

Editorials

EATING DISORDERS AND DIABETIC COMPLICATIONS

POOR metabolic control in adolescents with insulin-dependent diabetes mellitus (IDDM) is sometimes accepted as inevitable but likely to resolve when the patient's hormones, metabolism, and psyche finally come to terms with adult life. Unfortunately, such complacency is ill judged, because chronic diabetic tissue damage may begin in adolescence, and diabetic microvascular complications — especially retinopathy — may appear or worsen appreciably during puberty. Possible contributory factors include poor glycemic control, which appears to be consistently worse in adolescent girls, and increased serum growth hormone concentrations, which may be both a cause and a consequence of inadequately controlled hyperglycemia.¹

The paper by Rydall et al. in this issue of the *Journal*² highlights another putative risk factor for the development of diabetic complications in adolescent girls — namely, the abnormal forms of behavior defined loosely as eating disorders. These include food bingeing, self-induced vomiting, undereating, abuse of laxatives or diuretics, and underdosing or omission of insulin. Except for bingeing, these forms of behavior may be used deliberately to cause weight loss, and they have generally been attributed to disturbances of body image. They may affect up to 30 percent of young women with IDDM, and they are associated with poor diabetic control, especially chronic hyperglycemia.^{3,4} The association with IDDM remains unexplained, but the general body-image problems that confront teenage girls are probably compounded by strong advice to patients with diabetes to remain thin and by the obesity-promoting effects of insulin, especially at the high dosages that tend to be used in adolescents.⁵ There is some overlap between these patients with eating disorders and the subgroup of patients with “brittle” (chronically unstable) IDDM that consists largely of young women whose diabetes cannot be controlled by intensive insulin therapy, even under close supervision. Many patients with brittle diabetes omit injections of insulin or interfere with their treatment in other ways; some apparently intend to control their weight, whereas others deliberately destabilize their diabetes to escape from difficulties at home or school.⁶ Brittle diabetes ultimately imposes a high risk of microvascular disease,⁶ and the report by Rydall et al. supports earlier suspicions^{7,8} that eating disorders also predispose patients to these complications.

The prospective study by Rydall et al. of 91 ado-

lescent girls with IDDM confirmed that eating disorders were common (in 28 percent of cases initially) and that they tended to persist during 3.5 to 5 years of follow-up. Omission of insulin and undereating were particularly frequent. Eating disorders were associated with high glycosylated hemoglobin values, and most strikingly, highly disordered eating appeared to predict diabetic retinopathy more strongly than did either glycosylated hemoglobin values or the duration of diabetes. At the end of the study, retinopathy was more than three times as prevalent in the patients with highly disordered eating behavior as in those with nondisordered eating (86 percent vs. 24 percent).

Like many prospective observational studies, this one has some methodologic idiosyncrasies. Single measurements of glycosylated hemoglobin and baseline eating behavior were related statistically to retinal findings 3.5 to 5 years later. The predictive value of the study is diluted because we do not know whether any of the adolescent girls already had retinopathy (their eyes were not examined initially) and because neither glycemic control nor eating behavior was assessed in the interim. This is important, because the patients with highly disordered eating behavior had had diabetes longer than the others at entry and were therefore more likely to have retinopathy. It is also important to note that the key finding relates simply to the presence or absence of retinopathy and not to its severity or clinical importance. This all-or-none measure is of limited value, because background retinopathy is common in patients with IDDM (incidence, 50 to 90 percent after 15 years), but only 30 percent ultimately have sight-threatening retinopathy.

Measuring behavior is always problematic, because there are no biologic markers of eating disorders and no objective reporting systems. The questionnaires used by Rydall et al. depend on the patient's recall, which is known to be poor for hypoglycemic episodes,⁹ and leading questions about compliance with treatment may be evaded.⁶ The quantitation and categorization of eating disorders also require comment. The unitary scoring system used assumes that all types of behavior are equivalent, but it is unlikely that an episode of self-induced vomiting would have the same metabolic effect as omitting an insulin injection or “dieting to lose weight.” Curiously, a patient who admitted to six episodes of abnormal eating during the previous three months would be classified as moderately disordered, but one with five episodes would be classified as nondisordered. This might not agree with others' conceptions of normality. Also, it would be interesting to know what happened to the patients who did not admit to any eating disorders.

Nonetheless, this new study offers some important messages and raises some interesting questions.

It focuses attention on the thorny problem of eating disorders, which are undoubtedly common in women with IDDM and must be considered whenever diabetes proves difficult to control; the tendency of these disorders to persist implies that they must not be forgotten in older women with diabetes. The role of eating disorders in men, who seem to be much less at risk yet are equally prone to diabetic complications, is not known. It would be reassuring to learn that the treatment of eating disorders can ultimately reduce the risk of long-term complications as well as improve short-term glycemic control.¹⁰

Finally, and most challenging of all, is the hint that eating disorders contribute directly to microvascular disease. Further studies should aim to confirm this finding and may help us unravel the pathophysiologic mechanisms of diabetic tissue damage that cannot be attributed to hyperglycemia alone.

GARETH WILLIAMS, M.D.
GEOFFREY V. GILL, M.D.

Fazakerley Hospital
Liverpool L9 7AL, United Kingdom

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PREVENTION OF PRIMARY LIVER CANCER BY IMMUNIZATION

THE most common form of primary liver cancer is hepatocellular carcinoma. The other forms of primary liver cancer, including cholangiocarcinoma, angiosarcoma, and several others, are quite rare. Hepatocellular carcinoma is one of the 10 most common cancers in the world. It is particularly common among men in Southeast Asia, the western Pa-

cific region, sub-Saharan Africa, and a number of other developing regions. Epidemiologic data from case-control and cohort studies and from laboratory investigations indicate that there is a consistent and specific causal association between infection with hepatitis B virus (HBV) and hepatocellular carcinoma. Up to 80 percent of hepatocellular cancers are attributable to this virus. HBV is thus second only to tobacco among the known human carcinogens.¹

HBV has a propensity to persist after perinatal infection by a carrier mother, particularly among certain ethnic groups (e.g., the Chinese) or after infection in early life, but also after 10 to 15 percent of acute infections with HBV in adults. Persistent HBV infection is an essential factor in the development of hepatocellular carcinoma because of the relentless progression to chronic liver disease, including chronic active hepatitis and cirrhosis, in a large proportion of carriers (approximately 25 percent). The risk of hepatocellular carcinoma has been estimated on the basis of earlier studies carried out in Taiwan² to be 100 times as high in chronic HBV carriers as in uninfected populations. The incidence of hepatocellular carcinoma is highest in patients with cirrhosis, although the tumor also occurs in patients with chronic hepatitis or asymptomatic infections.

In addition to the epidemiologic evidence, another important link is provided by the related animal hepadnaviruses, and in particular by the woodchuck hepatitis virus.³ Liver cancer frequently develops in woodchucks in the wild infected chronically with woodchuck hepatitis virus, and liver tumors develop in virtually all animals infected experimentally during the neonatal period. The mechanisms of the hepatocarcinogenesis of HBV remain largely unknown, however. One key event is essential to the process — namely, the integration of viral DNA into the host-cell chromosomal DNA, where it may either activate or suppress cellular genes involved in cell growth and proliferation. Integration is known to occur at random and is likely to mediate the rearrangement of both cellular and viral DNA, which may lead to novel transactivation and alteration of functional cell proteins and cellular gene expression. A viral gene that is currently under investigation is the *HBV X* gene.⁴ It follows, therefore, that if the integration of viral DNA can be prevented, then cell transformation and neoplastic changes will not occur. The prevention of this crucial step by vaccination against hepatitis B is described in the report in this issue of the *Journal* by Chang et al.,⁵ and their data provide further evidence of a direct causal relation between HBV and hepatocellular carcinoma. The immunization program against hepatitis B in Taiwan, an area of hyperendemic infection, reduced the rate of HBV carriage in six-year-old children from about 10 percent in the period from 1981 to 1986 to between 0.9 percent and 0.8 percent in the peri-

od from 1990 to 1994. The drop in the rate of carriage occurred as the proportion of infants immunized against hepatitis B increased from 15 percent of children born to mothers at high risk during the earlier period to 84 to 94 percent of all newborn infants during the later period.

This significant reduction in the prevalence of hepatitis B surface antigen was accompanied by a decline in the average annual incidence of hepatocellular carcinoma in children 6 to 14 years of age, from 0.70 per 100,000 between 1981 and 1986 to 0.57 between 1986 and 1989 and 0.36 between 1990 and 1994. The incidence of hepatocellular carcinoma in children 6 to 19 years old fell even more dramatically, from 0.52 among those born between 1974 and 1984 to 0.13 among those born between 1984 and 1986.

Maintaining protection against HBV infection will be essential if the ultimate goal of reducing morbidity and mortality from chronic liver disease and hepatocellular carcinoma is to be achieved later in life, since the peak incidence of this tumor in Taiwan occurs in the sixth decade of life.⁶ This is not merely an academic consideration. The titer of vaccine-induced antibody to HBV (anti-HBs) declines, often rapidly, during the months and years after immunization. There are complex mathematical models with varying estimates of the half-life of anti-HBs, but there are still no empirical data that establish the titer of anti-HBs required for protection against particular routes of infection or the size of the infectious inoculum. Indeed, there is a debate over the minimal protective level of anti-HBs (10 IU per liter, or more likely, 100 IU per liter) and over the need for booster immunization rather than reliance on immunologic memory alone.⁷

In 1983, the World Health Organization (WHO) proposed as a medium-term objective trials of immunization against hepatitis B to prevent liver cancer, while recognizing the difficulties of randomization, the cost of the vaccine, and the complex logistics of long-term trials.¹ This objective has now been achieved in Taiwan through the rigorous application of universal immunization against hepatitis B and the prevention of the carrier state in children.⁶ Further studies are required in men who are at the peak age for this cancer risk but are without HBV markers. The earlier epidemiologic studies in Taiwan carried out by Beasley et al.² identified young male civil

servants as an ideal target population for immunization against HBV.

The implementation of a policy of universal immunization of infants against hepatitis B is now in place in 85 countries, including the United States, and it is expected to have a substantial impact on morbidity and mortality from acute and chronic liver disease, including HBV-related cirrhosis and hepatocellular carcinoma. For example, the European Regional Office of WHO estimates that 1 million people are infected with HBV in Europe each year. Of these, about 90,000 will become chronically infected and about 22,000 will die of cirrhosis and liver cancer. WHO recommends the adoption of universal hepatitis B immunization for infants, adolescents, or both by the end of this year. The implementation of this policy throughout the world will lead in due course to a marked reduction of the reservoir of HBV carriers, and ultimately it could lead to the eradication of HBV infection. The Taiwanese study of the effect of vaccination in reducing the carrier rate of HBV in children, with a concomitant reduction in hepatocellular carcinoma, leads us in this direction, provides crucial evidence, and represents a milestone in the annals of preventive medicine.

ARIE J. ZUCKERMAN, M.D., D.Sc.

Royal Free Hospital School of Medicine
London NW3 2PF, United Kingdom

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*Sounding Board***OVERRIDING A PATIENT'S REFUSAL OF TREATMENT AFTER AN IATROGENIC COMPLICATION**

AN iatrogenic complication is an unfavorable response to medical treatment that is induced by the therapeutic effort itself.¹ Although some are minor, others are life-threatening. Serious or fatal iatrogenic complications occur in 4 to 9 percent of hospitalized patients.²⁻⁴ One retrospective series found that 14 percent of cardiac arrests could be traced to an iatrogenic event.⁵

Physicians often treat conditions caused by iatrogenic complications differently from other medical conditions.⁶ In this article we shall consider various reasons that might be used to justify making a distinction, in particular the arguments used to justify overriding a do-not-resuscitate (DNR)⁷ order after an iatrogenic cardiac arrest.

Many authors have asserted that patients and their families must be informed of iatrogenic complications and have focused their discussion on safeguards to minimize the possibility of such complications.^{3,5,8,9} How should physicians respond to an iatrogenic complication in a patient with an advance directive to limit care? Consider the hypothetical case of a 69-year-old man with metastatic lung cancer who is undergoing chemotherapy. He is admitted to the hospital for pneumonia and requests a DNR order. He suffers a cardiac arrest due to an anaphylactic reaction to an antibiotic, and his physician insists on resuscitation, arguing that the patient's DNR order should not be invoked for an iatrogenic cardiac arrest. Although various ethical principles might be cited as justifications for overriding such a patient's advance directive, we believe that none have merit.

THE PRINCIPLE OF NONMALEFICENCE

Perhaps more than any other ethical principle, the exhortation to do no harm has permeated the culture of medicine and the minds of physicians.¹⁰ Although it was proposed as an ethical absolute, modern-day therapies such as chemotherapy and transplantation have led physicians to modify the adage to "do harm only if the benefits outweigh the harm."¹¹⁻¹³ Understood as a balance, the principle of nonmaleficence establishes only a partial or apparent duty to avoid harm. It does not dictate that this duty should outweigh the obligation to respect a patient's advance directive or that physicians therefore have a duty to remedy harm when it occurs. Nor can the principle of nonmaleficence establish that the bene-

fits of attempting resuscitation outweigh the harm of doing so. A discussion of harm in quantitative terms such as length of stay or survival to discharge is nearsighted because it defines harm only from the physician's perspective. The arguments for overriding a patient's directive must focus less on such outcomes and more on the need for invasive procedures and the patient's quality of life and dignity — a viewpoint that better accommodates the patient's perspective.

EFFICACY OF RESUSCITATION

Another justification for overriding a patient's advance directive after an iatrogenic cardiac arrest relies on the claim that treatment should be permissible simply because resuscitation is likely to be successful.⁵ This reasoning has been invoked to justify the routine suspension of DNR orders in the operating room¹⁴⁻¹⁶ and to question a patient's right to self-determination in particular situations.¹⁷ However, iatrogenic complications are not always so easily reversed,⁵ nor can predictions based on groups of patients be applied easily to individual patients. Furthermore, when physicians treat patients on the basis of probabilities rather than on an individual patient's consent, they forget that resuscitative efforts often cause precisely the type of harm that people commonly wish to avoid (discomfort, fear, and indignity) when they request a DNR order. To withdraw treatment only after it has been unsuccessful is too late, since many of these types of harm will already have occurred.

Furthermore, it is inconsistent to override a DNR order simply because resuscitation is likely to be successful. As Engelhardt explains, "taking freedom seriously means acknowledging the rights of competent individuals to dispose of their lives in ways that others may judge imprudent."¹⁸ For this reason, it is not logical for physicians to override prior directives after an iatrogenic complication when they are morally and legally obligated to respect the refusal by a competent patient to undergo other treatments that may have similar rates of efficacy.

PROXIMATE CAUSE

Proximate cause, a legal concept, is the idea that the primary cause of an event is the cause that is closest in time. From this perspective, a physician may feel obligated to resuscitate a patient because the physician, and not the patient's underlying disease, caused the arrest. Although intuitively appealing, such an argument assumes that the last link in a long chain of events is the most important. This argument ignores the fact that one action or omission is seldom either necessary or sufficient for an iatrogenic event to occur and that several iatrogenic complications may affect one patient.³ In the case we used as an example, the patient's cardiac arrest re-

sulted in part from the antibiotic, but also perhaps from his chemotherapy and from a failure to recognize the allergy. When multiple factors are involved, attributing causation entirely to the factor closest in time to the iatrogenic event is not justified.¹⁹

PHYSICIAN ERROR

Clinical errors contribute to about half of all iatrogenic events,^{20,21} and discussions of medical error continue to generate strong emotional reactions. In his observations of surgical training, Bosk noted that errors in judgment and technique are viewed as morally neutral, whereas failure to report or correct them is viewed as more serious.²² Physicians are taught to accept responsibility for all results, whether intended or not, and to seek to correct errors to promote a patient's well-being. Although accepting responsibility for an unpredictable outcome is one of the most laudable tenets of medical philosophy, an obligation to reverse complications does not necessarily follow.

In seeking to undo complications, physicians may need to perform additional procedures and provide additional therapies, each of which has its own benefits and risks. The occurrence of an iatrogenic complication does not give physicians the right to perform these interventions without the patient's consent. If a competent patient refuses to consent to compensatory tests and therapies, then the physicians should not override the patient's decision regardless of their good intent or the likelihood of success. Likewise, physicians should not presume consent for incompetent patients, especially if the patient has an advance directive that states otherwise. Treating physicians' errors as a special case perpetuates the common misconception that errors are avoidable evils of medicine, rather than expected results in our high-technology modern practice.²³ Drawing a moral line around error reinforces the conception that error is negligence and inhibits a frank and open discussion of the potential for error both within the medical community and with patients.

EXCEPTIONS TO THE RULE

Despite our arguments, there may be instances in which a patient's prior directive can be overridden. Although a DNR order may often be intended as a literal proscription, it can also be a more general statement, with several meanings and intents. Patients are often motivated to request a DNR order because of their goals, but their request is documented in terms of procedures. If the goals and procedures do not coincide when an iatrogenic event occurs, the results can be disastrous.

In our hypothetical case, resuscitation would be appropriate if there were reason to believe that it would be consistent with the patient's goals. A decision to resuscitate based on the patient's goals rather

than his or her stated preferences about particular procedures reflects respect for the beliefs, emotions, and intentions behind such preferences.

How do physicians determine what a patient intended when he or she requested a DNR order, and how should they evaluate potential discrepancies between these intentions and the directive as written? Optimally, the patient, family members, and the physician should discuss these matters when the patient requests the DNR order. However, communication between physicians and patients is often inadequate, particularly with regard to death, the limitation of treatment, and the use of cardiopulmonary resuscitation.^{24,25} When the patient's intentions are unknown and opportunity permits, they should be clarified with his or her surrogate decision maker. If there is time, a surrogate can authorize the physician to override the patient's DNR order if the surrogate believes that the patient's expressed preferences are not consistent with the patient's actual goals. Because physicians may feel obligated to treat out of a sense of guilt or a fear of litigation, physicians in most cases should not make such a decision themselves. If the patient is unable to communicate, and his or her preferences are undocumented and unknown, we believe that an advance directive should be taken literally and a DNR order should be respected.

CONCLUSIONS

Resuscitation after an iatrogenic complication becomes an issue largely because patients are not given an adequate opportunity to communicate their preferences regarding when to limit treatment. As an ethical issue, this problem is in part "iatrogenic," because it often results from physicians' failure to talk with their patients. The problem is further compounded by physicians' guilt and fear of litigation. However, to let these considerations justify overriding a patient's prior directive is to lose sight of the patient as a person.

When possible, physicians should discuss treatment goals and potential complications with their patients, including the possibility of iatrogenic injury. When evidence of such a discussion is unavailable and the patient's intent cannot be determined, the patient's advance directive should be followed. In the unusual case in which a person's intentions are known to be different from a stated preference to forgo life-sustaining treatment, resuscitation may be permissible. However, such a course should be rare, and the continuation of treatment must be directly clarified with the patient or a surrogate at the earliest opportunity.

DAVID CASARETT, M.D.

LAINIE F. ROSS, M.D., Ph.D.

University of Chicago
Chicago, IL 60637

Address reprint requests to Dr. Ross at the University of Chicago, MacLean Center for Clinical Medical Ethics, 5841 S. Maryland Ave., MC 6098, Chicago, IL 60637.

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