

The New England Journal of Medicine

Owned and Published by the
Massachusetts Medical Society

Philip E. McCarthy, M.D.
President

William M. McDermott, Jr., M.D.
Executive Vice President

Charles S. Amoroso, Jr.
Executive Secretary

THE COMMITTEE ON PUBLICATIONS OF THE MASSACHUSETTS MEDICAL SOCIETY

James F. McDonough, M.D., *Chairman*

Henry H. Banks, M.D. Edward E. Jacobs, Jr., M.D.
Frank E. Bixby, Jr., M.D. Daniel Miller, M.D.
Howard M. Ecker, M.D. Udayan Shah
James Froehlich, M.D. Percy W. Wadman, M.D.
James B. Hanshaw, M.D., John I. Sandson, M.D., *Advisers*

Arnold S. Relman, M.D., *EDITOR-IN-CHIEF EMERITUS*
Jerome P. Kassirer, M.D., *EDITOR-IN-CHIEF*
Marcia Angell, M.D., *EXECUTIVE EDITOR*
Edwin W. Salzman, M.D., *DEPUTY EDITOR*
Gregory D. Curfman, M.D., *DEPUTY EDITOR*
Edward W. Campion, M.D., *DEPUTY EDITOR*
Robert D. Utiger, M.D., *DEPUTY EDITOR*

ASSOCIATE EDITORS

Jane F. Desforges, M.D. Morton N. Swartz, M.D.
Ronald A. Malt, M.D. Franklin H. Epstein, M.D.
Lee Goldman, M.D.

Robert S. Schwartz, M.D., *BOOK REVIEW EDITOR*
Frederick Mosteller, Ph.D., Walter Willett, M.D.
STATISTICAL CONSULTANTS

John K. Iglehart, *NATIONAL CORRESPONDENT*

Marlene A. Thayer, *EDITORIAL OFFICE MANAGER*
Stephen E. Cinto, *MANAGER OF EDITORIAL PRODUCTION*
Lorraine W. Loviglio, *MANAGER OF MANUSCRIPT EDITING*

EDITORIAL BOARD

Mary Ellen Avery, M.D. Peter T. Macklem, M.D.
David Baltimore, Ph.D. Robert J. Mayer, M.D.
John G. Bartlett, M.D. Kenneth McIntosh, M.D.
Eugene Braunwald, M.D. Stuart H. Orkin, M.D.
Harvey R. Colten, M.D. Peter Reich, M.D.
Robert M. Donaldson, Jr., M.D. Uwe E. Reinhardt, Ph.D.
Richard H. Egdahl, M.D. B. Lawrence Riggs, M.D.
Bernard G. Forget, M.D. Lewis P. Rowland, M.D.
Antonio M. Gotto, Jr., M.D., D.Phil. Kenneth J. Ryan, M.D.
Thomas B. Graboyes, M.D. Harold C. Sox, M.D.
Martin S. Hirsch, M.D. Paul D. Stolley, M.D.
Norman K. Hollenberg, M.D., Ph.D. Jean D. Wilson, M.D.

EDITORIAL OFFICES

Timothy S. Anderson, *Editorial Production Assistant*; Karen M. Daly, *Editorial Assistant*; Briana Doherty, *Editorial Assistant*; Kathleen Eagan, *Editorial Assistant*; Dale R. Golden, *Editorial Assistant*; Christie L. Hager, *Research Assistant*; Susan L. Kaplan, *Editorial Production Layout Artist*; David F. March, *Manuscript Editor*; Sandra S. McLean, *Manuscript Editor*; Brian Middleton, *Editorial Assistant*; Henry S. Miller, Jr., *Manuscript Editor*; Stephen Morrissey, *Manuscript Editor*; Sylvia L. Parsons, *Editorial Assistant*; Marilyn Seaquist, *Receptionist*; Deborah A. Stone, *Senior Editorial Production Coordinator*; Pamela S. Stryjewski, *Editorial Production Proofreader*; Nancy B. Watkins, *Editorial Production Assistant*.

Robert D. Bovenschulte, *VICE PRESIDENT FOR PUBLISHING*

BREAST-FEEDING IN 1991

THE national and international medical community strongly advocates breast-feeding for the first three to six months of an infant's life.^{1,2} In less developed countries, the greatest virtues of breast milk are that it is economical, highly nutritious, and used instead of potentially contaminated or nutritionally inadequate alternatives. Commercial formulas may be diluted with contaminated water, and refrigerated storage is frequently unavailable. Illiterate and impoverished mothers may dilute formulas improperly or purposely overdilute them in an attempt to save money for other essential needs. It is thus not surprising that for areas with inadequate sanitation, well-designed epidemiologic studies usually conclude that breast-feeding reduces infants' morbidity from infectious diseases and mortality.^{3,4}

Human milk is remarkably rich in immune components.^{5,6} Community-based epidemiologic studies do not support the view that these components necessarily have a direct role in the protective effect of breast milk on infant mortality, but such components (especially organism-specific IgA) can modify diarrheal symptoms. A more direct role for breast milk in preventing infection and death is most convincingly shown in studies of hospitalized, high-risk newborns (those who are born prematurely or have intrauterine growth retardation).⁷ Thus, the immune components of breast milk may increase the chance of survival for at least low-birth-weight newborns in both underdeveloped and economically developed countries.

In countries such as the United States, sanitation is usually not a problem, and nutritionally adequate alternatives to breast milk are generally available. Thus, in the United States breast-feeding is usually not a measurable factor in infants' survival. Nonetheless, most physicians strongly encourage mothers of healthy, full-term infants to breast-feed their babies for at least three to six months. After six months, nutritional supplementation is needed but breast-feeding can continue. In the United States, breast-feeding can be most strongly defended in terms of its economic

PROSPECTIVE authors should consult "Information for Authors," which appears in the first issue of each month and may be obtained from the *Journal* Editorial Office (address below).

ARTICLES with original material are accepted for consideration with the understanding that, except for abstracts, no part of the data has been published, or will be submitted for publication elsewhere, before appearing here. NOTICES should be sent at least 30 days before publication date.

THE *Journal* does not hold itself responsible for statements made by any contributor. Statements or opinions expressed in the *Journal* reflect the views of the author(s) and not the official policy of the Massachusetts Medical Society unless so stated.

ALTHOUGH all advertising material is expected to conform to ethical standards, acceptance does not imply endorsement by the *Journal*.

MATERIAL printed in the *Journal* is covered by copyright. No part of this publication may be reproduced or transmitted in any form without written permission.

FOR information on subscriptions, permissions, reprints, and other services see the "Business Information for Readers" page preceding the Classified Advertising section.

EDITORIAL OFFICES: 10 Shattuck St., Boston, MA 02115-6094.

Telephone: (617) 734-9800. FAX: (617) 734-4457.

BUSINESS, SUBSCRIPTION OFFICES: 1440 Main St., Waltham, MA 02154-1649.

advantages (especially for low-income families), its potential effects on the clinical severity of gastrointestinal infections, the presumed beneficial effects on the maternal–infant interaction, the mother’s perceptions of that interaction, and its contribution to the mother’s confidence in her maternal capabilities. The importance of such intangible benefits of breast-feeding should not be underestimated.⁸

Breast milk is a truly impressive substance, but nothing human is perfect. In an article in this week’s issue of the *Journal*, Mennella and Beauchamp note in passing that the human immunodeficiency virus (HIV) — as well as other infectious agents — can be transmitted through breast milk.⁹ The authors’ concern about the potential transmission of HIV in their hypothetical “taste-testing” experiment is almost certainly alarmist in the context of their study. The probability of HIV infection in the breast-feeding women was likely to be extremely low, and their risk factors and antibody status could have been readily determined. In our culture, such hypothetical tasters are far more likely to be repelled by the idea of tasting breast milk from unknown women than to be infected with HIV through the tasting process. However, concern about transmission of HIV to the infant of an infected woman through her breast milk is valid, especially when risk factors for HIV infection are present.^{10,11} It has been recommended that infected mothers in locations with good sanitation should not breast-feed their infants. This recommendation does not apply to some less developed countries, however.^{12,13}

Mennella and Beauchamp discuss the deleterious effects of maternal alcohol consumption on the flavor of human milk and on the infants’ behavior.⁹ (Alcohol appears in breast milk in approximately the same concentration as in maternal serum.¹⁴) In the narrowest sense, their findings imply that physicians should be circumspect in recommending that mothers who have difficulty with breast-feeding consume small quantities of alcohol. In the trial-and-error path to resolving problems with breast-feeding, circumspection is always in order. Previous evaluations of alcohol have suggested that it may have either beneficial or harmful effects. Even more confusing, previous studies suggest that the beneficial effects of beer on lactation may be due to its nonalcoholic components.^{15,16} More broadly, physicians should review with breast-feeding mothers the transmissibility in breast milk of any drugs they may be taking, both prescription and nonprescription.^{14,17} Alcohol is only one of many drugs that have potential effects on the breast-feeding infant.

Finally, the authors elegantly document what most breast-feeding mothers have long known: to their infants, mothers are what they eat (and drink). An experienced nursing mother is usually aware of her infant’s reactions to her breast milk after her intake of various foods. The long-term effects of maternal intake on the breast-fed infant will probably remain conjectural for some time to come. One has only to taste the sweetness of breast milk or note its high sucrose content — approximated by artificial formulas — to wonder

whether it could contribute to a child’s subsequent affection for sweets.¹⁴ But that possibility is hardly reason to condemn breast milk. Concern about the long-term effects of alcohol in breast milk may be valid, but it is not supported by the studies cited by Mennella and Beauchamp and does not warrant proscribing an occasional alcoholic drink for a nursing mother. In the case of a nursing mother with substantial drug or alcohol intake I would be far more concerned about the effects on the mother’s parenting skills than about the effects on the infant’s own dietary preferences or substance use 30 years later.

With increasing urbanization and greater entry of women into the work force in both undeveloped and developed countries, it behooves physicians to remember that our encouragement of breast-feeding often conflicts with the practical imperatives faced by many young mothers. We should continue to encourage breast-feeding, but in individual instances this policy can safely be tempered with realism. For example, a young mother who must work despite her employer’s failure to support her attempts to breast-feed her child is poorly served by a physician who instills in her a sense of guilt or loss at not nursing her infant. Most important, if physicians are to encourage breast-feeding, we should support political and legislative initiatives that make this a practical choice for today’s mothers.

NAIEP, Centers for Disease Control
Atlanta, GA 30333

JANINE JASON, M.D.

This essay represents the opinion of Dr. Jason, and no official support or endorsement by the Centers for Disease Control is intended or should be inferred.

REFERENCES

1. World Health Organization. International code of marketing of breast-milk substitutes. Geneva: World Health Organization, 1981.
2. Committee on Nutrition, American Academy of Pediatrics. Pediatric nutrition handbook. 2nd ed. Elk Grove Village, Ill.: American Academy of Pediatrics, 1985.
3. Jason JM, Nieburg P, Marks JS. Mortality and infectious disease associated with infant-feeding practices in developing countries. Part 2. *Pediatrics* 1984;74:702-27.
4. Habicht J-P, DaVanzo J, Butz WP. Does breastfeeding really save lives, or are apparent benefits due to biases? *Am J Epidemiol* 1986;123:279-90.
5. Prentice A, Prentice AM, Cole TJ, Paul AA, Whitehead RG. Breast-milk antimicrobial factors of rural Gambian mothers. I. Influence of stage of lactation and maternal plane of nutrition. *Acta Paediatr Scand* 1984;73:796-802.
6. Hanson LA, Ahlstedt S, Andersson B, et al. Protective factors in milk and the development of the immune system. *Pediatrics* 1985;75:172-6.
7. Narayanan I, Prakash K, Prabhakar AK, Gujral VV. A planned prospective evaluation of the anti-infective property of varying quantities of expressed human milk. *Acta Paediatr Scand* 1982;71:441-5.
8. Jason J, van der Meer A. *Parenting your premature baby*. New York: Bantam/Dell Publishing, 1990.
9. Mennella JA, Beauchamp GK. The transfer of alcohol to human milk — effects on flavor and the infant’s behavior. *N Engl J Med* 1991;325:981-5.
10. Van de Perre P, Simonon A, Msellati P, et al. Postnatal transmission of human immunodeficiency virus type 1 from mother to infant — a prospective cohort study in Kigali, Rwanda. *N Engl J Med* 1991;325:593-8.
11. Pizzo PA, Butler KM. In the vertical transmission of HIV, timing may be everything. *N Engl J Med* 1991;325:652-4.
12. Special programme on AIDS statement: breast-feeding/breast milk and human immunodeficiency virus. Geneva: World Health Organization, 1987.
13. AAP issues statement on perinatal HIV infection. *Am Fam Physician* 1989;39(3):390-3.
14. Avery ME, Taeusch HW Jr, eds. *Shaffer’s diseases of the newborn*. 5th ed. Philadelphia: W.B. Saunders, 1984.
15. Grossman ER. Beer, breast-feeding, and the wisdom of old wives. *JAMA* 1988;259:1016.

16. De Rosa G, Corsello SM, Ruffilli MP, Della-Casa S, Pasargiklian E. Prolactin secretion after beer. *Lancet* 1981;2:934.
17. Committee on Drugs. The transfer of drugs and other chemicals into human breast milk. *Pediatrics* 1983;72:375-83.

CIRCADIAN VARIATION AND CARDIOVASCULAR DISEASE

A MORNING increase in the risk of acute cardiovascular disorders — transient myocardial ischemia, myocardial infarction, sudden cardiac death, and stroke — is now well documented and widely accepted by both the medical profession and the public. Over the past five years, several investigators have demonstrated that this apparent curiosity can offer clues to the mechanisms of onset of acute cardiovascular disease. The article by Panza et al. in this issue of the *Journal*¹ is an important addition to this emerging field of study.

The authors demonstrated convincingly in normal subjects that forearm vascular resistance, as determined by plethysmography, is higher in the morning than at other times of day. They then determined that the increase in resistance was due to alpha-adrenergic activity, since it was abolished by the intraarterial infusion of an alpha-blocking agent. The experiment was well designed, the difficult measurements were properly performed, and the appropriate controls were included. As the authors note, the importance of this morning increase in vascular tone is that it could “contribute to higher blood pressure and the increased incidence of cardiovascular events at this time of day.”

This highly focused study leaves several important questions unanswered. Would results be similar in patients with hypertension or coronary artery disease, who have a higher incidence of cardiovascular events than normal subjects? Is coronary-artery tone also increased in the morning, as suggested by the existence of a lower threshold for morning ischemia, which the same group of researchers demonstrated previously?² Do the vascular responses to postural change, physical exertion, and mental stress also show a circadian variation? What is the relation of the increase in vascular tone to plasma levels of catecholamines, renin, and atrial natriuretic factor, a vasoactive agent known to be released in a pattern with circadian variation?³ What is the importance of the absence of a morning increase in vascular tone in 2 of the 12 subjects studied? Would these subjects be more likely to have an acute event at a different time of day? Do patients with diabetes or heart failure, who have altered circadian patterns of the timing of myocardial infarction, have altered circadian patterns of vascular tone?⁴

The present study is important not only in explaining circadian variation but also for its contribution to the more general concept of the “triggering” of acute cardiovascular events at any time of day. The authors note that their study supports “the view that certain dynamic physiologic mechanisms contribute to, and even trigger, the onset of acute cardiovascular events.”

The concept of triggering is most clearly formulated in the case of myocardial infarction, the acute event for which the best information about onset is available. Data from autopsy and catheterization studies have clearly established that most myocardial infarctions are caused by an occlusive thrombus overlying a ruptured atherosclerotic plaque.^{5,6} This information, together with the recognition of circadian variation, has led to a hypothesis of the triggering of acute myocardial infarction.⁷ The first step in the process is postulated to be the rupture of a “vulnerable” atherosclerotic plaque caused by hemodynamic forces resulting from physical or mental stress. The resulting thrombus may then become occlusive because of conditions causing increased coagulability or vasoconstriction.

Myocardial infarction that occurs after shoveling snow — a trigger that has been recognized for many years — exemplifies the triggering hypothesis and underscores the potential importance of the present study of vasomotor tone.⁸ The myocardial infarction may occur when a person with a vulnerable atherosclerotic plaque arises in the morning and begins shoveling vigorously in the cold. The exertion causes a sudden increase in arterial pressure (potentiated by the cold temperature and the increased systemic arterial tone in the morning), and the plaque ruptures. Initially, a nonobstructive mural thrombus forms over the exposed collagen of the ruptured plaque, producing no acute symptoms. However, because of relatively increased platelet aggregability⁹ and decreased fibrinolytic activity in the morning,¹⁰ the thrombus grows rapidly and occludes the lumen. Increased coronary tone may also contribute to the complete obstruction of the lumen by the plaque and its thrombus. The infarction is thus caused by the simultaneous presence of a number of factors, benign when they appear alone but potentially lethal in combination.

Studies of aspirin and beta-adrenergic blockers — two agents that reduce the frequency of myocardial infarction — support this hypothetical sequence of events. In the Physicians' Health Study, aspirin, which reduces the activity of platelets, was most effective in preventing infarction in the morning, when platelet activity is increased.¹¹ Beta-adrenergic-blocking agents also appear to diminish the morning increase in rates of myocardial infarction and sudden cardiac death, presumably by blocking the morning surge in sympathetic activity.^{8,12}

The findings of Panza et al. do not yet have direct clinical importance. The broader topic of circadian variation, however, already suggests the importance of 24-hour protection for patients currently taking antiischemic or antihypertensive medications. Although some investigators have questioned the safety of morning exercise, any postulated short-term increase in the relative risk of morning as compared with evening exertion is likely to be far outweighed by the long-term beneficial effects of exercise.

The most exciting aspect of the knowledge gained thus far about the timing of the onset of cardiovascular events is the potential for extending recent progress in the treatment of the disease to include prevention