Editorials

DIETING AND EXERCISE IN OVERWEIGHT, LACTATING WOMEN

In this issue of the Journal, Lovelady et al.\(^1\) report the results of a 10-week intervention trial in which 40 overweight, lactating women were randomly assigned either to a diet-and-exercise group or to a control group at four weeks post partum. The goal was to determine whether restriction of energy intake compromised milk production and thereby the growth of the women's infants, and therefore whether such weight-loss programs are appropriate for overweight, lactating women soon after delivery. Lovelady et al. found that maternal loss of 0.5 kg of body weight per week did not affect the growth of the infants, given that gains in weight and length by the infants did not differ significantly between the intervention and control groups. However, a negative result such as this must be interpreted with caution. The 95 percent confidence interval for the mean difference in weight gain between groups (−280 g to 409 g) indicates that the true mean difference lies somewhere within this interval, but the study had limited statistical power to detect these differences.

Assurance that the intervention did not compromise the growth of any infant is necessary. The large standard deviation in weight gain of the infants suggests that the growth of some infants might have been inadequate. Among numerous causes of compromised growth, a negative effect of the diet-and-exercise program on the milk supply of some women cannot be ruled out. Regression analysis and a graph of maternal weight loss against the weight gain of the infants would have provided more support for the authors' main conclusion that the loss of 0.5 kg per week did not affect the growth of the infants. Other questions relevant to the interpretation of the study results are as follows: Were the infants of the women in the intervention group fussier than those of the women in the control group? Did the infants of the women in the intervention group require any supplementation with formula? Finally, were the frequency and duration of feeding similar in the two groups?

In addition, it is important to consider whether a diet-and-exercise program is appropriate for overweight, lactating women so soon after delivery. In this context, normal rates of postpartum weight loss, the effect of postpartum weight retention on obesity later in life, and the effect of other weight-reduction programs on lactation should be examined.

Lactation is a minor contributor to postpartum weight loss, despite the fact that the production of milk places an additional demand for energy on the mother and presumably causes mobilization of tissue stores of nutrients. Weight loss in women who are lactating is highly variable, averaging 0.6 to 0.8 kg per month, with a range between a loss of 5.6 kg and a gain of 5.5 kg per month.\(^2\)

During the postpartum period, women retain, on average, between 0.5 and 2.0 kg of the weight gained during the pregnancy.\(^3\) Although many women return to their approximate prepregnancy weight within a year, childbearing is a critical determinant of obesity in some. The 1988 National Maternal and Infant Health Survey revealed that 25 percent of white women and 45 percent of black women were heavier by 4.1 kg or more at 10 to 18 months post partum than they were before pregnancy.\(^4\) Postpartum retention of weight is clearly a function of gestational weight gain. Women whose weight gain during pregnancy is within the range recommended by the Institute of Medicine retain less weight post partum in all categories of body-mass index (the weight in kilograms divided by the square of the height in meters).\(^5\)

Women who are of normal weight before pregnancy and who gain an amount that is within the range recommended usually return to their prepregnancy body-mass index without requiring intervention. Women who are overweight before pregnancy and who gain more than the recommended amount would benefit from prenatal and postnatal nutritional counseling.

With overweight and obesity (defined as a body-mass index \(\geq 25\)) affecting about 50 percent of women in the United States,\(^6\) there is a need for prevention of excessive gestational weight gain and effective treatment for women who gain excessive amounts of weight during pregnancy. Clearly, the diet-and-exercise program of Lovelady et al.\(^1\) was successful in achieving accelerated weight loss in lactating women. However, the women's reactions to the program, such as hunger, fatigue, irritability, and psychosocial stress, should have been evaluated.

The effect of energy restriction on lactation has been addressed in a few other studies. In a 1-week study of women who were 12 weeks post partum, those who consumed more than 1500 kcal per day were able to lactate normally, but in those who consumed 1500 kcal or less per day the milk volume decreased by 15 percent during the following week.\(^7\) In another study of women who were 8 weeks post partum, an energy deficit of approximately 500 kcal per day for 10 weeks resulted in weight loss of 4.8 kg, with no apparent effect on milk production, but a third of the women dropped out of the study.\(^8\) In an 11-day study of lactating women who were 12 weeks post partum,\(^9\) the women in a diet group and those in a diet-plus-exercise group both lost approximately 1 kg per week, and their lactational performance (amount and composition of milk and growth of their infants) was similar to that of a control group; however, the short duration of that study limits its...
value. With some reservations, the overall conclusion to be drawn from these studies is that moderate weight reduction is compatible with normal lactation.

If a diet is to be prescribed for lactating women, it is important to review their energy requirements and to recommend energy intake that is only moderately restrictive. Given the energy demands of lactation, the reported mean energy intakes of 1736 kcal per day (at 9 weeks) and 1669 kcal per day (at 14 weeks) in the study by Lovelady et al. suggest that usual energy intake was underestimated, because greater weight loss than that reported would have been expected. The energy requirements of lactating women can be estimated by adding the total energy expenditure plus the energy cost of milk production, as Lovelady et al. did in a previous study. In that study, energy expenditure averaged 2414 kcal per day, with an additional 538 kcal needed to support full lactation, which brought the total energy requirement to 2952 kcal per day. The energy deficit incurred in the diet-and-exercise group in this new study was 446 kcal per day on the basis of changes in weight, or 534 kcal per day on the basis of changes in body composition (assuming energy equivalencies of 6500 kcal per kilogram of weight loss, or 9100 kcal per kilogram of fat mass and 1200 kcal per kilogram of fat-free mass). At these rates of weight loss, mean energy intake could not have been less than 2000 kcal per day.

For the health and well-being of both mothers and infants, the nutritional aim should be to achieve balance in maternal weight and body composition over the entire reproductive cycle, not only in the early postpartum period. Diet-and-exercise programs may be adversely postponed until four to six months post partum, when a mother’s milk is no longer the sole source of nutrition for her infant. Effective nutritional counseling to prevent excessive gestational weight gain and to promote gradual postpartum weight loss should be made available to all women at risk for retention of excessive weight post partum.

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EXERCISE — TONING UP THE ENDOTHELIUM?

PHYSICIANS generally accept the idea that exercise promotes cardiovascular health, a concept that enjoys considerable support from epidemiologic evidence. In both men and women, there is an inverse relation between the level of physical activity and the incidence of cardiovascular disease, and this relation persists after control for other risk factors for cardiovascular disease. Among patients with established cardiovascular disease, mortality is lower among those who participate in an exercise program than among those who do not. These and other data have prompted the inclusion of an exercise program in recommendations for the primary and secondary prevention of cardiovascular disease.

Despite the clear association between exercise and a reduced risk of cardiovascular disease, the precise mechanisms responsible for this association remain unclear. Exercise training has a favorable effect on the severity of traditional cardiovascular risk factors such as hypertension, diabetes, hypercholesterolemia, and obesity. However, such influences probably do not account for the overall effect of exercise on cardiovascular disease, since the effect of exercise is independent of the traditional risk factors. Exercise training also improves myocardial perfusion but has only a limited effect on the extent of atherosclerotic lesions, suggesting that morphologic changes in atherosclerotic lesions do not explain the benefits of exercise.

In addition to the presence of atherosclerotic lesions, cardiovascular disease is characterized by important abnormalities in vascular function. In particular, endothelial control of vascular tone, thrombosis, and platelet activity is impaired in patients with coronary artery disease. In this issue of the Journal, Hambrecht and colleagues provide evidence of an important link between endothelial function and exercise training in patients with established cardiovascular disease. In their study, patients referred for coronary angioplasty were divided into two groups. After an-
gioplasty, the patients in one group were hospitalized for four weeks, during which time they exercised on a bicycle for six 10-minute periods per day; the patients assigned to a control group maintained a sedentary lifestyle and received their usual outpatient care from private physicians.

Using well-accepted methods, the authors assessed coronary vasomotor function before and after this four-week period in an untreated vessel that contained a noncritical stenosis. Exercise training lessened vasocostriction and improved blood-flow changes in response to acetylcholine, indicating that coronary endothelial function in the patients who exercised had improved. Smooth-muscle function in the coronary microvasculature also improved with exercise training, as indicated by the increased blood-flow response to adenosine. These results could not be explained simply on the basis of improved levels of lipoproteins or use of medications.

Several limitations of this study warrant consideration. The number of patients studied was relatively small, and only men were included. In addition, because the exercise-training group, unlike the control group, was hospitalized during the study period, there may have been differences between the groups in diet and compliance with medical treatment. Finally, the exercise regimen was unconventional and may not lend itself to application in most cardiac-rehabilitation programs. Nevertheless, the findings of the study support the hypothesis that repetitive exercise improves endothelial function in the human coronary circulation.

The mechanisms responsible for these effects have been elucidated in animal models and in cell-culture systems. Physical exercise increases coronary blood flow, resulting in increased shear stress on the surface of the endothelium. Endothelial cells respond to short-term increases in shear stress by producing vasodilator compounds such as prostacyclin and nitric oxide. Sustained increases in shear stress elicit an adaptive response in endothelial cells that is manifested, in part, by increased expression of the enzyme that catalyzes nitric oxide production. Predictably, endothelial function in animals that perform regular exercise is improved as a result of increased endothelial nitric oxide production and is better than that in animals that do not exercise. The study by Hambrecht and colleagues suggests that such adaptive responses of the endothelium also apply to the coronary circulation in humans, even in those with coronary artery disease.

There is growing recognition that abnormal endothelial function is central to the development of atherosclerosis and symptoms of coronary artery disease. Normally, the endothelium performs several homeostatic functions: for instance, it maintains vasodilatation and prevents platelet and inflammatory cells from adhering to the vascular surface. Restoration of these normal properties would be expected to have a number of important consequences. For example, the progression of atherosclerosis is dependent on the recruitment of inflammatory cells into the vascular wall, a process that is normally limited by endothelium-derived nitric oxide. Consequently, improving the production of endothelium-derived nitric oxide by means of exercise training should limit the progression of atherosclerosis. Restoration of nitric oxide–dependent vasodilatation in conduit vessels and microvessels should improve myocardial perfusion and limit angina pectoris. Similarly, enhanced endothelial nitric oxide production should limit platelet activation and the risk of thrombus formation, which is an important event in the development of myocardial infarction. Thus, the overall effect of exercise training in restoring normal endothelial function would be expected to limit the clinical manifestations of coronary artery disease.

If improved endothelial function does translate into a lower risk of cardiovascular disease, other interventions that improve endothelial function might also be expected to have demonstrable effects on the risk of cardiovascular events. Available evidence supports this hypothesis. In patients with established coronary artery disease, cholesterol-lowering therapy and angiotensin-converting–enzyme inhibitors improve endothelial function, and in randomized trials these interventions also decreased the rate of cardiovascular events. Other factors associated with a lower risk of cardiovascular events, including smoking cessation and premenopausal status, are also associated with improved endothelial function.

In summary, the well-established beneficial effects of regular exercise on cardiovascular disease may be a consequence of a number of factors, including improvement of coronary-artery endothelial function, as demonstrated by Hambrecht and colleagues. These findings are consistent with the growing understanding that changes in vascular-wall function have important implications for the clinical manifestations of cardiovascular disease. Clearly, elucidating specific mechanisms and developing strategies to reverse abnormal vascular function in patients with atherosclerosis will provide new insights into the treatment of cardiovascular disease. In addition, examination of endothelial function has potential as a way to assess the risk of cardiovascular disease and to guide risk-modification strategies.

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NEW TREATMENT OPTIONS FOR TREMORS

THE revival and refinement of stereotactic neurosurgery represent the most important therapeutic advance in the treatment of movement disorders in the past 30 years. The majority of patients who undergo surgery have Parkinson’s disease, but this approach is also being used for patients with movement disorders such as dystonia and tremor, which is sometimes so severe that it cannot be adequately treated with medication. The study by Schuurman et al. in this issue of the Journal offers new information on neurosurgical treatment in such patients.

Tremor is the most common movement disorder. The majority of affected patients have Parkinson’s disease (prevalence, 110 per 100,000) or essential tremor (prevalence, 306 to 417 per 100,000). The remaining types of tremor, including various idiopathic forms and that caused by multiple sclerosis or brain trauma, are less frequent but often lead to severe disability.

Tremor is not a single entity. It is classified according to the underlying cause, such as Parkinson’s disease, or to the presence of syndromes that have various causes but similar symptoms at presentation, such as cerebellar tremor. Of the more than 10 types of tremor, the most incapacitating are essential tremor, tremor due to Parkinson’s disease, cerebellar tremor, and tremor due to neuropathy. The effect on the patient depends on the clinical manifestations. The more goal-directed movements are distorted by tremor, the more severe the resulting difficulty in performing daily activities. Rest tremor can be intolerable because it can severely restrict social interactions and is physically exhausting. In patients with Parkinson’s disease, tremor occurs mainly at rest. In patients with essential tremor, tremor often occurs during goal-directed movements, and in patients with cerebellar tremor, this is always the case. Tremor in patients with multiple sclerosis is usually cerebellar in nature but is accompanied by other cerebellar, sensory, and corticospinal impairments. The study by Schuurman et al. includes patients with tremor due to Parkinson’s disease, essential tremor, or multiple sclerosis.

The first-line treatment for tremor is oral medication. The average patient with tremor due to Parkinson’s disease can be treated with dopamine agonists, levodopa, anticholinergic agents, or budipine, and if all other types of medication have failed, clozapine is often effective. This kind of treatment generally results in a symptomatic improvement of more than 50 percent. Some patients, however, remain disabled by their tremor. Patients with essential tremor are treated with beta-blockers (mainly a nonselective blocker such as propranolol or a β2-selective blocker), pramipexole, or both, and 40 to 70 percent of these patients have symptomatic improvement of 50 to 70 percent. There is no generally accepted medical treatment for cerebellar tremor. Treatment with clonazepam is sometimes successful, as is treatment with levodopa and anticholinergic agents or clozapine when a clinically significant rest tremor is present. Unfortunately, for the most severely affected patients, the degree of improvement afforded by pharmacotherapy is insufficient. Therefore, new types of treatment are necessary, and the most promising is neurosurgery. The minimal criteria for a patient to be considered a candidate for neurosurgery are a lack of response to pharmacotherapy, severe disability resulting from the tremor, and the absence of contraindications to neurosurgery.

The use of neurosurgery dates back to the 1950s. In the 1960s the preferred neuroanatomical target was the nucleus ventralis intermedius thalami, in which a lesion was created with thermocoagulation. The creation of a lesion as small as 40 to 60 mm3 can suppress the tremor. The critical causative role of the nucleus ventralis intermedius thalami is not yet fully understood, but it is assumed that tremor is generated within loops between deep cerebral or cerebellar nuclei and cortical areas and that most of these loops pass through the ventrolateral thalamic nuclei. Initially, most of the patients who underwent sur-
surgery had Parkinson's disease, and the treatment of nonparkinsonian tremors was a secondary indication at many centers.

The quality of the assessments of early efforts can hardly be compared with that of the present day, but long-term studies suggest that the improvement in tremor was clinically significant. Speech problems and neuropsychological side effects were frequent, especially in patients who underwent bilateral operations. Therefore, bilateral thalamotomy was rarely performed. These efforts ended abruptly with the introduction of levodopa in the early 1970s. Levodopa helped patients with Parkinson's disease, but not those with essential tremor or cerebellar tremor. Only a few neurosurgical centers continued to operate on small numbers of patients, mainly those with nonparkinsonian tremors.

The renaissance of neurosurgery in the past 10 years has occurred for several reasons. First, in 1987 Benabid and colleagues described the use of deep-brain stimulation at the same location that was earlier targeted for thermoablation. These researchers implanted small electrodes into the nucleus ventralis intermedius thalami and connected them to a subcutaneously implanted stimulator. Stimulation at frequencies of more than 100 Hz is assumed to work by inhibiting the function of the stimulated area. This treatment promised similar benefits but fewer side effects than thermoablation. The electrical settings could be adapted for each patient, and even bilateral operations became relatively safe.

Second, the reevaluation of pallidotomy as a treatment for Parkinson's disease confirmed that this approach improved akinesia and decreased levodopa-induced dyskinesia. Third, the advent of new imaging and microelectrode recording techniques increased the safety and precision of the operations. Fourth, pathophysiological studies in animal models of Parkinson's disease showed that the thalamus is overinhibited and both the internal pallidum and the subthalamic nucleus are overactive. Lesions of the subthalamic nucleus decreased the parkinsonian symptoms in monkeys, prompting neurosurgeons to target this area for stimulation by electrodes. Meanwhile, the subthalamic nucleus, internal pallidum, and the nucleus ventralis intermedius thalami all became the subjects of ongoing studies of thermoablation and stimulation therapy. Thus, neurosurgery for Parkinson's disease suddenly became logical, and the reasons for its success became apparent. Since the pathophysiology of nonparkinsonian tremors is still unknown, the use of such surgery for nonparkinsonian tremors is purely empirical, with the thalamus the only target.

The effect of deep-brain stimulation on tremor in patients with Parkinson's disease or essential tremor has been well documented in two controlled, prospective studies. In smaller studies, patients with tremor due to multiple sclerosis have also had a favorable response to deep-brain stimulation. The study by Schuurman et al., however, is the first randomized, prospective trial that compares the effects of thalamotomy on tremor with those of stimulation, and it has solved two key questions. The degree of improvement in tremor was similar after deep-brain stimulation and thalamotomy, but overall function was better after stimulation. Schuurman et al. have convincingly demonstrated that perioperative morbidity is lower with deep-brain stimulation than with thalamotomy, thereby confirming uncontrolled data from centers with experience in the use of both techniques.

In the study by Schuurman et al., both approaches improved tremor in patients with multiple sclerosis but did not result in functional improvement. This result is not unexpected, since these patients also have other complications of their disease. Furthermore, this result confirms those of earlier studies that reported functional improvement in only about a third of patients with cerebellar tremor who were treated by the creation of lesions in the nucleus ventralis intermedius thalami. A rough estimate of the percentage of patients with long-term functional improvement after surgery on the nucleus ventralis intermedius thalami is 85 percent for patients with Parkinson's disease, 50 percent for those with essential tremor, and 30 percent for those with multiple sclerosis, although the percentages in whom the severity of tremor is reduced are much higher.

Do the results of Schuurman et al. signal the end of thalamotomy? They offer a strong argument for the use of deep-brain stimulation as the treatment of choice for eligible patients. But patients so treated must be followed closely at specialized centers, and the costs of therapy are much higher than those of thalamotomy. Studies of the cost effectiveness of thalamic stimulation are needed. The results of Schuurman et al. cannot be uncritically extrapolated to approaches involving other targets, such as the internal pallidum and the subthalamic nucleus.

Progress in the field of stereotactic surgery is very rapid. While Schuurman et al. were conducting their study, the main target of stimulation therapy in patients with Parkinson's disease shifted to the subthalamic nucleus, because stimulation of this nucleus improves not only tremor but also akinesia by about 70 percent. There is no evidence to date that stimulation of this nucleus will also improve nonparkinsonian tremors, but other targets may be discovered for them, too. The factor limiting therapeutic progress in patients with nonparkinsonian tremors is the lack of insight into the underlying mechanisms of tremor.

We need to understand the abnormally functioning motor loops within the central nervous system if we are to find better ways to inhibit them. It is unlikely that the same mechanisms underlie all nonparkinsonian tremors, and thus thermoablation or...
stimulation of different nuclei may be necessary. Further basic research and clinical work are necessary to find better ways to help patients with disabling tremor.

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Sounding Board

Pharmacologic Paralysis and Withdrawal of Mechanical Ventilation at the End of Life

The right of a patient or surrogate to refuse life-sustaining treatment, including mechanical ventilation, is firmly established in American law and bioethics. Moreover, practice standards now encourage clinicians to administer sedatives and analgesics in doses that fully relieve the pain and suffering of terminally ill patients, including patients from whom life support is being withdrawn. In addition to receiving these medications, however, some patients from whom mechanical ventilation is being withdrawn have been receiving or are given neuromuscular blocking agents at the time of death. By blocking neuromuscular transmission, these agents cause paralysis until they are metabolized or their action is pharmacologically reversed. Although some physicians choose to continue or to begin administering these medications when mechanical ventilation is being withdrawn, others insist that this practice is unethical. The following two case reports illustrate the issues.

A two-month-old infant had respiratory failure that had not responded to treatment. His family and physician together agreed that the time had come to withdraw life support and allow him to die. He was sedated with a combination of opioids and benzodiazepines and was made comfortable while making no spontaneous respiratory efforts. His physician administered a dose of pancuronium, a neuromuscular blocking agent. The child continued to appear peaceful as the physician removed the endotracheal tube and placed him in his mother's arms. Several minutes later, the physician pronounced him dead.

A 60-year-old woman was dying of pneumonia. Along with sedatives and analgesics, she required a continuous infusion of vecuronium (another neuromuscular blocking agent) to make the necessarily high ventilator settings tolerable. She had multiorgan involvement, with hepatic and renal insufficiency. Her family and physician concluded that the removal of life support would be most consistent with her expressed values and preferences. Because the physician believed that it is unethical to withdraw ventilation while a patient is pharmacologically paralyzed, he used a nerve stimulator to assess her level of neuromuscular blockade. The train-of-four test revealed no twitches, indicating profound blockade. This test was repeated every six hours, with no evidence of the return of neuromuscular function, for five days, when the results indicated that the effect of the neuromuscular blocking agent had diminished to a level at which it was pharmacologically reversible. After the paralysis was reversed, a combination of glycopyrrolate and neostigmine, the patient appeared sedated and comfortable. The endotracheal tube was removed, and additional doses of opioids and benzodiazepines were titrated to ensure the patient's comfort, and she died peacefully about an hour later.

These case reports illustrate the current range of practice in the use of neuromuscular blocking agents in patients at the end of life. The literature reflects this range. In one study, 3 of 33 patients (9 percent) continued to receive neuromuscular blocking agents during the withdrawal of life support. In another study, of 54 children from whom life support was being withdrawn, 14 (26 percent) received neuromuscular blocking agents at some time during the days preceding withdrawal of the ventilator as part of their therapeutic regimen. One survey of critical care physicians found that 6 percent use neuromuscular blocking agents at least occasionally in patients at the end of life, and another survey of pediatric intensive care specialists in the United Kingdom found that 12 percent would opt to continue the administration of neuromuscular blocking agents during removal of the ventilator. A Dutch study of 181 neonates who died reported the use of neuromuscular blocking agents in 12 infants “because of a very prolonged dying process.” Although the use of these agents has been criticized on ethical grounds, the variations in practice and their ethical implications have not been thoroughly explored.

A variety of neuromuscular blocking agents are used in intensive care medicine. They are used for brief periods to facilitate endotracheal intubation and are administered continuously to patients who require high ventilator settings or nonphysiologic ventilatory modes. The frequency of their use is suggested by two recent studies of severe respiratory failure, which reported the administration of neuromuscular blocking agents to 30 percent and 47 percent of the patients enrolled.

Neuromuscular blocking agents have no analgesic or sedative properties, a fact that may be overlooked by clinicians. They should therefore never be used in the absence of adequate sedation and analgesia. The half-life of neuromuscular blocking agents used in intensive care units ranges from minutes to hours, but it is often prolonged in patients with hepatic or renal dysfunction. Current guidelines recommend frequent testing with a nerve stimulator to avoid overdosage, but this type of testing can be difficult to perform and may produce unreliable results in the critical care setting. When overdosage does occur, the paralysis may be irreversible for as long as several days. Furthermore, in some patients a prolonged weakness of unclear cause develops that cannot be
pharmacologically reversed and that may last for weeks or months.¹⁹

The ethics of the use of neuromuscular blocking agents in patients at the end of life can be analyzed in terms of three categories of patients. The first category involves patients who have not been receiving neuromuscular blocking agents as part of their therapeutic regimen, such as the infant in the first case report. In that case, the clinician may well have been seeking to relieve the family’s suffering by guaranteeing that the patient would not have seizures or make any gasping respiratory efforts after the withdrawal of ventilation. Although families may indeed become very distressed by the dying process and although clinicians should seek to ease their anguish, the needs of the patient must always come first. These are best met by administering opioids, benzodiazepines, barbiturates, or other medications that produce actual comfort, not neuromuscular blocking agents, which produce only the appearance of comfort.²⁰ Indeed, unless the patient also receives adequate sedation and analgesia, the neuromuscular blocking agents may mask the signs of acute air hunger associated with the withdrawal of the ventilator, leaving the patient to endure the agony of suffocation in silence and isolation.

The second category involves patients who are already receiving neuromuscular blocking agents as part of their therapeutic regimen when the decision to withdraw life support is made, but in whom the effect of these agents can be reversed or allowed to wear off within a short period. Restoration of neuromuscular function allows mechanical ventilation to be withdrawn in the absence of the confounding effects of paralysis and is desirable whenever possible.

The third category also involves patients who are receiving neuromuscular blocking agents when the decision to withdraw life support is made, but includes only those whose neuromuscular function cannot be restored for several days or even weeks because of relative overdosage of the drug, the accumulation of active metabolites, or the syndrome of prolonged weakness described above. It is these circumstances that present the ethical conundrum, since insistence on the restoration of neuromuscular function before the withdrawal of ventilation will delay the termination of life support well beyond the point at which the patient and family have determined that the burdens of such treatments outweigh the probable benefits.

As illustrated in the second case report, however, some clinicians believe that neuromuscular function must be restored before the ventilator can be withdrawn. One argument supporting this position is that withdrawal of mechanical ventilation from a patient who is pharmacologically paralyzed is akin to killing the patient, because the neuromuscular blocking agents administered by the physician are the cause of the patient’s death.²¹

This concern arises from a failure to make a distinction between moral responsibility and causal responsibility. When a physician removes mechanical ventilation from a dying patient who is not paralyzed, he or she is responsible for the patient’s death in the causal sense, since the withdrawal of the ventilator is the immediate cause of death. The physician is not responsible for the patient’s death in the moral sense, however, because he or she is acting with the patient’s consent and within a socially defined role and standard of practice. In contrast, if a ventilator were withdrawn by a physician who was not authorized to do so, he or she would be regarded as both morally and causally responsible for the patient’s death.

Both the withdrawal of mechanical ventilation and the administration of neuromuscular blocking agents require physicians causally responsible for the patient’s death. The determination of moral responsibility, however, depends on a number of factors in addition to causation. Along with whether a physician is acting with the fully informed consent of the patient or surrogate and within a sanctioned professional role, there is the question whether withdrawal of ventilation in the presence of pharmacologic paralysis violates the physician’s obligation to be guided by beneficence.

At least three issues arouse concern that withdrawal of a ventilator from a patient who is pharmacologically paralyzed may not be consistent with the physician’s duty to be beneficent. The first is the possibility that the patient may actually survive separation from the ventilator. For some families and clinicians, withdrawal of the ventilator may provide the patient a last opportunity to demonstrate the potential to survive. Taken to an extreme, some may see the withdrawal of ventilation as the last chance for a miracle to occur. From this perspective, pharmacologic paralysis must always be eliminated, because its presence precludes the possibility of survival.

This objection confuses two very different clinical situations. In one, the patient has a small but clinically plausible chance of surviving the withdrawal of mechanical ventilation; in the other, the patient’s condition has failed to stabilize despite the use of maximal levels of respiratory support, and there is no plausible chance of survival once the ventilator is removed. In the first situation, the ventilator should be withdrawn in a way that ensures the patient’s comfort but also maximizes his or her chances of survival without the ventilator. Every effort should be made to optimize the patient’s pulmonary mechanics and respiratory drive, with special attention given to nutrition, positioning, bronchodilation, and minimizing the sedative and depressant effects of medications. As part of this effort, care should be taken to avoid the possibility of residual weakness from neuromuscular blocking agents.

The situation is very different for patients whose
conditions have not stabilized despite the use of maximal levels of respiratory support. At the time of ventilator withdrawal, these patients are receiving ventilation at high pressures, with high levels of supplemental oxygen and often with nonphysiologic ventilatory modes. Under these circumstances, there is no plausible possibility that the patient can survive, even briefly, once separated from the ventilator. Withdrawal of the ventilator results in the immediate cessation of effective ventilation, regardless of the presence of medications that may affect respiratory drive, and cardiac arrest occurs within minutes. In such cases of virtually certain death after the withdrawal of mechanical ventilation, the presence of residual paralysis from a neuromuscular blocking agent cannot be seen as precluding the possibility of survival.

A second reason why the withdrawal of ventilation while the patient is pharmacologically paralyzed may not be consistent with the physician’s obligation to be beneficent is that reversal of neuromuscular blockade facilitates the ability of clinicians to assess the patient’s comfort. The absence of oral or behavioral clues in paralyzed patients makes the assessment of pain and suffering difficult. Monitoring the patient for hypertension, tachycardia, and other autonomic signs is often the only course open to clinicians, and the physiologic instability of dying patients may make even these clues unreliable.

But although it is always desirable to be able to assess the patient’s comfort directly, it is not absolutely necessary in order to be confident that analgesia and sedation are adequate. Neuromuscular blocking agents are used routinely as part of the anesthetic regimen for a variety of common surgical procedures, and anesthesiologists are highly confident in their abilities to ensure a patient’s comfort, even in the presence of physiologic instability and rapidly fluctuating levels of noxious surgical stimulation. This is not to imply that patients never experience awareness under anesthesia, yet the rarity of this phenomenon serves to illustrate just how well anesthesiologists are able to gauge the effects of their medications and the comfort of the patient, even in the presence of neuromuscular blockade.

This analogy suggests that the challenge of providing analgesia and sedation to a dying patient with pharmacologic paralysis is not dissimilar from the routine work of anesthesiologists, and that with proper training, clinicians who care for dying patients should be able to have the same confidence in their ability to ensure the comfort of these patients. The sudden and rapid increase in noxious stimulation that accompanies the withdrawal of the ventilator is similar to the increase that occurs during surgical procedures and should also be manageable by trained and experienced clinicians.

Although we believe that the problems of assessing pain and suffering in patients who are receiving neuromuscular blocking agents can be overcome under ideal circumstances, we recognize that current practice is far from ideal. Even patients who are able to talk openly with their physicians about their pain and suffering do not necessarily have optimal or even satisfactory pain relief at the end of life. Furthermore, in many intensive care units the responsibility for withdrawing mechanical ventilation often falls to nurses and respiratory therapists. If physicians do not possess the training and skills to care for patients acceptably during the withdrawal of life support, it certainly would be unreasonable to expect a higher level of competence from others. These real-world considerations serve to emphasize that the withdrawal of life support from a patient with pharmacologic paralysis should be a rare exception, never undertaken without a full appreciation for the difficulties and importance of ensuring the comfort of the patient in circumstances in which behavioral clues to the patient’s perception of the event are severely limited.

A third argument for the restoration of neuromuscular function before life support is withdrawn stems from the goal of optimizing opportunities for interaction between dying patients and their families. The use of neuromuscular blocking agents thwarts this goal, by eliminating the possibility of communication between the patient and family as well as the patient’s ability to express his or her feelings and needs. Although this consideration is an important reason to avoid the use of neuromuscular blocking agents whenever possible, we do not think it is sufficient to support an absolute prohibition against the withdrawal of life support in patients who are pharmacologically paralyzed.

In conclusion, we suggest the following guidelines for the use of neuromuscular blocking agents at the time life-sustaining treatment is withdrawn. These agents should never be introduced when the ventilator is being withdrawn, and as a general rule, in patients who are already receiving neuromuscular blocking agents, neuromuscular function should be restored before the life support is withdrawn. The only exception to this rule should be when death is expected to be both rapid and certain after the removal of the ventilator and when the burdens to the patient and family of waiting for the neuromuscular blockade to diminish to a reversible level exceed the benefits of allowing better assessment of the patient’s comfort and the possibility of interaction with loved ones. Assuming that skilled and experienced clinicians are available and that the patient’s family has been informed and agrees with this assessment, we believe that the withdrawal of life support can ethically occur in the presence of pharmacologic neuromuscular blockade. Under these circumstances, clinical skill and judgment should guide the administration of sedatives and analgesics to ensure the comfort of the dying patient. We believe these recommendations
should be incorporated into practice guidelines for the care of patients at the end of life.

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