Correspondence

Meta-Analyses and Large Randomized, Controlled Trials

To the Editor: We were pleased to see that using an independent protocol, LeLorier et al. (Aug. 21 issue)[1] confirmed both our[2] previous estimates of the frequency of discrepancies between large trials and meta-analyses and those of Villar et al.[3] Their selection of 12 large trials from four influential journals may have inflated the frequency of apparent discrepancies. Such journals may tend to publish trials that are likely to change practice, whose results disagree with prior evidence.[4] Still, the estimates of LeLorier et al. are largely similar to prior estimates. However, we are concerned that several of their premises propagate outdated myths.

First, why is the latest single large trial always the gold standard against which all prior evidence (often including several large trials) must be measured? In 6 of the 12 cases discussed, the meta-analysis had more patients than the subsequent gold standard. Second, decision making based solely on which side of 0.05 the P value lies is potentially misleading; an odds ratio of 0.7 (95 percent confidence interval, 0.5 to 0.9; $P = 0.01$), although different in precision, is hardly discrepant with an odds ratio of 0.7 (95 percent confidence interval, 0.3 to 1.8; $P = 0.4$). The measure that LeLorier et al. use may misrepresent the true frequency of disagreement.

Third, even with appropriate measures, discrepancies between meta-analyses and large trials should be expected, given the variable characteristics and treatment responses in different persons, protocols, and populations. Not only are trials in meta-analyses frequently heterogeneous, but also the idea of the homogeneous single trial is often a myth. Discrepancies occur even within trials[5] and between large trials themselves, as studies of magnesium in myocardial infarction exemplify.[6] Meta-analysis has recently been evolving toward evaluating this heterogeneity. It is more constructive to quantify reasons for discrepancies[2] rather than wait for the latest larger and better trial that may nullify past experience. Unfortunately, LeLorier et al. did not explore such reasons systematically.

Fourth, potential biases exist in both meta-analyses and clinical trials. If nothing else, meta-analysis sensitizes us to several of these biases regarding the conduct and reporting of trials.[4] LeLorier and colleagues made use of such scientific advances to make their points. Meta-analysis is not statistical alchemy that makes life easier by distilling one magic number from confounded data; it is a scientific discipline that aims to quantify evidence and to explore bias and diversity in research systematically. We should keep trying to improve clinical trials and meta-analyses, not undermine them.

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INSTRUCTIONS FOR LETTERS TO THE EDITOR

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To the Editor: LeLorier et al. assume that the results of randomized, controlled trials correctly represent the true effect of an intervention and that the results of meta-analyses must be judged against this gold standard. This comparison, however, is not valid when there are major methodologic differences between the trials included in the meta-analysis and the subsequent randomized, controlled trial.

For example, the authors compare the results of a meta-analysis and a randomized, controlled trial that examined the efficacy of nitrates in patients with acute myocardial infarction. The meta-analysis, published in 1988,[1] found a benefit in terms of mortality from the use of nitrates (odds ratio, 0.65; 95 percent confidence interval, 0.51 to 0.82), but the randomized, controlled trial, published in 1994,[2] found no benefit (odds ratio, 0.94; 95 percent confidence interval, 0.84 to 1.05). However, both the interventions and the patient populations were markedly different. Patients in the meta-analysis were not treated with thrombolytic agents and were rarely treated with beta-blockers, and the control group had a high mortality rate (20.5 percent).[1] In contrast, patients in the randomized, controlled trial were intensively treated with multiple therapies (72 percent received thrombolytic agents and 31 percent received beta-blockers), and the mortality rate (6.9 percent) in the control group was much lower.[2] Rather than indicating that the meta-analysis is wrong, the findings suggest that nitrates decrease mortality only in patients who are not treated acutely with other therapies.

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2. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet 1994;343:1115-22.

To the Editor: . . . An overall estimate from a meta-analysis can be misleading if there is considerable heterogeneity among the included trials that has not been fully investigated. Similarly, it is misleading to compare the results of a single study with those of a meta-analysis without a careful examination of important characteristics of the patients and interventions included in these trials. Unfortunately, the study by LeLorier and colleagues, by giving the impression that the meta-analyses and the large trials were measuring the same thing, applies a simplistic analysis to a complex issue. These potentially misleading comparisons were seized on in the accompanying editorial (Aug. 21 issue)[1] to assert that a conventional narrative review is more reliable than a well-conducted meta-analysis, without providing any objective evidence to demonstrate the predictive accuracy of such narrative reviews. The reliability of large randomized, controlled trials, systematic reviews, meta-analyses, and narrative or ad hoc reviews and their respective roles in the field of clinical evaluation should be decided on the basis of careful scientific inquiry rather than prejudice.

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1. Bailar JC III. The promise and problems of meta-analysis. N Engl J Med 1997;337:559-61.

To the Editor: The study by LeLorier et al. comparing the results of meta-analyses and subsequent large randomized, controlled trials illustrates the importance of exploring the heterogeneity of research evidence, a point noticeably missing from the editorial by Bailar. It would surely have been informative for LeLorier et al. to have explored the heterogeneity evident in Figure 1 of their article, particularly with respect to the methodologic quality, numbers of patients, and the length of follow-up. Instead, the authors chose to summarize the results in terms of predictive ability, a simplistic approach, particularly when correlated outcomes from within the same studies were included.

Both the article and the editorial highlight pitfalls that are only too well known to reviewers in the Cochrane Collaboration.[1] However, LeLorier et al. failed to provide information about how closely the meta-analyses followed Cochrane Collaboration guidelines,[1] among which are identifying unpublished studies, specifying whether data on individual patients or aggregate data were used, and revealing the way in which the quality of the original trial design was evaluated and whether heterogeneity between trial results was investigated. None of these points were mentioned by Bailar. Similarly, the only indication of the rigor of the large, randomized trials selected in the study by LeLorier et al. is provided by the journal in which they were published and the number of patients randomized, rather than by the mention of any previously published standards,[2] despite the description and use of such trials as the gold standard in evaluations of the efficacy of clinical interventions. Although recognizing the key role of rigorous, large, randomized, controlled clinical trials, we must not throw out the baby with the bath water, or fall prey to the biases inherent in conventional narrative review,[3] by dismissing systematic reviews and, when appropriate, meta-analysis.

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1. Oxman A. Preparing and maintaining systematic reviews. Cochrane Collaboration hand book. Oxford, England: Cochrane Collaboration, 1996:Section VI.
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3. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers CT. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. JAMA 1992;268:240-8.

To the Editor: LeLorier et al. restrictively searched for trials in four high-profile journals that can be very selective about publication. It is possible that the trials identified were submitted or published for the very reason that their effect sizes differed from those in previous meta-analyses, whereas trials closely confirming meta-analyses may have appeared in less prestigious journals. A less biased approach might have been to have conducted a similar analysis in which primary selection was applied to the meta-analyses and all journals were searched for subsequent trials. . . .

In our opinion, the editorial presents the biased viewpoint of a single person (much like a conventional review), illustrated by the statement that "when both the trial and the meta-analysis seem to be of good quality, . . . I tend to believe the results of the trial." On what basis? Support of narrative over systematic reviews is worrying. The problems of traditional review are numerous and have been well documented.[1] The expression of such an opinion in a *Journal* editorial is a step back in this era of evidence-based medicine.

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1. Mulrow CD. The medical review article: state of the science. Ann Intern Med 1987;106:485-8.

To the Editor: LeLorier et al. make a key assumption that the meta-analyses and the randomized trials were both estimating the same underlying effect. They attempted to adjust for any error in this assumption by performing a sensitivity analysis on the determination of similarity by the reviewers.

We believe that more advanced techniques of meta-analysis that explore specific sources of heterogeneity would provide additional insight into why the meta-analyses and their corresponding large trials did not observe the same outcomes. For example, techniques such as hierarchical Bayes'[1] and regression methods could be used to identify specific points on which the large trials and the individual trials in the meta-analyses differ, and to quantify the associations of these sources of heterogeneity with the observed outcomes. These analyses might therefore generate fruitful new directions for research.

When we acknowledge that meta-analysis is a method for studying studies rather than a shortcut for conducting large, randomized trials, we will begin to find the proper place for meta-analysis in our biostatistical toolbag.

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1. DeMouchel WH, Harris JE. Bayes methods for combining the results of cancer studies in humans and other species. J Am Stat Assoc 1983;78:293-308.

To the Editor: Meta-analysis provides an opportunity to look for reasons for inconsistent results among studies, but LeLorier et al. mention only some hypothetical, generic reasons and overlook clinical information that might have explained the discrepant findings.

The discrepancies may be explained more by clinical heterogeneity and details of the study protocols and less by publication bias and analysis of random as opposed to fixed effects. For example, there was a statistically significant discrepancy between the meta-analysis[1] and the large randomized, controlled trial — the Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP)[2] — involving low-dose aspirin for the prevention of intrauterine growth retardation. Eligibility criteria for the study (women at 12 to 32 weeks of gestation with a sufficient risk of preeclampsia or intrauterine growth retardation according to the responsible clinician) were vastly different from those of the meta-analysis (women with prior preeclampsia, intrauterine growth retardation, or placental infarction; primiparas with either increased blood pressure in response to angiotensin II or abnormal uteroplacental blood flow). This difference is reflected in the base-line risks of intrauterine growth retardation in the control groups: 6.6 percent (95 percent confidence interval, 6.2 to 7.0 percent) for women enrolled in the CLASP trial and 28 percent (range, 18 to 63 percent) for the study groups in the meta-analysis. This difference in risk by more than a factor of 4 exists despite the use of a less stringent definition of intrauterine growth retardation in the CLASP trial. Differences in the base-line risk of preeclampsia further highlight the heterogeneity: 7.6 percent (95 percent confidence interval, 6.8 to 8.1 percent) in the CLASP trial and 33 percent (range, 17 to 52 percent) in the meta-analysis.

The difference in the base-line risks of intrauterine growth retardation and preeclampsia, despite an offsetting difference in the criteria for intrauterine growth retardation, is a plausible explanation for the discrepant results. In reality, the CLASP trial and meta-analysis results are not necessarily discrepant, but they may reflect a variation in the effect of treatment with low-dose aspirin as a function of the risk of intrauterine growth retardation.

Without a careful consideration of clinical homogeneity, the work of LeLorier et al. has the same limitations as meta-analyses that do not carefully consider the clinical aspects of data synthesis.

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1. Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease. JAMA 1991;266:260-4.
2. CLASP (Collaborative Low-Dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet 1994;343:619-29.

The authors reply:

To the Editor: Ioannidis et al., as well as Khan et al. and Stewart et al., suggest that the editors of the influential journals that published the trials we chose may tend to favor the publication of large trials whose results disagree with prior evidence. This is a new variation on publication bias that, unfortunately, cannot be proved. Ioannidis

et al. mention that our work confirms their own results[1] and those of Villar et al.,[2] but we want to respond to their comments.

First, we do not agree with the view that the six meta-analyses with more patients than the large randomized, controlled trials are more credible. Although the inclusion of more patients gives more statistical power, it cannot compensate for methodologic flaws. Second, we still think that the precision of an odds ratio is important, since it determines whether a therapy is adopted or rejected. An odds ratio whose confidence interval overlaps 1 will be considered, at best, to represent a tendency, and the null hypothesis will still stand. Third, we fully agree that the problems of heterogeneity are extremely important, and they are the object of our present work. Fourth, we are certainly in favor of having meta-analysis emphasize the systematic exploration of bias and diversity in research rather than the distillation of a magic odds ratio.

According to Bent et al., the higher base-line mortality rates in the meta-analysis[3] of the efficacy of nitrates in patients with myocardial infarction could explain the discrepancy between its results and those of the subsequent large randomized, controlled trial — the third study of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3).[4] The question is whether these differences alone could move the odds ratio from 0.5 to nearly 1, given that the meta-analysis includes studies with base-line mortality rates that are lower than the one in the GISSI-3 trial. The large randomized, controlled trial would thus have met the homogeneity criteria of the meta-analysis. It is fortunate that the investigators decided to examine the role of nitrates in acute myocardial infarction in the era of thrombolytic agents and beta-blockers by conducting a trial rather than a sequential meta-analysis.

Imperiale proposes that the differences in base-line rates of preeclampsia and intrauterine growth retardation can be used to explain why the positive results of his meta-analysis[5] on the effects of aspirin were not confirmed by the large randomized, controlled trial[6] (the CLASP trial). An alternative explanation would be that among the six studies in the meta-analysis, one was a nonrandomized trial[7] and two were not placebo-controlled.[7,8]

We agree with the proposal of Sim and Lavori for the development of statistical techniques to explore specific sources of heterogeneity and assist in the selection of studies. The choice of the data to be included constitutes the first and most fundamental step in a review and is, in our opinion, much more important than its eventual shape or form.

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8. Wallenburg HC, Rotmans N. Prevention of recurrent idiopathic fetal growth retardation by low-dose aspirin and dipyridamole. Am J Obstet Gynecol 1987;157:1230-5.

To the Editor: My objections to meta-analysis are purely pragmatic. It does not work nearly as well as we might want it to work. The problems are so deep and so numerous that the results are simply not reliable. My editorial cites a few relevant references, and I could have cited many more. The work of LeLorier et al. adds to the evidence that meta-analysis simply does not work very well in practice.

Khan et al. seem concerned that neither the meta-analyses nor the randomized, controlled trials were performed to their own standard of excellence. But that is just the point. As it is practiced and as it is reported in our leading journals, meta-analysis is often deeply flawed. Many people cite high-sounding guidelines, and I am sure that all truly want to do a superior analysis, but meta-analysis often fails in ways that seem to be invisible to the analyst. We cannot know whether improved implementation would alter the findings.

Stewart et al. suggest that leading journals may deliberately select and publish randomized, controlled trials that disagree with previously published meta-analyses, and they propose that all journals be searched for randomized, controlled trials. That could be useful, but it would pose a much bigger task than the work of LeLorier et al. and might miss the main point: the results of meta-analyses are often at variance with those of randomized, controlled trials. Certainly, randomized, controlled trials can be done as poorly as meta-analyses, and the analysis conducted by LeLorier et al. is also less than perfect. What we need is a guide through the imperfect world of science.

The advocates of meta-analysis and evidence-based medicine should undertake research that might demonstrate that meta-analyses in the real world — not just in theory — improve health outcomes in patients. Review of the long history of randomized, controlled trials, individually weak for this specific purpose, has led to overwhelming evidence of efficacy. Examples include the development of better vaccines, more effective screening for diseases, and improved treatments for childhood cancer, infections, mental illness, cardiovascular disease, and many others. I am not willing to abandon that history to join those now promoting meta-analysis as the answer, no matter how pretty the underlying theory, until its defects are honestly exposed and corrected. The knowledgeable, thoughtful, traditional review of the original literature remains the closest thing we have to a gold standard for summarizing disparate evidence in medicine.

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Hormone-Replacement Therapy Compared with Simvastatin for Postmenopausal Women with Hypercholesterolemia

To the Editor: With respect to the article by Darling et al. (Aug. 28 issue)[1] on the effects of hormone-replacement therapy and simvastatin in postmenopausal women with hypercholesterolemia: We carried out a study in which we assessed the effects of the combination of these two therapies. A total of 71 women with hypercholesterolemia (mean [±SD] age, 53±4 years) were recruited. The initial phase of the study consisted of three months of hormone-replacement therapy and a cholesterol-lowering diet, which resulted in low-density lipoprotein (LDL) cholesterol levels of less than 160 mg per deciliter in 15 of the women (21 percent). Those with persistently high LDL cholesterol levels entered the second phase, in which simvastatin (10 mg per day) was added. A total of 34 women completed nine months of combined therapy (Table 1).

Our results are consistent with those of Darling et al. — namely, simvastatin was more effective than hormone-replacement therapy. However, we believe that the conclusion suggested by Darling et al. is somewhat inaccurate. Although some women, especially those with mild hypercholesterolemia, will benefit from hormone-replacement therapy as a single cholesterol-lowering treatment, most women with hypercholesterolemia will need a specific, more potent hypercholesterolemic drug. Most studies of the effects of hormone-replacement therapy on the lipid profile have shown only a 5 to 15 percent reduction in persistently high LDL levels,[2] in contrast with the 24 percent reduction reported by Darling et al. Combined treatment with hormone-replacement therapy and low-dose simvastatin proved to be extremely effective in our study, with no serious adverse reactions. Moreover, this combined therapeutic regimen may have a synergistic antiatherogenic effect.

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1. Darling GM, Johns JA, McCloud PI, Davis SR. Estrogen and progestin compared with simvastatin for hypercholesterolemia in postmenopausal women. N Engl J Med 1997;337:595-601.
2. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. Circulation 1987;57:1102-9.

TABLE 1. MEAN (±SD) CHOLESTEROL LEVELS IN WOMEN WITH HYPERCHOLESTEROLEMIA TREATED FOR THREE MONTHS WITH HORMONE-REPLACEMENT THERAPY AND DIET AND FOR NINE MONTHS WITH SIMVASTATIN PLUS HORMONE-REPLACEMENT THERAPY AND DIET.*

VARIABLE	BASE LINE	HRT AND DIET	SIMVASTATIN PLUS HRT AND DIET	
Time during regimen (mo)	—	3	1	9
Cholesterol (mg/dl)				
Total	290±29	281±26	213±30†	214±22†
LDL	204±31	187±26‡	122±30†	124±22†
HDL	53±12	62±16‡	60±18‡	63±14‡
Triglycerides (mg/dl)	144±63	170±65	147±68	147±67

*HRT denotes hormone-replacement therapy, LDL low-density lipoprotein, and HDL high-density lipoprotein.

†$P<0.001$ for the comparisons with base line and HRT plus diet.

‡$P<0.05$ for the comparison with base line.

To the Editor: The report by Darling and colleagues ascribes a 27 percent reduction in Lp(a) lipoprotein levels to postmenopausal hormone therapy with combined estrogen and progestin. Unfortunately, the authors do not consider the effects of dietary changes on lipoproteins. According to their summary of the protocol, "At enrollment, all the women were given . . . dietary advice by a trained nurse. Although they were encouraged to continue the recommended diet for the remainder of the study, there was no formal assessment of their compliance." The usual Australian diet is notoriously high in fat, saturated fat, and cholesterol, and lipid profiles may be expected to improve as a result of relatively modest changes.

Although not ideal, brief instruction on appropriate dietary changes can result in significant improvements in lipid profiles. Rhodes et al.[1] reported serum lipid changes in adults with a mean serum cholesterol level of 260 mg per deciliter who were instructed by a nurse or physician on the Step 1 diet of the National Cholesterol Education Program.[2] Dietary fat decreased from 37 percent of energy at base line to 31 percent, and cholesterol intake dropped by approximately 25 percent. Mean reductions of 7 percent in the total serum cholesterol level and 10 percent in the LDL cholesterol level occurred after 12 weeks.[1]

The dramatic reduction in LDL cholesterol levels with only 10 mg of simvastatin per day (36 percent, vs. an expected reduction of approximately 25 percent) may well be attributable to the combined effect of dietary modification and pharmacologic treatment. For any trial that purports to demonstrate the effect of a therapy on lipoprotein levels, it is an absolute necessity to document dietary composition at base line and during treatment.

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1. Rhodes KS, Bookstein LC, Aaronson LS, Mercer NM, Orringer CE. Intensive nutrition counseling enhances outcomes of National Cholesterol Education Program dietary therapy. J Am Diet Assoc 1996;96:1003-10.
2. Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994;89:1333-445.

The authors reply:

To the Editor: Dr. Pines and colleagues are concerned that our article may promote postmenopausal hormone therapy as the sole pharmacotherapy for postmenopausal women with hypercholesterolemia. In fact, we are trying to promote its individualized use as first-line pharmacotherapy in such women, and we fully concur with the notion that many women will require the addition of conventional lipid-lowering agents to hormone therapy in order to achieve the level of LDL cholesterol currently recommended by the expert panel of the National Cholesterol Education Program.[1] However, it is notable that studies specifically designed to investigate the effect of oral postmenopausal hormone therapy in women with hyperlipidemia consistently show a greater reduction in LDL cholesterol levels (12 to 24 percent)[2-4] than that documented in studies of women with normal lipid levels (10 to 15 percent).

We have also been interested in clarifying the effect of the concurrent use of postmenopausal hormone therapy and simvastatin on lipoprotein. Our unpublished data support the conclusions of Dr. Pines and colleagues and even suggest that the effect of the two therapies may be additive. Thus, the stepwise introduction of diet, followed by individualized hormone therapy, followed by a statin may prove to be the preferred way of managing hypercholesterolemia in postmenopausal women.

We appreciate the comments of Drs. Cashin-Hemphill and Vailas regarding the potential effect of relatively modest dietary modifications on the lipoprotein profile in patients with hypercholesterolemia. The crossover design of our study was used to compare two therapies (postmenopausal hormone therapy and simvastatin) with each other, not to determine the effect of each therapy alone. We were therefore careful not to include P values for the change from base-line values for each therapy alone but to include only P values for the comparison between the two therapies. The mean percentage change from base line with 95 percent confidence intervals was retained to assist in clinical interpretation of the results. Given the comments of Drs. Cashin-Hemphill and Vailas, it might have been more prudent to label the two therapies "postmenopausal hormone therapy plus dietary advice" and "simvastatin plus dietary advice." Even so, the comparison remains valid.

As we stated in our article, "The groups did not differ significantly in any variables at base line or at the end of the washout period (week 0 and week 16)." The dietary advice was given only at week 0. One would expect that any effect of dietary modification that was independent of the pharmacologic therapy would have been detectable at week 16, when all pharmacotherapy had been "washed out." No such effect was observed.

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1. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA 1993;269:3015-23.
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Obesity

To the Editor: In their article on obesity, Rosenbaum et al. (Aug. 7 issue)[1] characterize sibutramine, currently undergoing regulatory review as a drug for the treatment of obesity, as having both catecholaminergic and serotonergic agonist effects. Sibutramine, in fact, is not an agonist at catecholamine or serotonin receptors but instead acts by inhibiting the reuptake of serotonin and norepinephrine at central synapses. Thus, sibutramine's mode of action is similar to that of other monoamine-reuptake inhibitors such as venlafaxine (an inhibitor of serotonin and norepinephrine reuptake) and fluoxetine (a selective serotonin-reuptake inhibitor). The mode of action of drugs that alter appetite by enhancing central monoamine activity has several implications. For instance, primary pulmonary hypertension has been associated with certain appetite-suppressant drugs[2] (e.g., fenfluramine), as well as other drugs (e.g., cocaine), that act by causing monoamine release.[3] Rosenbaum et al. characterize the implicated anorectic drugs as reuptake inhibitors. In fact, monoamine-reuptake inhibitors that do not cause monoamine release, such as tricyclic antidepressant drugs, selective serotonin-reuptake inhibitors, and serotonin- and norepinephrine-reuptake inhibitors, have not been associated with an increased risk of primary pulmonary hypertension or neurotoxicity[4] or with the cardiac valvulopathy reported by Connolly et al.[5] Given the diversity of the satiety-enhancing drugs currently being developed, attention to the details of the mechanism of action may be even more important in the future.

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To the Editor: The excellent review of obesity contains a contradiction. The authors say that insulin causes weight gain because it increases the expression of neuropeptide Y

messenger RNA, with subsequent central appetite stimulation. They later say that insulin reduces food intake by inhibiting the expression of neuropeptide Y, and in another section, insulin is said to increase the expression of leptin in adipose tissue. Can the authors clarify the role of insulin in the stimulation or inhibition of food intake?

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The authors reply:

To the Editor: We appreciate the letter from Seaton et al. concerning the mode of action of sibutramine. We wished to note only that sibutramine has agonist actions in both serotonin and catecholamine systems. The full delineation of the exact mode of action of centrally active anorexiant drugs will undoubtedly receive increased scrutiny because some of these drugs may be neurotoxic,[1] cause primary pulmonary hypertension, and cause valvular heart disease.[2] Since our review was published, the Food and Drug Administration (FDA) and Wyeth–Ayerst Laboratories, acting on the concern about these possible adverse effects, have removed fenfluramines from the market.

We thank Dr. Eisenbud for his careful reading of the text. On page 401 (left-hand column), the statement, "The expression of neuropeptide Y mRNA is increased by insulin and glucocorticoids," is incorrect. It should read, "The expression of neuropeptide Y mRNA is increased by androgens and glucocorticoids and decreased by leptin, insulin, and estrogen."

There are two other errors. First, on page 397 (right-hand column), the statement suggesting that lesions of the median forebrain bundle are equivalent to those of the ventromedial hypothalamus is incorrect. Lesions of the median forebrain bundle are more likely to induce anorexia in a manner similar to that of lesions of the lateral hypothalamus. Second, on page 403, in the third sentence under the heading "Drug Therapy," *fenfluramine* should be *dexfenfluramine*. Dexfenfluramine was approved by the FDA in 1996, but fenfluramine was approved in 1973.

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1. McCann UD, Seiden LS, Rubin LJ, Ricaurte GA. Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine: a systematic review of the evidence. JAMA 1997;278:666-72.
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Transient Renal Failure Due to Simultaneous Ibuprofen and Aminoglycoside Therapy in Children with Cystic Fibrosis

To the Editor: Ibuprofen can retard the decline in pulmonary function in children with cystic fibrosis.[1] Aminoglycosides are often given to treat pulmonary infections in children with cystic fibrosis. Both ibuprofen and aminoglycosides are nephrotoxic. We have seen four children with cystic fibrosis who had transient renal failure during exacerbations of their lung disease that we believe was caused by the intravenous administration of an aminoglycoside while maintenance treatment with ibuprofen was continued.

The first patient was a 16-year-old girl with severe lung disease in whom nausea and vomiting developed six days after admission and the commencement of therapy with intravenous tobramycin for exacerbation of her lung disease. She received furosemide for peripheral edema, and oliguria developed the next day. Her serum creatinine concentration rose from 0.5 mg per deciliter (48 μmol per liter) at the time of admission to 2.8 mg per deciliter (249 μmol per liter) six days later. The ibuprofen and tobramycin were discontinued, and the serum creatinine concentration was 0.8 mg per deciliter (74 μmol per liter) two days later. The maximal serum tobramycin concentration was 27 mg per milliliter. The patient died nine days later of lung disease; minimal tubulointerstitial nephritis was seen at autopsy.

The second patient was a 10-year-old girl with moderately severe lung disease in whom nausea, vomiting, and abdominal cramps developed two days after admission and the initiation of therapy with intravenous gentamicin for exacerbation of her chronic lung disease. She was found to have a supratherapeutic peak serum gentamicin concentration of 16 mg per milliliter, and her serum creatinine concentration had increased from 0.7 mg per deciliter (64 μmol per liter) at the time of admission to 2.4 mg per deciliter (211 μmol per liter). The ibuprofen and gentamicin were discontinued, and her serum creatinine concentration was 0.9 mg per deciliter (82 μmol per liter) five days later.

The other two patients were twin 23-month-old brothers who were hospitalized simultaneously for exacerbations of chronic lung disease. Both patients were treated with intravenous gentamicin. The ibuprofen they were taking before admission was inadvertently continued, despite the existence of a policy of stopping ibuprofen during hospitalization if aminoglycoside therapy was given. This policy was instituted as a result of the first two cases. One twin began vomiting four days after admission. Ibuprofen was discontinued nine days later, but lethargy, increased vomiting, and periorbital edema occurred the next day, followed by generalized edema and oliguria. The child's serum creatinine concentration rose from 0.2 mg per deciliter (20 μmol per liter; measured 3 months earlier) to 5.2 mg per deciliter (460 μmol per liter) 16 days after admission. He received peritoneal dialysis for eight days, by which time urine output was normal and his serum creatinine concentration was 0.4 mg per deciliter (32 μmol per liter). The other brother had a transient asymptomatic increase in the serum creatinine concentration, from 0.6 mg per deciliter (49 μmol per liter) at admission to 1.5 mg per deciliter (134 μmol per liter) 18 days later. In both cases, subsequent audiologic testing had normal results, although the more severely affected brother had transient ataxia.

Our observations suggest that the combination of intravenous aminoglycoside and ibuprofen can cause acute renal insufficiency. We have not seen this complication with ibuprofen alone or with ibuprofen and nebulized tobramycin.[2] Aminoglycoside-induced toxicity is potentiated by

extracellular volume depletion,[3] and ibuprofen and other nonsteroidal antiinflammatory drugs interfere with the intrarenal production of prostaglandin E_2 and prostacyclin, which cause renal vasodilatation in the presence of reduced circulating volume.[4] Our findings suggest that ibuprofen should be stopped during intravenous aminoglycoside therapy.

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Case 21-1997: Paraneoplastic Cerebellar Degeneration and Hodgkin's Disease

To the Editor: Dr. Eder, in his discussion of the paraneoplastic cerebellar degeneration associated with Hodgkin's disease (July 10 issue),[1] quoted the 1976 paper by Trotter and colleagues[2] but did not mention that the antibodies they described are now recognized as distinct antibodies associated with Hodgkin's disease. These antibodies have been designated anti-Tr antibodies.[3] They have a characteristic dotted staining pattern, suggestive of immunoreactivity of the dendritic spines of Purkinje cells, and are specific for Hodgkin's disease.

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Professionalism

To the Editor: Karen Ignagni, the president of the American Association of Health Plans, stated in the October 9 issue, "The editor of the *New England Journal of Medicine* is entitled to be a critic of managed care, but it is profoundly disturbing to see such an important and presumably dispassionate publication used as a sounding board for these critical views."[1] That managed care promotes the slogan "Putting patients first" says it all. That is the unspoken assumption of the medical profession. It has been the foundation of the physician–patient relationship since Hippocrates. This special relationship is based on honor, and honor need not be spoken. Doctors do not require a slogan for trust. When trust is gone, it cannot be restored, like a soul that has left the body. Trust that is honored cannot be captured by a managed-care contract. Grasp a butterfly with hot tongs and the butterfly dies.

What physician, including the editor, can be dispassionate about the current destruction of our medical family at the hands of profit-hungry CEOs? Putting profit first is their unspoken assumption. As a practicing neurosurgeon for 28 years, I recommend passion when compassion for the patient is first, foremost, and central. As a young resident, I remember Wilder Penfield's words: "Keep the businessman out of medicine." I challenge you, as editor, to continue to speak in strong terms about the heart of the matter. In medicine we are witnesses to, and to some extent accomplices in, the social revolution aimed at converting people into integers. As Osler said, we can have both, science and faith, if only we keep them separate. There is plenty of room for dispassionate science in the *Journal*, but honor, trust, and dignity are matters of faith, not science. Once we were knights, duty bound to protect each and every patient, regardless of monetary concerns.

We physicians have allowed the current gross decline in our once noble profession. We have been passive passengers, docile slaves obedient to the gag clause. We cannot rely on government or the profit-oriented insurance industry to correct the medical train wreck in progress. We must take over the engine. We must lift ourselves up, with passion.

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To the Editor: You point out how the fee-for-service system participates in the support of research and education.[1] You omit, however, an important aspect of that support: the countless hours that voluntary clinical faculty contribute as ward attendings, clinic attendings, and preceptors in their own offices. These physicians are culled from any area where there is a medical school (and often where there is not). They give willingly and generously of their time and expertise, believing that being a physician includes passing along their hard-won knowledge and skills to the next generation. Many of my colleagues and I have been preceptors and attending physicians year after year, for countless young medical students and physicians. We do this silently and without fanfare. Most of the general public does not even know about it, as witnessed by the reactions of my new patients (the old ones are used to it), who are surprised and usually delighted to see students in the office.

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