

Editorials

ALCOHOL FOR STROKE PREVENTION?

CEREBROVASCULAR disease accounts for a substantial worldwide burden of death and disability. In addition to well-established risk factors such as hypertension, myocardial infarction, diabetes mellitus, and smoking,¹ an increasing body of evidence suggests that lifestyle factors contribute to the risk of stroke. In this issue of the *Journal*, Berger et al.² report, on the basis of their study of U.S. male physicians 40 to 84 years of age who were participants in the Physicians' Health Study, that light-to-moderate alcohol consumption may prevent stroke. The overall relative risk of stroke was 0.79 (95 percent confidence interval, 0.66 to 0.94) for those who reported consuming as little as one alcoholic drink per week and remained near this level for alcohol intakes up to one or more drinks per day. This finding confirms most previous cohort and case-control studies, in which the risk reduction associated with light-to-moderate alcohol consumption ranged from 20 percent to 60 percent.³⁻⁵

Thus far, with regard to wine, beer, and spirits, no consistent evidence has emerged that any one beverage confers a greater health benefit than another.⁵ The protective effect has been found for both men and women,^{3,6} but only for adults over 35 years of age. Although an increased risk of stroke has been found to be associated with heavy drinking in studies worldwide — including in Japan⁷ and South America⁸ — no significant protective effect of light drinking has been reported in these studies.

The discrepancies among studies may be attributable to the small number of subjects in some, resulting in insufficient statistical power, or to the different categorization of drinking in different countries. Differences in susceptibility among ethnic groups are also possible. However, the Northern Manhattan Stroke Study found a protective effect of moderate alcohol intake against ischemic stroke among whites, blacks, and Hispanics.⁵ Moreover, since the early 1980s, the definition of light drinking has changed from less than 35 g per day⁷ to less than 12 g per day, especially in the United States.² The effect of light alcohol intake on hemorrhagic stroke remains controversial, whereas a large increase in the incidence of hemorrhagic stroke has regularly been reported among heavy drinkers.^{3,4}

When strokes of all types are considered together, the net benefit is due to the reduction in the incidence of ischemic stroke, the most frequent type, associated with moderate drinking. The existence of such a protective effect of alcohol consumption is support-

ed by the reduction in mortality observed by Thun et al. in a cohort of 490,000 U.S. adults.⁹ Among 5766 Scottish men, however, a dose-related increase in mortality has been reported that may be related to particular patterns of drinking in Scotland.¹⁰ Alcohol may also be beneficial in the prevention of dementia, another burdensome disorder in aging populations.¹¹

Certain biases and pitfalls may weaken studies on alcohol consumption. First, surveys of alcohol intake must take into account the quantity of alcohol consumed as measured by the number of drinks (corresponding, on average, to 12 to 15 g of pure alcohol per drink, the equivalent of 120 ml of wine) and the frequency of drinking per week. Therefore, subjects with unusual drinking patterns, such as sporadic binge drinking, which is related to an excess risk of stroke and death, may go unrecognized within a study population. Second, self-reported alcohol consumption can be misleading, because it may be underestimated by 50 percent, as compared with alcohol purchases.⁴ Even if there is a good correlation between a first and a second questionnaire, this does not exclude a systematic bias due to the underestimation of alcohol consumption by some respondents. Therefore, the assumption that this bias does not modify the relation between the categories, but only precludes conclusions about the absolute quantity of alcohol that has a beneficial effect, remains to be demonstrated. Third, subjects participating in a survey are more likely to be interested in their health status than those who drink very heavily and who may be less likely to agree to participate. This factor may explain why only 3.1 percent of the physicians in the data base used by Berger et al. reported having more than one drink per day.²

The pathophysiologic mechanisms by which alcohol may contribute to the prevention of cardiovascular disease and stroke remain unclear. An increase in high-density lipoprotein cholesterol has been documented but may not be causal.^{5,12} The effects of alcohol on thrombosis and on nitrous oxide metabolism, and their potential relation to the prevention of cardiovascular disease,^{2,13} are controversial. Moreover, the apparent protective effect of a single drink per week,² or even a single drink per month,⁵ suggests that other mechanisms may be involved. The anxiolytic properties of alcohol may reduce the deleterious cardiovascular consequences of stress. Moreover, regular moderate alcohol consumption may reflect a special way of life. We know more or less how to quantify drinking, smoking, physical activity,^{14,15} body-mass index, and diet. However, despite our best efforts to control for bias, we still are unable to quantify a lifestyle that integrates special attention to the quality of food consumed,^{1,12} regular physical activity,¹⁴ moderate alcohol consumption,¹² and a general concern for health. This way of life may be a factor in the prevention of stroke

and other diseases, and we may still be measuring its confounders.

Should doctors prescribe alcohol as a preventive measure as if it were a medication? It is well established that alcohol can induce dependence and that alcoholism is a major social, economic, and health burden associated with deviant behavior, violence, suicide, accidental death — particularly among teenagers and binge drinkers — and homicide. Moreover, heavy drinking can result in damage to the liver, pancreas, upper gastrointestinal tract, nervous system, and heart and to the developing fetus. However, the assumption that an increase in average alcohol intake would increase the number of heavy drinkers in a population is unproved. Still, the serious health problems associated with excessive alcohol intake demand that we take a cautious approach.

Since the health benefits of light-to-moderate alcohol consumption have been demonstrated, how should we advise individual patients? Among healthy adults over 35 years of age, the benefits attributable to alcohol have to be balanced against the risks. The greatest benefit of alcohol in the prevention of cardiovascular disease may be evident among persons with the highest base-line cardiovascular risk.^{2,9} The higher the base-line risk, the more likely it is that alcohol may be protective. Thus, alcohol may have a particular benefit in secondary prevention after stroke or myocardial infarction.

Finally, when advising patients about the prevention of cardiovascular disease and stroke, physicians must consider not only alcohol consumption, but also a host of other important risk factors, including hypertension, cigarette smoking, diabetes, body weight, physical activity, and abnormalities of blood lipids. Any recommendations about alcohol intake must be made in this broader context.

MARC HOMMEL, M.D.
ASSIA JAILLARD, M.D.

University Hospital of Grenoble
38043 Grenoble CEDEX, France

REFERENCES

1. Gorelick PB, Sacco RL, Smith DB, et al. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA* 1999;281:1112-20.
2. Berger K, Ajani UA, Kase CS, et al. Light-to-moderate alcohol consumption and the risk of stroke among U.S. male physicians. *N Engl J Med* 1999;341:1557-64.
3. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med* 1988;319:267-73.
4. Camargo CA Jr. Moderate alcohol consumption and stroke: the epidemiologic evidence. *Stroke* 1989;20:1611-26.
5. Sacco RL, Elkind M, Boden-Albala B, et al. The protective effect of moderate alcohol consumption on ischemic stroke. *JAMA* 1999;281:53-60.
6. Klatsky AL, Armstrong MA, Friedman GD. Alcohol use and subsequent cerebrovascular disease hospitalizations. *Stroke* 1989;20:741-6.
7. Iso H, Kitamura A, Shimamoto T, et al. Alcohol intake and the risk of cardiovascular disease in middle-aged Japanese men. *Stroke* 1995;26:767-73.
8. Jaillard AS, Hommel M, Mazetti P. Prevalence of stroke at high altitude (3380 m) in Cuzco, a town of Peru: a population based study. *Stroke* 1995;26:562-8.
9. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *N Engl J Med* 1997;337:1705-14.
10. Hart CL, Smith GD, Hold DJ, Hawthorne VM. Alcohol consumption and mortality from all causes, coronary heart disease, and stroke: results from a prospective cohort of Scottish men with 21 years of follow up. *BMJ* 1999;318:1725-9.
11. Lemeschow S, Letenneur L, Dartigues JF, Lafont S, Orgogozo JM, Commenges D. Illustration of analysis taking into account complex survey considerations: the association between wine consumption and dementia in the PAQUID Study. *Am J Epidemiol* 1998;148:298-306.
12. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 1992;339:1523-6.
13. Gorelick PB. The status of alcohol as a risk factor for stroke. *Stroke* 1989;20:1607-10.
14. Sacco RL, Gan R, Boden-Albala B, et al. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke* 1998;29:380-7.
15. Lee IM, Hennekens CH, Berger K, Buring JE, Manson JE. Exercise and risk of stroke in male physicians. *Stroke* 1999;30:1-6.

©1999, Massachusetts Medical Society.

THALIDOMIDE — A REVIVAL STORY

ONE of the most devastating tragedies of modern medicine was set into motion by the over-the-counter marketing of thalidomide in Europe during the late 1950s for the treatment of morning sickness. The drug was withdrawn in the 1960s after the appearance of reports of teratogenicity and phocomelia associated with its use. The recent return of thalidomide stems from the broad spectrum of its pharmacologic and immunologic effects.¹ Thalidomide has been approved by the Food and Drug Administration for the treatment of erythema nodosum leprosum, an inflammatory manifestation of leprosy,² and potential therapeutic applications span a wide spectrum of other diseases.

In 2000, multiple myeloma will be diagnosed in about 13,700 patients in the United States. This incurable bone marrow cancer accounts for 2 percent of cancer-related deaths.³ Treatment of this disease has been notoriously difficult. In this issue of the *Journal*, Singhal et al. report on the use of thalidomide as a single agent in the treatment of refractory myeloma.⁴ In their study, 76 of the 84 patients in the trial (90 percent) had received at least one cycle of high-dose chemotherapy, and 42 percent had high-risk cytogenetic abnormalities. The overall rate of response was 32 percent, as evidenced by a reduction of at least 25 percent in the level of the myeloma protein in serum or Bence Jones protein in urine. This response was associated with a decrease in the percentage of plasma cells in bone marrow, indicating a reduction in the tumor burden. Since the median time to disease progression among patients who had a response had not been reached after a median follow-up of 14.5 months, the responses appear in

some cases to be durable. Given that the patients in the study had relapsed after chemotherapy, which was usually given in massive doses, this effect of thalidomide is indeed remarkable.

Although the results of Singhal et al. indicate that a new drug can be added to the armamentarium of agents against myeloma, important questions remain. The study design called for a gradual increase in the dose, but only 55 percent of the patients received the intended maximal daily dose of 800 mg; it is unclear whether this was due to dose-limiting toxicity. Most patients received 400 mg of thalidomide daily, but whether there is a dose–response relation in the antimyeloma activity of thalidomide was not established. Both factors are critical, since somnolence, neuropathy, and other side effects were common with the higher dose of thalidomide. The optimal dose of thalidomide and schedule of administration therefore remain to be determined.

A low plasma-cell–labeling index, indicating a slow rate of tumor-cell replication, was associated with a response to thalidomide, but it is unclear whether other factors that are useful for predicting the outcome of conventional or high-dose chemotherapy will also apply to thalidomide. The absence of clinically significant treatment-related myelosuppression suggests that thalidomide can readily be tested in earlier stages of myeloma, both alone and with other types of chemotherapy.

New therapies for myeloma are urgently needed. The five-year survival rate for patients treated with chemotherapy has remained at 29 percent for more than four decades. In an overview of 6633 patients from 27 randomized trials in which combination chemotherapy was compared with melphalan plus prednisone, the response rates were higher with combination chemotherapy, but there was no difference in survival.⁵ A randomized, controlled trial conducted by the Intergroupe Français du Myélome showed that high-dose chemotherapy followed by autologous bone marrow transplantation resulted in better response rates, overall survival, and event-free survival than conventional chemotherapy, but few, if any, patients were cured.⁶ Moreover, the high mortality rate among patients with myeloma who undergo allogeneic bone marrow transplantation has limited the use of this procedure. More needs to be done to improve the outcome of high-dose chemotherapy and autologous hematopoietic stem-cell rescue and to make treatment of residual disease after transplantation more effective — for example, through the use of vaccination against the patient's own myeloma protein or other forms of immunotherapy.⁷

The mechanism of action of thalidomide in myeloma is unknown. Recent reports of increased blood-vessel formation (angiogenesis) in the bone marrow of patients with myeloma^{8,9} and the antiangiogenic properties of thalidomide¹⁰ provided the rationale

for the study by Singhal et al. of thalidomide in myeloma. Factors produced by myeloma cells stimulate angiogenesis in the marrow, and it is likely that progression of myeloma follows an increase in bone marrow neovascularization.⁹ Nevertheless, Singhal et al. found no correlation between signs of angiogenesis in the marrow and the response to thalidomide, suggesting that inhibition of angiogenesis may not be the primary mechanism of this drug in myeloma.³

Possible mechanisms of action of thalidomide, its *in vivo* metabolites, or both, in myeloma are shown in Figure 1. Thalidomide may directly inhibit the growth and survival of myeloma cells, bone marrow stromal cells, or both. Oxidative damage to DNA mediated by free radicals, which probably has a role in the teratogenicity of thalidomide,¹¹ may be important here. A second mechanism relates to the finding that adhesion of myeloma cells to bone marrow stromal cells triggers the secretion of cytokines that augment the growth and survival of myeloma cells¹² and induces drug resistance in them.¹³ Thalidomide, by modulating the profile of adhesion molecules,¹⁴ may influence the growth and survival of tumor cells. Cytokines that are secreted into the microenvironment of the marrow, such as interleukin-6, 1β , and 10 and tumor necrosis factor α , modulate the growth and survival of myeloma cells¹²; thalidomide may alter the secretion and biologic activity of such cytokines.¹⁵ Thalidomide may inhibit vascular endothelial growth factor and basic fibroblast growth factor 2, which stimulate angiogenesis.¹⁶ Finally, thalidomide may act against myeloma by inducing the secretion of interferon- γ and interleukin-2 by CD8+ T cells.¹⁷ Determining which of these mechanisms mediate the activity of thalidomide against myeloma will be critical in defining its clinical utility and deriving more potent analogues with fewer side effects. Two new classes of thalidomide analogues have already been identified: phosphodiesterase 4 inhibitors, which inhibit the production of tumor necrosis factor α but have little effect on the activation of T cells, and another class, which does not inhibit phosphodiesterase, but instead markedly stimulates T cells and the secretion of interferon- γ and interleukin-2.¹⁵

The efficacy of thalidomide treatment in patients with refractory, relapsed myeloma suggests that this drug can be used to overcome resistance to conventional chemotherapy. Its demonstrated efficacy in late-stage disease and its low toxicity provide the rationale for evaluating its effect in patients with early disease, either as a single agent or in combination with chemotherapy. Ongoing studies of the way in which thalidomide affects myeloma cells and of resistance to thalidomide in myeloma will guide the synthesis of analogues with enhanced activity and even less toxicity. Current clinical studies of thalidomide open

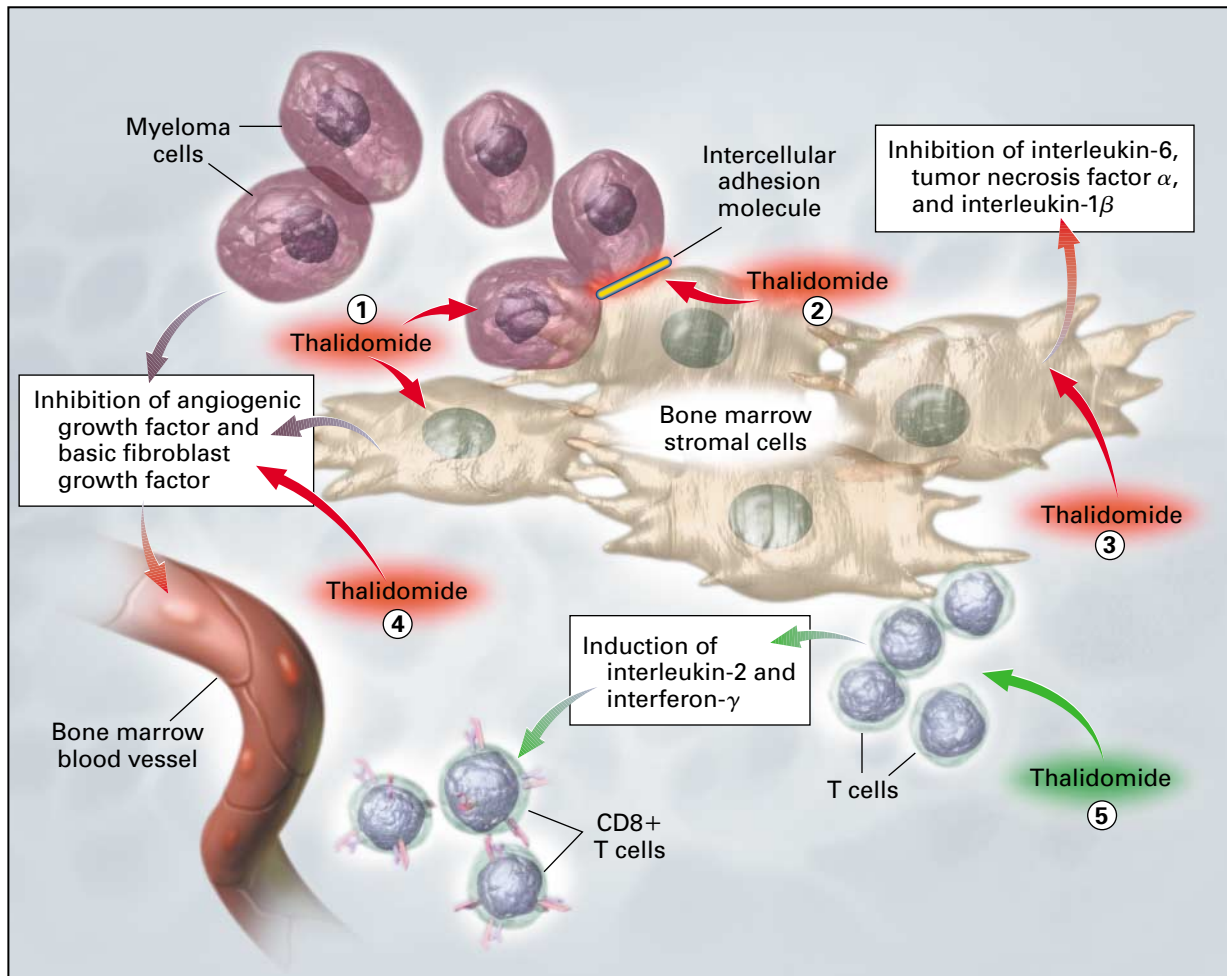


Figure 1. Potential Mechanisms of Action of Thalidomide and Its in Vivo Metabolites.

Thalidomide may inhibit the growth and survival of tumor cells, bone marrow stromal cells, or both (1); alter the profile of adhesion molecules and interactions between tumor cells and bone marrow stromal cells (2); modulate the cytokine milieu and thereby affect the growth and survival of tumor cells, bone marrow stromal cells, or both (3); inhibit angiogenesis (4); or increase the number of CD8+ T cells by means of its immunomodulatory effects (5).

possibilities for novel treatments that target the tumor cell and its microenvironment.

NOOPUR RAJE, M.D.
KENNETH ANDERSON, M.D.
Dana-Farber Cancer Institute
Boston, MA 02115

REFERENCES

1. Hales BF. Thalidomide on the comeback trail. *Nat Med* 1999;5:489-90.
2. Sampaio EP, Kaplan G, Miranda A, et al. The influence of thalidomide on the clinical and immunologic manifestation of erythema nodosum leprosum. *J Infect Dis* 1993;168:408-14.
3. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin* 1999;49:12.
4. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999;341:1565-71.
5. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. *J Clin Oncol* 1998;16:3832-42.
6. Attal M, Harousseau J-L, Stoppa A-M, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 1996;335:91-7.
7. Schlossman RL, Anderson KC. Bone marrow transplantation in multiple myeloma. *Curr Opin Oncol* 1999;11:102-8.
8. Ribatti D, Vacca A, Nico B, et al. Bone marrow angiogenesis and mast cell density increase simultaneously with progression of human multiple myeloma. *Br J Cancer* 1999;79:451-5.
9. Vacca A, Ribatti D, Presta M, et al. Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma. *Blood* 1999;93:3064-73.
10. D'Amato RJ, Loughman MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A* 1994;91:4082-5.
11. Parman T, Wiley MJ, Wells PG. Free radical-mediated oxidative DNA damage in the mechanism of thalidomide teratogenicity. *Nat Med* 1999;5:582-5.
12. Hallek M, Leif Bergsagel P, Anderson KC. Multiple myeloma: increasing evidence for a multistep transformation process. *Blood* 1998;91:3-21.

13. Damiano JS, Cress AE, Hazelhurst LA, Shtil AA, Dalton WS. Cell adhesion mediated drug resistance (CAM-DR): role of integrins and resistance to apoptosis in human myeloma cell lines. *Blood* 1999;93:1658-67.
14. Geitz H, Handt S, Zwingenberger K. Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. *Immunopharmacology* 1996;31:213-21.
15. Corral LG, Haslett PA, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J Immunol* 1999;163:380-6.
16. Bellamy WT, Richter L, Frutiger Y, Grogan TM. Expression of vascular endothelial growth factor and its receptors in hematopoietic malignancies. *Cancer Res* 1999;59:728-33.
17. Haslett PA, Corral LG, Albert M, Kaplan G. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. *J Exp Med* 1998;187:1885-92.

©1999, Massachusetts Medical Society.

FIREARMS AND SUICIDE

THE article by Wintemute et al.¹ in this issue of the *Journal* adds to the growing literature that connects firearms with increased risks of suicide and homicide.²⁻⁶ Some of these studies have examined the risks associated with the possession of firearms, and some, the risks associated with ownership; now, this article looks at the risks in relation to firearm purchase. The findings are of particular interest because they indicate that purchasers of handguns are at high risk for suicide, particularly during the period immediately after the purchase.¹ This association is especially strong among women.

There are other interesting findings in this study, as well as limitations. First, it is important to note that Wintemute et al. found that the risk of death from homicide among men who purchased handguns was actually lower than that among men in the general population. Although this finding did not apply to women who purchased a handgun, it may represent a true protective effect of handgun purchase and needs to be considered seriously and examined further. Second, the current findings do not demonstrate that the purchase of a firearm caused suicidal behavior or actually increased the risk of suicide among those who purchased handguns. Causes of suicidal behavior may include a variety of factors, ranging from depression and schizophrenia to a history of domestic violence or child abuse to impulsivity.⁷ Previous research indicates, however, that firearms are more likely to be lethal than other commonly used methods of attempting suicide.⁸⁻¹⁰ The data presented by Wintemute et al. suggest that people who are considering suicide may purchase a firearm in order to carry out their plan with the most lethal means available. This possibility challenges us to find a way to prevent such purchasers of handguns from committing suicide.

This is a serious challenge. The report by Winte-

mute et al. highlights the importance of firearm-related suicide as a critical component of the overall problem of firearm-related injuries. In fact, the most common cause of firearm-related deaths in this country is suicide. In 1997 in the United States, 32,436 people died from firearm injuries: 17,566 (54 percent) of these deaths were suicides and 13,252 (41 percent) were homicides. Despite these numbers, suicides by firearm have been virtually ignored in most discussions of how to prevent firearm-related violence.

We believe there are several explanations for this lack of attention. First, most people are not aware of how many suicides are committed with handguns. Second, when people think of "handgun violence," they often think only of homicide, and because media attention is focused primarily on homicide, suicide is less visible and inherently less threatening.

Third, many people are fatalistic about suicide, believing that little can be done to stop a person who is intent on committing suicide from doing so. In addition, it is commonly believed that the chosen method of suicide is not an important determinant of the outcome. Many people believe that access to firearms is of little consequence in this regard because people who are suicidal are so intent on killing themselves that they will find another means of doing so if a firearm is not readily available.

Fourth, those who study the prevention of firearm-related violence are usually separate from those who study the prevention of suicide in general. Firearm-related violence has traditionally been the domain of criminal justice, whereas suicide has been seen as part of mental health care. Wintemute et al. represent a new breed of public health professional, successfully bringing these two domains together to raise new questions and stimulate new responses.

The report by Wintemute et al. should make us ask, "What do we need to know and what do we need to do to prevent firearm-related suicides?" To seek answers, three areas need to be explored: What do we know about the frequency and characteristics of suicides by firearm? What are the causes of firearm suicides? And what interventions are effective in the prevention of firearm suicides?

First, we need to understand more about the circumstances under which suicides by firearm occur. Do those who commit suicide by this method have a history of domestic violence, child abuse, or depression? Have persons who committed suicide with firearms recently been involved in an interpersonal conflict, or have they suffered a traumatic loss? And what do we know about the firearms used to commit suicide? Information about the types of firearms, their storage, and their history of ownership and ownership transfer would be useful in developing strategies for prevention. For recent purchasers of handguns who used a handgun to commit suicide, was the handgun they used the same one that they

purchased recently? How can we use the methods developed by the Bureau of Alcohol, Tobacco, and Firearms for tracing firearm purchases in homicides and other crimes to examine these connections?

The study by Wintemute et al. included only adults, since only adults can legally purchase handguns. We need to look at the circumstances under which children and adolescents with suicidal thoughts obtain handguns originally purchased through legal channels or acquired through illegal channels. Progress in this area will require collecting data on large numbers of firearm purchases and firearm-related injuries. Wintemute et al. have been able to conduct many productive studies in this respect because California systematically collects data and makes them available for research. There have been multiple calls for a system of firearm-injury surveillance to ensure the collection of such data at a relatively low cost.^{11,12} Such a system would permit more systematic analysis and help to prevent firearm-related injuries and deaths.

Second, we need to understand a great deal more about the causes of firearm-related suicide, in particular how handgun purchase is related to suicidal behavior. For example, would persons who try to purchase a handgun with the intention of using it to commit suicide be successful in committing suicide if they were prevented from purchasing the gun? Are depression and other forms of mental illness important risk factors for firearm-related suicide among purchasers of handguns, or are handgun purchasers who are suicidal more likely to be characterized by impulsivity? Immediate access to a firearm may be a much more important risk factor for someone who is impulsive than for someone who is seriously depressed. The high risk that might be posed by impulsivity would not just be the risk associated with the impulse to purchase the handgun, but might also reflect the high risk associated with the impulse to use the handgun if it were available. Does violence perpetrated by an intimate partner play a part in suicidal behavior among women who purchase guns? Since Wintemute et al. found that only about 10 percent of all suicides by firearm were committed by recent purchasers of handguns, how did the other 90 percent of persons who committed suicide with a firearm gain access to the weapon?

Finally, at the time a handgun is purchased, there are often processes in place (such as waiting periods and background checks) that may help prevent suicide, but their effectiveness has not been evaluated. Do waiting periods prevent suicides among people who are impulsive by preventing them from having access to a handgun during the time they have the suicidal impulse? If waiting periods do prevent impulsive suicides, what is the optimal length of a waiting period for the prevention of the greatest number of these suicides? Can background checks be used to identify persons who are at high risk for suicidal behavior?

There do not appear to be any screening instruments for suicidal tendency that are sufficiently specific for use in preventing persons who are suicidal from taking possession of a firearm at the time of sale. The problem is that suicide is so rare among handgun purchasers that even a highly specific screening tool would yield many more false positives than it would identify real cases, so screening is probably not a good option.¹ Would it be more effective to screen all purchasers for mental health problems with the use of a questionnaire at the time of sale?

The issue is no longer whether we should apply science to the problem of firearm-related injuries, but how we should do so in the effort to prevent such injuries. Eleven years ago, an editorial in the *Journal* called for more scientific investigation of firearm injuries,¹³ as did a recent report by the Institute of Medicine.¹² Kassirer¹⁴ has called on the government, together with foundations and the private sector, to intensify efforts to describe the problem, identify risks and protective factors, and evaluate strategies for prevention. Scientific investment in this area remains limited despite the magnitude of the problem. Expanding efforts to answer some of the questions we have posed here may help to preserve the legality of firearm ownership while saving many lives. To use science to answer these questions is only common sense. We cannot afford not to do so.

MARK L. ROSENBERG, M.D., M.P.P.

Collaborative Center for Child Well-being
Decatur, GA 30030

JAMES A. MERCY, Ph.D.

Medical College of Wisconsin
Milwaukee, WI 53226

LLOYD B. POTTER, Ph.D., M.P.H.

Centers for Disease Control and Prevention
Atlanta, GA 30341

REFERENCES

1. Wintemute GJ, Parham CA, Beaumont JJ, Wright M, Drake C. Mortality among recent purchasers of handguns. *N Engl J Med* 1999;341:1583-9.
2. Brent DA, Perper JA, Goldstein CE, et al. Risk factors for adolescent suicide: a comparison of adolescent suicide victims with suicidal inpatients. *Arch Gen Psychiatry* 1988;45:581-8.
3. Brent DA, Perper JA, Allman CJ, Moritz GM, Wartella ME, Zelenak JP. The presence and accessibility of firearms in the homes of adolescent suicides: a case-control study. *JAMA* 1991;266:2989-95.
4. Kellermann AL, Rivara FP, Somes G, et al. Suicide in the home in relation to gun ownership. *N Engl J Med* 1992;327:467-72.
5. Kellermann AL, Rivara FP, Rushforth NB, et al. Gun ownership as a risk factor for homicide in the home. *N Engl J Med* 1993;329:1084-91.
6. Cummings P, Koepsell TD, Grossman DC, Savarino J, Thompson RS. The association between the purchase of a handgun and homicide or suicide. *Am J Public Health* 1997;87:974-8.
7. The Surgeon General's call to action to prevent suicide. Washington, D.C.: Public Health Service, 1999.
8. Annett JL, Mercy JA, Gibson DR, Ryan GW. National estimates of nonfatal firearm-related injuries: beyond the tip of the iceberg. *JAMA* 1995;273:1749-54.
9. Card JJ. Lethality of suicidal methods and suicide risk: two distinct concepts. *Omega J Death Dying* 1974;5(1):37-45.
10. Lee RK, Waxweiler RJ, Dobbins JG, Pascheta T. Incidence rates of

firearm injuries in Galveston, Texas, 1979–1981. *Am J Epidemiol* 1991; 134:511-21.

11. Teret SP. The firearm injury reporting system revisited. *JAMA* 1996; 275:70.

12. Bonnie RJ, Fulco CE, Liverman CT, eds. Reducing the burden of injury: advancing prevention and treatment. Washington, D.C.: National Academy Press, 1999.

13. Mercy JA, Houk VN. Firearm injuries: a call for science. *N Engl J Med* 1988;319:1283-5.

14. Kassirer JP. A partisan assault on science — the threat to the CDC. *N Engl J Med* 1995;333:793-4.

©1999, Massachusetts Medical Society.

*Sounding Board***MEDICAL PROFESSIONALISM
IN SOCIETY**

TODAY, at the dawn of a new century, genuine medical professionalism is in peril. Increasingly, physicians encounter perverse financial incentives, fierce market competition, and the erosion of patients' trust,¹⁻⁷ yet most physicians are ill equipped to deal with these threats.^{8,9} The role of professionalism has been so little discussed that it has virtually disappeared in the battle between those who favor market competition in a trillion-dollar industry and those who seek greater government regulation.⁸ Physicians, feeling trapped between these camps, are turning to unionization and other tactics.¹⁰

In the first half of this century, medical professionalism was generally understood according to the structural-functional approach of Talcott Parsons and his school.¹¹⁻¹³ This approach catalogued the distinctive characteristics of professions and then attempted to discern the social function of each. For instance, professional cooperation, rather than competition, was seen as serving the public good by increasing the speed of dissemination of new information. Parsons also believed that professionals were predisposed to public service because they were less interested in amassing wealth than in achieving recognition among their colleagues for doing good work.¹¹

Although their work was illuminating in many ways, the structural functionalists failed to consider the moral foundations of professionalism, and this failure resulted in a confusing conflation. Distinctive characteristics rather than moral premises were used to define professionalism. For example, self-regulation, which is a distinctive characteristic necessitated by the nature of professional work, was understood instead as the essence of professionalism. In the absence of an explicit moral base, critics could readily claim that self-regulation by physicians was nothing but a cover for the monopolization of trade.

In the 1960s, a critical academic literature seized on this weakness, combined it with empirical evidence of professional self-interest, and asserted that professional ethics were a cynical ploy.¹⁴⁻¹⁸ As Freidson noted, "When the leaders of the profession invoke ethics and the values of professionalism, [the] critics declare it a self-serving ideology that masks the reality of naked self-interest."¹⁹ Practical attacks on professionalism gained strength from these criticisms. Throughout the 1970s and 1980s, claims that physicians were exploiting their trade monopoly led to the use of antitrust legislation against physicians.²⁰

By the 1990s, many academics were reaffirming

the importance of professional self-regulation, especially in health care.^{19,21} Sociologists who study the professions have become less cynically focused on power. They have acknowledged that professional self-regulation, although susceptible to abuse, serves necessary social functions.^{19,22} Still, the earlier attacks on professionalism left this term with no coherent meaning. Lacking systematic knowledge about professionalism, many people use the term to refer to ill-defined, sometimes self-serving, concepts.²³⁻²⁵ A clarification of genuine medical professionalism is necessary if the current unraveling is to be reversed.^{8,26-28}

PROFESSIONALISM IN SOCIETY

Medical professionalism is more than merely an activity that straddles market competition and government regulation. Likewise, it is much more than a technical necessity for delivering a needed good or service, and it cannot be reduced to a "deal" negotiated with society. We think of professionalism as an activity that involves both the distribution of a commodity and the fair allocation of a social good but that is uniquely defined according to moral relationships.²⁹ Professionalism is a structurally stabilizing, morally protective force in society. Along with private-sector and public or government activities, it is a cornerstone of a stable society.

Dramatic failures of medical professionalism to provide moral protection have occurred in recent memory, each failure marking a time of social disarray or worse. Apartheid in South Africa overpowered core health care values,³⁰ as did the Soviet Union's misuse of psychiatric diagnoses.³¹ The perversion of medical values, and the complicity of physicians and other health care practitioners in this perversion, were an integral part of Nazism.³²⁻³⁴

The social role of professionalism as a stabilizing force is not unique to the medical profession. Complex societies in different times and places have had in common a need for meritocratic, dedicated subgroups that function to keep private interests and government power in balance through attention to greater social goods. For instance, de Tocqueville remarked that American lawyers of his time served as a stabilizing force in American society, tempering the excesses of government and private industry.³⁵ Similarly, the protected Mandarin class in pre-Communist China served this role for many years, criticizing both the state and the private sector in order to protect vulnerable social goods.³⁶

Professions protect not only vulnerable persons but also vulnerable social values. Many values are vulnerable: individuals and societies may abandon the sick, ignore due process in judging the guilt or innocence of a person accused of a crime, provide inadequate support for education, propagate information that suits those in power while stifling different perspectives, and so on. Values are so vulnerable that it

is hard to think of any society that has not at times lapsed in protecting them. Good civilizations, however, limit and reverse such lapses, in part by entrusting designated groups of people — physicians, lawyers, teachers, journalists, and others — to safeguard the values. When professionalism in these core social activities becomes unsteady, it marks the emergence of societal problems.

That the need for professionalism is more than technical does not undermine the legitimacy of the technical argument.¹⁹ In medical matters, neither patients as consumers nor government regulators have sufficient training, experience, or time to assess every health care product and service; the services purchased are too complex, rapidly changing, and difficult to correlate with measurable outcomes. Lay medical education can alter the scope of needed professional oversight, and this is desirable in many cases. But illness will always limit the ability of patients to “shop around” when important purchasing choices must be made.³ Professional groups, through the establishment of standards, education, and peer review, can go a long way toward supplying quality assurance.³⁷

In making a full case for professionalism, we do not wish to overstate the claim. In particular, we note that respect for human worth, trustworthiness, and the protection of important values are not the exclusive province of professionals; neither is competence. But they are particular obligations of professionals. We also remain mindful that professionals, no less than entrepreneurs or government officials, can misuse their power and have done so. The danger that power will be misused is inherent in any system that assigns authority to a group of people to police themselves. A full understanding of what professionalism entails provides some protection against this danger.

A MODEL OF PROFESSIONALISM

Three core elements of professionalism, each different in nature, are necessary for it to work properly. First, professionalism requires a moral commitment to the ethic of medical service, which we will call devotion to medical service and its values. This devotion leads naturally to a public, normative act: public profession of this ethic. Public profession of the ethic serves both to maintain professionals’ devotion to medical service and to assert its values in societal discussions. These discussions lead naturally to engagement in a political process of negotiation, in which professionals advocate for health care values in the context of other important, perhaps competing, societal values.

Devotion to Medical Service

Physicians should cultivate in themselves and in their peers a devotion to health care values by placing the goals of individual and public health ahead

of other goals. That is, physicians must be devoted to the work of providing health care.

Physicians who value individual and public health more than other social goods remain motivated to work hard even when the financial rewards for such work are not great. They criticize and police one another even when such actions have personal, social, and financial costs. They offer high-quality services whether or not patients are capable of judging their quality. They continue to provide health care even when, as during an epidemic, they risk their own health. And they maintain their obligations to care for financially disadvantaged patients.³⁸⁻⁴⁰ Today, the ascendancy of marketplace values puts health care for the poor at particular risk.^{3,41,42} Physicians should influence the organizations in which they practice to adopt policies that address the care of impoverished persons. Similarly, physicians must resist incentives that place the trust between patient and doctor and even patient care at risk.^{5,43,44} Devotion to medical service is so important that physicians must avoid even the appearance that they are primarily devoted to their own interests rather than to the interests of others. Dramatic rises in physicians’ incomes over the past four decades have fostered the trust-destroying belief, whether true or not, that physicians as a group are greedy and take advantage of patients.^{17,45-49}

Public Profession of Values

Physicians should speak out about their values. The word “profession” means, from the Latin, “speaking forth.” Public avowal of values has been a distinctive feature of the professions from before medieval times.

Although acting on one’s professional devotion to medical service is a form of public profession of values, it is not enough. The unique nature of the relationship between patient and physician requires an explicit and professionally protected moral base so that there can be legitimate shared expectations, even in circumstances, such as emergencies, in which individual relationships have not had time to mature. The patient–physician relationship is based on shared experiences of vulnerability and the potential for health or illness and on a resultant respect for the inestimable value of human life and health.⁵⁰ Furthermore, health care values focus on the public as well as the individual. As Samuel Johnson noted, “A decent provision for the poor is the true test of civilization.”⁵¹ Health care values reflect this assertion. Through public profession of health care values, patients and the public hear about these values as well as the standards that result from them. They hear that physicians’ commitment to such important standards as never exploiting patients’ inherent vulnerability and not abandoning patients is timeless. They hear that other, specific aspects of health care values are delineated in a continuous dynamic process with society, to which physicians bring their training, profes-

sional virtues, interprofessional relations, and above all, experiences in caring for patients. Finally, public profession of values — for example, by participating in “white-coat ceremonies,” posting ethics codes in waiting areas, and contributing to and espousing the standards of a professional association — demands commitment.^{52,53} A public, collective commitment to fulfill legitimate expectations implies an acceptance of accountability for one’s professional actions, as well as an acceptance of the shared standards of the profession, which may sometimes conflict with personal beliefs.

Negotiation Regarding Professional Values and Other Social Values

Public profession of values inevitably requires professionals to engage with the public in negotiating social priorities that balance medical values with other societal values. This political process of negotiation should lead to what is sometimes referred to as a social contract between physicians and the public.⁵⁴

The process of negotiation not only clarifies legitimate public and professional expectations but can also prevent counterproductive paternalistic behavior on the part of professionals. Individually, the process fosters patient-centered care by including each patient’s health goals in decision making. Collectively, it can help accommodate a suitable social disposition toward medical care. The process of negotiation can make clear professionals’ obligations to meet public needs, reminding the profession that it cannot have everything its own way and simultaneously demanding appropriate advocacy. Tension may develop between what society wants of physicians and physicians’ devotion to health care values. For example, portions of society today favor intense market competition among physicians as a way to lower the costs of care. But such competition encourages the development of trade secrets among physicians, such as proprietary practice guidelines,⁵⁵ and impedes the collegial interaction and information sharing that are needed to provide high-quality care. The challenge for physicians is to be accountable to the public and its changing values while protecting core health care values.

An Archetypal Model of Professionalism

We propose that an ideal archetypal model^{19,56} of medical professionalism entails the three elements of devotion, profession, and negotiation. The model is ideal in that it is not descriptive of the reality today or in any other era. It is archetypal because it is intended to describe only core elements of professionalism. The purpose of the model is to provide a normative guide.

Each element may fail, may be misapplied, or may not be in balance with the other two. A failure of devotion to the ethic of medical service leads to self-protective behavior on the part of physicians, as oc-

curred, for instance, in the difficult transition to managed care and at the start of the AIDS epidemic. Failure to profess health care values publicly may lead to uninformed, misinformed, or piecemeal public policies. And failure to negotiate an acceptable social contract leads the public to establish other contracts in order to obtain what it needs and wants. As one example, “alternative” practitioners and therapies become more attractive to the public when they provide something desirable that the profession has ignored in individual or social negotiations. Yet negotiation does not mean simply giving the public what it wants. An overemphasis on satisfying public demands, without attention to core health care values, will ultimately leave both professionals and society unprotected. In addition, professionalism may be misused if physicians become devoted, as individuals or groups, to values derived from other sources, such as business values. Finally, an exaggerated devotion to an ethic that is determined solely by professionals may lead to paternalism or to the refusal to consider other important perspectives.

A SPECTRUM OF PROFESSIONAL ACTIVISM

With this model of professionalism as devotion, profession, and negotiation, exactly how, in a practical sense, should physicians act on behalf of patients, the public, and health care values? What types of activity constitute professional advocacy?

The advocacy activities of individual professionals should fall along a spectrum, with more extreme actions requiring more stringent justifications.⁵⁷ At one end of the spectrum is routine advocacy for patients and public health. Routine advocacy constitutes physicians’ regular daily activity. Physicians working in health care delivery organizations — coordinating care, working to improve practice guidelines, and so on — should advocate health care values rather than government or corporate values, speaking on behalf of patients and health care. Occasionally, this type of advocacy may be personally risky. For instance, physicians who appeal adverse coverage decisions on behalf of their patients may put at risk their standing with health plans.

If advocacy fails, physicians have an obligation to express internal dissent with regard to activities or policies that undermine core health care values. This responsibility is what distinguishes genuine professionals from “company docs.” Although internal dissent is not always clearly distinct from routine advocacy, it is a negative form of activism that may go against an internal hierarchy. Internal dissent may require courage and skill to achieve a positive outcome, but it generally requires minimal moral justification.

Public dissent is next on the spectrum and should be used with more care. It may raise tensions and backfire, causing harm. For instance, the dissenter

may be demoted or fired, thereby perhaps harming patients' care, or a point of dissent may become more difficult to resolve because publicity can provoke denial or defensiveness. Public dissent is warranted only when internal dissent has demonstrably failed to remedy a harmful situation, when outside pressure is likely to be required to achieve change, when public silence allows the harmful situation to continue, and when the potential harms to patients from public dissent are relatively small. For example, the proposed closing of a clinic may justify efforts to galvanize community support through public dissent.

With direct professional disobedience, the fourth form of activism on the spectrum, professionals act against authorities, publicly disobeying rules or laws that are antithetical to health care. Direct professional disobedience has a clear potential to harm patients, the profession, and professionals themselves. It should therefore be reserved for situations in which both internal and public dissent have failed, direct disobedience is likely to be effective in remedying the problem, the problem is very serious (preferably, its seriousness can be documented empirically), and the action entails as little harm as possible.⁵⁸ Surreptitious disobedience, such as secretly "gaming" a billing code to obtain coverage for services, is not justifiable as a form of direct professional disobedience, since it is neither public nor aimed at achieving systemic change.⁵⁹ In contrast, delivering free care despite a policy to the contrary, urging colleagues not to comply with California's Proposition 187 (which called on physicians not to treat illegal immigrants), and openly breaking a contractual "gag rule" are examples of justifiable disobedience.^{60,61}

Indirect professional disobedience is the disobeying of otherwise unobjectionable rules in order to call attention to a wrong.⁵⁸ Indirect actions become appealing when it is not helpful to disobey directly. For example, physicians may not be effective in protesting a health plan's underprovision for the uninsured by directly caring for them — providing charity care is a normal part of professionalism and in an open system it may even facilitate the injustice. But an indirect action, such as collectively refusing to honor a dress code, might call attention to the situation. Although the danger of harm from such an action may seem remote, indirect disobedience can be more harmful than direct disobedience, because in the latter the action itself preserves patient care. Protestors may also overestimate the effectiveness of their campaigns.⁵⁸ To be justified, the disobedient act should, at a minimum, be clearly linked with the offensive situation, be seen as reasonable by the public, be unlikely to result in greater harm to patients or others, and be likely to result in lasting positive change.

Finally, a principled exit from medical practice within a health care system is justifiable in catastrophic circumstances. Patients will frequently be harmed by

a physician's exit, so it must be justifiable on the following moral grounds. The harm to be prevented must be obvious and large; advocacy, dissent, and disobedience must have been tried; and there must be a good prospect that health care overall will be substantially better served if the professional makes a principled exit than if he or she continues to exert a strong voice for change within the organization. Because a principled exit is sometimes easier than disobedience, particular care should be taken to avoid distorted versions of it. A self-righteous exit helps no one in need (and actually does harm by eliminating a potential source of advocacy) and primarily serves the dissenter's self-image. This type of exit is an act of self-righteousness or even cowardice masquerading as professionalism. In the right circumstances, however, an exit may be both honorable and courageous. In one very unusual circumstance, professional disobedience and exit were chosen simultaneously by a group of physicians as the only way to maintain the moral base of medical practice: Dutch physicians in World War II turned in their licenses but continued to practice underground, to avoid practicing under Nazi rule.³⁴ The extreme nature of this example illustrates the burden of proof that those who wish to exit must meet before claiming that such an action is necessary to maintain professionalism.

CONCLUSIONS

We believe there is an essential role for professionalism in society that market-driven and government-controlled health care alone cannot provide, and we propose three core elements of medical professionalism: devotion to service, profession of values, and negotiation within society. Each element can be misapplied, but in balance they offer normative guidance. The model calls on physicians to engage in professional activities along a spectrum of advocacy, thereby helping to preserve the decency and stability that are essential to civilized society.

MATTHEW K. WYNIA, M.D., M.P.H.

American Medical Association
Chicago, IL 60610

STEPHEN R. LATHAM, J.D., PH.D.

Quinnipiac School of Law
New Haven, CT 06518

AUDIEY C. KAO, M.D., PH.D.

JESSICA W. BERG, J.D.

LINDA L. EMANUEL, M.D., PH.D.

American Medical Association
Chicago, IL 60610

The opinions expressed in this article are those of the authors and may not reflect the official policies of the American Medical Association.

We are indebted to Professors Robert Baker, Edmund Pellegrino, Dennis Thompson, Eliot Freidson, Thomas Donaldson, and Henry Richardson and Mr. Robert Dwek for critiquing the manuscript in important ways, especially by insisting on a clear moral foundation for our understanding of professionalism; and to Julie Powers for assisting in the preparation of the manuscript.

REFERENCES

1. Grumbach K, Osmond D, Vranizan K, Jaffe D, Bindman AB. Primary care physicians' experience of financial incentives in managed-care systems. *N Engl J Med* 1998;339:1516-21.
2. Angell M. The doctor as double agent. *Kennedy Inst Ethics J* 1993;3:279-86.
3. Kassirer JP. Managed care and the morality of the marketplace. *N Engl J Med* 1995;333:50-2.
4. Feldman DS, Novack DH, Gracely E. Effects of managed care on physician-patient relationships, quality of care, and the ethical practice of medicine. *Arch Intern Med* 1998;158:1626-32.
5. Kao AC, Green DC, Zaslavsky AM, Koplan JP, Cleary PD. The relationship between method of physician payment and patient trust. *JAMA* 1998;280:1708-14.
6. Blumenthal D. Effects of market reforms on doctors and their patients. *Health Aff (Millwood)* 1996;15(2):170-84.
7. Anders G. Health against wealth: HMOs and the breakdown of medical trust. Boston: Houghton Mifflin, 1996.
8. Sullivan WM. What is left of professionalism after managed care? *Hastings Cent Rep* 1999;29:7-13.
9. Donelan K, Blendon RJ, Lundberg GD, et al. The new medical marketplace: physicians' views. *Health Aff (Millwood)* 1997;16(5):139-48.
10. Klein S. AMA to establish national collective bargaining unit. *American Medical News*. July 5, 1999;42:1, 34-5.
11. Parsons T. The professions and social structure. *Social Forces* 1939;17:457-67.
12. *Idem*. Essays in sociological theory. London: Free Press, 1954.
13. Vollmer HM, Mills DL. Professionalization. Englewood Cliffs, N.J.: Prentice-Hall, 1966.
14. Freidson E. Professional dominance: the social structure of medical care. Chicago: Aldine, 1970.
15. Krause EA. Death of the guilds: professions, states, and the advance of capitalism, 1930 to the present. New Haven, Conn.: Yale University Press, 1996.
16. Larson MS. The rise of professionalism: a sociological analysis. Berkeley: University of California Press, 1977.
17. Starr P. The social transformation of American medicine. New York: Basic Books, 1982.
18. Buchanan A. Is there a medical profession in the house? In: Spece R, Shimm D, Buchanan A, eds. Conflicts of interest in clinical practice and research. New York: Oxford University Press, 1996:105-36.
19. Freidson E. Professionalism reborn: theory, prophecy, and policy. Chicago: University of Chicago Press, 1994.
20. Curry R. Medicine for sale. Knoxville, Tenn.: Grand Rounds Press, 1992.
21. Gordon R, Simon S. The redemption of professionalism? In: Nelson R, Trubek D, Solomon R, eds. Lawyers' ideals/lawyers' practices: transformations in the American legal system. Ithaca, N.Y.: Cornell University Press, 1992:230-57.
22. Reuschmeyer D. Comparing legal professions cross-nationally: from a professions-centered approach to a state-centered approach. *Am Bar Found Res J* 1986(Summer):415-46.
23. Swick HM, Szenas P, Danoff D, Whitcomb ME. Teaching professionalism in undergraduate medical education. *JAMA* 1999;282:830-2.
24. Reynolds PP. Reaffirming professionalism through the education community. *Ann Intern Med* 1994;120:609-14.
25. Cruess RL, Cruess SR. Teaching medicine as a profession in the service of healing. *Acad Med* 1997;72:941-52.
26. Cruess RL, Cruess SR, Johnston SE. Renewing professionalism: an opportunity for medicine. *Acad Med* 1999;74:878-84.
27. Blumenthal D. The vital role of professionalism in health care reform. *Health Aff (Millwood)* 1994;13(1):252-6.
28. Emanuel L. Bringing market medicine to professional account. *JAMA* 1997;277:1004-5.
29. Pellegrino ED, Relman AS. Professional medical associations: ethical and practical guidelines. *JAMA* 1999;282:984-6.
30. Silove D. Doctors and the state: lessons from the Biko case. *Soc Sci Med* 1990;30:417-29.
31. Pellegrino ED. Guarding the integrity of medical ethics: some lessons from Soviet Russia. *JAMA* 1995;273:1622-3.
32. *Idem*. The Nazi doctors and Nuremberg: some moral lessons revisited. *Ann Intern Med* 1997;127:307-8.
33. Grodin MA, Annas GJ. Legacies of Nuremberg: medical ethics and human rights. *JAMA* 1996;276:1682-3.
34. Alexander L. Medical science under dictatorship. *N Engl J Med* 1949;241:39-47.
35. de Tocqueville A. Democracy in America. In: Mayer JP, translator. Garden City, N.Y.: Doubleday, 1969.
36. Dworkin R. Decline of the Mandarin class. *Baltimore Sun*. September 8, 1998:11A.
37. Orentlicher D. The influence of a professional association on physician behavior. *Albany Law Rev* 1994;57:582-605.
38. Council on Ethical and Judicial Affairs, American Medical Association. Caring for the poor. *JAMA* 1993;269:2533-7.
39. Lundberg GD, Bodine L. Fifty hours for the poor. *JAMA* 1987;258:3157.
40. Pellegrino ED. Altruism, self-interest, and medical ethics. *JAMA* 1987;258:1939-40.
41. Cunningham PJ, Grossman JM, St Peter RF, Lesser CS. Managed care and physicians' provision of charity care. *JAMA* 1999;281:1087-92.
42. Cunningham PJ. Pressures on safety net access: the level of managed care penetration and uninsurance rate in a community. *Health Serv Res* 1999;34(1):255-70.
43. Gray BH. Trust and trustworthy care in the managed care era. *Health Aff (Millwood)* 1997;16(1):34-49.
44. Kerr EA, Hays RD, Mittman BS, Siu AL, Leake B, Brook RH. Primary care physicians' satisfaction with quality of care in California capitated medical groups. *JAMA* 1997;278:308-12.
45. Jaklevic MC. Doc income still rising — AMA data. *Mod Healthcare* 1998;28(13):3.
46. Rodwin MA. Medicine, money, and morals: physicians' conflicts of interest. New York: Oxford University Press, 1993.
47. James C. "Hope" series returns with darker view of doctors. *New York Times*. September 23, 1999:B1, B9.
48. Cauthen DB. Luxurious cars: should physicians flaunt their wealth? *JAMA* 1989;262:1631.
49. Reinhardt UE. Resource allocation in health care: the allocation of life-styles to providers. *Milbank Q* 1987;65:153-76.
50. Pellegrino ED, Thomasma DC. A philosophical basis of medical practice. Oxford, England: Oxford University Press, 1981.
51. Boswell J. Life of Johnson. Oxford, England: Oxford University Press, 1904.
52. Pellegrino ED. The medical profession as a moral community. *Bull N Y Acad Med* 1990;66:221-32.
53. Orr RD, Pang N, Pellegrino ED, Siegler M. Use of the Hippocratic Oath: a review of twentieth century practice and a content analysis of oaths administered in medical schools in the U.S. and Canada in 1993. *J Clin Ethics* 1997;8:377-88.
54. Veatch RM. A theory of medical ethics. New York: Basic Books, 1981.
55. Brody H, Bonham VL Jr. Gag rules and trade secrets in managed care contracts: ethical and legal concerns. *Arch Intern Med* 1997;157:2037-43.
56. Weber M. Economy and society: an outline of interpretive sociology. New York: Bedminster Press, 1968.
57. Emanuel L. Professionalism and accountability in managed care. In: American Board of Internal Medicine Report of the 1996 Summer Conference. Philadelphia: American Board of Internal Medicine, 1996:67-72.
58. Cohen C. Militant morality: civil disobedience and bioethics. *Hastings Cent Rep* 1989;19(6):23-5.
59. Morreim EH. Balancing act: the new medical ethics of medicine's new economics. Washington, D.C.: Georgetown University Press, 1995.
60. Ziv TA, Lo B. Denial of care to illegal immigrants: Proposition 187 in California. *N Engl J Med* 1995;332:1095-8.
61. Woolhandler S, Himmelstein DU. Extreme risk — the new corporate proposition for physicians. *N Engl J Med* 1995;333:1706-8.

©1999, Massachusetts Medical Society.



INFORMATION FOR AUTHORS

These guidelines are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." (The complete document appears in N Engl J Med 1997;336:309-15.)

MANUSCRIPTS Manuscripts containing original material are accepted for consideration if neither the article nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the *Journal*. This restriction does not apply to abstracts or press reports published in connection with scientific meetings. Authors should submit to the Editor copies of any published papers or other manuscripts in preparation or submitted elsewhere that are related to the manuscript to be considered by the *Journal*. The *Journal* discourages the submission of more than one article dealing with related aspects of the same study.

Submit an original manuscript with one set of original figures and two copies of the complete manuscript. Manuscripts must be no longer than 3000 words. Please supply a word count (not including abstract or references). Use standard-sized paper, and triple-space throughout. Address all submissions to the Editor, New England Journal of Medicine, 10 Shattuck St., Boston, MA 02115-6094. A covering letter signed by all authors should identify the person (with the address and telephone number) responsible for negotiations concerning the manuscript; the letter should make it clear that the final manuscript has been seen and approved by all authors and that they have taken due care to ensure the integrity of the work. At least one person's name must accompany a group name — e.g., Thelma J. Smith, for the Boston Porphyria Group. As stated in the Uniform Requirements (see above), credit for authorship requires substantial contributions to: (a) conception and design, or analysis and interpretation of data; and (b) the drafting of the article or critical revision for important intellectual content. If more than 12 authors are listed for a multicenter trial, or more than 8 for a study from a single institution, each author must sign a statement attesting that he or she fulfills the authorship criteria of the Uniform Requirements. No more than 12 names will be listed under the title; other names will appear in a footnote. Acknowledgments will be limited to a column of *Journal* space, and those acknowledged will be listed only once. (See editorial, Nov. 21, 1991, issue.)

LETTERS TO THE EDITOR See the *Journal* correspondence section.

CONFLICT OF INTEREST Authors of research articles should disclose at the time of submission any financial arrangement they may have with a company whose product figures prominently in the submitted manuscript or with a company making a competing product. Such information will be held in confidence while the paper is under review and will not influence the editorial decision, but if the article is accepted for publication, the editors will usually discuss with the authors the manner in which such information is to be communicated to the reader.

Because the essence of reviews and editorials is selection and interpretation of the literature, the *Journal* expects that authors of such articles will not have any financial interest in a company (or its competitor) that makes a product discussed in the article.

COPYRIGHT Authors agree to execute copyright transfer forms as requested. Copyright in any contribution is owned by the Massachusetts Medical Society. The Society and its licensees have the right to use, reproduce, transmit, derivate, publish, and distribute the contribution, in the *Journal* or otherwise, in any form or medium. Authors will not use or authorize the use of the contribution without the Society's written consent, except as may be allowed by U.S. fair use law.

UNITS OF MEASUREMENT Authors should express all measurements in conventional units, with Système International (SI) units given in parentheses throughout the text. Figures and tables should use conventional units, with conversion factors given in legends or footnotes. In accordance with the Uniform Requirements, however, manuscripts containing only SI units will not be returned for that reason.

TITLES AND AUTHORS' NAMES With the manuscript, provide a page giving the title of the paper; titles should be concise and descrip-

tive (not declarative). Also include a running head of fewer than 40 letter spaces; the name(s) of the author(s), including the first name(s) and no more than two graduate degrees; the name of the department and institution in which the work was done; the institutional affiliation of each author; and the name and address of the author to whom reprint requests should be addressed. Any grant support that requires acknowledgment should be mentioned on this page.

ABSTRACTS Provide on a separate page an abstract of not more than 250 words. This abstract should consist of four paragraphs, labeled Background, Methods, Results, and Conclusions. They should briefly describe, respectively, the problem being addressed in the study, how the study was performed, the salient results, and what the authors conclude from the results.

KEY WORDS Three to 10 key words or short phrases should be added to the bottom of the abstract page; these will help us index the article and may be published with the Abstract. Use terms from the Medical Subject Headings from *Index Medicus*.

REFERENCES References must be triple-spaced and numbered consecutively as they are cited. References first cited in tables or figure legends must be numbered so that they will be in sequence with references cited in the text. The style of references is that of *Index Medicus*. List all authors when there are six or fewer; when there are seven or more, list the first three, then "et al." The following is a sample reference:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylprocainamide. *N Engl J Med* 1979;301:1382-5.

Numbered references to personal communications, unpublished data, and manuscripts either "in preparation" or "submitted for publication" are unacceptable (see "Permissions"). If essential, such material may be incorporated in the appropriate place in the text.

TABLES Double-space tables and provide a title for each. If an article is accepted, the *Journal* will arrange to deposit extensive tables of important data with the National Auxiliary Publications Service (NAPS); we will pay for the deposit and add an appropriate footnote to the text. This service makes available microfiche or photocopies of tables at moderate charges to those who request them.

ILLUSTRATIONS Figures should be professionally designed. Symbols, lettering, and numbering should be clear and large enough to remain legible after the figure has been reduced to fit the width of a single column.

The back of each figure should include the sequence number, the name of the author, and the proper orientation (e.g., "top"). Do not mount the figure on cardboard. Photomicrographs should be cropped to a width of 8 cm, and electron photomicrographs should have internal scale markers.

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permission to use the figure. Permission forms are available from the Editor.

Legends for illustrations should be triple-spaced on a separate sheet and should not appear on the illustrations.

Color illustrations are encouraged. Send both transparencies and prints for this purpose.

ABBREVIATIONS Except for units of measurement, abbreviations are discouraged. Consult *Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers* (Sixth edition. New York: Cambridge University Press, 1994) for lists of standard abbreviations. The first time an abbreviation appears it should be preceded by the words for which it stands.

DRUG NAMES Generic names should generally be used. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

PERMISSIONS Materials taken from other sources must be accompanied by a written statement from both author and publisher giving permission to the *Journal* for reproduction.

Obtain permission in writing from at least one author of papers still in press, unpublished data, and personal communications.

REVIEW AND ACTION Manuscripts are examined by the editorial staff and are usually sent to outside reviewers. We encourage authors to suggest the names of possible reviewers, but we reserve the right of final selection. Only one copy of rejected manuscripts will be returned, usually within six weeks. Decisions about potentially acceptable manuscripts may take longer.