Coffee

Facts and Controversies

Gale M. Etherton, Mahendr S. Kochar, MD

In this article, we review current literature on coffee, both regular and decaffeinated, and its potential effects in humans. Moderate coffee consumption is believed to have no persistent effect on blood pressure. Large intake of coffee may increase total cholesterol levels; boiled coffee increases cholesterol levels more than filtered coffee. Consuming more than four cups per day may be associated with increased risk of acute myocardial infarction. There appears to be an association between urinary bladder cancer and coffee consumption. No association was found between ingestion of coffee and incidence of duodenal ulcer and ulcerative colitis. Increased coffee consumption by pregnant women appears to decrease fetal birth weight. Fetal heart rate, respiration, and both maternal and fetal anemia are increased with coffee consumption but coffee has not been shown to be teratogenic. Coffee consumption appears to pose no particular threat in most people if consumed in moderation. Naturally decaffeinated, filter-brewed coffee further diminishes its potential harmful effects. *(Arch Fam Med. 1993;2:317-322)*

Coffee represents one of the world's leading commodities, and is considered by many to be America's national drink. Nearly 5.4 million kilograms of coffee is produced in the world every year.[1] Northern Scandinavian countries consume the most coffee. In 1989, over 50% of the US population older than 10 years drank coffee, the majority of whom were older than 30 years. Drinkers of decaffeinated coffee make up another 16.7% of the population. In the United States, nearly 5 kg of coffee is consumed per person per year, representing a total annual expenditure of nearly $2.5 billion.[1,2] In an effort to evaluate coffee's effects on humans, we conducted a search of world medical literature in English in the last 10 years using the databases of the National Library of Medicine and included articles on coffee with positive and negative findings in this review.

To assess the effects of coffee consumption on humans, we evaluated the population consuming coffee. One study of coffee drinkers in California found that men prefer caffeinated coffee at an early age and later switch to decaffeinated coffee, whereas women prefer decaffeinated coffee at all ages.[1] Furthermore, comparisons among coffee drinkers indicated that those who drink caffeinated coffee are more likely to smoke, drink alcohol, eat saturated fats and foods high in cholesterol, and exercise less frequently than those who drink decaffeinated coffee.[3] These findings suggest that the population of caffeinated coffee drinkers in general might have atherogenic behaviors that would put them at high risk for coronary heart disease. This possibility should be kept in mind when interpreting results from studies done on coffee and health.[3-6]

From the Medical College of Wisconsin and the Zablocki Veterans Affairs Medical Center, Milwaukee.

COMPOSITION OF COFFEE

Many factors influence the chemical composition of the beverage coffee, including

degree of roasting, brewing conditions, additives (such as sugar and cream), contaminants, and the nature and origin of the coffee itself. The percentage of volatile substances in household brew again varies according to method of preparation; in practice, however, 40% to 100% of the volatile substances present in dry coffee are extractable. Over 700 volatile substances have been identified in coffee, including carbonyl compounds, alcohols, acids, esters, terpenoid compounds, nitrogen- and sulfur-containing compounds, hydrocarbons, and heterocyclic and aromatic compounds. Of the nonvolatile soluble substances, caffeine is physiologically the most important. However, the other nonvolatile soluble substances include other purines, glycosides, lipids, melanoidins, and acids such as nicotinic and chlorogenic acids. Contaminants in green coffee include pesticides, nitrosamines, organic solvents, and mycotoxins due to the presence of moldy beans, although roasting destroys 80% to 99% of the mycotoxins. Some of these contaminants have recognized toxicologic and carcinogenic effects.[1]

CAFFEINE

As previously mentioned, the primary component of physiological concern in coffee is caffeine (1,3,7-trimethylxanthine). The typical caffeine content of brewed coffee is 85 to 100 mg per 175-mL (6-oz) cup and of instant coffee is 65 mg per cup. By comparison, there is 40 mg of caffeine in a cup of tea and 45 mg in 350 mL (12 oz) of caffeinated soft drink. Decaffeinated coffee has less than 2 mg of caffeine per cup. Caffeine is completely absorbed from the gastrointestinal tract, reaching a peak concentration in blood within 30 to 60 minutes after ingestion. Its concentration, and hence its effect, is additive with half-lives ranging from 2 to 12 hours and averaging 4 to 6 hours. Moderately heavy coffee drinkers have mean plasma caffeine concentrations of 4.4 mg/L over 24 hours. The effect of caffeine varies for each individual depending on how much is consumed, the schedule of consumption, and the elimination half-life.

PHARMACOLOGIC EFFECTS

In humans, caffeine is metabolized into more than 25 metabolites, the primary ones being paraxanthine, theobromine, and theophylline. These xanthine derivatives (1) act as an adenosine receptor antagonist, (2) inhibit cyclic nucleotide phosphodiesterase activity, (3) mobilize calcium, and (4) inhibit monoamine oxidase activity.[7-9] The most important effect of caffeine is antagonism to adenosine receptor found in the brain, kidney, cardiovascular system, respiratory system, gastrointestinal system, and adipose tissue. Adenosine inhibits cyclic adenosine monophosphate (cAMP) production within a cell by binding to high-affinity A1 receptors, or conversely, stimulates cAMP production within a cell by binding to low-affinity A2 receptors.[7] Cyclic adenosine monophosphate acts as a second messenger to activate a cAMP-dependent protein kinase, which in turn phosphorylates selected proteins within the cell. This phosphorylation may be inhibitory or stimulatory for that particular protein depending on the protein. Through this second messenger mechanism, a variety of cellular functions can be regulated. Caffeine nonselectively blocks both adenosine receptors (A1 and A2), thereby preventing any second messenger function. By binding to high-affinity A1 receptors, caffeine prevents adenosine from inhibiting cAMP production. Conversely, by binding to low-affinity A2 receptors, caffeine prevents adenosine from stimulating cAMP production. Thus, caffeine disrupts the second messenger function of cAMP with these mechanisms. Furthermore, the inhibitory effect of caffeine on cyclic nucleotide phosphodiesterase prevents the cellular breakdown of cAMP and thereby prolongs its effect.[10] Through these actions, caffeine exerts its varied effects such as diuresis, central nervous system stimulation, increased cardiac contractility, bronchodilatation, and analgesia as well as other functions.[7,9]

Tolerance to many of these and other effects of caffeine develop within a few days, such that coffee drinkers exhibit withdrawal symptoms when its intake is discontinued. Daily dose at which withdrawal occurs is approximately 2½ cups of coffee.[11] Symptoms of withdrawal include headache, drowsiness, fatigue, decreased performance, dysphoric mood change, muscle pain/stiffness, flulike symptoms, nausea/vomiting, anxiety, and caffeine craving.[7,12,13] Physicians should be aware that symptoms of caffeine withdrawal can occur in patients who are taking caffeine-containing prescription or over-the-counter analgesic or antihistaminic preparations after they stop taking them.

EPIDEMIOLOGIC STUDIES

Numerous epidemiologic and animal research studies have been conducted to assess the harmful effects of long-term coffee ingestion. Both case-control and cohort studies have been used to evaluate coffee's effects on humans, but, as yet, no clear picture has emerged. Often these studies are plagued with problems, resulting in inconclusive findings. Standards of measurement for the prescribed "one cup" of coffee are often neglected, or, instead, dose-dependency of coffee toward the related outcome is ignored. Brewing methods are not always standardized or even clarified. Furthermore, confounding factors, such as smoking, are not always evaluated, nor is the study group completely characterized. Because of these problems in design, many incongruencies are found in the literature.

ANIMAL STUDIES

Animal research studies have their own problems. Both quantitative and qualitative differences in metabolism of caffeine, for example, can be seen between humans and experi-

Association of Coffee With Various Conditions*

Condition	Association		
	Probable	None Probable	Inconclusive
Cancer	Urinary bladder	Breast, colon, rectal	Pancreatic, ovarian
Cardiovascular and lipid disorders	Transient increase in BP in nontolerant individuals, increased total and LDL cholesterol, increased risk of acute myocardial infarction with >4 cups per day	Permanent increase in BP in normotensive subjects, HDL cholesterol level	Elevated BP in hypertensive subjects, enhanced thrombogenesis, cardiac arrhythmias, risk of CVD
Gastrointestinal effects	Increased cholecystokinin concentration, increased gallbladder contractions	Duodenal ulcer, ulcerative colitis, gallstones	...
Mental and behavioral effects	Anxiety, depression, panic disorders, sleep disruption	...	Somnolence
Pregnancy	Reduced fetal birth weight with >3 cups per day, increased fetal heart rate, increased fetal respiration rate, maternal and fetal anemia	Teratogenic potential	Infertility, prematurity
Other effects	Osteoporosis with >2 cups per day, diuresis, bronchodilatation, analgesia, chromosomal aberrations and sister chromatid exchange in vitro, fibrocystic breast disease	Improvement in alcholol-related incidents	Decrease in alcoholism, impaired sports performance, reduced immune functions, reduced growth of thyroid neoplasms

**BP indicates blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and CVD, cardiovascular disease.*

mental animals.[1] In addition, many in vitro studies on lower organisms are extrapolated to higher organisms and do not address in vivo equivalency. Thus, research data on the effect of coffee on humans must be viewed with this in mind.

CARCINOGENIC POTENTIAL

The International Agency for Research on Cancer of the World Health Organization evaluated coffee's carcinogenic risk to humans. Its evaluation of the literature through March 1990 led it to conclude that there is limited evidence in humans that coffee drinking is carcinogenic in the urinary bladder; however, potential bias or chance cannot be ruled out.[1] Further studies support this finding and add that smoking is an effect modulator.[14,15] The Agency's review of the effect of coffee on pancreatic and ovarian cancer concludes that there is inadequate evidence to determine the presence or absence of causal association between coffee and cancer. There is substantial evidence to conclude that coffee does not cause cancer of the breast. However, the Agency concluded that there is a positive association between coffee intake and fibrocystic breast disease, but cautioned that differences in disease detection between drinkers and nondrinkers of coffee and may account for this finding. Nevertheless, decreasing the amount of caffeine in the diet may be beneficial in decreasing breast pain associated with fibrocystic breast disease.[16] Other recent studies have concluded that coffee is not a contributing risk factor for developing colon or rectal cancer.[17] Thus, only urinary bladder cancer has any association with coffee ingestion, and that association is not without potential bias.

CARDIOVASCULAR AND LIPID EFFECTS

Several investigations have evaluated the cardiovascular disease risk of coffee consumption. Several studies indicate that coffee ingestion, regardless of brewing method, does acutely increase blood pressure in individuals who have not developed tolerance, but that once tolerance is reached, blood pressure returns to baseline.[1,7,18,19] In other studies, a small 1– to 5–mm Hg decrease in blood pressure was observed in normotensive adults who replaced regular with decaffeinated coffee.[20-22] Many studies conclude that a decrease in coffee/caffeine intake may be helpful in lowering blood pressure in subjects with hypertension but this is not a consistent finding.[23]

Analysis of the influence of coffee on serum lipids suggests that increased intake of coffee contributes to an increase in total serum cholesterol levels.[24,25] There is no difference between caffeinated and decaffeinated coffee in terms of the effects on blood lipids, which implies that the effects of coffee on lipids are due to component(s) other than caffeine.[26,27] Filtering coffee appears to decrease its potentially harmful effect of raising levels of low-density lipoprotein and total serum cholesterol,[7,24,28] whereas boiling coffee appears to increase this negative effect.[1,7,24,29,30] High-density lipoprotein cholesterol levels appear to be unrelated to coffee consumption.[29,31-34] Unfortunately, these studies have some design problems in that not all of them checked levels of low- and high-density lipoprotein and triglyceride, nor did they all account for brewing method, amount consumed, or gender.

Risk of having an acute myocardial infarction appears to be weakly associated with ingesting more than four cups of coffee per day. This as-

sociation has been found to exist independent of smoking, diabetes mellitus, hyperlipidemia, hypertension, body mass index, or years of education.[35-38] However, no comparison was made between decaffeinated and regular coffee, nor was the brewing method specified.

The effect of coffee on hemostasis remains unclear, but it may enhance thrombotic tendency.[39-41] Caffeine may induce cardiac arrhythmia in humans.[42] Of the studies done to evaluate its effect on cardiovascular disease itself, four studies[42-45] concluded that coffee is a safe beverage and is not a risk factor for cardiovascular disease; yet, again, four other studies[43,46-48] concluded that coffee ingestion is a risk factor for cardiovascular disease, but only when over six cups per day is consumed.

GASTROINTESTINAL EFFECTS

No association has been found between coffee ingestion, regular or decaffeinated, and the incidence of duodenal ulcer or ulcerative colitis.[49,50] Although ingestion of coffee does appear to bring on dyspepsic symptoms in some,[49,51] it does not appear to affect any present ulcer activity.[49,52]

MENTAL AND BEHAVIORAL EFFECTS

Caffeine exacerbates the symptoms of anxiety[53] and depression[54] and can make panic disorders worse.[55] Two to four cups of coffee at bedtime can induce significant disruption of sleep but individual differences occur within a wide range.[56] This effect is compatible with the stimulant properties of caffeine.[57] Some people, on the other hand, get an idiosyncratic reaction and develop somnolence following caffeine ingestion.[58]

COFFEE AND PREGNANCY

Studies of the effect of coffee on infertility and prematurity are inconclusive.[59-61] However, ingestion of over three cups of coffee per day appears to decrease fetal birth weight.[1,7,62-64] Coffee, both decaffeinated and regular, increases fetal heart rate and respiration.[65] Another study found coffee to be independently associated with increased maternal and fetal anemia.[64] Coffee has not been shown to be teratogenic.[1,7,63]

OTHER EFFECTS

Various other studies have examined the effect of coffee on the body. Coffee ingestion of more than two cups per day has been implicated as a risk factor for osteoporosis because of the effect of caffeine on increasing urinary calcium output.[66] Caffeinated coffee's diuretic effects have been shown not to be mediated by atrial naturetic factor.[67] Both regular and decaffeinated coffee give rise to increments in plasma cholecystokinin concentration and increase gallbladder contractions.[68] No association was found between consumption of coffee and incidence of gallstones.[69] Finally, one study suggests that coffee may modify various immune functions.[70]

Mutagenicity studies on the effects of coffee indicate that brewed (both decaffeinated and regular) and instant coffee induce chromosomal aberrations and sister chromatic exchange in cultured human lymphocytes and/or cultured mammalian cells.[1] Other studies conclude that these sister chromatid exchanges are not mediated by dicarbonyls alone or by peroxides alone.[65,66,71,72]

THERAPEUTIC POTENTIAL

The therapeutic potential of coffee has also been examined. One study evaluated its effect on intoxicated individuals and noted that coffee did not decrease alcohol-induced driving-related incidents.[73] A preliminary study suggests that regular intake of coffee might help decrease alcoholism.[74] No conclusive evidence has been found to substantiate the belief that coffee/caffeine helps in the performance of sports; however, the National Collegiate Athletic Association of the United States has adopted bans on the use of caffeine prior to performance.[75,76] Known therapeutic uses of caffeinated coffee include antiasthmatic therapy and orthostatic and postprandial hypotension therapy, as well as analgesic therapy for migraine headaches.[7,77-79] A recent study has reported that caffeine can augment the analgesic effect of aspirin.[80] One study suggests that coffee may even play a protective role against the development of benign or malignant thyroid neoplasms by inhibiting cell growth through cAMP-mediated mechanisms.[81] The **Table** summarizes the effects of coffee and association between coffee drinking and various conditions.

In conclusion, coffee appears to pose no particular threat in most people when consumed in moderation (fewer than four cups per day) but individual differences exist, and some may be at risk of developing untoward effects. The potential dangers of caffeine could be further diminished by drinking only naturally decaffeinated, filter-brewed coffee.

Accepted for publication December 14, 1992.

Reprint requests to Department of Medicine and Pharmacology/Toxicology, The Medical College of Wisconsin, 5000 W National Ave, Milwaukee, WI 53295 (Dr Kochar).

REFERENCES

1. World Health Organization International Agency for Research on Cancer. Coffee, tea, mate, methylxanthines and methylgloxal. *IARC Monogr Eval Carcinog Risks Hum.* 1991;51:1-513.
2. Golenpaul A, ed. *The 1989 Information Please Almanac.* Boston, Mass: Houghton Mifflin Co; 1989:77.
3. Puccio EM, McPhillips JB, Barrett-Conner E, Ganiats TG. Clustering of atherogenic behaviors in coffee drinkers. *Am J Public Health.* 1990;80:1310-1313.
4. Jacobsen BK, Thelle DS. The Troms: Heart Study—is coffee drinking an indicator of a lifestyle with high risk for ischemic heart disease? *Acta Med Scand.* 1987;222:215-221.
5. Schreiber GB, Robins M, Maffeo CE, Masters MN, Bond AP, Morganstein D. Confounders contrib-

uting to the reported association of coffee or caffeine with disease. *Prev Med.* 1988;17:259-309.
6. Hemminiki E, Rankonen O, Rimpela A, Rimpela M. Coffee drinking among Finnish youth. *Soc Sci Med.* 1988;26:259-264.
7. Benowitz NL. Clinical pharmacology of caffeine. *Annu Rev Med.* 1990;41:277-288.
8. Denaro CP, Brown CR, Wilson M, Jacob P III, Benowitz NL. Dose dependency of caffeine metabolism with repeated dosing. *Clin Pharmacol Ther.* 1990;48:277-285.
9. Williams M, Jarvis MF. Adenosine antagonists as potential therapeutic agents. *Pharmacol Biochem Behav.* 1988;29:433-441.
10. Stryer L. *Biochemistry.* 2nd ed. San Francisco, Calif: WH Freeman Co; 1981:464.
11. Silverman K, Evans SM, Strain EC, Griffith RR. Withdrawal syndrome after the double blind cessation of caffeine consumption. *N Engl J Med.* 1992;327:1109-1114.
12. Hughes JR. Clinical importance of caffeine withdrawal. *N Engl J Med.* 1992;327:1160-1161.
13. Van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12-week double-blind trial. *BMJ.* 1990;300:1558-1559.
14. Clavel J, Cordier S. Coffee consumption and bladder cancer risk. *Int J Cancer.* 1991;47:207-212.
15. Ciccone G, Vineis P. Coffee drinking and bladder cancer. *Cancer Lett.* 1988;41:45-52.
16. Russell LC. Caffeine restriction as initial treatment for breast pain. *Nurse Pract.* 1989;14:36-37.
17. Rosenberg L. Coffee and tea consumption in relation to the risk of large bowel cancer: a review of epidemiologic studies. *Cancer Lett.* 1990;52:163-171.
18. Myers MG. Effects of caffeine on blood pressure. *Arch Intern Med.* 1988;148:1189-1193.
19. Jeong DU, Dimsdale JE. The effects of caffeine on blood pressure in the work environment. *Am J Hypertens.* 1990;3:749-753.
20. Bak AA, Grobbee DE. A randomized study on coffee and blood pressure. *J Hypertens.* 1990;4:259-264.
21. Van Dusseldorp M, Smits P, Thien T, Katan MB. Effect of decaffeinated versus regular coffee on blood pressure: a 12-week, double-blind trial. *Hypertension.* 1989;14:563-569.
22. Bak AA, Grobbee DE. Abstinence from coffee leads to a fall in blood pressure. *J Hypertens.* 1989;7(suppl):260-261.
23. MacDonald TM, Sharpe K, Fowler G, et al. Caffeine restriction: effect on mild hypertension. *BMJ.* 1991;303:1235-1238.
24. Pietinen P, Geboers J, Kesteloot H. Coffee consumption and serum cholesterol: an epidemiological study in Belgium. *Int J Epidemiol.* 1988;17:98-104.
25. Davis BR, Curb JD, Borhani NO, Prineas RJ, Molteni A. Coffee consumption and serum cholesterol in the hypertension detection and follow-up program. *Am J Epidemiol.* 1988;128:124-136.
26. Van Dusseldorp M, Katan MB, Demacker PNM. Effect of decaffeinated versus regular coffee on serum lipoproteins. *Am J Epidemiol.* 1990;132:33-40.
27. Superko HR, Bortz W Jr, Williams PT, Albers JJ, Wood PD. Caffeinated and decaffeinated coffee effects on plasma lipoprotein cholesterol, apolipoproteins and lipase activity: a controlled, randomized trial. *Am J Clin Nutr.* 1991;54:599-605.
28. Rosmarin PC, Applegate WB, Somes GW. Coffee consumption and serum lipids: a randomized, crossover clinical trial. *Am J Med.* 1990;88:349-356.
29. Zock PL, Katan MB, Merkus MD, van Dusseldorp M, Harryvan JL. Effect of a lipid rich fraction from boiled coffee on serum cholesterol. *Lancet.* 1990;335:1235-1237.
30. Pietinen P, Aro A, Tuomilento J, Uusitalo U, Korhonen H. Consumption of boiled coffee is correlated with serum cholesterol in Finland. *Int J Epidemiol.* 1990;19:586-590.
31. Aro A, Teirila J, Gref CG. Dose-dependent effect of serum cholesterol and apoprotein B concentrations by consumption of boiled, non-filtered coffee. *Atherosclerosis.* 1990;83:257-261.
32. Thelle DS, Heyden S, Fodor JG. Coffee and cholesterol in epidemiological and experimental studies. *Atherosclerosis.* 1987;67:97-103.
33. Tuomilehto J, Tanskanen A, Pietinen P, et al. Coffee consumption is correlated with serum cholesterol in middle aged Finnish men and women. *J Epidemiol Community Health.* 1987;41:237-242.
34. Donahue RP, Orchard TJ, Stein EA, Kuller LH. Lack of an association between coffee consumption and lipoprotein lipids and apolipoproteins in young adults: the Beaver County Study. *Prev Med.* 1987;16:796-802.
35. Klatsky AL, Freidman GD, Armstrong MA. Coffee use prior to myocardial infarction restudied: heavier intake may increase the risk. *Am J Epidemiol.* 1990;132:479-488.
36. Gramenzi A, Gentile A, Fasoli M, Negri E, Parazzini F, La Vecchia C. Association between certain goods and risk of myocardial infarction in women. *BMJ.* 1990;300:771-773.
37. La Vecchia C, Gentile A, Negri E, Parazzini F, Franceschi S. Coffee consumption and myocardial infarction in women. *Am J Epidemiol.* 1989;130:481-485.
38. Rosenberg L, Palmer JR, Kelly JP, Kaufman DW, Shapiro S. Coffee drinking and non-fatal myocardial infarction in men under 55 years of age. *Am J Epidemiol.* 1988;128:570-578.
39. Ammaturo V, Perricone C, Canazio A , et al. Caffeine stimulates in vivo platelet reactivity. *Acta Med Scand.* 1988;224:245-247.
40. Bak AA, Grobbee DE. Coffee, caffeine and hemostasis: a review. *Neth J Med.* 1990;37:242-246.
41. Bak AA, van Vliet HH, Grobbee DE. Coffee, caffeine and hemostasis: results from two randomized studies. *Atherosclerosis.* 1990;83:249-255.
42. Rosmarin PC. Coffee and coronary heart disease: a review. *Prog Cardiovasc Dis.* 1989;32:239-245.
43. Christensen L, Murray T. A review of the relationship between coffee consumption and coronary heart disease. *J Community Health.* 1990;15:391-408.
44. Wilson PW, Garrison RJ, Kannel WB, McGee DL, Castelli WP. Is coffee consumption a contributor to cardiovascular disease: insights from the Framingham Study. *Arch Intern Med.* 1989;149:1169-1172.
45. Grobbee DE, Rimm EB, Giovannucci E, Colditz G, Stampfer M, Willett W. Coffee, caffeine and cardiovascular disease in men. *N Engl J Med.* 1990;323:1026-1032.
46. Le Grady D, Dyer AR, Shekelle RB, et al. Coffee consumption and mortality in the Chicago Western Electric Company Study. *Am J Epidemiol.* 1987;126:803-812.
47. Lane JD, Manus DC. Persistent cardiovascular effects with repeated caffeine administration. *Psychosom Med.* 1989;51:373-380.
48. Tverdal A, Stensvold I, Solvoll K, Foss OP, Lund-Larson P, Bjartveit K. Coffee consumption and death from coronary heart disease in middle-aged Norwegian men and women. *BMJ.* 1990;300:556-559.
49. Elta GH, Behler EM, Colturi TJ. Comparison of coffee intake and coffee induced symptoms in patients with duodenal ulcer, non-ulcer dyspepsia and normal controls. *Am J Gastroenterol.* 1990;85:1339-1342.
50. Boyko EJ, Perera DR, Koepsell TD, Keane EM, Inui TS. Coffee and alcohol use and the risk of ulcerative colitis. *Am J Gastroenterol.* 1989;84:530-534.
51. Eisig JN, Zaterka S, Massuda HK, Bettarello A. Coffee drinking in patients with duodenal ulcer and a control population. *Scand J Gastroenterol.* 1989;24:796-798.
52. Kaneko E, Ooi S, Ito G, Honda N. Natural history of duodenal ulcer detected by the gastric mass surveys in men over 40 years of age. *Scand J Gastroenterol.* 1989;24:165-170.
53. Greden JF. Anxiety or caffeinism: a diagnostic dilemma. *Am J Psychiatry.* 1974;131:1089-1092.
54. Neil JF, Himmerhock JM, Mallinger AG, Mallinger J, Hamin I. Caffeinism complicating hyposomnic depressive episodes. *Compr Psychiatry.* 1978;4:377-385.
55. Charney DS, Heninger GR, Hatlow PI. Increased anxiogenic effects of caffeine in panic disorders. *Arch Gen Psychiatry.* 1985;42:233-243.
56. Goldstein A, Kaizer J. Psychotropic effects of caffeine in man. *Clin Pharmacol Ther.* 1969;10:477-488.
57. Rosenthal L, Roehrs T, Zwyghuizen-Doorenbos A, Plath D, Roth T. Alerting effects of caffeine after normal and restricted sleep. *Neuropsychology.* 1991;4:103-108.
58. Regestein QR. Pathogenesis of sleepiness induced by caffeine. *Am J Med.* 1989;86:586-588.
59. Joesoef MR, Beral V, Rolfs RT, Aral SO, Cramer DW. Are caffeinated beverages risk factors for delayed conception? *Lancet.* 1990;335:136-137.
60. Wilcox A, Weinberg C, Baird D. Caffeinated beverages and decreased fertility. *Lancet.* 1988;2:1453-1456.
61. Olsen J. Cigarette smoking, tea and coffee drinking, and subfecundity. *Am J Edipemiol.* 1991;133:734-739.
62. Berger A. Effects of caffeine consumption on pregnancy outcome: a review. *J Reprod Med.* 1988;33:945-956.
63. Narod SA, De Sanjose S, Victora C. Coffee during pregnancy: a reproductive hazard? *Am J Obstet Gynecol.* 1991;164:1109-1114.
64. Munoz LM, Lonnerdal B, Keen CL, Dewey KG. Coffee consumption as a factor in iron deficiency anemia among pregnant women and their infants in Costa Rica. *Am J Clin Nutr.* 1988;48:645-651.
65. Salvador HS, Koos BJ. Effects of regular and de-

caffeinated coffee on fetal breathing and heart rate. *Am J Obstet Gynecol.* 1989;160:1043-1047.
66. Kiel DP, Felson DT, Hannan MT, Anderson JJ, Wilson PW. Caffeine and the risk of hip fracture: the Framingham Study. *Am J Epidemiol.* 1990; 132:675-684.
67. Nussberger J, Mooser B, Maridor G, Juillerat L, Waeber B, Brunner HR. Caffeine induced diuresis and atrial naturetic peptides. *J Cardiovasc Pharmacol.* 1990;15:685-691.
68. Douglas BR, Jansen JB, Tham RT, Lamers CB. Coffee stimulation of cholecystokinin release and gall bladder contraction in humans. *Am J Clin Nutr.* 1990;52:553-556.
69. Jorgensen T. Gall stones in a Danish population: relation to weight, physical activity, smoking, coffee consumption and diabetes mellitus. *Gut.* 1989; 30:528-534.
70. Melamed I, Kark JD, Spirer Z. Coffee and the immune system. *Int J Immunopharmacol.* 1990; 12:129-134.
71. Aeschbacher HU, Wolleb U, Loliger J, Spadone JC, Liardon R. Contribution of coffee aroma constituents to the mutagenicity of coffee. *Food Chem Toxicol.* 1989;27:227-232.
72. Tucker JD, Taylor RT, Christensen ML, Strout CL, Hanna ML. Cytogenic response to 1,2-dicarbonyls and hydrogen peroxide in Chinese hamster ovary AUXB1 cells and human peripheral lymphocytes. *Mutagenesis.* 1989;4:343-348.
73. Fudin R, Nicastro R. Can caffeine antagonize alcohol-induced performance decrements in humans? *Percept Motor Skills.* 1988;67:375-391.
74. Santos RM, Lima DR. Effects of coffee in alcoholics. *Ann Intern Med.* 1991;115:400.
75. Jacobsen BH, Kulling FA. Health and ergogenic effects of caffeine. *Br J Sports Med.* 1989;23: 34-40.
76. Tarnopolsky MA, Atkinson SA, Mac Dougall JD, Sale DG, Sutter JR. Psychological responses to caffeine during endurance running in habitual caffeine users. *Med Sci Sports Exerc.* 1989;21:418-424.
77. Pagano R, Negri E, Decarli A, La Vecchia C. Coffee drinking and prevalence of bronchial asthma. *Chest.* 1988;94:386-389.
78. Ahmad RA, Watson RD. Treatment of postural hypotension: a review. *Drugs.* 1990;39:74-85.
79. Heseltine D, Dakkak M, Woodhouse K, MacDonald IA, Potter JF. The effect of caffeine on postprandial hypotension in the elderly. *J Am Geriatr Soc.* 1991;39:160-164.
80. Schachtel BP, Fillingim JM, Lane AC, Thoden WR, Baybutt RI. Caffeine as an analgesic adjuvant: a double-blind study comparing aspirin with caffeine to aspirin and placebo in patients with sore throat. *Arch Intern Med.* 1991;151:733-737.
81. Linos A, Linos DA, Vgotza N, Souvatzoglou A, Koutras DA. Does coffee consumption protect against thyroid disease? *Acta Chir Scand.* 1989; 155:317-320.