

Notice of Retraction

In 1995, *Annals* published an article titled “Changes in Energy Balance and Body Composition at Menopause” (1). The first author was Eric T. Poehlman, PhD, who was a professor of medicine at the University of Vermont in 1995. In July 2003, I received a letter from the provost of the University of Vermont. The letter reported on the outcome of an investigation into alleged scientific misconduct by Dr. Poehlman. The review panel concluded that Dr. Poehlman had published 3 articles that contained false and fabricated data. The articles reported the results of follow-up testing of members of a cohort of menopausal women. The University of Vermont investigation disclosed no convincing evidence that the women had undergone follow-up testing, and the panel concluded that the data had been fabricated. Dr. Poehlman’s 1995 article in *Annals* was 1 of the 3 articles that contained fabricated data. The review panel found that Dr. Poehlman alone was responsible for publishing the fabricated data; it exonerated his coauthors.

I am retracting Dr. Poehlman’s article in *Annals of Internal Medicine* because it contains fabricated data.

Harold C. Sox, MD
Editor

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COMMENTS AND RESPONSES

Hospitalist Care

TO THE EDITOR: In light of the findings of Auerbach and Meltzer and colleagues (1, 2), specifically that hospitalists’ efficiency of care became more evident during the second year of each of their studies, we would like to present a subanalysis of published data that also supports increased hospitalist efficiency (3). Rifkin and colleagues studied 455 patients who were hospitalized with community-acquired pneumonia and were cared for by a full-time hospitalist or a community-based primary care physician during 1 calendar year (3). After multivariate adjustment, the authors concluded that hospitalist care yielded shorter length of stay (6.5 vs. 5.6 days; $P < 0.001$) and lower costs (\$4501 vs. \$3907; $P = 0.03$), with mostly similar processes of care and no statistically significant difference in inpatient mortality rates. For the 9 hospitalists and 56 primary care physicians included in the analysis, the mean number of years since medical school graduation was 5.1 years and 20.6 years, respectively ($P < 0.001$). Thus, length of stay was shorter and costs were lower even though hospitalists had been in practice about 25% as long as the other physicians, although hospitalists may have had greater disease-specific experience.

Assuming that the “practice makes perfect” conclusions of Auerbach and Meltzer and colleagues are accurate, one would expect greater differences in length of stay, cost, and mortality in studies comparing models of care in which practitioners’ overall clinical experience is more similar. That is, if something specific about the hospitalist model, such as same-day rounding or more than 1 visit

per day, leads to more efficient and perhaps improved care, this will become only more obvious as experience accrues, assuming career retention is possible for hospitalists.

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- Meltzer D, Manning WG, Morrison J, Shah MN, Jin L, Guth T, et al. Effects of physician experience on costs and outcomes on an academic general medicine service: results of a trial of hospitalists. *Ann Intern Med.* 2002;137:866-74. [PMID: 12458986]
- Rifkin WD, Conner D, Silver A, Eichorn A. Comparison of processes and outcomes of pneumonia care between hospitalists and community-based primary care physicians. *Mayo Clin Proc.* 2002;77:1053-8. [PMID: 12374249]

TO THE EDITOR: As a general response to the articles and editorial about hospitalists (1–3), my comment is, “Let’s move on.” Hospitalist-style inpatient medicine is here to stay not because of an academic movement to improve inpatient medicine. Rather, its roots can be traced to the mundane issues of modern medical practice. An increasing number of office-based primary care physicians are transferring their hospital work to others. Therefore, physicians in the typical internal medicine group practice have had to devote a greater portion of their patient contact time to inpatient work. To meet the demands of this need for 24/7 care, cross-coverage schemes soon evolved into designated group physicians doing full-time hospital work. Even before the term *hospitalist* was coined, many hospitalized patients were already adjusting to these cross-coverage arrangements as a substitute for their primary care physicians. Therefore, further efforts to verify whether hospitalists have an impact on costs or length of stay seem moot. Many hospitalists, including myself, are products of this evolution from traditional internal medicine to hospitalist physician. The quality of our work can only improve if we dedicate our efforts to this niche. Hospitalists will be agents of change and seekers of improved quality, lower costs, and better outcomes as we struggle for recognition as a new specialty. No longer should the pundits ask if we should ascribe to the hospitalist model. It would be like questioning the need for dedicated emergency department physicians. As the Editors implied (3), modern health care is becoming increasingly complicated and specialized. The hospitalist physician has emerged as a natural product of these evolutionary forces.

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3. The who, what, when, where, whom, and how of hospitalist care [Editorial]. *Ann Intern Med.* 2002;137:930-1. [PMID: 12458994]

TO THE EDITOR: The 2 articles on academic hospitalist practices (1, 2) concluded that hospitalist services reduced cost. However, a detailed description of what is meant by “cost per case” is lacking. This precludes meaningful interpretation of cost reduction and comparison of cost-saving with previously reported studies.

Each health care system uses different algorithms, sometimes arbitrary, to tally costs and assign them to individual patients (3, 4). Because physicians have little impact on certain aspects of the total cost, failure to analyze these components may overestimate or underestimate the effectiveness of a hospitalist system. The total cost of hospitalization is a sum of the variable and fixed costs (5). Variable direct costs include expenses that increase incrementally with patient encounters. These include laboratory tests, radiology, and medications. Fixed direct costs are related to patient encounters but do not vary incrementally with volume. These include items such as equipment maintenance. Indirect costs are mostly fixed and include items such as plant depreciation and information services. Differences in assigning a particular expense, such as nursing, to variable-cost or fixed-cost groups will have a major influence on the cost components that are being compared (4), as will a year-to-year variation in cost-distributing algorithms. Consequently, the ratio of variable direct cost to total cost may vary markedly between institutions (3, 4). Describing the various components of the costs may have provided even more support for the authors’ conclusions.

Hospitalists are quickly becoming leaders in inpatient medicine. From my perspective as an academic hospitalist in an urban medical center, it is imperative that we familiarize ourselves with our institutions’ financial procedures. Variable direct cost is the most sensitive financial component of physician resource utilization and should be reported in future studies.

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al. Distribution of variable vs fixed costs of hospital care. *JAMA.* 1999;281:644-9. [PMID: 10029127]

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TO THE EDITOR: The studies by Auerbach and Meltzer and colleagues (1, 2) attempted to show that the clinical experience of hospitalists improved over time and that this improvement explained the modest but statistically significant reduction in mortality, shorter lengths of stay, and lower hospital costs observed for hospitalists’ patients compared with those of nonhospitalists. As the related editorial pointed out (3), the improved results in the second year of each study, most of which were related to shorter lengths of stay and lower costs, could also be attributed to improved logistic management of care, which would reflect hospitalists’ increased understanding of hospital resources. It was not clear from Auerbach and colleagues’ study how many years the hospitalists had been associated with the institution. Meltzer and colleagues seem to have converted nonhospitalists to hospitalists for the purpose of the study. Again, the relative familiarity of hospitalist physicians with the institution compared with physicians who were not selected as hospitalists (the control group) was not addressed.

Both study sites are large urban medical centers. Intuitively, the most important variable might be the knowledge hospitalists gained of the systems in which they were practicing, which allowed them to marshal resources more effectively. In future studies, hospitalists and a few nonhospitalists should have access to a care coordinator who manages the logistics of admission, diagnostic study and pharmacy ordering, discharge planning, patient transportation, consult notification, and other similar issues to normalize the influence of the system on delivery of care.

Auerbach and Meltzer and colleagues did not stratify mortality rates by type of discharge (for example, to a skilled-nursing facility or to home). Certainly, postdischarge destination may substantially influence postdischarge mortality rates. Choice of postdischarge destination could also reflect hospitalists’ knowledge of the system rather than any particular improvement in clinical acumen; therefore, this variable should be accounted for in similar studies. The cause of death was also not discussed. A detailed analysis of this variable might have shown whether differences in mortality were a function of shorter hospital stay (and reduced risk for iatrogenic disease) or postdischarge destination rather than in-hospital treatments.

If knowledge of the system can explain both studies’ results, then we must give some thought to how the system of delivering hospital care can be improved. Several specialty hospitals have recently been developed, usually by physicians wanting a more “user-friendly” environment in which to practice. We need a study that contrasts outcome and lengths of stay, properly stratified for case mix, to determine whether the primary flaw in our current hospital model is related to nonhospitalist care or to the difficulty of providing care in large institutions that in the past 50 years have grown increasingly unwieldy and complex.

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CPR for Patients Labeled DNR

TO THE EDITOR: In arguing that do-not-resuscitate (DNR) orders should sometimes be replaced by “limited aggressive therapy” orders (LATOs), Choudhry and colleagues (1) acknowledge that treatment-specific orders are potentially perilous: A given procedure may be consistent with a patient’s goals in certain situations but not in others. Choudhry and colleagues propose instead enumerating the situations in which cardiopulmonary resuscitation (CPR) might be initiated and specifying in which of those situations it should be attempted. This approach is analogous to Emanuel and Emanuel’s “Medical Directive” (2), which lists 4 clinical scenarios and asks in each case which of 11 interventions would be acceptable. Limited aggressive therapy orders are appealing to physicians for their apparent specificity, but they create the same difficulties as the Medical Directive: They fail to consider the patient’s goals and require an indefinitely long list of clinical situations.

An alternative is an advance care planning process that starts with the prioritization of patient goals. The patient’s predetermined priorities—life-prolonging treatment, maintenance of function, or maximization of comfort—would then have to be translated into practice at the time of an acute illness. For the patient whose major goal is maintaining function but for whom life prolongation remains a lesser but still important goal, CPR would be indicated for a witnessed arrest in the coronary care unit, one of the situations addressed by LATOs. However, CPR would not be attempted in the nursing home since, in the rare cases it is effective, it may lead to major functional impairment, which would be inconsistent with this patient’s goals.

Choudhry and colleagues were correct in saying that DNR orders are as problematic as other treatment-specific limitations. Attempting to define in advance in precisely which situations such limitations are applicable will not solve the problem. Perhaps it is time to consider eliminating intervention-specific directives altogether.

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TO THE EDITOR: Choudhry and colleagues (1) identified a major shortcoming of current resuscitation policies. A dichotomous CPR choice forces patients to choose DNR as the only way of avoiding the burden of prolonged CPR attempts in low-yield situations (such as unwitnessed arrests). Choudhry and colleagues’ proposed LATO offers one possible solution but is fraught with problems. Physicians (and nurses) do prefer dichotomous choices for CPR, presumably because of a need for simplicity when emergencies occur. Cardiopulmonary resuscitation is as effective as it is because so much happens automatically. Choudhry and colleagues’ proposal describes calling the code team, who would “determine whether the LATO applies.” In practice, such decision making in emergency situations would probably result in confusion and error.

Still, there is a need to offer patients the option of a high-yield treatment for “shockable” rhythms. The simplest way to do this is to offer what I will call a “short code.” A short code is simple to understand and implement. It is initiated as an ordinary code but is terminated if a stable rhythm with a pulse is not established within x minutes of starting the code (where x is a very short time, probably 5 minutes or less). Short codes are most likely to be successful in the types of scenarios Choudhry and colleagues describe, such as witnessed arrests during procedures. Availability of short codes would also allay the fear that staff might interpret DNR orders more broadly and forgo treatments other than CPR (2). It should be noted that a short code is in no way similar to a “slow code” and a “show code,” which are simply sham codes to circumvent a patient or family decision. Rather, it is an effective way to offer patients who are wary of CPR the option of a high-yield, low-morbidity resuscitation attempt.

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TO THE EDITOR: Choudhry and colleagues (1) suggested the addition of a new code status: LATO. I have 2 main concerns about their article. First, the exact problem that this new resuscitation status is meant to resolve is unclear. Is there a concern that individuals who might have benefited from resuscitation have somehow missed this opportunity? Certainly in the United States the problem is not one of inappropriately denying resuscitation but of inappropriately resuscitating the dying (2). Do-not-resuscitate orders are rarely written until late in the course of an illness, and even when living wills exist and the circumstances do not warrant it, resuscitation may still occur.

Second, I do not agree with the term *labeled DNR*. One of the concerns of our patients in discussing resuscitation status is that they

will somehow be labeled, looked at, and treated differently in circumstances other than those addressed by a DNR order. Choudhry and colleagues lend credence to that concern. Resuscitation status should not be a plan of care but a guide to what one does in specific circumstances. An advanced directive stating the desire for DNR status in the setting of advanced illness should not affect management of an acute myocardial infarction or arrest during a surgical procedure in an otherwise healthy person.

The only way to truly resolve DNR issues is to return this intervention to the status of other medical procedures that are offered only when medically appropriate and require consent to perform. Only resuscitation (an intervention with dismal results, as Choudhry and colleagues outlined) requires consent to withhold.

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TO THE EDITOR: Choudhry and colleagues (1) proposed the LATO for patients who currently have DNR orders but want to be resuscitated in circumstances when their chances of recovery are good. The authors suggested that certain circumstances, such as witnessed “shockable” rhythms, DNR in the operating room, and iatrogenic complications, warrant consideration of LATOs.

First, for patients with a DNR order who are being monitored and develop a “shockable” rhythm, one could argue that underlying comorbid illnesses should be taken into consideration. Comorbid illnesses play a substantial role in predicting survival to hospital discharge after CPR (2). The prognosis is particularly ominous for patients with noncardiac rather than cardiac comorbid conditions (2). One could also argue that an LATO would be interpreted as a full CPR order if the patient is in a monitored (that is, telemetry) setting.

Second, many patients with a DNR order consent to surgical procedures (3), and defining the perioperative period in which an LATO is effective could be difficult. Many patients, as well as many anesthesiologists, feel that DNR orders should be suspended in the operating room and reinstated after surgery (3). An LATO would be helpful if a predetermined time limit is set; otherwise, a preoperative reversal of the DNR order and postoperative reenactment is justified.

Third, according to 1 survey, 69% of physicians indicated that they would perform resuscitation in an iatrogenic arrest due to physician error (4). An LATO may be helpful in this situation and should be discussed before procedures requiring consent. The most common cause of iatrogenic arrests, however, is medication errors, which account for 44% of cases (5). Furthermore, should all adverse reactions to medications be considered iatrogenic errors? If so, how could one determine whether an LATO applies?

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IN RESPONSE: Resuscitation orders such as LATOs attempt to bridge the gap between patients’ expressed preferences regarding resuscitation and their intended goals. Values-based advance directives highlight this distinction but often fail to provide clinicians with practical guidance on how to act upon their patients’ values. In contrast, as pointed out by Dr. Gillick, intervention-specific directives are problematic because they fail to consider patients’ goals and often require long lists of clinical scenarios. The LATO is a hybrid that lies between these extremes. By requiring clinicians to explain some of the complexities of resuscitation choices, the LATO clarifies patients’ goals and also allows clinicians to determine how these goals should be practically implemented. Moreover, the LATO acknowledges that the effectiveness of resuscitation declines over time (as suggested by Dr. Freer’s “short code”) and that this information may be of interest to patients.

It is true, as suggested by Dr. LeGrand, that resuscitation may often be overused. This highlights the misalignment of patients’ expressed preferences and stated goals, albeit in reverse. We suggested that the LATO may be useful for patients who have existing DNR orders. However, it may also be useful for patients who have requested full resuscitation but may wish to be resuscitated only in certain circumstances.

Ideally, as recommended by Dr. Karnath, comorbid conditions should be considered when attempting to predict the outcome of resuscitation and when discussing resuscitation with patients. Unfortunately, there is an absence of evidence that can be used to make predictions on the basis of individual patient characteristics. Thus, we must use aggregate data (such as the cause of arrest, independent of other factors) to guide our decision making and, in the case of patients with LATOs, should restrict our actions to clear-cut situations. This is particularly true for iatrogenic events, the causes of which are often hard to determine. Overall, we feel that the value of an LATO outweighs its potential problems and suggest that the perfect should not be the enemy of the good.

Dr. Freer commented that it is potentially problematic for a code team to decide when an LATO applies. We agree. Ideally, the conditions in which an LATO applies and the circumstances surrounding an arrest would be apparent. With education and experience, LATOs could become standards of practice, much as the more complex Advanced Cardiac Life Support algorithms used to resuscitate patients have done.

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CLINICAL OBSERVATIONS

The Hungry Bone Syndrome after Medical Treatment of Thyrotoxicosis

TO THE EDITOR: *Background:* Hypocalcemia is a common complication of surgical therapy for thyrotoxicosis. The pathogenesis of the hypocalcemia is controversial; it is often attributed to hypoparathyroidism, but inadequate parathyroid hormone levels are not always found (1, 2). Hypocalcemia due to the hungry bone syndrome often complicates surgical parathyroidectomy for hyperparathyroidism (3). Unapposed bone formation, with decreased bone resorptive activity due to removal of the excess parathyroid hormone, results in hypocalcemia. To our knowledge, following is the first description of the hungry bone syndrome causing hypocalcemia after medical treatment of thyrotoxicosis.

Case Report: A 61-year-old woman with a history of nephrolithiasis was found to be thyrotoxic. In the 2 months before the diagnosis of hyperthyroidism, she had lost 14 kg and experienced new-onset tremor, anxiety, and palpitations. Laboratory testing revealed the following: a triiodothyronine level of 6.8 nmol/L (normal range, 0.9 to 2.8 nmol/L), a free thyroxine level of 144 pmol/L (normal range, 12 to 23 pmol/L), and a thyroid-stimulating hormone (TSH) level less than 0.05 mU/L. Treatment was initiated with methimazole and ultimately included radioactive iodine; symptoms improved and the patient gained weight.

Treatment of thyrotoxicosis resulted in laboratory and radiologic findings characteristic of the hungry bone syndrome (Table). The serum calcium level decreased from an initial value of 2.45 mmol/L (9.8 mg/dL) before treatment to a nadir of 2.07 mmol/L (8.3 mg/dL) 6 months later. Hypocalcemia was accompanied by marked hypocalciuria. The patient's intact parathyroid hormone level was elevated at 105.2 pg/mL (normal range, 10.0 to 65.0 pg/mL), suggesting secondary hyperparathyroidism. Other laboratory testing revealed normal 1,25-dihydroxyvitamin D₃ and 25-hydroxyvitamin D₃ levels and normalization of thyroid values; however, the serum alkaline phosphatase level was markedly elevated at

4.0 μ kat/L compared to the pretreatment level of 2.8 μ kat/L. Therapy with oral calcium carbonate was started at a dosage of 600 mg 4 times per day and was continued for 3 months until hypocalcemia resolved. At that time (Table) (9 months after initiation of thyrotoxicosis treatment), her intact parathyroid hormone and serum alkaline phosphatase levels had also normalized.

Bone mineral density was measured (Hologic QDR, Hologic, Waltham, Massachusetts) when the patient was hypocalcemic (6 months after initiation of thyrotoxicosis treatment) and 1 year after resolution of the hypocalcemia (Table) (22 months after initiation of thyrotoxicosis treatment). Consistent with the laboratory findings, bone mineral density increased by 21.8% at the lumbar spine (L1 to L4) and by 12.8% at the femoral neck (Table).

Conclusion: Thyrotoxicosis causes osteoporosis by increasing bone resorption (4). The increase in bone resorption can result in hypercalcemia, hypercalciuria, and renal calculi. Similar to parathyroidectomy for hyperparathyroidism, treatment of thyrotoxicosis increases bone mass by decreasing bone resorptive activity (3). In this patient, very active bone mineralization probably caused a marked decrease in serum calcium with consequent secondary hyperparathyroidism and hypocalciuria. Consistent with this conclusion, surgical thyroidectomy has been reported to cause hypocalcemia possibly related to the hungry bone syndrome (1, 2). As in this patient, treatment of thyrotoxicosis can markedly improve bone density (Table) (5). In cases of osteoporosis occurring with the diagnosis of thyrotoxicosis, clinicians should not start antiresorptive therapy until determining whether resolution of the thyrotoxicosis has improved bone density. In summary, patients treated medically for thyrotoxicosis may develop hypocalcemia due to the hungry bone syndrome, which results in an increase in bone mineral density. Dietary calcium supplements may help maximize the increase in bone density.

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Table. Laboratory and Radiologic Results before and after Treatment of Thyrotoxicosis

Variable	At Diagnosis of Thyrotoxicosis	6 Months Later	9 Months Later	22 Months Later
Serum calcium level, mmol/L (mg/dL)	2.45 (9.8)	2.07 (8.3)	2.27 (9.1)	2.25 (9.0)
Urinary calcium level, mmol/d (mg/d)		Undetectable	5.8 (234)	6.1 (244)
Intact parathyroid hormone level, pg/mL		105.2	65.7	
Alkaline phosphatase level, μ kat/L	2.8	4.0	2.6	1.7
Bone mineral density				
Lumbar spine				
g/m ²		0.800		0.975
t-score		-2.2		-0.7
Femoral neck				
g/m ²		0.622		0.701
t-score		-2.0		-1.3

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HFE Gene Mutations in Chile

TO THE EDITOR: *Background:* The prevalence of hereditary hemochromatosis varies among countries and geographic regions, apparently influenced by the ethnic origin of the local population and by the prevalence of allele variants C282Y and H63D in the *HFE* gene on chromosome 6 (1, 2). The current population of Chile is predominantly white but includes vestiges of an ancestral ethnic admixture between Spanish colonizers and local aboriginal inhabitants (mainly the Araucanian Indian groups Mapuches, Pehuenches, and Huilliches) that occurred between the 16th and 18th centuries.

Objective: To investigate the presence of C282Y and H63D mutations in 2 ethnic groups in Chile and compare it with data reported in the literature in ethnically related groups from Spain and North America.

Methods: The study included 156 healthy volunteers (hospital employees, voluntary blood donors, and medical students) who were older than 25 years of age, were from Santiago in central Chile, and had white phenotypic traits and Spanish or other European surnames but no family history of hereditary hemochromatosis. The study also included 78 persons born in the Araucanía region of southern Chile who had Araucanian Indian phenotypic traits and Araucanian surnames.

Genotyping was performed on genomic DNA isolated from peripheral blood leukocytes. The regions around the C282Y and H63D mutations were amplified separately by using polymerase chain reaction and oligonucleotide primer sequences, as described by

Feder and colleagues (3). Polymerase chain reaction products were screened by using restriction enzyme analysis with Rsa I (C282Y) and Mbo I (H63D). The mutations were confirmed by performing direct DNA sequencing of polymerase chain reaction products (4). Allele frequencies for C282Y and H63D mutations were obtained by direct count. The ethics committees of the University of Chile School of Medicine, the Chilean Air Force Hospital, and Universidad de La Frontera approved the study.

Results: Among 156 Chileans of white ethnicity, none were found to be homozygous for the C282Y mutation or compound heterozygous (C282Y/H63D). One hundred twenty-one (77.57%) did not show any of the mutations studied (Table). The allele frequency for C282Y was significantly lower in these persons than in 1001 Spanish persons pooled from 8 reports in the literature (1.28% vs. 3.14%; $P = 0.006$) (2, 5–8) but did not differ from the frequency among 2679 persons whose ethnicity was classified as Mexican, Hispanic, or Mexican American (1.28% vs. 1.55%; $P = 0.18$) (2, 9–11). The allele frequency for H63D was also significantly lower than in Spanish persons (10.58% vs. 22.1%; $P < 0.001$) and did not differ from the pooled data of frequency in Mexican, Hispanic, or Mexican-American persons (10.58% vs. 11%; $P > 0.2$).

Among 78 persons of Araucanian Indian descent, only 1 (who was heterozygous) had the C282Y allele. Four persons were heterozygous for the H63D allele, and 73 persons (93.59%) had a wild-type/wild-type genotype (Table). The allele frequency for C282Y was not significantly lower in persons of Araucanian Indian descent than in Chileans of white ethnicity (0.64% vs. 1.28%; $P > 0.2$), but H63D was significantly less prevalent (2.56% vs. 10.58%; $P = 0.002$). In addition, persons of Araucanian Indian descent had significantly lower allele frequencies for C282Y and H63D than did Spanish, Mexican, Hispanic, and Mexican-American persons ($P < 0.001$).

The genotype distribution observed in our population sample of Chilean persons of white ethnicity was close to expected numbers determined according to the Hardy–Weinberg equilibrium. This allowed us to predict that the prevalence of individuals homozygous for the C282Y mutation in Chile would be 0.00016 (that is, 1 in 6250 persons in the general population). This figure is roughly 6 times lower than that in Spain (6).

Conclusions: We propose that the original Araucanian Indians lacked *HFE* gene mutations C282Y and H63D. This ancestral characteristic could have been common to other groups of North and

Table. Genotypic Frequencies of HFE Gene Mutations C282Y and H63D in Chileans of White Ethnicity and Chileans of Araucanian Indian Descent*

Genotype	Chileans of White Ethnicity	Chileans of Araucanian Indian Descent
	n (%)	
C282Y/C282Y	0 (0)	0 (0)
C282Y/H63D	0 (0)	0 (0)
H63D/H63D	2 (1.28)	0 (0)
C282Y/wt	4 (2.56)	1 (1.28)
H63D/wt	29 (18.59)	4 (5.13)
wt/wt	121 (77.57)	73 (93.59)
Total	156 (100)	78 (100)

* wt = wild type. For all genotypes, $P < 0.05$ for Chileans of Araucanian Indian descent compared with Chileans of white ethnicity (chi-square and Fisher exact tests).

South American aboriginal inhabitants. The ethnic admixture of local aboriginal inhabitants and Spaniards and other Europeans may have led to a lower allele frequency of the C282Y and H63D mutations in white Chilean persons. This may also explain the low prevalence of *HFE*-related hemochromatosis in Chile.

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A Critical Overview of Homeopathy

TO THE EDITOR: Homeopathy has become increasingly popular with consumers throughout the world. It is also highly controversial. In this context, we welcome Jonas and colleagues' critical overview (1). Such an overview is not an easy task because of the different operator-dependent techniques used in homeopathic practice.

We wish to point out some shortcomings in this overview. A comprehensive review of homeopathy should consider adverse effects. A systematic review done by 2 of us (2) showed that the mean incidence of adverse effects was greater with homeopathic medicines than with placebo in 11 controlled clinical trials (relative risk, 1.8) but that the effects were minor, transient, and similar in type in both study groups. A single trial of influenza prophylaxis heavily biased the results. If this trial were excluded, the relative risk would be 1.3 (Table). The main risks associated with homeopathy seem to be indirect, relating to the prescriber rather than the medicine. To our knowledge, no studies have adequately investigated this, and government regulation of homeopathic practitioners varies widely among different countries and legislatures.

Homeopathic pathogenetic trials or "provings" are said to be the basis of the knowledge of homeopathic medicines, but Jonas and colleagues do not mention that many of these volunteer studies were done in the recent past. A systematic review by 2 of us (3) concluded that there is a strong negative correlation between quality and the number of pathogenetic effects (that is, low-quality studies yielded more symptoms). In other words, more subtle symptoms, mainly psychological, could be false and thus could bias criteria for homeopathic prescriptions.

Finally, we highlight the question of sample size. Trials of homeopathy and other forms of complementary medicine are frequently relatively small and statistically underpowered. Unfortu-

nately, perhaps because most scientists view homeopathy as having low "prior probability," they often interpret "absence of evidence" as "evidence of absence" of effect. For instance, in a recent study of the effect of homeopathic arnica, postoperative patients receiving placebo required 45% more analgesia than those receiving 1 of 2 homeopathic treatments (4). The study was interpreted as negative. The investigators did not report 95% confidence intervals, which is regrettable since the study was clearly underpowered to detect what was certainly a clinically relevant difference. The answer, of course, is larger, better-quality trials. But these also need larger budgets!

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Table. Adverse Effects of Homeopathic Medicine Reported in Placebo-Controlled Clinical Trials (1970–1995)*

Study, Year	Medicine, Dose	Incidence of Adverse Effect with Homeopathic Medicines, n/n	Incidence of Adverse Effect with Placebo, n/n	Reported Adverse Effect
Lökken et al., 1995	Arnica, D30 (mostly)	5/24	5/24	Nonspecific symptoms (headache, dizziness)
Reilly et al., 1994	Allergen, CH30	1/11	2/13	Aggravation of symptoms
Reilly et al., 1986	Pollen, CH30	11/56	11/52	Aggravation of symptoms
Reilly et al., 1985	Pollen, CH30	1/10	7/25	Aggravation of symptoms
Labrecque et al., 1992	Thuya, CH30 <i>Antimonium crudum</i> , CH7 <i>Nitricum acidum</i> , CH7	2/84	4/87	Stomach ache, loose stools, pimples, and tiredness
Attena et al., 1995	<i>Anas barbariae</i> , CH200	77/783	17/790	Aggravation of influenza-like syndrome: myalgia, low-grade fever, rhinorrhea, headache, skin rash, itching, ear ache
Wiesenauer, 1995	<i>Galphimia glauca</i> , D4	0/64	1/68	Slight nausea in the morning
Ernst, 1990	Plant complex, Ø–D4	0/31	0/30	None
Jansen, 1992	Individualized, 30–1000C	0/6	1/4	Repeated aggravations (with placebo)
Jacobs et al., 1994	Individualized, 30C	0/43	0/44	None
De Klerk, 1994	Individualized, 6–200C	12/86	13/84	Irritability, aggressive behavior (2 patients), fever, headache, eczema, vomiting, increased perspiration (2 patients), rash (2 patients), cross mood, obstinate behavior, hyperactivity, ear discharge, constipation, restlessness, cough, stomach ache, hyperactivity, nausea, epistaxis, convulsion, albuminuria

* C = centesimal; CH = centesimal hahnemannian; D = decimal.

arnica for prevention of pain and bruising: randomized placebo-controlled trial in hand surgery. *J R Soc Med.* 2003;96:60-5. [PMID: 12562974]

TO THE EDITOR: Jonas and colleagues (1) forgot some important “symptoms” that a homeopath has to look for when considering a *Pulsatilla* prescription: “flatulence, no two stools alike, averse to fat, drink and warm food” (2) and “morbid dread of the opposite sex, religious melancholy, given to extremes of pleasure and pain” (2), together with dozens of other unrelated signs, supposedly generated in healthy people by this “preeminently female remedy, especially for mild, gentle, yielding disposition . . . crying readily; weeps when talking” (2). Thus, the clear inverse correlation between the quality of a homeopathic study and its positive result comes as no surprise. When independent replication is demanded, it is even less surprising to see the positive results drop to zero.

For instance, consider 1 of Jonas and colleagues’ examples, in which the findings of 1 study (3) were nonindependently replicated by a second (4). Homeopathy was prescribed for diarrhea; some of the “symptoms” involved were head sweats during sleep and the presence of 1 red cheek and 1 pale cheek. Other investigators (5) have detailed the many inconsistencies and errors in the first of these 2 studies. In fact, the investigators of the original study seem to have manipulated variables and end points in search of a significant *P* value (which they found: *P* = 0.048). For instance, in the original study (3), a “significant difference in the average number of stools by day 3” is considered a positive outcome. However, in the second study (4), the difference appears by day 5 (in the first study, this had yielded a negative result). Yet Jonas and colleagues consider these to be high-quality studies!

Finally, 1 of the authors had a \$50 million budget solely for complementary and alternative medicine research. The authors’ statement that “more and better research is needed, unobstructed by belief or disbelief” (1) sounds like a cry for mercy for a pseudoscience disguised as an “alternative” therapy.

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TO THE EDITOR: Jonas and colleagues (1) sought to critically appraise homeopathy. This issue, along with the spread of other alternative medical therapies in western countries, is very important because it places all of scientific medicine in doubt (2). Jonas and colleagues’ paper only partially describes homeopathy—it does not

define the historical origin of this doctrine and discusses only its pharmacologic and therapeutic aspects.

Homeopathy was born in the 18th and 19th centuries, when “medical systems,” such as the doctrine of John Brown in England, dominated Europe. According to “medical systems,” each pathologic phenomenon consists of 2 opposing concepts (for example, Brown believed that all diseases were “hyposthenic” or “hypersthenic”) (3). The doctrine developed by Hahnemann was a medical system in which homeopathic and allopathic remedies were the opposing approaches. This distinction between allopathy and homeopathy now makes no sense because most drugs are given not to suppress symptoms but to break down etiopathogenic sequences. Hahnemann’s theory claims that all chronic diseases can be divided into 3 pathologic forms—psora, lues, and sycosis (which do not correspond to the current nosography)—that arise not from material causes but from a perturbation of the “vital spirit.” Accordingly, drugs act not because of their material structure but because of their power to influence the vital force of the living organism. Many orthodox homeopathic physicians still support this theory.

Every critical analysis of homeopathy must consider that homeopathy is not a scientific theory but a metaphysical doctrine based on concepts that cannot be defined or proven experimentally (4). Clinical trials of the properties of homeopathic preparations cannot demonstrate the truth of homeopathy or the likelihood of its effectiveness since the doctrine contains metaphysical concepts (5). Thus, Jonas and colleagues’ paper cannot supply any evidence in favor of homeopathy.

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IN RESPONSE: Dr. Dantas and colleagues point out that there are additional data beside those presented in our overview of homeopathy. Our purposely limited review omitted some less rigorous science. Determining the magnitude of adverse effects is even more difficult than determining efficacy since most studies are not designed to detect adverse effects. The rate of the latter is extremely low in homeopathy. A more fruitful approach than meta-analysis of efficacy studies is to investigate the potential toxic effects of homeopathic drugs in cell and animal studies (1). Likewise, homeopathic pathogenic trials or “provings,” while extensively reported in the literature, are generally not designed to detect effects over placebo. The few high-quality proving studies designed to test differences between homeopathic remedies and placebo do not show such dif-

ferences because symptoms in the placebo groups apparently covary in parallel with those in the remedy groups (2). Disentangling these remedy–placebo effects may require sequential rather than parallel study designs. Such studies have not been done.

The question of sample size is an important one for all clinical research. Sample size (not quality, as stated by Dr. Almeida) is the primary problem with the studies on the homeopathic treatment of diarrhea. Three studies (not 2), all rated as high quality by several independent reviewers, have demonstrated consistent effect sizes on the same outcome measure on the same day. As sample sizes increased, statistical significance improved and confidence intervals narrowed (3). Dr. Almeida's other comments are illogical and erroneous: 1) The symptoms of *Pulsatilla* and the criteria for study quality are completely unrelated; 2) the critique by Sampson has been thoroughly debunked (4, 5); 3) Dr. Almeida's failure to assess treatment model validity leads to erroneous research evaluation and conclusions, which is a common problem in complementary and alternative medicine (6); and 4) his statement that 1 author had \$50 million for alternative medicine research is incorrect.

We appreciate Dr. Federspil and colleagues' pointing out that some people practicing a medical system hold metaphysical beliefs about its action. This does not, of course, preclude science from examining the practice in the laboratory or in clinical trials to see whether it works. Walking the razor edge of Occam (that is, being

true to the data) is by far the most difficult task faced by investigators when confronted with controversial areas such as homeopathy. Good scientists, however, are willing to get their feet cut by the truth.

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