IS ACADEMIC MEDICINE FOR SALE?

In 1984 the Journal became the first of the major medical journals to require authors of original research articles to disclose any financial ties with companies that make products discussed in papers submitted to us. We were aware that such ties were becoming fairly common, and we thought it reasonable to disclose them to readers. Although we came to this issue early, no one could have foreseen at the time just how ubiquitous and manifold such financial associations would become. The article by Keller et al. in this issue of the Journal provides a striking example. The authors’ ties with companies that make antidepressant drugs were so extensive that it would have used too much space to disclose them fully in the Journal. We decided merely to summarize them and to provide the details on our Web site.

Finding an editorialist to write about the article presented another problem. Our conflict-of-interest policy for editorialists, established in 1990, is stricter than that for authors of original research papers. Since editorialists do not provide data, but instead selectively review the literature and offer their judgments, we require that they have no important financial ties to companies that make products related to the issues they discuss. We do not believe disclosure is enough to deal with the problem of possible bias. This policy is analogous to the requirement that judges recuse themselves from hearing cases if they have financial ties to a litigant. Just as a judge’s disclosure would not be sufficiently reassuring to the other side in a court case, so we believe that a policy of caveat emptor is not enough for readers who depend on the opinion of editorialists.

But as we spoke with research psychiatrists about writing an editorial on the treatment of depression, we found very few who did not have financial ties to drug companies that make antidepressants. (Fortunately, Dr. Jan Scott, who is eminently qualified to write the editorial, met our standards with respect to conflicts of interest.) The problem is by no means unique to psychiatry. We routinely encounter similar difficulties in finding editorialists in other specialties, particularly those that involve the heavy use of expensive drugs and devices.

In this editorial, I wish to discuss the extent to which academic medicine has become intertwined with the pharmaceutical and biotechnology industries, and the benefits and risks of this state of affairs. Bodenheimer, in his Health Policy Report elsewhere in this issue of the Journal, provides a detailed view of an overlapping issue — the relations between clinical investigators and the pharmaceutical industry.

The ties between clinical researchers and industry include not only grant support, but also a host of other financial arrangements. Researchers serve as consultants to companies whose products they are studying, join advisory boards and speakers’ bureaus, enter into patent and royalty arrangements, agree to be the listed authors of articles ghostwritten by interested companies, promote drugs and devices at companiesponsored symposiums, and allow themselves to be plied with expensive gifts and trips to luxurious settings. Many also have equity interest in the companies.

Although most medical schools have guidelines to regulate financial ties between their faculty members and industry, the rules are generally quite relaxed and are likely to become even more so. For some years, Harvard Medical School prided itself on having unusually strict guidelines. For example, Harvard has prohibited researchers from having more than $20,000 worth of stock in companies whose products they are studying. But now the medical school is in the process of softening its guidelines. Those reviewing the Harvard policy claim that the guidelines need to be modified to prevent the loss of star faculty members to other schools. The executive dean for academic programs was reported to say, “I’m not sure what will come of the proposal. But the impetus is to make sure our faculty has reasonable opportunities.”

Academic medical institutions are themselves growing increasingly beholden to industry. How can they justify rigorous conflict-of-interest policies for individual researchers when their own ties are so extensive? Some academic institutions have entered into partnerships with drug companies to set up research centers and teaching programs in which students and faculty members essentially carry out industry research. Both sides see great benefit in this arrangement. For financially struggling medical centers, it means cash. For the companies that make the drugs and devices, it means access to research talent, as well as affiliation with a prestigious “brand.” The time-honored custom of drug companies’ gaining entry into teaching hospitals by bestowing small gifts on house officers has reached new levels of munificence. Trainees now receive free meals and other substantial favors from drug companies virtually daily, and they are often invited to opulent dinners and other quasi-social events to hear lectures on various medical topics. All of this is done with the acquiescence of the teaching hospitals.

What is the justification for this large-scale breaching of the boundaries between academic medicine and for-profit industry? Two reasons are usually offered, one emphasized more than the other. The first is that ties to industry are necessary to facilitate technology transfer — that is, the movement of new drugs and devices from the laboratory to the marketplace. The term “technology transfer” entered the lexicon in 1980, with the passage of federal legislation, called the Bayh-Dole Act, that encouraged academic in-

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stitutions supported by federal grants to patent and license new products developed by their faculty members and to share royalties with the researchers. The Bayh–Dole Act is now frequently invoked to justify the ubiquitous ties between academia and industry. It is argued that the more contacts there are between academia and industry, the better it is for clinical medicine; the fact that money changes hands is considered merely the way of the world.

A second rationale, less often invoked explicitly, is simply that academic medical centers need the money. Many of the most prestigious institutions in the country are bleeding red ink as a result of the reductions in Medicare reimbursements contained in the 1997 Balanced Budget Act and the hard bargaining of other third-party payers to keep hospital costs down. Deals with drug companies can help make up for the shortfall, so that academic medical centers can continue to carry out their crucial missions of education, research, and the provision of clinical care for the sickest and neediest. Under the circumstances, it is not surprising that institutions feel justified in accepting help from any source.

I believe the claim that extensive ties between academic researchers and industry are necessary for technology transfer is greatly exaggerated, particularly with regard to clinical research. There may be some merit to the claim for basic research, but in most clinical research, including clinical trials, the “technology” is essentially already developed. Researchers are simply testing it. Furthermore, whether financial arrangements facilitate technology transfer depends crucially on what those arrangements are. Certainly grant support is constructive, if administered properly. But it is highly doubtful whether many of the other financial arrangements facilitate technology transfer or confer any other social benefit. For example, there is no conceivable social benefit in researchers’ having equity interest in companies whose products they are studying. Traveling around the world to appear at industry-sponsored symposiums has much more to do with marketing than with technology transfer. Consulting arrangements may be more likely to further the development of useful products, but even this is arguable. Industry may ask clinical researchers to become consultants more to obtain their goodwill than to benefit from their expertise. The goodwill of academic researchers is a very valuable commodity for drug and device manufacturers. Finally, it is by no means necessary for technology transfer that researchers be personally rewarded. One could imagine a different system for accomplishing the same purpose. For example, income from consulting might go to a pool earmarked to support research or any other mission of the medical center.

What is wrong with the current situation? Why shouldn’t clinical researchers have close ties to industry? One obvious concern is that these ties will bias research, both the kind of work that is done and the way it is reported. Researchers might undertake studies on the basis of whether they can get industry funding, not whether the studies are scientifically important. That would mean more research on drugs and devices and less designed to gain insights into the causes and mechanisms of disease. It would also skew research toward finding trivial differences between drugs, because those differences can be exploited for marketing. Of even greater concern is the possibility that financial ties may influence the outcome of research studies.

As summarized by Bodenheimer,5 there is now considerable evidence that researchers with ties to drug companies are indeed more likely to report results that are favorable to the products of those companies than researchers without such ties. That does not conclusively prove that researchers are influenced by their financial ties to industry. Conceivably, drug companies seek out researchers who happen to be getting positive results. But I believe bias is the most likely explanation, and in either case, it is clear that the more enthusiastic researchers are, the more assured they can be of industry funding.

Many researchers profess that they are outraged by the very notion that their financial ties to industry could affect their work. They insist that, as scientists, they can remain objective, no matter what the blandishments. In short, they cannot be bought. What is at issue is not whether researchers can be “bought,” in the sense of a quid pro quo. It is that close and renumerative collaboration with a company naturally creates goodwill on the part of researchers and the hope that the largesse will continue. This attitude can subtly influence scientific judgment in ways that may be difficult to discern. Can we really believe that clinical researchers are more immune to self-interest than other people?

When the boundaries between industry and academic medicine become as blurred as they now are, the business goals of industry influence the mission of the medical schools in multiple ways. In terms of education, medical students and house officers, under the constant tutelage of industry representatives, learn to rely on drugs and devices more than they probably should. As the critics of medicine so often charge, young physicians learn that for every problem, there is a pill (and a drug company representative to explain it). They also become accustomed to receiving gifts and favors from an industry that uses these courtesies to influence their continuing education. The academic medical centers, in allowing themselves to become research outposts for industry, contribute to the overemphasis on drugs and devices. Finally, there is the issue of conflicts of commitment. Faculty members who do extensive work for industry may be distracted from their commitment to the school’s educational mission.
All of this is not to gainsay the importance of the spectacular advances in therapy and diagnosis made possible by new drugs and devices. Nor is it to deny the value of cooperation between academia and industry. But that cooperation should be at arm’s length, with both sides maintaining their own standards and ethical norms. The incentives of the marketplace should not become woven into the fabric of academic medicine. We need to remember that for-profit businesses are pledged to increase the value of their investors’ stock. That is a very different goal from the mission of medical schools.

What needs to be done — or undone? Softening its conflict-of-interest guidelines is exactly the wrong thing for Harvard Medical School to do. Instead, it should seek to encourage other institutions to adopt stronger ones. If there were general agreement among the major medical schools on uniform and rigorous rules, the concern about losing faculty to more lax schools — and the consequent race to the bottom — would end. Certain financial ties should be prohibited altogether, including equity interest and many of the writing and speaking arrangements. Rules regarding conflicts of commitment should also be enforced. It is difficult to believe that full-time faculty members can generate outside income greater than their salaries without shortchanging their institutions and students.

As Rothman urges, teaching hospitals should forbid drug-company representatives from coming into the hospital to promote their wares and offer gifts to students and house officers. House officers should buy their own pizza, and hospitals should pay them enough to do so. To the argument that these gifts are too inconsequential to constitute bribes, the answer is that the drug companies are not engaging in charity. These gifts are intended to buy the goodwill of young physicians with long prescribing lives ahead of them. Similarly, academic medical centers should be wary of partnerships in which they make available their precious resources of talent and prestige to carry out research that serves primarily the interests of the companies. That is ultimately a Faustian bargain.

It is well to remember that the costs of the industry-sponsored trips, meals, gifts, conferences, and symposia and the honorariums, consulting fees, and research grants are simply added to the prices of drugs and devices. The Clinton administration and Congress are now grappling with the serious problem of escalating drug prices in this country. In these difficult times, academic medicine depends more than ever on the public’s trust and goodwill. If the public begins to perceive academic medical institutions and clinical researchers as gaining inappropriately from cozy relations with industry — relations that create conflicts of interest and contribute to rising drug prices — there will be little sympathy for their difficulties. Academic institutions and their clinical faculty members must take care not to be open to the charge that they are for sale.

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REFERENCES

6. Faculty policies on integrity in science. Cambridge, Mass.: Harvard University, February 1996.

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TREATMENT OF CHRONIC DEPRESSION

The majority of persons who have an acute episode of a major depressive disorder will have a response to the first or second treatment tried. In patients with mild or moderately severe episodes, treatment with antidepressant drugs and brief psychotherapies are equally effective; in those with severe episodes, medication is usually recommended. The treatment of chronic depression is more problematic, since in 20 to 30 percent of initial episodes, there is incomplete remission after two years. Patients with chronic depression have marked impairments in psychosocial function, poor responses to single therapies, and very high rates of use of health care resources. Furthermore, even if they have a partial remission, they have a risk of relapse of 50 to 80 percent.

The poor response of patients with chronic depression to treatment with antidepressant drugs alone is not fully understood, but it cannot be explained solely on the basis of inadequate dosing or the failure of patients to take their medication. Psychotherapy has been advocated as an alternative. Unfortunately, a review of nine studies of psychotherapy for chronic depression that were published before 1998 revealed that in only two trials were patients appropriately randomized, and the combined sample size was only 126 subjects.

Given the lack of empirical data, establishing the relative efficacy of pharmacotherapy and psychotherapy for this disorder has been difficult. Nonetheless, two trends in research results are apparent. First, there is a relatively low rate of response to placebo (about...
15 percent) in trials of psychotherapy or medication.\(^7\) Second, the combination of psychotherapy and medication results in greater improvement than either treatment alone (rate of response, approximately 60 percent vs. 40 percent).\(^8\) However, the evidence to date has not been strong enough to justify unequivocally the use of a combination of the two approaches.\(^2\)

In this issue of the *Journal*, Keller et al. report the results of a comparison of short-term treatment with an antidepressant (nefazodone), the cognitive behavioral-analysis system of psychotherapy (about 16 sessions), or the two in combination.\(^8\) The study included 681 adults with a chronic nonpsychotic major depressive disorder. After 12 weeks, the group that received the combined treatment had a significantly greater rate of response than the group treated with nefazodone alone or the group treated with psychotherapy alone. The results of Keller et al. confirm previous findings\(^9\) that there is a greater overall reduction in the severity of symptoms (by about 25 percent) among patients who receive combined treatment than among those who receive single therapies. The combined treatment had a less powerful effect when assessed in terms of the gold-standard outcome of complete remission, but the rate of remission was almost twice as high among patients who received both nefazodone and psychotherapy (42 percent) as among patients who received either nefazodone alone (22 percent) or psychotherapy alone (24 percent).

Should physicians now recommend the combination of an antidepressant drug such as nefazodone and the cognitive behavioral-analysis system of psychotherapy as the treatment of choice for patients with chronic depression? The answer is not straightforward. Concentrating on short-term outcomes creates a snapshot of depression and its treatment that is not easy to reconcile with the realities of clinical practice.\(^10\) Additional information is required about whether the reported gains are maintained beyond three months and whether the combined-treatment protocol can be generalized to day-to-day practice.

The findings of Keller et al. support the view that the rate of change — that is, the trajectory of improvement — is faster in patients who receive combined treatment than in those who receive a single treatment.\(^11\) However, physicians need to know whether the response rates continue to increase among those treated with antidepressant drugs or psychotherapy alone. If so, the differences among the groups could disappear over time. Most important, longer follow-up would establish how many patients with an early response or remission have sustained clinical improvement. Unfortunately, since Keller et al. used a crossover design in the subsequent long-term phase of the study (treatment was changed at 12 weeks), other studies will be needed to answer these questions.

Two recent randomized, controlled trials evaluated rates of relapse after therapy for chronic depression.\(^12,13\) The studies have important methodologic differences, but both used a brief psychotherapy (10 to 20 sessions), called cognitive therapy, which was adapted to meet the needs of their target population. Fava et al.\(^12\) reported the 6-year outcome in 40 patients, whereas Paykel et al.\(^13\) assessed 158 patients during 20 weeks of treatment and for a year afterward. Both studies demonstrated that the benefits of psychotherapy were sustained after treatment ended; the risk of relapse or persistent symptoms was reduced by 45 to 50 percent. Furthermore, patients who received cognitive therapy plus medication had significantly fewer unscheduled visits with their psychiatrists.\(^13\) Such findings are clearly important in a consideration of the overall benefits and costs of treatment.

The feasibility of combined treatment for chronic depression also depends on the clinical population treated and the case of delivery. The study subjects recruited by Keller et al.,\(^8\) Fava et al.,\(^12\) and Paykel et al.\(^13\) exemplify the heterogeneity that is typical of patients with chronic depression. The most clinically significant group of patients excluded from the study by Keller et al. and from other studies was the group with other coexisting conditions, such as substance abuse or severe personality disorders. Their inclusion would probably have reduced but not eliminated the additional benefit of combined therapy, although patients with complex problems may require a longer course of psychotherapy.\(^5,6\)

Delivery of the combined treatment poses the most challenging problem. There is no evidence that nefazodone has any special benefit as compared with other antidepressant drugs, but following clinical-practice guidelines with regard to the prescribing of these drugs does improve the outcome of case management.\(^2,8,13\) Therapists who can provide brief therapies are scarce, and it is important to know what the interventions entail. The cognitive behavioral-analysis system of psychotherapy helps motivate patients with chronic depression to change by targeting their cognitive and emotional functioning and the consequences of their behavior. The aim of therapy is to help patients develop their social problem-solving and relationship skills. A comparison of this model of psychotherapy with other brief psychotherapies such as cognitive therapy, interpersonal therapy, and behavioral therapy reveals considerable procedural overlap in the areas addressed and the techniques used.\(^10\) The emphasis of each approach varies, but they all assume that cognitive, behavioral, emotional, and interpersonal functions are related, and all attempt to change factors associated with the maintenance of depression.

Although the theoretical mechanisms of action of these approaches are not supported in practice,\(^10\) brief psychotherapies of proven effectiveness in the treatment of depression share a number of clinical characteristics.\(^14\) Each conceptualizes an individual patient’s problems and shares the model of this conceptual-
ization with the patient, involves the rational use of techniques in a logical sequence, emphasizes the development of skills that can be transferred to situations outside of the therapy sessions, and attributes changes to the patient’s efforts.

If a brief psychotherapy has these characteristics and has demonstrated efficacy in a randomized, controlled trial, the choice of approach will primarily depend on the availability of a competent therapist. Competency is defined by the therapist’s ability to use appropriate techniques skillfully and by his or her personal qualities (which affect the therapeutic alliance with the patient). Research has demonstrated a significant correlation between a therapist’s competency and the outcome of patients. In the treatment of chronic depression, a therapist’s expertise may account for 30 percent of the variance in outcome and for significant differences in the rate of dropping out of therapy. The therapist’s adherence to the manual for a given form of psychotherapy is also a critical component of effective treatment.

The results of Keller et al. and Paykel et al. suggest that the combination of optimal doses of antidepressant drugs with 12 to 20 sessions of competently delivered brief psychotherapy may significantly improve the immediate and long-term prognosis of patients with chronic depression. On the basis of current knowledge, the combined treatment may be of particular benefit to patients with chronic severe depression or those who have had only a partial remission when treated with antidepressant drugs alone. In such patients, the balance of evidence suggests that combined therapy has an additive effect. Future research needs to clarify which patients at risk for chronic depression will benefit more from combined therapy than from single therapy and to identify the key elements of the psychotherapy. The more intensive combined-treatment approach can then be reserved for those who are most likely to benefit. As the key elements of psychotherapy become better understood, it may be possible to develop a briefer therapeutic approach that will be easier to deliver in general clinical settings.

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REFERENCES

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A WAKE-UP CALL IN THE INTENSIVE CARE UNIT

In few other areas of medicine is the saying “you can’t get something for nothing” more true than in the intensive care unit. Modern advances in critical care have offered patients opportunities for survival that did not exist in earlier eras. The invasive therapeutic interventions and round-the-clock monitoring that constitute these advances, however, have created a potentially harrowing experience for many patients. The price often paid for survival includes sleep deprivation, pain, anxiety, depression, agitation, and delirium. Unfortunately, no data support the presumption that naturally occurring amnesia protects patients from these discomforts. More than 70 percent of patients vividly recollect their experiences in the intensive care unit, a third have memories of moderate-to-severe pain, and many have psychological problems akin to post-traumatic stress disorder that persist long after their medical recovery.

Because the environment in the intensive care unit is so stressful, intensive intravenous sedation has evolved from adjunct therapy to a central component of critical care. Initially administered as continuous infusions to promote comfort in patients receiving mechanical ventilation, various combinations of narcotics, benzodiazepines, major tranquilizers, and anesthetic agents are now given almost routinely for numerous indications. Physicians prescribe these drugs in stupor-producing doses for intubated patients to induce amnesia, prevent patients from removing their endotracheal tubes, decrease oxygen consumption, and promote synchronous breathing.
with mechanical ventilators. It is now common in a busy intensive care unit to find that most, if not all, patients receiving mechanical ventilation are in a drug-induced state of suspended animation.

Unfortunately, the benefits of intensive sedation do not come without a price. Observational studies have identified sedation as an independent risk factor for ventilator-associated pneumonia. Randomized trials have suggested that continuous infusions of sedatives, as compared with intermittent infusions, prolong mechanical ventilation. It appears that efforts to produce a humane experience in the intensive care unit and to facilitate care can interfere with the chance for a rapid and complication-free recovery from respiratory failure. Because there is no risk-free sedative drug, recent efforts to improve outcomes for patients in the intensive care unit have shifted toward investigations of the manner in which sedatives are administered.

The study by Kress and coworkers in this issue of the Journal is the most recent effort to improve the care of patients who require mechanical ventilation and who are receiving continuous infusions of sedative drugs. These investigators found that daily interruption of continuous infusions of sedatives provides patients an opportunity to wake up and undergo clinical assessment, which promotes more rapid withdrawal of ventilatory support than would be possible without such assessment.

Remembering that one can’t get something for nothing in the intensive care unit, we should consider what price might accompany a daily awakening. The authors monitored patients for only a few adverse events, all of which related to the effectiveness or lack of effectiveness of sedatives used for what might be called “chemical restraint.” Although the incidence of patients’ removal of their own endotracheal tubes or central venous catheters did not increase, the authors emphasized the low power of their study for assessing safety. Other important adverse events, however, were not examined. For instance, patients’ perceptions of distress during daily awakenings or recollections of discomfort after their stay in the intensive care unit were not studied. We should wonder whether patients would perceive a daily lurch into drug-free dysphoria followed by a slide back into sedative-induced torpor as worse than the few extra days of mechanical ventilation that may be necessary when sedation is not interrupted.

The cardiovascular effects of daily awakenings were also not assessed. Some critically ill patients have hyperadrenergic stress responses that can be attenuated with intravenous sedation. Patients with coronary artery disease who are receiving mechanical ventilation commonly have electrocardiographic evidence of myocardial ischemia during trials of weaning from ventilation. We should wonder what effect a sudden interruption of sedation might have on myocardial oxygen balance in patients who are at risk for cardiac disease.

The number of patients in the study did not permit the authors to evaluate the potential for daily awakenings to precipitate acute drug-withdrawal syndromes in patients who have become drug-dependent. In a recent study, 9 of 28 patients receiving mechanical ventilation in whom sedative and analgesic therapy that had lasted a week or more was gradually discontinued had acute withdrawal symptoms that included anxiety, irritability, vomiting, and seizures. Sudden interruptions of sedative infusions to allow a morning awakening could likewise conceivably trigger withdrawal symptoms, which are associated with a 15 percent mortality rate when the drug withdrawn is a benzodiazepine.

Perhaps the most important adverse consequence of the current study, however, would be the further institutionalization of the routine use of intensive sedation in all intubated patients on the premise that daily awakenings help prevent unnecessarily prolonged mechanical ventilation. Despite the widespread use of high-dose, continuous infusions of sedatives in the intensive care unit, there is little evidence that such sedation improves patients’ outcomes. In fact, one study has suggested that an inability to recall experiences during a critical illness leads to psychological distress after recovery.

Continuous infusion of sedatives held promise in the 1980s as a method for providing sedation at precise levels that promoted comfort and sleep but allowed easy arousal. Unfortunately, this promise remains unfulfilled. No data indicate that sedation in the intensive care unit promotes physiologic sleep. Moreover, practical and validated scoring systems to allow accurate adjustment of the doses of sedatives given to patients receiving mechanical ventilation do not exist. Consequently, the initial goal of light sedation is lost, since continuous infusions of sedatives result in high tissue concentrations of drug, precipitating obtundation. This seems to have occurred in the study by Kress et al., as demonstrated by the greater need for neurologic evaluation among patients in the control group than among those in the group whose infusions were interrupted daily.

It is humbling to realize that most of our knowledge of the pharmacokinetics of sedative drugs derives from short-term studies in normal subjects. Critical illnesses and drug interactions alter the volumes of distribution, availability, and elimination of drugs, essentially converting “short-acting” sedatives to drugs with long-term effects. There have been few rigorous studies of the comparative usefulness of various sedative drugs administered in the intensive care unit. Appropriate administration of these drugs is further complicated by the poor understanding of their pharmacokinetics and therapeutic properties on the part of many caregivers in the intensive care unit. Perhaps most disturbing is the observation, in some hospitals, that the intensity of sedation varies inversely with
the number of nurses on a shift, suggesting that “compliant” patients permit understaffing of intensive care units.10

We can thank Kress and coworkers for a superb study that examines approaches to care for patients receiving continuous sedative infusions in the intensive care unit. Considering the gaps in our knowledge, however, this investigation may represent not so much a call for daily wake-ups of patients undergoing mechanical ventilation as a wake-up call for practitioners in the intensive care unit to examine practices of sedation more critically. We need better methods of ensuring that the lowest effective doses of the most appropriate sedative, analgesic, and tranquilizing drugs are given for the shortest required time to critically ill patients receiving mechanical ventilation. Use of appropriate doses throughout a patient’s stay in the intensive care unit may prevent the need for sudden discontinuation of drug administration.

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INFORMATION FOR AUTHORS

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