Sweet Syndrome Associated With *Pasteurella multocida* Bronchitis

Acute febrile neutrophilic dermatosis, also referred to as Sweet syndrome, was first described in 1964.[1] This disease can be associated with infectious diseases or other conditions, but it is more frequently idiopathic (70% of cases). We report the first case, to our knowledge, of the concomitant occurrence of Sweet syndrome and *Pasteurella multocida* bronchitis.

Report of a Case. A 52-year-old woman who was living with several dogs and had long-term bronchiectasis was admitted to the hospital for painful skin lesions that were located on the arms and were associated with general malaise. A few days before, a pulmonary involvement was noted, which was characterized by an aggravation of her chronic cough and expectoration. On the day of admission, she presented with fever (38.2°C), asthenia, arthritis of the left ankle, and raised erythematous and tender plaques that were "mountain range–like" over her forearms, chest, and legs. Pulmonary examination revealed some sonorous rales in the pulmonary fields. Laboratory tests detected moderate neutrophilia (7.4×10^9/L neutrophils) and an inflammatory syndrome (erythrocyte sedimentation rate, 72 mm/h; C-reactive protein level, 118 mg/L; and coagulation factor I [fibrinogen], 7 g/L). Viral serologic test results for hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus, and cytomegalovirus were negative; bacterial serologic test results for *Yersinia*, *Mycoplasma pneumoniae*, and streptococci were also negative, as was the tuberculin intradermal test result. The cytobacteriological analysis of the expectoration revealed numerous *Pasteurella multocida* organisms. Histopathological examination of a skin biopsy specimen showed an intense edema of the upper dermis and an inflammatory infiltrate consisting mainly of neutrophils with leukocytoclasis but without vasculitis, suggesting Sweet syndrome. Chest x-ray film did not show a pleural or parenchymatosus evolutive lesion. Abdominal ultrasonogram, results of gynecologic investigation, and mammogram were normal. The patient was treated with prednisolone, 30 mg/d (quickly tapered over 9 days), and ampicillin, 2 g/d for 10 days, which resulted in a remission of fever within 2 days, arthralgias within 3 days, and respiratory symptoms and skin lesions within 10 days.

Comment. Sweet syndrome is frequently isolated but can be associated with numerous diseases: inflammatory diseases in 16% of cases or neoplastic diseases (hemoproliferative disorders or solid malignant tumors) in 11% of cases. Five percent of cases are associated with drug sensitivity and 2% with pregnancy.[2-4] Various infectious agents are reported to be associated with the syndrome, including bacterial agents (ie, *Yersinia enterolitica*, *Salmonella*, *Entamoeba coli*, *Helicobacter pylori*, *Staphylococcus*, *Streptococcus*, *Borrelia burgdorferi*, nontuberculous mycobacteria, and tubercle bacilli), viral agents (ie, human immunodeficiency virus, cytomegalovirus, and hepatitis), fungi, and parasites.

Pasteurella multocida is a small gram-negative bacterium that colonizes the upper respiratory or digestive tracts of healthy domestic animals (55% of dogs and 60%-90% of cats). Human infection usually follows direct contact, such as bites or licking, and results in cellulitis[5]; no associated reactive dermatoses, such as Sweet syndrome, have yet been reported. *Pasteurella* infections associated with atraumatic animal exposure are rare. The most common site of such infections is the respiratory tract (62% of cases), usually resulting in bronchitis, pneumopathy, or sinusitis.[6] These infections result from airborne contamination and occur in patients with underlying chronic respiratory disease, most commonly bronchiectasis, as was the case for our patient.

It is highly probably that Sweet syndrome was induced by the *Pasteurella* infection in our patient. Indeed, with the exception of the positive expectoration culture results for *P multocida*, all test results were negative. Moreover, pulmonary involvement occurred 8 days before dermatosis, suggesting that bacterial particles play a role in the occurrence of Sweet syndrome. Finally, it must be pointed out that the cutaneous lesions quickly improved despite the short duration of corticotherapy, and no recurrence was observed after a 6-month follow-up period. We conclude that a systematic analysis of expectoration should be performed in every case of Sweet syndrome that is associated with respiratory manifestations.

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1. Sweet RD. An acute febrile neutrophilic dermatosis. *Br J Dermatol*. 1964;74:349-356.
2. Von den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis). *J Am Acad Dermatol*. 1994;31:535-556.
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6. Sazon A, Soo Hoo GW, Santiago S. Hemoptysis as the sole presentation of *Pasteurella multocida* infection. *South Med J*. 1998;91:484-486.

Data Without a Prayer

The literature on religious activity and health outcomes is fraught with methodological difficulties.[1] Regrettably, the article by Harris et al[2] on the impact of intercessory prayer in the coronary care unit (CCU) continues this tradition. Evidence for the conclusion that prayer has an impact on clinical course in the CCU and "may be an effective adjunct to standard medical care"[2] is weak at best. Although the intercessors were instructed to pray for a speedy recovery, the prayer and control groups did not differ in length of stay in the CCU or in the hospital, nor did they differ on the Byrd scale. They only differed on the unvalidated Mid American Heart Institute–Cardiac Care Unit (MAHI-CCU) scale constructed for the purpose of this study. The lack of construct validity raises serious questions about this finding.

On both the unweighted and weighted scales, the prayer group showed a slightly but significantly better clinical course (ie, lower scores) than the control group. The unweighted scale is completely meaningless, as the authors' own example illustrates: a patient who dies in the CCU (1 event) has a lower unweighted score than one who requires antibiotics, arterial monitoring, and antianginal agents (3 events). The significance of the group difference on the weighted scale assumes that it has construct validity (eg, that the need for an electrophysiologic study [3 points] is 3 times as bad as the need for antibiotics [1 point], as the scale indicates). This is by no means clear. High interrater agreement (96%) on the scores for 11 randomly selected cases is not a substitute for construct validity. Raters also will agree substantially on hair color, but that does not make it a meaningful clinical index.

Finally, there is the significant ethical issue raised by the conclusion that prayer should be added to the list of medical interventions. All intercessors in this study were Christian. Should only Christian prayer be recommended? Should we conduct studies to determine if Christian prayer is more effective than Jewish or Muslim prayer? Religion does not need medical science to validate its rituals. To attempt this trivializes religion.

As we have indicated elsewhere,[1] there is little doubt that for many people, religion brings comfort when illness strikes. This does not, however, mean that medicine should take on religious practices as adjunctive treatments. To do so flies in the face of the vast majority of empirical evidence and raises serious ethical issues.

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1. Sloan RP, Bagiella E, Powell T. Religion, spirituality, and medicine. *Lancet*. 1999;353:664-667.
2. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med*. 1999;159:2273-2278.

Intercessory Prayer

We have found a discrepancy and possible error in the data regarding intercessory prayer presented by Harris et al.[1] Table 3 in the article lists the number of events for each component of the Mid America Heart Institute–Cardiac Care Unit (MAHI-CCU) score. Summing these numbers, being careful not to include the interventional coronary procedures twice (as both the total number and the number for the different procedures are listed in Table 3), gives the total number of events as 1436 for the usual care group and 1173 for the prayer group. Dividing by the number of patients in each group (524 control group patients and 466 prayer group patients) results in an unweighted MAHI-CCU score of 2.74 for the usual care group and 2.52 for the prayer group, instead of the scores of 3.00 and 2.70 reported in Table 4 in the article.

If our calculations are correct, the absolute difference between the control and prayer group is 0.22 instead of 0.30, and the relative difference is 8% rather than 10%. Assuming that the SEM remains about 0.1, the corrected numbers would not result in a statistically significant difference between the control and prayer groups.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med*. 1999;159:2273-2278.

Waiving Informed Consent for Research on Spiritual Matters?

When I first picked up the article by Harris et al,[1] I read with open-minded interest: Would such prayer have any effect on the course of illness of the subjects studied? If so, or even if not, how could it hurt? Even for the agnostic, when critically ill, wouldn't most be of the opinion that anything that might help is worth trying, particularly if there is no harm done in the trying?

As I read the study, however, it was not the findings that intrigued me, but the method of study—specifically, the rationale, approved by the institutional review board, to bypass the informed consent of prospective subjects. The authors made a point of elaborating on this choice, anticipating that there would be some reader concern. They offered or implied a number of reasons to support circumventing the informed consent process and justify proceeding with the study: (1) that there is "no known risk" associated with the procedure, (2) that the informed consent discussion with prospective subjects would be likely to bias the study toward inclusion of a propensity of "prayer-receptive" subjects, and (3) that the informed consent inquiry itself could cause distress for the patient, in that the patient would be forced

to think about issues of faith at a time when it may not have been that patient's desire to do so.

I believe that these very reasons, rather than supporting the skirting of informed consent, actually demand either requesting informed consent or scrapping the study.

No Known Risk of the Procedure. With this rationale, the investigators are playing both sides of the game. It appears that their prestudy hypothesis was that intercessory prayer, as performed in the study, would beneficially affect the course of illness, as measured by the given physiologic parameters. If proven to be true, the conclusion would be that intercessory prayer has a positive therapeutic effect, medically speaking. Any intervention that might have a positive therapeutic effect might also have a negative effect. That there are no known risks to prayer is a given, a leap of faith. But could there be risks? Are the prayers reaching a Higher Power that might, upon having Its attention called to a nonbeliever, actually respond to the request unfavorably? Of course, we will never know. But in imposing a scientific template (ie, performing a scientific study to assess therapeutic effect) on a faith-based intervention, it is incumbent upon the investigators to follow the science-based rules by naming the uncertainty and allowing the subject to choose.

Selection Bias. While it is probably true that requesting consent of potential subjects would result in a bias toward inclusion of "prayer-receptive" patients, this is not an adequate reason to bypass informed consent. It would serve as a variable to discuss in the article or, at the discretion of the investigators, a reason not to attempt the study according to the scientific template attempted.

Patient Distress. As discussed above, this is not an adequate reason to avoid requesting consent, especially given the argument against "no known risks." In fact, the investigators themselves cite a prior study in which almost 13% of patients did decline to be involved because of religious or personal reasons. Again, perhaps this would serve as a reason not to perform such a controlled study.

I am uncomfortable with the concept that the team chose to look at prayer as a "therapeutic intervention" and investigate it as such and yet used the uncertainty embedded in such an intervention as the rationale for bypassing the usual procedures for the protection of research subjects. I imagine that there are potential subjects who would fear faith-based uncertainty as much as or more than earthly uncertainties. I wonder whether at least some members of the study group were of non-Christian faiths or were agnostics or atheists. It would be surprising to discover, if interviewed in retrospect, that *none* of the 1013 subjects objected to being included in this study without their consent.

Intercessory prayer has always been practiced, with or without the consent of the subject, by believers for believers and nonbelievers alike. Obviously, there is no way to regulate this, and it is beyond the realm of the medical code of protection of subjects. My objection is to the practice of studying this intervention in a scientific framework (ie, a randomized, double-blinded, controlled trial published in a major peer-reviewed medical journal), and yet bypassing the relevant requirements of that framework.

Finally, I am concerned with the potential effect of such a study and its publication on the reputation of the hospitals involved and on the integrity of health care organizations in general. Not every patient who enters a particular health care institution is a believer. Nonbelievers, or those of non-Christian faiths, may experience distress resulting from the recognition that they may be included in studies such as this, without their knowledge or consent, while they are most vulnerable and need to trust their health care team to act in their best interest and according to their autonomous wishes.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med.* 1999;159:2273-2278.

A Randomized, Controlled Trial of Prayer?

Extraordinary claims require extraordinary evidence. However, is the evidence sufficient for the claim by Harris et al[1] that prayer may be an effective adjunct to standard medical care? Patients in the coronary care unit (CCU) who were randomized to receive remote, intercessory prayer (plus usual care) stayed as long in the CCU and in the hospital as patients who received usual care only. Furthermore, there were no differences between groups on 34 clinical outcome characteristics, but the prayer group had 11% lower scores on a new, unvalidated summary statistic describing clinical CCU course. The only alternative explanation that the authors discuss is chance, which they consider unlikely given one statistically significant ($P=.04$) difference between groups. The authors do not realize, however, that by making 34 comparisons using separate t tests with α set at .005 and another 3 with α set at .05, the chance of finding 1 significant difference is not 1 out of 25, but

$$1-(1-0.05)^3+1-(1-0.005)^{34}=0.14+0.16=0.30,$$

almost 1 out of 3.[2] Furthermore, with groups of more than 400, the smallest differences become statistically significant.

Finally, the authors fail to consider further alternative explanations for their findings. Consider the following: As a clairvoyant and telepath, I was aware (unlike the patients in the CCU and the staff involved) that this study was going on. Wanting to take advantage of the careful registration of CCU courses, I have subsequently used my telepathic powers to influence the CCU course of the experimental group. Admittedly, the effect was a little weaker than I anticipated, but that should be attributed to the fact that this was my first transatlantic telepathy work. My influence has worked quite satisfactorily in a recent European trial that some people think was investigating a new analgesic. I wonder whether

Harris et al have convincing arguments favoring their interpretation of their data over mine. They might point to the fact that more people believe in prayer than in my clairvoyant and telepathic powers. There were times, however, that everyone believed that the earth was flat, and everyone was wrong. Which will it be in this study—prayer, telepathy, or a summary statistic of uncertain validity? I am willing to reveal that I will settle for chance.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med.* 1999;159:2273-2278.
2. Hays WL. *Statistics*. 2nd ed. London, England: Holt Rinehart & Winston Inc; 1973.

P Value Out of Control

As suggested by Harris et al,[1] effective remote, intercessory prayer could be explained by one of two mechanisms. It might represent a miracle: the intervention of God in the physical world by a supernatural force in ways that are incompatible with natural law. It might also represent a form of telekinesis: the movement (healing) of an object (human body) at a distance (remotely) with thought or will (prayer) by an unknown natural force. Miracle or telekinesis has never been shown to exist by credible, replicable scientific experimentation.

Harris et al state that their purpose is not to speculate on mechanisms, but rather to convey results. This approach seems to miss the heart of the issue. It is the very improbability of the mechanism that raises doubts concerning the validity of the results. Goodman[2] has cautioned against overreliance on *P* values in assessing the efficacy of studies. He emphasizes that *P* values must be evaluated within the context of the prestudy probability of efficacy. For years, skeptics have warned that extraordinary claims require extraordinary proof. This is another way of stating Goodman's theme that results that are inconsistent with a well-validated scientific precedent (low prestudy probability of efficacy) require a higher burden of proof (lower *P* value). Within this context, the study of Harris et al actually suggests that remote, intercessory prayer has no effect on outcome.

Harris et al draw an analogy between their study and James Lind's scurvy trials. If Lind's studies had been subjected to statistical analysis, I suggest that the *P* value would have been far more impressive. Such a *P* value would have probably justified a reevaluation of the then current theories regarding the mechanism of scurvy. However, Harris et al are not merely testing the efficacy of a medication. On the basis of a *P* value of .04, Harris and his colleagues are suggesting the need to reassess 500 years of scientific advancement in our understanding of how the physical world is organized.

As science has advanced, we have actually become more confident that the earth is round, that lemons cure scurvy, that no miraculous forces suspend natural law, and that unknown forces do not move objects from a distance. Rather than doubting the fundamental nature of the scientific worldview, shouldn't we be questioning the meaning of a *P* value of .04? Is it not more likely that the results of the study conducted by Harris et al have occurred by chance (1 in 25) or by bias rather than postulating a mechanism that requires a seminal paradigm shift in physics? Do not their results suggest the need to reassess our statistical methods for judging efficacy rather than the need to reassess the fundamental theories of science?

The study by Harris et al is a wonderful example of a *P* value out of context and out of control. It is out of context because of the failure to properly adjust for mechanistic improbabilities. It is out of control because of its propensity to encourage much pseudoscientific mischief.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med.* 1999;159:2273-2278.
2. Goodman SN. Toward evidence-based medical statistics, 2: the Bayes factor. *Ann Intern Med.* 1999;130:1005-1013.

No Effect of Intercessory Prayer Has Been Proven

In the recent article by Harris et al,[1] the effects of remote, intercessory prayer on the medical course of patients in the coronary care unit (CCU) had borderline statistical significance at best. Of 40 measures (35 Mid America Heart Institute–Cardiac Care Unit [MAHI-CCU] score components, the weighted and unweighted overall MAHI-CCU scores, length of CCU stay, length of hospital stay, and Byrd score), 2 were significant ($P<.05$). One in 20 is classically what one would expect to be significant by chance; the 2 significant measures reported by Harris et al were the overall MAHI-CCU scores—essentially the same thing.

Statistical significance is not the only way to look at the value of a treatment, however. One can calculate the effect or the number of people one would need to pray for to produce an improvement. It is appropriate, of course, to keep in mind the confidence interval (CI) of these estimates. The unweighted MAHI-CCU score counted the patients' treatments and new diagnoses. With an estimated difference of 0.30 fewer such events for patients in the prayer group (2.7 vs 3.0), the number needed to treat is 3.33. One would have to pray for 3.33 CCU patients to prevent 1 such event (95% CI, 1.7-41.3) or for 10 patients to produce an event-free course (95% CI, 5.2-123.8). Concerns about capitalizing on chance might lead us to acknowledge a wider CI. If we adjust our α value by the Bonferroni procedure (divide the α level selected by the number of measures tested [.05/40=0.00125]), then the 99.875% CI for the differences is –0.16 to 0.76, which corresponds to a CI for the number needed to treat of 1.3 to –6.4.[2] That is, it is possible that an adverse CCU event may be prevented for every 1.3 people prayed for; on the other hand, it is also pos-

sible that we would be better off if we prevented praying, since preventing as few as 6.4 people from praying would prevent 1 event.

With the present results, I will neither organize intercessory prayer groups nor organize to prevent intercessory prayer—which is precisely where I was before reading the study.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med*. 1999;159:2273-2278.
2. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998; 317:1309-1312.

Does Prayer Really Set One Apart?

In the article by Harris et al,[1] I was struck by the data for Swan-Ganz (S-G) catheterization. In their Table 3, this item appears with a significance level of $P=.03$. This is not significant because of the number of comparisons made, as properly pointed out by the authors. However, considering the Mid America Heart Institute–Cardiac Care Unit (MAHI-CCU) score weight of 3 for S-G catheterization and the sheer differential number (n=49, 9.4% of the usual care group), it struck me that this may be a possible source of the reported group difference.

I contacted the primary author, Dr Harris, about this issue, and he replied, paraphrasing, that there were many comparisons that could be made and that, regardless, the unweighted CCU scores confirmed his result (W. S. Harris, PhD, written communication, November 1999). This simply restates the published position of Harris et al and does not address the possibility of a statistical anomaly due to short-term, nonrandom S-G catheter use, making the result unrepresentative of the inferred population(s) and not truly supportive of the seemingly demonstrated efficacy of prayer.

Essentially, looking at this from a step back, I see something similar to an omnibus analysis of variance that is significant, but none of the components are! It is my bet that if Harris et al remove that 1 item, it will all fall apart and end up the other side of .05.

With this in mind, I decided to play with the presented data a bit. The revised MAHI-CCU scores and unweighted MAHI-CCU scores without the S-G item vs the actual published means of the total scale appear in the **Table**.

Looking very roughly at these differences by applying the SEM to these means and assuming that the variance stays the same (with a score of 3; however, I am doubtful), we see that the tails still do not mesh, indicating a possibly significant result—but note the new differences in the Table.

In essence, without the S-G item, the tails of the possible MAHI-CCU score means are only .06 score points away from each other (still no overlap), but as originally presented with the item they are .25 score points away from each other. Similarly, we move from one tenth of an intervention in the unweighted measure as the tail separation down to three hundredths of an intervention by dropping this 1 item.

Effects of Intercessory Prayer on Mid America Heart Institute–Cardiac Care Unit (MAHI-CCU) Scores Without the Swan-Ganz (S-G) Catheter Score Component*

	Without S-G Catheter		Total MAHI-CCU Scale	
	Usual Care Group	Prayer Group	Usual Care Group	Prayer Group
Unadjusted				
MAHI-CCU score	6.15	5.56	7.13	6.35
Unweighted MAHI-CCU score*	2.67	2.44	3.00	2.70
With SEM Adjustment				
MAHI-CCU score	5.88	5.82	6.86	6.61
Unweighted MAHI-CCU score*	2.57	2.54	2.90	2.80

**A simple count of events (diagnoses, drugs prescribed, and procedures) from the MAHI-CCU score in Table 1 of Harris et al,[1] presented as events per patient.*

I would interpret this as a need to reanalyze these data without the S-G score, thus applying the actual new variance rather than my rough assumptions here. This singular item may or may not account for the reported finding, but if indeed dropping the S-G item does eliminate the prayer effect, I am left to wonder whether the result is not simply another chance hit on a significant result and whether it is inappropriate to infer that prayer, when the recipient is unaware of it, creates a separate population of patients.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med*. 1999;159:2273-2273.

Does Prayer Need Testing?

The recent study of the effects of remote, intercessory prayer on patient outcome by Harris et al[1] appears to have both philosophical and study design issues that need further clarification.

To an average reader like myself, the statements that "we have not proven that God answers prayer or that God even exists. It was the intercessory prayer and not the existence of God that was tested here," seem a contradiction. If the intent of the study was to determine whether God answers prayer, then God's will and His existence were also being tested de facto, since the prayer was directed to God for the healing of 466 patients in the prayer group.

People of all faiths have been praying since the dawn of civilization on this planet. For those who truly believe in God's existence, the question why people get sick and how they are healed has a very different meaning. Their entire attitude towards prayer and their expectations from prayer are quite different as well. In the guise of prayer,

they do not demand that God perform healing, and they do not give God a timetable to do the task. In other words, they do not put God to a test ("Don't put Lord your God to test," Matthew 5:7). Instead, they accept His will and His timetable and understand that the answer to their petition might be negative as part of God's greater providence. It should be pointed out that the analogy of James Lind's observation on the healing potential of lemons and limes (citrus fruits) in scurvy might not be applicable when it comes to spirituality. To illustrate the point, a person completely deprived of vitamin C will develop scurvy, but one can manage to stay physically healthy without praying or even believing in God's existence.

The second issue that requires further clarification is study design. If medical record numbers were assigned to the prayer and usual care (no prayer) group participants on a sequential basis, how did the study end up with only 466 subjects in the prayer group and 524 subjects in the usual care group? Also, since in the "Comment" section it was stated that pure randomized intercessory prayer was not possible (and I certainly agree with that), the validity of this study's outcome remains in question. Additionally, since the intercessors were not given the diagnosis and update information, the intensity of prayer and commitment of the intercessors (in other words, the effectiveness of prayer) remains in question as well (see Luke 11:8 on persistence of prayer). Despite these perceived concerns, it was encouraging to note a *P* value of .04 on the unweighted Mid America Heart Institute–Cardiac Care Unit (MAHI-CCU) score and an MAHI-CCU score in favor of the prayer group corroborating the findings of 2 other randomized controlled trials[2,3] that also studied the potential benefit of intercessory prayer.

Since pure randomization for intercessory prayer is not possible (as the authors pointed out), I fail to understand their reason for suggesting a need for further randomized studies on intercessory prayer. Will those who believe in God's existence want to see God's will put to test? What message, if any, will such a study have for those who firmly believe in only the theory of evolution?

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med.* 1999;159:2273-2278.
2. Byrd RC. Positive therapeutic effects of intercessory prayer in a coronary care unit population. *South Med J.* 1988;81:826-829.
3. Sicher F, Targ E, Moore D II, Smith HS. A randomized double-blind study of the effect of distant healing in a population with advanced AIDS: report of a small-scale study. *West J Med.* 1998;169:356-363.

Ethical and Practical Problems in Studying Prayer

I have both scientific and ethical concerns about the study by Harris et al[1] on intercessory prayer.

First, the study was not randomized. Patients were systematically assigned to study groups by a method that the authors expected to be random in net effect; that is not the same thing. The approach used by Harris et al more often results in accidental unblinding and systematic bias from unexpected systematic behavior than does true randomization. Although this is relatively unlikely to have caused problems in this specific study, the term *randomized* should be reserved for studies that are actually randomized.

More importantly, the statistical analysis is problematic. The authors used the *t* test to compare results on a clinical outcomes scale. Such scale values are not ordinary number-line numbers in their representation of clinical severity; one cannot in any clinical sense say that a unit increment in one portion of the scale in one patient means exactly the same thing as a unit increment in a different part of the scale or in a different patient. Without that uniformity, ordinary arithmetic does not work, and a test like the *t* test does not work. The net effect is that the authors have directly compared the numbers, but not the clinical events. This subtlety can conveniently be ignored if the differences between groups are large and the statistical significance is great; in this study, that is hardly the case. A 10% difference in a *P* value of .04 in this context is not a robust challenge to the null hypothesis.

The authors requested and were granted a waiver of the requirement for prospective informed consent; they discuss only 2 of the several criteria that are ordinarily applied to determine if such a waiver is appropriate, and it is not clear that even those 2 criteria were satisfied. (Indeed, the criteria they cited are those for waiving the need for a written consent form but not those for a waiver of consent itself.) For example, it appears that someone uninvolved in the patients' care had to have access to the medical records or to summary data with identifiers in order to record the study's outcomes; this is normally a consent-requiring activity. I find it hard to imagine that all 990 patients executed blanket waivers for the use of their records for research and that all 990 did so at a time in which they were suitably free of outcome anxiety and sedative analgesia so that such a waiver could be meaningful. Moreover, federal regulations provide that, when prospective consent is waived, the information should be provided to the subjects post hoc if practicable and appropriate (45 CFR §46.116[a][4]). I see no indication that this ethical and regulatory expectation was addressed.

More subtly, but perhaps most importantly of all, it may have been inappropriate to waive consent because a substantial number of patients would be expected to find the study offensive to their religious sensibilities. The authors divorced the concept of prayer from the concept of deity in framing their hypothesis; not all patients will do so as facilely.

There are many proscriptions (in the Old Testament, New Testament, and Koran) against "putting God to the test"; it is predictable that at least some patients will view the study as doing exactly that. Out of respect for autonomy, one should think long and hard before enrolling an uninformed, nonconsenting patient as a subject in a study that he or she might find blasphemous.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med.* 1999;159:2273-2278.

Therapeutic Efficacy of Prayer

I read with interest the study by Harris et al,[1] which suggests that prayer may be an effective adjunct to standard medical care. The authors failed to cite 2 other studies that arrived at a similar conclusion.[2,3] Both studies, however, were criticized on methodological and statistical grounds.[4]

More than a century ago, Galton[5] pleaded for a scientific inquiry into the efficacy of prayer. But does the efficacy of prayer have to be scientifically proved? Prayer can ameliorate or prevent despair and despondency. Prayer sets a psychological frame of mind to allow the body's psyche to be at rest with itself. Since ancient times, it has been known that the state of mind of a sick person influences the response to treatment.

The general use of prayer as a modality of treatment for the sick is not in itself a prima facie argument in favor of the efficacy of prayer. The fact remains, however, that the majority of mankind prays for the sick at one time or another. The prayers may differ in content, in the manner in which they are offered, or to whom they are addressed, but both religious and nonreligious people alike offer prayers for recovery when they are sick.

One should never be discouraged from praying even under the most difficult and troublesome conditions. The Talmud states that "even if a sharp sword rests upon a man's neck, he should not desist from prayer"(Tractate Berachot, folio 10a).

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Is It Prayer, or Is It Parity?

Harris and coauthors[1] arranged for prayers to be said for patients in the cardiac care unit who had even medical record numbers; they found borderline significant advantages for this group in one measure of patient scores. Unfortunately, they failed to realize that investigators of seemingly paranormal effects must consider a much wider range of possibilities than those that occur in ordinary scientific work.

It is true, as they say, that intercessory prayer has been common for millennia. But it is equally true that mystic powers have been attached to numbers from time immemorial,[2] and the specific distinction of even and odd has been considered significant in cultures ranging from China to ancient Greece.[3] Thus, the assignment of even numbers is just as likely an explanation of the data as the prayers.

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Questions on the Design and Findings of a Randomized, Controlled Trial of the Effects of Remote, Intercessory Prayer on Outcomes in Patients Admitted to the Coronary Care Unit

Harris et al[1] did not evaluate or comment on what appears to be the strongest statistical association in their study: 3.7% (18/484) of those in the prayer group were discharged within 24 hours compared with only 0.9% (5/529) of those in the usual care group ($P<.005$ by χ^2 test if observations are independent). Since these discharges occurred before the intervention began (mean ± SE, 1.6 ± 0.16 days after admission), we are concerned that the statistical methods used by Harris et al,[1] which assume independence of the observations, may not be appropriate for their data. While their article states that "new patients were randomly assigned," it is not clear whether the same person who was readmitted for a new episode would have constituted a new patient; Figure 1 of their article does not indicate that readmissions of the same patient were excluded.[1] Since patient assignment was based on an (odd or even) identification number that never changed, readmitted patients would remain in the same treatment group. For example, a patient with an even identification number who was admitted several times during the study period and tended to stay in the coronary care unit less than 24 hours (or to have a low Mid America Heart Institute–Cardiac Care Unit [MAHI-CCU] score) would always be in the prayer group. Statistical methods that require independent observations would not treat the data from this individual correctly.[2] Thus, we believe that the authors should comment on the following: Were multiple admissions from the same individuals included in their analysis? What were the potential reasons for the significantly higher (preintervention) 24-hour discharge rate of patients in the prayer group?

Even if the data of Harris et al[1] are taken at face value, we think their conclusions that the study "suggests that prayer may be an effective adjunct to standard medical care" is exaggerated, given the statistical weakness of the data and lack of a scientific basis for the hypothesis. Out of 40 "post-prayer" outcomes examined in Tables 3, 4, and 5 of their article, only 3 were significant at $P<.05$, and none was significant at $P<.02$. While these outcomes were positively correlated with each other, from

a statistical standpoint this finding is not unexpected once multiple comparisons are considered.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled clinical trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med*. 1999;159:2273-2278.
2. Dixon WJ, Massey FJ. *Introduction to Statistical Analysis*. New York, NY: McGraw-Hill Co; 1969.

The Effect of Remote Intercessory Prayer on Clinical Outcomes

In October 1999, Harris et al[1] published the results of a randomized, controlled, double-blind study, which indicated that patients who were admitted to the coronary care unit of a major hospital and prayed for by external intercessors on a daily basis for 28 days experienced significantly fewer clinical events during their hospital stay (either weighted for severity [$P=.04$] or unweighted [$P=.04$]) than patients who were admitted to the same unit and not prayed for. There was no significant difference between the 2 groups with respect to length of hospital stay or length of stay in the coronary care unit.

We believe there is a serious flaw in this study in that patients were not randomly allocated to each group, but were allocated on a systematic basis according to whether the patient's medical record number was odd or even. This method of allocation was specified in the protocol (obtained through the courtesy of Dr Harris), so it was presumably known by all investigators. The choice as to which group was to receive the intercessory prayers was made by the study coordinator tossing a coin at the start of the study; this knowledge was to be kept secret from all other participants until the close of the study.

This feature of the study makes it highly vulnerable to the introduction of bias. If the investigator who extracted the data on clinical events from the patients' charts had any idea or guessed as to which was the prayer group, it could lead, consciously or unconsciously, to bias, since the medical record number would be visible throughout each patient's chart. If the investigator had guessed wrongly and the bias had been against the actual prayer group, the results might never have been written up and published. After all, it may be difficult to publish an article showing that remote intercessory prayer had no effect on clinical outcomes.

The fact that the outcome that was open to subjective interpretation, namely the clinical events, showed a significant difference between groups, but that the outcome that was not subject to interpretation, namely length of stay, did not lends weight to the suspicion that the study was not truly blind.

If the authors had randomized the patients according to an acceptable randomization method, eg, random number tables, randomized blocks, or adaptive biased coin, and kept the random allocation of each patient secret, the "blindness" of the clinical investigator assessing the medical charts would not have been in question. However, the use of a systematic method of patient allocation throws doubt on this aspect of the study. As the hypothesis tested by this study is an extraordinary one, a high standard of evidence is required for it to be believed. This study did not achieve this standard.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med*. 1999;159:2273-2278.

Prayer Can Help

The article by Harris et al[1] on the effect of prayer on the outcome in patients admitted to a coronary care unit (CCU) in the October 25 issue of the ARCHIVES, which showed lower (improved) "CCU course scores" of patients who were being prayed for by others, gives us another, much-needed tool for the care of our patients. Other recent articles also indicate that prayer and religious faith can contribute to the recovery and well-being of our patients.[2-8]

Lately, I have run across several patients in my practice who found answers to some of their problems in a book entitled *The Awakening: One Man's Battle With Darkness*[9]; it is about a congregation in south Germany that experienced remarkable relief of many of its members' needs 150 years ago after recognizing and dealing with the causes of many of their *problems of living*, to use the terminology and concept of Thomas Szasz.[10]

Such problems of living as depression, the one labeled *attention deficit hyperactivity disorder*, and many other garden-variety functional disturbances may often respond better to an approach that attends to the root causes of the disorder with an inner-oriented reflection, prayer, or whatever you want to call it, which is then shared with another person, rather than undergoing drug "treatment" that can only suppress symptomatology. The efficacy of prayer, while not so easy to manipulate or prove, has been relied on and used by many people, professional and nonprofessional, for many years. It has its place in 21st century health care.

Thanks for publishing practical articles that address the whole gamut of patients' needs, which require a wider scope of effective management approaches.

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God, Prayer, and Coronary Care Unit Outcomes: Faith vs Works?

I wish to share a few comments on the study of Harris et al[1] that appeared in the October 25, 1999, issue of the ARCHIVES. The purpose of this study was to see if there was any scientifically measurable effect of remote, intercessory prayer on the outcome of seriously ill patients in the coronary care unit.

The analysis of Harris et al seems to indicate that the main effect of intercessory prayer was on physicians and their medical decisions and not on patient outcome itself. That the same outcome was achieved with fewer controversial medical interventions in the prayer group is a bit sobering. In reading this study, I asked myself: Why should God allow the patients who received the remote, intercessory prayer to do better than the control group? Does God love those for whom strangers pray more than those who were randomly assigned not to receive their prayers? I was taught that God is not capricious and that faith is not a matter of scientific proof.

Perhaps the irony of this study is that the outcome was the same despite fewer interventions in the prayer group. Perhaps the real conclusion is that God's grace is greater than our skills and immeasurable by our tools. Like many before them, the investigators may have missed the real message of their "study": that despite our arrogance, God's omnipotence is beyond our ability to add or detract.

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1. Harris WS, Gowda M, Kolb JW, et al. A randomized, controlled trial of the effects of remote, intercessory prayer on outcomes in patients admitted to the coronary care unit. *Arch Intern Med*. 1999;159:2273-2278.

In reply

We welcome the opportunity to respond to readers of the ARCHIVES regarding our study of intercessory prayer. Research on intercessory prayer is in its infancy, and there is much we do not understand. Our trial was an attempt to replicate and improve upon the earlier trial of Byrd.[1] We asked whether the ancient tradition of praying for the sick could help them get better. We concluded that further studies were warranted "to explore the potential role of prayer as a possible adjunct to standard medical care."[2] Several readers questioned whether the evidence we presented was strong enough to justify that conclusion. Given that it was supported by the positive outcomes of 2 blinded, prospective, controlled trials that were conducted more than a decade apart in 2 different research centers, we feel that it was justified.

Whether our study was conducted in an ethical manner was also questioned. As we described in our article, serious consideration was given to the potential risks that prayer might pose to patients. We were unable to find any evidence that prayer with beneficial intent has ever been harmful to humans. We thus requested that our institutional review board waive the requirement for written informed consent. The issue was also addressed by our hospital ethics committee, which agreed that there was no need to obtain informed consent, and by the reviewers of the manuscript, who raised no ethical concerns. We do not feel that we violated patient autonomy by praying for them; indeed, patients are often prayed for without their express permission by many people who are unknown to them through prayer chains and announcements in churches and synagogues.

As we acknowledged in our article, the Mid American Heart Institute–Cardiac Care Unit (MAHI-CCU) scale has not been validated. It was developed by a team of cardiologists as an intuitively reasonable tool to describe the nature of the hospital course. It was applied equally and blindly to both groups to attempt to detect differences in overall hospital experience. We are currently developing and validating new methods for use in future studies.

In an attempt to decipher which components of the MAHI-CCU score were most responsible for the observed difference between groups, the Swan-Ganz catheter procedure stood out as contributing more than other events. It was not, however, a major determinant of the treatment effect, since removing it only changes the difference between the groups from 11% to 9%.

Hoover and Margolick questioned our definition of a new patient. If a patient who was first admitted to the coronary care unit (CCU) (and was thus entered into the trial) was then discharged to the floor and then readmitted to the CCU prior to hospital discharge, that patient's readmission to the CCU counted as an "event" that occurred in association with the original admission. No patient was counted twice. They also asked why there were more short stays (<24 hours) in the prayer group (3.7%) than in the usual care group (1%). Although we have no ready explanation for this, it seems unlikely that the randomization procedure we used could have been responsible.

A few statistical concerns were raised. First, it was suggested that the multiple comparisons we examined made it more likely that some statistically significant difference between groups would be found. Multiple comparison adjustment of the MAHI-CCU scores was not warranted, since these were defined in advance as the primary outcome measures. Thus, the type I error rate for assessing significance in this study was preserved. Very conservative (Bonferroni) significance levels (P<.001) were used for each of the 34 individual events that make up the score. Other summary outcomes (CCU and length of hospital stay) were considered secondary end points. Secondly, Karis and Karis noted that the unweighted MAHI-CCU score was too high based on the data presented in Table 3 of our article. When we reexamined our calculations, we noted that we failed to make it clear that patients who received percutaneous transluminal coronary angioplasty and a stent or rotablator were given 2 points; any patient receiving all 3 interventions was given 3 points. In addition, the need for a cardiovascular stress test was in-

cluded as an event in the score calculation but was omitted from Tables 1 and 3 in our article.

See Correction below

Smith and Fisher are correct in noting that an even-odd medical record number randomization scheme is less than optimal; in future trials, we would use, as they suggest, a system that is more impervious to detection. Nevertheless, there is little room for subjectivity in a chart review method that simply records the presence or absence of a set of predetermined events. Thus, we do not believe that our findings were biased by this approach. These writers also raise the issue of "file-drawer bias," ie, the reluctance of some investigators to publish no-effect studies. We clearly have no control over what others may have done, and while this charge can be leveled at any field of inquiry, the fact that in this very young field several studies with negative findings have been published[3-5] *argues against such bias. We hope that most investigators, in addressing an important question and having designed their study to the best of their abilities, would make (as we did) an a priori commitment to publish their results regardless of outcome for the good of the overall scientific enterprise.*

Several letters raised questions regarding the theological implications of our study. As we noted in our article, we cannot draw any conclusions regarding the existence or nature of God from this trial.

A critically important attribute of any scientist is open-mindedness, the willingness to objectively consider new or alternative concepts and hypotheses. There is a growing demand among patients that we acknowledge their need to be treated as whole persons who have not only physical but emotional and spiritual needs as well. Practicing as we do in a large metropolitan hospital among a wide variety of religious traditions, we are acutely sensitive to the need for a nonsectarian approach to addressing spiritual issues. This diversity is mirrored in the spectrum of religious practices among our authors, which ranged from a variety of Protestant and Roman Catholic traditions to Hinduism. Since spiritual factors may play some role in healing, additional studies are needed to clarify the place of intercessory prayer in maintaining and restoring health.

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Correction

Errors in Results. In the Original Investigation titled "A Randomized, Controlled Trial of the Effects of Remote, Intercessory Prayer on Outcomes in Patients Admitted to the Coronary Care Unit," published in the October 25, 1999, issue of the ARCHIVES (1999;159:2273-2278), the authors, Harris et al, were prompted by questions raised in postpublication correspondence to reevaluate their calculations and feel that 2 points need to be clarified. In Table 3 of their article, a percutaneous transluminal coronary angioplasty procedure (PTCA) with a stent and/or a rotablator appeared to count as one event. However, when they calculated the unweighted score, they gave one point for PTCA and an additional point for stent and one for rotablator when these occurred in the same patient. Thus, a patient receiving all 3 procedures was given 3 points, not 1, as was implied in Table 3. Second, the need for a cardiovascular stress test (such as a thallium test or an echocardiogram) was included in the calculation of the Mid American Heart Institute–Cardiac Care Unit (MAHI-CCU) scores but was omitted from Tables 1 and 3 of their article. There were 44 of these events in the usual care group (8.4%) and 26 (5.6%) in the prayer group ($P=.11$). The following tabulation clarifies how Harris et al arrived at the scores reported in Table 4:

	Usual Care Group	Prayer Group
Sum of points from Table 3 as published	1436	1173
Extra points for PTCA + stent	79	59
Extra points for PTCA + rotablator	5	0
Extra points for PTCA + stent + rotablator	4*	0
Cardiovascular stress test	44	26
Total events	1568	1258
No. of patients	524	466
Unweighted MAHI-CCU score as published	3.0	2.7†

*Two patients × 2 extra points each.
†$P=.04$.

In the calculation of the weighted MAHI-CCU score, the need for cardiovascular stress tests was ranked as a category 4 event; if reclassified as a category 2 event, the mean ± SEM scores become 6.97 ± 0.26 for the usual care group and 6.24 ± 0.26 for the prayer group ($P=.05$); the effect size remains 10% to 11%.

In Table 4, the number of patients in the Usual Care Group was incorrectly reported as "(n = 52)"; it should have been "(n = 524)."