weight loss.

In the Nelson syndrome, rapid growth of an adrenocorticotropic pituitary adenoma following bilateral adrenalectomy causes extreme elevation of melanocortin levels and hyperpigmentation. The Nelson syndrome is a human model in which temporal associations among body weight, skin pigmentation, and high circulating levels of melanocortins might be observed.

**Objective:** To investigate these associations, we tracked body weight, hormone levels, and intensity of skin and scar pigmentation over 20 years in a patient with the Nelson syndrome.

**Case Report:** In 1982, a previously healthy 29-year-old woman experienced weight gain and was treated unsuccessfully with gastric stapling in 1983. In early 1984, she developed biochemical evidence of the Cushing syndrome and underwent unilateral adrenalectomy for an adrenal nodule. The contralateral adrenal gland was removed in late 1984 because of persistent hypercortisolemia, and physiologic replacement of hydrocortisone and fludrocortisone was started. In 1987, after attaining her peak body mass (body mass index, 44.7 kg/m²), the patient experienced pronounced skin darkening and lost 37.3 kg (body mass index, 27.6 kg/m²), followed by headaches and bitemporal hemianopsia. Diagnosis of the Nelson syndrome with pituitary macroadenoma and elevated plasma ACTH levels (6000 pg/mL [normal value, <65 pg/mL]) led to partial transsphenoidal tumor resection in late 1988. All symptoms resolved, followed over the next year by a weight gain of 7.3 kg with skin lightening. Six years later, in 1994, the Nelson syndrome recurred, with marked skin darkening, a weight loss of 7.5 kg, headaches, and hemianopsia; the patient underwent a second transsphenoidal resection. The pituitary tumor contained both ACTH and MSH on immunohistochemical analysis. Plasma ACTH levels then decreased, associated with weight gain (8.2 kg), lightening of the skin, and resolution of all symptoms. Since 1995, the patient’s weight, skin color, and health have remained stable. Euthyroidism and euglycemia were noted.

**Figure:** Inverse relationship of body weight and plasma adrenocorticotropic hormone (ACTH) levels or intensity of scar pigmentation as biomarker.

![Graph showing inverse relationship of body weight and plasma ACTH levels or intensity of scar pigmentation.](https://annals.org)
throughout the course, with normal gonadotropin and prolactin levels from 1987 to 1997.

The intensity of pigmentation in scars formed at different times also varied inversely with weight changes. Scars from the gastric stapling and adrenalectomies that predated the Nelson syndrome (and that formed as the patient gained weight) were pale, indicating that contemporaneous melanocortin levels were not excessive, consistent with the normal plasma ACTH levels in 1985 and early 1987 (Figure). In contrast, scars from a gastric stapling reversal procedure (late 1987) and the pituitary resection (1988), which formed as the patient lost weight, were dark. A scar from a minor injury in 1991, which formed as the patient gained weight, was pale, indicating that circulating melanocortin levels were not excessive in this period, whereas the scar from the second pituitary resection in 1995, formed as the patient lost weight again, was dark because of supraphysiologic circulating melanocortin levels at that time. For photographs of the patient over time, see Appendix Figures 1 and 2, available at www.annals.org.

Discussion: This patient’s body weight fluctuations correlated inversely with plasma ACTH levels, suggesting that excessive ACTH (and α-MSH) secretion by the Nelson tumor could be responsible. Of importance, the data exclude confounding metabolic influences of altered glucocorticoid levels, which were effectively held steady by fixed glucocorticoid replacement therapy after total adrenalectomy. The dramatic decreases in body weight during the initial growth and later recurrence of the pituitary tumor suggest that endogenous circulating melanocortins, at least at supraphysiologic levels, can induce weight loss in humans.

The melanogenic actions of POMC products provided a striking interpretive tool in this case. Human melanocytes are highly sensitive to both MSH and ACTH, and melanocortin administration can cause skin darkening. Therefore, the intensity of eumelanin (dark) skin pigmentation was a temporal biomarker of supraphysiologic circulating melanocortin levels, supported by biochemical and immunocytochemical ACTH and MSH determinations. Furthermore, the increased melanization of dark scars provided a novel, permanent record of the excessive circulating melanocortin levels that prevailed during their formation, in contrast with the transient hyperpigmentation of normal skin. (Melanization of scars occurs weeks after wound formation and persists because of the negligible turnover and desquamation rates of scar keratinocytes relative to those in normal skin.) Conversely, the absence of melanization in scars that formed during periods of steady weight gain (1983 to 1984, 1991) indicates that the prevailing blood melanocortin levels at those times were not excessive.

Melanocortin neurons project to MC4R-rich hypothalamic nuclei implicated in appetite regulation (4); they also inhibit feeding and increase energy expenditure. In animals, MC4R agonists cause weight loss (1) and MC4R antagonists cause hyperphagia (5). Inactivating mutations of the POMC and MC4R genes in some obese humans (2, 3) indicate that blunted melanocortin signaling can cause weight gain, but there is little evidence for the converse phenomenon, or that changes in endogenous circulating melanocortin levels can dynamically alter body weight. This patient dramatically demonstrates such dynamic regulation, with the novel finding that excessive melanocortin production is associated with marked weight loss.

Conclusion: The repeated inverse correlations between plasma ACTH levels or bioactivity and body weight strongly suggest that excessive circulating levels of melanocortins can cause weight loss in humans.

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Potential Financial Conflicts of Interest: None disclosed.

References

CORRECTION

Correction: A Randomized, Double-Blind, Placebo-Controlled Trial of Rifaximin To Prevent Travelers’ Diarrhea

A recent paper on rifaximin to prevent travelers’ diarrhea (1) contained an error. In the Methods section, under “Interventions,” the beginning of the first sentence should read, “Eligible participants who came to the clinic without diarrhea were randomly assigned to the next available study number.”

Reference
Appendix Figure 1. Dynamic changes of skin and scar pigmentation with fluctuations of plasma levels of adrenocorticotropic hormone.

Appendix Figure 2. Abdominal scars with variable pigmentation reflecting the plasma level of adrenocorticotropic hormone at the time of formation.

1 = laparotomy for gastric stapling (light scar); 2 = adrenalectomy (light scar); 3 = reversal of gastric stapling (dark scar); 4 = first hypophysectomy (dark scar); 5 = second hypophysectomy (dark scar).