

ressed a  
latively  
virtually  
CPR we  
as we  
that pa-  
ergoing  
no con-  
acts, we  
o often  
atient's  
is. Both  
are im-  
CPR. In  
ess, the  
atient's  
rder for  
ditions  
fficient  
f CPR  
ecision  
ted un-  
it and  
eir pa-  
sion to

t, how-  
re, the  
al care  
in the  
sponse  
atment  
h cases  
CPR.  
terms  
death

, M.D.

rdiac mas-

diopulmo-

itation in  
4ed 1984;

uglas RG  
hysicians'  
JA 1986;

oulton C,  
ions in a  
hospitals.

rders for  
at is their

ventions:  
ed 1986;

9. Gulati RS, Bhan GL, Horan MA. Cardiopulmonary resuscitation of old people. *Lancet* 1983; 2:267-9.
10. Bedell SE, Delbanco TL, Cook EF, Epstein FH. Survival after cardiopulmonary resuscitation in the hospital. *N Engl J Med* 1983; 309: 569-76.
11. Peatfield RC, Sillett RW, Taylor D, McNicol MW. Survival after cardiac arrest in hospital. *Lancet* 1977; 1:1223-5.
12. Hershey CO, Fisher L. Why outcome of cardiopulmonary resuscitation on general wards is so poor. *Lancet* 1982; 1:31-4.
13. Johnson AL, Tanser PH, Ulan RA, Wood TE. Results of cardiac resuscitation in 552 patients. *Am J Card* 1967; 20:831-5.
14. Füsgen I, Summa J-D. How much sense is there in an attempt to resuscitate an aged person? *Gerontology* 1978; 24:37-45.
15. Messert B, Quagliari CE. Cardiopulmonary resuscitation: perspectives and problems. *Lancet* 1976; 2:410-2.
16. Scott RPF. Cardiopulmonary resuscitation in a teaching hospital: a survey of cardiac arrests occurring outside intensive care units and emergency rooms. *Anaesthesia* 1981; 36:526-30.
17. Hollingsworth JH. The results of cardiopulmonary resuscitation: a 3-year university hospital experience. *Ann Intern Med* 1969; 71:459-66.
18. Castagna J, Weil MH, Shubin H. Factors determining survival in patients with cardiac arrest. *Chest* 1974; 65:527-9.
19. Camarata SJ, Weil MH, Hanashiro PK, Shubin H. Cardiac arrest in the critically ill. I. A study of predisposing causes in 132 patients. *Circulation* 1971; 44:688-95.
20. DeBard ML. Cardiopulmonary resuscitation: analysis of six years' experience and review of the literature. *Ann Emerg Med* 1981; 10:408-16.
21. Lemire JG, Johnson AL. Is cardiac resuscitation worthwhile? A decade of experience. *N Engl J Med* 1972; 286:970-2.

**CORRESPONDENCE**

**ALCOHOL AND BREAST CANCER**

To the Editor: The editorial on alcohol and breast cancer (May 7 issue)<sup>1</sup> underscores the need for more research on the topic because of several shortcomings of the epidemiologic information available: (1) the incidence of breast cancer is higher in upper socioeconomic groups, (2) follow-up studies in the past have been based on insufficient numbers of subjects or have had too short a period of follow-up, and (3) selection bias in hospitals may be due to admission practices or a particular organization of the health care delivery system in a given general population. To this list could be added a lack of record linkage and means of identification.

Since most of these difficulties were overcome in the Gothenburg Population Cohort Study,<sup>2-4</sup> it might be of interest to report that in the general population of Gothenburg, no association at all was evident between breast cancer and alcohol-related conditions among native-born Swedish women who were 30 to 59 years old at the outset of 10 years of follow-up (Table 1). Moreover, although alcohol-related conditions varied significantly with the preceding marital status, breast cancer did not (Table 2).

Thus, within the study design of a general white population that was both ethnically and socioeconomically homogeneous, among

Table 1. Expected and Observed Cases of Breast Cancer with Coexisting Alcohol-Related Conditions among Gothenburg Women Followed for 10 Years.\*

	EXPECTED†	OBSERVED
Breast cancer (n = 1123) and alcoholism (n = 229)	3.19	5
Breast cancer (n = 1123) and liver cirrhosis (n = 232)	3.23	3
Breast cancer (n = 1123) and pancreatitis (n = 204)	2.84	3

\*The Gothenburg Population Cohort Study population contained 80,563 subjects.<sup>2-4</sup>

†Values are underestimates because of excess mortality and, hence, a reduced average period of observation.

Table 2. Ten-Year (1970-1979) Prevalence Rate of Breast Cancer and Selected Alcohol-Related Conditions, According to Age Group and Preceding Marital Status.\*

	WOMEN BORN IN 1911-22 (AGED 48-59 AT START OF FOLLOW-UP)			
	NEVER MARRIED (N = 3665)	MARRIED (N = 27,497)	DIVORCED (N = 3577)	WIDOWED (N = 2479)
	cumulated prevalence rate/1000 general population, as of November 1969			
Breast cancer	21.8	19.2	18.5	17.4
Alcoholism	1.1	2.3	8.1	5.7
Liver cirrhosis	2.2	3.4	6.2	5.7
Pancreatitis	3.0	2.7	5.9	4.0
	WOMEN BORN IN 1923-40 (AGED 30-47 AT START OF FOLLOW-UP)			
	NEVER MARRIED (N = 4795)	MARRIED (N = 34,120)	DIVORCED (N = 3826)	WIDOWED (N = 604)
	cumulated prevalence rate/1000 general population, as of November 1969			
Breast cancer	11.1	9.2	9.2	6.6
Alcoholism	2.1	1.9	11.5	1.7
Liver cirrhosis	1.7	1.6	7.8	3.3
Pancreatitis	2.1	1.7	4.7	5.0

\*Distributional heterogeneity with marital status for breast cancer non-significant (P>0.05), for alcoholism P<0.001, for liver cirrhosis P<0.01 (older women) and P<0.001 (younger women), and for pancreatitis P<0.01 (older women) and P<0.001 (younger women).

the 1123 cases of breast cancer seen at the only general hospital serving this population during a 10-year follow-up period, we were unable to confirm the suggested association between breast cancer and alcohol consumption.

BENGT LINDEGÅRD, M.D.

S-421 05 Västra Frölunda, Sweden University of Gothenburg

1. Graham S. Alcohol and breast cancer. *N Engl J Med* 1987; 316:1211-3.
2. Lindegård B, Langman MJS. Marital state, alcohol consumption, and liability to myocardial infarction, stroke, diabetes mellitus, or hypertension in men from Gothenburg. *Br Med J* 1985; 291:1529-33.
3. Lindegård B. Survival and age at diagnosis in breast cancer. *N Engl J Med* 1987; 316:750-1.
4. Lindegård B, Hillbom M, Brody S. High-dose estrogen-progestagen oral contraceptives: a risk factor for aneurysmal subarachnoid hemorrhage. *Acta Neurol Scand* 1987; 76:37-45.

Letters to the Editor are considered for publication (subject to editing and abridgment), provided that they are submitted in duplicate, signed by all authors, typewritten in double spacing, and do not exceed 40 typewritten lines of manuscript text (excluding references). Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various editions (print, data base, and optical disk) in anthologies, revisions, and any other form or medium. Letters should not duplicate similar material being submitted or published elsewhere, and they should not contain abbreviations. Financial associations or other possible conflicts of interest should always be disclosed.

Letters referring to a recent *Journal* article must be received within six weeks of the article's publication. We are unable to provide pre-publication proofs, and unpublished material will not be returned to authors unless a stamped, self-addressed envelope is enclosed.

*To the Editor:* In the article by Schatzkin et al. (May 7 issue),<sup>1</sup> Table 1 shows their identified risk factors, including body-mass index, which was divided into three categories. The formula for body-mass index is given as  $(wt[kg]/ht[cm]^2)$ . Body-mass index closely correlates with body fat,<sup>2</sup> but the formula listed in Table 1 is not correct, although the categories reflect a correct use of the formula. The correct formula is  $(wt[kg]/ht[meters]^2)$ .

HERBERT L. MUNCIE, JR., M.D.  
University of Maryland  
School of Medicine  
Baltimore, MD 21201

- Schatzkin A, Jones DY, Hoover RN, et al. Alcohol consumption and breast cancer in the Epidemiologic Follow-up Study of the first National Health and Nutrition Examination Survey. *N Engl J Med* 1987; 316:1169-73.
- Bray GA. The obese patient. In: Smith LH Jr, ed. Major problems in internal medicine. Vol. 9. Philadelphia: W.B. Saunders, 1976.

*To the Editor:* Recently, results of two epidemiologic studies linked even moderate alcohol consumption with significant increases in the likelihood of development of breast cancer (the relative risk ranged from 1.4 to 1.6).<sup>1,2</sup> Considering that alcohol consumption is almost universally associated with psychosocial factors, including stress,<sup>3,4</sup> it is important that these data be interpreted within the framework of alcohol "covariants," or behaviors that accompany or are triggered by alcohol consumption.

Although the confounding influence of several alcohol and cancer risk "covariants" (i.e., parity, dietary fat, and body weight) was considered by Willett et al.,<sup>2</sup> psychosocial factors were not. However, results from epidemiologic<sup>5,6</sup> and animal<sup>7,8</sup> studies indicate that emotionality (depression) and stress modify the risk of cancer. More important, these variables have been consistently linked to alcohol use.<sup>3,4</sup>

There are at least two routes of psychosocial modulation of the risk of breast cancer. First, the neurochemical correlates that accompany states of chronic stress, inadequate ways of coping with stress, and depression could produce functional disruption of systems whose integrity is instrumental in cancer risk (i.e., immunity).<sup>9</sup> For example, chronic elevation of the serum cortisol level is consistently associated with stress and depression<sup>10</sup> as well as alcoholism.<sup>11</sup> Furthermore, stress-associated increases in corticosterone have resulted in immunodeficiency and increased tumorigenicity in animals.<sup>9</sup>

Second, the presence of a given psychological state, such as stress, may increase the likelihood or frequency of a variety of behaviors, including smoking and alcohol consumption, that may also alter the risk of cancer.

Within this framework, Willett and colleagues' interpretation that both the dose-response effect of alcohol on cancer risk and the differential effect observed between wine consumption (no increase in risk) and the use of other alcoholic beverages (increased risk) enhance the likelihood of causality may be questioned. Rather, the finding of a different breast-cancer risk with wine as opposed to beer and liquor adds to the likelihood of confounding by psychosocial variables and reduces the likelihood of causality.

Confounding of alcohol intake as a factor in breast-cancer risk by extraneous psychosocial variables may be minimized by using animal models of mammary carcinogenesis.

GEORGIA ANDRIANOPOULOS, PH.D.  
RICHARD L. NELSON, M.D.  
University of Illinois at Chicago  
Chicago, IL 60680

- Schatzkin A, Jones DY, Hoover RN, et al. Alcohol consumption and breast cancer in the Epidemiologic Follow-up Study of the first National Health and Nutrition Examination Survey. *N Engl J Med* 1987; 316:1169-73.
- Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med* 1987; 316:1174-80.
- Powers R, Kutash IL. Stress and alcohol. *Int J Addict* 1985; 20:461-82.
- Linsky AS, Strauss MA, Colby JP. Stressful events, stressful conditions and alcohol problems in the United States: a partial test of Bale's theory. *J Stud Alcohol* 1980; 46:72-80.

- Graham S, Snell LM, Graham JB, Ford L. Social trauma in the epidemiology of cancer of the cervix. *J Chronic Dis* 1971; 24:711-25.
- Grossarth-Maticek R. Psychosocial predictors of cancer and internal diseases: an overview. *Psychother Psychosom* 1980; 33:122-8.
- Justice A. Review of the effects of stress on cancer in laboratory animals: importance of time of stress application and type of tumor. *Psychol Bull* 1985; 98:108-38.
- Riley V, Fitzmaurice MA, Spackman DH. Psychoneuroimmunologic factors in neoplasia: studies in animals. In: Ader R, ed. *Psychoneuroimmunology*. New York: Academic Press, 1981:31-94.
- Stein M, Keller SE, Schleifer SJ. Stress and immunomodulation: the role of depression and neuroendocrine function. *J Immunol* 1985; 135:827s-833s.
- Baumgartner A, Gräf K-J, Kürten I. The dexamethasone suppression test in depression, in schizophrenia, and during experimental stress. *Biol Psychiatry* 1985; 20:675-9.
- Swartz CM, Dunner FJ. Dexamethasone suppression testing of alcoholics. *Arch Gen Psychiatry* 1982; 39:1309-12.

*To the Editor:* Two recent *Journal* reports have confirmed earlier studies and clearly demonstrated that even moderate consumption of alcoholic beverages is an important risk factor for breast cancer.<sup>1,2</sup> Both papers offered a list of potential mechanisms for the alcohol effect, but concluded that the pathophysiologic mechanism or mechanisms remains to be established. Very recent data suggest an additional etiologic agent with respect to consumption of alcoholic beverages. Specifically, the phyto-estrogen biochanin A, as well as the ubiquitous plant steroidal compound  $\beta$ -sitosterol, have been isolated from and identified in bourbon; in addition, concentrates of bourbon have been shown to interact with uterine estrogen receptors in rabbits in a dose-dependent manner and to produce dose-related estrogenic responses in both the uterine mass and serum levels of luteinizing hormone in ovariectomized rats.<sup>3-5</sup>

Phyto-estrogens are nonsteroidal estrogenic substances of plant origin; known phyto-estrogens include flavonoids such as biochanin A and formononetin and their isoflavonoid metabolites, genistein and daidzein, respectively. The isoflavonoids are metabolized in the intestine by gut microflora to the estrogenic compound equol, in both animals and humans.<sup>6-9</sup> The estrogenic effects of some forage crops have long been recognized, and the responsible compounds have been isolated and identified.<sup>10-13</sup> More recent studies have shown that the above flavonoids, isoflavonoids, and equol interact with estrogen receptors.<sup>14,15</sup>

With respect to the link between alcoholic-beverage consumption and the development of breast cancer, it is particularly interesting to note that the phyto-estrogen biochanin A, which has been identified in bourbon, has been shown to interact with estrogen receptors in human breast-cancer cells,<sup>16</sup> and that  $\beta$ -sitosterol, which has also been found in bourbon, was long ago isolated and identified in human breast-cancer tissue.<sup>17</sup> Whether or not other alcoholic beverages also contain biologically active phyto-estrogens remains to be demonstrated; nevertheless, the results of the studies of bourbon suggest yet another pathway to be explored.

JUDITH S. GAVALER, PH.D., ELAINE R. ROSENBLUM, M.S.,  
PATRICIA K. EAGON, PH.D., DAVID H. VAN THIEL, M.D.,  
AND CLIFF POHL, PH.D.  
University of Pittsburgh School of Medicine

IAIN M. CAMPBELL, PH.D.  
University of Pittsburgh  
Faculty of Arts and Sciences  
Pittsburgh, PA 15261

- Schatzkin A, Jones DY, Hoover RN, et al. Alcohol consumption and breast cancer in the Epidemiologic Follow-up Study of the first National Health and Nutrition Examination Survey. *N Engl J Med* 1987; 316:1169-73.
- Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med* 1987; 316:1174-80.
- Gavaler JS, Imhoff AF, Pohl CR, Rosenblum ER, Van Thiel DH. Alcoholic beverages: A source of estrogenic substances? In: Lindros KO, Ylikahri R, Kianmaa K, eds. *Advances in biomedical alcohol research*. Oxford: Pergamon Press, 1987; 545-9.

4. Rosenblum ER, Van Thiel DH, Campbell IM, Eagon PK, Gavalier JS. Separation and identification of phyto-estrogenic compounds isolated from bourbon. In: Lindros KO, Ylikahri R, Kiianmaa K, eds. *Advances in biomedical alcohol research*. Oxford: Pergamon Press, 1987:551-5.
5. Gavalier JS, Rosenblum ER, Van Thiel DH, et al. Biologically active phytoestrogens are present in bourbon. *Alcoholism (NY)* 1987; 11:399-406.
6. Nilsson A, Hill JL, Davies HL. An *in vitro* study of formononetin and biochanin A metabolism in rumen fluid from sheep. *Biochim Biophys Acta* 1967; 148:92-8.
7. Lindsay DR, Kelly RW. The metabolism of phyto-oestrogens in sheep. *Aust Vet J* 1970; 46:219-22.
8. Griffiths LA, Barrow A. The fate of orally and parenterally administered flavonoids in the mammal: the significance of biliary excretion. *Angiologia* 1972; 9:162-74.
9. Axelson M, Kirk DN, Farrant RD, Cooley G, Lawson AM, Setchell KD. The identification of the weak oestrogen equol [7-hydroxy-3-(4'-hydroxyphenyl)chroman] in human urine. *Biochem J* 1982; 201:353-7.
10. Biggers JD, Curnow DH. Oestrogenic activity of subterranean clover. 1. The oestrogenic activity of genistein. *J Biochem (Tokyo)* 1954; 58:278-82.
11. Booth AN, Bickoff EM, Kohler GO. Estrogen-like activity in vegetable oils and mill by-products. *Science* 1960; 131:1807-8.
12. Guggolz J, Livingston AL, Bickoff EM. Detection of daidzein, formononetin, genistein, and biochanin A in forages. *J Agric Food Chem* 1961; 9:330-2.
13. Shutt DA. The effects of plant oestrogens on animal reproduction. *Endeavour* 1976; 35:110-3.
14. Shutt DA, Cox RI. Steroid and phyto-oestrogen binding to sheep uterine receptors *in vitro*. *J Endocrinol* 1972; 52:299-310.
15. Tang BY, Adams NR. Effect of equol on oestrogen receptors and on synthesis of DNA and protein in the immature rat uterus. *J Endocrinol* 1980; 85:291-7.
16. Martin PM, Horwitz KB, Ryan DS, McGuire WL. Phytoestrogen interaction with estrogen receptors in human breast cancer cells. *Endocrinology* 1978; 103:1860-7.
17. Gordan GS, Fitzpatrick ME, Lubich WP. Identification of osteolytic sterols in human breast cancer. *Trans Assoc Am Physicians* 1967; 80:183-9.

2. Schatzkin A, Jones DY, Hoover RN, et al. Alcohol consumption and breast cancer in the Epidemiologic Follow-up Study of the first National Health and Nutrition Examination Survey. *N Engl J Med* 1987; 316:1169-73.
3. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med* 1987; 316:1174-80.
4. Reiter RJ, ed. *The pineal gland*. Vols. I, II, III. Boca Raton, Fla.: CRC Press, 1981.
5. Lewy AJ, Wehr TA, Goodwin FK, Newsome OA, Markey SP. Light suppresses melatonin secretion in humans. *Science* 1980; 210:1267-9.
6. Cohen M, Lippman M, Chabner B. Role of pineal gland in aetiology and treatment of breast cancer. *Lancet* 1978; 2:814-6.
7. Tamarkin L, Cohen M, Rosele D, Reichert C, Lippman M, Chabner B. Melatonin inhibition and pinealectomy enhancement of 7,12-dimethylbenz(a)anthracene-induced mammary tumors in the rat. *Cancer Res* 1981; 41:4432-6.
8. Shah PN, Mhatre MC, Kothari LS. Effect of melatonin on mammary carcinogenesis in intact and pinealectomized rats in varying photoperiods. *Cancer Res* 1984; 44:3403-7.
9. Blask DE, Hill SM. Effects of melatonin on cancer: studies on MCF-7 human breast cancer cells in culture. *J Neural Transm [Suppl]* 1986; 21:433-49.
10. Stevens RG. Electric power use and breast cancer: a hypothesis. *Am J Epidemiol* 1987; 125:556-61.
11. Wilson BW. Chronic exposure to ELF fields may induce depression. *Bioelectromagnetics* (in press).
12. Moss HB, Tamarkin L, Majchrowicz E, Martin PR, Linnoila M. Pineal function during ethanol intoxication, dependence, and withdrawal. *Life Sci* 1986; 39:2209-14.
13. Wetterberg L. Melatonin in humans: physiological and clinical studies. *J Neural Trans [Suppl]* 1978; 13:289-310.

*To the Editor:* Evidence is mounting that alcohol consumption may increase the risk of breast cancer in women.<sup>1-5</sup> A possible biologic mechanism for this effect may be an ethanol-induced alteration of the normal circadian rhythm of melatonin secretion from the pineal gland. Melatonin has strong effects on mammalian gonadal function,<sup>4</sup> and its circulating levels are acutely suppressed by light.<sup>5</sup> Cohen et al.<sup>6</sup> have suggested that suppression of the normal nocturnal rise in melatonin production may increase the risk of breast cancer by leading to unopposed estrogen production. Tamarkin et al.<sup>7</sup> tested this hypothesis in rats and found that pinealectomy enhanced, and melatonin injection inhibited, chemically induced mammary cancer. Constant exposure to light produces a "functional pinealectomy" and can also enhance chemically induced mammary cancer in rats.<sup>8</sup> Shah et al.<sup>9</sup> postulated that nighttime suppression of melatonin may lead to nighttime elevation of prolactin and estrogen production, which in turn may lead to increased turnover of the breast epithelial stem cells at risk. Melatonin also exerts mitostatic action on certain cancer cell lines,<sup>9</sup> and hence reduction of melatonin may increase the chances that a breast-cancer cell would survive. Disruption of melatonin rhythm has been suggested as a possible mechanism by which the use of electrical power may affect the risk of breast cancer<sup>10</sup> and depression.<sup>11</sup>

Alcohol consumption can reduce melatonin production in rats,<sup>12</sup> and persons with chronic alcoholism studied by Wetterberg had a depressed nocturnal peak in serum melatonin.<sup>13</sup> Alcohol may therefore increase the risk of breast cancer because of a reduction in the nocturnal rise in melatonin. This hypothesis can be tested by measuring nocturnal melatonin production in humans at various levels of alcohol consumption.

RICHARD G. STEVENS, PH.D.  
Pacific Northwest Laboratory  
Richland, WA 99352

ROBERT A. HIATT, M.D.  
Kaiser-Permanente Medical Care Program  
Oakland, CA 94611

1. Hiatt RA, Bawol RD. Alcoholic beverage consumption and breast cancer incidence. *Am J Epidemiol* 1984; 120:676-83.

*To the Editor:* Epidemiologic studies have demonstrated strong associations between alcohol consumption and an increased risk of carcinoma. Willett et al.<sup>1</sup> reported a statistically slightly higher frequency of breast cancer among women drinking beer and hard liquor, but not among those drinking wine. An earlier study, by Pollack et al.,<sup>2</sup> demonstrated an association between beer (but not wine) and carcinoma of the colon. These studies suggested the hypothesis that the relatively high sulfite content of wine as compared with other alcoholic beverages might have a protective or mitigating role with respect to carcinogenesis.

Sulfites are added to most wines and are used in their processing to prevent spoilage and discoloration. They are capable of interacting with free radicals that could play a part in carcinogenesis.<sup>3</sup> They have received recent attention because some people, notably asthmatics, have allergic reactions to sulfites. Wines generally have a much higher sulfite content than do other alcoholic beverages, and may be a major source of exogenous sulfite. Indeed, estimated consumption levels among U.S. citizens indicate a per capita intake of sulfite from food (expressed in sulfur dioxide equivalents) of approximately 6 mg per day. Beer and wine contribute additional amounts of 10 mg per liter and 30 mg per 200 ml, respectively.<sup>4</sup>

We recently demonstrated *in vitro* that the metabolism of ethanol by alcohol dehydrogenase in the presence of xanthine oxidase produces superoxide (as indicated by malondialdehyde generation from lipid membranes) due to the metabolism of acetaldehyde.<sup>5</sup> The addition of ferritin promoted this peroxidation, suggesting mobilization of catalytic iron superoxide. Acetaldehyde produced in the gastrointestinal tract and liver during the metabolism of ethanol (primarily by alcohol dehydrogenase) can be further metabolized by the ubiquitous enzyme xanthine oxidase, which is especially rich in these organs but is found in others as well. The resulting superoxide by itself, or through interconversion to other free radicals by catalytic iron, has been implicated in carcinogenesis due to activation of procarcinogens or direct cellular injury.<sup>6</sup> In bacterial mutagenicity studies *in vitro*, sulfites have been found to suppress mutagenic activity.<sup>7</sup>

In our own *in vitro* studies, we observed that sulfites in micromolar concentrations readily inhibit the generation of superoxide (from acetaldehyde-xanthine oxidase) (Table 1).

Differences in intake, metabolism (by sulfite oxidase), and other variables, including iron content and other congeners found in alco-

Table 1. Inhibition of Generation of Superoxide by Sulfite.

SULFITE ADDED	% INHIBITION OF MDA PRODUCTION*
1 $\mu$ M	21.5
5 $\mu$ M	70.5
10 $\mu$ M	100.0

\*Malondialdehyde (MDA) produced from acetaldehyde-xanthine oxidase, according to the method of MacLeod et al.<sup>3</sup>

holic beverages, may confound the relation between carcinogenesis and sulfite. For example, in the study by Pollack et al.<sup>2</sup> wine and whiskey but not beer were associated with an increased risk of cancer of the lung.

Investigation of the possible inhibitory or enhancing roles of sulfite in inducing and promoting cancer may provide useful insights into the mechanisms of alcohol-induced carcinogenesis.

VICTOR HERBERT, M.D., J.D.  
ELIZABETH JAYATILLEKE, M.S.  
SPENCER SHAW, M.D.

Bronx, NY 10468

Veterans Administration Medical Center

1. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med* 1987; 316:1174-80.
2. Pollack ES, Nomura AMY, Heilbrun LK, Stemmermann GN, Green SB. Prospective study of alcohol consumption and cancer. *N Engl J Med* 1984; 310:617-21.
3. MacLeod RM, Farkas W, Fridovich I, Handler P. Purification and properties of hepatic sulfite oxidase. *J Biol Chem* 1961; 236:1841-6.
4. Bush RK, Taylor SL, Busse W. A critical evaluation of clinical trials in reactions to sulfites. *J Allergy Clin Immunol* 1986; 78:191-202.
5. Shaw S, Jayatilake E. Acetaldehyde-mediated hepatic lipid peroxidation: role of superoxide and ferritin. *Biochem Biophys Res Commun* 1987; 143:984-90.
6. Ames BN. Dietary carcinogens and anticarcinogens: oxygen radicals and degenerative diseases. *Science* 1983; 221:1256-64.
7. Suwa Y, Nagao M, Kosugi A, Sugimura T. Sulfite suppresses the mutagenic property of coffee. *Mutat Res* 1982; 102:383-91.

*To the Editor:* The epidemiologic papers by Schatzkin and Willett and their colleagues report that moderate consumption of alcohol by women is associated with an increased risk of breast cancer. Although both groups indicate that the mechanism for this association is unknown, they speculate about whether prolactin, a known promoter of mammary cancer in rodents, could in some way link alcohol and an increased breast-cancer risk.

Both articles note the possibility that alcohol increases the risk of breast cancer through increased release of prolactin, as first suggested by Williams.<sup>1</sup> However, Williams did not show that alcohol had an effect on prolactin release, but merely speculated on such a possibility.<sup>3</sup> The available data on the relation between alcohol ingestion and serum prolactin levels in animals are conflicting. As pointed out by Willett et al., Schrauzer et al.<sup>2</sup> found that alcohol depressed serum prolactin levels in C3H mice while accelerating the appearance of spontaneous mammary cancers. Since the alcohol regimen in that study was excessive (15 percent ethanol in drinking water for 28 days), mammary carcinogenesis may have been promoted by some nonspecific mechanism (such as stress, nutritional imbalance, or poor health of the animals). Other studies document decreases,<sup>3</sup> increases,<sup>4</sup> or no apparent effect<sup>5,6</sup> of dietary ethanol on serum prolactin levels in rats. Most studies in humans have dealt with serum prolactin levels in chronic alcoholism and alcohol withdrawal, which has little relevance to the issue of breast cancer and moderate alcohol consumption. However, measurement of serum prolactin levels in healthy premenopausal women after acute ingestion of alcohol<sup>7,8</sup> does not support Williams' original suggestion.

As an outgrowth of our longstanding interest in mechanisms of prolactin action in normal and neoplastic target cells,<sup>9</sup> we recently

examined the effects of dietary ethanol on membrane prolactin-receptor concentrations in target tissue in rats. In both sexes, ethanol decreased membrane prolactin receptors,<sup>5</sup> a change consistent with decreased rather than increased responsiveness of a target tissue to the hormone.

In summary, the available laboratory data support neither serum prolactin nor target-organ responsiveness to prolactin as a mediator of the increased risk of breast cancer associated with alcohol consumption. In view of the myriad of unidentified confounding factors that may be associated with an increased risk of this disease, the effect attributed to alcohol should be interpreted with caution.

RAPHAEL J. WITORSCH, PH.D.  
Medical College of Virginia

Richmond, VA 23298

1. Williams RR. Breast and thyroid cancer and malignant melanoma promoted by alcohol-induced pituitary secretion of prolactin. *T.S.H.*, and *M.S.H.* *Lancet* 1976; 1:996-9.
2. Schrauzer GN, McGinnes JE, Ishmael D, Bell LJ. Alcoholism and cancer. I. Effects of long-term exposure to alcohol on spontaneous mammary adenocarcinoma and prolactin levels in C3H/St mice. *J Stud Alcohol* 1979; 40:240-6.
3. Lee M, Wakabayashi K. Pituitary and thyroid hormones in pregnant alcohol-fed rats and their fetuses. *Alcoholism (NY)* 1986; 10:428-31.
4. Sanchis R, Esquifino A, Guerci C. Chronic ethanol modifies estrous cyclicity and alters prolactin and LH levels. *Pharmacol Biochem Behav* 1985; 23:221-4.
5. Seilicovich A, Rettori V, Koch OR, Duvilanski B, Diaz M del C, Debeljuk L. The effect of acute and chronic ethanol administration on prolactin secretion in male rats. *J Androl* 1982; 3:344-8.
6. Dave JR, Krieg RJ Jr, Witorsch RJ. Modulation of prolactin binding sites in vitro by membrane fluidizers: effects on male prostatic and female hepatic membranes in alcohol-fed rats. *Biochim Biophys Acta* 1985; 816:313-20.
7. Välimäki M, Härkönen M, Ylikhärri R. Acute effects of alcohol on female sex hormones. *Alcoholism (NY)* 1983; 7:289-93.
8. Mendelson JH, Mello NK, Ellingboe J. Acute alcohol intake and pituitary gonadal hormones in normal human females. *J Pharmacol Exp Ther* 1981; 218:23-6.
9. Witorsch RJ, Dave JR, Adler RA. Prolactin receptors: the status of knowledge and current concepts concerning the mechanism of action of prolactin. In: Kalimi MY, Hubbard JR, eds. *Peptide hormone receptors*. Berlin: Walter de Gruyter, 1987:63-127.

The above letters were referred to the authors and editorialist in question, who offer the following replies:

*To the Editor:* The formula for body-mass index in Table 1 of our article, as Muncie indicates, should have read  $w(\text{kg})/h(\text{cm} \times 100)^2$ . The correct formula was used in all our analyses.

The other letters raise a number of interesting points regarding possible mechanisms underlying the association between alcohol and breast cancer. The epidemiologic data do seem sufficiently strong at this time to justify further efforts to elucidate these mechanisms. It would be particularly useful for investigators to model the biologic effects of long-term "moderate" alcohol consumption, since it is plausible that these effects differ from those induced by acute high-dose intake.

We emphasize, though, that the epidemiology of alcohol and breast cancer is by no means definitive. Further confirmatory studies are needed, especially in populations with a greater range of alcohol consumption, as are more refined efforts to evaluate age at effect, dose, and type of beverage.

ARTHUR SCHATZKIN, M.D., DR.P.H.,  
ROBERT N. HOOVER, M.D., SC.D.,  
CHRISTINE L. CARTER, PH.D., M.P.H., LOUISE BRINTON, PH.D.,  
MARSHA REICHMAN, PH.D., D. YVONNE JONES, PH.D.,  
REGINA G. ZIEGLER, PH.D., M.P.H.,  
AND PHILIP R. TAYLOR, M.D., S.M.  
Bethesda, MD 20892  
National Cancer Institute

*To the Editor:* The repeated observations of a direct association between alcohol intake and breast cancer demand careful consider-

Vol. 3  
ation  
or bio  
Drs  
tors s  
observ  
suppo  
breast  
ated w  
to mod  
from E  
consum  
gumen  
smokin  
hypoth  
cancer  
gardin  
find a  
dence  
beer as  
other s  
have a  
Cava  
than al  
ages m  
amount  
ment of  
the risk  
Expla  
need to  
present  
observa  
from an  
mental  
the mos  
amount  
to explo  
inciden  
reviewe  
ther exp  
intrigui  
of the a  
prolacti  
mechani  
inciden  
as our p  
develop

Boston,

1. LA MC breast 7.
2. Talam cancer.
3. La Ved hol con 61-5.
4. Buring postme Epidem
5. Ames Science

*To the Editor:* The repeated observations of a direct association between alcohol intake and breast cancer demand careful consideration. First of all, diagnosis is hardly a study of a

ation of possible explanations, whether they be confounding factors or biologic mechanisms.

Drs. Andrianopoulos and Nelson suggest that psychosocial factors such as depression and stress may explain the association we observed. Few data exist, including those that they have cited, to support a relation between depression or stress and the risk of breast cancer. Although heavy alcohol consumption may be associated with stress, there is little evidence that this is true for the light to moderate use in our study population. In addition, three studies from France and Italy,<sup>1-3</sup> with a different social context of alcohol consumption, showed similar findings, thereby weakening their argument further. Andrianopoulos and Nelson suggest that cigarette smoking also reflects stress; if so, our data do not support their hypothesis, since smoking was not related to an excess risk of breast cancer. Andrianopoulos and Nelson misrepresent our statement regarding the association with wine consumption; although we did not find a significant independent relation with this beverage, the confidence intervals for wine consumption included the effects found for beer and liquor. Since an association with wine has been seen in other studies, the overall evidence suggests that wine is likely to have a similar relation to breast cancer.

Gavaler et al. raise the interesting possibility that factors other than alcohol — specifically, phyto-estrogens — in alcoholic beverages may explain our findings. However, it is unclear whether the amounts are large enough to cause physiologic effects; even replacement estrogen given in pharmacologic doses has little influence on the risk of breast cancer.<sup>4</sup>

Explanations for the association, other than alcohol, certainly need to be considered. However, the alcohol in these beverages is present in sufficient concentrations to have a wide variety of readily observable biochemical and physiologic effects. In reviewing data from animal and in vitro studies of the relative potency of environmental carcinogens, Ames et al.<sup>5</sup> concluded that alcohol is among the most important potential chemical carcinogens because of the amounts consumed. We therefore believe it will be most profitable to explore possible mechanisms whereby alcohol may influence the incidence of breast cancer. Thus, the evidence regarding melatonin reviewed by Drs. Stevens and Hiatt is interesting and deserves further exploration. The findings of Herbert et al. provide both an intriguing potential mechanism and a possible modifier of the effect of the alcohol. The data of Witorsch reduce the likelihood that prolactin is a mediating factor. These efforts to identify possible mechanisms are worthy of pursuit because of the extremely high incidence rates of breast cancer in the industrialized world, as well as our present failure to understand the cause of this disease or to develop effective preventive measures.

WALTER C. WILLETT, MEIR J. STAMPFER,  
GRAHAM A. COLDITZ, BERNIE A. ROSNER,  
CHARLES H. HENNEKENS, AND FRANK E. SPEIZER  
Boston, MA 02115 Channing Laboratory

1. L&MG, Hill C, Kramar A, Flamant R. Alcoholic beverage consumption and breast cancer in a French case-control study. *Am J Epidemiol* 1984; 120:350-7.
2. Talamini R, La Vecchia C, Decarli A, et al. Social factors, diet and breast cancer in a northern Italian population. *Br J Cancer* 1984; 49:723-9.
3. La Vecchia C, Decarli A, Franceschi S, Pampallona S, Tognoni G. Alcohol consumption and the risk of breast cancer in women. *JNCI* 1985; 75: 61-5.
4. Buring JE, Hennekens CH, Lipnick RJ, et al. A prospective cohort study of postmenopausal hormone use and risk of breast cancer in U.S. women. *Am J Epidemiol* 1987; 125:939-47.
5. Ames BN, Magaw R, Gold LS. Ranking possible carcinogenic hazards. *Science* 1987; 236:271-80.

*To the Editor:* The brevity of Dr. Lindegård's report on the findings in the Gothenburg Population Cohort Study makes it difficult to evaluate. But one or two potential sources of bias do stand out. First of all, his measure of alcohol ingestion is based simply on a diagnosis of alcoholism, cirrhosis of the liver, or pancreatitis. This is hardly a measure of the amount ingested. It does not permit a study of a dose-response effect or of the effect of anything except a

large amount of drinking, and it does not include heavy drinkers in whom alcohol-related disorders have not developed. His expected number of cases is minute, and a small change in the cases observed could yield significance. Secondly, in view of the facts that in most previous studies, women who never married had a higher risk of breast cancer than those who were ever married and, in addition, nulliparity or low parity carries a higher risk than multiparity, his finding that breast cancer does not vary with marital status is somewhat surprising.

He cites shortcomings in previous studies. One has to do with socioeconomic status, but the cohort studies of both Schatzkin and Hiatt and their colleagues adjusted for socioeconomic status, as did many others. Moreover, the studies of both Willett and Hiatt involved series of patients similar in size to the series of the Gothenburg study. A few of the studies completed in the past were conducted in patients drawn from one hospital only, like those of Dr. Lindegård, but most came from many hospitals.

The fact that more than 15 cohort and case-control studies carried out in three countries, using a variety of methods and, in most cases, adjusting for known risk factors for breast cancer, all suggest an increased risk of breast cancer with an increase in the ingestion of alcohol leads me again to suggest that the relation may be real. Two of the three studies that showed no relation could not have been expected to because of methodologic idiosyncrasies. The same might be said of the Gothenburg inquiry. The volume of congruent findings on this question is large indeed, and I am still forced to conclude that in view of the high incidence of this difficult-to-treat disease and its high case fatality rate, one should make recommendations that might reduce its incidence.

SAXON GRAHAM, PH.D.  
State University of New York  
School of Medicine

Buffalo, NY 14214

#### APLASTIC ANEMIA, MALIGNANT LYMPHOMA, AND THE ACQUIRED IMMUNODEFICIENCY SYNDROME

*To the Editor:* The acquired immunodeficiency syndrome (AIDS) has been complicated by multiple hematologic abnormalities, including single or multiple cytopenias associated with variable bone marrow morphology.<sup>1</sup> A case of aplastic anemia in a homosexual man with AIDS and Kaposi's sarcoma has previously been reported<sup>2</sup>; however, antibodies to human immunodeficiency virus (HIV) were not measured. We report the association of severe aplastic anemia, malignant lymphoma, and positive HIV-antibody status.

A 19-year-old black woman was transferred to University Hospitals of Cleveland on April 11, 1987, with a presumptive diagnosis of aplastic anemia. A complete blood count showed a hematocrit of 26 percent, with a reticulocyte count of less than 1 percent. The white-cell count was 900 per microliter, and the platelet count 12,000 per microliter. A bone marrow biopsy showed 5 to 10 percent cellularity consisting entirely of lymphocytes, plasma cells and histiocytes, and focal aggregates of large, pleomorphic lymphoid cells suggestive of malignant lymphoma. Immunocytochemical analysis showed rare kappa and IgG staining of the large atypical lymphoid population. Staging CT scanning showed multiple 1- to 2-cm retroperitoneal nodes. An enzyme-linked immunosorbent assay for antibody to HIV was strongly reactive. Western blot analysis confirmed HIV positivity. Risk factors for HIV transmission included a blood transfusion in January 1987 and a suspected history of drug abuse.

The patient's hospital course was marked by persistent severe cytopenias, respiratory deterioration attributed to intrapulmonary hemorrhage, and massive retroperitoneal hemorrhage. Despite vigorous supportive measures, the patient died on May 11, 1987. Her family refused to grant permission for an autopsy.

The diagnosis of aplastic anemia in this case was established by the presence of severe pancytopenia, reticulocytopenia, and persistent marrow cellularity of less than 10 percent. Atypical marrow lymphoid aggregates have commonly been observed in patients with AIDS,<sup>3</sup> but the marked cellular atypia and presence of sur-